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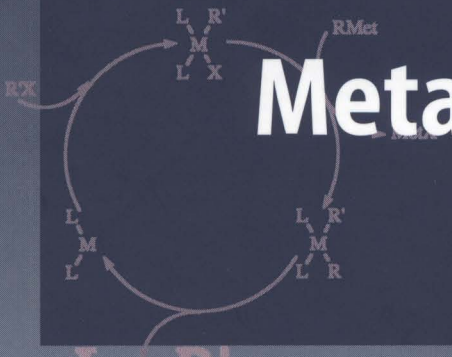
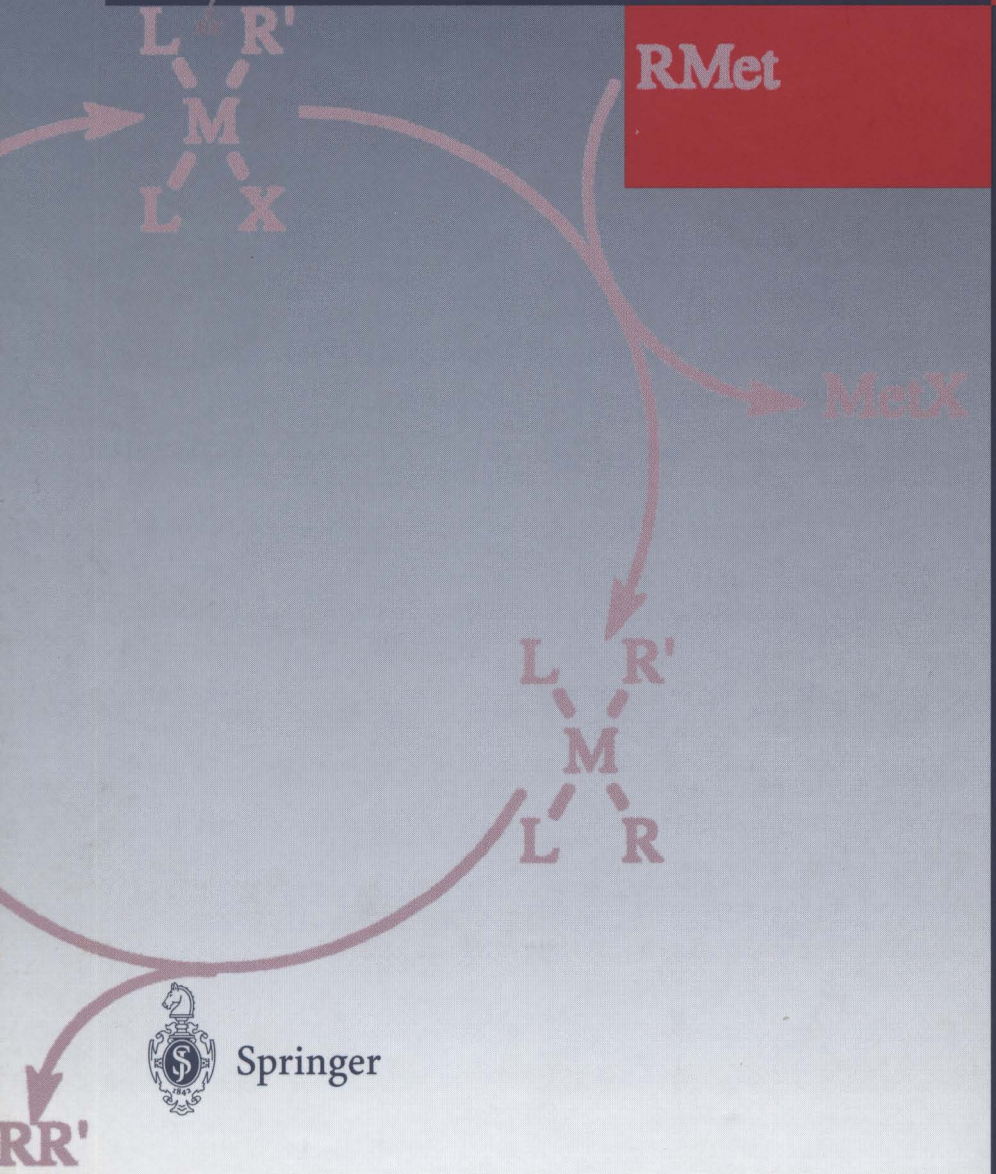
Application of Transition Metal Catalysts in Organic Synthesis





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With 20 Tables

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Preface

The present book may be considered as a continuation of our laboratory manuals dealing with the chemistry of acetylenes, allenes and polar organometallics. It contains a number of experimental procedures for the catalytic use of copper, nickel and palladium compounds in organic synthesis based on methods described in literature and carried out by the authors of this book and their coworkers. The original plan was to cover a much broader field of transition metal chemistry, but this was soon dropped as being too ambitious. It would take too much time and effort to become familiar with all experimental methods in the extensive field of transition metal-catalyzed organic synthesis, a necessary condition to develop reliable procedures. We therefore decided to restrict ourselves to sub-fields in which some experience had been acquired in our laboratory. The various methods are exemplified with procedures on a preparative scale, usually 50 or 100 mmolar, using normal laboratory glassware and reagents and starting compounds which are either relatively cheap or readily preparable. In addition, literature surveys of the various subjects are given.

We are indebted to Diosynth, DSM and Shell for additional financial and material support.

Utrecht, November 1997 Lambert Brandsma

Table of Contents

1 Catalysts, Ligands and Reagents

Although several transition metal catalysts are commercially available, one may prefer to make them oneself if larger quantities are needed. The procedures described in this chapter are taken from the literature, but in some of them modifications have been introduced in order to facilitate their performance.

1.1 Catalysts

1.1.1 Copper Halides

Copper(I) chloride and the corresponding *bromide* and *iodide* (CuX or Cu_2X_2) are almost colourless compounds. Molecular weights for CuX are 98.9, 143.4 and 190.4, respectively. Due to oxidation a light-green or – in the case of CuI – light-brown colour appears during storage, but the small traces of Cu(II) present in most cases do not affect the intended result of a reaction in which the salts are used in catalytic amounts. The preparations of CuBr and CuCl are described in Vogel's Textbook of Practical Organic Chemistry, 5th ed., Longman, London (1991) p. 428 and by C.S. Marvel and S.M. Mc Elvain in Org. Synth., Coll. Vol. 1 (1941), 170, respectively.

For some reactions the use of the *complex* $Cu(I)Br{\cdot}(CH_3)_2S$ (molecular weight 205.5) is recommended (e.g. by H.O. House, C.-Y. Chu, J.M. Wilkins and M.J. Umen, J. Org. Chem. (1975) 40, 1460). Catalytic reactions are sometimes carried out in the presence of additional amounts of dimethyl sulfide, which serve to increase the solubility of the intermediary complex. A serious disadvantage is the stench of the sulfide liberated during the work-up.

1.1.1.1 Solubilization of Copper(I) Halides

Copper(I) halides can be *solubilized* by shaking the powders with a solution of an excess of anhydrous lithium bromide in tetrahydrofuran. In this way (concentrated) solutions of the *cuprate LiCuXBr* can be prepared. These may have a rather dark green or brown colour, caused by the presence of small amounts of Cu(II). The advantage of using these solubilized copper(I)halides over addition of the powders in a catalytic reaction with an organometallic reagent is that the catalyst is quickly and homogeneously distributed.

1.1.2 Nickel Catalysts

1.1.2.1 Nickel(II)bromide·bis(triphenylphosphane)

$NiBr_2(Ph_3P)_2$, mol. weight 742.8, air-stable, green powder.

Preparation: (Cf. K. Yamamoto, Bull. Chem. Soc. Japan (1954) 27, 501.) At 70 °C, 60.0 g (0.23 mol) of triphenylphosphane was dissolved in 350 ml of 96% ethanol. A solution of 27.3 g (0.10 mol) of $NiBr_2 \cdot 3H_2O$ in 100 ml of ethanol (70 °C) was added over a few min with efficient mechanical stirring. After stirring for 1 h at 60–65 °C, the thick suspension was allowed to cool to room temperature. The precipitate was filtered off on a sintered-glass funnel (G-3), washed three times with 75 ml-portions of ethanol and subsequently dried in vacuo (rotary evaporator-water aspirator, then oil pump, <1 mmHg pressure). The yield was 50 g.

1.1.2.2 Nickel(II)chloride·bis(triphenylphosphane)

$NiCl_2(Ph_3P)_2$, mol. weight 653.9, dark-green powder, can be prepared in an analogous way.

1.1.2.3 Nickel(II)chloride·1,3-bis(diphenylphosphino)propane

$NiCl_2 \cdot Ph_2P(CH_2)_3PPh_2$ ($NiCl_2$·dppp), mol. weight 541.8, red, air-stable powder.

Preparation: (Cf. G.R. Van Hecke, W. DeW. Horrocks, Jr., Inorg. Chem. (1960) 5, 1968.) Nickel(II)chloride·$6H_2O$ (4.8 g, 0.02 mol) was dissolved in 100 ml of methanol. A warm (~60 °C) solution of 8.2 g (0.02 mol) of 1,3-bis(diphenylphospino)propane (see Sect. 1.2.1.2) in 70 ml of tetrahydrofuran was added over 1 min with efficient stirring. After an additional half hour (at ~60 °C) the suspension was cooled to room temperature and then filtered on a sintered-glass funnel (G-3). The solid was washed twice with 30-ml portions of methanol and subsequently three times with 30-ml portions of water. The red powder was dried in vacuo (rotary evaporator, then oil-pump vacuum of <1 mmHg). Yield 10.1 g (86.4%).

1.1.2.4 Nickel(II)chloride·1,2-bis(diphenylphosphino)ethane

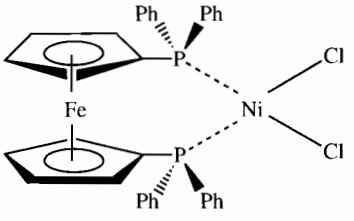
$NiCl_2 \cdot Ph_2PCH_2CH_2PPh_2$ ($NiCl_2$·dppe), mol. weight 527.8, orange-yellow, air-stable powder was prepared in a similar way from $NiCl_2 \cdot 6H_2O$ and $Ph_2PCH_2CH_2PPh_2$ (see Sect. 1.2.1.1).

1.1.2.5 Nickel(II)chloride·1,4-bis(diphenylphosphino)butane

$NiCl_2 \cdot Ph_2P(CH_2)_4PPh_2$ ($NiCl_2$·dppb), mol. weight 555.8 (purple powder), was obtained in a similar way from $NiCl_2 \cdot 6H_2O$ and $Ph_2P(CH_2)_4PPh_2$ (see Sect. 1.2.1.3) in almost quantitative yield.

1.1.2.6 Nickel(II)chloride·1,1′-bis(diphenylphosphino)ferrocene

($NiCl_2$·dppf), mol. weight 683.8, dark green, air-stable powder.



Preparation: Dppf (1,1'-bis(diphenylphosphino)ferrocene) (Sect. 1.2.2), (5.54 g, 0.01 mol) was dissolved in 35 ml of toluene heated at ~65 °C. A solution of 0.01 mol (2.4 g) of $NiCl_2 \cdot 6H_2O$ in 15 ml of ethanol was added to the stirred warm solution. After stirring for 1 h at ~60 °C, the suspension was cooled to −10 °C and filtered on a sintered-glass funnel (G-3). The solid was successively washed with cold (0 °C) ethanol and pentane. The solid was dried in vacuo (rotary evaporator, then oil-pump vacuum <1 mmHg). The yield was 5.4 g (79%).

1.1.2.7 Nickel(II)bromide·1,1′-bis(diphenylphosphino)ferrocene

($NiBr_2$·dppf), mol. weight 772.7, black, air-stable powder, was prepared in a similar way from dppf and $NiBr_2 \cdot 3H_2O$. The yield was ~90%.

1.1.2.8 trans-Chloro(1-naphthyl)bis(triphenylphosphane)nickel

$C_{10}H_7NiCl(PPh_3)_2$, mol. weight 745.2, yellow, air-stable powder.

Preparation: (Cf. J. van Soolingen, H. D. Verkruijsse, M.A. Keegstra, L. Brandsma, Synth. Commun. (1990) 20, 3153.) A stirred mixture of 48.0 g (0.20 mol) of $NiCl_2 \cdot 6H_2O$, 115.3 g (0.44 mol) of triphenylphosphane and 900 ml of 96% ethanol was heated until a gentle reflux started. 1-Chloronaphthalene (0.4 mol, 65 g, excess) was then added, followed by zinc dust (13 g, ~0.2 mol, Merck, analytical grade) over 5 min. The dark-green mixture very soon turned yellow. After stirring and heating under reflux for 1.5 h (under nitrogen), the mixture was cooled to 20 °C. Four 20-ml portions of 30% aqueous hydrochloric acid were added over 15 min. After stirring for ~1.5 h, the solid was filtered off on a sintered-glass funnel and successively washed with 200 ml of ethanol, twice with 200 ml of 1M aqueous hydrochloric acid, twice with 200 ml of 96% ethanol and once with 200 ml of pentane. The yellowish solid was dried in vacuo (first rotary evaporator, then oil-pump vacuum <1 mmHg, bath temperature not higher than 45 °C). The yield was at least 80%.

1.1.2.9 trans-Bromo(1-naphthyl)bis(triphenylphosphane)nickel and trans-Bromo(phenyl)bis(triphenylphosphane)nickel

trans-Bromo(1-naphthyl)bis(triphenylphosphane)nickel, $C_{10}H_7NiBr(PPh_3)_2$, mol. weight 790.0, orange, air-stable powder, and *trans*-bromophenyl)bis(triphenylphosphane)nickel, C_6H_5NiBr-$(PPh_3)_2$, mol. weight 740.0, orange, air-stable powder, can be prepared by a procedure, similar to 1.1.2.8, from PPh_3, the corresponding aryl bromides and $NiBr_2 \cdot 3H_2O$.

1.1.3 Palladium Catalysts

1.1.3.1 Palladium(II)chloride·bis(acetonitrile)

$PdCl_2(CH_3CN)_2$, mol. weight 259.3, yellow, air-stable powder.

Preparation: A mixture of 3.0 g of finely powdered palladium dichloride and 200 ml of dry acetonitrile was stirred magnetically and heated under reflux until the $PdCl_2$ had dissolved completely (~2–3 h), then the hot solution was concentrated in vacuo. The last traces of acetonitrile were removed at a pressure of <1 mmHg.

1.1.3.2 Palladium(II)chloride·bis(benzonitrile)

$PdCl_2(PhCN)_2$, mol. weight 383.5, can be prepared by a similar procedure (cf. M.S. Kharash, R.C. Seyler, F.R. Mayo, J. Am. Chem. Soc. (1938) 60, 882).

1.1.3.3 Palladium(II)chloride·bis(triphenylphosphane)

$PdCl_2(PPh_3)_2$, mol. weight 701.6, light-yellow, air-stable powder.

Preparation: A stirred mixture of 3.54 g (0.02 mol) of finely powdered palladium(II) chloride and 4 g of anhydrous lithium chloride in 150 ml of methanol was heated at 60 °C until the red-brown solid had dissolved (~15 min). A solution of 13.1 g (0.05 mol, excess) of triphenylphosphane in 25 ml of warm (50 °C) tetrahydrofuran was added in one portion. The mixture was stirred at ~50 °C until the brown colour had disappeared completely (1 to 2 h). The yellow suspension was cooled to room temperature and then filtered on sintered glass (G-3 filter). The solid was successively washed twice with 30-ml portions of methanol and once with dry ether. After drying in vacuo (rotary evaporator, then oil-pump vacuum), the product was obtained in 90–95% yield.

For another procedure, which uses DMF as a solvent, see A.O. King, E. Negishi, J. Org. Chem. (1978) 43, 358.

1.1.3.4 Palladium(II)chloride·1,4-bis(diphenylphosphino)butane

$PdCl_2 \cdot Ph_2P(CH_2)_4PPh_2$, ($PdCl_2$·dppb), mol. weight 603.5, light-yellow, air-stable powder.

Preparation: (Cf. D.R. Coulson, Inorg. Synth. (1972) 13, 121.) A stirred mixture of 0.02 mol (3.54 g) of finely powdered palladium(II) chloride, 4 g of anhydrous lithium chloride and 300 ml of methanol was heated at 60 °C until a clear solution had formed. A warm solution of 0.02 mol (8.5 g) of 1,4-diphenylphosphinobutane (dppb) (see Sect. 1.2.1.3) in 60 ml of tetrahydrofuran was added over a few seconds. After 45 min (at ~50 °C) the light-yellow suspension was cooled to 20 °C and filtered on sintered glass (G-3 filter). After washing twice with 30-ml portions of methanol (20 °C) and twice with ether, the solvent was removed in vacuo (rotary evaporator, then oil-pump vacuum, <1 mmHg) to give the complex in greater than 90% yields.

1.1.3.5 Palladium(II)chloride·1,1'-bis(diphenylphosphino)ferrocene

$PdCl_2$·dppf, mol. weight 731.5, air-stable orange-red powder.

Preparation: (Cf. T. Hayashi, M. Konishi, M. Kumada, Tetrahedron Lett. (1979) 1871.) 1,1-Bis(diphenylphosphino)ferrocene (0.02 mol, 11.1 g) (see Sect. 1.2.2) was dissolved at 65 °C in 75 ml of toluene. To the stirred solution was added a solution of 3.54 g (0.02 mol) of palladium(II)chloride and 3 g of anhydrous lithium chloride in 100 ml of 96% ethanol (for complete dissolution of $PdCl_2$ heating for ~1 h at 70 °C was required). After an additional 30 to 45 min (at 70 °C) the suspension was cooled to 20 °C and filtered on sintered glass (G-3 filter). The solid was washed three times with 25-ml portions of ethanol and subsequently twice with dry ether. After drying in vacuo (bath temperature ~40 °C) $PdCl_2$·dppf was obtained in almost quantitative yield.

1.1.3.6 Tetrakis(triphenylphosphane)palladium(0)

$Pd(PPh_3)_4$, mol. weight 1155, yellow, microcrystalline powder. It should be stored under inert gas, since it slowly turns brown upon exposure to air (without seriously affecting the catalytic activity, however).

Preparation: (Cf. D.R. Coulson, Inorg. Synthesis (1972) 13, 121.) In a 500-ml one-necked round-bottomed flask 3.54 g (0.02 mol) of finely powdered $PdCl_2$ and 26.2 g (0.10 mol) of triphenylphosphane were dissolved in 240 ml of dimethylsulfoxide with heating and magnetic stirring (we found cautious heating with an open flame more practical than with an oil bath). When at ~140 °C all $PdCl_2$ had dissolved, heating was stopped and hydrazine hydrate ($NH_2NH_2 \cdot H_2O$) (4.1 g) was added over ~1 min by syringe. The colour became darker, while nitrogen was evolved. One minute after this addition the mixture was cooled (water-bath) until the solution became turbid. The still hot suspension was stirred (without cooling bath) for an additional 20 min and subsequently cooled to 20 °C. The solid was filtered off on sintered glass (G-3), washed three times with 35-ml portions of ethanol and subsequently twice with 40-ml portions of diethyl ether. After drying in vacuo (rotary evaporator, then oil-pump vacuum <1 mmHg, bath temperature ~45 °C), 22 g (~95% yield) of yellow powder remained.

1.1.3.7 Tris(dibenzylideneacetone)dipalladium(0)·chloroform

$Pd_2(dba)_3 \cdot CHCl_3$, mol. weight 1035, purple crystals (dba = PhCH=CH-CO-CH=CHPh)

Preparation: (T. Ukai, H. Kawazura, Y. Ishii, J.J. Bonnet, J.A. Ibers, J. Organometal. Chem. (1974) 65, 253.) Palladium(II) chloride (1.05 g, 5.92 mmol) was added to a solution of 4.60 g (19.6 mmol) of dibenzylideneacetone and 3.90 g (47.5 mmol) of sodium acetate in 150 ml of methanol, heated at 50 °C. After stirring for 4 h at 40 °C, the mixture was allowed to cool. The purple precipitate was filtered off on sintered glass and successively washed with water and acetone. After drying in vacuo, the solid (3.39 g) was dissolved in 120 ml of chloroform (60 °C). The violet solution was filtered and the filtrate diluted with 170 ml of ether. After cooling to 10-15 °C, the purple precipitate was filtered on sintered glass, washed with ether and dried in vacuo. The yield was ~80%.

1.2 Ligands

A variety of phosphorus-containing mono- and bidentate ligands have been (and may be) used to tune the reactivity of transition-metal catalysts. Some can be prepared rather easily by one-pot procedures using relatively cheap reagents. The synthesis of potentially interesting ligands, such as $R_2P(CH_2)_nPR_2$ (with R = *prim-*, *sec-*, and *tert-*alkyl) and 1,1'-bis(diisopropylphosphino)ferrocene, is experimentally very demanding, since it involves the preparation of extremely air-sensitive secondary phosphanes (R_2PH) or water-sensitive chlorodialkylphosphanes (R_2PCl).

In this section, experimental instructions are given for the synthesis of some frequently used bidentate ligands and of triarylphosphanes.

1.2.1 1,n-Bis(diphenylphosphino)alkanes (n= 2,3,4)

These can be prepared in liquid ammonia as well as in tetrahydrofuran:

$$Ph_3P + 2\,M \xrightarrow{\text{liq. } NH_3} Ph_2PM + PhH + MNH_2 \quad (M = Li \text{ or } Na)$$

$$2\,Ph_2PM + X(CH_2)_nX \xrightarrow{\text{liq. } NH_3} Ph_2P(CH_2)_nPPh_2 \quad (X = Cl \text{ or } Br)$$

(if n=2, the dichloride must be used)

$$Ph_2PH + n\text{-}BuLi \xrightarrow{THF} Ph_2PLi$$

$$2\,Ph_2PLi + X(CH_2)_nX \xrightarrow{THF} Ph_2P(CH_2)_nPPh_2$$

(if n=2, the dichloride must be used)

1.2.1.1 1,2-Bis(diphenylphosphino)ethane

(dppe), mol. weight 398.2, air-stable solid.

Preparation: (Cf. T. Yoshida, M. Iwamoto, S. Yuguchi, JP 11, 934 (1967); C. A. (1968) 68, 105358 e; W. Hewertson, H.R. Watson, J. Chem. Soc. (1962) 1490.) In a 3-l round-bottomed, three-necked flask, equipped with an efficient mechanical stirrer and two outlets, was placed 1.5 L of anhydrous liquid ammonia (see Note 1). A solution (~35 °C) of 52 g (0.20 mol) of triphenylphosphane in 75 ml of tetrahydrofuran was cautiously poured into the flask (with both outlets temporarily being removed). Sodium (see Note 2) was cut in pieces of ~0.5 g each and these were introduced into the efficiently stirred mixture over 45 min. Usually, somewhat more than the theoretically required amount of 0.40 mol (9.2 g) was needed to cause a persisting (for at least 15 min) very dark colour of the solution (between brown and blue, the colours of dissolved Ph_2PNa and Na, respectively). Fifteen min after this addition a powder funnel was placed on one of the necks and finely powdered ammonium chloride (8 g) was introduced in 0.5 g-portions over 15 min with vigorous stirring (to neutralize most of the sodamide formed in the cleavage reaction). The powder funnel was then replaced with a dropping funnel containing a mixture of 0.10 mol (~10 g) of 1,2-dichloroethane (see Note 3) and 20 ml of diethyl ether. This mixture was added dropwise over 45 min to the vigorously stirred suspension (if 10 min after completion of this addition the mixture is still brown, an additional small amount of dichloroethane has to be added dropwise until the brown colour disappears). The ammonia was allowed to evaporate overnight. After addition of 500 ml of water, the product was extracted with small portions of chloroform. The organic solution was dried over magnesium sulfate and subsequently the solvent was completely removed by evacuation (rotary evaporator, then oil-pump vacuum <1 mmHg). The white solid was purified by crystallization from a 1 : 5 mixture of tetrahydrofuran and diethyl ether. The yield was ~70%.

^1H NMR spectrum ($CDCl_3$): 7.1–7.4 (m, 20H); 2.15; (t, 4H) ppm.

Notes:

1. Small amounts of water (<0.1 to 0.2%) do not seriously affect the result, since these are „neutralized" by the alkali amide formed in the cleavage. The greater part (but not all) of the water in the ammonia can be neutralized by adding small (0.1 to 0.2 g) pieces of sodium or potassium (at intervals of 1 to 2 min) until the blue colour persists longer than 10 min.
2. Lithium may also be used.
3. Dibromoethane cannot be used, since Ph_2PPPh_2 is formed by attack of Ph_2P^- on Br and subsequent fast reaction of Ph_2P^- with Ph_2PBr produced in the first step.

1.2.1.2 1,3-Bis(diphenylphosphino)propane

(dppp), mol. weight 412.2, air-stable solid, was prepared in an excellent yield as described in Sect. 1.2.1.1. Instead of 1,3-dichloropropane the dibromide may be used.

^1H NMR spectrum ($CDCl_3$): 7.1-7.4 (m, 20 H); 2.1-2.3 (m, 4H); 1.3-1.8 (m, 2 H) ppm.

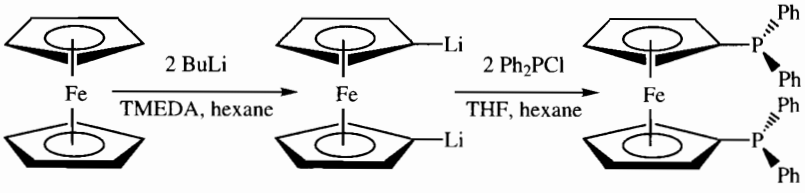
1.2.1.3 1,4-Bis(diphenylphosphino)butane

(dppb), mol. weight 426.1, air-stable solid, was prepared in excellent yields by reaction of Ph_2PNa or Ph_2PLi with $Cl(CH_2)_4Cl$ or $Br(CH_2)_4Br$ as described in Sect. 1.2.1.1.

^1H NMR spectrum (C_6D_6): 7.11-7.37 (m, 20H); 1.50 (m, 8H) ppm.

1.2.2 1,1'-Bis(diphenylphosphino)ferrocene

(dppf), mol. weight 554.2, orange, air-stable crystals.



Preparation: (Cf. J.J. Bishop, A. Davison, M.L. Katcher, D.W. Lichtenberg, R.E. Merril, J.C. Smart, J. Organometal. Chem. (1971) 27, 241; J.D. Unruh, J.R. Christenson, J. Mol. Catal. (1982) 14, 19.) A 1-l-three-necked, round-bottomed flask was equipped with a magnetic stirrer, a thermometer-gas inlet combination, and a reflux condenser. The flask was purged with nitrogen and charged with 9.2 g (50 mmol) of ferrocene and 250 ml of hexane. A solution of 1.6 M *n*-butyllithium in hexane (67 ml, 107 mmol) was quickly added and the resulting red suspension was stirred at room temperature while 12.0 g (103 mmol) of tetramethylethylenediamine (TMEDA) was added in one portion. The temperature rose to 30–35 °C within 5 min. The reaction mixture was heated on a water bath at 60 °C for one hour, during which the red suspension turned orange. The water bath was removed and 100 ml of dry THF (distilled from $LiAlH_4$/benzophenone) was added. The orange suspension was cooled to -40 °C. After removing the cooling bath, a mixture of 24.0 g (109 mmol) of chlorodiphenylphosphane and 50 ml of THF was added in three portions over five minutes. The temperature of the reaction mixture rose to about -25 °C and a yellow suspension was formed. The reaction mixture was stirred for an additional 15 min at room temperature. Subsequently it was concentrated to *ca.* 20% of its original volume using a rotatory evaporator, and then filtered on a G-3 glass filter. The precipitate was successively washed with 50 ml of 2 M hydrochloric acid, 50 ml of water, 50 ml of ethanol and 50 ml of ether. The resulting fine yellow powder was dried in vacuo to afford 20–22 g, corresponding to 75–80% yield of the desired product. The compound was pure according to NMR.

^1H-NMR spectrum: (300 MHz, $CDCl_3$): 7.3 (m, 20H), 4.3 (s, 4H), 4.0 (s, 4H) ppm; ^{13}C-NMR spectrum (75MHz, $CDCl_3$): 138.7 (d, 4C), 133.3 (d, 8C), 128.2 (d, 8C), 128.1 (s, 4C), 76.5 (d, 2C), 73.6 (d, 4C), 72.4 (d, 4C) ppm; ^{31}P-NMR spectrum (121 MHz, $CDCl_3$, 85% H_3PO_4 as external standard): -16.6 (s) ppm.

1.2.3 Triarylphosphanes and Tri(hetaryl)phosphanes

$$3\,RLi + PCl_3 \xrightarrow[-80 \rightarrow 20\,^{\circ}C]{\text{THF-hexane}} R_3P + 3\,LiCl$$

A number of triarylphosphanes and corresponding tri(hetaryl)phosphanes can be successfully prepared by addition of phosphor trichloride to a solution of three molar equivalents of the aryl- or hetaryllithium derivative in tetrahydrofuran. The most general methods for the generation of aryl- and hetaryllithium intermediates – deprotonation and bromine – lithium exchange using a strongly basic reagent such as *n*-butyllithium – are amply illustrated with experimental procedures in L. Brandsma, H.D. Verkruijsse, Preparative Polar Organometallic Chemistry, Vol. 1, Springer-Verlag, Heidelberg (1987). Therefore it will be sufficient if we describe a general procedure for the reaction of phosphor trichloride with aryl- or hetaryllithium compounds.

Preparation: In a 1-l round-bottomed flask, equipped with a thermometer-gas inlet combination, a mechanical stirrer and an outlet, is prepared (under inert gas) 0.105 mol of the organolithium intermediate (see Note 1) in 100 ml of tetrahydrofuran and 68 ml of hexane. After cooling to between –80 and –90 °C (bath with liquid nitrogen, occasional cooling), a mixture of 4.1 g (0.03 mol) of freshly distilled phosphor trichloride and 20 ml of diethyl ether is added dropwise over 15 min, while maintaining the low temperature. After the addition the cooling bath is removed and the temperature is allowed to rise to above 10 °C. Water (100 ml) is then added with vigorous stirring (see Note 2). The organic layer is dried over magnesium sulfate and subsequently concentrated in vacuo to give the product. It may be crystallized from a suitable solvent or mixture of solvents.

Notes:

1. If the organolithium intermediate is generated by bromine–lithium exchange, the solution contains *n*-butyl bromide. It is essential to keep the mixture below –60 °C in order to prevent subsequent butylation. This general procedure cannot be applied if for the generation of the organolithium compound lithium diisopropylamide has been used. The diisopropylamine liberated presumably will react very fast with PCl_3.
2. Some triarylphosphanes are moderately soluble in the THF–hexane mixture and the aqueous work-up may be troublesome because part of the product precipitates. In such cases the THF and hexane should be first removed in vacuo on the rotary evaporator. After addition of water to the residue, the product can be extracted with chloroform or dichloromethane.

1.3 Organometallic Reagents

Organomagnesium and -zinc halides are frequently used intermediates in transistion metal-catalyzed cross-couplings and substitutions. In a number of cases, Grignard derivatives are directly accessible by reaction of magnesium with an organic halide. A more generally applicable method for obtaining organomagnesium halides is the reaction of an organolithium compound with magnesium halide. Organozinc halides are usually prepared by an analogous metal exchange reaction.

The use of organoaluminium, -boron and -tin intermediates provides additional possibilities for realizing cross-couplings.

1.3.1 Preparation of Grignard Reagents from Mg and Organic Halides

Problems with the preparation of frequently used Grignard reagents, such as C_2H_5MgBr and PhMgBr, are mostly effectively solved by following the usual advice (addition of a crystal of iodine or using perfectly dry ether or tetrahydrofuran, compare Vogel's Textbook of Practical Organic Chemistry, 5th ed., Longman, London (1991) p. 531). The difficulties faced with during preparations of Grignard solutions from *chlorides* may be more serious. In this section we describe as extensively as possible the preparation of these Grignard reagents, the problems that may occur, and give some hints to prevent or solve them. For extensive practical information about the preparation of several special Grignard compounds the manual of B.J. Wakefield [Organomagnesium Methods in Organic Synthesis, Academic Press, London (1995)] should be consulted.

The usual protocol for the preparation of Grignard reagents consists of covering magnesium turnings (preferably an excess of at least 20 mol% with respect to the organic halide) with a relatively small amount of diethyl ether or tetrahydrofuran (~150 ml for each mol of Mg) in a flask filled with inert gas. Part (e.g. 10%) of the halide is then added in one portion (in preparations on a small scale, <0.10 molar, the *total* amount of solvent and halide is often added in one portion). The start of the reaction is marked by a *distinct* rise of the temperature (by at least 15 °C) in the solvent or from a beginning reflux (in the case of diethyl ether), and from the appearance of a turbidity. Sometimes, the reaction stops and heat is no longer evolved. This may be due to inactivation of the magnesium by a covering layer of alkoxide (presence of ROH in the halide RX) or hydroxide (uncarefully dried solvents). The white turbidity may change into a more coarse white suspension. In these cases it makes little sense to continue the experiment. If the initial reaction has started smoothly, however, the addition of the halide is continued (after the starting reaction has subsided). The desired amount of solvent (not less than 500 ml per mol of halide) is added dropwise in admixture with the halide. The turbidity gradually disappears and a dark-grey solution is formed. Generally, the temperature in the flask is kept (by heating or cooling) at a moderate level (gentle reflux in the case of ether, between 35 and 55 °C in

THF). If too strong cooling is applied during preparations of RMgX in THF, salty suspensions may be formed and the reaction may stop completely. As a rule, the preparations are completed by additional heating during 30 to 60 minutes. Large volumes of Grignard solutions, intended to be used for a number of syntheses, can be decanted from the excess of magnesium in a calibrated flask (filled with inert gas) using the Schlenck technique. Most Grignard reagents are stable at room temperature. The stopper of the storage flask should be *regularly greased* during storage in order to prevent it from getting stuck. Grignard reagents in THF often partly crystallize out at room temperature: therefore, the flask must be warmed (with manual swirling) at 30–40 °C prior to using part of the solution. This rather boring operation may be avoided in most cases by keeping the concentration below 0.8 mol/l. Estimation of Grignard solutions may be carried out with butan-2-ol using an indicator, such as 2,2'-bipyridyl or 1,10-phenanthroline (see Vogel's Textbook of Practical Organic Chemistry, 5th ed., Longman, London (1991), p. 443). Most of the alkyl- and arylmagnesium halides can be prepared with "yields" between 85 and 90%, for H_2C=CH–CH_2MgBr (see below) and *t*-BuMgCl ~80% and ~70%, respectively are attainable.

In addition to using perfectly dried solvents (carefully stored under nitrogen), the following measures may be taken to make the chance of a smooth start of a Grignard preparation as high as possible.

1. Stirring the alkyl halides with a substantial amount of finely powdered anhydrous calcium chloride (the use of alumina also may be considered) and calcium carbonate to remove traces of alcohol, water or hydrogen halide, followed by distillation.
2. Mechanically activating the magnesium by *slowly* stirring (under inert gas) the metal with a small amount of solvent (~150 ml for 1 mol of Mg) for at least 2.5 h, so that a greyish-black solution is formed. Pieces (0.5 to 1 cm) of glass from a broken Pasteur pipette may be added to assist in the activation.
3. Some special Grignard reagents, e.g. H_2C=CH-CH_2–MgBr and H_2C=C=CH–MgBr can be successfully prepared in diethyl ether at temperatures in the region of 0 °C (for H_2C=C=CH-MgBr see L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988). The metal is activated first by stirring it for half an hour at room temperature with a solution of mercury(II)chloride in a small amount of diethyl ether (1 to 2 g $HgCl_2$ for 1 mol of Mg). Subsequently, a small portion (~5%) of the halide is added at 0 to 5 °C to the turbid grey solution. This should result in a significant rise of the temperature to at least 10 °C in spite of cooling in an ice-water bath. After the reaction has subsided, the remaining amount of halide is added dropwise together with the desired amount of ether while maintaining the temperature between 0 and 5 °C. By using a large excess (at least 20 mol%) of magnesium, activating the metal and adding the halide slowly at low temperatures, Würtz-dimerization is effectively suppressed.
   Using mechanically activated magnesium, benzylmagnesium chloride in diethyl ether can be prepared with limited dimerization at temperatures between 10 and 25 °C.
   Some organomagnesium halides, e.g. 1-naphthylmagnesium bromide, are not very soluble in ether or THF. As a consequence, the preparation may be troublesome. If a sufficient amount of benzene is used as a cosolvent, no solid appears and the preparation may be carried out without problems.

1.3.2 Preparation of Organomagnesium and Organozinc Halides by Lithium–Magnesium or Lithium-Zinc Exchange

$$RLi + MgX_2 \longrightarrow RMgX + LiX$$

Organomagnesium halides can be readily prepared by the quantitatively proceeding exchange reaction:

Usually, the reaction with the $MgBr_2 \cdot (C_2H_5)_2O$ complex is completed within a few minutes even at temperatures in the region of –50 °C. Magnesium *chloride* is added as a solid (commercially available) and for a complete exchange stirring for 0.5 to 1 h may be necessary. A good quality of the powder can be maintained by storing it in a *rubber-stoppered* flask.

Preparation of a stock solution of $MgBr_2 \cdot (C_2H_5)_2O$*:* To a stirred mixture of 16 g of magnesium turnings and 150 ml of diethyl ether 0.52 mol of 1,2-dibromoethane is added over 1 h. During the addition a further 100 ml of ether is added portionwise. Stirring and heating under reflux are continued for an additional 45 min. As a rule, only a small upper layer appears. This consists mainly of diethyl ether and can be removed by warming and temporarily passing a fast stream of nitrogen (or dry air) through the flask. The oily, grey solution is decanted from the excess of metal into another flask and weighed. It is assumed to contain 0.50 mol of $MgBr_2$. Since the etherate does not crystallize out during storage at room temperature, the amount needed for some reaction can be determined by weighing. Regular greasing of the stopper of the storage flask is desired.

Lithium-zinc exchange reactions ($RLi + ZnCl_2 \rightarrow RZnCl + LiCl$) also proceed very smoothly. The zinc chloride is added most conveniently as a concentrated solution in tetrahydrofuran to the lithium derivative. Water present in the commercial anhydrous salt may be removed azeotropically using toluene as a solvent. Most of the toluene can be removed by decantation, followed by washing of the dried salt with pentane and finally evacuation.

Warning: It seems risky to leave strongly activated magnesium residues exposed to air. Small amounts may be dissolved in dilute aqueous hydrochloric acid, quantities larger than 10 gram can be destroyed (slowly) by aqueous ammonium chloride in a beaker.

1.3.3 Preparation of Organoaluminum Intermediates (see also Chapter 11)

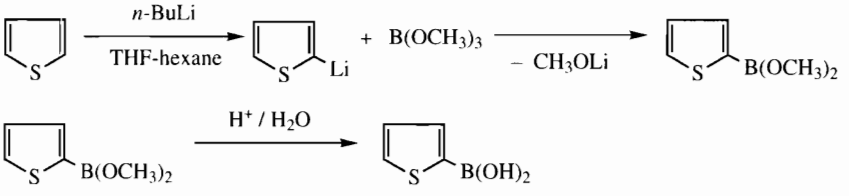
Representative procedures for the stereospecific addition of diisobutylaluminum hydride and trimethylaluminum to acetylenes can be found in Org. Synth. (1988) 66, 60 and Org. Synth., Coll. Vol. 7 (1990) 245.

1.3.4 Preparation of Organoboron and Organotin Intermediates (for Refs. see Chapter 11)

Stereo-defined adducts can be made from acetylenes and diisoamylborane or catechylborane and tributyltin hydride. Unfortunately, the possibilities for checking the literature procedures were seriously limited by the high price of the boron and tin reagents.

Useful boron and tin intermediates can be prepared by simple procedures from organolithium and -magnesium compounds and trialkylborates or trialkyltin chloride. A number of experimental procedures using the relatively cheap trimethyl borate and tributyltin chloride are given below.

1.3.4.1 2-Thiopheneboronic Acid



Scale: 0.10 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a thermometer-nitrogen inlet combination, a mechanical stirrer and an outlet

Procedure: Under an atmosphere of nitrogen a solution of 0.10 mol of BuLi in ~65 ml of hexane was added over a few sec (by syringe) to a mixture of 11 g (excess) of thiophene and 70 ml of THF cooled at –10 °C. During the addition the temperature was allowed to rise (without external cooling) to between 20 and 30 °C. After an additional 15 min (at ~25 °C) the solution was cooled to –90 °C. Trimethyl borate (0.20 mol, 20.6 g, see Note 1) was added in *one portion* (see Note 2) with vigorous stirring, after which the cooling bath was removed. Above –70 °C the evolution of heat was clearly visible. The temperature was allowed to rise to above 10 °C. The reaction mixture became somewhat less viscous. A mixture of 30 g of 30% hydrochloric acid and 50 ml of water was added at 10 °C followed by vigorous stirring at ~30 °C for half an hour. After separation of the layers, four extractions with ether were carried out. Each organic layer was washed twice with a saturated aqueous solution of ammonium chloride (50-ml portions) and the aqueous layers combined with the original one. The combined washings were extracted twice with small portions of ether and the extracts washed once with saturated aqueous ammonium chloride. The combined organic solutions (almost colourless) were dried over anhydrous $MgSO_4$ and subsequently concentrated in vacuo (in the last stage $p < 1$ mmHg). The weight of almost white crys-

talline material corresponded to a yield of ~90%. The product was not further purified. It was stored in the refrigerator.

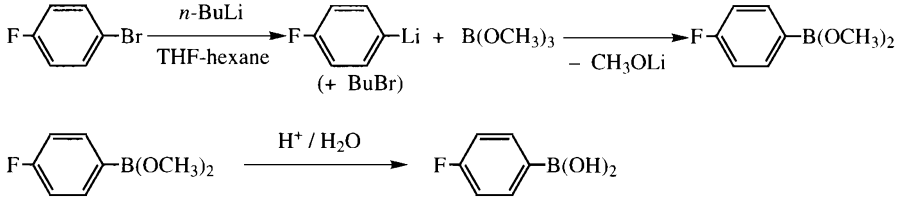
Notes:
1. Trimethylborate is very volatile and moisture-sensitive.
2. The use of this large excess and the rapid addition should prevent formation of di- and tri-substitution products $(2\text{-Th})_2B(OCH_3)$ and $(2\text{-Th})_3B$.

1.3.4.2 2-Furanboronic Acid

This procedure is very similar to the preceding one. For the lithiation a 50 mol% excess of freshly distilled furan was used. Upon addition of trimethylborate at ~–80 °C a clear solution was formed. After the acid hydrolysis, 15 extractions with small portions of ether were carried out. The organic solutions were not washed with water (see Note), but after drying over $MgSO_4$ and removal of the solvent on the rotary evaporator (bath temperature not higher than 35 °C), the remaining traces of solvent and possibly some hydrochloric acid were removed in an oil-pump vacuum (≤0.5 mmHg), while heating the flask in a bath at ~35 °C. The almost white crystalline material (yield ~85%) was used without further purification. It should be stored in the refrigerator

Note: Washing with water would lead to partial dissolution.

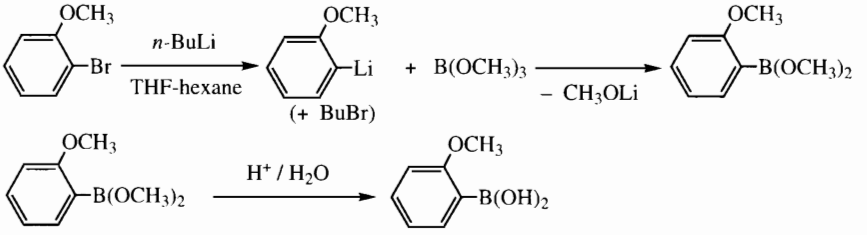
1.3.4.3 4-(Fluorophenyl)boronic Acid



Scale, equipment and notes: same as in preceding experiments.

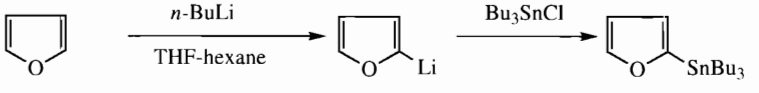
Procedure: Under an atmosphere of nitrogen a solution of 0.10 mol of *n*-BuLi in ~65 ml of hexane was added to 90 ml of THF with cooling below 0 °C. After cooling the solution to –90 °C, 0.11 mol (19.3 g) of 1-bromo-4-fluorobenzene was added over a few sec, while keeping the temperature between –70 and –85 °C. After an additional 15 min (at ~–75 °C) the suspension was cooled to –95 °C and 0.20 mol (20.6 g) of trimethylborate was added in *one* portion with vigorous stirring and intensive cooling. After the addition, the cooling bath was removed and the temperature of the colourless solution allowed to rise to –10 °C. The acid hydrolysis and work-up were carried out in a way similar to the procedure for 2-thiopheneboronic acid. The yield of white crystalline material was 85%. The product was used as such for cross-couplings. It should be stored in the refrigerator.

1.3.4.4 (2-Methoxyphenyl)boronic Acid



Scale, equipment and performance: Same as in preceding experiments. As the acid hydrolysis of the boronic ester proceeded somewhat less easily, the treatment with dilute acid was carried out for half an hour at 40 °C (instead of 30 °C). The crude boronic acid was obtained ~80% yield. The product should be stored in the refrigerator.

1.3.4.5 2-Tributylstannylfuran



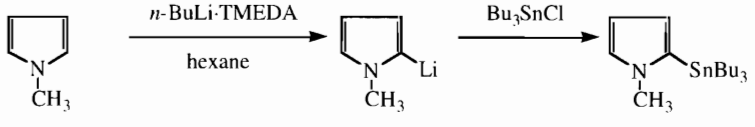
Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, a mechanical stirrer and an outlet

Procedure: Under nitrogen a solution of 0.12 mol of 2-furyllithium was prepared as described above for 2-thiopheneboronic acid and 2-furanboronic acid. The solution was cooled to –80 °C, after which 0.10 mol (32.6 g) of tributyltin chloride was added in one portion. A few min after this addition, the cooling bath was removed and the temperature allowed to rise to –10 °C. Water (100 ml) was then added with vigorous stirring, after which the layers were separated. The organic layer was dried over anhydrous $MgSO_4$ and subsequently concentrated in vacuo. Reasonably pure 2-furyl tributyltin remained as an almost colourless liquid (yield almost quantitative). Distillation at <2 mmHg is possible.

^{1}H-NMR spectrum (CCl_4): 7.61 (m, 1H); 6.40 (m, 1H); 6.28 (m, 1H) ppm.

1.3.4.6 1-Methyl-2-tributylstannylpyrrole



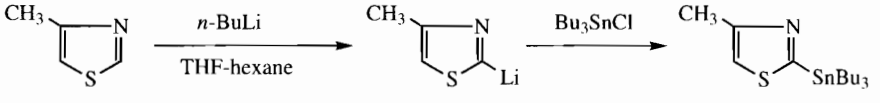
Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a thermometer-nitrogen inlet combination, a mechanical stirrer and a reflux condenser

Procedure: After perfusing the flask with nitrogen, a solution of 0.12 mol of *n*-BuLi in ~75 ml of hexane and 0.12 mol (13.9 g) of TMEDA (dried over potassium hydroxide) were added, followed by 0.15 mol (12.4 g) of freshly distilled 1-methylpyrrole. The mixture was heated under gentle reflux for 15 min and subsequently allowed to cool to room temperature. THF (80 ml) was then added at 20 °C to the suspension, whereupon the solution was cooled to −90 °C. Tributyltin chloride (0.10 mol, 32.6 g) was added in one portion, after which the temperature was allowed to rise to 0 °C. After hydrolysis and drying the organic layer over anhydrous $MgSO_4$, the solvent was removed in vacuo. The excess of 1-methylpyrrole was removed in a vacuum of less than 0.5 mmHg. The product was obtained in almost quantitative yield. If desired, the product can be distilled at <2 mm pressure.

^{1}H-NMR spectrum (CCl_4): 6.48 (m, 1H); 6.03 (m, 2H); 3.54 (s, 3H) ppm.

1.3.4.7 4-Methyl-2-tributylstannylthiazole



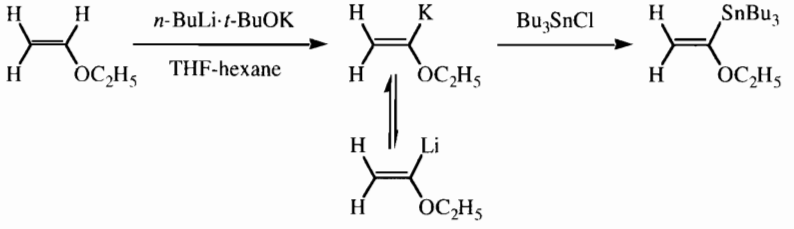
Scale and equipment: same as in preceding experiments.

Procedure: Under an atmosphere of N_2 ,4-methylthiazole (0.11 mol, 11 g) was added over a few sec to a solution of 0.11 mol of *n*-BuLi in ~70 ml of hexane and 70 ml of THF, while keeping the temperature between −65 and −80 °C. After stirring the suspension for 15 min at ~−75 °C, it was cooled to −90 °C and 0.10 mol (32.6 g) tributyltin chloride was added over 1 min with vigorous stirring and cooling between −70 and −90 °C. The reaction mixture was kept for an additional 15 min at ~−70 °C, then the cooling bath was removed and the temperature was allowed to rise to −50 °C. Pentane (75 ml) was added (see Note) and the suspension was warmed to 10 °C. It was then filtered through a 1-cm layer of anhydrous K_2CO_3 on a G-3 glass filter. The solid was rinsed well with dry ether. Concentration of the clear filtrate in vacuo (in the final stage a vacuum of <0.5 mm was applied with heating at 60 °C) gave the product in ~100% yield.

^{1}H-NMR spectrum (CCl_4): 6.92 (1H); 2.50 (3H) ppm.

Note: Aqueous work-up leads to cleavage of the Sn–C bond with partial or complete recovery of the unsubstituted thiazole.

1.3.4.8 Stannylation of Ethyl Vinyl Ether



Scale: 0.10 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: After perfusing with nitrogen, a solution of 0.12 mol of *n*-BuLi in ~75 ml of hexane was placed in the flask. A solution of 0.12 mol (13.4 g) of potassium *t*-butoxide (the commercially available base was used) in 80 ml of THF was added over 5 min with efficient stirring, while keeping the temperature between –85 and –100 °C (occasional cooling in a bath with liquid nitrogen). Subsequently, 0.3 mol (21 g, a large excess) of freshly distilled ethyl vinyl ether was added over 5 min. The solution was stirred for 10 min at –80 °C, after which the temperature was allowed to rise over 15 min to –40 °C. Tributyltin chloride (0.10 mol, 32.5 g) was added over 5 min at –60 to –70 °C, after which the cooling bath was removed and the temperature allowed to rise to 0 °C. Water (100 ml) was added with vigorous stirring. The organic layer was dried over anhydrous $MgSO_4$. Concentration in vacuo gave the product in almost 100% yield. If desired, the product can be distilled at a low pressure through a very short column.

^{1}H-NMR spectrum (CCl_4): 4.55 (d, 1H); 3.87 (d, 1H); 3.60 (q, 2H) ppm.

2 Procedures for the Preparation of Halogen Compounds

Halogen compounds are frequently used and often indispensable substrates for cross-coupling reactions and nucleophilic substitutions. In this chapter experimental procedures are given for a number of halides with relatively simple structures that are either not (yet) commercially available, very expensive or have a limited stability. The procedures are modifications or optimizations of published ones. A number of substituted aryl halides can be prepared by well-established methods. Several experimental procedures can be found in B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, "Vogel's Textbook of Practical Organic Chemistry", 5th ed., Longman Scientific & Technical, London (1991).

2.1 sp-Halides

2.1.1 1-Bromo-1-propyne and 1-Bromo-1-butyne

$$2\,KOH + Br_2 \longrightarrow KOBr + KBr + H_2O$$

$$RC{\equiv}CH + KOBr \xrightarrow[0 \rightarrow 20\,^{\circ}C]{H_2O,\ \text{petroleum ether}} RC{\equiv}C{-}Br + KOH$$

Scale: 0.40 molar.

Apparatus: 1-l round-bottomed, three-necked flask[1], equipped with a nitrogen inlet-thermometer combination, an efficient, gas-tight mechanical stirrer and a cold finger filled with dry ice and acetone (for the preparation of the hypobromite solution the flask was equipped with a dropping funnel, a mechanical stirrer and a thermometer-outlet combination).

Procedure: (Cf. L. Brandsma, H.D. Verkruijsse, Synthesis (1990) 984.) Bromine (0.60 mol, 96 g) was added over ~15 min to a vigorously stirred solution of 90 g of potassium hydroxide (technical quality, ~15% H_2O) in 200 ml of water, while keeping the temperature between –5 and 0 °C (bath with dry ice and acetone). The yellow solution

1 In all preparations described in this book round-bottomed flasks with vertical necks were used.

was covered with 40 ml of high-boiling petroleum ether (b.p. >190 °C/760 mmHg) and the flask equipped for the reaction with the alkyne. After the air had been replaced completely by nitrogen, the mixture was brought to 0 °C in the case of propyne, or +5 °C in the case of butyne. A cold (–20 °C) solution of 0.40 mol (16.0 and 21.6 g, respectively) of the alkyne in 120 ml of high-boiling petroleum was added in five portions over 15 min with vigorous stirring (the inlet being removed during the additions). The temperature of the mixture gradually rose to between 15 and 20 °C. A slow stream of nitrogen was passed through the flask. After addition of the last portion, the reaction was monitored by determining the refractive index of the supernatant layer (stirring was temporarily stopped). Stirring was continued for an additional half hour after the n_D had become maximal. After addition of 200 ml of water, the layers were separated under nitrogen. The organic layer was transferred into a 2-l round-bottomed flask (filled with nitrogen) containing boiling stones and 10–15 g of anhydrous magnesium sulfate. After vigorous shaking, the flask was equipped for a vacuum distillation: 40-cm Vigreux column, condenser and single receiver cooled at –75 °C. The system was evacuated (water aspirator) and the temperature of the heating bath gradually raised, until the petroleum began to reflux in the upper part of the column. Repetition of this procedure with the contents of the receiver (raising the bath temperature gradually from 10 to 40 °C) gave pure 1-bromo-1-propyne, n^{20}_D 1.472, and 1-bromo-1-butyne, n^{20}_D 1.470, in greater than 80% yields.

Warnings:

1. 1-Halo-1-alkynes, especially 1-bromo-1-propyne, are oxygen-sensitive. All operations therefore should be carried out under *inert gas*. Vapours of 1-bromo-1-propyne may ignite upon contact with air. The compounds should be stored in well-sealed bottles in the refrigerator.
2. In view of the suspected physiological effects, all operations should be carried out in a *well-ventilated hood*. The characteristic smell of 1-bromo-1-alkynes is easily noticed.

2.1.2 1-Bromo-1-pentyne and 1-Bromo-1-hexyne

$$RC{\equiv}CH + KOBr \xrightarrow[20 \rightarrow 40\ ^\circ C]{H_2O} RC{\equiv}C{-}Br + KOH$$

Scale: 0.30 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, an efficient mechanical stirrer and an outlet; see also preceding experiment.

Procedure: A solution of potassium hypobromite was made as described in the preceding experiment (the same amounts were used). After the air in the flask had been replaced by nitrogen, the 1-alkyne (0.30 mol, 20.4 and 24.6 g, respectively) was added

in one portion and the vigorously stirred mixture was brought at 20 °C (1-pentyne) or 40 °C (1-hexyne). The temperature in the reaction with 1-pentyne rose within 15 min to between 35 and 40 °C, in the case of 1-hexyne, the observed heating effect was relatively small. When the temperature began to drop, stirring was interrupted and the refractive index of the upper layer was determined (a sample of the upper layer was taken with a Pasteur pipette). The mixtures were stirred for an additional period (about half an hour) at 40 °C until the refractive index had reached a maximum. The work-up was carried out by extraction with the smallest possible amounts of pentane (twice) drying the organic solutions over anhydrous magnesium sulfate and distilling the greater part of the solvent off under nitrogen through a 40-cm Vigreux column (bath temperature not higher than 100 °C) at atmospheric pressure. Careful distillation of the remaining liquid in vacuo gave 1-bromo-1-pentyne, b.p. 40 °C/50 mmHg, n^{20}_D 1.468, and 1-bromo-1-hexyne, b.p. 35 °C/12 mmHg, n^{20}_D 1.466, in excellent yields.

Warnings: See preceding experiment.

2.1.3 Other 1-Bromo-1-alkynes

The bromination of 1-heptyne and higher homologues with potassium hypobromite exp. 1.1 proceeds much more slowly, because of their decreased solubility in the aqueous phase. The following method is recommended:

$$RC{\equiv}CH \xrightarrow[Et_2O\text{-hexane}]{\text{n-BuLi}} RC{\equiv}CLi \xrightarrow[\text{low temp.}]{B_2} RC{\equiv}C\text{–}Br$$

Instead of *n*-butyllithium an ethereal solution of ethylmagnesium bromide may be used for the metallation of the alkyne.

The kinetically and thermodynamically more acidic enynes RCH=CH-C≡CH, diynes RC≡C-C≡CH and aryl- or hetarylacetylenes can be easily brominated by the KOBr-method. Also for acetylenic alcohols, e.g. HC≡C-C$(CH_3)_2$OH, this method is applicable. In the case of primary or secondary acetylenic alcohols, e.g. HC≡C-CH(CH_3)OH, inversed addition must be applied in order to avoid subsequent reactions.

For the various procedures L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988) should be consulted.

Warnings: (See also preceding experiments.) Bromoalkynes with a conjugated system, e.g. Ar-C≡C–Br and RC≡C-C≡C–Br have a decreased thermal stability. Distillative purification of bromides with a conjugated diyne system should not be carried out.

2.1.4 Reaction of Alkynyllithium with Iodine in Organic Solvents

[See L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988) p. 152.]

$$RC{\equiv}CLi + I_2 \xrightarrow[<-20\,^{\circ}C]{THF\ or\ Et_2O\text{-}hexane} RC{\equiv}CI + LiI$$

Scale: 0.20 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping (or powder) funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: Finely powdered iodine (0.20 mol, the dropping funnel was replaced with a powder funnel) or a saturated solution of 0.20 mol of iodine in Et_2O or THF was added over 15 to 30 min to a solution or suspension of 0.20 mol of the lithiated acetylene (see literature mentioned above) in a mixture of Et_2O and hexane or THF and hexane with cooling between –15 and –30 °C. After this addition, the cooling bath was removed and the temperature was allowed to rise to about 0 °C (*suspensions* of RC≡CLi may react more slowly). Water (200 ml) was then added with vigorous stirring, and, after separation of the layers, the aqueous layer was extracted with Et_2O (small amounts of I_2 can be removed with an aqueous $Na_2S_2O_3$ solution). The organic solutions were dried over $MgSO_4$ and subsequently concentrated in vacuo, followed by distillation of the remaining liquid. $C_4H_9C{\equiv}CI$, b.p. 60 °C/10 mmHg, $n^{20}{}_D$ 1.5166, was obtained in >80% yield. Volatile iodoacetylenes (b.p. <40 °C/10 mmHg) can best be prepared by using Et_2O as the only solvent. The lithium alkynylide is generated from the acetylene and EtLi.LiBr in Et_2O. For another useful procedure for volatile iodoacetylenes see the exp. in Sect. 2.1.5. Acetylenic Grignard derivatives in Et_2O or THF also give iodoalkynes upon addition of iodine at –10 to –20 °C.

2.1.5 Preparation of Iodoacetylenes from Lithiated Acetylenes and Iodine in Liquid Ammonia

$$RC{\equiv}CLi + I_2 \xrightarrow[<-40\,^{\circ}C]{liq.\ NH_3} RC{\equiv}CI + LiI$$

Scale and Apparatus: Same as in the exp. in Sect. 2.1.4

Introduction: In the presence of water iodine reacts with ammonia to give explosive NI_3 as a black precipitate. In anhydrous liquid ammonia at –33 °C (or at lower tem-

peratures), however, practically no conversion takes place. This appears most convincingly from the fact that aryl- or heteroaryl iodoacetylenes can be prepared in excellent yield by stirring a mixture of equimolar amounts of iodine and the acetylene in liquid ammonia for several hours. For the less acidic *alkyl*acetylenes, this method has no practical importance, since very long reaction times are needed. A much quicker procedure is to add iodine as a solution in Et_2O or THF to an ammoniacal solution of the lithiated acetylene, cooled to below -33 °C: this reaction is almost instantaneous and generally gives iodoacetylenes in excellent yields. The volatile iodopropyne, for example, can be prepared by adding an ethereal solution of iodine to a solution of propynyllithium in ammonia cooled to below -60 °C. Under these conditions the iodination proceeds almost instantaneously.

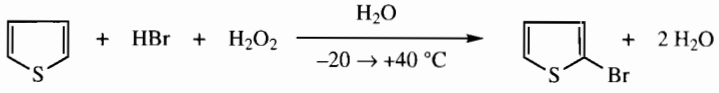
The alternative method for volatile iodoacetylenes – $RC{\equiv}CLi + I_2$ in Et_2O – is more time consuming, since it requires preparation of a solution of EtLi.LiBr from ethyl bromide and lithium in Et_2O.

Procedure: A solution of 0.20 mol of alkynyllithium in about 250 ml of liquid ammonia was prepared by addition of a 10% molar excess of the alkyne to a suspension of 0.20 mol of $LiNH_2$. *Propynyl*lithium and *butynyl*lithium can best be prepared by dropwise addition (over 20 min) of the 1,2-dibromoalkanes (0.20 mol) to a suspension of a slight excess of $LiNH_2$ (0.70 mol) in ~600 ml of liquid ammonia. The solutions in ammonia were cooled to below -60 °C (occasional cooling in a bath with liquid N_2), while N_2 was passed through the flask (0.5 L/min). A solution of 0.25 mol (excess) of iodine in Et_2O (~300 ml) or THF (250 ml) was then added over ~15 min with efficient stirring, while keeping the temperature between -50 and -70 °C (for the volatile iodoalkynes with b.p. <50 °C/15 mmHg, Et_2O should be used). After an additional 15 min (at ~-50 °C) the reaction mixture was cautiously poured onto 500 g of finely crushed ice, contained in a 2 to 3-l wide-necked conical flask. The reaction flask was rinsed with a small amount of ice water. A solution of 20 g of $Na_2S_2O_3$ in 150 ml of water was then added to the mixture. After melting of the ice (some warming might be applied) and vigorous shaking, the layers were separated. The aqueous layer was extracted three to five times with small portions of pentane (this gives a better separation than Et_2O). The combined organic solvents were dried over $MgSO_4$, after which the greater part of the solvent was removed: in the cases of $CH_3C{\equiv}CI$, $C_2H_5C{\equiv}CI$ and $C_3H_7C{\equiv}CI$, the Et_2O was distilled off at atmospheric pressure through a 40-cm Vigreux column under reduced pressure. $CH_3C{\equiv}CI$, b.p. ~50 °C/100 mmHg, n^{20}_D 1.5500, and $C_5H_{11}C{\equiv}CI$, b.p. 78 °C/10 mmHg, n^{20}_D 1.5105, were obtained in excellent yields.

2.2 Aryl and Hetaryl Halides

2.2.1 2-Bromothiophene

[See also M.A. Keegstra, L. Brandsma, Synthesis (1988) 890.]



Scale: 3 molar (thiophene).

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a dropping funnel, an efficient mechanical stirrer and a thermometer-outlet combination.

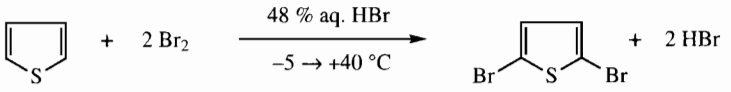
Procedure: The flask was charged with 3.0 mol (252 g) of thiophene, 400 ml of 48% aqueous hydrobromic acid (roughly corresponding to 3.5 mol) and 100 ml of diethyl ether. A 35% aqueous solution (see Note 1) of hydrogen peroxide (300 g, corresponding to 3.0 mol, was added in portions of 25-30 ml from the dropping funnel, while cooling the flask in a bath with dry ice and acetone. After addition of each portion the solution became temporarily light-brown. Initially, the temperature of the efficiently stirred mixture was kept between −10 and −20 °C, but as the heating effect caused by further additions became less strong, the temperature of the mixture was gradually raised to between +10 and 20 °C (see Note 2). After completion of the addition stirring was continued for an additional period of ~3 h, during which the temperature was allowed to rise above 30 °C. The layers were then separated. The heavier organic layer was washed twice with water and subsequently dried over anhydrous magnesium sulfate. The aqueous layer was extracted three times with small (~30 ml) portions of pentane. After washing with water and drying, the extracts were combined with the main portion. Most of the solvent was distilled off at atmospheric pressure through a 40-cm Vigreux column. After cooling to room temperature, the remaining liquid was subjected to careful distillation through a 30 or 40-cm Widmer column. 2-Bromothiophene was collected at between 40 and 80 °C/15 mmHg. A small amount (between 10 and 25 g) of 2,5-dibromothiophene passed over between 80 and 105 °C/15 mmHg. Redistillation of the first fraction gave pure 2-bromothiophene, b.p. 45 °C/15 mmHg, n^{20}_D 1.5868, in 80% or higher yields. The compound is stable at room temperature.

^{1}H-NMR spectrum (CCl_4): multiplet between 6.7 and 7.2 ppm.

Notes:

1. Since contact of the skin with 35% hydrogen peroxide causes very painful white spots, protection of skin and eyes is essential.
2. If too much of hydrogen peroxide is added at low temperatures, the reaction may become very vigorous and no longer controllable at somewhat higher temperatures. Temperature observation after each addition therefore is absolutely necessary.

2.2.2 2,5-Dibromothiophene



Scale: 0.50 molar (thiophene).

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel, an efficient mechanical stirrer and a thermometer-outlet combination.

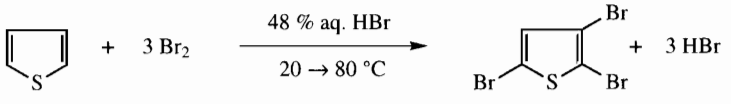
Procedure: The flask was charged with 0.50 mol (42 g) of thiophene, 150 ml of a 48% aqueous solution of hydrogen bromide, and 50 ml of diethyl ether. A mixture of 1.0 mol (160 g) of bromine and 75 ml of 48% aqueous hydrogen bromide was added dropwise with efficient stirring over 15 min. The temperature of the mixture, initially kept between −5 and +5 °C, was raised to ~20 °C towards the end of the addition. After disappearance of the brown colour caused by bromine, the layers were separated. The upper layer was extracted four times with very small portions of dichloromethane (see Note). The combined organic solutions were washed with water, dried over anhydrous magnesium sulfate (or vigorously shaken with the smallest possible amount of phosphorus pentoxide), and then concentrated under reduced pressure. Careful distillation through a 40-cm Vigreux column gave 2,5-dibromothiophene, b.p. 85 °C/15 mmHg, n^{20}_D 1.6288, in an excellent (~90%) yield. The product is rather stable at room temperature.

^{1}H-NMR spectrum (CCl_4): 6.75 ppm.

Note: After dilution with a small amount of water, the upper layer can be used for repetition of the experiment.

2,5-Dibromothiophene can also prepared by the hydrogen peroxide method (see exp. in Sect. 2.2.1). In this case the double molar amounts of H_2O_2 and HBr are used. The last portions of peroxide react at temperatures above 30 °C.

2.2.3 2,3,5-Tribromothiophene



Scale: 0.50 molar (thiophene).

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, an efficient mechanical stirrer and a thermometer-outlet combination.

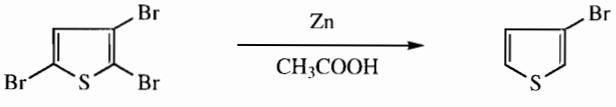
Procedure: (Cf. also exp. in Sect. 2.2.2.) To a mixture of 0.50 mol (42 g) of thiophene, 200 ml of a 48% aqueous solution of hydrogen bromide and 50 ml of diethyl ether was added dropwise over 15 min a mixture of 1.7 mol (272 g) of bromine and 150 ml of 48% aqueous hydrogen bromide. During the addition the temperature of the mixture was allowed to rise from room temperature to ~80 °C (some gaseous hydrogen bromide may escape, therefore small amounts of water may be added when the temperature rises). The bromination was terminated by stirring the mixture for a short additional period at 80 °C. After cooling to room temperature, the layers were separated and the upper layer (see Note 1) extracted twice with very small amounts of dichloromethane. The organic solutions were dried over anhydrous magnesium sulfate (vigorous shaking with a few g of phosphorus pentoxide presumably will be more effective). After removal of the solvents and excess of bromine under reduced pressure, the remaining liquid was carefully distilled through a 30 cm-Vigreux column. After a small first fraction, mainly consisting of 2,5-dibromothiophene, 2,3,5-tribromothiophene, b.p. 120 °C/15 mmHg, n^{21}_D 1.665, was obtained in >80% yield (see Note 2). The product solidified upon some cooling.

^{1}H-NMR spectrum (CCl_4): 6.84 (1H) ppm.

Notes:

1. After dilution with water, the upper layer can be used for further brominations.
2. An air condenser was used.

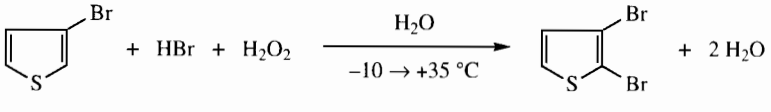
2.2.4 3-Bromothiophene



Following the Organic Synthesis procedure (Org.Synth., Coll. Vol. 5 (1973) 149) we always obtained good results. For 2,3,5-tribromothiophene we recommend our short procedure (see exp. in Sect. 2.2.3).

^{1}H-NMR spectrum (CCl_4): 7.0-7.2 (2H); 6.8-6.95 (1H) ppm.

2.2.5 2,3-Dibromothiophene



Scale: 0.5 molar.

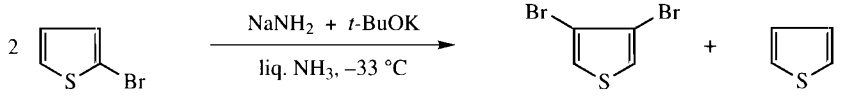
Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, an efficient mechanical stirrer and a theremometer-outlet combination.

Procedure: (Cf. M.A., Keegstra, L. Brandsma, Synthesis (1988) 890.) 3-Bromothiophene (0.5 mol, 81 g), diethyl ether (50 ml) and 100 ml of a 48% aqueous solution of hydrogen bromide were placed in the flask. A 35% aqueous solution of hydrogen peroxide (see Note) (50 g, corresponding to ~0.5 mol H_2O_2) was added dropwise over 30 min, while allowing the temperature of the mixture to rise gradually from −10 to +35 °C. After stirring for an additional half hour at 35-40 °C, the layers were separated and the aqueous layer extracted twice with small portions of dichloromethane. The combined organic solutions were washed with water and subsequently dried over anhydrous magnesium sulfate (shaking with a small amount of P_2O_5 is presumably more effective). After removal of the solvents under reduced pressure, the remaining liquid was carefully distilled through a 30-cm Vigreux column. 2,3-Dibromothiophene, b.p. 90 °C/15 mmHg, was obtained in ~90% yield.

^{1}H-NMR spectrum (CCl_4): two doublets centered around 6.85 and 7.15 ppm.

Note: For precautions when working with hydrogen peroxide see exp. in Sect. 2.2.1.

2.2.6 3,4-Dibromothiophene



Scale: 0.6 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a mechanical stirrer and two outlets for the preparation of sodamide; 2- or 3-l round-bottomed, three-necked flask, equipped with two outlets and a mechanical stirrer for the disproportionation reaction.

Procedure: (See also L. Brandsma, H.D. Verkruijsse, Synth. Comm. (1990) 20, 2119.) Anhydrous liquid ammonia (see Note 1) (~500 ml) was introduced from a cylinder into the first flask. About 1 g of the total amount of 0.2 mol (4.6 g) of sodium was introduced in two pieces with vigorous stirring and introduction of air (or oxygen from a cylinder, see Note 2) during 1 minute. Ferric nitrate (n H_2O) (~250 mg) was then introduced. When after a short time the blue colour had changed into grey, the remaining sodium was quickly introduced in ~1 g portions. As a rule, the conversion into sodamide is complete within half an hour. Powdered potassium *tert*-butoxide (0.2 mol, 22 g, commercially available) was then cautiously introduced through a powder funnel, which temporarily replaced one of the outlets. A very fine suspension (almost solution) was formed.

In the other flask were placed 98 g (0.6 mol) of 2-bromothiophene (exp. in Sect. 2.2.1) and 1 l of liquid ammonia. The solution in the first flask was added over half an hour (about 10 equal portions and equal intervals) to the efficiently stirred mixture in the second flask (for each addition one of the outlets of the second flask was temporarily removed). In the case of strong foaming during these additions a few ml of

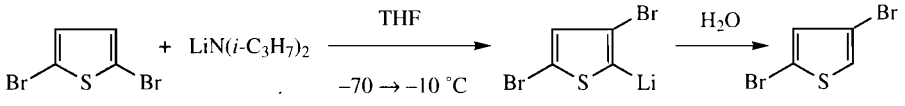
diethyl ether should be added. After stirring for 4 h, 25 g of finely powdered ammonium chloride was cautiously introduced (powder funnel) over 10 min (the outlets being removed), then the ammonia was evaporated by placing the flask (without outlets) in a water bath at 40 °C, or allowed to evaporate overnight (with outlets on the flask). To the remaining slurry was added 300 ml of water, after which the product was extracted with diethyl ether. The combined organic solutions were concentrated under reduced pressure after drying over anhydrous magnesium sulfate. Careful fractionation through a 30-cm Vigreux column gave, after a first fraction of 10-15 g, 3,4-dibromothiophene, b.p. 100 °C/12 mmHg, n^{20}_D 1.6403, in 65–71% yield. The first fraction consisted mainly of 3-bromothiophene, the small residue was a mixture of tribromo- and tetrabromothiophenes, formed in subsequent "halogen-dance" reactions.

^{1}H-NMR spectrum (CCl_4): one signal at 7.20 ppm.

Notes:

1. The quality of ammonia in the cylinder may be variable. If the quality is good, the blue colour of sodium persists already after introduction with intervals of 0.5 g Na in small pieces, while passing nitrogen through the flask. For making ammonia "super-dry" see L. Brandsma, Recl. Trav. Chim. Pays-Bas (1995) 114, 35.
2. From sodium and oxygen sodium peroxide is formed, which assists in the conversion of sodium into the amide under the catalytic influence of Fe_0.

2.2.7 2,4-Dibromothiophene



Scale: 0.20 molar.

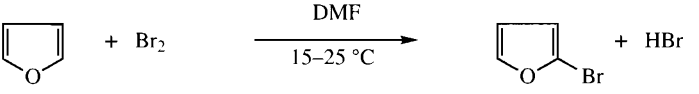
Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet, a mechanical stirrer and a thermometer-outlet combination.

Procedure: (Cf. S. Kano, Y. Yuasa, T. Yokomatsu, S. Shibuya, Heterocycl. (1983) 20, 2035.) A solution of 0.22 mol of *n*-butyllithium in ~135 ml of hexane was added to a mixture of 0.22 mol (24 g) of diisopropylamine and 120 ml of THF, while keeping the temperature between 0 and −20 °C (cooling in a bath with nitrogen allows a quick addition by syringe). The solution of lithium diisopropylamide was cooled to −75 °C, after which 0.20 mol (48.4 g) of 2,5-dibromothiophene was added in one portion. The temperature was allowed to rise to −10 °C (a purple solution was formed) at which level stirring was continued for an additional 15 min. The dark mixture was then poured into 500 ml of an aqueous solution of 30 g of ammonium chloride. After vigorous shaking, the layers were separated. The aqueous layer was extracted twice with diethyl ether or pentane and the combined organic solutions were dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by careful

distillation through a 30-cm Widmer column gave 2,4-dibromothiophene, b.p. 90 °C/ 15 mmHg, n^{20}_D 1.629, in 85% yield.

^{1}H-NMR spectrum (CCl_4): doublets at 6.90 and 7.05 ppm.

2.2.8 2-Bromofuran



Scale: 1.0 molar (bromine).

Apparatus: 1-l three-necked round-bottomed flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer-outlet combination.

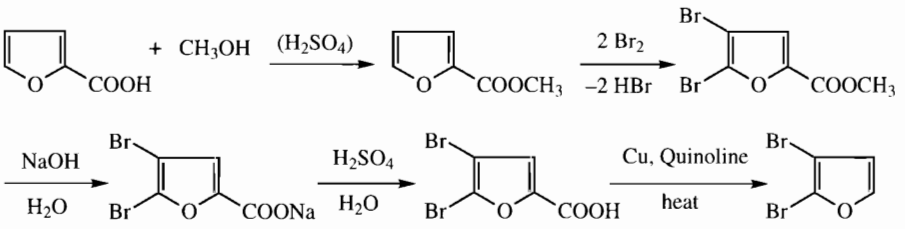
Procedure: (See also M.A. Keegstra, A.J.A. Klomp, L. Brandsma, Synth. Comm. (1990) 20, 3371.) A mixture of 1.5 mol (102 g) of freshly distilled furan and 150 ml of *N,N*-dimethylformamide was placed in the flask. The dropping funnel was filled with a *cold* mixture of 1 mol (160 g) of bromine and 150 ml of DMF which had been prepared by adding the bromine to cold (–25 °C) DMF. This solution was added over 1.5 h while keeping the temperature of the light-brown solution closely around +15 °C. After the addition, the temperature was allowed to rise to between 20 and 25 °C (~1 h additional stirring), then the mixture was poured into 1.5 l of ice water. After vigorous shaking and separation of the layers, the aqueous layer was extracted five times with small portions of pentane (50 ml and 4 × 30 ml). The main portion and extracts were combined, washed with water and dried over anhydrous magnesium sulfate. After addition of ~5 ml of *N,N*-diethylaniline (see Note) to the solution the pentane and the excess of furan were slowly distilled off at atmospheric pressure through a 40-cm Widmer column. The remaining liquid was distilled through a 30-cm Vigreux column to give 2-bromofuran, b.p. 102 °C/760 mmHg, n^{20}_D 1.498, in 68–73% yield. Distillation of the residue in vacuo gave a small amount of 2,5-dibromofuran (*ca* 15 g, b.p. ~55 °C/15 mmHg).

2-Bromofuran should be stored at –20 °C in the presence of a trace (<1%) of *N,N*-diethylaniline.

^{1}H-NMR spectrum (CCl_4): doublet at 7.3 (1 H) and multiplet around 6.3 ppm (2H) ppm.

Note: Small amounts of *addition* products are formed which give off HBr during the distillation, sometimes causing vigorous decomposition of the product. *N,N*-Diethylaniline binds the HBr.

2.2.9 2,3-Dibromofuran



This procedure has been carried out by us only once. It is based upon R. Sornay, c.s., Bull. Soc. Chim. France (1971) 990.

Scale: 1.0 molar (furancarboxylic acid).

Apparatus: 1-l round-bottomed flask, equipped with a dropping funnel and a very efficient condenser (a so-called cold finger, filled with ice and ice water, is recommended) for the bromination; 2-L, wide-necked, round-bottomed flask for the saponification; 1-l round-bottomed flask, equipped with an efficient reflux condenser for the decarboxylation.

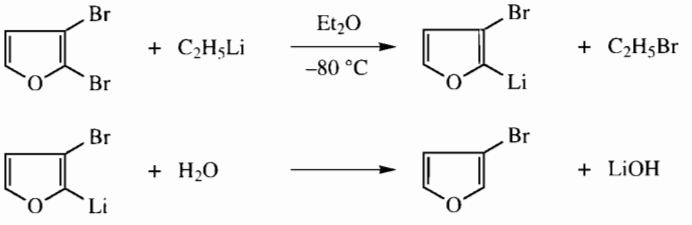
Procedure: To a mixture of 1.0 mol (112 g) of (commercially available) 2-furancarboxylic acid and 140 ml of methanol was cautiously added under manual swirling and some cooling 40 ml of 96% sulfuric acid. After refluxing during 7 h, the mixture was poured into 1 l of ice water. Extraction (3 times) was carried out with dichloromethane. The combined organic solutions were dried over anhydrous magnesium sulfate and subsequently concentrated in vacuo. Distillation through a 30-cm Vigreux column gave the ester, b.p. 75 °C/15 mmHg, in 85% yield.

Bromine (1.2 mol, 176 g) was added over 3 h to a mixture of 0.50 mol (63 g) of methyl 2-furancarboxylate and 70 ml of carbon tetrachloride which was kept under reflux. After the addition, heating was continued until the bromine vapor was (practically) no longer visible (several hours). Subsequently, the solvent was removed in vacuo, the last traces in an oil-pump vacuum. The remaining brown oil was added over a few min to 900 ml of a vigorously stirred 4 M NaOH solution in water. The temperature of the mixture gradually rose to 50 °C (or higher), while a yellow suspension was formed. Stirring at ~50 °C was continued for two days ("several hours" is presumably sufficient), then the mixture was poured into a mixture of 60 ml of 96% sulfuric acid and 500 g of crushed ice. The precipitate was filtered off on sintered glass and rinsed with 150 ml of ice water. Most of the water was removed under reduced pressure (rotary evaporator). The product was dried in an oil-pump vacuum. The yield of the crude, dry product was 62% (calculated on methyl 2-furancarboxylate). The product was mixed with 40 g of copper powder and 350 ml of quinoline and the mixture was heated in an oil bath at 180 °C until the evolution of carbon dioxide had ceased. After cooling to room temperature, 2,3-dibromofuran, b.p. 52 °C/15 mmHg, n^{20}_D 1.5466,

was obtained in 65% yield by careful fractional distillation through a 30-cm Widmer-column. The compound is stable at room temperature.

^{1}H-NMR spectrum (CCl_4): 6.42 ppm (2H) and 7.35 ppm (2H).

2.2.10 3-Bromofuran

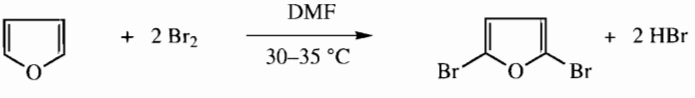


Scale: 0.50 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: A mixture of 0.50 mol (113 g) of 2,3-dibromofuran and 50 ml of dry diethyl ether was placed in the flask. A solution of 0.50 mol of ethyllithium [see L. Brandsma, H.D. Verkruijsse, Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier, Amsterdam (1981) and L. Brandsma, H.D. Verkruijsse, Preparative Polar Organometallic Chemistry, Vol. 1, Springer-Verlag, Berlin, Heidelberg (1987)] in ~500 ml of diethyl ether was added over about half an hour, while keeping the reaction mixture (with occasional cooling in a bath with liquid nitrogen) at ~–80 °C. Ten minutes after completion of the addition the cooling bath was removed and the solution was transferred into a 2-l round-bottomed flask. The solution was concentrated under reduced pressure to a volume of ~150 ml (bath temperature ≤ 20 °C). The remaining solution was poured (occasional manual swirling) into 400 ml of deoxygenated ice water. After separation of the layers two extractions with small volumes of pentane were carried out. The combined organic solutions were dried over anhydrous $MgSO_4$, after which the solvents were slowly distilled off through a 40-cm Widmer column. The remaining liquid was distilled through a shorter column to give 3-bromofuran, b.p. 105 °C/760 mmHg, n^{20}_D 1.493, in ~75% yield. The compound is fairly stable at room temperature.

2.2.11 2,5-Dibromofuran



Scale: 0.5 molar.

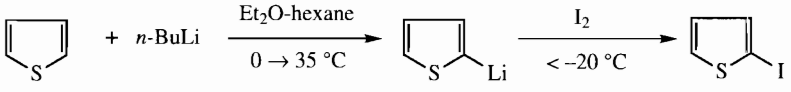
Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer-outlet combination.

Procedure: (See also M.A. Keegstra, A.J. Klomp, L. Brandsma, Synth. Comm. (1990) 20, 3371.) A cold mixture of 1.0 mol (160 g) of bromine and 200 ml of dimethylformamide (prepared by adding the bromine to cold (−20 °C) *N,N*-dimethylformamide) was added dropwise over 1 h to a mixture of 0.50 mol (34 g) of freshly distilled furan and 240 ml of *N,N*-dimethylformamide. During the addition the temperature of the mixture was kept between 30 and 35 °C. After heating at 50 °C for 30 min, the brown solution was poured into 2 l of ice water. After vigorous shaking for 2 min, three extractions with a pentane–diethyl ether (1 : 1) mixture were carried out (200 ml for the first extraction). The combined extracts were washed with water and dried over anhydrous magnesium sulfate. After addition of ~5 ml of *N,N*-diethylaniline (see Note), the greater part of the solvent was distilled off at normal pressure through a 40-cm Vigreux column. Careful distillation of the remaining liquid in vacuo gave 2,5-dibromofuran, b.p. 52 °C/12 mmHg, n^{20}_D 1.5522, in 49% yield. It is advisable to store the product in the refrigerator after adding a trace of *N,N*-diethylaniline.

^{1}H-NMR spectrum (CCl_4): 6.26 ppm.

Note: Small amounts of addition products are present. During heating they eliminate hydrogen bromide wich may initiate decomposition of the product. Diethylaniline effectively neutralizes the acid.

2.2.12 2-Iodothiophene



Scale: 0.50 molar (iodine).

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet, a mechanical stirrer and a reflux condenser for the lithiation; for the iodination the flask was equipped with a thermometer-inlet combination, a mechanical stirrer and a powder funnel; the reactions were carried out under nitrogen.

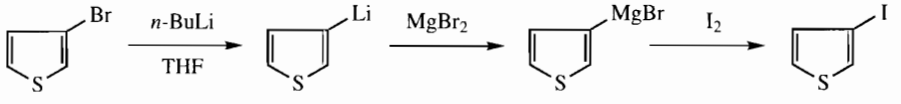
Procedure: A solution of 0.50 mol of *n*-butyllithium in 320 ml of hexane was placed in the flask. Dry diethyl ether (300 ml) was added and the solution was cooled to 0 °C. Thiophene (0.6 mol, 50 g) was added in one portion, after which the cooling bath was removed. The temperature of the solution rose gradually and after 20 to 30 min the ether began to reflux. After heating the solution under reflux for 1.5 h, the solution was cooled to −50 °C. A slurry of 0.50 mol (127 g) of finely powdered iodine in 300 ml of diethyl ether was added portionwise through the powder-funnel. During this addition, which occurred over 30 min, the mixture was vigorously stirred, while its temperature was kept below −10 °C. After stirring for an additional 10 min at −10 to 0 °C, 200 ml of an aqueous solution of 10 g of $Na_2S_2O_3 \cdot 5H_2O$ was added with vigorous stir-

ring. The organic layer was dried over anhydrous magnesium sulfate and subsequently concentrated under reduced pressure. Distillation of the remaining liquid through a 30-cm Vigreux column gave 2-iodothiophene, b.p. 60 °C/15 mmHg, n^{20}_D 1.6505, in ~80% yield. The compound should be stored at a dark place, preferably in the refrigerator.

^{1}H-NMR spectrum (CCl_4): multiplets centered around 7.2 (2H) and 6.7 (1H) ppm.

When THF-hexane was used instead of Et_2O-hexane, appreciable amounts of 2,3- and 2,5-diodothiophene were formed as a result of metallation of 2-iodothiophene by 2-lithiothiophene and subsequent iodination.

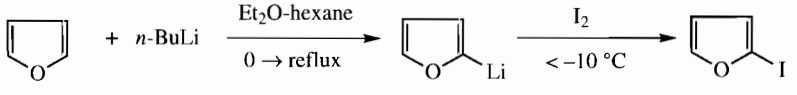
2.2.13 3-Iodothiophene



The procedure is described in L. Brandsma, H.D. Verkruijsse, Preparative Polar Organometallic Chemistry, Vol. I, p. 157, Springer-Verlag, Heidelberg (1987).

^{1}H-NMR spectrum (CCl_4): multiplets, centered around 7.3 (1H) and 7.05 (2H) ppm.

2.2.14 2-Iodofuran



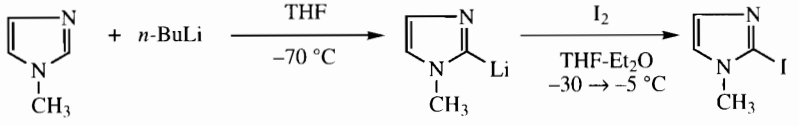
Scale: 0.50 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, an efficient mechanical stirrer and a reflux condenser; for the iodination the condenser was replaced by a powder funnel.

Procedure: A solution of 0.50 mol *n*-butyllithium in 320 ml of hexane was placed in the flask. The hexane was removed by evacuation (water aspirator) and heating the flask in a bath at 30 to 40 °C. To the remaining viscous liquid was added 300 ml of cold (−30 °C), dry diethyl ether. Furan (0.70 mol, 46.9 g, freshly distilled) was added in one portion, after which the equipment was placed on the flask. The solution was stirred for half an hour in a bath at 20 °C, and then heated under reflux for 1.5 h. After cooling the light-brown solution to −40 °C, a slurry of 0.50 mol (127 g) of finely powdered iodine in 300 ml of dry diethyl ether was added portionwise over half an hour with vigorous stirring while keeping the temperature between −40 and −20 °C (in the last stage somewhat higher). After an additional 10 min a cold (0 °C) solution of 10 g of $Na_2S_2O_3 \cdot 5H_2O$ in 200 ml of water was added with vigorous stirring. The organic

layer was dried over anhydrous magnesium sulfate, after which the greater part of the solvent was distilled off at normal pressure through a 30-cm Vigreux column (before beginning the distillation, 1 or 2 g of *N,N*-diethylaniline may be added as stabilisator, compare exp. in Sect. 2.2.8). Distillation of the remaining liquid gave 2-iodofuran, b.p. ~35 °C/15 mmHg, n^{20}_D 1.5622, in an excellent yield. The compound should be stored in the refrigerator.

2.2.15 2-Iodo-1-methylimidazole



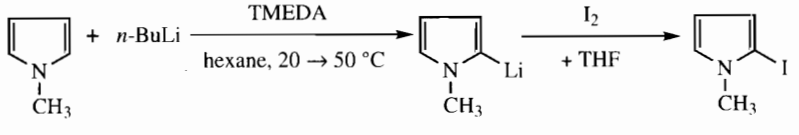
Scale: 0.10 molar (*n*-BuLi).

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, an efficient mechanical stirrer and an outlet; during the addition of iodine the outlet was replaced with a powder funnel.

Procedure: A mixture of 0.12 mol (9.9 g) of 1-methylimidazole and 80 ml of THF was cooled to between −80 and −75 °C, after which a solution of 0.10 mol of *n*-butyllithium in 64 ml of hexane was added over a few min by syringe, while keeping the temperature of the solution at ~−70 °C by occasional cooling in a bath with liquid nitrogen. The temperature was allowed to rise to −40 °C, after which 200 ml of diethyl ether was added. Subsequently, a slurry of 0.10 mol (25.4 g) of iodine in 50 ml of THF was added portionwise over 10 min, while allowing the temperature to rise to +5 °C. Water (25 ml) (if there is still a brown colour, a few ml of an aqueous solution of $Na_2S_2O_3 \cdot 5H_2O$) were added with vigorous stirring. The almost colourless upper layer was dried over anhydrous potassium carbonate and combined with ten ethereal extracts of the aqueous layer. The liquid remaining after evaporation of the solvent under reduced pressure was distilled through a 30-cm Vigreux column to give the product, b.p. ~80 °C/0.1 mmHg (air condenser), in 85% yield. It soon solidified upon standing at room temperature. It should be stored in the refrigerator.

^{1}H-NMR spectrum (CCl_4): 7.12 (s, 2H); 3.70 (s, 3H) ppm.

2.2.16 2-Iodo-1-methylpyrrole



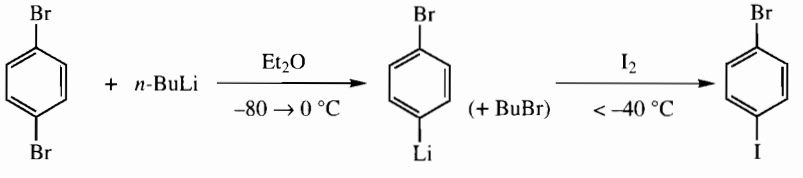
Scale: 0.30 molar.

Apparatus: 1-l round-bottomed, three-necked flask equipped with a nitrogen inlet-thermometer combination, an efficient mechanical stirrer and a reflux condenser; for the iodination the condenser was replaced with a combination of dropping funnel and outlet.

Procedure: A solution of 0.30 mol of *n*-butyllithium in 192 ml of hexane was placed in the flask. TMEDA (0.30 mol, 35 g) was added over a few sec through the condenser. To the warm (~40 °C) solution was subsequently added in one portion 0.32 mol (25.9 g) of freshly distilled 1-methylpyrrole. The temperature of the mixture rose to about 50 °C and was kept at that level for an additional half hour. Upon cooling to room temperature, a fine suspension formed. Dry THF (200 ml) was added, after which the solution was cooled to ~–80 °C (bath with liquid nitrogen). A solution of 0.31 mol (78.7 g) of iodine in 250 ml of THF was added portionwise over half an hour with vigorous stirring, while keeping the mixture between –50 and –70 °C. After the addition, the temperature of the yellow-brown suspension was allowed to rise to –30 °C and a solution of 10 g of $Na_2S_2O_3 \cdot 5H_2O$ in 200 ml of water was added, likewise with vigorous stirring. After separation of the layers, two extractions with diethyl ether were carried out. The combined organic solutions were dried over anhydrous magnesium sulfate and subsequently concentrated under reduced pressure. The remaining, brown liquid was subjected to a flash distillation through a very short column at the lowest possible pressure. The distillate, collected in a strongly cooled, single receiver, was redistilled through a 20-cm Vigreux column. 2-Iodo-1-methylpyrrole, b.p. 80 °C/15 mmHg, n^{20}_D 1.599, was obtained in yields of up to ~91%.

In general it is advisable to distill smaller portions at water-aspirator pressure, as 2-halopyrroles are unstable. The product should be stored at –20 °C.

2.2.17 1-Bromo-4-iodobenzene



Scale: 0.10 molar.

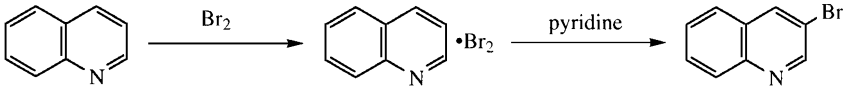
Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, a mechanical stirrer and an outlet; for the iodination the outlet was replaced by a powder funnel.

Procedure: A solution of 0.11 mol of *n*-butyllithium in 71 ml of hexane was added over a few minutes (by syringe, the outlet was temporarily removed) to a mixture of 0.10 mol (23.6 g) of 1,4-dibromobenzene and 200 ml of dry diethyl ether. During this addition the temperature was kept between –80 and –40 °C (cooling in a bath with liquid nitrogen allows a quick addition). After the addition, the cooling bath was removed

and the temperature allowed to rise to 0 °C. The solution was stirred for an additional 15 min at 0 °C, then it was cooled to below –55 °C. Finely powdered iodine (0.11 mol, 27.9 g) was introduced portionwise over 15 min, while keeping the temperature around –40 °C. After the addition the temperature was allowed to rise to 0 °C. The mixture was then treated with a solution of 10 g of $Na_2S_2O_3 \cdot 5H_2O$ in 100 ml of water under vigorous stirring. The organic layer was dried over anhydrous magnesium sulfate, after which the solvents and other volatile products (especially *n*-butyl bromide) were removed under reduced pressure (in the last stage <0.5 mmHg). The remaining solid was purified by crystallization from diethyl ether. 1-Bromo-4-iodo-benzene was obtained in greater than 80% yields.

^{1}H-NMR spectrum(CCl_4): 7.45 (d, 2H) and 7.15 (d, 2H) ppm.

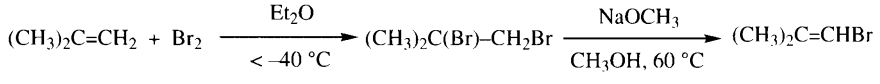
2.2.18 3-Bromoquinoline



The procedure of J.J. Eisch (J. Org. Chem. (1962) 27, 1318) was modified. Pyridine was added over ~30 min at a temperature close to the b.p. of CCl_4. A weakly exothermic reaction was observed. After the addition of the pyridine, the mixture was stirred for 2 h under reflux (Eisch: 20 h). The light-yellow CCl_4 solution was decanted from the brown viscous mass, which was rinsed twice with hot CCl_4 (50-60 °C). 3-Bromoquinoline was obtained by careful distillation: b.p. 140–145 °C/15 mmHg, n^{20}_D 1.6628, yield 72%.

2.3 Olefinic, Cycloolefinic and Allenic Halides

2.3.1 1-Bromo-2-methylpropene



Scale: 1.0 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a combination of thermometer and outlet for the addition of bromine and the dehydrobromination; for the preparation of $NaOCH_3$ the same apparatus with a reflux condenser instead of the outlet-thermometer combination was used.

Procedure: Dry diethyl ether (300 ml) was cooled to –40 °C, after which 1.2 mol (68 g) of isobutene was quickly added from a cold trap (–50 °C) in which it had been con-

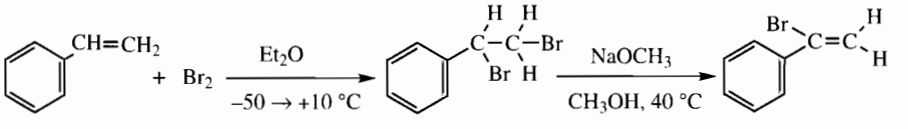
densed. Bromine (1.0 mol, 160 g) was added dropwise over 45 min with cooling between −30 and −50 °C. After the addition, the diethyl ether was *thoroughly* removed at water-aspirator pressure.

A solution of sodium methoxide was prepared from 1.3 mol (~31 g) of sodium and 600 ml of methanol. After dissolution of the metal the solution was concentrated to a volume of ~250 ml, using a water aspirator and a rotary evaporator.

The adduct from isobutene and bromine was added portionwise over 15 min, while allowing the temperature to rise to 60 °C. After the exothermic reaction had subsided, the suspension was stirred for an additional hour at 60 °C. The mixture was then poured into 1 l of ice water and the organic layer was isolated, washed twice with a small amount of water and dried over $MgSO_4$. The aqueous layer was extracted four times with 40-ml portions of high boiling (b.p. >170 °C) petroleum. The combined extracts were washed with water and dried over $MgSO_4$, after which the volatile product was "distilled off" at 10–20 mmHg through a 40-cm Vigreux column and collected in a single receiver cooled at −70 °C (the "distillation" was stopped as soon as petroleum began to pass over at >55 °C/15 mmHg). The main portion and the condensate were combined and carefully distilled through a 40-cm Vigreux column to give 1-bromo-2-methylpropene, b.p. 92 °C/760 mmHg, n^{20}_D 1.4608, in 78% yield.

^{1}H-NMR spectrum (CCl_4): 5.8 (m, 1H), 1.8 (m, 6H) ppm.

2.3.2 α-Bromostyrene

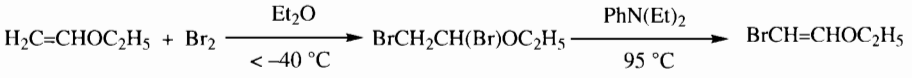


Scale: 0.50 molar.

Apparatus: 1-L, round-bottomed, three-necked flask, equipped with a dropping funnel, an efficient mechanical stirrer and a thermometer-outlet combination.

Procedure: A mixture of 0.50 mol (52 g) of freshly distilled styrene and 400 ml of dry diethyl ether was placed in the flask. Bromine (0.50 mol, 80 g) was added dropwise over 30 min with cooling, in the beginning at −50 °C, but as more slightly soluble adduct was formed, at higher temperatures. After the addition, the suspension was allowed to warm up to room temperature. A solution of 0.6 mol of sodium methoxide in 200 ml of methanol (obtained by dissolving sodium in a larger amount of methanol and subsequently concentrating the solution under reduced pressure) was added portionwise over 30 min, while allowing the temperature to rise to 40 °C. Stirring was continued for another half hour, then the suspension was poured into 1 l of ice water and the product was extracted with a diethyl ether-pentane (1 : 1) mixture. The combined extracts were washed with water, dried over anhydrous magnesium sulfate and concentrated in vacuo. Subsequent distillation gave α-bromostyrene, b.p. 80 °C/15 mmHg, n^{20}_D 1.589, in greater than 85% yield.

2.3.3 2-Bromo-1-ethoxyethene



Scale: 1.0 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer-outlet combination.

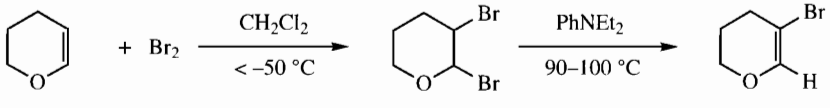
Procedure: In L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988) p. 196, the preparation of an *E/Z* mixture (usually mainly *Z*) of 1-ethoxy-2-bromoethene is extensively described.

Bromine (1.0 mol) was added dropwise to a mixture of 1.2 mol of freshly distilled ethoxyethene and 200 ml of diethyl ether at low temperatures, then the solvent was removed in vacuo, using a rotary evaporator. The remaining liquid was mixed with 2.0 mol (100% excess) of *N,N*-diethylaniline. After heating the mixture for ~30 min at 95–100 °C (occasional cooling may be necessary), it was cooled to between 50 and 60 °C. The relatively volatile bromovinyl ether was then distilled off from the salt slurry through a 40-cm Vigreux column and the distillate redistilled. Alternatively, ice water was added to the salt mass, after which the upper layer, a mixture of 2-bromovinyl ether and the excess of *N,N*-diethylaniline, was subjected to fractional distillation. In a third alternative the salt slurry (after cooling to room temperature) was treated with cold dilute hydrochloric acid, just enough to bind the 1 mol excess of diethylaniline. The mixture was then extracted with diethyl ether or pentane and b-bromovinyl ether was isolated in yields between 60 and 70% by distillation. The *E/Z*-mixture has a rather long boiling range (between ~30 and 50 °C/15 mmHg).

The *E/Z*-ratio may vary to some extent. Traces of acid adhering to the glass of the distillation flask may cause some *Z*- to *E* isomerization. The product should be stored in the refrigerator, preferably in the presence of a trace of an amine.

^{1}H-NMR spectrum (CCl_4): The *Z*-isomer shows doublets at ~6.6 and 5.05 ppm, the *E*-isomer doublets at 6.65 and 5.30 ppm.

2.3.4 3-Bromo-5,6-dihydro-4H-pyran



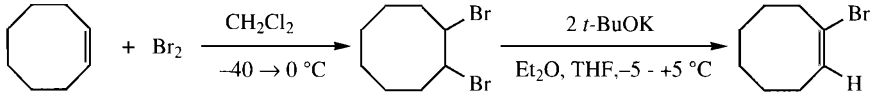
Scale: 1.0 molar.

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer-outlet combination.

Procedure: Bromine (1.0 mol, 160 g) was added dropwise over 30 min to a mixture of 1.2 mol (101 g) of freshly distilled dihydropyran and 400 ml of dichloromethane, while keeping the temperature below –40 °C. After the addition, 15 ml of *N,N*-diethylaniline was added, whereupon the solvent was removed under reduced pressure using a rotary evaporator. To the remaining liquid was added 450 g of *N,N*-diethylaniline. The mixture was heated at ~85 °C, after which a weakly exothermic reaction started. The temperature of the mixture was carefully kept between 90 and 100 °C (occasional cooling or heating) during 30 min. After cooling to 60 °C, 200 ml of ice water was added with vigorous stirring, subsequently a cold (–5 °C) mixture of 190 g of 36% aqueous hydrochloric acid and 200 ml of water was added with vigorous stirring, while keeping the mixture below 10 °C. The lower layer was separated off and the aqueous layer extracted twice with dichloromethane. The combination of lower layer and extracts was washed with water and dried over anhydrous magnesium sulfate, after which the dichloromethane was removed under reduced pressure. Careful distillation of the remaining liquid through a 30-cm Widmer column gave 3-bromo-5,6-dihydro-4*H*-pyran, b.p. 56 °C/15 mmHg, n^{20}_D 1.5074, in 70% yield. The compound should be stored in the refrigerator.

^{1}H-NMR spectrum (CCl_4): 6.55 (br s, 1H); 3.90 (m, 2H); 2.30 (m, 2H) and 1.95 (m, 2H) ppm.

2.3.5 1-Bromocyclooctene



Scale: 0.50 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer-outlet combination.

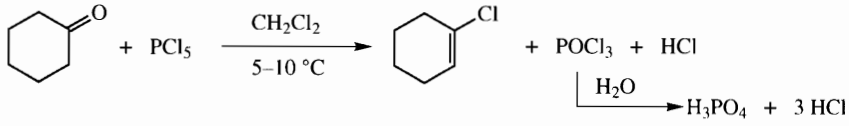
Procedure: (Cf. L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988) p.195-198 and L. Brandsma, H.D. Verkruijsse, Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier, Amsterdam (1981) p. 120.) To a mixture of 0.55 mol (60 g) of freshly distilled cyclooctene and 150 ml of dichloromethane was added at temperatures below –40 °C 0.50 mol (80 g) of bromine. After the addition, which took ~30 min, the temperature was allowed to rise to 0 °C. The solvent was completely removed under reduced pressure, using a rotary evaporator. The remaining liquid was mixed with 250 ml of diethyl ether. A solution of 0.8 mol (90 g) of potassium *tert*-butoxide (commercially available) in 200 ml of THF was added portionwise over 30 min, while keeping the temperature at –5 °C. After stirring for an additional period of 2.5 h at 0 to +5 °C, the mixture was poured into 1 l of ice water. After vigorous shaking and separation of the layers, the aqueous layer was extracted three times with diethyl ether. The combined organic solutions were washed twice with a saturat-

ed aqueous solution of ammonium chloride and subsequently dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. Careful distillation of the remaining liquid through a 40-cm Vigreux column gave 1-bromocyclooctene, b.p. 88 °C/15 mmHg, n^{20}_D 1.519, in 70-74% yield.

^{1}H-NMR spectrum (CCl_4): 6.0 (t, 1H); 2.6 (m, 2H); 2.2 (m, 2H) and 1.6 (4 H) ppm.

2.3.6 1-Chlorocyclohexene

For an extensive description see L. Brandsma, H.D. Verkruijsse, Preparative Polar



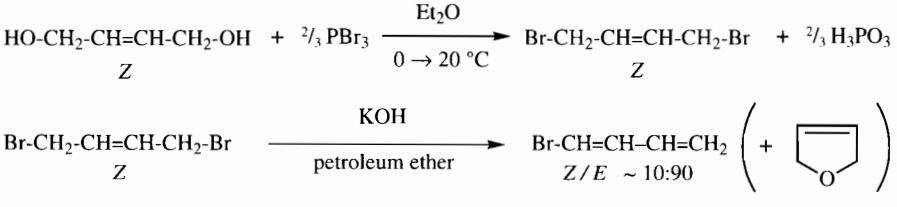
Organometallic Chemistry, Vol. I, Springer-Verlag, Heidelberg (1987) p. 65 and E.A. Braude, J.A. Coles, W.F. Forbes, E.A. Evans, J. Chem. Soc. (1950) 2014 and (1953) 2202.

The ^{1}H-NMR spectrum showed inter alia a multiplet around 5.7 (1H) ppm.

1-Chlorocycloheptene was prepared in a similar way.

2.3.7 Z-1,4-Dibromo-2-butene and 1-Bromo-1,3-butadiene (E/Z ≥ 90:10)

Scale: 1,4-dihydroxy-2-butene: 0.30 molar. 1,4-dibromo-2-butene: 0.20 molar.



Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer-outlet combination for the preparation of 1,4-dibromo-2-butene; for the dehydrobromination a 2-l round-bottomed, three-necked flask, equipped with an efficient, gas-tight mechanical stirrer was connected to a distillation apparatus consisting of a 30-cm Vigreux column, condenser and a 100-ml receiver cooled in a bath at –75 °C.

Procedure:

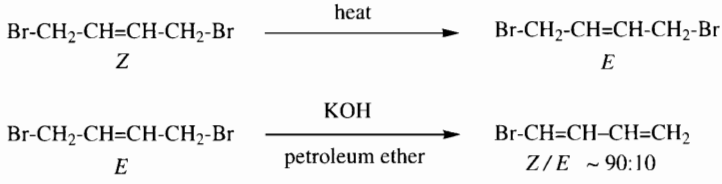
Z-1,4-Dibromo-2-butene: Phosphorus tribromide (0.21 mol, 58 g) was added over 1.5 h to a mixture of 0.30 mol (28.2 g) of *Z*-1,4-dihydroxy-2-butene (commercially available) and 80 ml of diethyl ether, while keeping the temperature at 0 to 10 °C. After the

addition, the cooling bath was removed and the mixture was stirred for another 1 h at room temperature, then it was poured into 500 ml of ice water. After shaking, an additional amount of diethyl ether was added in order to effect a good separation of the layers. The upper layer and one ethereal extract were combined and washed with a saturated aqueous solution of sodium chloride. After drying over anhydrous magnesium sulfate, the ether was removed under reduced pressure. Since the product may isomerize into the *E*-isomer upon heating, the bath temperature was kept below 25 °C during the evaporation of the solvent. The last traces of ether were removed in an oil-pump vacuum (<1 mmHg). The remaining liquid has to be either used immediately for the preparation of *E*-1-bromo-1,3-butadiene or has to be stored at temperatures below –20 °C. The weight of the crude product was close to the theoretically expected one. The NMR spectrum showed a *Z* / *E* ratio of at least ~90:10.

1-Bromo-1,3-butadiene (E/Z ≥ 9): In a 2-l round-bottomed flask was made by vigorous shaking during 1 to 2 min a mixture of 0.20 mol (43 g) of the freshly prepared crude 1,4-dibromobutene (mainly *Z*-isomer), 150 ml of high-boiling petroleum ether (b.p. ≥ 100 °C/15 mmHg) and 250 g of freshly machine-powdered potassium hydroxide. The flask was then immediately connected to the column of the distillation apparatus and the system was evacuated (water aspirator). The mixture was vigorously stirred. The formation of the volatile product caused rather strong foaming. As soon as foaming became less serious, the flask was heated until the petroleum ether began to reflux in the lower part of the column. The condensate in the strongly cooled receiver consisted mainly of *E*-1-bromo-1,3-butadiene. Small amounts of dihydrofuran could be removed by repeated (three or four times) shaking with 10-ml portions of concentrated (30%) hydrochloric acid in a small dropping funnel, the acid layers being discarded. The under layer was transferred into a 250-ml round-bottomed flask containing a small amount (~5 g) of anhydrous magnesium sulfate. After vigorous shaking, the flask containing the mixture was connected to a distillation apparatus consisting of a 30-cm Vigreux column, condenser and single receiver cooled at –75 °C. During evacuation (water aspirator) and moderate heating (bath temperature not higher than 50 °C at the end) the 1-bromo-1,3-butadiene condensed in the receiver. The contents consisted for ~95% of a ~9 : 1 mixture of *E*- and *Z*-bromobutadiene. The compound boils at 90-94 °C/760 mmHg, n^{20}_D 1.512. Yields were generally at least 50%. The compound was stored in the refrigerator.

^{1}H-NMR spectrum (acetone-d_6): 6.73 (m, 1H); 6.35 (m, 1 H); 6.26 (m, 1H); 5.25 (m, 1H) and 5.14 (m, 1 H) ppm; ^{13}C-NMR spectrum (acetone-d_6): 138.98, 135.26, 118.89 and 110.43 ppm.

2.3.8 E-1,4-Dibromo-2-butene and 1-Bromo-1,3-butadiene (Z/E ≥ 90:10)



Scale: 0.20 molar (1,4-dibromo-2-butene).

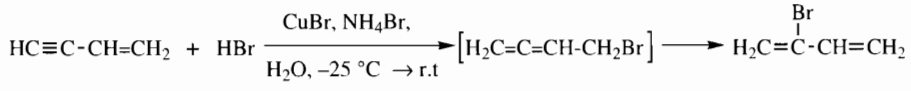
Apparatus: Round-bottomed flask, equipped with a reflux condenser for the conversion of *Z*- into *E*-1,4-dibromo-2-butene; for the dehydrobromination the same apparatus as in the exp. in Sect. 2.3.7 was used.

Procedure:
E-1,4-Dibromo-2-butene: The *Z*-isomer (see exp. in Sect. 2.3.7) was heated under reflux in a water-aspirator vacuum for a number of hours. Distillation (using an air condenser) in vacuo (b.p. ~82 °C/15 mmHg) gave mainly the *E*-isomer. The pure isomer, m.p. 51–52 °C, was obtained by crystallization from pentane.

1-Bromo-1,3-butadiene (Z/E ≥ 90:10): The procedure was similar to that described for the *E*-isomer. As no dihydrofuran was formed, the treatment with concentrated hydrochloric acid was not carried out. The yield was usually higher than 80%. The product was a mixture of the *E*- and *Z*-isomer, the latter predominating (ratio *Z/E* 90:10). The boiling point at atmospheric pressure was 90–94 °C, n^{20}_D 1.510. The compound was stored in the refrigerator.

^{1}H-NMR spectrum (acetone-d_6): 6.56-6.70 (m, 2H); 6.12-6.25 (m, 1 H) and 5.32-5.57 (m, 2 H) ppm; ^{13}C-NMR spectrum (acetone-d_6): 133.93, 133.22, 122.0 and 109.39 ppm.

2.3.9 2-Bromo-1,3-butadiene



Scale: 0.50 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with an efficient gas-tight mechanical stirrer, a thermometer and a cold finger filled with dry ice and acetone.

Procedure: (Cf. I.M. Dolgopol'ski, Yu.V. Trenke, M.Kh. Blyumental, J. Gen. Chem. (USSR) (1963) 33, 1059.) After the flask had been charged with 250 g of a 48% aqueous solution of hydrobromic acid, 20 g of copper(I) bromide and 30 g of ammonium bromide, the air in the apparatus was completely replaced by nitrogen. The dark solution was cooled in a bath at –30 °C and the gas inlet was replaced by a thermometer. Vinylacetylene (0.50 mol, 25 g, (see Note)), condensed in a trap at –75 °C, was added in one portion. The cooling bath was removed. The mixture was vigorously stirred. In the case of a too vigorous reflux in the cold finger, occasional cooling was applied. After ~2 h the temperature in the flask had risen to above 0 °C while the intensivity of the reflux had considerably diminished. Stirring was continued for an additional period of 10 h (the condenser was no longer cooled as the unconverted vinylacetylene remained in solution). The mixture was poured into 500 ml of water, after which three extractions with high-boiling petroleum ether (b.p. >170 °C, 50 and 2 × 30 ml), were carried out. The extracts were washed with water and then dried over 10 g anhydrous magnesium sulfate in a 1-l round-bottomed flask. The flask was equipped for a vacuum distillation: 40-cm Vigreux column, condenser, and single receiver cooled in a bath at –75 °C. The apparatus was evacuated (water aspirator) and the temperature of the heating bath gradually increased until the petroleum began to pass over at >55 °C/15 mmHg. Repetition of this procedure with the contents of the receiver (not allowing the petroleum to pass over) gave pure 2-bromo-1,3-butadiene in ~60% yield, n^{20}_D 1.498. Distillation at atmospheric pressure was not carried out. The product slowly polymerized, even at –20 °C in the refrigerator.

NMR spectrum (CCl_4): 6.30 (dd, 1H); 5.81 (d, 1H); 5.66 (s, 1H); 5.59 (d, 1H) and 5.31 (d, 1H) ppm.

Note: For the preparation of $HC{\equiv}CCH{=}CH_2$ see L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988) p. 178.

2.3.10 1-Bromo-3-methyl-1,2-butadiene

$$HC{\equiv}C{-}C(CH_3)_2OH \xrightarrow[H_2O,\ 40\ ^\circ C]{HBr,\ NH_4Br,\ CuBr,\ Cu^0} BrCH{=}C{=}C(CH_3)_2$$

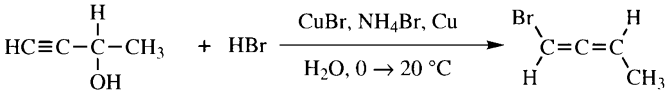
Scale: 0.20 molar.

Apparatus: 250-ml round-bottomed, three-necked flask equipped with a mechanical stirrer, a thermometer and an outlet.

Procedure: (Cf. P.M. Greaves, M. Kalli, Ph.D. Landor, J. Chem. Soc. (C) (1971) 667 and S.R. Landor, A.N. Patel, P.E. Whiter, P.M. Greaves, J. Chem. Soc., (C) (1966) 1223.) A mixture of 50 ml of 48% aqueous hydrobromic acid, 10 g of copper(I) bromide, 8 g of ammonium bromide, 0.5 g of copper bronze and 0.20 mol (16.8 g) of (commercially available) 2-methyl-3-butyn-2-ol was stirred for 15 min under nitrogen at 40 °C (internal temperature). After cooling to room temperature, the layers were separated

as completely as possible. The upper layer was transferred into a 500-ml round-bottomed flask containing 10 g of sodium hydrogen carbonate. After vigorous shaking for a few min, the flask was equipped for a vacuum distillation: 30-cm Vigreux column, condenser and single receiver cooled at −75 °C. By evacuation (10-15 mmHg) and gentle (~50 °C) heating the product distilled and condensed in the receiver. The yield of 1-bromo-3-methyl-1,2-butadiene, n^{20}_D 1.518, was between 70 and 80%.

2.3.11 1-Bromo-1,2-butadiene

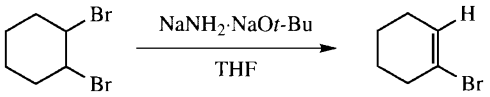


Scale: 0.40 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet, an efficient mechanical stirrer and a thermometer-outlet combination.

Procedure: (Cf. lit. cited for the exp. in Sect. 2.3.10.) A mixture of 200 ml of 48% aqueous hydrogen bromide and 0.40 mol (108 g) of phosphorus tribromide was vigorously stirred at ~25 °C until the system had become homogeneous (~1 h). The solution was cooled to 0 °C, after which 0.4 mol (~40 g) of ammonium bromide, 0.1 mol (~14 g) of copper(I) bromide, 2 g of copper bronze and 0.40 mol (28 g) of the (commercially available) acetylenic alcohol and 40 ml of pentane were added. The air in the flask was replaced by nitrogen and the mixture was stirred for 5 h at 0 °C and subsequently for 18 h at 15 to 20 °C. During this period a slow stream of nitrogen was passed through the flask. After separation of the layers, two extractions with pentane were carried out. The combined organic solutions were washed with water and then dried over anhydrous magnesium sulfate. Most of the pentane was distilled off at atmospheric pressure through a 40-cm Vigreux column, keeping the bath temperature below 100 °C. Subsequent careful distillation through a 40-cm Widmer column gave 1-bromo-1,2-butadiene, b.p. ~60 °C/160–170 mmHg, n^{20}_D 1.523, in yields varying from 60-75%.

2.3.12 1-Bromocyclohexene



Scale: 0.28 molar (1,2-dibromocyclohexane).

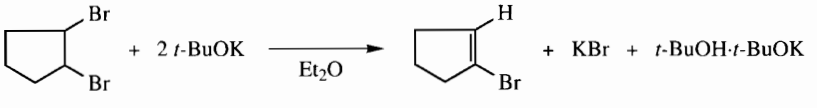
Apparatus: 2-l round-bottomed, three-necked flask, equipped with a combination of a dropping funnel and a gas inlet, a mechanical stirrer and a thermometer-outlet com-

bination; for the preparation of sodamide the flask was equipped with a mechanical stirrer and two outlets (diameter ≥5 mm).

Procedure: (Cf. G. Guillaumet, V. Lemmel, G. Coudert, P. Caubère, Tetrahedron (1974) 30, 1289.) Anhydrous liquid ammonia [1 l, water content <0.1%, see L. Brandsma, H.D. Verkruijsse, Preparative Polar Organometallic Chemistry, Vol. I, Springer-Verlag (1987) p. 21] was placed in the flask. Sodium (2 g) was added in ~0.2 g pieces. When the solution had become uniformly blue, ~300 mg of ferric nitrate (hydrate) was added and air was passed through the flask for 30 sec. When a grey solution had formed, sodium (1.25 mol, 29 g) was added in pieces of ~1 g (as a rule, the conversion into sodamide is complete within half an hour). After completion of the conversion the ammonia was removed by placing the flask in a water bath at 40 °C (one of the outlets was removed). When the volume of the suspension had decreased to ~100 ml, dry THF (300 ml) was cautiously added and the evaporation procedure was continued, while heating the flask in a bath at 50–55 °C and passing a flow of nitrogen through the flask (~500 ml/min). When the flow of escaping ammonia had become very weak, the suspension was cooled to 30 °C and a mixture of 0.38 mol (28 g) of *t*-butyl alcohol and 20 ml of THF was added dropwise over 30 min, while keeping the temperature between 30 and 45 °C. After stirring for an additional 2 h at ~45 °C, a mixture of 0.28 mol (67.8 g) of 1,2-dibromocyclohexane (prepared from cyclohexene and Br_2) was added over 4 h, while keeping the temperature between 20 and 25 °C. The thick brown suspension was stirred for an additional 2.5 h at 20–25 °C, then it was poured into 1 l of ice water containing 100 g of ammonium chloride. After vigorous shaking, the aqueous layer was extracted twice with small portions of pentane. The combined organic solutions were dried over anhydrous $MgSO_4$, after which the greater part of the solvents was distilled off at atmospheric pressure through a 30-cm Vigreux column. Careful distillation of the remaining liquid through a 30-cm Widmer column gave 1-bromocyclohexene, b.p. 50 °C/12 mmHg, n^{22}_D 1.5112, in ~50% yield.

^{1}H-NMR spectrum (CCl_4): 6.0 (1H) ppm.

2.3.13 1-Bromocyclopentene



Scale: 0.30 molar (1,2-dibromocyclopentane).

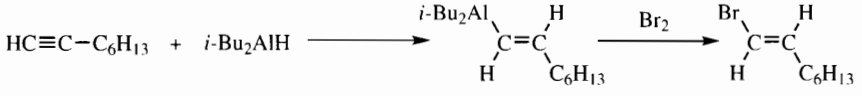
Apparatus: 1-l round-bottomed, three-necked flask, equipped with a stopper (during the addition of *t*-BuOK being replaced with a powder funnel), a mechanical stirrer and a reflux condenser.

Procedure: [This procedure is more simple than the one of Caubère et al. (Tetrahedron (1974) 30, 1289) which also gives good results in this case.] To a mixture of 0.30 mol (69 g) of 1,2-dibromocyclopentane (prepared in the usual way from cyclopentene and

bromine) and 600 ml of ether was added in one portion 0.30 mol (34 g) of finely powdered (commercially available) *t*-BuOK. The reaction was mildly exothermic and after some time the ether began to reflux. After refluxing had stopped, an additional 0.30 mol of *t*-BuOK was added in two equal portions with an interval of half an hour. The thick suspension was heated under reflux until GC indicated disappearance of 1,2-dibromocyclopentane (~5 h). After cooling to room temperature, the mixture was hydrolyzed with a solution of 30 g of ammonium chloride in 150 ml water. The aqueous layer was extracted once with ether. The combined organic solutions were washed five times with 1 M aqueous hydrochloric acid (in order to remove the *t*-butyl alcohol) and subsequently dried over anhydrous $MgSO_4$. The ether was then distilled off at atmospheric pressure through a 30-cm Vigreux column. Careful distillation of the remaining liquid afforded 1-bromocyclopentene, b.p. 130 °C/760 mmHg, n^{20}_D 1.5025, in 50% yield.

^{1}H-NMR spectrum (CCl_4): 5.8 (1H) ppm.

2.3.14 E-1-Bromo-1-octene

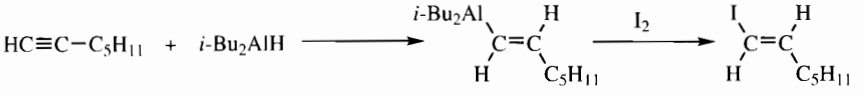


Scale: 20 mmolar.

Procedure: (Cf. G. Zweifel, R.B. Steele, J. Am. Chem. Soc. (1967) 89, 2754; checked in the laboratory of Prof. G. Linstrumelle, Paris.) To a solution of 1-octyne (2.2 g, 20 mmol) in heptane (5 ml) was added diisobutylaluminum hydride 1 M (20 ml, 20 mmol), while keeping the temperature below 40 °C. After the exothermic reaction had subsided, the reaction mixture was heated for 2 h at 50 °C. The mixture was cooled at −50 °C, after which a solution of bromine (1.025 ml, 20 mmol) in cold anhydrous THF (15 ml) (bromine was dissolved in cold THF) and heptane (4 ml) was added over 10 min, while keeping the temperature between −40 and −60 °C. The mixture was then allowed to reach room temperature and a 20% aqueous solution of H_2SO_4 was added dropwise with efficient stirring and cooling in an ice-water bath. After this operation the mixture was poured into dilute aqueous sulfuric acid and 5 extractions with pentane were carried out. After drying over $MgSO_4$ and removal of the solvent under reduced pressure the product was distilled: b.p. 70 °C/15 mmHg, yield 71%.

^{1}H-NMR spectrum (200 MHz, $CDCl_3$): 6.16 (dt, 2H, $J_{1,2}$ = 13.6 Hz, $J_{2,3}$ = 6.9 Hz); 5.98 (dt, 2H, $J_{1,3}$ = 1.1 Hz) ppm.

2.3.15 E-1-Iodo-1-heptene



Scale: 20 mmolar

Procedure: (Cf. G. Zweifel, R.B. Steele, J. Am. Chem. Soc. (1967) 89, 2753; checked in the laboratory of Prof. G. Linstrumelle, Paris.) This compound was prepared in a way similar to the procedure of 2-3-14. The iodine was added as a solution (20 mmol) in THF (20 ml) at ~−50 °C. The extract was washed with aqueous $Na_2S_2O_3$ in order to remove some free iodine. Distillation (b.p. 62 °C/15 mmHg) gave the product in ~70% yield.

^{1}H-NMR spectrum (200 MHz, $CDCl_3$): 6.52 (dt, 2H, $J_{1,2}$ = 14.3 Hz, $J_{2,3}$ = 7.1); 6.00 (dt, 2H, $J_{1,3}$ = 1.4 Hz) ppm.

3 Cross-Coupling Between 1-Alkynes and 1-Bromoalkynes

3.1 Introduction

In 1957 W. Chodkiewicz, who collaborated with P. Cadiot in Paris, published his thesis with the modest title "Contributions to the synthesis of acetylenic compounds" [1]. In his thesis he described the copper(I)-catalyzed coupling of a large number of acetylenes and bromoacetylenes:

$$RC{\equiv}C{-}H \;+\; Br{-}C{\equiv}CR' \xrightarrow[\text{amine}]{\text{Cu(I)}} RC{\equiv}C{-}C{\equiv}CR'$$

In fact, this synthesis of unsymmetrically substituted butadiynes is one of the most useful and versatile methods in acetylenic chemistry [2–5]. The reaction, usually referred to as Cadiot-Chodkiewicz coupling, has been found particularly useful in syntheses of naturally occurring poly-unsaturated compounds [6].

About the mechanism little is known. Copper acetylides are likely intermediates.

Cadiot-Chodkiewicz cross-couplings have been applied to synthesize amphiphilic diynes containing an ester group. Their polymers are used for obtaining Langmuir-Blodgett films [7–10].

The present chapter is mainly based on the reviews [1–5] and on our own experimental data.

References (Sect. 3.1)

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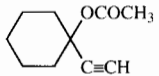
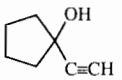
Table 1. Cadiot-Chodkiewicz couplings selected from literature

Acetylene RC≡CH	Bromoacetylene BrC≡CR'	Conditions	Reported yield (%)	Literature
Alkylacetylenes				
C_2H_5-C≡CH	BrC≡C-CH_3	20°C, THF	13	Bull. Soc. Chim. France (1965) 1525
C_2H_5-C≡CH	BrC≡C-CH=CH_2	20-30°C, CH_3OH	80–90	J. Prakt. Chem. (1969) 153
Arylacetylenes				
Ph-C≡CH	BrC≡C-COOH	20°C, NMP	75	Ann. Chim. (Paris) (1957) 819
p-NO_2-Ph-C≡CH	BrC≡C-Ph	40°C, DMF	79	Ann. Chim. (Paris) (1957) 819
p-NO_2-Ph-C≡CH	BrC≡C-CH_2OH	40°C, DMF	80	Ann. Chim. (Paris) (1957) 819
p-Br-Ph-C≡CH	BrC≡C-Ph	25°C, DMF	86	Ann. Chim. (Paris) (1962) 785
Ph-C≡CH	BrC≡C-C$(CH_3)_2OH$	$C_4H_9NH_2$	70	C.A. (1973) 79, 18257e
Ph-C≡CH	BrC≡C-CH=O	CH_3OH	71	Houben-Weyl (1977) 5/2a, p. 931
Ph-C≡CH	BrC≡C-CH$(OC_2H_5)_2$	$(C_2H_5)_3N$	39	Houben-Weyl (1977) 5/2a, p. 931
Enynes				
C_2H_5CH=CH-C≡CH	BrC≡C-COOH	CH_3OH, little H_2O, then decarboxylation with Cu(II)	?	J. Prakt. Chem. (1969) 153
1,3-Diynes				
CH_3C≡C-C≡CH	BrC≡C-C$(CH_3)_2OH$	30°C, CH_3OH, Et_2O	91	Ann. Chim. (Paris) (1957) 819
CH_3C≡C-C≡CH	BrC≡C-Ph	30°C, CH_3OH	91	Bull. Soc. Chim. France (1961) 2171
CH_3C≡C-C≡CH	BrC≡C-CH_2OH	30°C, CH_3OH	97	Ann. Chim. (Paris) (1957) 819
Amines				
$(CH_3)_2NCH_2$-C≡CH	BrC≡C-Ph	25°C, H_2O	86	Ann. Chim. (Paris) (1957) 819
$(CH_3)_2NCH_2$-C≡CH	BrC≡C-C$(CH_3)_2OH$	20°C, H_2O	97	Ann. Chim. (Paris) (1957) 819
$(CH_3)_2NCH_2$-C≡CH	BrC≡C-C$(Ph)_2OH$	20°C, CH_3OH	90	Ann. Chim. (Paris) (1957), 819
$(CH_3)_2NCH_2$-C≡CH	BrC≡C-C≡CCH_3	20°C, H_2O	91	Ann. Chim., (Paris) (1957) 819
$H_2NCH_2CH_2$-C≡CH	BrC≡C-C$(Ph)_2OH$	–	65	Ch. Acetylenes (1969) 612

Ethers, sulfides				
$C_2H_5OCH_2$-C≡CH	BrC≡C-C(Ph)$_2$OH	20°C, CH_3OH	90	Ann. Chim. (Paris) (1957) 819
Esters, amides				
$CH_3OOCCH_2CH_2$-C≡CH	BrC≡C-n-C_4H_9	10°C, CH_3OH	89	Ann. Chim. (Paris) (1957) 819
H_2NCO-C≡CH	BrC≡C-Ph	< 10°C, DMF	76	Ann. Chim. (Paris) (1957) 819
H_2NCO-C≡CH	BrC≡C-CH=CHCOOH	DMF	92	Bull. Soc. Chim. France (1961) 2171
H_2NCO-C≡CH	BrC≡C-C(CH$_3$)$_2$OH	< 5°C, DMF	77	Ann. Chim. (Paris) (1957) 819
H_2NCO-C≡CH	BrC≡C-CH(OC$_2$H$_5$)$_2$	CH_3OH, DMF, Et_2O	41	J. Chem. Soc. (Perkin I) (1975) 424
	BrC≡C-n-C_4H_9	10°C, CH_3OH	83	Ann. Chim. (Paris) (1957) 819
Acetals				
(C$_2$H$_5$O)$_2$CH-C≡CH	BrC≡C-CH=CHCOOH	–	80	Ch. Acetylenes (1969) 612
(C$_2$H$_5$O)$_2$CH-C≡CH	BrC≡C-Ph	CH_3OH	71	Houben-Weyl (1977) 5/2a, p.931
(C$_2$H$_5$O)$_2$CHC≡C-C≡CH	BrC≡C-Ph	CH_3OH	76	Houben-Weyl (1977), 5/2a, p.931
Acids				
HOOC-C≡CH	BrC≡C-p-BrPh	25-30°C	92	Compt. Rend (1969) 1905
HOOC-CH_2CH_2-C≡CH	BrC≡C-C≡CCH_3	20°C, H_2O	86	Ann. Chim. (Paris) (1957) 819
HOOCCH=CH-C≡CH	BrC≡C-C≡CCH_3	20°C, H_2O	88	Ann. Chim. (Paris) (1957) 819
HOOCCH=CH-C≡CH	BrC≡C-Ph	20°C, CH_3OH	74	Compt. Rend (1957) 1634

Abbreviations: Ch. Acetylenes = Chemistry of Acetylenes, H.G. Viehe (ed.), Marcel Dekker, New York, (1969).

Table 1. (Continued)

Acetylene RC≡CH	Bromoacetylene BrC≡CR'	Conditions	Reported yield (%)	Literature
Alcohols				
$HOCH_2$-C≡CH	BrC≡C-CH_3	40°C, H_2O	89	Ann. Chim. (Paris) (1957) 819
$HOC(CH_3)_2$-C≡CH	BrC≡C-CH_3	20°C, H_2O	93	Ann. Chim. (Paris) (1957) 819
$HOC(Ph)_2$-C≡CH	BrC≡C-CH_3	20°C, CH_3OH	90	Ann. Chim. (Paris) (1957) 819
$HOCH_2$-C≡CH	BrC≡C-n-C_3H_7	45°C, H_2O	81	Ann. Chim. (Paris) (1957) 819
$HOC(Ph)_2$-C≡CH	BrC≡C-Ph	20°C, CH_3OH	87	Ann. Chim. (Paris) (1957) 819
	BrC≡C-$C(CH_3)_2OH$	20°C, CH_3OH	94	Ann. Chim. (Paris) (1957) 819
$HOCH_2$-C≡CH	BrC≡C-COOH	35°C, H_2O	84	Ann. Chim. (Paris) (1957) 819
$HOCH_2CH_2$-C≡CH	BrC≡C-COOH	20°C, H_2O	94	Ann. Chim. (Paris) (1957) 819
$HOC(CH_3)_2$-C≡CH	BrC≡C-$CH_2CH(OH)CH_3$	20°C, CH_3OH	71	C.A. (1969) 70, 11015e
$HOC(CH_3)_2$-C≡CH	BrC≡C-$CH_2SC_2H_5$	20-30°C, CH_3OH	70	Bull. Soc. Chim. France (1966) 3024

Abbreviations: Ch. Acetylenes = Chemistry of Acetylenes, H.G. Viehe (ed.), Marcel Dekker, New York, (1969).

3.2 Scope and Limitations

(For literature see Refs. [1–5, 7] of Sect. 3.1.) The Cadiot-Chodkiewicz coupling gives access to a wide variety of unsymmetrically substituted butadiynes, RC≡C–C≡R'.

Some hetero-substituted acetylenes do not survive the conditions of the coupling. For example, trimethylsilylacetylene, $(CH_3)_3SiC{\equiv}CH$, and trialkylstannylacetylenes, $R_3SnC{\equiv}CH$, undergo C-heteroatom cleavage under the influence of the amine present in the coupling mixture. However bromotriethylsilylacetylene, $BrC{\equiv}C\text{-}Si(C_2H_5)_3$, has been successfully used in Cadiot-Chodkiewicz couplings (J. Chem. Soc., Chem. Commun. (1968) 204). According to Cadiot and Chodkiewicz acetylenic phosphines, $R_2P\text{-}C{\equiv}CH$, cannot be used, because of strong P–Cu complexation.

Table 1 gives a number of representative asymmetric couplings, reported in literature and arranged according to the nature of the acetylene RC≡CH.

3.3 Relative Reactivities of the Acetylene and the Bromoacetylene

There seems to exist some relation between the acidity of the acetylene (pK) and the ease with which it couples with the bromoalkyne. Acetylenic hydrocarbons with a non-conjugated triple bond, e.g. $HC{\equiv}CC_4H_9$, are less reactive than arylacetylenes, e.g. $PhC{\equiv}CH$, presumably because the intermediary copper alkynylides, e.g. $C_4H_9C{\equiv}C\text{-}Cu$, are formed less easily. Our experimental results confirm the reports of Cadiot and Chodkiewicz: whereas $PhC{\equiv}CH$ and $C_2H_5C{\equiv}CBr$ gave the unsymmetrical acetylene $PhC{\equiv}C\text{-}C{\equiv}CC_2H_5$ in a good (~70%) yield, $PhC{\equiv}CBr$ and $C_2H_5C{\equiv}CH$ reacted under similar conditions to give the unsymmetrical and symmetrical ($PhC{\equiv}C\text{-}C{\equiv}CPh$) product in comparable amounts. From the reaction (at ~30 °C) between $C_6H_{13}C{\equiv}CH$ and $C_2H_5C{\equiv}CBr$ the coupling product $C_6H_{13}C{\equiv}C\text{-}C{\equiv}CC_2H_5$ was isolated in a modest (~50%) yield. The formation of appreciable amounts of homo-coupling products may become a serious problem in large-scale preparations of RC≡C–C≡CR' in which both R and R' contain long carbon chains.

The chain length in the acetylenic compound also seems to influence the yield: Chodkiewicz (Ann. Chim. (Paris) (1957) 855) reported that yields with $HC{\equiv}C\text{-}C(CH_3){=}CH_2$ are higher than with $HC{\equiv}C\text{-}C(C_5H_{11}){=}CH_2$. We succeeded in obtaining good (> 65%) yields of cross-coupling products from $C_2H_5C{\equiv}CBr$ and the alcohols $HC{\equiv}C(CH_2)_nOH$ with n = 1, 2, 4, 5 and 7 by carrying out the reactions at suitable temperatures (see Table 2). However, the alcohol $HC{\equiv}C(CH_2)_9OH$ and bromobutyne gave yields of maximally 45% and ~25% of $C_2H_5C{\equiv}C\text{-}C{\equiv}C(CH_2)_9OH$ when performed at 30 to 35 °C and 15 to 20 °C, respectively, homo-coupling of $C_2H_5C{\equiv}CBr$ being the main reaction. An unfavourable factor in the case of $HC{\equiv}C(CH_2)_9OH$ might be the slight solubility of the copper derivative, which appears as a white suspension upon addition of copper(I) halide. Most of the other acetylenic derivatives investigated formed almost colourless solutions with copper(I) halide.

Table 2. Cadiot-Chodkiewicz couplings performed in the author's laboratory

Acetylene RC≡CH	Bromoacetylene BrC≡CR'	Temp. range (°C)	Scale (mmol)	Isolated yield[a] (%)	Remarks
C_6H_{13}-C≡CH	BrC≡C-Et	30–35 or 15–20	100	50–55	
Ph-C≡CH	BrC≡C-Et	44–48	50	70	Addition time 1 h; 20 % excess PhC≡CH
Et-C≡CH	BrC≡C-Ph	25–30	100	~45	
$HOCH_2$-C≡CH	BrC≡C-Et	45–50	100	86	Addition time 1 h; 20 % excess $HC{\equiv}CCH_2OH$
$HOCH_2$-C≡CH	BrC≡C-Et	25–45	100	71	Addition time 45 min; 20 % excess $HC{\equiv}CCH_2OH$
$HOC(CH_3)_2$-C≡CH	BrC≡C-Et	20–25	100	81	25 % excess $HC{\equiv}CC(CH_3)_2OH$
$HOCH_2CH_2$-C≡CH	BrC≡C-Et	25–28	100	74	20 % excess $HC{\equiv}C(CH_2)_2OH$
$HOCH_2CH_2$-C≡CH	BrC≡C-Et	9–11	100	87	20 % excess $HC{\equiv}C(CH_2)_2OH$
$HO(CH_2)_4$-C≡CH	BrC≡C-Et	15–17	100	69	15 % excess $HC{\equiv}C(CH_2)_4OH$
$HO(CH_2)_4$-C≡CH	BrC≡C-Et	28–32	100	57	15 % excess $HC{\equiv}C(CH_2)_4OH$
$HO(CH_2)_4$-C≡CH	BrC≡C-Et	42–47	50	45	
$HO(CH_2)_7$-C≡CH	BrC≡C-Et	25–30	100	64	
$HO(CH_2)_9$-C≡CH	BrC≡C-Et	45–50	50	36	15 % excess $HC{\equiv}C(CH_2)_9OH$
$HO(CH_2)_9$-C≡CH	BrC≡C-Et	35–40	200	45	
$HO(CH_2)_9$-C≡CH	BrC≡C-Et	15–20	70	25	
R"OCH_2-C≡CH R" = $-CH(CH_3)OEt$	BrC≡C-C_5H_{11}	30–35	200	> 80	L. Brandsma, Preparative. Acetylenic Chemistry, Elsevier, Amsterdam (1988) p.213
$EtSCH_2$-C≡CH	BrC≡C-Et	15–18	50	80	Addition time 1 h
$EtSCH_2$-C≡CH	BrC≡C-Et	40–45	50	70	Addition time 1 h
Et_2NCH_2-C≡CH	BrC≡C-Et	30–35	200	> 80	
R"$O(CH_2)_2$-C≡CH R" = $-CH(CH_3)OEt$	BrC≡C-Et	17–20	50	74	15 % excess $HC{\equiv}C(CH_2)_2OR"$
R"$O(CH_2)_4$-C≡CH R" = $-CH(CH_3)OEt$	BrC≡C-Et	17–20	50	80	5 % excess EtC≡CBr

$Et_2NCH_2CH_2$-C≡CH	BrC≡C-Et	25–30	50	< 10	15 % excess amine
$Et_2NCH_2CH_2$-C≡CH	BrC≡C-Et	10–13	50	55	15 % excess amine
$(EtO)_2CH$-C≡CH	BrC≡C-Et	24–27	50	77	20 % excess $HC{\equiv}CCH(OEt)_2$
EtSCH=CH-C≡CH	BrC≡C-t-Bu	30–35	100	> 80	Undistilled, purity > 95 % by NMR
$NH_2C(CH_3)_2$-C≡CH	BrC≡C-Et	37–40	100	43	Addition time ~80 min Undistilled, purity ~98 % by GLC
$NH_2C(CH_3)_2$-C≡CH	BrC≡C-Et	11–13	100	67	Addition time ~80 min Undistilled, purity ~99 % by GLC

[a] Products were isolated by careful fractional distillation through a 25 cm Vigreux column at 10–15 mm Hg pressure; $C_2H_5C{\equiv}C$-C≡$C(CH_2)_9OH$ was distilled at ~0.5 mm Hg. Products with R" = $-CH(CH_3)OC_2H_5$ may decompose under the influence of traces of acid adhering to the glass wall: prior to distillation 1 gram of tetramethylethanediamine was added.

The presence of an alcoholic function in the acetylene is said to have a favourable influence while variations in the structure of the bromoacetylene, R'C≡CBr, are reported to have little influence upon the results.

Domnin and coworkers (Ref. [7] of Sect. 3.1) found significantly lower yields of conjugated diynes in Cadiot-Chodkiewicz couplings with long-chain aliphatic alkynes. They could not give a satisfactory explanation.

3.4 Conditions for the Coupling

(For literature see Refs. of Sect. 3.1.) The general procedure involves dropwise addition of the bromoacetylene (mixed with a solvent) to a well-stirred mixture of the acetylene, water or an organic solvent, aqueous ethylamine, hydroxylamine. HCl and a catalytic quantity (1–5 mol%) of copper(I)chloride or bromide. The ethylamine serves to neutralize the hydrobromic acid produced in the coupling. The use of a large(~70 mol%) excess is recommended by Chodkiewicz and Cadiot. If the acetylene contains a COOH group, more ethylamine has to be used. Bromoacetylenes containing a COOH group are most conveniently added as a solution of their sodium or ethylamine salts.

The function of the hydroxylamine salt is to reduce any Cu(II), which might be formed by the presence of traces of oxygen, to Cu(I), and which may give rise to oxidative dimerization of the acetylene RC≡CH.

Methanol, ethanol and water are the most frequently used solvents. For reactions with compounds that are slightly soluble in these solvents, diethyl ether, tetrahydrofuran, dimethylformamide or *N*-methylpyrrolidinone may be used.

The coupling reaction is usually very fast at concentrations of the order of 0.5 to 1 mol/l and can be easily followed by the heating effect. Most couplings in the presence of ethylamine proceed at a convenient rate within the temperature range of 10 to 35 °C, but the rate may decrease strongly if the temperature is lowered by 10 to 20 °C. Cadiot and Chodkiewicz recommend "optimum temperatures" depending upon the nature of the acetylene: these are 15–25 °C for non-conjugated acetylenes, RC≡CH, and 30 °C for enynes RCH=CH-C≡CH, and diynes, RC≡CC≡CH.

If the product is neutral or contains weakly basic groups (NH_2, R_2N), a small amount of alkali cyanide is added prior to carrying out the work-up. This converts Cu(I) into the inactive complex. If relatively much methanol or ethanol has been used, it seems practical to remove these solvents under reduced pressure before carrying out the extraction procedure. Carboxylic acids can be isolated after treatment with mineralic acid. After addition of the bromoacetylene (no cyanide may be added!) methanol or ethanol are removed in vacuo, the neutral by products that might have formed are removed by extraction, finally dilute acid is added to liberate the coupling product.

Bromoacetylenes are far more reactive than chloroacetylenes, while iodoacetylenes cannot be used because they very readily undergo homo-coupling. J. Wityak and J.B. Chan (Synth. Comm. (1991) 21, 977), however, described some examples of successful

cross-couplings between 1-iodoacetylenes and acetylenic compounds. They used conditions similar to the ones applied for coupling between acetylenes and sp^2 halides (see Chapter 10).

$$R'C{\equiv}CI + HC{\equiv}CR \xrightarrow[THF,\ (i\text{-}Pr)_2NH,\ 25\ °C]{PdCl_2{\cdot}(PPh_3)_2,\ CuI} R'C{\equiv}C{-}C{\equiv}CR$$

In the laboratory of G. Linstrumelle (G.L., personal communication) similar cross-couplings have been investigated, using the same combination of catalysts. The coupling was performed with a number of amines with or without another organic solvent and 100 mol% excess of an acetylenic derivative. By far the best results were obtained when the reaction was carried out in pyrrolidinone. In the absence of the copper catalyst the reactions proceeded sluggishly and yields were low. The Pd-catalyst, however, could be omitted without affecting the yields. 1-Bromo-1-alkynes also coupled satisfactorily. Here, the best results were obtained with the combination of a Pd- and a Cu-catalyst. 1-Chloroalkynes gave yields between 15 and 30% only.

3.5 Choice of the Reaction Partners

An unsymmetrically substituted compound RC≡C–C≡CR' can, in principle, be obtained by two alternative couplings:

$$RC{\equiv}C{-}H + Br{-}C{\equiv}CR' \xrightarrow{a} RC{\equiv}C{-}C{\equiv}CR' \xleftarrow{b} RC{\equiv}C{-}Br + H{-}C{\equiv}CR'$$

The decision which alternative to take depends upon a number of factors, such as yield, accessibility and stability of the reaction partners and ease of purification of the product. If, for example, $C_6H_5C{\equiv}C{-}C{\equiv}CC_2H_5$ is to be prepared, route a is preferred ($PhC{\equiv}C{-}H + Br{-}C{\equiv}CC_2H_5$), since couplings with more acidic acetylenes give better results. For the preparation of $HOC(CH_3)_2C{\equiv}C{-}C{\equiv}CCH_2N(CH_3)_2$ the combination of $BrC{\equiv}CC(CH_3)_2OH$ and $HC{\equiv}CCH_2N(CH_3)_2$ seems better than $HC{\equiv}CC(CH_3)_2OH$ + $BrC{\equiv}CCH_2N(CH_3)_2$, since the latter bromide is expected to be very unstable.

3.6 Side Reactions

Under the catalytic influence of Cu(I) the bromoacetylene may be converted into the symmetrical product:

$$2\ R'C{\equiv}C{-}Br + 2\ Cu^+ \longrightarrow R'C{\equiv}C{-}C{\equiv}CR' + 2\ Cu^{2+}$$

Cu^{2+} is reduced to Cu^+ by the hydroxylamine present in the solution. Ammonia is said to favour this homo-coupling, whereas primary amines repress it. The possibility of

this undesired reaction can be further reduced by using Cu(I) salts in *small* amounts, by slow addition of the bromoacetylene with efficient stirring and by a careful control of the operating temperature (low is better, but not always).

The use of large amounts of primary amine (more than the usual excess) involves the risk of addition across the triple bond of the bromoacetylene, e.g. (see Sect. 3.1, Ref. [3]):

$$PhC{\equiv}CBr + RNH_2 \xrightarrow[NH_2OH{\cdot}HCl,\ CuCl]{RNH_2,\ EtOH} PhCH_2C(NHR){=}NR + PhCH_2C(NHR){=}NOH$$

3.7 Experimental Part

3.7.1 General Remarks and Some Observations

In addition to the experiments described by Cadiot, Chodkiewicz and others we have carried out several couplings on a 0.05 to 0.10 molar scale with readily available bromoalkynes and acetylenes. The amount of copper halide (we always used copper(I) *bromide*) was ca. 5 mol%, while ethylamine was used in large excess (15 gram 70% aqueous solution for 0.10 molar-scale reactions). The solvent for our reactions was methanol. For the coupling of propargyl alcohol with the lower bromo-alkynes we also did experiments with water-methanol mixtures, but the results were similar to those obtained with methanol as the only solvent. The bromoalkyne was added as a solution in methanol.

According to Cadiot and Chodkiewicz the reaction can be easily monitored by temperature observation. We can fully confirm this: addition of a few drops of a methanolic solution of bromoalkyne to a mixture of the acetylenic partner, methanol and the other reagents usually caused the temperature to rise by several degrees within a temperature range of 10 to 40 °C. When the addition was stopped, the temperature did not continue to rise. The couplings with propargyl alcohol were exceptions to this rule: the heating effect during addition of the bromoalkyne was weak below 40 °C. This lower reactivity might be caused by a slight solubility of the copper acetylide $Cu{-}C{\equiv}CCH_2OH$. It appeared as a yellow suspension upon addition of the catalytic amount of copper halide. In couplings with 1-butyne and its homologues also a yellow turbidity or suspension was visible, but in these cases the heating effect was strong. It is, in general, advisable to perform the couplings at temperatures as low as possible, but with maintenance of the prompt temperature response after addition of a few drops of the solution of the bromoacetylene or after interruption of the addition. Chemists have learned that slow addition gives better results: over 1 hour is better than over 15 minutes. The prompt temperature response in most Cadiot-Chodkiewicz couplings indicates that these reactions can be performed very quickly and the work-up carried out shortly after completion of the addition of the bromoalkyne.

Furthermore it seems important to stir efficiently during the addition of the bromoalkyne: too high local concentrations of the latter may give rise to homo-coupling.

Most of our reactions have been done within the temperature range of 15 to 35 °C and (isolated) yields were generally satisfactory, though seldom as high as reported

by Chodkiewicz and his French colleagues. The results of some reactions, which gave low or moderate yields when performed between 25 and 30 °C, could be improved by working at considerably lower temperatures. For example, $C_2H_5C{\equiv}C{-}Br$ and $HC{\equiv}CCH_2CH_2N(C_2H_5)_2$ gave almost no coupling product at ~30 °C, but at 10 °C a yield of 60% could be obtained. When the temperature was lowered still further to 0 °C, the reaction still seemed rather fast, but the yield was lower. Also couplings with acetylenic alcohols of the general formula $HC{\equiv}C(CH_2)_nOH$ with $n > 1$ gave better results when carried out in the region of 15 °C (with $HC{\equiv}C(CH_2)_9OH$ as an exception). For reactions with propargyl alcohol, however, higher temperatures (around 50 °C) appeared to be somewhat more favourable. It is not possible on the basis of our (limited) experimental data to predict whether for a given reaction a higher or a lower temperature will lead to improved results. Higher temperatures seem more favourable when the copper acetylide is slightly soluble.

Another possibility for obtaining optimal results consists in varying the molar proportions of the reaction partners. If the acetylenic compound $RC{\equiv}CH$ is readily available and relatively cheap, e.g. $HC{\equiv}CCH_2OH$ or $HC{\equiv}CC(CH_3)_2OH$, one may use a large excess of it. An additional favourable circumstance is that these compounds can be easily separated from the much less volatile and less soluble (in water) coupling products. If, however, an acetylenic alcohol $HC{\equiv}C(CH_2)_nOH$ with $n = 2$ or higher, is to be coupled, one may decide to use the bromoalkyne in excess in the expectation that all $HC{\equiv}C(CH_2)_nOH$ will be converted into $RC{\equiv}CC{\equiv}C(CH_2)_nOH$. Especially in the case of a long carbon chain, separation of the starting alcohol and the coupling product may be troublesome.

3.7.2 Performance of Cu-Catalyzed Cadiot-Chodkiewicz Couplings

Our couplings were carried out by the following standard procedure. An atmosphere of inert gas was carefully maintained.

In a 250-ml round-bottomed, three-necked flask, equipped with a dropping funnel combined with a nitrogen inlet, a thermometer and an outlet were placed 0.10 mol of the acetylenic compound, 15 gram of a 70% aqueous solution of ethylamine, 5 g of hydroxylamine.HCl and 50 ml of methanol. After replacing the air by nitrogen, magnetic stirring was started and 0.7 g of finely powdered copper(I) bromide was added. In the case of propargyl alcohol and aliphatic 1-alkynes and some other acetylenes a yellowish suspension was formed. In most cases, however the solution remained clear and almost colourless (Note). The bromoalkyne (0.10 mol, dissolved in 25 ml of methanol) was added dropwise over ~40 min to 1 h with efficient stirring and maintaining the temperature of the reaction mixture at the level indicated in Table 2 (ice bath or water bath). Twenty minutes after completion of the addition a solution of 2 g of KCN or NaCN in 10 ml of water was added. The greater part (~50 ml) of the methanol was then removed under reduced pressure (rotary evaporator). The remaining liquid was extracted five times with 40-ml portions of diethyl ether. The combined organic solutions were washed once with a concentrated aqueous solution of ammonium chloride and subsequently dried over anhydrous magnesium sulfate

(potassium carbonate in the case of amines). The products were isolated by distillation under reduced pressure.

Products with a highly conjugated system (e.g. C≡C–C≡C–C≡C or C≡C–C≡C–C=C) should not be distilled.

Note: Acetylenes with a conjugated system, e.g. $CH_3C{\equiv}CC{\equiv}CH$, may give a red suspension.

The results are given in Table 2.

3.7.3 Typical Procedure for the Pd/Cu-Catalyzed Cross Coupling Between 1-Bromo-1-alkynes and Acetylenes

Scale: 1.3 mmolar.

Procedure: (Adapted from Prof. G. Linstrumelle, École Normale Supérieure, Paris.) To a stirred solution of 1-bromo-1-heptyne (227 mg, 1.3 mmol), 46 mg $PdCl_2{\cdot}(PPh_3)_2$ (0.0065 mmol) of and copper(I)iodide (25 mg, 0.13 mmol) in 3 ml of pyrrolidinone was added a solution of 216 mg (1.56 mmol) of 1-decyne in 2.5 ml of pyrrolidinone. After stirring for 1 h at 25 °C, aqueous NH_4Cl and diethyl ether were added. The product was isolated in 61% yield by chromotography on silicagel.

$HOCH_2C{\equiv}C–C{\equiv}C\text{-}C_5H_{11}$ was obtained in 80% yield from $HC{\equiv}CCH_2OH$ (100 mol% excess and $BrC{\equiv}C\text{-}C_5H_{11}$ in the presence of the Pd- and Cu-catalysts as described above.

Other successful examples are the preparation of $(CH_3)_2NCH_2C{\equiv}C–C{\equiv}CC_5H_{11}$ (82% yield) and $PhC{\equiv}CC{\equiv}CC_5H_{11}$ (61% yield).

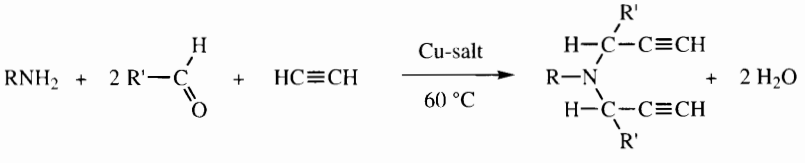
4 Copper-Catalyzed Aminoalkylation of Acetylenes

4.1 Introduction, Scope and Mechanism

The reaction of acidic acetylenes such as phenylacetylene with formaldehyde and secondary amines was reported by Mannich and Chang in 1933 [1].

$$PhC{\equiv}CH + HCH{=}O + R_2NH \xrightarrow[100\ °C]{\text{dioxane}} PhC{\equiv}C{-}CH_2NR_2 + H_2O$$

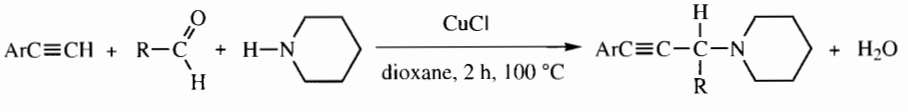
After prolonged heating the substituted propargylic amines were obtained in good yields. Vinylacetylene, $HC{\equiv}CCH{=}CH_2$, behaved in a similar way [2]. With the lesser acidic aliphatic acetylenes the aminoalkylation proceeds very sluggishly. Reppe reported that copper salts considerably facilitate this reaction [3, 4]. Acetylene itself (under pressure) gives mainly $R_2N\text{-}CH_2C{\equiv}CCH_2\text{-}NR_2$. Applying high acetylene pressure Moore and Vitcha [5] carried out the reaction of *primary* amines with aldehydes:



Russian investigators [6] performed an analogous reaction with *N,N*-diethylpropargyl amine and formaldehyde under mild conditions:

$$(C_2H_5)_2NCH_2C{\equiv}CH + C_2H_5NH_2 + H_2C{=}O \xrightarrow[20\text{-}60\ °C,\ 5\ h]{\text{Cu-salt}} [(C_2H_5)_2NCH_2C{\equiv}CCH_2]_2NC_2H_5$$

Kotlyarevsky et al. [15] obtained good yields in Mannich couplings between arylacetylenes, benzaldehyde or 2-pyridinecarboxaldehyde and piperidine:



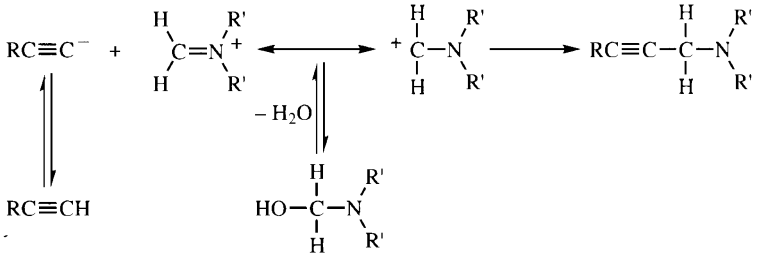
Some Mannich reactions have been successfully performed under the catalytic influence of ferric chloride [7]. We found that also cobalt(III)chloride has a catalytic effect in the dialkylaminomethylation of phenylacetylene. In the reaction with 1-hexyne, however, only copper salts were shown to be effective catalysts [8].

A wide variety of acetylenic derivatives can be aminomethylated under relatively mild conditions and within one hour, using small (1 to 5 mol%) amounts of a copper(I) (CuCl or CuBr) or copper(II) salt, e.g. $Cu(OAc)_2$. Yields are generally higher than 75%. Many examples of Mannich reactions with secondary amines and formaldehyde are listed in Refs. [12] and [13].

For the Mannich couplings with acetylenic *alcohols*, especially propargyl alcohol, special conditions are necessary. If the usual protocol is followed, yields are often unsatisfactory, because the hydroxyl group reacts preferentially, affording *O,N*-acetals ($-C{\equiv}C-CR_2-OCH_2NR'_2$, (compare [9,10]). Salvador and Simon [11], however, obtained *N,N*-acetals $H_2C(NR'_2)_2$ as the main products. The problems may be circumvenced by protecting the OH group in the acetylenic alcohol, e.g. by etherification, but Salvador and Simon [11] performed the reaction with (unprotected) propargyl alcohol and secondary amines in aqueous medium at different pH-values. The most favourable ones were between 8 and 9. Since the products contain both the OH and the NR'_2 function, their solubility in water is very good, so that a time-consuming continuous extraction with diethyl ether is necessary. A simplified procedure developed by us [8] is described in the experimental part of this chapter. Ethoxyacetylene, $HC{\equiv}COC_2H_5$ and other acetylenic ethers do not give the normal Mannich reaction [16].

1-Butyn-3-ol, $HC{\equiv}C-CH(CH_3)OH$, reacts with R'_2NCH_2OH in acetic acid in the presence of a copper catalyst to give the expected Mannich product. Using dioxane as a solvent, this condensation has been achieved with anhydrous zinc chloride or primary sodium phosphate (without Cu-catalyst), though yields were moderate [14].

The Mannich condensation of an acetylene with formaldehyde and a secondary amine may be visualized as the reaction of the acetylenic anion with the intermediary imonium ion, formed by elimination of water from dialkylaminomethanol:



It is not clear in what manner copper salts can catalyze most of the Mannich reactions and why iron and cobalt salts do so only in the case of acetylenes with a higher acidity, such as phenylacetylene.

The use of Mannich condensation products from acetylenes as pharmaceutics, insecticides and intermediates for the production of solvents and dyes has been reported (see Ref. [12], p. 97).

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4.2 Experimental Part

4.2.1 Reaction of Acetylenic Alcohols with Dimethylaminomethanol

$$(CH_3)_2NH + (CH_2O)_n \xrightarrow[20 \rightarrow 65\ °C]{\text{dioxane}} (CH_3)_2NCH_2OH$$

$$(CH_3)_2NCH_2OH + HC{\equiv}C(CH_2)_nOH \xrightarrow[H_2SO_4,\ H_2O \quad n = 1,2]{\text{dioxane, } Cu(OAc)_2} (CH_3)_2NCH_2{-}C{\equiv}C(CH_2)_nOH$$

Scale: 0.30 molar ($HC{\equiv}C(CH_2)_nOH$).

Apparatus: 500-ml round-bottomed flask + reflux condenser.

Procedure: The flask was charged with 12.5 g (corresponding to 0.4 mol of the monomer) of paraformaldehyde and 30 g of dioxane. Liquified dimethylamine (18.5 g, ~0.4 mol) was added (weight increase of the flask) in three equal portions over 20 min with manual swirling and cooling in a bath at 15 °C. After addition of the last portion the bath was removed. The temperature of the mixture rose to above 30 °C. The flask was heated for an additional ten min in a bath at 70 °C (occasional manual swirling). The resulting turbid solution was cooled to ~–10 °C, after which 10 ml of a 50% (w/w) mixture of 96% sulfuric acid (see Note 1) and water were added with manual swirling. Subsequently 1.2 g of powdered cupric acetate and 0.30 mol of the freshly distilled (in a partial vacuum) acetylenic alcohol were added. A reflux condenser was placed on the flask and the mixture was brought to gentle reflux. The greenish yellow slurry soon disappeared and the solution gradually became dark red

to brown. After 15 min the mixture was cooled to room temperature and 120 ml of diethyl ether was added, followed by 20 g of anhydrous potassium carbonate. After vigorous shaking, the brown supernatant layer was decanted from the brown slurry. This extraction procedure was repeated at least ten times (see Note 2) with 25-ml portions of ether. The combined organic solutions were shaken with 20 g of anhydrous potassium carbonate and subsequently concentrated in vacuo. Distillation through a 20-cm Vigreux column gave the Mannich products as somewhat viscous liquids, b.p. 110 °C/ 15 mmHg (n = 1), and 115 °C/ 15 mmHg (n = 2), in 85% and 90% yield, respectively.

^{1}H-NMR-spectra (CCl_4):

(n = 1): 4.11 ppm (t, CH_2O); 3.20 (t, CH_2N); 2.26 (NCH_3) ppm.

(n = 2): 3.53 ppm (t, CH_2O); 3.10 (t, CH_2N); 2.22 (NCH_3); 2.2 (t, CH_2) ppm.

Notes:

1. If 15 ml of this solution were added instead of 10, the yield was considerably lower.
2. The progress in the extraction can be followed by pouring some of the extract on to a clean and dry ground-glass stopper. If after evaporation of the ether no residue remains on the surface, no further extraction is necessary.

Closely similar procedures (same relative molar amounts of reagents) with $(C_2H_5)_2NH$, morpholine, piperidine, $HC{\equiv}CCH_2OH$ and $HC{\equiv}CC(CH_3)_2OH$ gave the coupling products in yields varying from ~70 to ~90%. The period of refluxing was about half an hour. The products were distilled under a pressure of ~1 mmHg through a short column.

4.2.2 General Procedure for the Mannich Reaction of Acetylenes Without an OH-Function

$$RC{\equiv}CH + R'_2N\text{-}CH_2OH \xrightarrow[\text{dioxane, 70-100 °C}]{Cu(OAc)_2} RC{\equiv}C\text{-}CH_2NR'_2 + H_2O$$

Scale: 0.40 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a combination of a thermometer and an outlet for reactive acetylenes: het(aryl)C≡CH, R"CH=CH-C≡CH, R"C≡CC≡CH, R"SCH=CHC≡CH, RSC≡CH; for less acidic acetylenes, e.g. $C_4H_9C{\equiv}CH$ and $CH_3OCH_2C{\equiv}CH$ a reflux condenser was used instead of the thermometer-outlet combination.

Procedure: The dialkylaminomethanol R'_2NCH_2OH was prepared (cf. exp. 4.2.1) from 12.6 g (corresponding with 0.42 mol of monomeric formaldehyde) of paraformaldehyde, 40 ml of dioxane and 0.40 mol of the amine R'_2NH. Copper(II)acetate (1.5 g, (see Note 1)) was added, after which the temperature of the blue solution was brought to ~75 °C. The reactive acetylene (0.40 mol) was added dropwise or portionwise over

~10 min. The conversion was completed by stirring for an additional half hour at 85–90 °C (internal temperature).

The less acidic acetylene (0.40 mol) was added portionwise over about 20 min, while keeping the bath temperature between 80 and 85 °C (see Note 2). After an additional 2 to 2.5 h the conversions were considered to be finished (usually, the colour of the reaction mixtures turns brown towards the end of the conversion, while some metallic copper is formed). The most convenient way of working up consists of adding (after cooling to below 30 °C) 100 to 150 ml of diethyl ether and subsequently introducing anhydrous potassium carbonate (with vigorous stirring) in small portions until a viscous slurry has formed (~7 g of water is formed in the coupling). The solution is decanted and the slurry extracted a sufficient number of times (see preceding exp.). The combined ethereal solutions are dried over a small amount of anhydrous potassium carbonate, subsequently concentrated under reduced pressure and the remaining liquid distilled in vacuo (see Note 3).

The following Mannich products were prepared:

$C_4H_9C{\equiv}C{-}CH_2N(CH_3)_2$, b.p. 60 °C/12 mmHg;

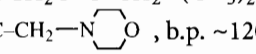
$C_4H_9C{\equiv}C{-}CH_2N(C_2H_5)_2$, b.p. 86 °C/12 mmHg;

$C_2H_5CH{=}CHC{\equiv}C{-}CH_2N(C_2H_5)_2$ (*E* + *Z*), b.p. 92-98 °C/12 mmHg;

Z-$C_2H_5SCH{=}CHC{\equiv}C{-}CH_2N(C_2H_5)_2$, b.p.142 °C/12 mmHg;

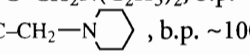
$C_4H_9C{\equiv}CC{\equiv}C{-}CH_2N(C_2H_5)_2$, b.p. ~92 °C/0.5 mmHg;

$CH_3OCH_2C{\equiv}C{-}CH_2N(CH_3)_2$, b.p. 60 °C/15 mmHg;



, b.p. ~120 °C/0.1 mmHg;

$PhC{\equiv}C{-}CH_2N(C_2H_5)_2$, b.p. ~110 °C/0.5 mmHg;



, b.p. ~100 °C/0.2 mmHg

Yields were generally higher than ~80%.

Notes:

1. An additional small amount of copper(II) acetate may be added~15 min after the addition of the acetylene.
2. Portionwise addition is relevant, if the acetylene is very volatile (e.g. 1-pentyne, b.p. 42 °C). If the total amount of the volatile acetylene is added in one portion, the temperature in the reaction flask remains for a relatively long time on a low level due to refluxing of the acetylene.
3. In view of serious foaming during distillation it is advisable to use a relatively big distillation flask.

4.2.3 Mannich Reactions with Gaseous Acetylenes

$$RC{\equiv}CH + R'_2NCH_2OH \xrightarrow[\text{dioxane, 90-105 °C}]{Cu(OAc)_2} RC{\equiv}CCH_2NR'_2 + H_2O$$

(R = CH_3, C_2H_5, $H_2C{=}CH$)

Scale: 0.40 molar.
Apparatus: 500-ml, round-bottomed, three-necked flask, equipped with a gas inlet tube, a gas-tight, efficient mechanical stirrer and a reflux condenser, filled with a mixture of dry ice and acetone (~–70 °C). The inlet tube was connected with a trap containing 0.40 mol of the liquified acetylene and the top of the condenser with a trap, cooled in a bath at –70 °C; all connections were fixed well and made gas-tight.

Procedure: A mixture of the aminoalcohol (0.40 mol) and dioxane (~40 ml) was prepared in the reaction flask as described in the exp. of Sect. 4.2.1. After adding 2 g of copper(II) acetate, the temperature of the mixture was brought at ~90 °C (heating in an oil bath at 100–105 °C). Vigorous stirring was started and the trap containing the acetylene was placed in a water bath: 0 °C in the case of propyne or 20 °C in the cases of 1-butyne and vinylacetylene. At these temperatures the evaporation of the acetylene was not too fast. When, after 45 min to 1 h, all of the acetylene had evaporated and the second trap contained some acetylene, the traps were interchanged, an additional gram of $Cu(OAc)_2$ was added, and stirring at ~90 °C was continued for another half hour. If the second trap was empty and a brown suspension had formed in the flask, the reaction mixture was cooled to room temperature and 150 ml of ether was added, followed by ~20 g of anhydrous potassium carbonate (under vigorous stirring). The work-up was carried out as described in the preceding experiments. The following coupling products were obtained in greater than 75% yields.

$CH_3C{\equiv}C{-}CH_2N(C_2H_5)_2$, b.p. 45 °C/ 12 mmHg;
$C_2H_5C{\equiv}C{-}CH_2N(C_2H_5)_2$, b.p. 63 °C/10 mmHg;
$H_2C{=}CHC{\equiv}C{-}CH_2N(C_2H_5)_2$, b.p. 68 °C/10 mmHg.

5 Copper(I)-Halide-Catalyzed Oxidative Coupling of Acetylenes

5.1 Introduction

More than a century ago Glaser described the oxidation with air of phenylacetylene to diphenylbutadiyne [1]. The original procedure using preformed copper acetylide has evolved to a number of variants in which the acetylene is oxidized with oxygen or air in the presence of *catalytic* amounts of copper(I)halide. The overall equation is:

$$2\,RC{\equiv}CH + 1/2\,O_2 \longrightarrow RC{\equiv}C{-}C{\equiv}CR + H_2O$$

Instead of oxygen, copper(II) salts can be used in stochiometrical amounts.
The various coupling methods have been reviewed [2, 3].

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5.2 Methods, Scope and Limitations

A large variety of acetylenic compounds have been oxidatively "dimerized". Several examples are mentioned in the reviews, listed under 5.1. In many cases the reaction has been carried out with relatively large amounts of copper salts, often much more than stochiometrically required.

Depending upon the acidity of the ethynyl proton in RC≡CH, the nature of R and other factors, the oxidative coupling may be carried out in an organic solvent or in aqueous medium, following the general procedures (a) and (b) which are described below:

(a) Introduction of oxygen into a vigorously agitated mixture of RC≡CH and an organic solvent containing a catalytic amount (up to ~10 mol%) of copper(I)halide [1]. In order to solubilize the copper salt, pyridine or tetramethylethane diamine (TMEDA) (formation of the bidentate complex) is used. The amine also facilitates the (reversible) proton removal from RC≡CH. Pyridine can be used as solvent, though many chemists will prefer the non-smelling dimethylformamide. The easily remov-

able acetone (rotary evaporator) is particularly attractive [1, 2]. Aryl- or hetarylacetylenes (ArC≡CH), enynes (R'CH=CHC≡CH), diynes (R'C≡CC≡CH) [3] and triethylsilylacetylene [2] ($Et_3SiC{\equiv}CH$) react very smoothly under the influence of CuX·pyridine or CuX·TMEDA and yields are generally excellent. Also acetylenic tertiary alcohols ($HC{\equiv}CC(R^1)(R^2)OH$) react satisfactorily [1], but for primary alcohols and the acetylenic amines $HC{\equiv}CC(R^1)(R^2)NH_2$ the aqueous procedure b is more suitable. Acetylenes without conjugation, e.g. aliphatic 1-alkynes, react sluggishly, but addition of the more strongly basic diazabicycloundecene (DBU) greatly facilitates their oxidative coupling [3–5].

(b) Reaction of oxygen with a mixture of the acetylene and an aqueous solution of ammonium chloride containing copper(I)halide. The amount of copper halide is generally much larger than that used in method a, but Reppe et al. [6] could convert more than 50 moles of propargyl alcohol into 2,5-hexadiyn-1,6-diol by using 1 mol of CuCl and by adding the alcohol portionwise. The method can be used also for the oxidative couplings of secondary [6] ($HC{\equiv}CCH(R)OH$) and tertiary ($HC{\equiv}CC(R^1)(R^2)OH$) alcohols [6], acetylenic acids [6] (e.g. $HC{\equiv}CCH_2CH_2COOH$) and amines [7] (e.g. $HC{\equiv}CCH_2NH$-*t*-C_4H_9). Successful conversion of $HC{\equiv}CCH{=}CH_2$ into $H_2C{=}CHC{\equiv}C\text{-}C{\equiv}CCH{=}CH_2$ has been achieved by using diethyl ether as a cosolvent [6]. Oxidative couplings of $HC{\equiv}C(CH_2)_8COOCH_3$, $H_2C{=}CHCH_2C{\equiv}CH$, $HC{\equiv}C(CH_2)_nOH$, $HC{\equiv}CCH_2CH_2COCH_3$, $HC{\equiv}CCH{=}CHCH_2OH$ in water or alcohol-water mixtures have been described in Refs. [8, 9, 10, 11 and 12], respectively.

As the oxidative couplings proceed smoothly over a wide pH range, acid- as well as base-sensitive acetylenes can be dimerized with satisfactory results. Acetylenic amines can be coupled as their HCl salts.

A number of heterosubstituted acetylenes do not give the coupling products, due to the presence of strongly complexing groups ($HC{\equiv}CPR_2$ [13]), C-heteroatom cleavage ($HC{\equiv}CSnR_3$, $HC{\equiv}CPbR_3$ [13]) or reactions involving strongly activated triple bonds (e.g. $HC{\equiv}COC_2H_5$ [14]). Several attempts to couple the ester $HC{\equiv}CCOOCH_3$ and the amine $HC{\equiv}CCH_2NH_2$ failed [15].

References (Sect. 5.2)

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5.3 About the Mechanism

In spite of the several physical-organic investigations on the copper-catalyzed oxidative coupling of acetylenes, the mechanism has not yet been completely elucidated [1]. Copper seems to have an unique role: salts of cobalt and iron are not capable of catalyzing the coupling [2]. Klebanski et al. [3] arrived at the conclusion that Cu^{2+} is the actual oxidizing reagent. In the first, slow step, the ethynyl proton is removed. The acetylenic anion is subsequently converted into the alkynyl radical. Its dimerization gives the diyne. Cu^{2+} is produced from oxygen, Cu^{+} and water:

$$RC{\equiv}CH \rightleftharpoons RC{\equiv}C^- + H^+ \quad \text{(slow)}$$

$$2\,Cu^+ + {}^1/_2\,O_2 + H_2O \longrightarrow 2\,Cu^{2+} + 2\,{}^-OH$$

$$RC{\equiv}C^- + Cu^{2+} \longrightarrow RC{\equiv}C\bullet + Cu^+ \quad \text{(fast)}$$

$$2\,RC{\equiv}C\bullet \longrightarrow RC{\equiv}C{-}C{\equiv}CR \quad \text{(fast)}$$

Bohlmann's investigations [4] provide some support for the mechanistic proposal of the Russian investigators: under basic conditions the order of the reaction rates of oxidative couplings was found to be parallel with the expected order of acidities of the acetylenes. Thus, enynes R'CH=CHC≡CH, and diynes, R'C≡CC≡CH, reacted faster than did acetylenes with an unconjugated triple bond, RC≡CH. Fedenok et al. [5] also found that more acidic acetylenes react more easily.

Under acidic conditions (H_2O, CH_3OH, CuCl, $HOCH_2CH_2NH_2{\cdot}HCl$, $CuCl_2$ and a small amount of HCl to bring the pH to 3), the order was PhC≡CH > RC≡CH > RC≡CC≡CH > PhC≡CC≡CH. According to Bohlmann the rate-determining step in acidic medium is the formation of a copper complex, which dissociates into $RC{\equiv}C^-$ and H^+.

$$RC{\equiv}CH \rightleftharpoons RC{\equiv}C{-}H \rightleftharpoons RC{\equiv}C^-\,H^+$$
$$\qquad\qquad\quad \downarrow Cu^+ \qquad\qquad\quad \downarrow Cu^+$$

Such a π-complex formation should facilitate the removal of the ethynyl proton.

Clifford and Waters [6] performed kinetic investigations on the oxidation of $HC{\equiv}CCH_2OH$ with Cu(II) acetate in the absence of air in pyridine. It was found that the rate of oxidation depends in a complex manner on the concentration of Cu(I) and $HC{\equiv}CCH_2OH$, suggesting π-complex formaton. In the resulting mechanistic propos-

al, the actual oxidation step is an electron transfer from copper(I) acetylide to copper(II) acetate:

$$RC{\equiv}CH + B \rightleftharpoons RC{\equiv}C^- + BH^+ \quad \text{(slow)}$$

$$RC{\equiv}C^- + CuOAc \rightleftharpoons RC{\equiv}CCu + {}^-OAc \quad \text{(slow)}$$

$$RC{\equiv}CCu + Cu(OAc)_2 \longrightarrow RC{\equiv}C\bullet + 2\,CuOAc \quad \text{(fast)}$$

$$2\,RC{\equiv}C\bullet \longrightarrow RC{\equiv}C{-}C{\equiv}CR \quad \text{(fast)}$$

Based upon the results of kinetic studies of the coupling of RC≡CH with Cu(II) in pyridine (using a $(C_2H_5)_3N$-CH_3COOH buffer), Fedenok et al. [5] proposed the formation of a complex between Cu^{2+} and PhC≡CH, which dissociates into Cu^{2+} (PhC≡C^-) and H^+:

$$Cu^{2+}{\cdot}py + PhC{\equiv}CH \rightleftharpoons Cu^{2+}{\cdot}py\,(PhC{\equiv}CH) + py$$

$$Cu^{2+}{\cdot}py\,(PhC{\equiv}CH) \rightleftharpoons Cu^{2+}{\cdot}py\,(PhC{\equiv}C^-) + H^+$$

$$2\,Cu^{2+}{\cdot}py\,(PhC{\equiv}C^-) \longrightarrow 2\,Cu^+ + PhC{\equiv}C{-}C{\equiv}CPh$$

It should be noted that in this proposal no ethynyl radicals occur (cf. [4]).

Reppe et al. [7] carried out the preparative oxidative coupling of propargyl alcohol with copper(I) chloride in an aqueous solution of ammonium chloride under an atmosphere of oxygen. Their experimental observations are in agreement with the assumption of a complex consisting of CuCl, NH_4Cl and $HC{\equiv}CCH_2OH$. If the concentration of the acetylenic compound is too high, the reaction is retarded because the equilibrium of reaction (1) is shifted to the right side and reaction (2) cannot proceed at a sufficiently high rate due to a too low concentration of Cu^{2+} (Cu(OH)Cl).

$$2\,RC{\equiv}CH + 2\,CuCl + 2\,NH_4Cl \rightleftharpoons 2\,[RC{\equiv}CH{\bullet}CuCl{\bullet}NH_4Cl] \quad (1)$$

$$2\,CuCl + H_2O + {}^1/_2\,O_2 \longrightarrow 2\,Cu(OH)Cl \quad (2)$$

$$2\,[RC{\equiv}CH{\bullet}CuCl{\bullet}NH_4Cl] + 2\,Cu(OH)Cl \longrightarrow [RC{\equiv}CC{\equiv}CR{\bullet}2CuCl{\bullet}2NH_4Cl] + CuCl + 2\,H_2O \quad (3)$$

$$[RC{\equiv}CC{\equiv}CR{\bullet}2CuCl{\bullet}2NH_4Cl] + 2\,RC{\equiv}CH \rightleftharpoons RC{\equiv}CC{\equiv}CR + 2\,[RC{\equiv}CH{\bullet}2CuCl{\bullet}2NH_4Cl] \quad (4)$$

Our experimental observations are in agreement with those of Reppe et al.: if propargyl alcohol was added to the mixture of ammonium chloride, water and copper(I) chloride too quickly, the increase of the temperature in the reaction mixture was retarded. After stopping the addition, a gradual rising of the temperature was observed, while the intensity of the green colour of Cu(OH)Cl became stronger.

References (Sect. 5.3)

1. For discussions on the various mechanistic proposals the reader is referred to the following reviews:
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5.4 Experimental Part

5.4.1 Oxidative Coupling of Propargyl Alcohol Catalyzed by Copper(I) Chloride in an Aqueous Medium

$$HC{\equiv}CCH_2OH \xrightarrow[H_2O,\ \sim 40\ ^\circ C]{O_2,\ CuCl,\ NH_4Cl} HOCH_2C{\equiv}C\text{-}C{\equiv}CCH_2OH$$

Scale: 0.50 molar.

Instead of using a shaking apparatus connected to a mercury manometer and carrying out the reaction under pressure (1.5 atm.), as in the procedure of Reppe et al. (Justus Liebigs Ann. Chem. (1955) 596, 1) conventional laboratory equipment may be used. At least one mol of propargyl alcohol can be converted within 3 hours using between 5 and 10 g of copper(I) chloride (for a quicker method see 5.4.2, experiments with acetone as solvent). Performance of our procedure requires continuous observation. We presume that a number of other acetylenic compounds (as in the paper of Reppe) can be oxidatively coupled by a similar procedure.

Procedure: A 1-l round-bottomed, three-necked flask was equipped with a gas inlet tube, an efficient mechanical stirrer and a combination of an outlet and a thermometer. After completely replacing the air in the flask with oxygen, the rate of introduction of oxygen was adjusted at ~100 ml/min. The flask was charged with a cold (~5 °C), saturated solution of ammonium chloride in 100 ml of water and 5 g of finely powdered copper(I) chloride (technical grade may be used). After addition of 4 g of freshly distilled propargyl alcohol (under gentle stirring) at room temperature, the colour of the mixture (first green) became very light. The rate of stirring was increased, in

order to effect intensive mixing of the reaction mixture and oxygen (high turbulence). The mixture was brought to 30 °C, after which the temperature gradually rose to above 35 °C. By occasional cooling (water bath) the temperature was maintained in the region of 40 °C. When the green colour began to return, a second portion of ~4 g of propargyl alcohol was added (stirring was temporarily stopped). The remainder of the 0.50 mol was added in 4-g portions over ~1.5 h. Stirring (at 40 °C) after addition of the last portion was continued for an additional period of 30 to 45 min. The green suspension was cooled to room temperature, after which six to eight extractions with a 1 : 3 mixture of THF and ether were carried out (first twice with 100-ml portions, for the other extractions 50-ml portions). The light-brown extracts were combined and stirred during 30 min with 50 g of anhydrous potassium carbonate. After filtration and thorough extraction of the drying agent with the ether-THF mixture, the solution was concentrated under reduced pressure. The remaining light-brown solid was powdered (mortar) and subsequently heated at 50 °C (with occasional manual swirling) in a vacuum of <1 mmHg in order to remove the last traces of solvent. The yield of pure product was greater than 85%.

5.4.2 Oxidative Couplings Catalyzed by Copper(I) Chloride·TMEDA in Acetone

5.4.2.1 Oxidative Coupling of Methyl Propargyl Ether

$$HC{\equiv}CCH_2OCH_3 \xrightarrow[\text{acetone, 40–50 °C}]{\text{CuCl, TMEDA}} CH_3OCH_2C{\equiv}C\text{-}C{\equiv}CCH_2OCH_3$$

Scale: 0.30 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a gas inlet tube, an efficient mechanical stirrer and a combination of a gas outlet and a thermometer. Oxygen was slowly introduced (100 to 200 ml/min).

Procedure: After replacing the air in the flask completely with oxygen, 90 ml of acetone (technical grade may be used), 5 g of freshly distilled methyl propargyl ether, 2 g of TMEDA and 2 g of finely powdered copper(I) chloride were successively placed in the flask (intervals between the various additions a few seconds) while stirring at a moderate rate. The mixture was brought at 40 °C, after which very vigorous stirring (high turbulence) was started. After formation of a blue-green solution the heating effect became stronger and the temperature rose to over 50 °C within a few min. By occasional cooling the temperature was kept around 50 °C. When the reaction had subsided, another portion of 5 g was added. The remaining amount was added in two 5-g portions with intervals of ~10 min. After the temperature had begun to drop fast, the mixture was stirred for an additional half hour at 50 °C. The acetone was then removed under reduced pressure, after which a solution of 10 g of ammonium chloride in 50 ml of water, containing some ammonia was added. The mixture was

extracted five times with small portions of ether. The combined organic solutions were dried over anhydrous magnesium sulfate and subsequently concentrated under reduced pressure. The remaining colourless liquid was distilled through a short column: b.p. ~70 °C/ 0.3 mmHg, n^{20}_D 1.4988, yield ~80%.

^{1}H-NMR spectrum (CCl_4): 4.12 (CH_2); 3.32 (OCH_3) ppm.

5.4.2.2 Oxidative Coupling of 3-Butyn-2-ol

$$HC{\equiv}C\text{-}CH(CH_3)OH \xrightarrow[\text{acetone, 45–50 °C}]{O_2,\ CuCl,\ TMEDA} HO\text{-}CH(CH_3)C{\equiv}C\text{–}C{\equiv}CCH(CH_3)\text{-}OH$$

Scale: 0.50 molar (for the equipment see Sect. 5.4.2.1).

Procedure: After filling the flask with oxygen, 90 ml of acetone, 3.2 g of TMEDA, 3.2 g of finely powdered copper(I) chloride and ~5 g of of the acetylenic alcohol (commercially available) were introduced with intervals of a few seconds and with stirring at a moderate rate. The flow of oxygen was adjusted at ~100 ml/min and very vigorous stirring was started (intensive mixing of the solution with oxygen). The mixture was brought to 45 °C, after which the temperature of the green-blue solution rose to over 50 °C within a few min. Occasional cooling was applied to keep the temperature between 45 and 50 °C. When the temperature had begun to drop (without cooling) and the colour of the solution had become darker, a second portion of 5 g of the acetylenic alcohol was added. The remaining amount was introduced in 5g-portions over about half an hour. When, after addition of the last portion, the temperature began to drop, the reaction mixture was heated in a bath at 45 °C. After an additional half hour most of the acetone was removed under reduced pressure (rotary evaporator). The residue was treated with 100 ml of a saturated solution of ammonium chloride containing some ammonia, after which five extractions with ether were carried out. The combined extracts (washing was not carried out) were dried over anhydrous potassium carbonate. After concentration in vacuo (in the last stage a high vacuum was applied) a viscous light-brown oil remained, which solidified upon standing at room temperature. The NMR-spectrum (4.45 ppm, (q, 1H); 1.42 ppm, (d, CH3)) indicated that the product had a satisfactory purity. The yield was almost quantitative.

5.4.2.3 Oxidative Coupling of 2-Methyl-3-butyn-2-ol

$$HC{\equiv}C\text{-}C(CH_3)_2OH \xrightarrow[\text{acetone, 45–50 °C}]{O_2,\ CuCl,\ TMEDA} HO\text{-}C(CH_3)_2C{\equiv}C\text{–}C{\equiv}CC(CH_3)_2\text{-}OH$$

Scale: 0.15 molar (for the equipment see Sect. 5.4.2.1).

Procedure: Acetone (70 ml), 0.15 mol of 2-methyl-3-butyn-2-ol (commercially available), 1.2 g of freshly powdered copper(I) chloride and 1.2 g of TMEDA were successively placed (with intervals of a few seconds) in the flask which had been filled with

oxygen. Vigorous stirring was started, while oxygen was introduced at a rate of 100 ml/min. The temperature of the mixture rose within a few minutes to over 40 °C, but was kept between 45 and 50 °C by occasional cooling. After the exothermic reaction had subsided, the mixture was stirred for an additional 20 min at ~45 °C. The greater part of the acetone was removed on the rotary evaporator, then 500 ml of an aqueous solution of 20 g of ammonium chloride containing some ammonia was added. The product was isolated by extraction with ether. The yield of pure crystalline material was almost quantitative.

5.4.2.4 Oxidative Coupling of 3-Butyn-1-ol

$$HC{\equiv}CCH_2CH_2OH \xrightarrow[\text{acetone, 45 °C}]{O_2,\ CuCl,\ TMEDA} HO\text{-}CH_2CH_2C{\equiv}C\text{–}C{\equiv}CCH_2CH_2\text{-}OH$$

Scale: 0.15 molar (for the equipment see Sect. 5.4.2.1).

Procedure: The flask was filled with oxygen, after which 80 ml of acetone, 0.15 mol of 3-butyn-1-ol, 1.1 g of finely powdered copper(I) chloride and 1.3 g of TMEDA were introduced with intervals of a few seconds. Very vigorous stirring was started, while oxygen was slowly (100 ml/min) passed through the flask. The temperature of the blue solution rose to above 40 °C within a few min, but was kept betwen 40 and 45 °C by occasional cooling. Stirring and introduction of oxygen were continued until the temperature had dropped to below 35 °C. After addition of 5 ml of water, the acetone was removed on the rotary evaporator. The greenish residue was thoroughly extracted (at least five times) with ether. The combined extracts were dried (without washing) over anhydrous potassium carbonate. After filtration and thorough rinsing of the potassium carbonate with ether, the solvent was removed under reduced pressure. In the last stage a vacuum <1 mmHg (heating in a bath at 45 °C) was applied. The remaining viscous liquid (yield >95%) was 3,5-octadiyne-1,8-diol. The product solidified slowly at room temperature.

^{1}H-NMR spectrum ($CDCl_3$): 3.7 (t, OCH_2); 2.5 (t, $C{\equiv}C\text{-}CH_2$) ppm.

5.4.2.5 Oxidative Coupling of 1-Methoxy-1-buten-3-yne

$$Z\text{-}HC{\equiv}CCH{=}CHOCH_3 \xrightarrow[\text{acetone, 45–50 °C}]{O_2,\ CuCl,\ TMEDA} Z,Z\text{-}CH_3OCH{=}CHC{\equiv}C\text{–}C{\equiv}CCH{=}CHOCH_3$$

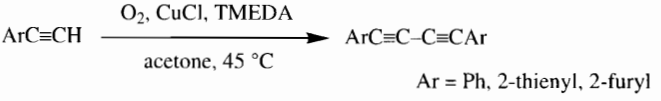
Scale: 0.10 molar (for the equipment see Sect. 5.4.2.1).

Procedure: A vigorously stirred mixture of 80 ml of acetone, 1 g of copper(I) chloride, 1 g of TMEDA and 0.10 mol of *Z*-$HC{\equiv}CCH{=}CHOCH_3$ was warmed under introduction of oxygen to ~35 °C, after which the suspended material passed into solution and an exothermic reaction started. The temperature was maintained between 40 and 45 °C. After an additional period of 15 min (at 40–45 °C) the greater part of the acetone was

removed under reduced pressure and the residue was treated with an aqueous solution of ammonium chloride containing some ammonia. The ethereal extract was concentrated in vacuo. The remaining brown liquid was distilled through a very short column (b.p. 130–140 °C/0.5 mmHg). The yield of pure product was 75%.

^{1}H-NMR spectrum (CCl_4): 6.45 (d, J ~8 Hz, OCH); 4.5 (d, J ~8Hz, C(C-CH); 3.80 (OCH_3) ppm.

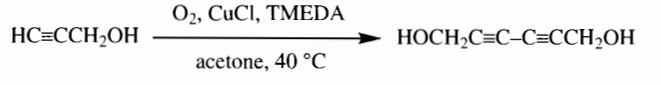
5.4.2.6 Oxidative Coupling of Arylacetylenes



Scale: 0.10 molar (for the equipment see Sect. 5.4.2.1).

Procedure: (See also preceding experiments.) A mixture of 75 ml of acetone, 0.10 mol of the freshly distilled arylacetylene, 1 g of copper(I) chloride and 1 g of TMEDA was vigorously stirred while passing oxygen through the flask (~100 ml/min). The temperature rose to above 40 °C within a few min. After the temperature had dropped to below 35 °C, 300 ml of water containing some ammonia were added and the product was extracted with ether. The extract was dried and then filtered through a 3 cm-layer of neutral Al_2O_3. Evaporation of the ether in vacuo gave the pure products as white solids in almost quantitative yields.

5.4.2.7 Oxidative Coupling of Propargyl Alcohol



Scale: 0.50 molar (for the equipment see Sect. 5.4.2.1).

Procedure: To a mixture of 80 ml of acetone, 2 g of finely powdered copper(I) chloride and 2.2 g of TMEDA (greyish suspension) was added at room temperature 5 g of freshly distilled propargyl alcohol. The flow of oxygen was adjusted at ~100 ml/min. Vigorous stirring was started. The temperature rose within a few min to above 35 °C. A light-green solution was formed. The temperature was kept between 37 and 42 °C by occasional cooling. When the temperature had begun to drop and the solution had become dark green, a second portion of 4 g of the alcohol was added (the rate of stirring was temporarily decreased) (if too much was added in one portion, a yellow suspension was formed). The remaining amount of alcohol was added under similar conditions. Stirring after addition of the last portion was continued until the temperature had dropped to 25 °C. A saturated aqueous solution of ammonium chloride (30 ml) was then added, after which 10 extractions with ether were carried out. The combined ethereal solutions (washing with water was not carried out) were vigorously shaken or stirred with 20 g of anhydrous potassium carbonate for 15 min. The supernatant solution and five ethereal rinsings of the drying agent were dried again over (fresh) potas-

sium carbonate and subsequently concentrated in vacuo. A light-brown solid, practically pure 2,4-hexadiyne-1,6-diol, remained. Yield ~90%. This experiment can be carried out within 1 hour (cf. exp. 5.4.2.1: 3 h).

^{1}H-NMR spectrum ($CDCl_3$/ DMSO-d_6 ~ 4 : 1): 4.25 ppm.

In the cases of *trimethylsilylacetylene*, $Me_3SiC{\equiv}CH$, and *ethyl propargyl sulfide*, $HC{\equiv}CCH_2SC_2H_5$, the reaction stopped after some minutes and brown solutions were formed. *Propargyl aldehyde diethylacetal*, $HC{\equiv}CCH(OC_2H_5)_2$, reacted rather slowly at 45 °C. The *enyne* $HC{\equiv}CC(t\text{-}C_4H_9){=}CH_2$ reacted smoothly to give the crystalline "dimer" in an excellent yield.

5.4.3 Oxidative Couplings Catalyzed by Copper(I) Chloride·TMEDA in N,N-Dimethylformamide

5.4.3.1 Oxidative Coupling of 1,1-Diethoxy-2-propyne

$$HC{\equiv}CCH(OC_2H_5)_2 \xrightarrow[DMF,\ 45\text{–}50\ ^\circ C]{O_2,\ CuCl,\ TMEDA} (C_2H_5O)_2CH\text{-}C{\equiv}C\text{–}C{\equiv}C\text{-}CH(OC_2H_5)_2$$

Scale: 0.10 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a gas inlet tube, an efficient mechanical stirrer and a combination of gas outlet and thermometer. Oxygen was introduced at a rate of ~100 ml/min.

Procedure: After completely replacing the air with oxygen, 70 ml of DMF, 1.3 g of freshly powdered copper(I) chloride, 3.5 g of TMEDA and 0.10 mol of freshly distilled propargyl aldehyde diethylacetal were introduced at intervals of a few seconds. A greyish suspension was formed. After starting very vigorous stirring, the temperature rose to above 45 °C within a few min. After the exothermic reaction had subsided (dropping of the temperature) the mixture was stirred for an additional 20 min at 40 to 45 °C. The bluish-green solution was then treated with 500 ml of water and five extractions with a 1 : 1 mixture of ether and pentane were carried out. The combined extracts were washed with water and dried over anhydrous potassium carbonate. After removal of the solvent in vacuo the pure diyne remained as an almost colourless liquid. Yield ~95%.

^{1}H-NMR spectrum (CCl_4): 5.20 (CH<); 3.3–3.8 (m, OCH_3); 1.20 (t, CH_3) ppm.

5.4.3.2 Oxidative Coupling of Ethyl Propargyl Sulfide

$$HC{\equiv}CCH_2SC_2H_5 \xrightarrow[DMF,\ 40\ ^\circ C]{O_2,\ CuCl,\ TMEDA} C_2H_5SCH_2C{\equiv}C\text{–}C{\equiv}CCH_2SC_2H_5$$

Scale: 0.10 molar (for the equipment see Sect. 5.4.3.1).

Procedure: A mixture of 0.10 mol of freshly distilled ethyl propargyl sulfide, 70 ml of DMF, 0.8 g of finely powdered copper(I) chloride and 1 g of TMEDA was brought to 35 °C, after which the heating bath was removed. The temperature of the mixture was kept (occasional cooling or heating) at ~40 °C for 30 min, then the brownish green solution was poured into 400 ml of water. The mixture was extracted five times with a 1 : 1 mixture of ether and pentane; the combined organic solutions were washed with water and dried over anhydrous magnesium sulfate. The liquid remaining after evaporation of the solvent under reduced pressure (in the last stage a vacuum of ~0.5 mm was applied in order to remove traces of the starting compound), the diyne remained as a light-brown oil. Yield ~85%.

^{1}H-NMR spectrum (CCl_4): 3.31 ($CH_2C\equiv$) ppm.

5.4.4 Oxidative Couplings Catalyzed by Copper(I) Chloride in Pyridine

5.4.4.1 Oxidative Coupling of 4-Butyn-1-ol

$$HC\equiv C(CH_2)_4OH \xrightarrow[\text{pyridine, 40–45 °C}]{O_2,\ CuCl} HO(CH_2)_4C\equiv C{-}C\equiv C(CH_2)_4OH$$

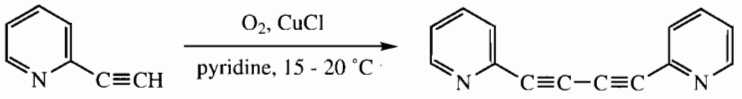
Scale: 0.20 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a gas inlet tube, an efficient mechanical stirrer and a combination of gas outlet and thermometer. Oxygen was introduced at a rate of ~100 ml/min.

Procedure: The acetylenic alcohol (0.20 mol) was dissolved in 70 ml of pyridine and 1 g of finely powdered copper(I) chloride was added with stirring at a moderate rate. The green solution was then stirred vigorously and the temperature rose within 15 min to ~40 °C. The temperature of the mixture was kept between 40 and 45 °C (occasional cooling). After the exothermic reaction had subsided and the temperature had begun to drop, the mixture was stirred for another half hour at ~40 °C, during which period the colour gradually became dark-green. The greater part of the pyridine was removed on the rotary evaporator. The remaining liquid was treated with a sufficient amount of cold (0 °C) dilute aqueous hydrochloric acid (4 M). The solution was extracted four times with ether. The combined extracts were washed with water and subsequently dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo small amounts of the starting compound were distilled off in a high-vacuum. The residue (yield ~85%) was almost pure diol. It solidified after cooling to room temperature.

^{1}H-NMR spectrum ($CDCl_3$) showed triplets around 3.6 (CH_2O), 2.3 ($CH_2C\equiv$) and 1.6 (CH_2CH_2) ppm.

5.4.4.2 Oxidative Coupling of 2-Ethynylpyridine



Scale: 0.10 molar.

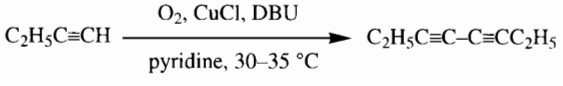
Apparatus: 250-ml instead of 500-ml flask (cf. procedure in Sect. 5.4.4.1). Oxygen was introduced at a rate of ~100 ml/min.

Procedure: A mixture of 0.10 mol of 2-ethynylpyridine, 1.0 g of finely powdered copper(I) chloride and 50 ml of pyridine was vigorously stirred, while keeping the temperature of the mixture between 15 and 20 °C (if the temperature was allowed to rise above 30 °C, much brown tarry material was formed). After 1.5 h the dark mixture was poured into 300 ml of water. The mixture was extracted four times with small portions of chloroform. The combined extracts were dried over anhydrous potassium carbonate, after which the solvent was removed under reduced pressure. The last traces of solvent were removed in an oil-pump vacuum (<0.5 mmHg). The remaining solid (m.p. 119-120 °C) was pure di(2-pyridyl)butadiyne. Yield ~80%.

Oxidative couplings of *phenylacetylene, 2-furylacetylene,* $t\text{-}C_4H_9C{\equiv}C\text{-}C{\equiv}CH$, $HC{\equiv}CCH_2N(C_2H_5)_2$ and *3-ethynylpyridine* were successfully carried out by similar procedures at ~35 °C. Stirring and introduction of oxygen were stopped when the temperature began to drop fast and the colour of the mixture had become very dark-green or greenish brown. Yields were generally excellent.

5.4.5 Oxidative Couplings Catalyzed by Copper(I) Chloride and Diazabicycloundecene

5.4.5.1 Oxidative Coupling of 1-Butyne



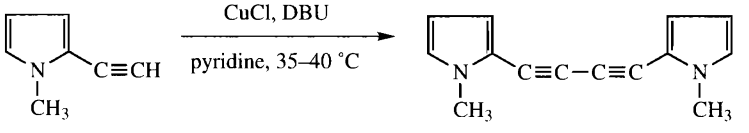
Scale: 0.50 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with an inlet tube, an efficient mechanical stirrer and a combination of thermometer and outlet. The outlet was connected to a cold trap (–78 °C). Oxygen was passed through the flask at a rate of 100 to 150 ml/min. All connections were made gas-tight.

Procedure: After the air in the flask had been completely replaced by oxygen, 250 ml of pyridine, 2 g of finely powdered copper(I) chloride and 3 ml of diazabicycloundecene (DBU) were introduced. The mixture was cooled to ~10 °C and 0.50 mol of 1-butyne

(liquified in a cold trap, ~–70 °C) was added. Vigorous stirring with introduction of oxygen was started. The temperature of the mixture gradually rose, but was kept between 25 and 30 °C by occasional cooling in a bath at –50 °C. When the reaction had subsided, the contents of the cold trap were poured into the flask (usually not more than a few ml). Stirring at 35 °C was then continued for an additional period of 30 min. The dark-green solution was poured into 1 L of ice water, after which ten extractions with small (first portion 70 ml, subsequently ~30 ml) portions of pentane were carried out. The combined extracts were washed with cold dilute hydrochloric acid and subsequently dried over anhydrous magnesium sulfate. Most of the pentane was distilled off at normal pressure through a 30-cm Widmer column. The remaining liquid was distilled in vacuo. 3,5-Octadiyne, b.p. 40 °C/ 15 mmHg, n^{20}_D 1.4907, was obtained in greater than 75% yield.

5.4.5.2 Oxidative Coupling of 2-Ethynyl-1-methylpyrrole



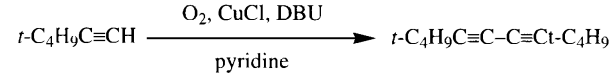
Scale: 0.05 molar.

Apparatus: 250-ml round-bottomed, three-necked flask, equipped with a gas inlet tube, a mechanical stirrer and a thermometer-outlet combination. Oxygen was introduced at a rate of ~100 ml/min.

Procedure: A mixture of 0.05 mol of 2-ethynyl-1-methylpyrrole, 50 ml of pyridine, 1 g of finely powdered copper(I) chloride and 2 g of diazabicycloundecene was vigorously stirred. The temperature of the mixture, initially 20 °C, rose to above 35 °C, but was kept between 35 and 40 °C by occasional cooling. After the temperature had begun to drop, stirring was continued for an additional half hour at 30 to 35 °C. The mixture was poured into 500 ml of water, after which five extractions with ether were carried out. The combined extracts were dried over anhydrous potassium carbonate and subsequently concentrated in vacuo. The last traces of pyridine were removed in a high vacuum of <0.5 mmHg. The coupling product remained as a light-brown solid. Yield >80%.

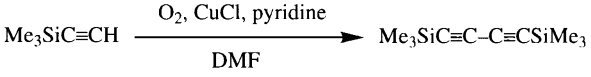
In the absence of DBU no reaction took place.

5.4.5.3 Oxidative Coupling of t-Butylacetylene



The reaction was carried out at ~40 °C and gave, via aqueous work-up and extraction with pentane the diyne as white crystals in an excellent yield.

5.4.6 Oxidative Coupling of Trimethylsilylacetylene



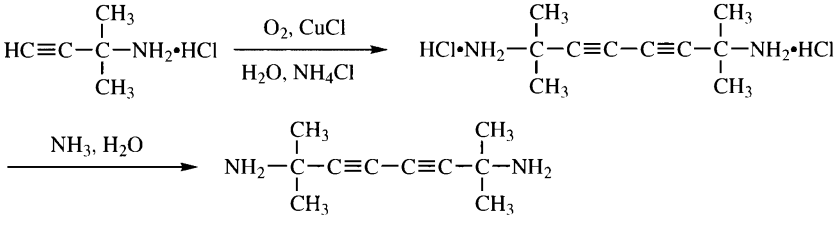
Scale: 0.10 molar.

Apparatus: 500-ml three-necked, round-bottomed flask, equipped with a gas inlet tube, an efficient mechanical stirrer and a combination of thermometer and gas outlet. Oxygen was introduced at a rate of ~100 ml/min.

Procedure: After completely replacing the air in the flask by oxygen, 50 ml of *N,N*-dimethylformamide, 2 ml of pyridine, 1 g of finely powdered copper(I) chloride and 0.10 mol of trimethylsilylacetylene were placed in the flask. Vigorous stirring was started, causing the temperature to rise within a few min from 20 to ~40 °C. Occasional cooling was necessary to keep the temperature between 35 and 40 °C. After the temperature had begun to drop (from 40 °C) stirring was continued until the colour of the mixture had become brown. The mixture was poured into 500 ml of ice water, after which four extractions with small portions of pentane were carried out. The combined organic solutions were washed with cold (0 °C) 2 M hydrochloric acid in order to remove traces of pyridine and subsequently dried over anhydrous magnesium sulfate. After evaporation of the pentane in vacuo bis(trimethylsilyl)butadiyne remained as light-brown crystals. Yield ~80%.

Using CuCl in pyridine or CuCl·TMEDA in acetone, poor results were obtained.

5.4.7 Oxidative Coupling of the HCl-Salt of 3-Amino-3-methyl-1-butyne



Scale: 0.10 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a gas inlet tube, an efficient mechanical stirrer and a combination of thermometer and outlet. Oxygen was introduced at a rate of ~100 ml/min.

Procedure: Concentrated, aqueous hydrochloric acid (36%) was added dropwise at 0 °C to a mixture of 0.10 mol of the amine and 70 ml of a saturated aqueous solution of

ammonium chloride until the pH had become 6. Finely powdered copper(I) chloride (5 g) was introduced, after which the mixture was warmed to 45 °C. A yellowish solution was formed. The whole flask was insulated in cotton wool and very vigorous stirring was started. The temperature rose within half an hour to above 50 °C. Stirring was continued until the the temperature had dropped to 30 °C, then 30 ml of a concentrated aqueous solution of ammonia and 100 ml of water were added to the light-green suspension. The blue solution was extracted 7 times with ether. The ethereal solutions were dried (without washing) over anhydrous potassium carbonate and subsequently concentrated under reduced pressure. The pure coupling product remained as a light-brown solid. Yield ~85%.

^{1}H-NMR spectrum ($CDCl_3$): 1.80 (broadened signal, NH_2) and 1.42 (CH_3) ppm.

Under similar conditions *propargylamine* $HC{\equiv}CCH_2NH_2$ gave an amorphous red solid.

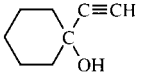
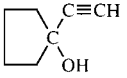
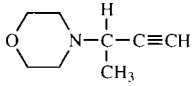
5.5 Summary of Experimental Conditions for Oxidative Couplings

Based on rather extensive experience with oxidative couplings, we can draw the following conclusions with regard to the most favorable conditions for couplings of the various acetylenic derivatives using oxygen as oxidant and copper(I) halide as catalyst.

(a) None of the various solvents is generally applicable. Several acetylenic derivatives can be successfully coupled in pyridine, which is a good complexator for copper compounds. However, for many chemists this solvent is less attractive because of its unpleasant smell. Moreover, some couplings of acetylenic compounds containing polar groups such as OH and C=O do not give optimal results in pyridine, while the work-up may be laborious. Application of *N,N*-dimethylformamide, acetone (or other volatile organic solvents) provides complementary possibilities for oxidative couplings. Water is particularly suitable for couplings of the lower acetylenic alcohols (e.g. $HC{\equiv}CCH_2OH$), though also some more lipophilic acetylenes have been successfully coupled using a two-phase system of water and an organic solvent. In some cases the coupling may stop or proceed very sluggishly due to formation of some slightly soluble copper compound. The only general advice that we can give is: try another solvent.

(b) Aryl- or hetarylacetylenes (except 2-ethynyl-1-methylpyrrole), enynes (R'CH=CHC≡CH) and diynes (R'C≡C-C≡CH) very readily dimerize and the choice of the solvent is determined only by considerations involving the ease of the work-up.

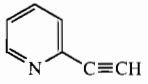
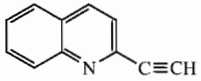
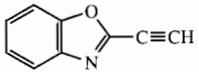
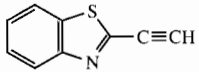
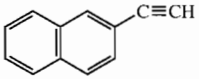
Table 3. Oxidative couplings of acetylenic compounds selected from literature

Acetylenic compounds	Scale (mmol)	Reaction conditions	Yield (%)	Literature
Alcohols				
$HOCH_2CH{=}CHC{\equiv}CH$	410	CuCl (150 g!), NH_4Cl (240 g), H_2O (600 ml), air, 55°C, 2.5 h	65	JCS (1947) 1586
1-naphthyl-CH(OH)-C≡CH	38	CuCl (2 mmol), TMEDA, acetone, 20 → 40°C, 6 h	80	BCS.Jpn (1970) 3567
$HOCH_2C{\equiv}CC{\equiv}CH$	15	CuCl (5 g!), NH_4Cl (8 g), H_2O (50 ml), CH_3OH (10 ml), O_2, 15°C, 2.5 h	74	JCS (1952) 2014
$HOC(CH_3)_2$-C≡CH	200	CuCl (1 g), TMEDA (1.2 g), acetone (135 ml), O_2, 42°C	85	JOC (1962) 3320
	200	CuCl (1 g), TMEDA (1.2 g), acetone (135 ml), O_2, 42°C	93	JOC (1962) 3320
	200	CuCl (1 g), TMEDA (1.2 g), acetone (135 ml), O_2, 42°C	89.5	JOC (1962) 3320
$HO(CH_2)_3C{\equiv}CH$	200	CuCl (6 g), NH_4Cl (20 g),H_2O (65 ml), conc. HCl (0.5 g)	~100	BSC.Fr (1953) 417
Amines				
$CH_3(Ph)N$-C≡CH	60	CuCl (6 g), NH_4OH (conc., 35 ml), CH_3OH (70 ml), O_2, room temp, 30 min	60	BSC.Fr (1974) 1535
t-$C_4H_9NHCH_2$-C≡CH	40	CuCl (8.5 g), NH_4Cl (26 g), 2 M HCl (26 ml), H_2O (25 ml), O_2, 55°C, 6 h	81	T (1973) 4111
$Et_2NCH_2CH{=}CH$-C≡CH	30	CuCl (0.65 g), NH_4Cl (1.9 g), 2 M HCl (14 ml), H_2O (2.25 g), air, room temp, 5.5 h	65	JCS (1949) 782
	180	CuCl (4 g), NH_4Cl (12 g), 2 M HCl (85 ml), H_2O (14 g), air, room temp, 5.5 h	88	JCS (1949) 782

Acids and esters				
$CH_3OOC(CH_2)_8$-C≡CH	610	CuCl (160 g),NH_4Cl (280 g), conc. HCl (8 ml), C_2H_5OH(800 ml), H_2O (1200 ml), 55°C, air, 2.5 h	77	JCS (1953) 2193
$HOOC(CH_2)_2$-C≡CH	200	CuCl (11 g), NH_4Cl (60 g), H_2O (200 ml), O_2, 0°C	100	LAC (1955) 596, 72
HOOCCH=CH-C≡CH trans	17	CuCl (4 g), NH_4Cl (14 g), acetone (10 ml), H_2O (20 ml), O_2, 5°C	>90	JCS (1958) 950
Ketones				
	1000	CuCl (30 g), NH_4Cl (100 g), conc. HCl (2,4 g), H_2O (400 ml), O_2-shake	95	BSC.Fr (1960) 1914
Ethers and thioethers				
t-C_4H_9O-C≡CH (also other RO-C≡CH)	20	CuCl.TMEDA (1 mmol), acetone (15 ml), O_2, ~20°C, 1 h	77	JACS (1990) 7405
C_2H_5S-C≡CH	131	CuCl (13.4 g), NH_4OH (conc., 75 ml), CH_3OH (300 ml), O_2, room temp., 1 h	72	RTC (1956) 1459
Hydrocarbons, (het)arylacetylenes and silylacetylenes				
PhCH=CH-C≡CH	16	CuCl (10.3 g), NH_4Cl (16.2 g), H_2O (200 ml), C_2H_5OH (30 ml), O_2-shake, 6 h	60	JCS (1959) 933
H_2C=CH-C≡CH (30 % soln. in Et_2O)	–	CuCl (30 g), NH_4Cl (90 g), H_2O (300 ml), O_2, 0°C	100	LAC (1955) 596, 71
H_2C=$CHCH_2$-C≡CH	4500	CuCl (24 g), NH_4Cl (80 g), H_2O (260 mL), HCl (conc., 2 mL)	86	BSC.Fr (1953) 417

Abbreviations of literature references: BCS.Jpn = Bull. Chem. Soc. Japan; BSC.Fr = Bull. Soc. Chim. France; JACS = J. Am. Chem. Soc; JCS = J. Chem. Soc.; JOC = J. Org. Chem.; LAC = Lieb. Ann. Chem.; RTC = Recl. Trav. Chim. Pays-Bas; T = Tetrahedron; TL = Tetrahedron Lett.

Table 3. (Continued)

Acetylenic compounds	Scale (mmol)	Reaction conditions	Yield (%)	Literature
Hydrocarbons, (het)arylacetylenes and silylacetylenes				
	50	CuCl (10 mmol), TMEDA (13 mmol), $CH_3OCH_2CH_2OCH_3$ (50-70 mL), 30 -35°C, 20-60 min	79	TL (1972) 4831
	20	CuCl (6 mmol), TMEDA (10 mmol), $CH_3OCH_2CH_2OCH_3$ (50-70 mL), 30-35°C, 20-60 min	64	TL (1972) 4831
	20	CuCl (5 mmol), TMEDA (9 mmol), $CH_3OCH_2CH_2OCH_3$ (50-70 mL), 30-35°C, 20-60 min	50	TL (1972) 4831
	16	CuCl (5 mmol), TMEDA (9 mmol), $CH_3OCH_2CH_2OCH_3$ (50-70 mL), 30-35°C, 20-60 min	90	TL (1972) 4831
	50	CuCl (15 mmol), TMEDA (19 mmol), $CH_3OCH_2CH_2OCH_3$ (50-70 mL), 30-35°C, 30-60 min	97	TL (1972) 4831
Et_3Si-C≡CH	100	CuCl.TMEDA (~0.4 g), acetone (50 mL), air, ~20°C, 6 h	86	T (1972) 4601
Et_3Si-C≡CC≡CH	32	CuCl.TMEDA (~1 g), acetone (100 mL), air, ~20°C, 1.5 h	80	T (1972) 4601

Abbreviations of literature references: BCS.Jpn = Bull. Chem. Soc. Japan; BSC.Fr = Bull. Soc. Chim. France; JACS = J. Am. Chem. Soc; JCS = J. Chem. Soc.; JOC = J. Org. Chem.; LAC = Lieb. Ann. Chem.; RTC = Recl. Trav. Chim. Pays-Bas; T = Tetrahedron; TL = Tetrahedron Lett.

6 Copper(I)-Halide-Catalyzed Substitution of sp^2-Halogen by Alkoxide

6.1 Introduction

Uncatalyzed substitution of halogen in sp^2-halides by ether groups can proceed by addition-elimination mechanisms. In the olefinic or cyclo-olefinic series such reactions are facilitated by electron-withdrawing groups. In the chemistry of aromatic compounds the analogous reactions are called S_NAr substitutions. Although the processes are considerably promoted by electron-withdrawing groups, e.g. NO_2, in the *ortho*- or *para*-position [1, 4], they can occur also with unactivated aryl compounds, if strongly polar solvents such as hexamethylphosphoric triamide (HMPT) are used. Shaw at al. [1] succeeded in displacing one chlorine atom in *o*- and *m*-dichlorobenzene by OCH_3 using HMPT as a solvent. Even (mono)chlorobenzene and 1-chloronaphthalene reacted at somewhat higher temperatures. Similar reactions may be effected by using a crown ether [2]. Italian investigators [3–5] showed that the nucleophiles RO^-, RS^- and RSe^- can substitute chlorine, and in a few cases, even bromine. In all substitutions strongly polar solvents such as *N,N*-dimethylformamide (DMF) and hexamethylphosphoric triamide (HMPT) were used. Some of these reactions have preparative significance. The same group of Italian chemists [6] showed that fluor in unactivated aryl fluorides can be substituted by thioether groups (RS), while Cram [7] mentioned the formation of *o*-cresol from *tert*-butoxide and *o*-fluorotoluene (proceeding through *o*-*t*-butoxytoluene) in dimethylsulfoxide. We [8] could convert 1,3,5-trifluorobenzene at will into difluoro-methoxybenzene or 1,3,5-trimethoxybenzene. The mono-substitution was achieved by heating the trifluoro compound for one hour at 75 °C with sodium methoxide in *N*-methylpyrrolidinone (NMP), while heating for 18 hours at 130 °C was necessary for substituting all of the fluorine atoms. Even (mono)-fluorobenzene could be converted into anisole under relatively mild conditions (DMF, 100 °C) [8]. All reactions mentioned presumably are of the S_NAr type.

Copper salts or copper oxides are capable of catalyzing alkoxy- and aryloxy-dehalogenations of a number of unactivated aryl and hetaryl halides (RX). The earlier investigations have been reviewed by Moroz and Shvartsberg [9] and by Lindley [10]. In the review of the Russian chemists the Ullmann synthesis of aryl ethers is treated, while Lindley has reviewed copper-assisted substitutions of aryl halogen with several types of nucleophilic reagents.

$$RX + R'OM \xrightarrow{\text{Cu-catalyst}} ROR' + MX$$

R = aryl, hetaryl, alkenyl or cycloalkenyl;
X = I, Br or (in some cases) Cl

References (Sect. 6.1)

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2. Sam DJ, Simmons HE (1974) J Amer Chem Soc 96, 2252
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6. Cogolli P, Maiolo F, Testaferri L, Tingoli M, Tiecco M (1979) J Org Chem 44, 2642
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8. Keegstra MA, Brandsma L, unpublished
9. Moroz AA, Shvartsberg MS (1974) Russ Chem Rev 43, 679
10. Lindley J (1984) Tetrahedron 40, 1433

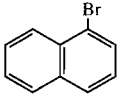
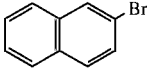
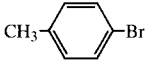
6.2 Scope and Limitations of the Copper-Catalyzed Nucleophilic Substitution of sp^2-Halogen by Alkoxy Groups

Table 4 shows a number of copper(I) halide catalyzed substitutions with alkoxides and sp^2-halides. Some less successful reactions are included for the sake of comparison. The data have been taken from literature as well as from investigations in our laboratory. For examples of the Ullmann synthesis of diaryl ethers the reader is referred to the review of Moroz and Shvartsberg (see Sect. 6.1, Ref. 9). Bacon and coworkers [1, 2] carried out copper(I)-iodide-catalyzed methoxy- and ethoxydehalogenations with a large number of aryl halides in mixtures of collidine and methanol or ethanol. Although the large amount of catalyst (50 mol%) used and the long reaction times (generally >12 hours) make the procedure not very attractive from a preparative point of view, the papers give valuable information on the influence of substituents. For example, benzene derivatives having the bromine atom situated between two *ortho*-methoxy groups are poor substrates for Cu-catalyzed substitutions, reductive debromination being the main reaction [2]. With iodides the results are even worse. Phenyl bromides containing a CH_3 or COOH substituent give ethyl or methyl ethers in good yields, whereas the presence of OH or NH_2 substituents gives rise to reduced yields, probably because of competing reactions. In the case of a NO_2, CH=O or $C(=O)CH_3$ group no ethers are obtained. Chlorine is substituted very sluggishly [1,3–5].

3-Bromopyridine, 2- and 3-bromothiophene have been successfully converted into ethers. Fair yields have been obtained from the reactions of methoxide with 2,4-, 2,5- and 3,4-dibromothiophene, but in the case of 2,3-dibromothiophene reductive debromination with formation of 3-bromothiophene and subsequent conversion into 3-methoxythiophene were the only reactions. Methoxy- and ethoxy-debromination of 2-bromofuran proceeded with moderate to fair yields [4].

Reactions of methoxide with aryl halides containing an SR substituent proceeded very slowly, presumably due to strong complexation of Cu with sulfur [8].

Table 4. Copper catalyzed alkoxy-dehalogenations

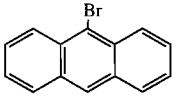
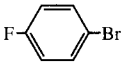
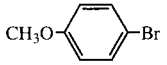
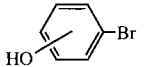
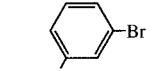
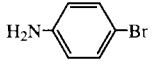
Reactant A (mmol)	Reactant B (mmol)	Reaction Conditions[a]	Yield	Literature[b]
PhBr (200)	CH_3ONa (300)	DMF-CH_3OH, 110°C, 45 min	High	T (1989) 5565
PhBr (100)	C_2H_5ONa (150)	C_2H_5OH, NMP, 110°C, 50 min	>90 %	T (1992) 3633
PhBr (100)	*i*-C_3H_7ONa (150)	*i*-C_3H_7OH, NMP, 110°C, 3.5 h	Good	T (1992) 3633
PhBr (100)	*n*-$C_5H_{11}ONa$ (150)	*n*-$C_5H_{11}OH$, NMP, 110°C, 0.5 h	Good	T (1992) 3633
PhBr (100)	F_3CCH_2ONa (150)	F_3CCH_2OH, NMP, 110°C, 50 min	High	T (1992) 3633
PhBr (100)	$CH_3OCH_2CH_2ONa$ (150)	$CH_3OCH_2CH_2OH$, NMP, 110°C, 2 h	High	T (1992) 3633
PhBr (100)	$Me_2NCH_2CH_2ONa$ (150)	$Me_2NCH_2CH_2OH$, NMP, 110°C, 1.5 h	High	T (1992) 3633
 (100)	CH_3ONa (150)	CH_3OH, NMP, 110°C, 0.5 h	High	T (1992) 3633
Same (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuBr, 115°C, 6 h	High	JCS (1969) 312
Same (10)	C_2H_5ONa (30)	C_2H_5OH, collidine, 50 mol % CuBr, 115°C, 6 h	High	JCS (1969) 312
Same (10)	*i*-C_3H_7ONa (30)	*i*-C_3H_7OH, collidine, 50 mol % CuBr, 115°C, 49 h	Low	JCS (1969) 312
Same (10)	*c*-Hex-ONa (30)	*c*-Hex-OH, collidine, 50 mol % CuBr, 115°C, 24 h	Good	JCS (1969) 312
Same (10)	*n*-C_3H_7ONa (30)	*n*-C_3H_7OH, collidine, 50 mol % CuBr, 115°C, 16 h	High	JCS (1969) 312
PhI (10)	C_2H_5ONa (30)	C_2H_5OH, collidine, 50 mol % CuBr, 115°C, 16 h	High	JCS (1969) 312
 (10)	C_2H_5ONa (30)	C_2H_5OH, collidine, 50 mol % CuBr, 115°C, 15 h	High	JCS (1969) 312
 (10)	C_2H_5ONa (30)	C_2H_5OH, collidine, 50 mol % CuBr, 115°C, 13 h	High	JCS (1969) 312

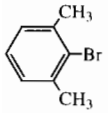
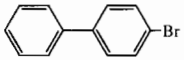
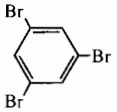
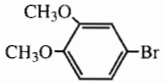
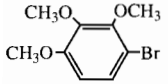
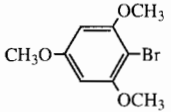
Abbreviations: DMF = N,N-dimethylformamide; NMP = N-methylpyrrolidinone

[a] Amount of copper-catalyst: 10-15 mol %, unless indicated otherwise.

[b] AK = Arkiv. Kemi; JCS = J. Chem. Soc.; JMC = J. Mol. Catal.; RTC = Recl. Trav. Chim., Pays-Bas; SC = Synth. Commun.; T = Tetrahedron.

Table 4. (Continued)

Reactant A (mmol)	Reactant B (mmol)	Reaction Conditions[a]	Yield	Literature[b]
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuBr, 115°C, 16 h (also 9 % anthracene formed)	Good	JCS (1969) 312
 (100)	CH_3ONa (150)	CH_3OH, 95-100°C, 4 h	Good	T (1992) 3633
 (10)	CH_3ONa (60) di-substitution	CH_3OH, collidine, 50 mol % CuBr, 115°C, 16 h	High	JCS (1969) 312
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuBr, 115°C, 16 h	High	JCS (1969) 312
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuBr, 115°C, 16 h	Moderate to fair	JCS (1969) 312
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuBr, 115°C, 16 h	High	JCS (1969) 312
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuBr, 115°C, 16 h	Fair	JCS (1969) 312

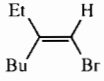
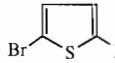
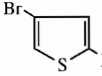
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuBr, 115°C, 16 h	Moderate	JCS (1969) 312
 (10)	C_2H_5ONa (30)	C_2H_5OH, collidine, 50 mol % CuBr, 115°C, 24 h	High	JCS (1969) 312
	CH_3ONa Tri-substitution	CH_3OH, DMF, 110°C	High	SC (1974) 35
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuI, 115 → 170°C, 15–20 h (some reductive debromination)	Good	JCS (1969) 1978
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuI, 115 → 170°C, 15–20 h (much reductive debromination)	Fair	JCS (1969) 1978
 (10)	CH_3ONa (30)	CH_3OH, collidine, 50 mol % CuI, 115 → 170°C, 15–20 h (mainly reduction)	Low	JCS (1969) 1978
 (100)	CH_3ONa (150)	CH_3OH, 90°C, 3 h, (very concentrated solution)	Fair	T (1992) 3633
 (200)	CH_3ONa (300)	CH_3OH, 100°C, 5 h (very concentrated solution)	High	SC (1990) 213

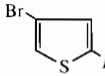
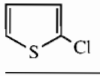
Abbreviations: DMF = N,N-dimethylformamide; NMP = N-methylpyrrolidinone

[a] Amount of copper-catalyst: 10-15 mol %, unless indicated otherwise.

[b] AK = Arkiv. Kemi; JCS = J. Chem. Soc.; JMC = J. Mol. Catal.; RTC = Recl. Trav. Chim., Pays-Bas; SC = Synth. Commun.; T = Tetrahedron.

Table 4. (Continued)

Reactant A (mmol)	Reactant B (mmol)	Reaction Conditions[a]	Yield	Literature[b]
Same (200)	C_2H_5ONa (300)	C_2H_5OH, 100°C, 2.5 h (very concentrated solution)	High	T (1992) 3633
 (300)	CH_3ONa (800)	CH_3OH, CuO (11,2 g), 70°C, 100 h	High	AK (1958) 239
Same (200)	CH_3ONa (300)	CH_3OH, NMP, 110°C, ~1 h	High	SC (1990) 213
Same (100)	C_2H_5ONa (150)	C_2H_5OH, DMF, 110°C, 1 h	High	T (1992) 3633
Same (100)	*i*-C_3H7ONa (150)	*i*-C3H7OH, DMF, 110°C, 8 h	High	T (1992) 3633
Same (165)	F_3CCH_2ONa (230)	F_3CCH_2OH, DMF, 110°C, 5 h	Good	JMC (1992) 299
Same (150)	$F_3C(CF_2)nCH_2ONa$ (76)	DME, CuI (37 mmol), 90°C, 15 h	Fair to good	JMC (1992) 299
 (100)	CH_3ONa (150)	CH_3OH, NMP, 110°C, 90 min	Good	T (1992) 2681
 (100)	CH_3ONa (150)	CH_3OH, NMP, 110°C, 75 min, (retention of configuration)	High	T (1992) 2681
 (50)	CH_3ONa (150) di-substitution	CH_3OH, reflux, 6 h (very concentrated solution)	Fair	T (1992) 3633
 (50)	CH_3ONa (150) di-substitution	CH_3OH, reflux, 6 h (very concentrated solution)	35 %	T (1992) 3633
 (50)	CH_3ONa (150) di-substitution	CH_3OH, reflux, 6 h (very concentrated solution)	Fair	T (1992) 3633

 (50)	CH_3ONa (50) mono-substitution	CH_3OH, reflux, 12 h	Moderate	T (1992) 3633
 (100)	F_3CCH_2ONa (200)	F_3CCH_2OH, reflux, 5 days	Good	RTC (1991) 299
 (100)	F_3CCH_2ONa (200)	F_3CCH_2OH, reflux, 5 days	Good	RTC (1991) 299

Abbreviations: DMF = N,N-dimethylformamide; NMP = N-methylpyrrolidinone

[a] Amount of copper-catalyst: 10-15 mol %, unless indicated otherwise.

[b] AK = Arkiv. Kemi; JCS = J. Chem. Soc.; JMC = J. Mol. Catal.; RTC = Recl. Trav. Chim., Pays-Bas; SC = Synth. Commun.; T = Tetrahedron.

Olefinic and cyclo-olefinic bromides (or iodides) that do not readily undergo 1,2-dehydrohalogenation can be smoothly converted into the corresponding methyl ethers [6].

Bacon and Rennison [1] investigated the Cu(I)-catalyzed reaction of 1-bromonaphthalene with a number of alkoxides. They obtained good to excellent results from the reactions with $NaOCH_3$, $NaOC_2H_5$, NaO-*n*-C_3H_7 and NaO-*c*-hexyl. With the alkoxides $NaOCH_2CH_2ONa$, $NaOCH_2Ph$, NaO-*i*-C_3H_7 and NaO-*t*-C_4H_9 reductive dehalogenation with the formation of naphthalene predominated: we had similar experiences with $NaOCH_2CH_2ONa$ and NaO-*t*-C_4H_9, but our reactions with *iso*-propoxide gave the expected ether in a good yield [4]. It should be mentioned in this connection that Whitesides at al. [10] obtained excellent yields of *t*-butoxybenzene in the (stochiometric) reaction of *t*-C_4H_9OCu with iodobenzene in pyridine at 115 °C . Attempts to introduce $H_2C{=}CHCH_2O$, *t*-$BuCH_2O$ or $HC{\equiv}CCH_2O$ groups into the aromatic ring failed completely, either due to decomposition of the catalyst (abundant formation of metallic copper) or to decomposition of the alkoxide ($HC{\equiv}CCH_2ONa$). The slow and very incomplete reaction of bromobenzene with $C_2H_5SCH_2CH_2ONa$ [4] may be explained by Cu–S complexation. Substitution of bromine in bromobenzene and 2- or 3-bromothiophene by $(CH_3)_2N\text{-}CH_2CH_2O$, F_3CCH_2O or other polyfluoro-alkoxy [9] and $CH_3OCH_2CH_2O$ groups proceeded without problems [4,8].

We obtained aryl and hetaryl *t*-butyl ethers in low yields from the copper(I)-catalyzed reaction of the corresponding bromides with sodium *tert*-butoxide in DMF or in mixtures of DMF and *tert*-butyl-alcohol. We also failed to convert 3-bromopyridine and 2-bromofuran and the corresponding bromothiophenes into the *tert*-butyl ethers [7].

References (Sect. 6.2)

1. Bacon RGR, Rennison SC (1969) J Chem Soc (C) 312
2. Bacon RGR, Wright JR (1969) J Chem Soc (C) 1978
3. Aalten HL, van Koten G, Grove DM, Kuilman T, Piekstra OG, Hulshof LA, Sheldon RA (1989) Tetrahedron 45, 5565
4. Keegstra MA, Peters THL, Brandsma L (1992) Tetrahedron 48, 3633
5. Nobel D (1993) J Chem Soc, Chem Commun 419
6. Keegstra MA (1992) Tetrahedron 48, 2681
7. Brandsma L, de Lang RJ, unpublished
8. Klumpers EG, den Besten R, Brandsma L, unpublished
9. El Kassimi A, Héraud G, Büchner W, Fache F, Lemaire M (1992) J Mol Catal 72, 299
10. Whitesides GM, Sadowski JS, Lilburn J (1974) J Amer Chem Soc 96, 2829

6.3 Mechanistic Investigations

Whitesides and coworkers [1] prepared copper(I) alkoxides by the reaction of alcohols with methylcopper and, in a more practical way, from lithium alkoxides and copper(I) chloride.

$$ROH + CH_3Cu \xrightarrow[0\ ^\circ C]{Et_2O} ROCu + CH_4$$

$$ROLi + CuCl \xrightarrow[0\ ^\circ C]{CH_3O(CH_2)_2OCH_3} ROCu{\cdot}LiCl\ (complex)$$

Subsequent reactions with aryl bromides or iodides and with 1-bromocyclohexene afforded alkyl-aryl ethers and 1-alkoxycyclohexene. Pyridine and mixtures of 1,2-dimethoxyethane and hexamethyl-phosphoric triamide were shown to be good solvents. Although even at room temperature some reaction took place, good yields could be obtained only after heating at temperatures in the region of 110 °C . The copper(I) alkoxides showed reasonable stability at room temperature.

These results indicate that copper(I) alkoxides are intermediates in the copper(I)-halide-catalyzed alkoxy-dehalogenations of aryl, hetaryl, and alkenyl halides with alkali alkoxides. Litvak and Shein arrived at the same conclusion [2]. Aalten at al. [3] concluded from their experiments that the reactive intermediate in the copper-catalyzed conversion of bromobenzene to anisole is the cuprate $Cu(OCH_3)_2^-Na^+$. In both mechanistic proposals the next steps are the formation of a coordinative complex of the aryl halide with copper(I) and electron transfer from the metal to the nucleus. In the mechanistic scheme of the Russian investigators, the reaction products are formed through a radical-like four-membered transition state, in which copper is monovalent.

Experiments in which substituted bromobenzenes (*p*-OCH_3, *m*-OCH_3, *p*-CH_3, *m*-CH_3, *p*-Cl, *m*-Cl) were allowed to compete with bromobenzene for sodium methoxide showed no strong differences in reactivities [3].

References (Sect. 6.3)

1. Whitesides GM, Sadowski JS, Lilburn J (1974) J Amer Chem Soc 96, 2829
2. Litvak VV, Shein SM (1974) J Org Chem, USSR, 2373
3. Aalten HL, van Koten G, Grove DM, Kuilman T, Piekstra OG, Hulshof LA, Sheldon RA (1989) Tetrahedron 45, 5565

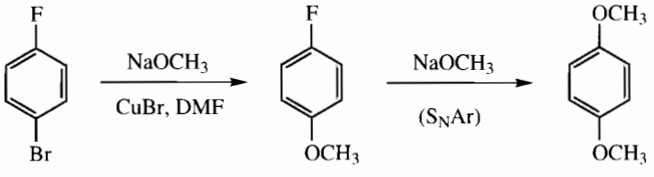
6.4 Reaction Conditions

6.4.1 Solvent and Reaction Temperature

Bacon et al. [1] used in their reactions of aryl halides with sodium methoxide 2,4,6-collidine as a co-solvent. The methanol was gradually distilled off or its vapor was

swept away in a stream of nitrogen, while allowing the temperature in the reaction mixture to rise from about 110 to 170 °C. In earlier investigations [2, 3] with halothiophenes, methanol was the only solvent and complete conversion under such conditions required prolonged heating under reflux.

In more recent investigations [4–8] dimethylformamide and *N*-methylpyrrolidinone (NMP) have been used as co-solvents. Replacement of alcohol by these dipolar aprotic solvents has not the dramatic accelerating effect on the reaction rates as in the familiar S_N2 substitutions with alkyl halides and in S_NAr reactions [9, 10]. It is more likely that these solvents serve to solubilize the catalyst and to attain a sufficiently high temperature. In some cases dimethylformamide was found to have a detrimental effect: notably alkoxylations of 2-bromo- and 2,5-dibromothiophene gave much intractable product when DMF was used as a co-solvent. When the desired product has hydrophylic properties due to the presence of polar groups, application of a polar co-solvent may necessitate a laborious extraction procedure. Especially fluorine-containing aryl bromides or iodides may undergo undesired substitution by fluorine by an S_NAr-mechanism if a dipolar aprotic solvent is present in a high con-centration, e.g. [5]:



In general, we recommend the use of very concentrated solutions of alkoxides in the corresponding alcohol as the only solvent for copper-catalyzed substitutions of sp^2-halogen. In these systems the attainable temperature is at least 95 °C , sufficiently high to effect completion of most conversions within a few hours. During reactions with sodium methoxide the temperature in the reaction mixture gradually drops as methoxide is consumed and complexed methanol is liberated. In order to bring the temperature back to the desired level, part of the alcohol can be distilled off.

6.4.2 The Catalyst

The most generally applied catalyst is copper(I) bromide. It is added in well-powdered form to the mixture of the alkoxide, alcohol, substrate and co-solvent. Since copper(II) halide was found to exert a comparable catalytic effect [4], the commercially available copper(I) halide, which sometimes contains small amounts of copper(II) impurities, can be used in general. In the reaction mixture copper(II) bromide is readily converted into copper(I) bromide [11].

Copper(II) oxide has been used in the successful conversions of 2-iodothiophene and 3-bromothiophene into the corresponding methoxythiophenes [2, 3].

Using the copper(I) oxide-collidine system, Bacon and Rennison isolated considerable amounts of arenes (ArH) from the reactions of aryl halides (ArHal) with a number of sodium alkoxides [12].

In a recent communication Nobel [13] reported very good results in a number of methoxy-dehalogenations, using the catalyst $Cu(OH)_2 \cdot CuCO_3$. Unfortunately, few experimental data were given.

Whereas Bacon et al. used amounts of copper halide as large as 50 mol% (e.g. [11]), more recent investigations have shown that with 10 to 15 mol% aromatic nucleophilic substitutions can be completed within a few hours at temperatures in the range 100–110 °C [4–7]. In cases of limited stability of the intermediary copper(I) alkoxide (e.g. $CuOC_2H_5$) it seems advisable to add the copper halide portionwise over a certain period.

Pd- and Ni compounds do not catalyze nucleophilic alkoxy-dehalogenations [14].

References (Sects. 6.4.1 and 6.4.2)

1. Bacon RGR, Wright JR (1969) J Chem Soc (C) 1978
2. Gronowitz S (1958) Arkiv för Kemi 12, 239
3. Sicé J (1953) J Amer Chem Soc 75, 3697
4. Aalten HL, van Koten G, Grove DM, Kuilman T, Piekstra OG, Hulshof LA, Sheldon RA (1989) Tetrahedron 45, 5565
5. Keegstra MA, Peters THA, Brandsma L (1992) Tetrahedron 48, 3633
6. Keegstra MA, Peters THA, Brandsma L (1990) Synth Comm 20, 213
7. Keegstra MA (1992) Tetrahedron 48, 2681
8. El Kassmi A, Héraud G, Büchner W, Fache F, Lemaire M (1992) J Mol Catal 72, 299
9. Testaferri L, Tiecco M, Tingoli M, Chianelli D, Montanucci M (1983) Tettrahedron 39, 193
10. Cogolli P, Maiolo F, Testaferri L, Tingoli M, Tiecco M (1979) J Org Chem 44, 2642
11. Bacon RGR, Rennison SC (1969) J Chem Soc (C) 312
12. Bacon RGR, Rennison SC (1969) J Chem Soc (C) 308
13. Nobel D (1993) J Chem Soc, Chem Comm 419
14. Keegstra MA, Brandsma L, unpublished

6.5 Differences in the Reactivities of the Various sp^2-Halides

As is usual in catalyzed displacements of halogen, sp^2-iodides are more reactive than the corresponding bromides. Aryl and hetaryl *chlorides* show little reactivity. Attempts to substitute chlorine by methoxy or ethoxy groups have so far been unsuccessful [1]. Displacement of chlorine in chlorobenzene and 2-chlorothiophene by CF_3CH_2O has been effected by refluxing a mixture of CF_3CH_2ONa, CF_3CH_2OH, Cu(I)Br and the halogen compound for several days [2]. The limiting factor in realizing other alkoxy-dechlorinations is the insufficient stability of the intermediary copper alkoxide.

Copper(I)-catalyzed substitutions with haloolefins and cycloolefins proceed more easily than the reactions with aryl and hetaryl halides [3]. This is illustrated by the fact that iodonorbornene gave the corresponding methyl ether in a reasonable yield when heated with sodium methoxide in the presence of 10 mol% of copper(I) bromide. The reaction with iodonorbornene proceeded easily at temperatures in the region of 50 °C , considerably lower than the usual level for Cu-catalyzed alkoxy-

dehalogenations. Even 1-chlorocycloheptene reacted rather smoothly with sodium methoxide in a methanol–DMF mixture at 100–110 °C, though the conversion did not proceed satisfactorily due to abundant formation of metallic copper [3].

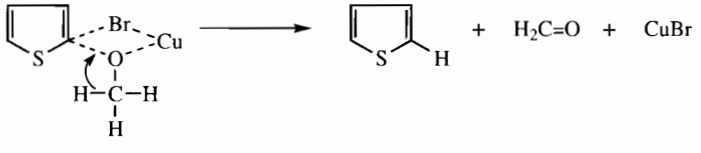
Reaction of 2,4-dibromothiophene with excess sodium methoxide gave the corresponding 2,4-dimethyl ether. When the reaction was stopped at an early stage, 2-methoxy-4-bromothiophene could be obtained in a fair yield [4].

References (Sect. 6.5)

1. See [4, 5 and 13] of Sect. 6.4.
2. KEEGSTRA MA, BRANDSMA L (1991) Recl Trav Chim, Pays-Bas 110, 299
3. KEEGSTRA MA (1992) Tetrahedron 48, 2681
4. KEEGSTRA MA, PETERS THA, BRANDSMA L (1992) Tetrahedron 48, 3633

6.6 Side Reactions

In many cases reductive dehalogenation accompanies the nucleophilic substitution. It is not always clear whether this side reaction is catalytic or stochiometric with respect to copper. In the latter case the copper(I) alkoxide decomposes with formation of metallic copper, which subsequently reduces the sp^2-halide. Especially dibromothiophenes were found to be reduction-responsive. The main product from the copper(I)-bromide-catalyzed reaction of 2,3-dibromothiophene with sodium methoxide in methanol was 3-methoxythiophene, presumably the result of a copper-assisted reduction at the 2-position and subsequent methoxylation of 3-bromothiophene [1]. Bacon and Wright [2] found quite a lot of reduced product in reactions of bromobenzenes that have one or more methoxy groups in the vicinity of the halogen atom. The Cu-catalyzed reductive debromination of 2-bromothiophene may be represented as follows:



We found considerable differences in the ratios of substitutive and reductive debromination of 2-bromothiophene, depending on the solvent system used [3]. With *N*-methylpyrrolidinone, *N,N*-dimethylformamide or dimethylsulfoxide as co-solvent reduction predominated. In the absence of such a solvent, using very concentrated solutions of sodium alkoxide, the 2-alkoxythiophenes were the main products. Alkoxylations with 3-bromothiophene were much less dependent on the solvent composition.

Low yields of 2-methoxy- and 2-ethoxythiophene were obtained when commercial sodium alkoxides were used [3]. The general advice therefore is to carry out copper-catalyzed substitutions with freshly prepared alkoxides. Furthermore it seems necessary to carefully maintain an atmosphere of inert gas, especially in reactions with sodium ethoxide and higher alkoxides: the accidental inflow of air when samples

were taken from the ethoxylation reaction mixtures sometimes caused the reaction to stop [3].

If a fluorine atom is present, its substitution by RO may be a very important side reaction. This S_NAr-substitution can be suppressed completely, however, by carrying out the copper-catalyzed substitution in the absence of a dipolar aprotic cosolvent [1].

References (Sect. 6.6)

1. KEEGSTRA MA, PETERS THA, BRANDSMA L (1992) Tetrahedron 48, 3633
2. BACON RGR, WRIGHT JR (1969) J Chem Soc (C) 1978
3. KEEGSTRA MA, PETERS THA, unpublished observations

6.7 Applications

If the aryl bromide is readily available, the copper(I)-halide-catalyzed alkoxylation may be preferred to other methods for the preparation of alkyl aryl ethers, such as the (uncatalyzed) alkylation of phenolates. This holds especially for the introduction of the more complex alkoxy substituents $CH_3OCH_2CH_2O-$ and $(CH_3)_2NCH_2CH_2O-$.

$$Ar\text{–}Br + NaOCH_2CH_2OCH_3 \xrightarrow{CuBr} ArOCH_2CH_2OCH_3$$

$$Ar\text{–}Br + NaOCH_2CH_2N(CH_3)_2 \xrightarrow{CuBr} ArOCH_2CH_2N(CH_3)_2$$

Copper(I)-catalyzed nucleophilic substitution is the method of choice for the preparation of mono- or dialkoxythiophenes and for 3-alkoxypyridines.

6.8 Experimental Part[1]

6.8.1 General

6.8.1.1 Reaction Conditions and Observations

In all reactions **an atmosphere of inert gas** was carefully maintained. For the preparation of sodium methoxide and sodium ethoxide the water-free alcohols were used. The commercially available solid alkoxides (sometimes brown-coloured) gave poor results in many cases. All reactions were carried out with technical grade copper(I) bromide.

A detailed description of all operations carried out during the reactions and the isolation procedures can be of considerable help, especially for inexperienced performers. Although mention of the changes in appearance of the reaction mixtures (especially colours) may also be useful, one should be sure that the phenomena described are reproducible. In some cases minute impurities in the starting materials, solvents

1 With the collaboration of Mr. T.H.A. Peters

or auxiliary reagents may cause strong colours. A suspension may appear or disappear depending on relatively small variations in the composition of the solvent system, in the temperature of the reaction mixture or in the composition of the atmosphere in the reaction flask (presence of traces of oxygen).

The operations given below are carefully and accurately described. As regards the phenomena, a few general observations will suffice.

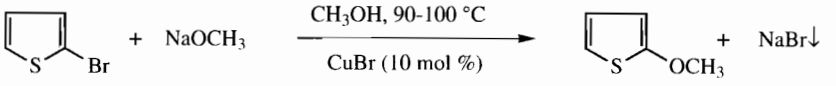
1. Addition of *N,N*-dimethylformamide (DMF) or *N*-methylpyrrolidinone (NMP) to a very concentrated suspension of sodium methoxide or ethoxide in the corresponding alcohol and gentle heating causes dissolution of the alkoxide.
2. Upon addition of copper(I) bromide at temperatures below 90 °C the solution turns blue.
3. After subsequent addition of the sp^2-bromide (or iodides) and heating to above 90 °C the colour often changes to grey or brown, announcing the start of the substitution reaction.
4. If the co-solvents mentioned are absent (only the alcohol present) the introduction of the catalyst gives a grey or light-brown suspension. Subsequent addition of the sp^2-halide and heating at temperatures above 90 °C may give rise to a variety of colours (usually brown) depending on the nature of the halide.
5. The progress of the reactions with methoxide or ethoxide can be easily followed by observing the temperature. As alkoxide is consumed, the strongly complexed alcohol is liberated. While maintaining a sufficiently strong reflux, the temperature in the reaction mixture drops due to the formation of free alcohol. If this fall in temperature is too slow at the beginning, part of the alcohol may be distilled off or otherwise an additional amount of copper(I) halide may be added, since the catalyst may have been inactivated, e.g. by the inflow of oxygen.
6. Decomposition of the intermediary copper(I) alkoxide is visible by the appearance of (brown) metallic copper.
7. A very dark-brown aqueous layer – and in some cases difficult separation of the layers due to the presence of brown solid material – often predicts a low yield of the expected product.

6.8.1.2 Apparatus and Equipment

Since the copper-catalyzed reactions are usually performed with high concentrations of substrate and alkoxide, syntheses on a laboratory scale (up to 0.3 molar) can be conveniently carried out in flasks that are not larger than 500 ml. Stirring is carried out magnetically, using an efficient stirring bar. The flask is equipped with a thermometer reaching into the reaction mixture and a 10-cm long tube through which the catalyst and substrate are introduced and can be added from time to time. On the third neck is placed a Dean-Stark device, by which solvent can be withdrawn from the reaction mixture. In this way, temperature control during the reaction is possible to a certain extent. When removal of solvent has to be stopped, the liquid in the receiver is allowed to run over. In order to maintain this possibility in the later stage of the reaction, one should draw off the condensate in small portions, leaving space of a few ml only.

6.8.2 Methoxylation

6.8.2.1 2-Methoxythiophene



Scale: 0.20 molar.

Apparatus: Equipment described in Sect. 6.8.1.2, size of the flask 250 ml.

Procedure: A solution of 0.30 mol of sodium methoxide in 175 ml of methanol was prepared from 7.0 g of clean sodium and absolute methanol (p.a. quality). From the solution 120 ml was distilled off under N_2. After addition of 0.20 mol (32.6 g) of 2-bromothiophene and 2.9 g of finely powdered copper(I) bromide, more methanol was (slowly) distilled off until the temperature of the reaction mixture had reached 98 °C. When, after about half an hour, the temperature had dropped to 94 or 95 °C, a small amount of methanol was distilled off in order to bring the temperature back to the original level. After the temperature had dropped to ~90 °C a second portion of methanol was distilled off, so that the temperature could rise by a few °C. After one or two repetitions of distilling off the methanol, the temperature remained practically constant. GLC showed complete conversion after a total period of 3 to 4 h refluxing. The mixture was cooled to below 30 °C, after which a solution of 20 g of ammonium chloride in 150 ml of water was added. The mixture was extracted at least six times with small portions of pentane (the aqueous layer became blue). After washing the combined extracts 3 times with water and drying over anhydrous magnesium sulfate, the solvent was distilled off at atmospheric pressure through a 30-cm Widmer column. Subsequent distillation in vacuo through an efficient column gave 2-methoxythiophene, b.p. 40 °C /15 mmHg, n^{20}_D 1.5262, in yields of 75% or higher.

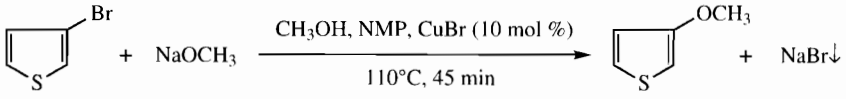
^{1}H-NMR spectrum (CCl_4): 6.3-6.7 (m, 2H); 6.0-6.15 (m, 1H); 3.75 (s, 3H) ppm.

General notes:

1. A slow stream of nitrogen (~100 ml/min) was passed through the apparatus during the time of the reaction. During the addition of 2-bromothiophene and copper(I) bromide (through the tube on the flask) the intensity of the flow of nitrogen was temporarily increased. This was also done during the taking samples for GLC with a Pasteur pipette.
2. If during the reaction the methanol is distilled off at too fast a rate, some of the bromothiophene or methoxythiophene may be swept away with it.
3. Some thiophene is formed by reductive dehalogenation. This can be separated from the desired product only by very careful distillation.

6.8.2.2 3-Methoxythiophene

Whereas the reaction of 2-bromothiophene with sodium methoxide proceeds unsatisfactorily if DMF or NMP are present as co-solvents, high yields of 3-methoxythiophene can be obtained when 3-bromothiophene is reacted with sodium methoxide in a mixture of methanol and NMP.



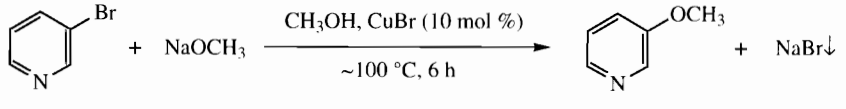
Scale: 0.20 molar.

Apparatus: Equipment described in Sect. 6.8.1.2, size of the flask 250 ml.

Procedure: After preparing a solution of 0.30 mol of sodium methoxide in 150 ml of methanol, ~120 ml of methanol were distilled off (see equipment described in Sect. 6.8.1.2). *N*-Methylpyrrolidinone (dried over machine-powdered potassium hydroxide and subsequently distilled in vacuo, 50 ml) was added. Subsequently 0.20 mol (32.6 g) of 3-bromothiophene and 2.9 g of finely powdered copper(I) bromide were added to the clear solution (which was at ~80 °C). The suspension was heated until methanol began to reflux. The temperature in the flask rose to between 110 and 120 °C , but soon began to drop. Methanol was distilled off until the temperature had risen again to ~110 °C . After about 45 min GLC indicated complete conversion. The mixture was cooled to below 30 °C and the product, b.p. 44 °C /15 mmHg, n^{20}_D 1.5292, was isolated as described for its 2-isomer (exp. in Sect. 6.8.2.1) in greater than 80% yield.

^{1}H-NMR spectrum (CCl_4): 7.0-7.2 (m, 1H); 6.5-6.7 (m, 1H); 6.0-6.2 (m, 1H); 3.8 (s, 3H) ppm.

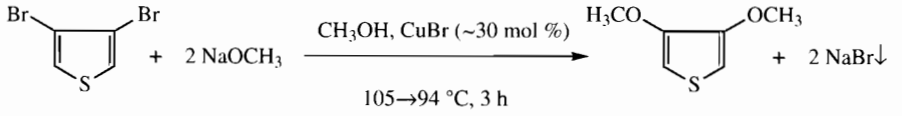
6.8.2.3 3-Methoxypyridine



Apparatus: Equipment described in Sect. 6.8.1.2, size of the flask 250 ml.

Procedure: The preparation of this compound from 3-bromopyridine and sodium methoxide was carried out in a way similar to the procedure for 2-methoxythiophene (exp. in Sect. 6.8.2.1). For the extraction, a 1 : 1 mixture of ether and pentane was used. The extracts were not washed with water. After drying over anhydrous potassium carbonate, the solvent was removed under reduced pressure. 3-Methoxypyridine, b.p. 71 °C /15 mmHg, n^{20}_D 1.5208 was obtained in >85% yield.

6.8.2.4 3,4-Dimethoxythiophene



Scale: 0.10 molar.

Apparatus: Equipment described in Sect. 6.8.1.2, size of the flask 250 ml.

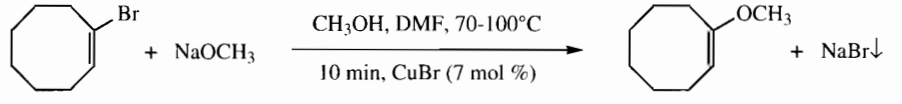
Procedure: Using 0.10 mol (24.2 g) of 3,4-dibromothiophene, 0.40 mol of sodium methoxide and ~3 g of copper(I) bromide this procedure was carried out in a way similar to the preparation of 2-methoxythiophene.

Methanol was distilled off from a solution of 0.40 mol of sodium methoxide. When the temperature had reached 90 °C , 0.10 mol of 3,4-dibromothiophene and 1.4 g of finely powdered copper(I) bromide were added. More methanol was distilled off until the temperature had reached 105 °C . After refluxing for 3 h, during which two additional portions of 1.4 g of CuBr were introduced, the product was isolated. 3,4-Dimethoxythiophene, b.p. 105 °C /15 mmHg, n^{20}_D 1.539, was obtained in 60% yield after a careful distillation.

^{1}H-NMR spectrum (CCl_4): 6.04 (s, 2H); 3.08 (s, 6H) ppm.

The *isomeric dimethoxythiophenes* were prepared in a similar way.

6.8.2.5 1-Methoxycyclooctene



Scale: 0.10 molar.

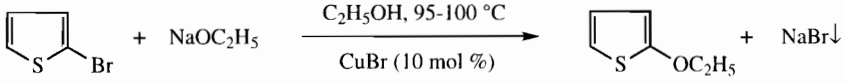
Apparatus: Equipment described in Sect. 6.8.1.2, size of the flask 250 ml.

Procedure: A solution of 0.15 mol of sodium methoxide in 75 ml of methanol was prepared from clean sodium and absulute methanol (p.a. quality). Methanol was distilled off until a white slurry had formed. Dry DMF (20 ml) was added at ~50 °C , causing dissolution of the methoxide. Subsequently 0.10 mol (19 g) of 1-bromocyclooctene and 1 g of finely powdered copper(I) bromide were added at 70 °C . A vigorous reaction started and the temperature rose above 90 °C . The conversion was completed by heating the mixture for an additional 10 min at 95–100 °C . After cooling below 30 °C 150 ml of an aqueous solution of 30 g of ammonium chloride was added and the mixture was extracted five times with small portions of diethyl ether. The combined extracts were washed twice with water and were subsequently dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by distillation gave 1-methoxycyclooctene, b.p. 70 °C /15 mmHg, n^{20}_D 1.475, in 92% yield.

^{1}H-NMR spectrum (CCl_4): 4.42 (t, 1H); 3.43 (s, 3H) ppm.

6.8.3 Other Alkoxylations

6.8.3.1 2-Ethoxythiophene



Procedure: This synthesis was carried out in a way similar to the preparation of 2-methoxythiophene (see exp. in Sect. 6.8.2.1). This reaction was more sensitive to oxygen. It seemed to be effective to add the copper(I) bromide in three or four equal portions at intervals of 45 min (with a temporary increase in the flow of nitrogen during the additions). The time required for complete conversion was about 4 h.
2-Ethoxythiophene, b.p. 65 °C /15 mmHg, n^{20}_D 1.5195, was obtained in yields of at least 70%.

^{1}H-NMR spectrum (CCl_4): 6.25-6.70 (m, 2H); 6.0-6.15 (m, 1H) ppm.

6.8.3.2 3-Ethoxythiophene

This compound was prepared (>80% yield) in the same way as 3-methoxythiophene (see exp. in Sect. 6.8.2.2), using DMF instead of NMP as a co-solvent.

6.8.3.3 3-Isopropoxythiophene

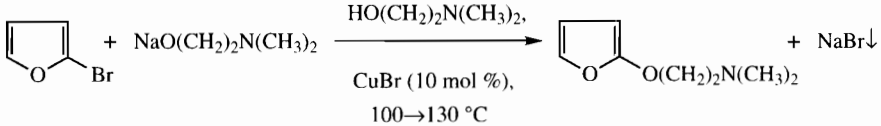
Scale: 0.10 molar.

Apparatus: Equipment described in Sect. 6.8.1.2, size of the flask 250 ml.

Procedure: In the flask was prepared a solution of 0.15 mol of sodium isopropoxide in 100 ml of dry isopropylalcohol. DMF (20 ml) was then added and the alcohol was distilled off, until the temperature had reached 110 °C . 3-Bromothiophene (0.10 mol, 16.3 g) and 1.4 g of finely powdered copper(I) bromide were added. The mixture was stirred at 110–115 °C until GLC indicated complete disappearance of 3-bromothiophene (6-8 h !). 3-Isopropoxythiophene, b.p. 80 °C /15 mmHg, was obtained in 75% yield.

^{1}H-NMR spectrum (CCl_4): 6.9-7.1 (m, 1H); 6.5-6.7 (m, 1H); 6.0-6.15 (m, 1H); 4.1-4.5 (q, 1H) ppm.

6.8.3.4 2-(2'Dimethylaminoethoxy)furan



Scale: 0.10 molar.

Apparatus: Equipment described in Sect. 6.8.1.2, size of the flask 250 ml; a normal reflux condenser was used instead of the Dean-Stark device.

Procedure: 2-Dimethylaminoethanol (50 ml) was placed in the flask. Sodium (4 g, 0.15 mol) was introduced in small pieces. When, at temperatures between 80 and 110 °C , all the sodium had dissolved, the mixture was cooled to 70 °C . Finely powdered copper(I) bromide (1.4 g) and 0.10 mol (14.7 g) of 2-bromofuran were added, after which the temperature was raised to above 90 °C . A vigorous reaction started and the temperature rose to above 125 °C . After heating for an additional 10 min at 120 °C , the very dark mixture was cooled to below 30 °C and a solution of 20 g of ammonium chloride in 150 ml of water was added. The mixture was extracted 5 times with small portions of diethyl ether. The combined extracts were washed with water and subsequently dried over anhydrous potassium carbonate. After removal of the solvent under reduced pressure 9 g (~60%) of 2-(2'-dimethylaminoethoxy)furan remained as a light brown liquid.

^{1}H-NMR spectrum (CCl_4): 6.78 (m, 1H); 6.12 (m, 1H); 5.05 (m, 1H); 4.00 (t, 2H); 2.55 (t, 2H); 2.20 (s, 6H) ppm.

The same procedure with *3-bromofuran* gave the expected derivative in a low yield.

6.8.3.5 2-(2'Dimethylaminoethoxy)thiophene

Procedure: This compound (b.p. 110 °C /15 mmHg) was prepared (78% yield) in a way similar to the synthesis of the analogous furan derivative. After the exothermic reaction had ceased, the mixture was heated for 20 min at 140 °C .

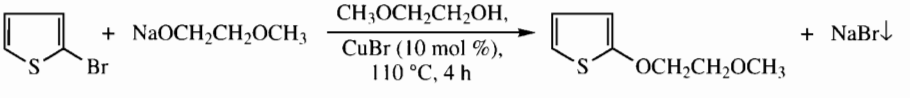
^{1}H-NMR spectrum (CCl_4): 6.58 (m, 1H); 6.40 (m, 1H); 6.11 (m, 1H); 3.99 (t, 2H); 2.57 (t, 2H); 2.20 (s, 6H) ppm.

6.8.3.6 1-(2'Dimethylaminoethoxy)cyclooctene

Procedure: This compound (undistilled) was prepared from 1-bromocyclooctene in almost quantitative yield ana-logous to the preparation of 2-(2'-dimethylaminoethoxy)furan.

^{1}H-NMR spectrum (CCl_4): 4.40 (t, 1H); 3.62 (t, 2H); 2.50 (t, 2H) ppm.

6.8.3.7 2-(2'Methoxyethoxy)thiophene



Scale: 0.10 molar.

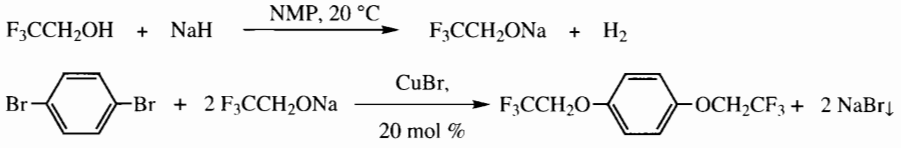
Apparatus: Equipment described in Sect. 6.8.1.2, size of the flask 250 ml: a normal reflux condenser was used instead of the Dean-Stark device.

Procedure: 2-Methoxyethoxide was prepared by dissolving at 20–100 °C clean sodium (4.6 g, 0.20 mol) in 100 ml of 2-methoxyethanol. 2-Bromothiophene (0.10 mol, 16.3 g) and 1.4 g of finely powdered copper(I)bromide were added at 80 °C , after which the

mixture was stirred for 4 h at 110 °C . The mixture was then poured into a solution of 25 g of ammonium chloride in 500 ml of water. Five extractions with pentane (or low boiling petroleum ether) were carried out. The combined extracts were washed three times with water, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. 2-(2'Methoxyethoxy)thiophene, b.p. ~70 °C /0.5 mmHg, was obtained in 70% yield.

^{1}H-NMR spectrum ($CDCl_3$): 7.08 (m, 1H); 6.71 (m, 1H); 6.17 (m, 1H); 3.98 (t, 2H); 3.61 (t, 2H); 3.28 (s, 3H) ppm.

6.8.3.8 1,4-Bis(2,2,2-trifluoroethoxy)benzene



Scale: 0.10 molar.

Apparatus: 250-ml round-bottomed, three-necked flask, equipped with a thermometer-nitrogen inlet combination, dropping funnel and a reflux condenser. The reaction mixture was stirred magnetically; the reaction was carried out under nitrogen.

Procedure: A 50% dispersion of sodium hydride in mineral oil (15 g, corresponding to ~0.3 mol of NaH) was placed in the flask, which was equipped with a gas inlet, a stopper and an outlet. After replacing the air by nitrogen, 75 ml of dry diethyl ether or pentane were added (with stirring). After 30 sec the stirring was stopped and the sodium hydride allowed to settle. Most of the ether or pentane was then cautiously removed by syringe. This procedure was repeated once. The remaining small amount of supernatant ether or pentane was removed by evaporation. After charging the flask with 75 ml of *N*-methylpyrrolidinone (dried over machine-powdered potassium hydroxide and subsequently distilled in vacuo), the equipment was placed on the flask and a mixture of 0.30 mol (30 g) of 2,2,2-trifluoroethanol and 15 ml of NMP was added dropwise over 1 h. After stirring for an additional 1 h at 20 °C , when the evolution of gas had stopped completely (some heating may be applied), 0.10 mol (23.6 g) of *p*-dibromobenzene and 2.8 g of finely powdered copper(I) bromide were added. The mixture was stirred for 2 h at 100 °C and was subsequently poured into 350 ml of an aqueous solution of 5 g of sodium cyanide. After vigorous shaking (under air), the brown solid was filtered off on sintered glass. The solid was washed twice with 50 ml of water, subsequently once with cold methanol and dried in vacuo. The pure product was obtained in 76% yield after crystallization from hexane.

^{1}H-NMR spectrum ($CDCl_3$): 6.89 (s, 4H); 4.29 (q, 4H, J_{HF} = 8.2 Hz) ppm.

Note: The reaction can also be carried out in 2,2,2-trifluoroethanol as solvent (for the apparatus see Sect. 6.8.1.2). Sodium was dissolved in 100 ml of the alcohol, in the last stage under reflux. Then part of the alcohol was distilled off (at normal pressure) until

the temperature of the solution had risen to 135 °C . 1,4-Dibromobenzene (0.10 mol, 23.6 g) and 2.8 g of finely powdered copper(I) bromide were added at ~125 °C . After refluxing for one night, the greater part of the alcohol was distilled off from the grey suspension (at slightly lowered pressure). After cooling to room temperature, the residue was treated with a solution of 5 g of sodium cyanide in 200 ml of water. The product was isolated in almost quantitative yield *via* extraction with diethyl ether.

7 Copper-Catalyzed Carbon-Carbon Bond Formation by 1,1- and 1,3-Substitution Reactions

7.1 Introduction

A wide variety of organic reactions are promoted by copper in copper salts or in organocopper compounds. Chapters 3–6 dealt with Cadiot-Chodkiewicz couplings, oxidative "dimerizations", Mannich reactions and alkoxy-dehalogenations.

The present chapter is devoted to a number of substitution reactions, mainly with Grignard intermediates, in which copper salts are used in catalytic amounts. The substrates include saturated halides or esters (acetates, tosylates), allylic or propargylic halides, esters, ethers, acetals derived from α,β-unsaturated aldehydes (C=C–$CH(OR)_2$ or C≡C–$CH(OR)_2$), allenic ethers (C=C=COR) and cyclic ethers (epoxides, oxetanes and larger ring systems) having either a saturated carbon atom or a vinylic or acetylenic group linked to the α-carbon atom in the ring.

Successful catalytic use of copper salts in reactions with organolithium or magnesium compounds is possible if the formation of the organocopper intermediates and the subsequent reaction with the substrate are much faster than the reaction of the latter with the organolithium or magnesium compound. Under these conditions a reactive copper intermediate can be continuously regenerated.

An extensive review on the stochiometric and catalytic use of copper salts and complexes in organic synthesis, with many experimental procedures, has been provided by Lipshutz [1], while the earlier review by Erdik [2] is confined to catalytic reactions. Copper-catalyzed cross-couplings of acetylenic compounds with allylic and propargylic substrates are extensively reviewed in [3].

References (Sect. 7.1)

1. Lipshutz BH (1994) In: Schlosser M (ed) Organometallics in Synthesis, A Manual. John Wiley, New York p 284-382
2. Erdik E (1984) Tetrahedron 40, 641-657
3. Jäger V (1977) In: Houben-Weyl, Methoden der Organischen Chemie, Band 5/2a, Georg Thieme Verlag, Stuttgart, p 463-495

7.2 Displacement of Halide, Tosylate and Acetate in Saturated Compounds

Substitution of halogen (often iodine) or tosylate in saturated substrates by alkyl or aryl groups in many cases has been performed with preformed cuprates, mostly R_2CuLi [1, 2]. It has been found, however, that smooth and successful displacement of halogen or tosylate is possible under the influence of catalytic amounts of copper salts. The latter are added as solutions of the complex $Cu_2Li_2Cl_4$ [3] or $CuLiBr_2$ [4]. Whitesides et al. [5] were the first to use a copper salt in catalytic amounts to promote a substitution reaction. In the absence of the catalyst the substitution was very slow:

$$n\text{-}C_8H_{17}I + CH_3Li \xrightarrow[Et_2O,\ 12\ h]{5\ mol\%\ CuI} n\text{-}C_8H_{17}\text{–}CH_3 + LiI$$

Using $(CH_3)_2LiCu$ in a 200 mol% excess, the reaction was complete within half an hour and even gave a better yield.

Tetrahydrofuran is an ideal solvent for catalytic substitutions with Grignard derivatives. Generally the following reactivity order is observed [6]:

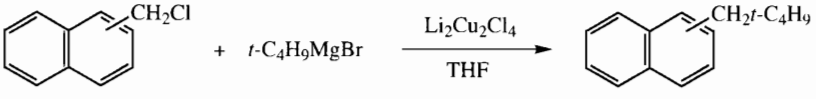
tert-alkylMgX > *sec*-alkylMgX > *prim*-alkylMgX > arylMgX > benzylMgX > hetarylMgX.

Some examples of successful substitutions are represented in the schemes below. Other examples are mentioned in Table 5.

$$C_8H_{17}OTs + t\text{-}C_4H_9MgBr \xrightarrow[THF]{4\%\ CuI} C_8H_{17}\text{–}t\text{-}C_4H_9 \qquad [7]$$

$$Br(CH_2)_{12}Br + 2\ BrMg(CH_2)_{11}OTHP \xrightarrow[THF]{Cu_2Li_2Cl_4} THPO(CH_2)_{34}OTHP \qquad [8]$$

$$\underset{\text{excess}}{Br(CH_2)_nBr} + \underset{(1\ \text{equiv})}{C_6H_5MgBr} \xrightarrow[THF\ \ n > 2]{LiCuBr_2\ \text{or}\ Cu_2Li_2Cl_4} Br(CH_2)_nC_6H_5 \qquad [9, 10]$$



[17]

Interaction between Grignard reagents and 1,2-dibromoethane, $Br(CH_2)_2Br$, leads to debromination [11]. Successful Cu-catalyzed disubstitutions with CH_2Br_2 and arylmagnesium halides have been reported by Japanese chemists [12]:

$$2\ ArMgBr + CH_2Br_2 \xrightarrow[THF,\ NMP]{CuBr} ArCH_2Ar$$

Reaction of 1,2-halohydrines with two equivalents of $H_2C{=}CHMgCl$, $H_2C{=}CHCH_2MgCl$, $(CH_3)_2C{=}CH{-}CH_2MgCl$ and PhMgCl in the presence of 5 mol% CuBr resulted in the desired substitution of the halogen. Bromohydrines gave the best results [13]:

$$CH_3CH(Br)\text{-}CH_2OMgCl + RMgCl \xrightarrow[THF]{CuBr\ (5\%)} CH_3CH(R)CH_2OH \quad 60\text{-}73\%\ \text{yield}$$

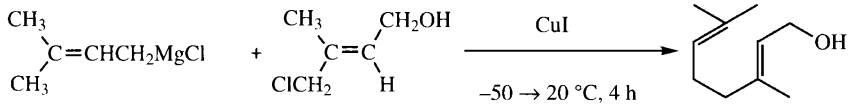
Bromoethanol $BrCH_2CH_2OH$ and *n*-alkylMgCl in the presence of a catalytic amount of CuI gave the expected alcohols $alkylCH_2CH_2OH$ in fair to excellent yields [14].

Allylic Grignard compounds were found to react smoothly with alkyl iodides under copper catalysis [15], e.g.:

$$\underset{(excess)}{(CH_3)_2C{=}CH{-}CH_2MgX} + RI \xrightarrow[Et_2O]{CuI} (CH_3)_2C{=}CH{-}CH_2R$$

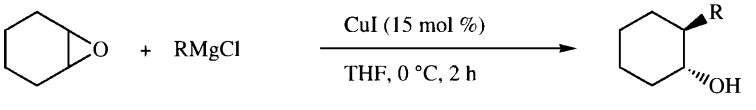
When CuI was absent, allylic transposition was the main reaction in this example.

The copper-catalyzed reaction with the prenyl Grignard reagent was applied in a successful synthesis of geraniol [15]:

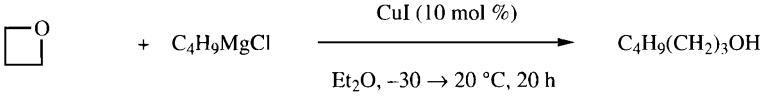


7.3 Ring Opening of Saturated Epoxides

Copper(I) halides considerably facilitate the ring opening of saturated epoxides and oxetanes by Grignard reagents [16]. An exception is the reaction of cyclohexene oxide with benzylmagnesium halide, which proceeded with better yield without a catalyst.



R = Ph, *n*-alkyl



A remarkable difference in regiochemistry was found, when allylic Grignard reagents were reacted with epoxides in the presence or absence of copper salts. Without the catalyst the conversions proceeded completely with allylic transposition, whereas in the presence of CuI (10%) no transposition occurred [18] (see Table 5, p.139).

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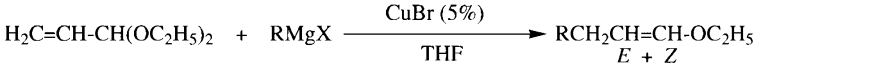
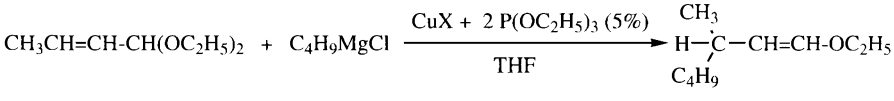
7.4 Reactions with Allylic Substrates

Allylic substrates (with leaving groups such as halide, tosylate, ester, sulfonyl, etc.) are much more reactive than the saturated substrates mentioned in Sect. 7.2. They can undergo copper-catalyzed substitution reactions with acetylenic Grignard derivatives, which do not react with saturated halides (except benzyl halides) and tosylates. Allylic substrates can undergo attack at the α-position with respect to the leaving group (1,1-substitution) or at the γ-position (1,3-substitution). In the latter case the double bond shifts (transposition or allylic rearrangement). Furthermore, stereochemistry is involved. The reactions of allylic substrates with nucleophilic species has been the subject of several studies: for leading reviews see [1–3]. Important mechanistic studies on copper-catalyzed displacement reactions with allylic halides and esters have been published by Goering, Bäckvall and coworkers [4, 5].

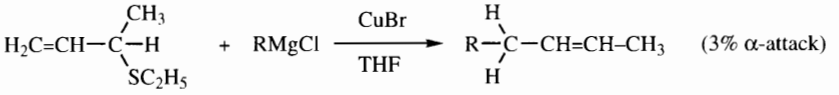
Transposition (1,3-substitution) is observed in reactions of Grignard reagents with allylic acetals [6]:

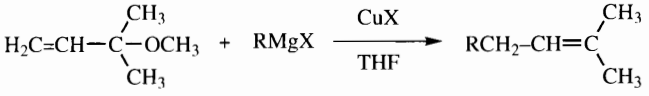




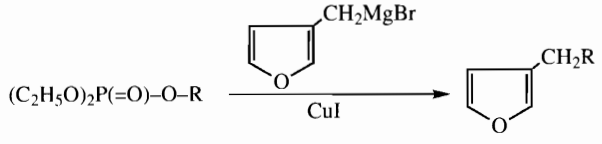
Since good yields can be obtained, these substitutions provide an attractive method for some special aldehydes, such as $t\text{-}C_4H_9CH_2CH{=}O$, formed from the substitution products by acid hydrolysis.

Allylic transposition is the predominant reaction if the α-position is hindered, e.g. [6,8]:



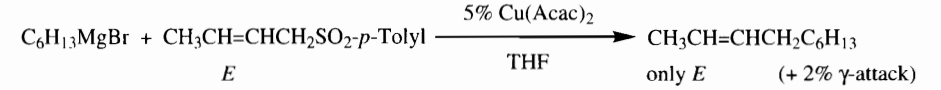


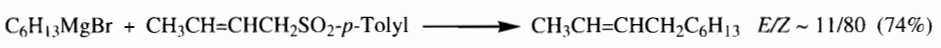
If both γ-positions are occupied, the organometallic reagent is forced to attack the α-carbon atoms, e.g. [8]:

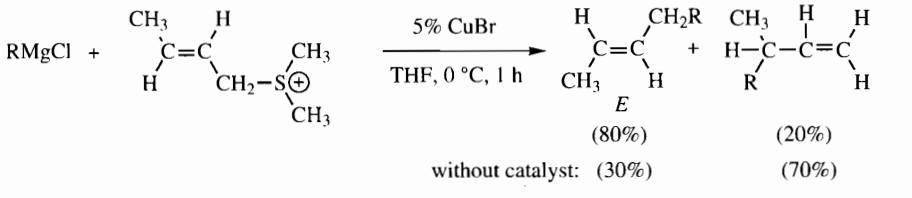


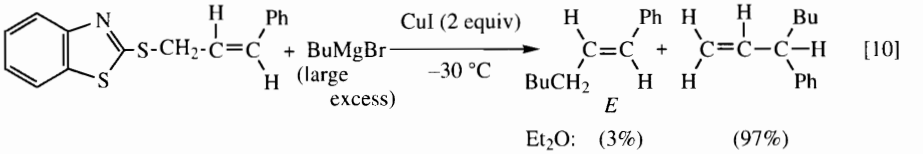
$R = CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$

With γ-(= 3-)monosubstituted allylic substrates the ratio of 1,1- or and 1,3(= γ)-substitution may vary, depending on the configuration of the double bond, the nature of the leaving group and the reaction conditions [8,9] (especially solvent [10]):





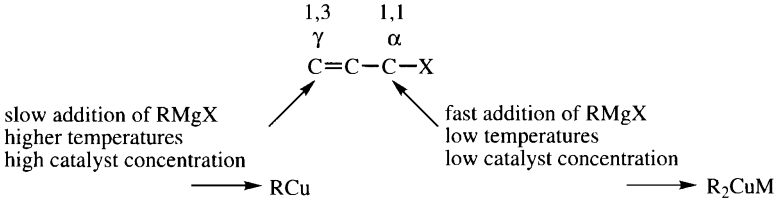




[10]

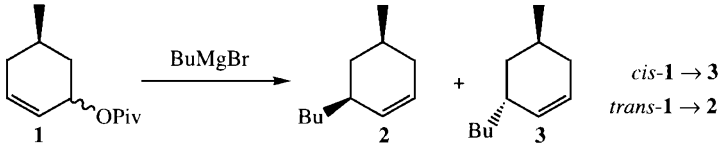
Goering et al. [4, 11] studied reactions of Grignard reagents with allylic esters in the presence of copper(I) salts. They found the catalytic reactions to be more satisfactory than those involving the stochiometric use of preformed copper intermediates, which often appeared to decompose during the reaction. Similar investigations were carried out more recently by Bäckvall and associates [5]. The results of the studies in both groups can be summarized as follows:

Highly selective α(1,1)- or γ(1,3)-attack in copper-catalyzed (CuCN, CuHal) reactions of a number of allylic substrates (especially esters) with Grignard compounds can be achieved by proper choice of the reaction conditions. Under conditions favouring the formation of a dialkylcuprate (R_2CuM) (fast addition of RMgX, low temperature, low catalyst concentration) α(1,1)-substitution predominates, whereas γ(1,3)-substitution is the main process when the reaction conditions are suitable for formation of monoalkylcopper (RCu) (slow addition of RMgX, higher temperature, higher concentration of the catalyst)

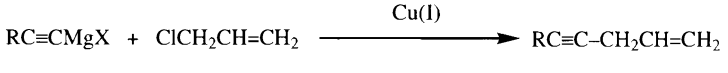


In the cases of $C_3H_7CH{=}CHCH_2OAc$ and geranyl acetate it appeared to be possible to reverse the site of attack from α(1,1)- to γ(1,3)-substitution by using diethyl ether (20 °C) instead of tetrahydrofuran in the CuCN-catalyzed reactions with *n*-butylmagnesium bromide [5]. These findings are in line with the results obtained in [10]. Also the counter ion of copper in the catalyst was shown to have an important influence on the regiochemistry [11]. In the reaction of *n*-C_4H_9MgBr with *E*-PhCH=CH-$CH(CH_3)$O-C(=O)-*t*-C_4H_9 in ether at room temperature γ-substitution predominated (≥ 97%) when CuCN was used (1 mol%). When using CuCl, CuBr, CuI or CuSCN, α-substitution was the main reaction (>85% α-attack). In the presence of CuCN, a catalyst which favoured in other cases γ-attack, PhMgBr and the last-mentioned substrate gave almost exclusively the α-substitution product.

The copper-catalyzed alkylation of *cis*- and *trans*-5-methyl-2-cyclohexyl pivalate with C_4H_9MgBr gave almost exclusively *trans*- and *cis*-substitution products, respectively [4]:



Copper halides catalyze the coupling between allylic halides and acetylenic Grignard intermediates (for several examples see [12]):



Successful copper halide-catalyzed reactions of allyl halides with free acetylenes have been carried out in aqueous or alcoholic medium [13].

$$RC{\equiv}CH + ClCH_2CH{=}CHR' \xrightarrow{Cu(I),\ H_2O} RC{\equiv}C{-}CH_2CH{=}CHR' + HCl$$

The pH has to be kept between 7 and 9 by continuous addition of alkali or ammonia, in order to suppress hydrolysis of the allylic halide. 1-Penten-1,4-yne, $HC{\equiv}CCH_2CH{=}CH_2$, can be obtained in an excellent yield from acetylene and allyl chloride in aqueous solution. The pH is maintained by slow dropwise addition of a NaOH solution. In a similar way 5-hexen-2-yne-1-ol, $H_2C{=}CHCH_2C{\equiv}CCH_2OH$ is prepared from allyl chloride and $HC{\equiv}CCH_2OH$.

Homologs of allyl chloride or bromide, e.g. $CH_3CH{=}CHCH_2$-X as well as α-substituted halides $H_2C{=}CH$-CH(R)Cl, give mixtures containing comparable amounts of 1,1- and 1,3-substitution products [13].

Reactions of Grignard reagents with butadiene monoxide under the influence of copper salts proceed as exemplified below [14]:

$$H_2C{=}CH{-}\underset{\diagdown\,\diagup}{O} + R_2C{=}CHCH_2MgX \xrightarrow[THF]{CuBr} R_2C{=}CH\text{-}CH_2CH_2CH{=}CHCH_2OH \quad (95\%\ E)$$

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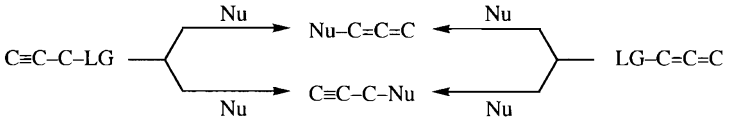
7.5 Reactions with Propargylic and Allenic Substrates

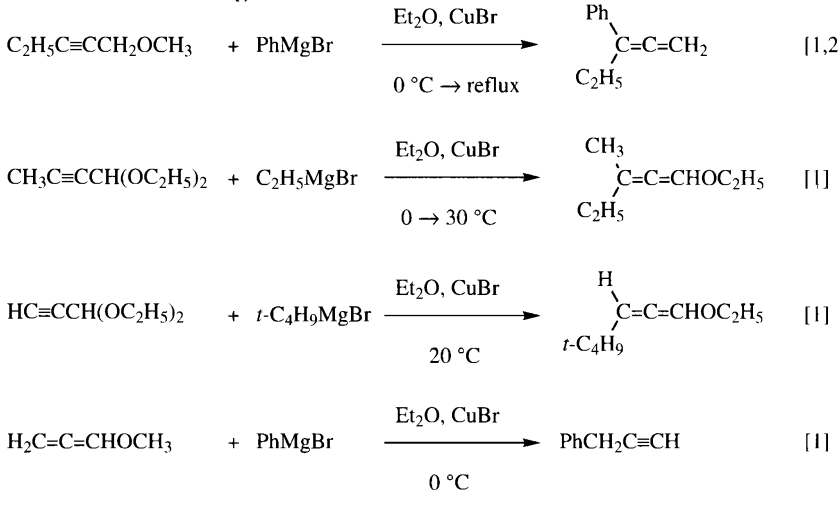
Substitutions with propargylic and allenic substrates can proceed with or without transposition of the unsaturation (1,3- or 1,1-substitution):



LG = Hlg, OAc, OTs, O-SOCH$_3$, OR etc.

Several substitutions can be successfully achieved using catalytic amounts of copper salts. The regiochemistry (1,1-versus 1,3-substitution) depends upon a number of factors, such as solvent, nature of the attacking reagent, leaving group. Some empirical rules derived from ample experience in the author's laboratory and literature data with copper-catalyzed substitutions are given below.

(a) Propargylic ethers or acetals and allenic ethers always react with transposition of the unsaturation, e.g.:



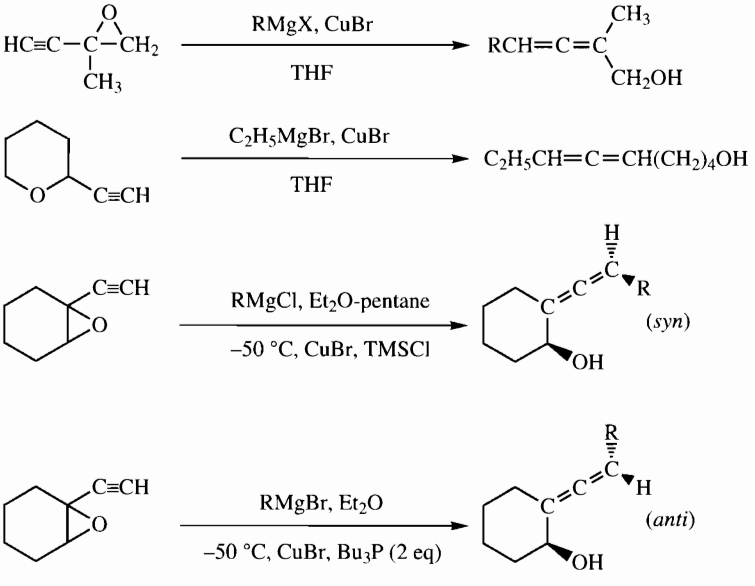
Grignards derived from heteroaromates, such as 2-furyl- and 2-thienylmagnesium bromide and acetylenic Grignard reagents are not sufficiently reactive to displace OR groups in propargylic and allenic ethers [3].

(b) The extent to which 1,1- and 1,3-substitution occur in copper-catalyzed substitutions with propargylic halides and tosylates, depends upon the nature of R in the Grignard reagent RMgX. With acetylenic Grignard reagents RC≡CMgX 1,1-substitution predominates (generally >85%) [4]. Also some hetaryl magnesium halides (e.g. 2-thienyl-MgBr, 2-furyl-MgBr and 1-methyl-2-pyrrylmagnesium bromide) reacted with propargyl bromide in THF at very low temperatures to give >85% of RCH$_2$C≡CH [5]. Arylmagnesium halides under similar conditions gave comparable amounts of ArCH=C=CH$_2$ and HC≡CCH$_2$Ar. From the reactions with (cyclo-)alkyl-MgX (except

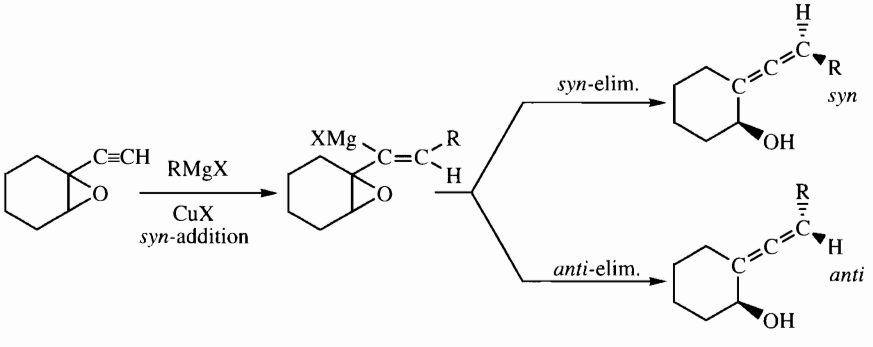
CH_3MgX, which gave a mixture of allene and acetylene) the sole product was the allene [5]. The strong tendency of alkylMgX to attack the γ-carbon atom is illustrated by the following conversion, in which no trace of acetylenic product is formed [1]:

$$t\text{-}C_4H_9MgCl + t\text{-}C_4H_9C{\equiv}CCH_2OTs \xrightarrow{\text{THF, CuBr}} (t\text{-}C_4H_9)_2C{=}C{=}CH_2$$

(c) Acetylenic epoxides and other cyclic ethers are attacked exclusively at the terminal acetylenic carbon atom by Grignard reagents [6–8]:

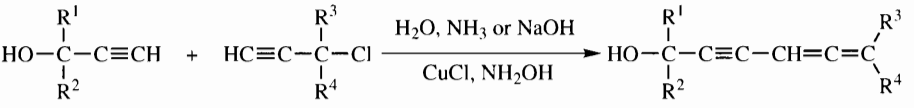


Alexakis et al. [8] succeeded in controlling the stereochemistry (*syn* or *anti*) of the copper-catalyzed reaction of Grignard reagents with acetylenic epoxides, which in fact may proceed *via* addition and elimination:



The diastereoselectivity in reactions of Grignard reagents with non-cyclic acetylenic epoxides could be similarly controlled [8]. An important determining factor appeared to be the nature of halogen (Cl or Br) in the Grignard reagent.

Cross-couplings between acetylenic compounds and propargylic halides (mostly chlorides) have been successfully carried out in an aqueous medium containing catalytic amounts of copper(I) chloride. Ammonia or sodium hydroxide was added to neutralize the hydrogen chloride produced in the coupling. Reactions with $HC{\equiv}CCH_2Cl$, $HC{\equiv}CCH(R)Cl$ and $HC{\equiv}CC(R^3)(R^4)Cl$ proceeded with exclusive formation of allenynes:



γ-Substituted propargyl chlorides e.g. $CH_3C{\equiv}CCH_2Cl$ gave, in general, mixtures of 1,1- and 1,3-coupling product [9,10].

References (Sect. 7.5)

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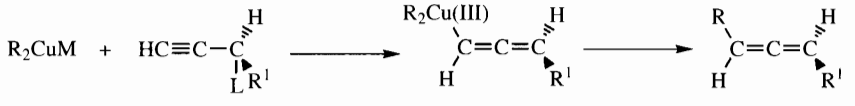
7.6 About the Mechanism of Copper-Catalyzed Substitutions

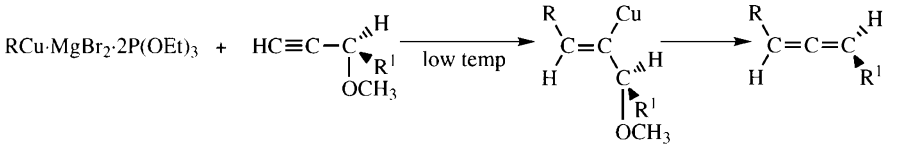
The mechanism of copper-assisted substitutions is a matter of continuous discussion [1, 2]. One point of uncertainty, when one is dealing with reactions of intermediary diorganocuprates, R_2CuM (M = Li or MgBr), is the nature of the reactive intermediate in solution [3, 4]. Investigations on the substitution reaction of lithium diorganocuprates with tosylates and halides showed the same characteristics as in the familiar S_N2 reactions [5]. Possible intermediates are a Cu(III) species or oxidative addition products of the substrates R^1X and the dimer of R_2CuLi.

In a number of papers dealing with the reactions of R_2CuM with chiral propargylic substrates the 1,3-substitution is assumed to proceed through a copper(III) intermediate [6–9]:



L = halogen or various ester groups

In the case of propargylic ethers, having the more poorly leaving OR group, a (*syn*-)-addition-(*anti*-)elimination mechanism was considered more likely [10, 11]:



Vermeer et al. [12] performed the reaction of $PhC{\equiv}CCH_2OTs$ with "CH_3Cu" at low temperatures in tetrahydrofuran and obtained $PhC(D)C{=}C{=}CH_2$ upon quenching the reaction mixture with deuteromethanol. When prior to quenching the temperature was allowed to rise to above 0 °C, only the expected 1,3-substitution product $PhC(CH_3){=}C{=}CH_2$ was obtained. The results may be considered as strong evidence for the intermediate occurrence of a Cu(III) species.

References (Sect. 7.6.)

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7.7 Experimental Section[1]

Note: All experiments were carried out under nitrogen. For all reactions commercial copper salts were used without purification.

7.7.1 Alkylation Reactions with Halides and Tosylates

7.7.1.1 2,2,7,7-Tetramethyloctane

$$2\ t\text{-}C_4H_9MgCl + Br(CH_2)_4Br \xrightarrow[THF]{CuBr\cdot LiBr} t\text{-}C_4H_9\text{-}(CH_2)_4\text{-}t\text{-}C_4H_9 + 2\ MgBrCl\downarrow$$

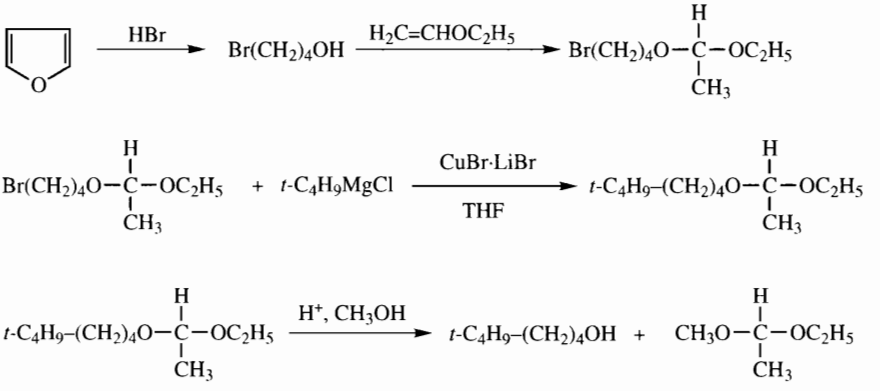
Scale: 0.08 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: A mixture of 0.08 mol (17.3 g) of 1,4-dibromobutane and 50 ml of THF was placed in the flask, and a solution of 1 g of copper(I) bromide and 3 g of anhydrous lithium bromide in 10 ml of THF was added. Subsequently a solution of 0.20 mol (excess) of *t*-butylmagnesium chloride in ~120 ml of THF was added dropwise over 20 min. Initially, the temperature of the black to purple reaction mixture was kept between −20 and −10 °C, but as more salt was formed, the temperature had to be increased gradually to +30 °C. During the addition much heat was evolved. Suddenly, the suspension turned dark-brown and further addition of the Grignard solution did not cause any noticable heating effect. The dark slurry was poured into a solution of 5 g of potassium cyanide and 50 g ammonium chloride in 150 ml of water. After vigorous shaking (under air) and separation of the layers, the aqueous phase was extracted twice with small portions of pentane. The almost colourless and dried (anhydrous $MgSO_4$) organic solution was concentrated under reduced pressure (bath temperature 240 °C) and the remaining liquid distilled through a 30-cm Vigreux column to give the product, b.p. 66 °C/14 mmHg, as a wax-like solid (purity by GC >99%) in 88% yield.

1 With the collaboration of Mr. H. Andringa

7.7.1.2 5,5-Dimethylhexan-1-ol



Scale: 0.10 molar.

Apparatus: Same as for the exp. in Sect. 7.1.1.

Procedure: A solution of 0.13 mol of *t*-BuMgCl in ~90 ml of THF was added drop- or portionwise to a mixture of 0.10 mol (22.2 g) of protected bromobutanol, 50 ml of THF and 1 g of CuBr (as a solution with 3 g of anhydrous LiBr in 10 ml of THF), while gradually allowing to the temperature of the yellowish suspension to rise to +20 °C. After an additional period of 20 min (at 20 °C) the product was isolated as described in Sect. 7.7.1.1: b.p. 87 °C/15 mmHg, n^{20}_D 1.4156, yield 90%.

The product was mixed with 30 ml of methanol, three drops of 30% aqueous hydrochloric acid were added and the solution was heated for 15 min at 45 °C. The excess of methanol and the acetal of acetaldehyde were removed under reduced pressure (bath temperature <40 °C) and the remaining liquid distilled through a 20-cm Vigreux column. The alcohol, b.p. 76 °C/15 mmHg, n^{20}_D 1.427, was obtained in 77% overall yield.

^{1}H-NMR spectrum (CCl_4): 3.5 (t, 2H); 0.8 (s, 9H) ppm.

Preparation of $Br(CH_2)_4OCH(CH_3)OC_2H_5$: Gaseous hydrogen bromide (from a cylinder, or generated by dropwise addition of the calculated amount of water to a vigorously stirred mixture of PBr_3 and CCl_4 (ratio ~0.25 v/v) in a two-necked flask, equipped with a dropping funnel-gas inlet combination and a reflux condenser having an outlet on the top) was led together with air or nitrogen (to prevent sucking-back of the THF) into 100 ml of dry THF. During this introduction the temperature of the THF was kept between 40 and 50 °C. The introduction was stopped when the weight of the THF solution had increased by 40 g. After standing for an additional 15 min at ~50 °C, the solution was cooled to room temperature, and added over 30 min to 1.0 mol (72 g) of freshly distilled ethyl vinyl ether, while keeping the solution between 0 and 5 °C. After the addition ~300 mg of *p*-toluenesulfonic acid was added at −5 to 0 °C in order to ensure complete reaction (as a rule this addition does not give rise to an observable heating effect). After an additional 15 min (at 0 °C) the solution

was vigorously stirred (or shaken) with 10 ml of a concentrated aqueous solution of potassium carbonate. The organic phase was dried on the anhydrous salt, after which 5 ml of triethylamine or diethylamine was added. After removal of the solvents under reduced pressure, the product was distilled in an apparatus which had been previously rinsed with a solution of triethylamine or diethylamine in acetone (to ensure the absence of traces of acid on the glass, which may cause deprotection). The protected bromobutanol, b.p. 100 °C/15 mmHg, was obtained in an excellent yield. The compound should be stored at –20 °C in the presence of some anhydrous K_2CO_3.

7.7.1.3 Selective Substitution of Bromine in 1-Bromo-4-chlorobutane

$$2\ t\text{-}C_4H_9MgCl + Br(CH_2)_4Cl \xrightarrow[THF]{CuBr\cdot LiBr} t\text{-}C_4H_9\text{–}(CH_2)_4\text{–}Cl$$

Scale: 0.20 molar.

Apparatus: Same as for the exp. in Sect. 7.7.1.1.

Procedure: An ~10% molar excess (see Note) of the Grignard reagent (added at –15 to 20 °C) was used. At the end of the addition the colour of the suspension changed from yellow to greyish. After an additional 15 min (at 15–20 °C) the reaction mixture was hydrolyzed. After extraction and drying over anhydrous $MgSO_4$, the greater part of the solvents was distilled off at atmospheric pressure through a 30-cm Vigreux column. Careful fractional distillation of the remaining liquid gave the product, b.p. 50 °C/15 mmHg, n^{20}_D 1.4268, in 80% yield.

^{1}H-NMR spectrum (CCl_4): 3.5 (CH_2Cl) ppm.

Note: If a larger excess of t-C_4H_9MgCl was used, t-C_4H_9–$(CH_2)_4$–t-C_4H_9 (somewhat less volatile) was also formed in significant amounts. With the lesser reactive reagents, such as ArylMgX the chance of disubstitution seems smaller.

7.7.1.4 Selective Mono-substitutions with 1,n-Dibromoalkanes

$$Br(CH_2)_nBr + RMgX \xrightarrow[THF]{CuBr\cdot LiBr} R\text{–}(CH_2)_n\text{–}Br$$

Scale: 0.10 molar (RMgX).

Apparatus: Same as for the exp. in Sect. 7.7.1.1.

Procedure: To a mixture of 0.30 mol (see Note) of 1,4-dibromobutane (65 g) and 90 ml of THF was added a solution of 1 g of copper(I) bromide and 2 g of anhydrous lithium bromide in 10 ml of THF. The mixture was warmed to 40 °C and a solution of 0.10 mol of phenylmagnesium bromide in 100 ml of THF was added dropwise over 1 h, while

keeping the temperature of the reaction mixture between 50 and 55 °C. After an additional 1 h (at ~50 °C) the mixture was cooled to 20 °C and then treated as described in exp. 7.7.1.1.

$Ph(CH_2)_4Br$, b.p. ~80 °C/0.8 mmHg, was obtained in 85% yield by careful fractional distillation.

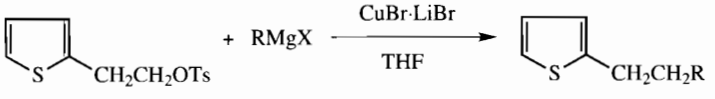
Note: The use of a smaller (or no) excess of 1,4-dibromobutane led to the formation of significant amounts of $Ph(CH_2)_4Ph$.

Cyclohexylmagnesium bromide or *p-fluorophenylmagnesium bromide* and three equivalents of *1,4-dibromobutane* reacted under similar conditions to give the *monosubstitution products* in good yields. Good results were obtained also with a large excess of *1,3-dibromopropane*. *2-Thienylmagnesium bromide* and *benzylmagnesium bromide* reacted very sluggishly giving the expected products in low yields.

n-, sec- and tert-Alkylmagnesium halides are sufficiently reactive, but it is very difficult to separate the desired product from the excess of dibromoalkane because of the small differences in boiling points.

In the reactions with *1,2-dibromoethane* elimination predominates.

7.7.1.5 Displacement of Tosylate in Alkyl Tosylates



Scale: 0.05 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: The tosylate (0.05 mol, 14.1 g), THF (50 ml) and copper(I) bromide(1 g, as a solution with 2 g of anhydrous lithium bromide in 10 ml of THF) were placed in the flask. A solution of 0.08 mol of *t*-butylmagnesium chloride in ~80 ml of THF was added over 15 min at ~–20 °C. The reaction mixture became almost colourless. After an additional 20 min (at ~–10 °C) the temperature was allowed to rise to 15–20 °C. Between 0 and 10 °C a distinct heating effect was observable. The greyish reaction mixture was worked-up as described in the preceding exps. to give 2-thienylCH_2CH_2-*t*-C_4H_9, b.p. 87 °C/13 mmHg, n^{22}_D 1.4920, in 89% yield.

^{1}H-NMR spectrum (CCl_4): 6.6–7.0 (m, 3H); 2.6–2.9 (m, 2H); 1.45–1.75 (m, 2H); 1.0 (s, 9H) ppm.

In the absence of CuBr a heating effect was also observed at ~–20 °C. After raising the temperature to 20 °C and subsequent work-up, all starting compound was recovered, however.

The *reaction with PhMgBr* proceeded only at temperatures higher than +20 °C. During the addition of the Grignard reagent (20% molar excess) the temperature of the reaction mixture was allowed to rise to +50 °C. After an additional half hour (at 40-45 °C) the product (solid) was isolated. 2-ThienylCH_2CH_2Ph was obtained in ~90% yield.

^{1}H-NMR spectrum (CCl_4): 6.7–7.2 (m, 8H); 2.95 (narrow multiplet, 4H) ppm.

2-Thienylmagnesium bromide reacted with 2-thienylCH_2CH_2OTos at ~60 °C (2 h reflux) to give a mixture consisting of comparable amounts of 2-thienyl-CH_2CH_2-2-thienyl and 2-thienyl-CH_2CH_2Br

7.7.1.6 Neopentylbenzene

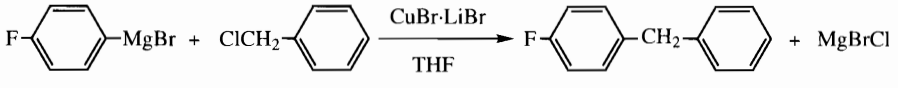
$$t\text{-}C_4H_9MgCl + ClCH_2Ph \xrightarrow[THF]{CuBr\cdot LiBr} t\text{-}C_4H_9\text{–}CH_2Ph$$

Scale: 0.10 molar.

Apparatus: Same as for the exp. in Sect. 7.7.1.1.

Procedure: To a mixture of 0.10 mol (12.6 g) of benzyl chloride and 60 ml of THF was added a solution of 1 g of copper(I) bromide and 2 g of anhydrous lithium bromide in 10 ml of THF. Subsequently a solution of 0.14 mol of *t*-butylmagnesium chloride in ~80 ml of THF was added during 15 min, while keeping the reaction mixture between 0 and 5 °C. After the addition, the temperature was allowed to rise to 20 °C and stirring of the greyish reaction mixture was continued for an additional half hour. After the usual work-up (see exp. in Sect. 7.7.1.1) neopentylbenzene, b.p. 67 °C/15 mmHg, n^{20}_D 1.486, was obtained in 76% yield. There was a small high-boiling residue.

7.7.1.7 Benzyl–Aryl Couplings



Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a nitrogen inlet-dropping funnel combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: A solution of 0.10 mol (12.6 g) of benzyl chloride in 100 ml of THF was placed in the flask, after which a solution of 1 g of copper(I) bromide and 2 g of anhydrous lithium bromide in 10 ml of THF was added. A solution of 0.12 mol of *p*-fluorophenylmagnesium bromide in ~80 ml of THF was added over 20 min while keeping the temperature of the reaction mixture between 25 and 35 °C. After the addition, the mixture (initially almost colourless) was heated for 1 h at ~40 °C (dark-green solu-

tion). After aqueous work-up (KCN, NH_4Cl) as described in the exp. in Sect. 7.7.1.1 the product (b.p. ~90 °C/0.5 mmHg) was isolated in 80% yield.

^{1}H-NMR spectrum (CCl_4): 6.8–7.2 (m, 9H); 3.81 (s, 2H) ppm.

p-CH_3O-C_6H_4-CH_2Ph, b.p. ~125 °C/0.5 mmHg, was obtained in an excellent yield from *p*-CH_3O-C_6H_4MgBr and benzyl chloride.

^{1}H-NMR spectrum (CCl_4): 6.55–7.12 (m, 9H); 3.76 (s, 2H); 3.57 (s, 3H) ppm.

Under similar conditions, copper-catalyzed reactions with *more highly substituted arylmagnesium halides and benzylic halides* were found to proceed with considerable cross-homo scrambling. Using *palladium catalysts* the desired cross-couplings proceeded satisfactorily.

7.7.1.8 t-Butylallene

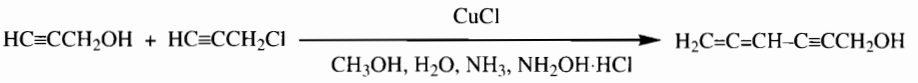
$$t\text{-}C_4H_9MgCl + HC{\equiv}CCH_2Cl \xrightarrow[THF]{CuBr{\cdot}LiBr} t\text{-}C_4H_9\text{–}CH{=}C{=}CH_2 + MgCl_2$$

Scale: 0.50 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel-gas inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: Freshly distilled propargyl chloride (0.50 mol, 37 g), 80 ml of THF and a solution of 4 g of copper(I) bromide and 8 g of anhydrous lithium bromide in 25 ml of THF were placed in the flask. A solution of 0.60 mol of *t*-butylmagnesium chloride in ~350 ml of THF was added over 1 h, initially with cooling between –10 and –15 °C, but, as more salt began to separate, the temperature was gradually raised to +15 °C (at the end). After an additional 1 h (at 15–20 °C) the suspension was poured into 500 ml of an aqueous solution of 150 g of ammonium chloride and 10 g of potassium cyanide. After vigorous shaking and separation of the layers, the upper layer was diluted with 150 ml of high-boiling petroleum ether (b.p. 3 170 °C (760 mmHg). The mixture was washed at least 10 times with 150-ml portions of 3 M hydrochloric acid in order to remove the THF. The combined aqueous layers were extracted once with 100 ml of the petroleum ether and this extract was also washed several times with 3 M HCl. The petroleum ether solutions were combined, dried over anhydrous $MgSO_4$ and subjected to vacuum distillation (10–15 mmHg, using a 40-cm Vigreux column and a single receiver cooled at –78 °C). The "distillation" was stopped when the petroleum ether began to distill (b.p. ~50–60 °C/15 mmHg). Redistillation of the contents of the receiver through a 40-cm Vigreux column at atmospheric pressure gave *t*-butylallene, b.p. ~80 °C/760 mmHg, n^{25}_D 1.4196, in ~75% yield (if some THF is still present, the product should be shaken with 3 M HCl in a small separating funnel).

7.7.1.9 Coupling Between Propargyl Alcohol and Propargyl Chloride in Aqueous Solution



Scale: 0.25 molar.

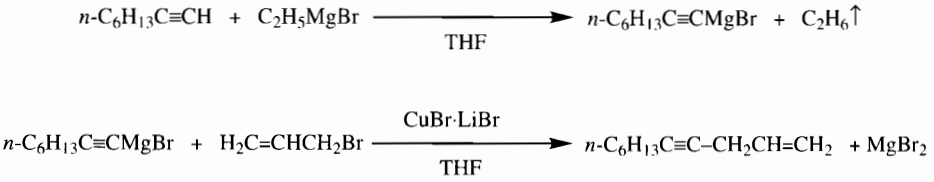
Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: (Cf. A. Sevin et al., Tetrahedron Lett. (1965) 1953.) Methanol (70 ml), 25% aqueous NH_3 solution (30 ml), freshly distilled propargyl alcohol (0.50 mol, 28 g), powdered copper(I) chloride (1.5 g, technical grade) and hydroxylamine.HCl (2 g) were placed in the flask. After flushing with nitrogen, a mixture of 0.25 mol (19 g) of freshly distilled propargyl chloride and 40 ml of methanol was added dropwise over 1 h, while keeping the temperature of the reaction mixture between 25 and 30 °C. After an additional 45 min a solution of 30 g of KCN or NaCN in 150 ml of water was added (under air) with vigorous stirring. Ten extracts with ether were carried out. The combined extracts were dried (without washing) over anhydrous $MgSO_4$ and concentrated in vacuo (the last traces of $HC{\equiv}CCH_2OH$ were removed at <0.5 mmHg, keeping the bath temperature below 40 °C). Almost pure $H_2C{=}C{=}CHC{\equiv}CCH_2OH$, ($n^{20}_D$ 1.5405) was obtained in ~80% yield. Distillation in small (~5 g) portions at <0.5 mmHg is possible, but usually results in partial polymerization.

$H_2C{=}C{=}CHC{\equiv}CC(CH_3)_2OH$, n^{25}_D 1.5405, was obtained from $HC{\equiv}CC(CH_3)_2OH$ and $HC{\equiv}CCH_2Cl$ in ~70% yield by a similar procedure.

Coupling between $H_2C{=}CHCH_2Cl$ and $HC{\equiv}CCH_2OH$, $HC{\equiv}CCH(CH_3)OH$ or $HC{\equiv}C\text{-}C(CH_3)_2OH$ by similar procedures is described by Kurtz, Liebigs Ann. Chem. (1962) 658, 6.

7.7.1.10 Couplings Between Acetylenic Grignard Reagents and Allyl Bromide or Propargyl Bromide



Scale: 0.30 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination (for the preparation of *n*-$C_6H_{13}C{\equiv}CMgBr$ a reflux condenser was used instead).

Procedure: 1-Octyne (0.30 mol, 33 g) was added at 20 °C to a solution of 0.30 mol of ethylmagnesium bromide in 200 ml of THF. After the exothermic reaction (evolution of ethane) had subsided, the mixture was heated for 1 h under reflux. The solution was then cooled to 20 °C and a solution of 2 g of copper(I) bromide and 4 g of anhydrous lithium bromide in 20 ml of THF was added. Freshly distilled allyl bromide (0.35 mol, 42 g) was added over 15 min, while keeping the temperature of the reaction mixture between 45 and 55 °C. After heating for an additional half hour at 60 °C, the suspension was cooled to room temperature and 200 ml of an aqueous solution containing 50 g of ammonium chloride and 15 ml of 30% aqueous hydrochloric acid were slowly added with vigorous stirring and cooling in an ice bath. The organic layer and one ethereal extract were dried over anhydrous $MgSO_4$. The coupling product, b.p. 79 °C/10 mmHg, n^{20}_D 1.4480, was obtained in 75% yield.

n-$C_6H_{13}C{\equiv}CCH_2C{\equiv}CH$, b.p. 82 °C/10 mmHg, was obtained in ~60% yield by a similar procedure, using a 10% molar excess of $HC{\equiv}CCH_2Br$. The contamination $C_6H_{13}C{\equiv}CCH{=}C{=}CH_2$ was removed by strongly (~120 °C) heating the product under N_2 for ~45 min, followed by distillation.

The preparation of *PhC≡CCH₂C≡CH* from $PhC{\equiv}CMgBr$ and $HC{\equiv}CCH_2Br$ by a similar procedure is described by Miller et al., Org. Synth., Coll. Vol. 6 (1988) 925.

7.7.1.11 Reactions of Grignard Reagents with Propargylic Tosylates

$$t\text{-}C_4H_9C{\equiv}CCH_2OTs + t\text{-}C_4H_9MgCl \xrightarrow[THF]{CuBr\cdot LiBr} (t\text{-}C_4H_9)_2C{=}C{=}CH_2 + TsOMgCl$$

Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: The tosylate (0.10 mol) and 100 ml THF were placed in the flask, after which a solution of 1 g of copper(I) bromide and 2 g of anhydrous lithium bromide in 10 ml of THF was added. A solution of 0.13 mol of *t*-butylmagnesium chloride in ~80 ml of THF was added over 20 min, while keeping the temperature between 0 and −5 °C. After the addition the cooling bath was removed and the mixture was stirred for an additional half hour, then 150 ml of 2 M aqueous hydrochloric acid was slowly added with vigorous stirring and cooling in an ice bath. The aqueous layer was extracted twice with 50-ml portions of pentane. The combined organic solutions were washed ten times

with 50-ml portions of a saturated aqueous solution of ammonium chloride in order to remove the greater part of the THF. The organic solution was dried over anhydrous $MgSO_4$, after which the greater part of the solvent was distilled off at atmospheric pressure through a 40-cm Vigreux column. Careful distillation of the remaining liquid gave di-*t*-butylallene, b.p. 38 °C/15 mmHg, n^{20}_D 1.4538, in ~75% yield.

The ratio of the 1,3- and 1,1-substitution products from reactions of Grignard reagents with propargylic tosylates depends strongly upon the nature of the Grignard reagent. Alkyl- or cycloalkylmagnesium halides and $HC{\equiv}CCH_2OTs$ or $RC{\equiv}CCH_2OTs$ give almost exclusively the allene by 1,3-substitution, whereas acetylenic Grignard derivatives give at least 85% (rel.) of the acetylenic derivative (1,1-substitution), compare H.D. Verkruijsse, M. Hasselaar, Synthesis (1979) 292.

7.7.2 Substitutions with Cyclic and Non-Cyclic Ethers

7.7.2.1 Preparation of 1-Alkenyl Ethers from Grignard Reagents and 1,1-Diethoxy-2-propene

$$H_2C{=}CHCH(OEt)_2 + t\text{-}C_4H_9MgCl \xrightarrow[THF]{CuBr{\cdot}LiBr} t\text{-}C_4H_9CH_2CH{=}CHOEt + EtOMgCl$$

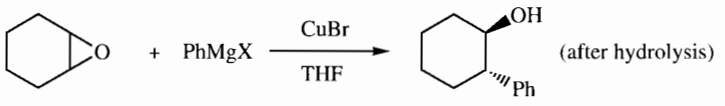
Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: (Cf. J.F. Normant et al., Tetrahedron Lett. (1975) 3833.) To a mixture of 0.10 mol (13 g, see Org. Synth. Coll. Vol. 4, p. 21) of acrolein diethylacetal and 50 ml of THF was added a solution of 0.3 g of copper(I) bromide and 1 g of anhydrous lithium bromide in 7 ml of THF. Subsequently a solution of 0.13 mol of *t*-butylmagnesium chloride in 75 ml of THF was added over ~10 min, while keeping the temperature between −10 and −15 °C. After the addition a second, equal portion of copper(I) bromide solution was added to effect complete conversion. The cooling bath was removed and the temperature allowed to rise to above 10 °C. The dark-brown slurry was cautiously hydrolyzed with 100 ml of a saturated solution of ammonium chloride containing 5 g of KCN or NaCN. The aqueous phase was extracted with pentane. After drying the organic solution over anhydrous $MgSO_4$, the greater part of the solvent was distilled off at atmospheric pressure through a 30-cm Vigreux column. The vinylic ether was obtained in 76% yield by careful distillation (b.p. 40 °C/15 mmHg). The product was a 77/13 mixture of the *Z* and *E* isomer.

n-$C_4H_9CH_2CH{=}CHOC_2H_5$ (*Z*/*E* ~2), b.p. 57 °C/15 mmHg, was obtained in 83% yield by a similar procedure from *n*-C_4H_9MgBr (in ether) and $H_2C{=}CHCH(OC_2H_5)_2$ (in THF) at 0–7 °C.

7.7.2.2 Reaction of Phenylmagnesium Bromide with Cyclohexene Oxide

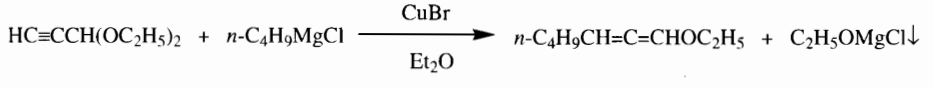


Scale: 0.05 molar.

Apparatus: Same as for the exp. in Sect. 7.7.2.1.

Procedure: (Cf. A. Schwartz et al., Org. Synth., Coll. Vol. 8 (1993) 516 and Huynh et al., Tetrahedron Lett. (1979) 1503.) To a mixture of 0.05 mol (5 g) of cyclohexeneoxide and 50 ml of THF was added with stirring 1.6 g of finely powdered copper(I) bromide. Subsequently a solution of 0.07 mol of phenylmagnesium bromide in ~60 ml of THF was added over 10 min. During the addition the temperature was allowed to rise from 20 to 40 °C. The mixture was stirred for 1 h at 30–35 °C, after which a solution of 20 g of ammonium chloride and 3 g of NaCN or KCN in 100 ml of water was added over a few min with vigorous stirring (under air). After three extractions with ether the combined organic solutions were dried over anhydrous $MgSO_4$. Concentration in vacuo, followed by distillation through a short column (an air condenser was used) gave the pure product, b.p. 90 °C/12 mmHg, as a solid in 88% yield.

7.7.2.3 Preparation of Allenic Ethers from Propargylaldehyde Diethylacetal and Grignard Reagents



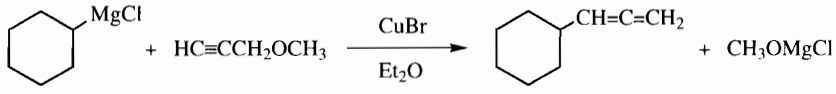
Scale: 0.10 molar.

Apparatus: Same as for the exp. in Sect. 7.7.2.1.

Procedure: (Cf. G. Tadema et al., Recl. Trav. Chim. Pays-Bas (1976) 95, 66.) Finely powdered copper(I) bromide (0.5 g) was added to a mixture of 75 ml of diethyl ether and 0.10 mol (13 g, see L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988)) of 1,1-diethoxy-2-propyne. After cooling the mixture to −30 °C, dropwise addition of a solution of 0.13 mol of *n*-butylmagnesium chloride in ~80 ml of ether was started. During this addition, taking 20 min, the temperature of the rather thick suspension was gradually raised to −10 °C. After an additional half hour at 0 °C, a solution of 3 g of KCN or NaCN and 20 g of ammonium chloride in 200 ml of water was added in small portions with vigorous stirring and cooling in an ice bath (air was admitted in order to facilitate complexation of copper). After extraction with ether and drying over anhydrous potassium carbonate, the ether was removed under reduced pressure and the allenic ether, b.p. 63 °C/15 mmHg, n^{20}_D 1.4471, was obtained in 78% yield.

t-$C_4H_9CH{=}C{=}CHOC_2H_5$, b.p. 42 °C/15 mmHg, n^{20}_D 1.4378 was obtained by a similar procedure in 72% yield.

7.7.2.4 Cyclohexylallene



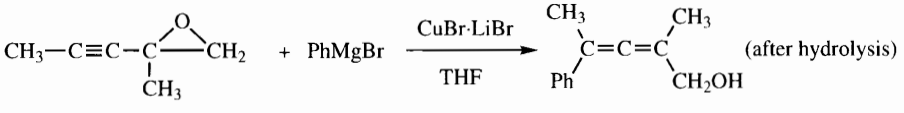
Scale: 0.10 molar.

Apparatus: Same as in preceding exps.

Procedure: (Cf. J.-L. Moreau et al., J. Organometal. Chem. (1976) 108, 159.) Freshly distilled methyl propargyl ether (0.10 mol, 7.0 g, see L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988)) and 70 ml of ether were placed in the flask. Finely powdered copper(I) bromide (1 g) was added with stirring. A solution of 0.13 mol of cyclohexylmagnesium chloride in ~90 ml of ether was added over 30 min, while keeping the temperature between −10 and 5 °C (bath with dry ice and acetone). A brown suspension or slurry was formed. After the addition the mixture was stirred for an additional half hour without cooling. Cyclohexylallene, b.p. 54 °C/15 mmHg, n^{20}_D 1.4812, was obtained in ~70% yield by a procedure of working-up similar to the one described in the preceding exp.

Allenes may also be obtained from RMgX and $HC{\equiv}CCH_2Cl$ or (Br).

7.7.2.5 Preparation of Allenic Alcohols from Acetylenic Epoxides and Grignard Reagents

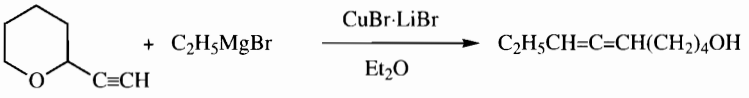


Scale: 0.10 molar.

Apparatus: Same as for the exp. in Sect. 7.7.2.1.

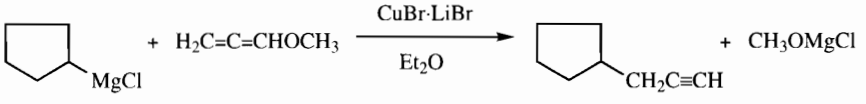
Procedure: (Cf. P. Vermeer et al., Recl. Trav. Chim. Pays-Bas (1974) 93, 46.) A solution of 1 g of copper(I) bromide and 2 g of anhydrous lithium bromide in 8 ml of THF was added to a mixture of 0.10 mol of the epoxide (0.10 mol, 9.6 g, see L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988)) and 100 ml of THF. A solution of 0.14 mol of phenylmagnesium bromide in ~100 ml of THF was added dropwise over 20 min at 20–30 °C. After an additional half hour the dark reaction mixture was hydrolyzed with a solution of NH_4Cl and KCN or NaCN as described in the preceding experiments. After extraction with ether and drying over anhydrous $MgSO_4$, the product was isolated in the usual way: b.p. ~100 °C/0.2 mmHg, n^{20}_D 1.5705, yield ~75%.

7.7.2.6 Reaction of 2-Ethynyltetrahydropyran with a Grignard Reagent



Reaction of 2-ethynyltetrahydropyran (for the preparation see L. Brandsma, Preparative Acetylenic Chemistry, 2nd ed., Elsevier, Amsterdam (1988)) with a 10% molar excess of ethylmagnesium bromide in the presence of the copper catalyst was performed at ~0 °C (with an additional period of 30 min at room temperature) in a way similar to the procedure described in the preceding exp. The allenic alcohol, b.p. 95 °C/12 mmHg, n^{20}_D 1.4768, was obtained in 82% yield. For the procedure compare D.J. Nelson, W.J. Miller, J. Chem. Soc., Chem. Comm. (1973) 444.

7.7.2.7 3-Cyclopentyl-1-propyne



Scale: 0.20 molar.

Apparatus: Same as for the exp. in Sect. 7.7.2.1.

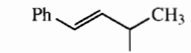
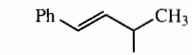
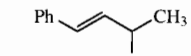
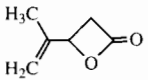
Procedure: (Cf. J. Meijer, P. Vermeer, Recl. Trav. Chim. Pays-Bas (1974) 93, 183.) Freshly distilled methoxyallene [0.20 mol, 14 g, see L. Brandsma, H.D. Verkruijsse, Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier, Amsterdam (1981)], 100 ml of diethyl ether and a solution of 1 g of copper(I) bromide and 2 g of anhydrous lithium bromide in 10 ml of THF were placed in the flask. A solution of 0.25 mol of cyclopentylmagnesium bromide in ~150 ml of ether was added over 30 min, while maintaining the temperature between −5 and +5 °C. After the addition, the cooling bath was removed and the white suspension was stirred for an additional 45 min, then the suspension was cautiously poured into 200 ml of an aqueous solution of 30 g of ammonium chloride and 5 g of NaCN or KCN. After one extraction with ether, the product b.p. 30 °C/20 mmHg, n^{20}_D 1.4502, was isolated in ~76% yield as described in the preceding exps.

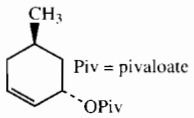
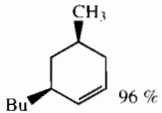
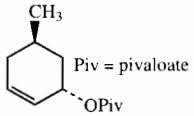
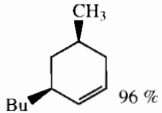
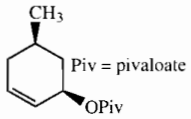
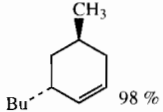
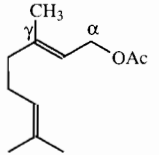
For other examples see literature mentioned above.

2-Thienylmagnesium bromide appeared to be insufficiently reactive.

From *n*-$C_4H_9CH=C=CHOCH_3$ and *n*-C_4H_9MgBr ***(n-C₄H₉)₂CHC≡CH*** was obtained in an excellent yield.

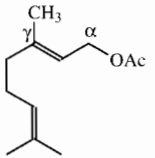
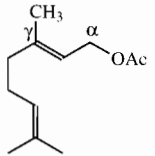
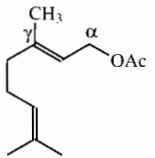
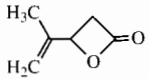
Table 5. Copper(I) catalyzed substitutions with sp^3-halides and various esters

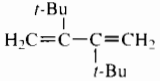
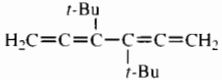
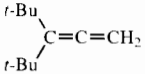
Organometallic intermediate	Substrate	Reaction conditions	Remarks	Literature[a]
CH_3Li	n-$C_8H_{17}I$	Et_2O, 12 h	Nonane 64 % yield, without CuI only 6 % nonane	JACS (1969) 4871
C_2H_5MgBr	c-$C_6H_{11}OTs$	THF, $-70 \rightarrow 20°C$	only 3 % yield	AC.Int (1974) 82
C_2H_5MgBr	$PhCH{=}CHCH_2OAc$	THF, –25°C, 25 mol % CuBr, EtMgBr	$PhCH{=}CHCH_2Et$ (84 %) reduction products (16 %) (total yield 70 %)	TL (1978) 5049
n-C_4H_9MgCl	$EtOCH_2CH_2Br$	THF, –10°C, 4 h	t-BuMgCl gives no product	TL (1977) 3263
n-C_4H_9MgCl	$AcOCH_2CH_2Br$	THF, –15°C	i-PrMgCl: fair yield t-BuMgCl: no product	TL (1977) 3263
n-C_4H_9MgBr	$CH_3CH{=}CHCH_2OAc$	Et_2O-THF, $-78 \rightarrow +20°C$	$CH_3CH{=}CHCH_2Bu$ retention of configuration	AC.Int (1974) 82
n-C_4H_9MgBr	 Piv = pivaloate OPiv	Et_2O, 0°C, 1 % CuCN	$PhCH(Bu)CH{=}CHCH_3$ E/Z (2-3 % α-attack)	JOC (1986) 2884
n-C_4H_9MgBr	 Piv = pivaloate OPiv	Et_2O, 0°C, 1 % CuCl	 (11 % γ-attack) C_4H_9	JOC (1986) 2884
n-C_4H_9MgBr		THF, –78°C, 1 h	n-$BuCH_2C(CH_3){=}CHCH_2COOH$ E/Z = 73/27	CL (1981) 1307

n-C_4H_9MgBr		Et_2O, 0°C, 1 % CuCN		JOC (1986) 2892
n-C_4H_9MgBr		Et_2O, 0°C, 10 % CuCl		JOC (1986) 2892
n-C_4H_9MgBr		Et_2O, 0°C, 2 % CuCN		JOC (1986) 2892
n-C_4H_9MgBr		THF, –30°C, 10 % Li_2CuCl_4	Fast addition (2 min) of n-BuMgBr giving >91 % a-attack	JACS (1990) 6615

[a] Abbreviations: AAC = L. Brandsma, H.D. Verkruijsse, Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier, Amsterdam, (1981); AC = Angew. Chem.; AC.IntEd = Angew. Chem., Int. Ed.; AL = Author's laboratory; CA = Chem. Abstr.; CB = Chem. Ber.; CC = J. Chem. Soc., Chem. Comm.; CL = Chem. Lett.; JACS = J. Am. Chem. Soc.; JOC = J. Org. Chem.; OOP = Org. Prep. and Proc., Int.; OS = Organic Syntheses; OS, ..., C... = Organic Synthesis, Collective Volume; PrAcCh = L. Brandsma, Preparative Acetylenic Chemistry, Elsevier, Amsterdam, (1988); RTC = Recl. Trav. Chim. Pays-Bas; S = Synthesis; SC = Synthetic Communications; TL = Tetrahedron Lett.

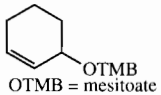
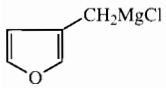
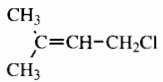
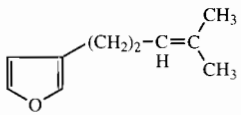
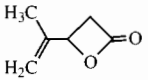
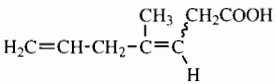
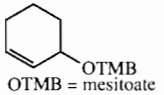
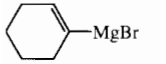
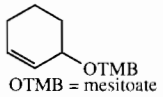
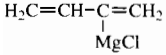
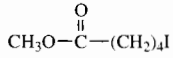
Table 5. (Continued)

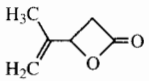
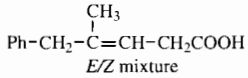
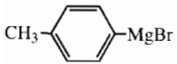
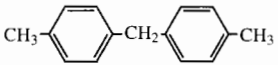
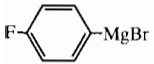
Organometallic intermediate	Substrate	Reaction conditions	Remarks	Literature[a]
n-C_4H_9MgBr		THF, 0°C, 10 % Li_2CuCl_4	Slow addition (30 h) of *n*-BuMgBr giving 60 % a-attack 40 % g-attack	JACS (1990) 6615
n-C_4H_9MgBr		THF, 0°C, 10 % CuCN	In THF 94 % α-attack 6 % γ-attack	JACS (1990) 6615
n-C_4H_9MgBr		Et_2O 20°C, 10 % CuCN	In Et_2O, 97 % γ-attack	JACS (1990) 6615
t-C_4H_9MgCl		THF, –78°C	*t*-$BuCH_2C(CH_3)$=$CHCH_2COOH$ E/Z mixture	CL (1981) 1307
t-C_4H_9MgCl	$HC{\equiv}CCH_2Cl$	Et_2O, –5°C, 30 min	*t*-C_4H_9CH=C=CH_2 See also exp. section	AAC, p. 158

t-C_4H_9MgCl (2 eq)	$ClCH_2C{\equiv}CCH_2Cl$	THF, −20 → 0°C		CC (1980) 923
t-C_4H_9MgCl (2 eq)	$ClCH_2C{\equiv}C{-}C{\equiv}CCH_2Cl$	THF, −40 → 0°C		AAC, p.168
t-C_4H_9MgBr	n-$C_8H_{17}OTs$	THF/Et_2O, −78 → 20°C, + 12 h	–	AC.Int (1974) 82
t-C_4H_9MgBr	$TsO(CH_2)_{11}OTs$	−78 → 20°C	–	AC.Int (1974) 82
t-C_4H_9MgBr	t-$C_4H_9C{\equiv}CCH_2OTs$	THF, −5 → 10°C, 30 min	 See exp. section	AAC, p. 162; PrAcCh, p.224
t-C_4H_9MgBr	1-Naphthyl-CH_2Cl	THF, 30°C, 2 h	–	S (1977) 316
n-$C_5H_{11}MgBr$	$BrMgOOC(CH_2)_{11}Br$	THF, −20°C	–	TL (1976) 4697
c-$C_6H_{11}MgCl$	$Br(CH_2)_3Br$	THF, 40-50°C, 1 h	–	SC (1990) 2349
c-$C_6H_{11}MgBr$	PhOTs	THF, −70 → 20°C	Fair yield (with EtMgBr and t-BuMgBr no product)	AC.Int (1974) 82
THPO-$(CH_2)_4MgCl$	$EtC{\equiv}CCH{=}CH(CH_2)_2Br$	THF, −20 → +20°C, 12 h	–	CB (1978) 1446

[a] Abbreviations: AAC = L. Brandsma, H.D. Verkruijsse, Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier, Amsterdam, (1981); AC = Angew. Chem.; AC.IntEd = Angew. Chem., Int. Ed.; AL = Author's laboratory; CA = Chem. Abstr.; CB = Chem. Ber.; CC = J. Chem. Soc., Chem. Comm.; CL = Chem. Lett.; JACS = J. Am. Chem. Soc.; JOC = J. Org. Chem.; OOP = Org. Prep. and Proc., Int.; OS = Organic Syntheses; OS, ..., C... = Organic Synthesis, Collective Volume; PrAcCh = L. Brandsma, Preparative Acetylenic Chemistry, Elsevier, Amsterdam, (1988); RTC = Recl. Trav. Chim. Pays-Bas; S = Synthesis; SC = Synthetic Communications; TL = Tetrahedron Lett.

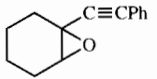
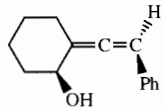
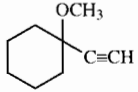
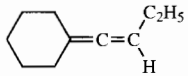
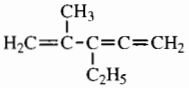
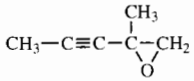
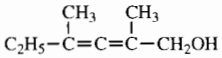
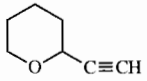
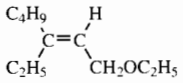
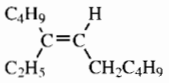
Table 5. (Continued)

Organometallic intermediate	Substrate	Reaction conditions	Remarks	Literature[a]
$H_2C{=}CHCH_2MgBr$	 OTMB = mesitoate	Et_2O, $-60 \rightarrow 0°C$ 25 % CuCN	–	JOC (1986) 2884
		THF, 0°C, 5 min		TL (1982) 3115
$Ph\text{-}(CH_2)_2MgCl$	$HOOC(CH_2)_2Br$	THF, –20°C	–	TL (1976) 4697
$H_2C{=}CH\text{–}MgBr$		THF, $-30 \rightarrow 0°C + 2$ h	Fair yield of E +Z 	CL (1981) 1307
$CH_3CH{=}CHMgBr$	 OTMB = mesitoate	THF/ Et_2O, 0°C, 3 % CuCN	–	JOC (1986) 2884
	 OTMB = mesitoate	Et_2O, 0°C, 3 % CuCN	–	JOC (1986) 2884
		THF, 0-20°C, 16 h	–	JOC (1983) 1912

$HC{\equiv}CMgBr$	$HC{\equiv}CCH_2OTs$	THF, 0 → 15°C	~5 % $HC{\equiv}CCH{=}C{=}CH_2$	PrAcCh, p. 227
$HC{\equiv}CMgBr$	$CH_3C{\equiv}CCH_2OTs$	THF, 0 → 15°C	–	PrAcCh, p. 227
n-$C_6H_{13}C{\equiv}CMgBr$	$H_2C{=}CHCH_2Br$	THF, 40 → 60°C	–	PrAcCh, p. 224
$PhC{\equiv}CMgBr$	$HC{\equiv}CCH_2Br$	THF, reflux 60-80 min	–	OS, C6 (1988) 925
$H_2C{=}C{=}CHMgBr$	$HC{\equiv}CCH_2Br$	Et_2O, ≤ 20°C	$(H_2C{=}C{=}CH{-})_2$ (solution in Et_2O)	OS (1981) 60, 41
$Me_3SiC{\equiv}CMgBr$	$HC{\equiv}CCH_2OTs$	THF, 0 → 15°C	5–7 % $Me_3SiC{\equiv}C{-}CH{=}C{=}CH_2$	AAC, p. 71
$EtOC{\equiv}CMgBr$	$CH_3C{\equiv}CCH_2OTs$	THF, 0 → 15°C	–	PrAcCh, p. 227
$ROCH_2C{\equiv}CMgBr$	$HC{\equiv}CCH_2Br$	THF, 40 → 60°C	–	PrAcCh, p. 225
PhMgBr	$Br(CH_2)_4Br$	THF, 40 → 50°C	–	SC (1990) 2349
PhMgBr		THF, –78°C, 1h	 *E/Z* mixture	CL (1981) 1307
	CH_2Br_2	THF-HMPT, reflux, 2 h	Product is 	OPP (1991) 617
	$Br(CH_2)_4Br$	THF, 40 → 50°C, 1 h	Excess $Br(CH_2)_4Br$	SC (1990) 2349

[a] Abbreviations: AAC = L. Brandsma, H.D. Verkruijsse, Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier, Amsterdam, (1981); AC = Angew. Chem.; AC.IntEd = Angew. Chem., Int. Ed.; AL = Author's laboratory; CA = Chem. Abstr.; CB = Chem. Ber.; CC = J. Chem. Soc., Chem. Comm.; CL = Chem. Lett.; JACS = J. Am. Chem. Soc.; JOC = J. Org. Chem.; OOP = Org. Prep. and Proc., Int.; OS = Organic Syntheses; OS, ..., C... = Organic Synthesis, Collective Volume; PrAcCh = L. Brandsma, Preparative Acetylenic Chemistry, Elsevier, Amsterdam, (1988); RTC = Recl. Trav. Chim. Pays-Bas; S = Synthesis; SC = Synthetic Communications; TL = Tetrahedron Lett.

Table 6. Copper(I) catalyzed substitutions with cyclic and non-cyclic ethers, and acetals

Organometallic intermediate	Substrate	Reaction conditions	Remarks	Literature[a]
$Me_2C{=}CHCH_2Li$ (a) ⇅ $H_2C{=}CH{-}CMe_2Li$ (b)		THF	Without CuX only reaction as (b); with CuX reaction as (a) as well as (b)	TL (1978) 4069
n-C_4H_9Li (LiBr)		Et_2O, (5 % CuBr + 2 Bu_3P)		TL (1989) 2391
C_2H_5MgBr	$PhCH{=}CH{-}CH_2OCH_3$	THF, –25°C	Only reduction to $PhCH{=}CHCH_3$ and $PhCH_2CH{=}CH_2$	TL (1978) 5049
C_2H_5MgBr		Et_2O, 0-20°C, 1 h		AAC, p. 163
C_2H_5MgBr		Et_2O, 0-20°C, 30 min		AAC, p. 165
C_2H_5MgBr		THF, 20 → 30°C, 15 min		RTC (1974) **46**
C_2H_5MgBr		Et_2O, –15°C, 30 min	$EtCH{=}C{=}CH(CH_2)_4OH$	AAC, p. 173
n-C_4H_9MgCl	$HC{\equiv}CCH_2OCH_3$	Et_2O, –5°C, 30 min	*n*-$C_4H_9CH{=}C{=}CH_2$	AAC, p. 157
n-C_4H_9MgCl		THF, 15-20°C, 3 h		TL (1975) 3837

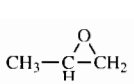
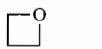
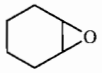
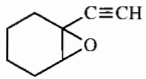
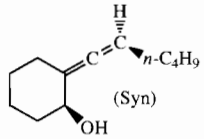
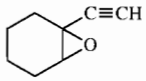
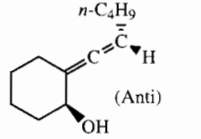
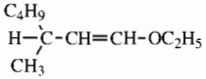
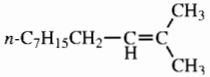
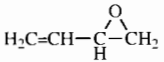
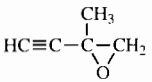
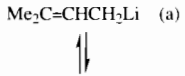
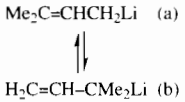
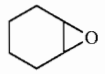
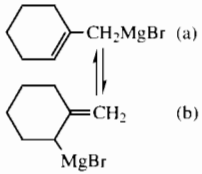
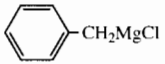
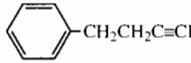
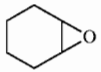
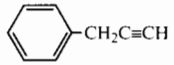
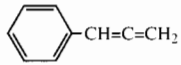
n-C_4H_9MgCl		THF, 0°C, 2 h	Without CuBr lower yield	TL (1979) 1503
n-C_4H_9MgCl		Et_2O, −30 → 20°C, 20 h	–	TL (1979) 1503
n-C_4H_9MgCl		THF, 0°C, 2 h	Without CuBr low yield	TL (1979) 1503
n-C_4H_9MgCl (analogous with other RMgX)		Et_2O/pentane, −50°C, CuBr (5 %), TMSCl		TL (1989) 2387
n-C_4H_9MgBr	n-$C_4H_9CH{=}C{=}CHOCH_3$	20-30°C, 40 min	$(n\text{-}C_4H_9)_2CHC{\equiv}CH$	AAC, p. 186
n-C_4H_9MgBr (analogous with t-BuMgBr and PhMgBr)		Et_2O, −50°C, CuBr (5 %), 2 eq Bu_3P		TL (1989) 2387
n-C_4H_9MgBr	$H_2C{=}CH{-}CH(OC_2H_5)_2$	Et_2O/THF, 0 → 25°C	n-$C_4H_9CH_2CH{=}CHOC_2H_5$ $Z + E$	AL; TL (1975) 3833
t-C_4H_9MgBr	$H_2C{=}CH{-}CH(OC_2H_5)_2$	Et_2O/THF, −40 → 15°C	t-$C_4H_9CH_2CH{=}CHOC_2H_5$ $Z + E$	AL; TL (1975) 3833
n-C_4H_9MgCl	$CH_3CH{=}CHCH(OC_2H_5)_2$	THF, −15 → 10°C CuX + 2 $P(OEt)_3$		TL (1975) 3837
t-C_4H_9MgBr	$HC{\equiv}CCH(OC_2H_5)_2$	THF, 0°C, 2 h	t-$C_4H_9CH{=}C{=}CHOC_2H_5$	AAC, p.167; RTC (1976) 66

Table 6. (Continued)

Organometallic intermediate	Substrate	Reaction conditions	Remarks	Literature
n-$C_7H_{15}MgCl$	$H_2C{=}CHC(CH_3)_2OCH_3$	THF 15-20°C, 6 h		TL (1975) 3837
c-C_5H_9MgBr	$HC{\equiv}CCH(OC_2H_5)_2$	Et_2O, 30°C	*c*-$C_5H_9CH{=}C{=}CHOC_2H_5$	RTC (1976) 66
c-$C_6H_{11}MgCl$	$H_2C{=}C{=}CHOCH_3$	Et_2O, 20°C, 20 min	*c*-$C_6H_{11}CH_2C{\equiv}CH$	RTC (1974) 183
c-$C_6H_{11}MgCl$	$HC{\equiv}CCH_2OCH_3$	Et_2O, −10 → 20°C, 30 min	*c*-$C_6H_{11}CH{=}C{=}CH_2$	AAC, p.159
$C_2H_5CH{=}CHCH_2CH_2MgBr$	$HC{\equiv}CCH(OC_2H5)_2$	Et_2O, −25°C	$RCH{=}C{=}CHOC_2H_5$ (R = $C_2H_5CH{=}CHCH_2CH_2$)	RTC (1976) 66
$H_2C{=}CHCH_2MgBr$		Et_2O, −30 → 20°C, 20 h	Fair yield	TL (1979) 1503
$H_2C{=}CHCH_2MgBr$		THF, −25°C, 1 h	$H_2C{=}CHCH_2CH_2CH{=}CH\text{-}CH_2OH$ mainly *E*	S (1978) 528
$H_2C{=}CHCH_2MgBr$		Et_2O, −20°C, 1 h	$H_2C{=}CHCH_2CH{=}C{=}C(CH_3)CH_2OH$	S (1978) 528
		THF, −30°C, 1.5 h	With 10 % CuBr, reaction as (a), yield 98 % Without CuBr, reaction as (b), yield 98 %;	TL (1978) 4069
		THF, −30°C, 1.5 h	With 10 % CuBr, reaction as (a); Without CuBr, reaction as (b)	TL (1978) 4069

		THF	With CuBr reaction as (a); Without CuBr, reaction as (b)	TL (1978) 4069
	$H_2C{=}C{=}CHOCH_3$	Et_2O, reflux, 30 min		RTC (1974) 183
PhMgCl		THF, 0°C, 2h	Without catalyst low yield	TL (1979) 1503
PhMgBr	$H_2C{=}C{=}CHOCH_3$	Et_2O, $0 \rightarrow 10°C$, 20 min		AAC, p.186
PhMgBr	$HC{\equiv}CCH_2OCH_3$	Et_2O, 0-5°C, 20 min		AAC, p.159
PhMgBr		THF, $-30 \rightarrow 20°C$, 20 h	Fair yield	TL (1979) 1503
PhMgBr	$H_2C{=}CHCH(OC_2H_5)_2$	Et_2O/THF	$PhCH_2CH{=}CHOC_2H_5$ $Z + E$	TL (1975) 3833
PhMgBr	$HC{\equiv}CCH(OC_2H_5)_2$	Et_2O, -3°C	$PhCH{=}C{=}CHOC_2H_5$	RTC (1976) 66

8 Nickel Catalyzed Iodo-Dechlorination and Iodo-Debromination of sp^2-Halides

8.1 Introduction

"Contrathermodynamic" conversion of allylic, propargylic and other reactive chlorides or bromides into the corresponding iodides is readily achieved by heating with an alkali iodide in a suitable organic solvent. These reactions, which take place in the absence of any catalyst, proceed to completion thanks to the slight solubility of the alkali chloride or bromide in the applied solvent.

Takagi et al. [1–3] (cf. [4]) found that under the influence of nickel catalysts olefinic and (hetero)aromatic bromides can be converted into the iodides:

$$RBr + KI \xrightarrow{\text{"Ni"}} RI + KBr\downarrow$$

This catalytic method complements the existing ones, such as the synthesis of Normant et al. (addition of $RCuMgBr_2$ to acetylenes, followed by reaction with iodine [5]), the reaction of aryldiazonium compounds with an alkali iodide [6], and metallation with a strongly basic reagent followed by addition of iodine [7].

In this chapter the catalytic method and its variants including one adapted for the conversion of olefinic *chlorides* into the iodides, are discussed and exemplified by experimental procedures.

References (Sect. 8.1)

1. Takagi K, Hayama N, Inokawa S (1978) Chem Lett 1435
2. Takagi K, Hayama N, Okamoto T (1978) Chem Lett 191
3. Takagi K, Hayama N, Inokawa S (1980) Bull Chem Soc Jpn 53, 3691
4. Tsou TT, Kochi JK (1980) J Org Chem 45, 1930
5. Normant JF, Alexakis A (1981) Synthesis 841
6. March J Advanced Organic Chemistry, John Wiley and Sons, New York, various editions
7. Brandsma L, Verkruijsse HD (1987) Preparative Polar Organometallic Chemistry, Vol. I, Springer-Verlag, Heidelberg

8.2 Scope and Limitations

The following procedures have been proposed for the conversion of olefinic and (hetero)aromatic chlorides and bromides into the corresponding iodine compounds.

(a) Heating a mixture of the chloride or bromide with a large (100 to 200 mol %) excess of potassium iodide at 150 °C in *N,N*-dimethylformamide in the presence of

catalytic amounts of nickel(II) bromide and tri(*n*-butyl)phosphane. Triphenylphosphane is much less suitable as a ligand.

$$RX + KI \xrightarrow[DMF,\ \sim 150\ ^\circ C]{NiBr_2 + Bu_3P} RI + KX\downarrow \qquad X = Cl, Br$$

(b) Heating the substrate at ~50 °C with KI in hexamethylphosphoric triamide in the presence of $NiBr_2$ and zinc powder.

(c) Heating the olefinic or aryl chloride with sodium iodide in dimethylformamide at ~150 °C in the presence of 2–5 mol % of bis(cyclooctadienyl)nickel $Ni(COD)_2$. This method has recently been published [1].

Although Method (a) has been exemplified by a few reactions only [2], it seems to be rather generally applicable [3]. In our laboratory it was found that 3-bromo-5,6-dihydropyran does not undergo the exchange reaction, while in 3,4-dibromothiophene only one bromine atom could be replaced by iodine [3].

A serious draw-back of Method (b) in its original form is the use of the cancer-suspect solvent HMPT. In solvents such as DMF the generation of Ni(0) does not proceed at a sufficiently high rate at temperatures in the region of 50 °C. In our laboratory the $NiBr_2$/Zn/DMF combination has been successfully applied to generate the active catalyst for the iodo-dechlorination of olefinic *chlorides* at reflux temperatures [1].

In Method (c) the oxygen-sensitive and not conveniently preparable [4] $Ni(COD)_2$ is used. Fortunately, in most cases successful substitutions with chlorides can be achieved by applying Method (b) (olefinic chloride with $NiBr_2$/Zn/DMF at 150 °C [3]). We have not extensively investigated the scopes of the three methods. An important reason was that in many cases the organic iodides are more easily accessible by other methods.

References (Sect. 8.2)

1. VAN HOOIJDONK MCJM, PETERS THA, VASILEVSKY SF, BRANDSMA L (1994) Synth Comm 24, 1261
2. TAKAGI K, HAYAMA N, OKAMOTO T (1978) Chem Lett 191
3. PETERS THA, VAN HOOIJDONK MCJM, WALDA B, VASILEVSKY SF, unpublished
4. KRYSAN DJ, MACKENZIE PB (1990) J Org Chem 55, 4229

8.3 Mechanistic Investigations

In their investigations of the mechanism of the nickel-catalyzed halogen exchange Tsou and Kochi obtained strong evidence for the occurrence of a Ni(I) species as the active catalyst. Ni(II) compounds can be reduced to Ni(0) in the presence of suitable ligands [1, 2].

$$NiBr_2 + 2\,Bu_3P \rightleftharpoons NiBr_2(PBu_3)_2$$

$$NiBr_2(PBu_3)_2 + 2\,KI \rightleftharpoons NiI_2(PBu_3)_2 + 2\,KBr$$

$$NiI_2(PBu_3)_2 \overset{150\,^\circ C}{\rightleftharpoons} Ni(0)(PBu_3)_2 + I_2$$

$$Ni(0)(PBu_3)_2 + RX \longrightarrow RNiX(PBu_3)_2 + NiX(PBu_3)_3 \text{ or}$$

$$NiX_2(PBu_3)_2 + Ni(PBu_3)_4 \longrightarrow 2\,NiX(PBu_3)_3$$

Instead of tributylphosphane the solvent can function as ligand.

Zerovalent nickel can also be generated from $NiBr_2$ and zinc powder or by heating $Ni(COD)_2$.

For the halogen exchange proceeding through Ni(I) species Tsou and Kochi propose the following two possibilities (a) and (b); in both cases the first step(1) is the reaction of the organic halide with the Ni(I) intermediate:

$$Ni^{I}XL_3 + RX' \rightleftharpoons RX'Ni^{I}XL_2 + L \quad (1)$$

$$RX'Ni^{I}XL_2 \rightleftharpoons \begin{array}{c} X' \\ R \diagdown\diagup NiL_2 \\ X \end{array} \rightleftharpoons RXNi^{I}X'L_2 \quad (a)$$

or

$$RX'Ni^{I}XL_2 \overset{\text{oxid. add.}}{\rightleftharpoons} \begin{array}{c} X' \\ | \\ R{-}Ni^{III}L_2 \\ | \\ X \end{array} \overset{\text{Red. elim.}}{\rightleftharpoons} RXNi^{I}X'L_2 \quad (b)$$

References (Sect. 8.3)

1. Tsou TT, Kochi JK (1980) J Org Chem 45, 1930
2. Tsou TT, Kochi JK (1979) J Am Chem Soc 101, 7547; (1979), 101, 6319

8.4 Side Reactions

The principal side reactions are homo-coupling of RX to RR, reductive dehalogenation with the formation of RH and the formation of phosphonium salts $RPBu_3I$ [(in the case of Method (a)].

Homo-coupling possibly proceeds by the following mechanism:

$$2\ RNiI(PBu_3)_2 \rightleftharpoons NiI_2(PBu_3)_2 + R_2Ni(PBu_3)_2$$

$$R_2Ni(PBu_3)_2 \longrightarrow Ni(PBu_3)_2 + RR$$

$$NiI_2(PBu_3)_2 \rightleftharpoons Ni(PBu_2)_2 + I_2$$

The observations of Tsou and Kochi [1] were in agreement with the following sequence:

$$Ni^{I}X + RX \longrightarrow RNi^{III}X_2$$

$$RNi^{III}X_2 + RNi^{II}X \longrightarrow Ni^{II}X_2 + R_2Ni^{III}X$$

$$R_2Ni^{III}X \longrightarrow RR + Ni^{I}X$$

Semmelhack et al. [2] proposed a sequence of oxidative addition to organonickel(II) halide and reductive elimination from the Ni(IV) complex:

$$RNi^{II}X + RX \rightleftharpoons R_2Ni^{IV}X_2 \longrightarrow RR + Ni^{II}X_2$$

Reductive dehalogenation might proceed through zero- and monovalent-nickel intermediates [3]:

$$Ni^{0}L_n + RX \xrightarrow{\text{solvent}} Ni^{I}XL_3 + R^{\bullet} \longrightarrow RH$$

$$Ni^{I}XL_3 + RX \xrightarrow{\text{solvent}} Ni^{II}X_2L_2 + R^{\bullet} \longrightarrow RH$$

Phosphonium salts are formed only in the presence of the Ni-catalyst. They might result from an oxidative addition of the substrate to Ni^0, followed by a reductive elimination [4] (for an alternative mechanism see [1])

$$Ni(PBu_3)_3 + RX \longrightarrow RNiX(PBu_3)_2 + PBu_3$$

$$RNiX(PBu_3)_2 + 2\ PBu_3 \longrightarrow R(PBu_3)^{+}\ X^{-} + Ni(PBu_3)_3$$

Applying Method (c) (Sect. 8.2) we found only traces of the homo-product RR. Reduction products were detected in the reaction of 1-bromocyclooctene and 2-bromothiophene with KI in the presence of $NiBr_2$ and Bu_3P. Phosphonium salts $RBu_3P^{+}\cdot I^{-}$ appeared as viscous residues after distillation or during the aqueous work up.

Formation of the Ullmann products RR may be a serious side reaction if the Ni(0) species is generated from nickel bromide and zinc powder [5]. Using *stochiometrical* amounts of zinc, in the presence of phosphane ligands and catalytic amounts of nickel bromide, RR may be obtained in good yield from organohalides [6–10].

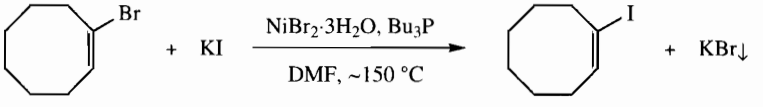
References (Sect. 8.4)

1. Tsou TT, Kochi JK (1979) J Am Chem Soc 101, 7547; (1979) 101, 6319
2. Semmelhack MF, Hellquist PM, Jones LD (1971) J Am Chem Soc 93, 5908; Semmelhack MF, Ryono LS (1975)J Am Chem Soc 97, 3873
3. Fahey DR, Mahan JE (1977) J Am Chem Soc 99, 2501
4. Cassar L, Foa M (1974) J Organometal Chem 74, 75
5. Takagi K, Hayama N, Okamoto T (1978) Chem Lett 191
6. Takagi K, Hayama N, Inokawa S (1979)Chem Lett 917
7. Takagi K, Hayama N (1983) Chem Lett637
8. Takagi K, Hayama N, Inokawa S (1980) Bull Chem Soc Jpn 53, 3691
9. Colon I, Kelsey DR (1986) J Org Chem 51, 2627
10. Tiecco M, Testaferri L, Tingoli M, Chianelli D, Montanucci M (1984) Synthesis 736

8.5 Experimental Procedures[1]

Note: All experiments were carried out under inert gas.

8.5.1 Conversion of 1-Bromocyclooctene into 1-Iodocyclooctene



Scale: 0.20 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a mechanical stirrer, a thermometer gas inlet combination and a short reflux condenser (a 30-cm Vigreux column may also be used).

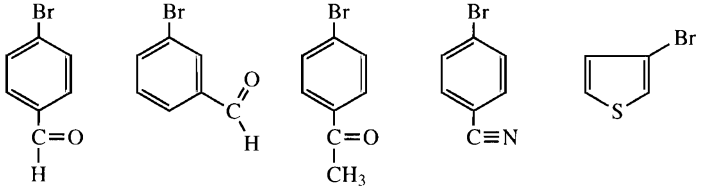
Procedure: The flask was charged with 80 g of finely powdered potassium iodide, 2 g of finely powdered nickel(II) bromide·$3H_2O$, 100 ml of *N,N*-dimethylformamide and 0.20 mol (38.0 g) of 1-bromocyclooctene. The system was evacuated and subsequently filled with inert gas. Stirring was started and 3.5 g of freshly distilled tributylphosphane was added. During heating the initial very dark green colour changed to dark brown. The potassium iodide gradually dissolved. After the temperature had risen to ~120 °C, a fine salt suspension became visible. The mixture was heated to between 150 and 155 °C (gentle reflux) and potassium bromide began to separate abundantly. After 20 to 30 min gas-liquid chromatography showed a conversion of >75%. (When, after another 1 h, the final ratio of ~90/10 of product and starting compound has not yet been reached, an additional small amount of ~1 g of tributylphosphane and ~0.5 g of $NiBr_2 \cdot 3H_2O$ has to be introduced). After the conversion had been completed

1 With the collaboration of Mr. T.H.A. Peters, Mr. M.C.J.M. van Hooijdonk and Mr. B. Walda

(~90/10 ratio), the mixture was cooled to below 50 °C and 200 ml of water was added. The mixture was extracted five times with diethyl ether (some viscous slurry, possibly a phosphonium salt, may appear). The combined organic solutions were washed twice with water, dried over anhydrous magnesium sulfate and subsequently concentrated in vacuo. Careful fractionation (the difference in b.p. of the starting compound and the product is ~20 °C only) through a 30 cm column gave 1-iodocyclooctene, b.p. 105 °C/15 mm Hg, in 70% yield. The purity was about 97%.

^{1}H-NMR spectrum ($CDCl_3$): 6.35 (J = 8.45 Hz, CH=) ppm.

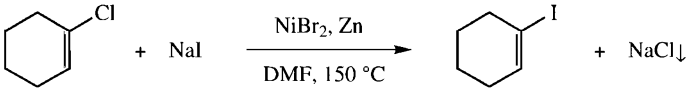
The following bromides were converted in a similar way into the iodides. Isolated yields (after distillation and crystalization from ether–pentane mixtures of pure (>97%) products were between 60 and 70%.



solid solid solid solid liquid

The catalyzed reactions of 3,4-dibromothiophene and 1,3-dibromobenzene with potassium iodide afforded the bromo–iodo compounds relatively smoothly. Exchange of the remaining bromine proceeded very sluggishly (in the case of 3,4-dibromothiophene, 3-iodothiophene was detected in the reaction mixture). 3-Bromo-5,6-dihydropyran did not give the iodo compound in this procedure, but remained unchanged. Free iodine was found in the reaction mixture.

8.5.2 1-Iodocyclohexene from 1-Chlorocyclohexene (Zn/$NiBr_2$)



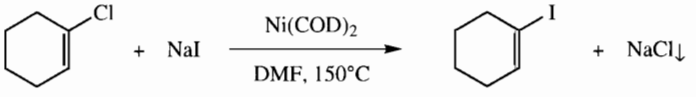
Scale: 0.10 molar.

Apparatus: 500-ml three-necked, round-bottomed flask equipped with a thermometer-gas inlet combination, a reflux condenser with a gas outlet and a magnetic stirring bar; the reaction was carried out under nitrogen.

Procedure: The flask was charged with 0.30 mol (45 g) of sodium iodide, 80 ml of *N,N*-dimethylformamide, 0.10 mol of 1-chlorocyclohexene, 0.5 g of nickel(II) bromide.$3H_2O$ and 0.5 g of zinc powder (Merck, analar grade). The apparatus was evacuated and subsequently filled with inert gas (this operation was repeated twice). Stirring was started and the mixture was heated to gentle reflux. After 3 to 5 hours gas chromatography indicated maximal conversion (ratio RI/RCl at least 9). The very dark grey mixture was

cooled to room temperature and then treated with 300 ml of water. The product was isolated by extraction with a 1 : 1 mixture of ether and pentane, washing the extracts with water, drying over anhydrous magnesium sulfate and careful distillation. 1-Iodocyclohexene, b.p. 70 °C/15 mm Hg, was obtained in 58% yield (purity ~97%). ^{1}H-NMR spectrum ($CDCl_3$): 6.3 (t, HC=) ppm.

8.5.3 1-Iodocyclohexene from 1-Chlorocyclohexene ($Ni(COD)_2$)



Scale: 0.10 molar.

Apparatus: Same as in Sect. 8.5.2; the reaction was carried out under nitrogen.

Procedure: The flask was charged with the solvent and reagents (same amounts as in exp. 8.5.2) and successively evacuated, and filled with inert gas. Cyclooctadienylnickel (0.5 g, see D.J. Krysan, P.B. Mackenzie, J. Org. Chem. (1990) 55, 4229.) was introduced and the stirred mixture was heated at 150 °C. When, after ~3 h (see Note), GLC indicated maximal conversion, the mixture was cooled, water was added and the product was isolated as described in the preceding experiment. 1-Iodocyclohexene was isolated in ~60% yield (purity 97%).

In a similar way *C_6H_5CH=CHI* (>90% *E*), *n-$C_8H_{17}CH$=CHI*, *$C_3H_7C\equiv CCH$=CHI* (>90% *E*) were isolated in modest (~60%) yields with reasonable (≥96%) purities.

3-Iodo-5,6-dihydropyran was obtained in ~80% yield from the corresponding bromo compound.

3-Iodoquinoline was obtained from 3-bromoquinoline in 56% yield after crystallization from a 1 : 2 (v/v) mixture of hexane and methanol. The extraction was carried out with dichloromethane.

Note: If the conversion stops at an early stage, an additional small amount of $Ni(COD)_2$ should be added.

8.6 Conclusions from our Investigations

1. The exchange reactions afford equilibrium mixtures of the starting halide and the corresponding iodide with ratios between ~15 : 85 and ~10 : 90. The yields of pure iodides, obtained by fractional distillation or crystallization therefore are seldom higher than 70%.
2. The excess of potassium iodide can be reduced to 100 mol % without affecting the rate of the reaction and the equilibrium ratios.

3. Most reactions with the $KI/Bu_3P/NiBr_2$ system can be completed within 3 hours, provided that additional small amounts of Bu_3P are added during the reaction to compensate for losses due to formation of phosphonium salts. Olefinic halides react faster than do aryl halides.
4. There are no dramatic differences in ratio between the various substituted aryl halides.
5. Very small amounts of water do not affect the results, but they rather seem to accelerate the reactions. Therefore, $NiBr_2 \cdot 3H_2O$ can be used instead of the anhydrous salt.
6. Reduction of the volume of the solvent does not lead to a significant improvement of the equilibrium ratio RI/RBr or RCl.
7. Hexamethylphosphoric triamide (HMPT) used by Takagi et al. (Bull. Chem. Soc. Jpn. (1980) 53, 3691) in the $NiBr_2/Zn$ method can be replaced by *N,N*-dimethylformamide, though the reduction to Ni(0) proceeds somewhat less easily in the latter solvent.
8. Iodo-dehalogenations of olefinic halides proceed with retention of the configuration of the double bond.
9. The rates of conversion were much lower when triphenylphosphane was used as a ligand instead of tri(*n*-butyl)phosphane. Remarkably, considerably higher rates were found when using tri(*tert*-butyl)phospane. Unfortunately, the preparation of this compound is laborious.

9 Nickel- and Palladium-Catalyzed Cyanation of sp^2-Halides and sp^2-Triflates

9.1 Introduction

One of the most commonly used laboratory methods for the preparation of sp^2-nitriles is the Rosenmund–von Braun reaction [1]. The procedure involves heating of an aryl or hetaryl bromide or iodide with copper(I) cyanide at elevated temperatures, using high-boiling solvents such as DMF. 1-Bromo-1-alkynes (RC≡C–Br) react under milder conditions to give alkynenitriles [2].

$$RX + CuCN \longrightarrow RC{\equiv}N + CuX$$

Apparently the reaction does not proceed to completion with a combination of alkali cyanide and *catalytic* amounts of copper(I) cyanide.

At the beginning of the 1970s Italian chemists [3] published an efficient method for the cyano-dehalogenation of aryl halides using catalytic amounts of nickel-triarylphosphane complexes. Japanese investigators [4] found palladium(II) salts to be catalytically active in cyanations. Based on these preliminary reports, several papers dealing with variants and extensions have appeared during the last two decades.

$$RX + MCN \xrightarrow{\text{Ni- or Pd-catalyst}} RC{\equiv}N + MX \quad (M = \text{mostly Na or K})$$

References (Sect. 9.1)

1. Review, also dealing with catalyzed cyanations: Ellis GP, Romney-Alexander TM (1987) Chem Revs 87, 779
2. Brandsma L (1988) Preparative Acetylenic Chemistry, 2nd ed, Elsevier, Amsterdam, p 229
3. Cassar L J (1973) Organometal Chem 54, C57; Cassar L, Ferrara S, Foá M (1974) Adv Chem Ser 132, Homogeneous Catalysis, p 252
4. Takagi K, Okamoto T, Sakakibara Y, Oka S (1973) Chem Lett 471

9.2 Scope and Limitations

A large number of cyanations with aryl, hetaryl and olefinic halides and triflates are summarized in Table 7. Many of them have been performed on a small scale, yields being determined by GLC. The published data indicate that cyanation of a wide variety of sp^2-halides and -triflates is, in principle, possible.

Most of the publications deal with cyanations in the aryl series. Although the reactivity order I ~ OTf > Br > Cl is observed, substitutions of chlorine generally proceed

satisfactorily under the influence of nickel catalysts [4, 5]. Compounds containing nitro groups are unsuitable substrates for nickel-catalyzed cyanations, since the catalyst is destroyed by the NO_2 group [5]. Nickel-catalyzed cyanation of *para*-bromoaniline gives reduced yields due to the formation of a phosphonium salt [5].

$$H_2NC_6H_4Br + P(C_6H_5)_3 + NaC{\equiv}N \xrightarrow{Ni(PC_6H_5)_3} H_2NC_6H_4P(C_6H_5)_3C{\equiv}N + NaBr$$

Also with *para*-bromodimethylaniline a moderate result has been reported [6]. 1,2-Dichlorobenzene and 1-chloro-2-fluorobenzene react extremely slowly in the presence of $Ni(PPh_3)_4$, but successful mono- and disubstitution with the dichloride in the presence of a nickel-bis(diphenylphosphino)ferrocene catalyst has been reported [6]. Bromomesitylene shows little reactivity [5]. For the cyanation of substrates containing thioether groups nickel catalysts seem unsuitable due to strong Ni–S complexation.

3-Bromofuran, 2- and 3-bromothiophene, and 3-bromopyridine have been successfully converted into the corresponding nitriles under the action of nickel catalysts. Also in the cyano-dehalogenations of a number of olefinic chlorides and bromides nickel catalysts have been shown to be effective.

Using palladium catalysts, selective substitution of iodine or bromine in chloroiodo- or bromochlorobenzenes by C≡N, difficultly realizable with nickel-catalysts, have been reported [1–3]. Because NO_2 and SR groups do not interact with Pd, cyanations of aryl halides containing such substituents seem to be feasible with the aid of Pd-catalysts [2, 7].

References (Sect. 9.2)

1. Chatani N, Hanafusa T (1986) J Org Chem 51, 4714
2. Takagi K, Okamoto T, Sakakibara Y, Ohno A, Hayama N (1975) Bull Chem Soc Japan 48, 3298
3. Takagi K, Sasaki K, Sakakibara Y (1991) Bull Chem Soc Japan 64, 1118
4. Takagi K, Sakakibara Y (1989) Chem Lett 1957
5. Cassar L, Ferrara S, Foá M (1974) Adv Chem Ser 132, 252
6. Sakakibara Y, Okuda F, Shimobayashi A, Kirino K, Sakai M, Uchino N, Takagi K (1988) Bull Chem Soc Japan 61, 1985
7. Procházka M, Siroky M (1983) Coll Czech Chem Comm 48, 1765

Table 7. Nickel- or palladium-catalyzed cyanation of sp^2-halides and -triflates (R–X → R–C≡N). For each entry the following data are given: catalyst; cyanation reagent; solvent; yield (G = GLC; I = isolated); literature reference number. The list of references is given at the end of the table

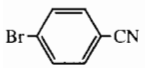
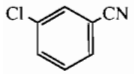
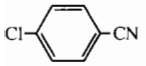
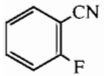
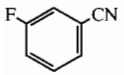
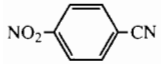
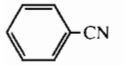
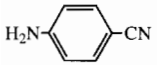
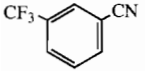
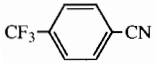
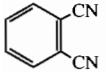
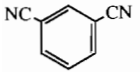
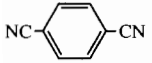
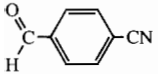
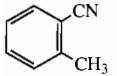
R–CN	X = I	X = Br	X = Cl	X = OTf
	$Pd(PPh_3)_4$; Me_3SiCN; Et_3N; 58 % (I) (13 % dicyanation) [1]			
	$Pd(OAc)_2$, NaOEt; KCN; HMPT; 70 % (G) (21 % dicyanation) [2]			
	$Pd_2(dba)_3 \cdot CHCl_3$, dppf; KCN; NMP; 93 % (I) [3]			$NiBr_2(PPh_3)_2$, PPh_3, Zn; KCN; NMP; 60 % (G) (31 % dicyanation) [4]. $Pd_2(dba)_3 \cdot CHCl_3$, dppf; KCN; NMP; 94 % (G) [3,4]
			$Ni(PPh_3)_3$; NaCN, DMF, H_2O; 5 % (G) [5]	
			$NiCl_2 \cdot (PPh_3)_2 \cdot PPh_3$, Mn/Fe; NaCN; EtOH; 84 % (G) [5]. $NiBr_2(PPh_3)_2$, PPh_3, Zn; KCN; HMPT; 99 % (G) [6]	
	$Pd(OAc)_2$, NaOEt; KCN; HMPT; 70 % (G) [2]		$NiCl_2 \cdot (PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH; 0 % (G) [5]	$Pd_2(dba)_3 \cdot CHCl_3$, dppf; KCN; NMP; 90 % (I) [3]
	$NiCl_2 \cdot (PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH;75 % (G) [5]. $Pd_2(dba)_3 \cdot CHCl_3$, dppf; KCN; NMP; 97 % (G) [7]. $Pd(PPh_3)_4$; $NaCN/Al_2O_3$; toluene; 98 % (G) [8]	$NiCl(C10H7) \cdot (PPh_3)_2$; NaCN; EtOH; 97 % (G) [5]. $Pd(PPh_3)_4$; $NaCN/Al_2O_3$; toluene; 99 % (G) [8]	$NiCl_2 \cdot (PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH; 95 % (G) [5]. Several Ni-catalysts/solvent-systems in [6]	$NiBr_2 \cdot (PPh_3)_2$, PPh_3, Zn; KCN; NMP; 98 % (G) [4]. $Pd_2(dba)_3 \cdot CHCl_3$, dppf; KCN; NMP; 94 % (G) [3,4]

Table 7. (Continued)

R–CN	X = I	X = Br	X = Cl	X = OTf
			$NiCl(C_{10}H_7)\cdot(PPh_3)_2$; NaCN; EtOH; 30 % (G) [5]	
			Ni-cat.; 80 % (I) [9c]	
			Ni-cat.; 81 % (I) [9c]	
			From Cl-C_6H_4CN: $NiBr_2$, dppf, Zn; KCN; HMPT; 82 % (G) [6]	
			From $C_6H_4Cl_2$: $NiCl_2\cdot(PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH; 86 % (G) [5]	
	From $C_6H_4I_2$: $Pd(PPh_3)_4$; Me_3SiCN; Et_3N; 53 % (I) [1]		From C_6H_4ClCN: $NiBr_2\cdot(PPh_3)_2$, PPh_3, Zn; KCN; CH_3CN; 95 % (G) [6]. From $C_6H_4Cl_2$: $NiCl_2\cdot(PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH; 91 % (G) [5]	From NC-C_6H_4OTf: $Pd_2(dba)_3\cdot CHCl_3$, dppf; KCN; NMP; 95 % (I) [3]
			Ni-cat.; 80 % (I) [9c]	
	$Pd(PPh_3)_4$; Me_3SiCN, Et_3N; 76 % (I) [1] $Pd_2(dba)_3\cdot CHCl_3$, dppf; KCN; NMP; 87 % (I) [3]	$Ni(PPh_3)_3$; NaCN; DMF, H_2O; 90 % (G) [5]	$NiBr_2\cdot(PPh_3)_2$, PPh_3, Zn; KCN; HMPT; 86 % (G) [6]	$NiBr_2\cdot(PPh_3)_2$, PPh_3; Zn; KCN; CH_3CN; 92 % (G) [4]

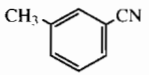
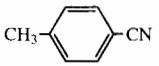
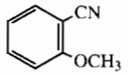
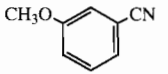
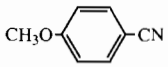
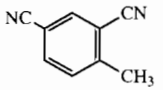
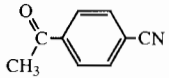
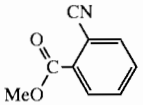
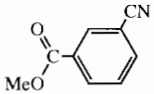
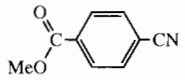
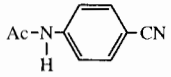
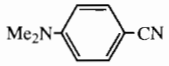
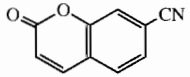
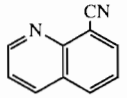
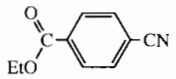
	$Pd(PPh_3)_4$; NaCN/Al_2O_3; toluene; 95 % (G) [8]	$NiCl_2 \cdot (PPh_3)_2$, PPh_3 Mn/Fe; NaCN; EtOH; 84 % (G) [5]	$NiBr_2 \cdot (PPh_3)_2$, PPh_3, Zn; KCN; HMPT; 95 % (G) [6]	
	$Pd(OAc)_2$, NaOEt; KCN; HMPT; 93 % (I) [2]. $Pd_2(dba)_3 \cdot CHCl_3$, dppf; KCN; NMP; 94 % (I) [3]		$Ni(PPh_3)_3$, PPh_3, dicyclohexyl-18-crown-6; KCN; C_6H_6; 77 % (I) [11]	$Pd_2(dba)_3 \cdot CHCl_3$, dppf; KCN; NMP; 87 % (I) [3]. $NiBr_2 \cdot (PPh_3)_2$, PPh_3, Zn; KCN; CH_3CN 85 % (I) [4]
		$Ni(PPh_3)_3$; NaCN; DMF, H_2O; 90 % (G) [5]	$NiBr_2 \cdot (PPh_3)_2$, PPh_3, Zn; KCN; HMPT; 96 % (G) [6]	
			$NiBr_2 \cdot (PPh_3)_2$, PPh_3, Zn; KCN; HMPT; 97 % (G) [6]	
	$Pd_2(dba)_3 \cdot CHCl_3$; dppf, KCN; NMP; 92 % (I) [3]	$NiCl(C_{10}H_7) \cdot (PPh_3)_2$; NaCN; EtOH; 97 % (G) [5]	$NiBr_2 \cdot (PPh_3)_2$, PPh_3, Zn; KCN; HMPT; 92 % (G) [6]	$Pd_2(dba)_3 \cdot CHCl_3$,dppf; KCN; NMP; 45 % (G) [3]. 89 %; (I) [4]
			From 2,4-dichlorotoluene: $NiCl(C_{10}H_7) \cdot (PPh_3)_2$, PPh_3, aliquat 336; NaCN; C_6H_6, H_2O; 37 % (G) and 40 % (G) from 4-Cl-1-CN-toluene [11]	
	$Pd_2(dba)_3 \cdot CHCl_3$, dppf; KCN; NMP; 94 % (I) [3]		$NiBr_2 \cdot (PPh_3)_2$, PPh_3, Zn; KCN; CH_3CN; 92 % (G) [6]. $NiCl(C_{10}H_7) \cdot (PPh_3)_2$, PPh_3, aliquat 336; NaCN; C_6H_6, H_2O; 96 % (G) [11]	$NiBr_2 \cdot (PPh_3)_2$,PPh_3, Zn; KCN; CH_3CN; 89 % (I) [4]. $Pd_2(dba)_3 \cdot CHCl_3$,dppf; KCN; NMP; 92 % (I) [3]

Table 7. (Continued)

R–CN	X = I	X = Br	X = Cl	X = OTf
	$Pd_2(dba)_3{\cdot}CHCl_3$, dppf; KCN; NMP; 93 % (I) [3]			
	$Pd_2(dba)_3{\cdot}CHCl_3$, dppf; KCN; NMP; 96 % (I) [3]			
	$Pd(PPh_3)_4$; Me_3SiCN; Et_3N; 68 % (I) [1]		$NiBr_2{\cdot}(PPh_3)_2$, PPh_3 Zn; KCN; CH_3CN; 96 % (G) [6]	$Pd_2(dba)_3{\cdot}CHCl_3$, dppf; KCN; NMP; 94 % (I) [3]
				$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; CH_3CN; 70 % (G) [12]. $Pd_2(dba)_3{\cdot}CHCl_3$, dppf; KCN; NMP; 35 % (G) [3]
		$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; HMPT; 48 % (G) [6]		
				$Pd_2(dba)_3{\cdot}CHCl_3$, dppf; KCN; NMP; 98 % (I) [3]
				$Pd_2(dba)_3{\cdot}CHCl_3$, dppf; KCN; NMP; 95 % (I) [3]
				$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; CH3CN; 76 % (I) [12]

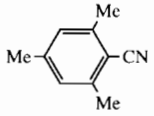
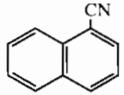
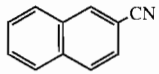
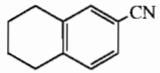
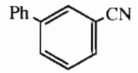
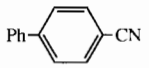
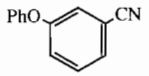
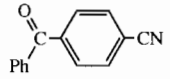
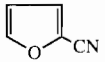
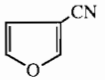
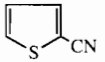
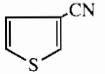
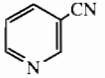
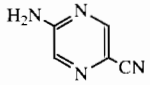
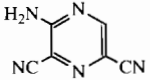
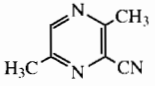
	$NiCl_2{\cdot}(PPh_3)_2$, PPh_3, Mn/Fe, NaCN; EtOH; 5 % (G) [5]		$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; CH_3CN; 32 % (I) [12]
	$Pd(PPh_3)_4 + Al_2O_3$; NaCN; toluene; 90 % (G) [8]	$NiCl_2{\cdot}(PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH; 90 % (G) [5]	$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; CH_3CN; 69 % (I) [12]
		$NiCl_2{\cdot}(PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH; 91 % (G) [5]	$Pd_2(dba)_3{\cdot}CHCl_3$, dppf; KCN; NMP; 91 % (I) [3]
			$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; CH_3CN; 86 % (I) [12]
		$NiCl_2{\cdot}(PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH; 85 % (G) [5]	
		$NiCl(C_{10}H_7){\cdot}(PPh_3)_2$; NaCN; EtOH; 94 % (G) [5]	$Pd_2(dba)_3{\cdot}CHCl_3$, dppf; KCN, NMP; 92 % (I) [3]
		$NiCl(C_{10}H_7){\cdot}(PPh_3)_2$; NaCN; EtOH; 98 % (G) [5]	
		$NiCl_2{\cdot}(PPh_3)_2$, PPh_3, Mn/Fe; NaCN; EtOH; 83 % (G) [5]	

Table 7. (Continued)

R–CN	X = I	X = Br	X = Cl	X = OTf
		$NiCl(C_{10}H_7)\cdot(PPh_3)_2$, PPh_3; KCN; C_3H_7OH (!); 95 % (G) (with EtOH the main product is 2-furyl-C(OEt)=NH) [13]		
		$NiBr_2\cdot(PPh_3)_2$, PPh_3, Zn; KCN; HMPT; 80 % (I) [17]		
		$NiCl(C_{10}H_7)\cdot(PPh_3)_2$, PPh_3; KCN; EtOH; 70 % (I) [14]		
		$NiCl(C_{10}H_7)\cdot(PPh_3)_2$, PPh_3; NaCN; EtOH; 79 % (I) [14]		
		$NiBr_2\cdot(PPh_3)_2$, PPh_3, Zn; KCN; MeCN; 57 % (G) [6]. $NiBr_2\cdot(PPh_3)_2$, PPh_3, Zn; NaCN; acetone; 90 % (G) [17]		
		$Pd(PPh_3)_4$, 18-crown-6; KCN, CuCN; DMF; 88 % (I) [15]		
		From dibromo compound: $Pd(PPh_3)_4$, 18-crown-6; KCN, CuCN; DMF; 50 % (I) [15]		
			$Pd(PPh_3)_4$; KCN; DMF; 80 % (I) [16]	

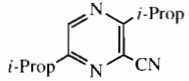
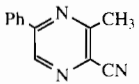
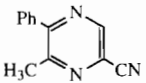
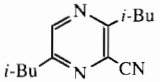
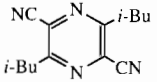
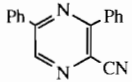
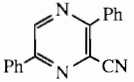
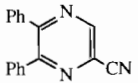
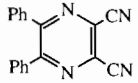
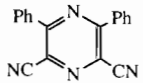
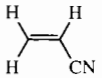
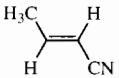
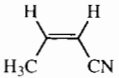
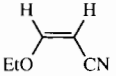
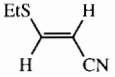
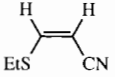
	$Pd(PPh_3)_4$; KCN; DMF; 47 % (I) [16]
	$Pd(PPh_3)_4$; KCN; DMF; 58 % (I) [16]
	$Pd(PPh_3)_4$; KCN; DMF; 66 % (I) [16]
	$Pd(PPh_3)_4$; KCN; DMF; 77 % (I) [16]
	From dichloro compound: $Pd(PPh_3)_4$; KCN; DMF; 76 % (I) [16]
	$Pd(PPh_3)_4$; KCN; DMF; 98 % (I) [16]
	$Pd(PPh_3)_4$; KCN; DMF; 31 % (I) [16]
	$Pd(PPh_3)_4$; KCN; DMF; 81 % (I) [16]

Table 7. (Continued)

R–CN	X = I	X = Br	X = Cl	X = OTf
			From dichloro compound: $Pd(PPh_3)_4$; KCN; DMF; 16 % (I) [16]	
			From dichloro compound: $Pd(PPh_3)_4$; KCN; DMF; 68 % (I) [16]	
		$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 20 % (G) [19]		
		$Pd(PPh_3)_4$, 18-crown-6; C_6H_6; 89 % (G) [10]		
		$Pd(PPh_3)_4$, 18-crown-6; C_6H_6; 92 % (G) [10]		
		$Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 0 % (G) [10]		
		$Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 15 % (G) [10]		
		$Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 0 % (G) [10]		

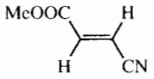
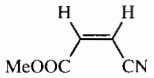
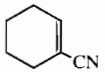
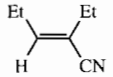
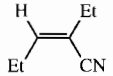
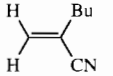
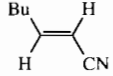
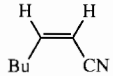
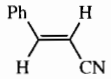
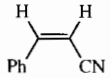
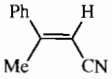
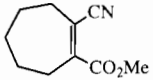
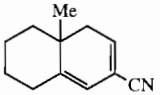
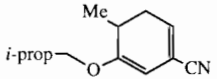
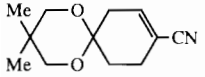
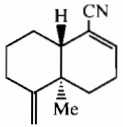
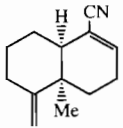
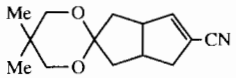
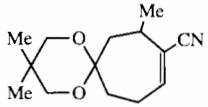
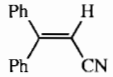
	$Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; (only polymerization) [10]	
	$Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; (only polymerization) [10]	
		$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 91 % (G) [19]
		$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 20 % (G) [19]
	$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 27 % (G) [19]	
	$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 90 % (G) [19]	
	$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 69 % (G) [19]. $Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 96 % (G) [18]	$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 50 % (G) [19]
	$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 83 % (G); [19]. $Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 98 % (G) [18]	

Table 7. (Continued)

R–CN	X = I	X = Br	X = Cl	X = OTf
		$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 96 % (G); [19]. $Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 94 % (I) [18]	$Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 84 % (G) [18]	
		$NiBr_2{\cdot}(PPh_3)_2$, PPh_3, Zn; KCN; DMF; 73 % (G); [19]. $Pd(PPh_3)_4$, 18-crown-6; KCN, C_6H_6, 94 % (I) [18]		
		$Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 93 % (I) [18]		
				$Pd(PPh_3)_4$, 12-crown-4; LiCN; C_6H_6; 59 % (I) [20]
				$Pd(PPh_3)_4$, 12-crown-4; LiCN; C_6H_6; 78 % (I) [20]
				$Pd(PPh_3)_4$, 12-crown-4; LiCN; C_6H_6; 85 % (I) [20]
				$Pd(PPh_3)_4$, 12-crown-4; LiCN; C_6H_6; 78 % (I) [20]

	$Pd(PPh_3)_4$, 12-crown-4; LiCN; C_6H_6; 87 % (I) [20]
	$Pd(PPh_3)_4$, 12-crown-4; LiCN; C_6H_6; 82 % (I) [20]
	$Pd(PPh_3)_4$, 12-crown-4; LiCN; C_6H_6; 76 % (I) [20]
	$Pd(PPh_3)_4$, 12-crown-4; LiCN; C_6H_6; 78 % (I) [20]
	$Pd(PPh_3)_4$, 18-crown-6; KCN; C_6H_6; 98 % (I) [18]

References of Table 7

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9.3 Mechanism of the Nickel Catalyzed Cyanation

The nickel- and the palladium-catalyzed cyanations are believed to proceed according to similar mechanisms. The mechanism of the nickel-catalyzed cyanation has been studied in some detail and is represented in Fig. 1 for $Ni(PPh_3)_4$ as catalyst and chlorobenzene as substrate. The proposed mechanism is the same for other aryl halides and triflates as well as for vinyl halides and triflates.

In solution, an equilibrium between $Ni(PPh_3)_4$ and $Ni(PPh_3)_3$ exists. In benzene this equilibrium is completely shifted to the side of $Ni(PPh_3)_3$, as has been proven by spectroscopic studies [1, 2]. Since further dissociation of a second PPh_3 moiety to form $Ni(PPh_3)_2$ could not be detected, $Ni(PPh_3)_3$ (complex *I*) is regarded as the actual catalyst. Recently, the crystal structure of $Ni(PPh_3)_3$ has been reported [3], showing a trigonal planar coordination sphere of nickel with all values of the P–Ni–P angles being 120°. The average value of the Ni–P bond distances of 2.147(6) Å is somewhat shorter than that in comparable nickel complexes, probably due to the less steric hindrance of the triphenylphospine groups as well as to coordinative unsaturation of the nickel centre.

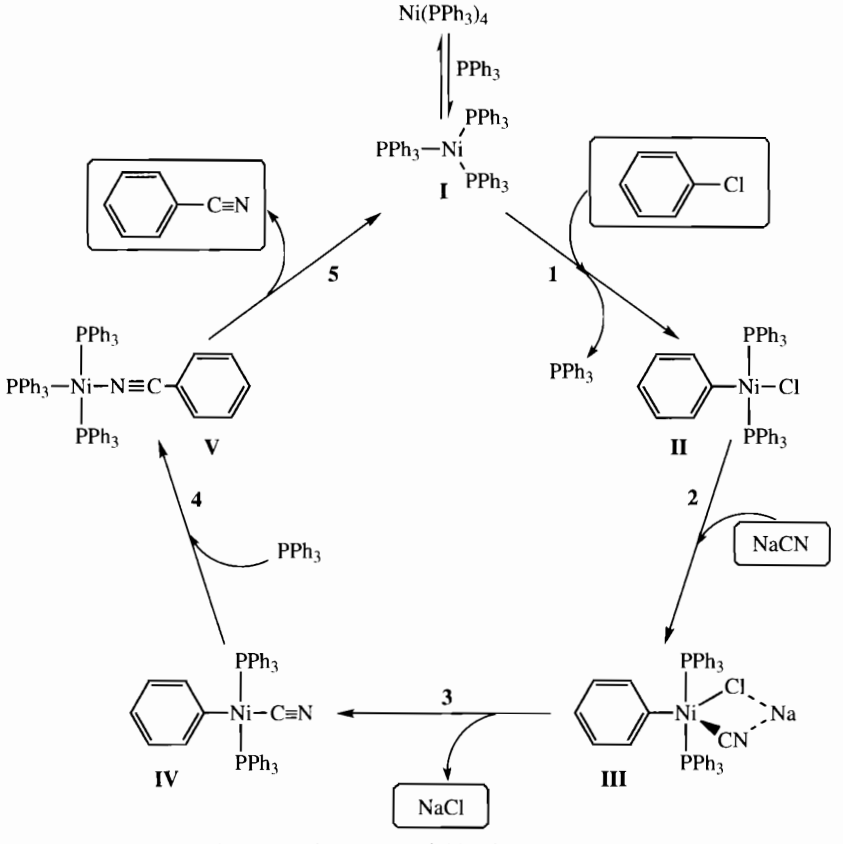

Fig. 1. Mechanism of $Ni(PPh_3)_4$-catalyzed cyanation of chlorobenzene

The first step in the catalytic cycle is the *oxidative addition* of chlorobenzene to the zero-valent $Ni(PPh_3)_3$ and the simultaneous dissociation of one PPh_3 group (step 1) to form the divalent oxidative addition complex *II*, in which nickel has been inserted into the carbon-chlorine bond to form a stable σ-bond between nickel and the phenyl group. This oxidative addition step is generally accepted since complex *II* can be isolated, and moreover, this isolated species has been shown to catalyze the cyanation reaction according to the proposed catalytic cycle (see Sect. 9.2, Ref.5). Kinetic studies have revealed that (excess) PPh_3 retards oxidative addition, and that electron-withdrawing substituents on the substrate accelerate it. Electron-releasing substituents show hardly any effect [4] (see also Sect. 9.2, Ref. 5). Various other oxidative addition complexes have been prepared by the action of zerovalent nickel phosphane complexes on aryl or vinyl halides [5–10]. These oxidative addition complexes are thought to be diamagnetic [11], having *trans* square planar geometry [11, 12] (see also Sect. 9.2, [5]). This geometry has been confirmed by crystal structures of arylnickel-bromide complexes with $P(Me)Ph_2$ [13, 14] and vinylnickeliodide complexes with PMe_3 [15], PEt_3 [16], and PPh_3 [17]. The thermodynamic stability of these complexes is often explained by the existence of a positive divalent nickel centre (both the aryl and the halogen bear a negative charge) and by the π-back donation of electron density from the phosphane ligands towards the nickel centre. However, Hidai et al. [11] proved with X-ray photoelectron spectroscopy (XPS) that the charge on nickel in these complexes is clearly less than 2^+. Moreover, both Tolman and Hidai [1, 5] found that the assumed effect of π-back donation is almost negligible, so that the reason for the stability remains a subject of discussion. Oxidative addition complexes of nickel with triphenylphopsphane are fairly air-stable in the solid state [5, 8]. They tend to decompose forming biaryls [18–21] (or bivinyls [9]) and nickel(I) or nickel(II) salts, when dissolved in the absence of nucleophiles under a nitrogen atmosphere, especially at elevated temperatures. When treated with proton acids, the nickel–carbon bond is broken with the quantitative formation of ArH [4] (or vinyl–H [9, 31]).

Complex *III*, which is formed by the addition of NaCN (step 2), is assumed to be a transition state and has not been isolated. It might be considered as an ion pair of the negatively charged nickel complex and the positively charged sodium ion. Its proposed existence was demonstrated by IR spectroscopy during cyanation (Sect. 9.2, [5]) and is in agreement with the general finding that substitution reactions of d^8 square planar complexes proceed via a five-coordinated trigonal bipyramidal intermediate [22, 23].

Complex *IV* is formed by elimination of NaCl (step 3). Athough the use of this complex has been reported in another context [24], it could not be isolated from the catalytic cycle but its existence has been demonstrated by IR spectroscopy during the cyanation reaction (Sect. 9.2, [5]). However, by using 1,2-dichlorobenzene as substrate *or* nickel trialkylphosphane complexes instead of $Ni(PPh_3)_4$, it is possible to isolate analogues of complex *IV* from the catalytic cycle, though there was no formation of aryl cyanides in these cases. In a similar way both aryl [25–29] and vinyl [30, 31] trialkylphosphane analogues of complex *IV* have been isolated from the stochiometric reaction between the corresponding oxidative addition complex and an alkalimetal cyanide. Finally, both vinyl and aryl analogues of complex *IV* have been prepared by the oxidative addition of benzonitrile to zero-valent trialkylphosphane complexes [32–35].

The action of PPh_3 results in the formation of the zero-valent complex V (step 4) by the reductive elimination of benzonitrile from divalent complex *IV* (see Sect. 9.2, Ref. 5). This reaction is thought to proceed via a five-coordinated trigonal bipyramidal transition state [35]. A mechanistic study on the *reductive elimination* of the trialkylphosphane analogue of complex *IV* revealed that the formation of benzonitrile was only observed in the presence of free ligand, even at elevated temperatures [35]. Therefore, it can be concluded that the cyanation reaction only proceeds when more than two extra equivalents of PPh_3 (with respect to nickel) are used and that (excess) PPh_3 accelerates the *reductive elimination.* Complex V has been prepared by an alternative method by the addition of benzonitrile to tris(triphenylphosphane)nickel(0). Its crystal structure has been determined [36] showing a distorted tetrahedral coordination sphere of nickel with an average value of the P–Ni–P and N–Ni–P angles being 115.8° and 104.6° respectively. The average value of the Ni–P bond distances of 2.190(5) Å is normal for this kind of complex. The same is true for the Ni–N bond distance of 1.889(11) Å (benzonitrile is N-coordinated to nickel).

In the last step benzonitrile is liberated and the starting complex *I* is re-formed (Step 5).

References (Sect. 9.3)

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9.4 Methods of Performing Nickel-Catalyzed Cyanations

In accordance with the proposed mechanism of cyano-dehalogenations (see Sect. 9.3) a zero-valent nickel compound such as $Ni(PPh_3)_3$ may be used as a catalyst. Cassar et al. [1] found this complex as well as $Ni(p\text{-tolyl})_3$ and $Ni[Ph_2P(CH_2)_4]PPh_2]_2$ to be effective catalysts, whereas with the complexes of Ni and tricyclohexylphosphane, tri-*n*-butylphosphane and cyclooctadiene poor results were obtained.

Since working with the extremely air-sensitive Ni^0-complexes is very troublesome, these are preferably generated in situ by reaction of a Ni(II) compound with a reducing metal in the presence of a suitable ligand. This bivalent-nickel compound may be the nickel(II)-halide-phosphane complex or even a combination of (free) nickel(II) bromide and the phosphane [5] e.g.:

$$\underset{(Cl_2)}{NiBr_2(PPh_3)_2} + 2\,Ph_3P \xrightarrow[\text{organic solvent}]{Zn} Ni^0(PPh_3)_{3\text{ or }4}$$

The use of the air-stable aryl-$Ni^{II}Cl(PPh_3)_2$ (or corresponding bromides) as catalysts for cyanations in ethanol [1] is particularly convenient. The intermediary Ni^0-compound is formed by a sequence of nucleophilic substitution and reductive elimination:

$$ArylNi^{II}Cl(PPh_3)_2 \xrightarrow{^-CN} ArylNi^{II}(CN)(PPh_3)_2 \longrightarrow Ni(PPh_3)_2 + Aryl\text{–}CN$$

It is essential to keep the concentration of dissolved cyanide low since the Ni^0-intermediate as well as the pre-catalyst with bivalent nickel can be inactivated ("poisoned") by excess cyanide. An atmosphere of inert gas should be maintained, since the intermediary Ni^0-compounds are oxygen-sensitive.

All of the procedures summarized below are carried out at temperatures within the range 40–80 °C. Complete conversions of most sp^2-halides can be effected within a few hours, provided that a sufficient amount of catalyst is used.

Based on the present, relatively scarce, knowledge it is not possible to predict whether or not a procedure will give a satisfactory result in the cyanation of a given halide. Procedure 1 below has proved to be successful with many substrates.

1. Addition of trans-chloro(aryl)bis(triphenylphosphane)nickel (or corresponding bromine compound) to a heated mixture of sp^2-halide, absolute ethanol, an additional amount of triphenylphosphane and alkali cyanide [1]. If the catalyst is added at room temperature, appreciably more of it is needed, especially in the case of sodium cyanide. It seems that a considerable part of the catalyst is spoilt at a relatively low temperature in some deactivation reaction. Methanol is totally unsuitable as a solvent for cyanations with sodium cyanide [2] since the much higher solubility of this salt leads to poisoning of the catalyst or of a Ni^0-intermediate. Also the presence of water is detrimental: in 96% ethanol the cyanation of bromobenzene with sodium cyanide did not take place [2]. Addition of an excess [that is more than necessary for formation of $Ni(PPh_3)_3$ or $Ni(PPh_3)_4$] of triphenylphosphane results in a faster cyanation [1].

By adding the catalyst last, at a higher temperature, one may roughly determine the minimal amount needed for a given cyanation. In the procedure proposed by Cassar et al. [1], the alkali cyanide is added as the last component to a heated solution of the substrate and the catalyst. If the solubility of the alkali cyanide is sufficiently low, e.g. in ethanol, all the cyanide can be added in one portion. Using methanol, in which sodium cyanide dissolves much better, a satisfactory yield of the nitrile can be obtained only if the alkali cyanide is slowly added as a concentrated aqueous solution.

The *trans*-halogeno(aryl)bis(triphenylphospane)nickel complexes are readily available by a modified procedure [3] (see Chapter I).

2. Generation in absolute ethanol of $Ni(PPh_3)_3$ or $Ni(PPh_3)_4$ from $NiCl_2{\cdot}(PPh_3)_2$ or $NiBr_2{\cdot}(PPh_3)_2$ and zinc powder (or an Mn-Fe alloy [1]) in the presence of an additional amount of triphenylphosphane, followed by the addition of the sp^2-halide and (at elevated temperatures) sodium or potassium cyanide. Using amounts of 1 to 5 mol % of nickel(II) halide-triphenylphospane complexes, chloro-, bromo- and iodobenzene, *m*-bromotoluene, *m*-chlorofluorobenzene, *m*-chlorobiphenyl, *m*- and *p*-dichlorobenzene, *p*-chlorobenzonitrile, 1- and 2-chloronaphthalene and *p*-chlorobenzophenone have been converted into the corresponding nitriles with excellent yields [1].

3. Controlled addition of acetone cyanohydrine and triethylamine to a mixture of the sp^2-halide, aryl–$NiCl(PPh_3)_2$, additional triphenylphosphane and acetone [1]. This procedure, carried out under mild conditions (30 °C), has been reported to give excellent results with bromobenzene and 1-chloronaphthalene. With pyridine, instead of triethylamine, we observed no reaction, possibly due to strong complexation of pyridine to the nickel ion (we found that pyridine also inhibits cyanations according to procedure 1). Our results with 2-bromothiophene and 4-bromoanisole were disappointing: soon after starting the addition of triethylamine and the cyanohydrine, the reaction mixtures became almost colourless and practically no conversion was found.

4. Using a phase-transfer catalyst such as tricaprylammonium chloride, cyanations of some aryl halides have been carried out in the system water-aryl halide. As cyanation catalyst, *trans*-chloro-(1-naphthylnickel)bis(triphenylphosphane) was used [4]. This method requires careful control of the rate of addition of an aqueous solution of alkali cyanide over a period of several hours.

5. Generation of the Ni^0-intermediate from nickel(II) halide-phosphane complexes, additional phophane and zinc powder or from anhydrous nickel(II) bromide, additional phosphane and zinc powder in solvents with very low solubility for NaCN and KCN [5, 6]. The most conveniently performable variant is the procedure in which Ni-catalyst and all of the necessary reagents are mixed at room temperature and the mixture is subsequently heated. Possibly, the zinc(II) halide formed in the reduction serves as a phase-transfer catalyst by forming a complex with the alkali cyanide which dissolves better, and which reacts with the sp^2-halide under the influence of the Ni-catalyst. Using THF and acetonitrile as solvents, the catalyst-ligand combinations 2 Ph_3P + $NiCl_2(Ph_3P)_2$, 2Ph_3P + $NiBr_2(Ph_3P)_2$, dppf + dppf·$NiCl_2$, dppf + dppf·$NiBr_2$ in amounts varying from 1 to 3 mol % and zinc as the reducing metal, we obtained unsatisfactory results with the model substrates chlorobenzene and bromobenzene. In these cases the reaction stopped at an early stage, possibly due to "poisoning" of the catalyst. Remarkable exeptions were the cyanations of *p*-chlorobenzotrifluoride, *p*-chloroacetophenone, methyl-*p*-chlorobenzoate and 2-chlorothiophene, which proceeded to almost 100% completion in the same systems of solvent, catalyst and reducing metal.

Hexamethylphosphoric triamide was not investigated because its suspected carcinogeneous properties make it less attractive as a solvent.

References (Sect. 9.4)

1. Cassar L, Ferrara S, Foá M (1974) Adv in Chem Ser 132, 252; Cassar L (1973) J Organometal Chem 54, C57
2. Brandsma L, van Soolingen J, unpublished observations
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9.5 Relative Reactivities of sp^2-Halides

Cassar et al. (see Ref. 1 of Sect. 9.4) derived relative rates of cyanations of substituted aryl halides from competition experiments. As catalyst 1-naphthylNiCl$(PPh_3)_2$ was used. Their results suggested that in most cases there are only small differences with the cyanation of chlorobenzene and bromobenzene. CN- and $COCH_3$-groups in the *para*-position, however, considerably facilitated the substitution of Cl or Br by CN (relative rates ranging from 3.7×10^2 to 5.2×10^3)

9.6 Side Reactions

As mentioned before, the nickel catalysts are inactivated by too high concentrations of cyanide. Since this reaction has not been studied, nothing is known about the nature

of this "poisoning". Possibly, catalytically inactive complexes such as $Ni(CN)(PPh_3)_3^-$ and $Ni(CN)_2(PPh_3)_2^{2-}$ are formed [1].

Also reductive dehalogenation and homo-coupling results in the loss of catalyst [2]:

$$RHal + Ni(PPh_3)_3 + H^+ \longrightarrow RH + 3\,Ph_3P + Ni^+ + Hal^-$$

$$2\,RHal + Ni(PPh_3)_3 \longrightarrow R\text{–}R + NiHal_2 + 3\,Ph_3P$$

The homo-coupling was found to be favoured at higher temperatures.

Formation of quarternary phosphonium salts occurs if electron-releasing substituents are present in the aryl halide. An outstanding example is the reaction of *p*-aminochlorobenzene with sodium cyanide, which gives appreciable amounts of the quaternary salt [2]:

$$ArX + PPh_3 \xrightarrow{Ni(PPh_3)_3} ArPPh_3X$$

References (Sect. 9.6)

1. Sakakibara Y, Okuda F, Shimobayashi A, Kirino K, Sakai M, Uchino N, Takagi K (1988) Bull Chem Soc Japan 61, 1985
2. Cassar L, Ferrara L, Foá M (1974) Adv in Chem Ser 132, 252

9.7 Catalysis by Palladium Compounds

Japanese chemists [1] reported in 1975 the Pd(II)-catalyzed cyanation of a number of aryl halides:

$$ArX + KCN \xrightarrow{Pd(II)} ArC{\equiv}N + KX$$

The substitution is facilated by small amounts of co-catalysts, such as KOH, K_2CO_3 and $NaOC_2H_5$. Whereas in the nickel-catalyzed cyanodehalogenation no strong differences in reactivity between aryl iodides and the corresponding chlorides and bromides are observed, the differences in the Pd-catalyzed reactions are more pronounced. This situation allows selective substitution of Cl in chloroiodobenzene. *p*-NO_2-C_6H_4I could be converted into the nitrile in a satisfactory yield; with a Ni-catalyst this substitution is not possible.

Although hexamethylphosphoric triamide (HMPT) is an outstanding solvent for this Pd-catalyzed cyanation, DMF and *N*-methylpyrrolidinone also gave satisfactory results at somewhat higher temperatures. Using HMPT as a solvent and ~1 mol % of Pd(II)acetate, the cyanations of aryl iodides could be completed within a few hours at temperatures in the region of 100 °C.

More recently [2] the same group of chemists proposed the use of the system tris-(dibenzylideneacetone)dipalladium(0)–chloroform (1 : 1) – 1,1'-bis(diphenylphosphino)ferrocene for cyanations of iodides and triflates. The reactions were carried out in *N*-methylpyrrolidinone (NMP) at temperatures as low as 60 °C with a very economic use of the catalyst (0.5 mol %). The potential of this method may be illustrated by the converversion of *p*-iodochlorobenzene into *p*-chlorobenzonitrile, which proceeded in

NMP within two hours at 60 °C with an excellent yield and selectivity. Using nickel-catalysts such a result is not attainable.

Trimethylsilyl cyanide $Me_3SiC{\equiv}N$ has been successfully used [3] as a reagent for the $Pd(PPh_3)_4$-catalyzed cyanation of aryl iodides. The reactions are advantageously carried out in triethylamine, which strongly complexes with the side product of the reaction, Me_3SiI, and thus prevents its subsequent reaction with OR and COOR groups. The differences in reactivities between Cl, Br and I permitted the substitution of iodine in 4-chloroiodobenzene and 4-bromoiodobenzene with reasonable selectivities.

Using neutral alumina either as a support for sodium cyanide or as a cocatalyst, some aryl bromides and iodides have been converted into the corresponding nitriles [4]. The reactions were carried out in toluene at temperatures in the region of 80 °C. Unfortunately, relatively large amounts of $Pd(PPh_3)_4$ (10 mol %) seem to be required.

2-Cyanopyrazines have been prepared in good yields by heating chloro derivatives with potassium cyanide in DMF at reflux temperature in the presence of $Pd(PPh_3)_4$ [5].

Using $Pd(PPh_3)_4$ (3 mol %) as a catalyst and 18-crown-6- as a phase-transfer reagent, a number of vinylic bromides have been converted into nitriles [6]. The reactions were carried out with excess alkali cyanide in refluxing benzene. The reaction of a number of structurally more complicated enol triflates with lithium cyanide in benzene at room temperature and $Pd(PPh_3)_4$ and 12-crown-4 as catalysts has been reported to provide nitriles in high yields [7].

References (Sect. 9.7)

1. Takagi K, Okamoto T, Sakakibara Y, Ohno A, Oka S, Hayama N (1975) Bull Chem Soc, Japan 48, 3298
2. Takagi K, Sasaki K, Sakakibara Y (1991) Bull Chem Soc, Japan 64, 1118
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9.8 Experimental Part

Notes:

(a) *All reactions were carried out under nitrogen.*

(b) The alkali cyanides used for the cyanations had a purity of >97% and were used as such.

9.8.1 General Procedure for the Nickel Catalyzed Cyanation of sp^2-Halides in Absolute Ethanol

(Cf. Cassar et al., Adv. in Org. Chem. Ser. (1974) 132, Homogeneous Catalysis II, p. 252)

Introduction: In this procedure the formation of sp^2-nitriles from the corresponding bromides (and some chlorides) and alkali cyanide under the influence of a Ni^0-catalyst is described. This catalyst is formed during the reaction from the stable Ni^{II}-pre-catalyst $ArNiCl(PPh_3)_2$ that has been added to the mixture of reactants. Although Cassar et al. in their procedure add the alkali cyanide at higher temperatures after generation of the Ni^0-catalyst, for reasons mentioned below we prefer to add the pre-catalyst latest. During the experimental investigations, which we did as a basis for this procedure, we noticed that the minimal amount (in mol %) of pre-catalyst needed for a sufficiently smooth cyanation depends upon the substrate. Whereas in the case of bromobenzene slightly more than 0.5 mol % may suffice, the cyanation of 2-bromothiophene and 3-bromopyridine started only after 5 to 7 mol % had been added. If the catalyst was added at temperatures below 60 °C, appreciably more was needed. This was also the case when large excesses (»20%, relative to substrate) of alkali cyanide were used, or when the amount of ethanol was large. During the addition (at 70 to 80 °C) of the pre-catalyst a brownish colour appeared, but usually the colour caused by the first additions soon faded. When approaching the "critical" amount of catalyst, the brown colour persisted longer, in some cases for 5 to 10 minutes. In order to maintain the brown colour, somewhat more had to be added. If nevertheless GC-monitoring and the decrease in intensity of the brown colour indicated unsatisfactory progress, more catalyst was added.

Since Cassar et al. had found that the cyanation proceeds faster if the amount of additional (free) triphenylphosphane is increased, in our experiments we always used more than two equivalents relative to $ArNi(Cl)(PPh_3)_2$. In the case of *p*-bromoanisole we observed that the reaction proceeded unsatisfactorily when using exactly two or less than two equivalents of PPh_3, but the cyanation of bromobenzene proceeded smoothly when the molar ratio of PPh_3 and 1-naphthylNiCl$(PPh_3)_2$ was only 2.

The dependence of the required amount of pre-catalyst on the nature of the substrate might be explained by assuming that the ratios of the rates of the poisoning reaction of the pre-catalyst or the Ni^0-intermediate with cyanide and the overall cyanation reaction (substitution of the halogen by CN^-, reductive elimination, oxidation) differ for the various sp^2-halides.

Since in our experience the cyanation of aryl halides can be carried out with less than 5 mol % of the pre-catalyst, one may apply a procedure in which the alkali cyanide is gradually added to a heated mixture of the aryl halide, a fixed, limited amount of pre-catalyst, additional triphenylphosphane and ethanol. In the hope of suppressing the toxic effect of the cyanide, and so to reduce the amount of catalyst, we have done experiments in which sodium cyanide was added in small portions over 0.5 to 1 hour to such a mixture containing a limited amount (2 to 3 mol %) of pre-catalyst. These attempts were applied to the cyanation of 2-bromothiophene, but they did not lead to reduction in the amount of catalyst. During the addition of alkali cyanide, the

colour of the reaction mixture gradually faded, and more catalyst had to be added in order to maintain satisfactory progress. Potassium cyanide is less soluble in ethanol, and therefore one may expect that the toxic effect caused by high concentrations of dissolved CN^-, will be suppressed. In the cyanation of 2-bromothiophene with potassium cyanide, indeed somewhat less of the catalyst was needed, but the reaction time was appreciably longer than when using sodium cyanide.

The reactions with *aryl* halides generally gave the nitriles in excellent yields, and were reproducible. As has been mentioned by Cassar et al., *o*-fluorochlorobenzene, *o*-dichlorobenzene and bromomesitylene could not be converted into the nitriles, while the reaction of *p*-chloronitrobenzene with NaCN gave intractable material. Selective substitution of bromine by CN in the bromochlorobenzenes could not be satisfactorily achieved.

Using ~3 mol % of 1-naphthylNiCl$(PPh_3)_2$, a smooth cyanation of 3-bromothiophene with excellent yields was achieved. Although very many experiments have been done with the 2-isomer, we cannot guarantee a satisfactory reproducibility for the general procedure. In a number of attempts, a smooth conversion (within 1 hour) with 70 to 80 % yields was attained using 5–6 mol % of 1-naphthylNiCl$(PPh_3)_2$. In other reactions the conversion proceeded incompletely: much insoluble material was precipitated during the aqueous work-up and yields were moderate. In some cases the reaction mixture suddenly turned green (from brown) before the reaction had finished.

Attempts to convert 2,5- and 3,4-dibromothiophene into cyano derivatives were unsuccessful.

The two isomeric bromofurans reacted smoothly with sodium cyanide in ethanol under the influence of 1-naphthylNiCl$(PPh_3)_2$. As in the cases of the thiophene analogues, the 2-bromo derivative required appreciably more (~7 mol %) of the catalyst than did the 3-isomer (~3 mol %). From both reactions a mixture of the desired nitrile and the adduct $RC(OC_2H_5)=NH$ (R = 2- or 3-furyl) was obtained.

The cyanations of 3-bromopyridine, 3-bromoquinoline, 1-bromo- and 1-chlorocyclohexene and 1-bromocyclooctene proceeded successfully, though much (5 to 8%) pre-catalyst was needed.

Scale: 0.10 molar

Apparatus: 250-ml round-bottomed, three-necked flask equipped with a reflux condenser, a thermometer and a powder funnel combined with a gas inlet. The reaction was carried out under inert gas with magnetic stirring.

Procedure: The flask was charged with 0.10 mol of the sp^2-halide, 30 ml (see Note 1) of absolute ethanol and 5 g of triphenylphosphane (see Note 1). After replacing the air in the flask completely with nitrogen, the stirred mixture was brought to ~75 °C. Powdered sodium cyanide (5.7 g, see Note 2) was quickly introduced, immediately followed by portions of ~0.5 g of 1-naphthylNiCl$(Ph_3P)_2$ or 1-phenylNiCl$(Ph_3P)_2$ (see Note 3). During these additions a gentle reflux was maintained. A next portion of pre-catalyst was introduced immediately after the brown or yellow-brown colour caused by the preceding addition had disappeared or after the intensity of the colour had

decreased considerably (see Note 4). Occasionally, introduction of an additional portion of pre-catalyst may be necessary in a later stage, if monitoring by GLC indicates that the reaction is not progressing well. When the conversion was complete (see Note 5), the reaction mixture was cooled to room temperature. Depending upon the volatility, or the solubility of the product in water a dry or an aqueous work-up may be carried out (see Note 6). In the first case, a sufficient amount of ether or a 1 : 1 mixture of ether and pentane (~120 ml) is added and air is bubbled through the stirred mixture for ~15 min (oxidation of the catalyst). The salt is filtered off on a sintered-glass funnel and rinsed well with ether. The filtrate is concentrated under reduced pressure and the remaining liquid distilled in vacuo (see Note 7). In the aqueous work-up, the reaction mixture is diluted with150 ml of an aqueous solution of 20 g of ammonium chloride, after which a sufficient number of extractions with ether or a mixture of ether and pentane are carried out (see Note 7). Yields of *aryl* cyanides were generally excellent. The following nitriles were prepared:

o- and *p*-tolunitrile from the bromides; *p*- and *m*-fluorobenzonitrile from the bromides; 1- and 2-naphthyl cyanide from the bromides; *o*-, *m*- and *p*-methoxybenzonitrile from the bromides; *p*-acetyl-benzonitrile from the bromide; *m*- and *p*-dicyanobenzene from the bromochlorobenzenes (0.05 molar scale).

The reactions of 3-bromothiophene, 3-bromopyridine and 3-bromoquinoline with sodium cyanide gave the nitriles in good (>70%) yields. From 2- and 3-bromofuran mixtures of comparable amounts of the nitriles and the adducts, furyl-C(OC_2H_5)=NH were obtained. The results with 2-bromothiophene were very variable.

The cyanodehalogenation of 1-bromocyclooctene proceeded with a reasonable (~70%)yield.

Notes:

1. Although in the case of 3-bromopyridine, 3-bromoquinoline, 2- and 3-bromofuran 45 ml of ethanol were used, smaller amounts also might give good results.
2. In the case of 2-bromothiophene we showed that considerably more of the pre-catalyst was needed if large excesses (e.g. 100 mol %) of sodium cyanide were used. It seems to us that generally a 10 to 20 mol % excess is sufficient.
3. For the preparation of relatively volatile nitriles (b.p. <100 °C/15 mm Hg) 1-naphthylNiCl(PPh_3)$_2$ (or the bromide) should be used. The small amount of 1-naphthyl cyanide formed during the reaction can be easily separated from the product by distillation. If less volatile nitriles are to be prepared $C_6H_5NiCl(Ph_3P)_2$ (or the bromide), should be used.
4. A directly visible indication for a proceeding reaction is a persisting, intensive brown or yellowish brown colour.
5. The colour of the reaction mixture at the end of the reaction may vary (dark brown, yellow, purple, green, etc.) depending upon the substrate, and is no good indication.
6. Aqueous work-up is recommended for products having a b.p. <60 °C/15 mm Hg; 3-cyanopyridine is soluble in water and therefore should be isolated via a dry work-up.
7. If the product is solid at room temperature, an air condenser should be used.

9.8.2 General Procedures for Cyanations Proceeding Under the Influence of a Ni^0-Catalyst Generated by Reducing a Ni^{II}-Precatalyst with Zinc Powder

(Cf. Sakakibara et al., Bull. Chem. Soc. Japan (1988) 61, 1985; Bull. Chem. Soc., Japan (1995) 68, 3137 and Cassar et al., Adv. in Chem. Series, Homogeneous Catalysis II (1974) 132, 252.)

Introduction: In the experimental procedure of Sect. 9.8.1 the actual Ni^0-catalyst is assumed to be formed by a sequence of nucleophilic substitution and reductive elimination:

$$ArNiCl(PPh_3)_2 \xrightarrow{\ominus CN} ArNi(CN)(PPh_3)_2 \xrightarrow{-ArCN} Ni(PPh_3)_2$$

By portionwise addition of the Ni^{II}-pre-catalyst to the mixture of substrate, additional triphenylphosphane, alkali cyanide and solvent one can roughly determine the amount of catalyst needed for maintaining the reaction with a particular sp^2-halide. A different approach is to generate the Ni^0 intermediate by reduction of a Ni^{II}-catalyst with a metal, in the presence of a protecting ligand:

$$NiBr_2 \cdot L_2 \xrightarrow{Zn} Ni^0L_2 \underset{}{\overset{2\,L}{\rightleftharpoons}} Ni^0L_4$$

Depending upon the solubility of the alkali cyanide in the solvent used, there are some variants of the reduction-cyanation procedure:

A. Performance of the reduction of $NiBr_2 \cdot L_2$ (or $NiCl_2 \cdot L_2$) in the presence of the alkali cyanide as well as the sp^2-halide. This variant is applicable if the solubility of the alkali cyanide in the solvent is low, so that the reaction of the Ni^{II}-halide or its reduction product with cyanide cannot seriously compete with the intended sequence of reduction to Ni^0, oxidative addition of the sp^2-halide, substitution of halogen by CN^- and reductive elimination. This procedure is, in principle, applicable for acetonitrile, tetrahydrofuran and hexamethylphosphoric triamide. In the cases of the activated substrates *p*-chlorobenzotrifluoride and *p*-chloroacetophenone this procedure worked excellently and almost complete conversion could be attained by us within a few hours using 1 mol % or less of the Ni^{II}-catalyst. When the same catalytic systems ($NiCl_2$·dppf + dppf + Zn; $NiCl_2(Ph_3P)_2$ + 2 Ph_3P + Zn were used for the cyanation of chlorobenzene, the reaction stopped after 40 to 75% conversion (with the same amount of catalysts). Peculiarly, with bromobenzene only 10 to 15% conversion was attained under similar conditions. Contrary to the general expectation of catalyst efficiency, the cyanation of *p*-chlorobenzotrifluoride in THF with the system $NiCl_2(Ph_3P)_2$ + 2 Ph_3P + Zn (or the $NiBr_2$-complex) gave the same or even better results than when using $NiCl_2$.dppf + dppf + Zn (less homo-coupling, faster conversion). In the cyanation of chlorobenzene, however, $NiCl_2$·dppf + dppf + Zn worked better than did $NiCl_2$·$(Ph_3P)_2$+2 Ph_3P+Zn. For the cyanation (in THF) of F_3C–C_6H_4–*p*-Cl the catalytic system $NiBr_2$·$(PPh_3)_2$ + 2 Ph_3P + Zn was shown to be very

efficient, but under similar conditions no conversion at all was observed in the case of 2-chlorothiophene.

B. Generation of the actual catalyst from the ligated Ni(II) halide and a reducing metal (preferably zinc powder) in the presence of an additional amount of ligand, followed by the addition of the substrate and (at higher temperatures) of the alkali cyanide. This order of additions has to be applied if solvents are used in which the alkali cyanide is appreciably better soluble than in the solvents of Variant A. In such solvents (ethanol, DMF) application of Variant A would lead to inactivation of the catalyst due to a too high concentration of dissolved cyanide. Using ethanol (100%) as a solvent, Cassar et al. (vide infra) reported good results for cyanations with a number of aryl bromides and chlorides. We applied this method to cyanate some olefinic halides in DMF and found $NiCl_2$.dppf more efficient than $NiCl_2(PPh_3)_2$.

An unsatisfactory aspect of Variants A and B is the use of a fixed amount of pre-catalyst for all cyanations, which may turn out to be not sufficient for certain substrates.

9.8.2.1 Cyanation of p-Chlorobenzotrifluoride

Scale: 0.25 molar for CF_3–C_6H_4–*p*-Cl
0.10 molar for CH_3CO–C_6H_4–*p*-Cl
0.05 molar for 1-bromocyclooctene.

Apparatus: 250-ml three-necked, round-bottomed flask equipped with a gas inlet, a thermometer and a gas outlet (for reactions in DMF and acetonitrile) or reflux condenser having a gas outlet on the top. In both cases the mixture was stirred magnetically and the reaction was carried out under nitrogen.

Procedure: The flask was charged with *p*-chlorobenzotrifluoride (0.25 mol, 45 g), sodium cyanide (15 g, 0.30 mol, excess), dry THF (40 ml), $NiBr_2 \cdot (PPh_3)_2$ (1.6 g, 0.8 mol %, note 1), triphenylphosphane (2.2 g) and zinc dust (2 g, Merck). After evacuation and flushing with nitrogen, the mixture was brought over 30 min to gentle reflux. After 10 to 15 min the colour of the mixture became yellowish brown. Within 4 h GLC-monitoring (note 2) indicated >95% conversion. The suspension was cooled to room temperature and 150 ml of diethyl ether was added. The salt was filtered off on sintered glass (G-2 filter) and the solid was washed well with ether. After concentration under reduced pressure, the product was distilled, using an air condenser. The nitrile, b.p. ~75 °C/15 mm Hg (m.p. 40 °C), was obtained in 85% yield (note 3).

Notes:

1. A more economic use of the pre-catalyst seems possible. The systems $NiCl_2(PPh_3)_2$ + 2 PPh_3 + Zn and $NiCl_2$dppf + dppf + Zn also gave good results.
2. It was noticed during this and other cyanations that the conversion during the first 30 to 60 minutes was very slow. We assume that first a sufficient amount of zinc halide has to produced, which serves to bring the cyanide into solution by forming a soluble complex with ^-CN.

3. Examples of similar experiments:
   p-Cl-C_6H_4*-*$COCH_3$ + 1 mol % $NiBr_2(PPh_3)_2$ + PPh_3 + Zn + Na/KCN in THF: complete con-version into the nitrile within 3 h.
   p-Cl-C_6H_4*-*$COCH_3$ + 3 mol % $NiBr_2(PPh_3)_2$ + PPh_3 + Zn + KCN in acetonitrile, 50 °C: after 2 h complete conversion into the nitrile.
   p-Cl-C_6H_4*-*OCH_3 + 1 mol % $NiBr_2$dppf + dppf + Zn + Na/KCN in THF: reaction stopped after 2 h at 35% conversion.
   2-Chlorothiophene (0.20 mol) + 1 mol % $NiCl_2$dppf + 1 mol % dppf + 1.1 g Zn + 12 g NaCN in THF: after 7 h ~95% conversion. After the dry work-up described above, *2-cyanothiophene*, b.p. 78 °C/15 mm Hg, was obtained in 87% yield.
   1-Chlorocycloheptene (0.10 mol), 1.0 g $NiCl_2$dppf + 1.0 g dppf + 1 g Zn powder + 7 g NaCN in THF: after 3 to 4 h complete conversion. After a dry work-up *1-cyanocycloheptene*, b.p. 88 °C/15 mm Hg, n^{20}_D 1.4865, was obtained in ~80% yield.

9.8.2.2 Cyanation of 1-Bromocyclooctene

(For the equipment see preceding exp.)

$NiCl_2$dppf (1.7 g, 5 mol %), dppf (1.4 g, 5 mol %) (see Note 1), zinc dust (0.50 g , Merck) and DMF (60 ml) were placed in the flask. After evacuation and flushing with nitrogen, the mixture was stirred, and heated at 50 °C. The initial green colour gradually changed to orange. After 1 h, 1-bromocyclooctene (9.3 g, 50 mmol) was added, followed by powdered sodium cyanide (2.7 g, 55 mmol) after a further period of 0.5 h. GLC-monitoring showed that the conversion was complete within 1 h (at 50 °C) (see Note 2). The reaction mixture was diluted with 300 ml of water, after which five extractions with a 1 : 1 mixture of ether and pentane were carried out. The combined organic solutions were washed three times with water and subsequently dried over magnesium sulfate. Distillation of the liquid remaining after concentration of the extract under reduced pressure gave the nitrile, b.p. 105 °C/15 mm Hg, in 70% yield (see Note 3).

^{1}H-NMR spectrum (CCl_4): 6.5 (t, 1H) ppm.

Notes:
1. With $NiCl_2 \cdot (PPh_3)_2$ the conversions proceeded more slowly.
2. Using KCN, ~3 h were needed for completion.
3. *n-*C_8H_{11}*CH=CHCl* and *1-chlorohexene* gave the nitriles in 60–70% yields after a reaction time of 20–24 h.

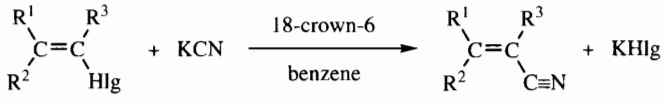
9.8.3 Palladium-Catalyzed Cyanation of Aryl Iodides

$$ArI + KC{\equiv}N \xrightarrow[NMP]{Pd^0 + dppf} ArC{\equiv}N + KI$$

General procedure: (From K. Takagi, K. Sasaki, Y. Sakakibara, Bull. Soc. Chem., Jpn. (1991) 64, 1118, unchecked.) To dry potassium cyanide (139 mg, 2 mmol), $Pd_2(dba)_3$ $CHCl_3$ (5.2 mg, 0.005 mmol), dppf (11.1 mg, 0,02 mmol), *p*-chloroiodobenzene (238 mg, 1 mmol) and 5 ml of *N*-methylpyrrolidinone were added. After flushing with nitrogen, the stirred mixture was heated for 2 h at 60 °C. Purification by chromatography on silicagel afforded *p*-chlorobenzonitrile in an excellent yield.

A number of other iodoarenes are reported to give the nitrile in high yields.

9.8.4 Palladium-Catalyzed Cyano-Debromination of Bromoolefins



Procedure: (From K. Yamamura, S. Murahashi, Tetrahedron Lett. (1977) 4429, unchecked.) A mixture of 10 mmol of *trans*-β-bromostyrene, 20 mmol of KCN, 0.3 mmol of $Pd(PPh_3)_4$, 0.76 mmol of 18-crown-6 and 10 ml of dry benzene was stirred at room temperature for 20 min and subsequently heated at 70–75 °C for 2 h. The product was isolated in 94% yield after aqueous work-up. Also the chloride gave the nitrile in a high yield after refluxing for 15 h. Some other bromoolefins were successfully converted into the nitriles. Generally, the reactions proceeded with retention of the configuration of the double bond.

10 Couplings of Acetylenes with sp^2-Halides

10.1 Introduction

In 1975 Japanese investigators [1] reported the coupling of acetylene and some derivatives with a number of sp^2-halides under the joint influence of palladium(II) chloride and copper(I) iodide. Somewhat earlier, in the same year, two other research groups [2, 3] had communicated similar couplings under different conditions, using only palladium catalysts. Such *sp* to sp^2-couplings were earlier only possible under forced conditions (Stephens-Castro couplings with copper acetylides [4, 5]). Couplings of free acetylenes with iodoheteroaromates in the presence of potassium carbonate and catalytic amounts of metallic copper or CuI have been reported by a research group in Novosibirsk [11]. The newly introduced method can be schematically represented as follows:

$$\text{R–Hlg} + \text{HC}{\equiv}\text{CR'} \xrightarrow{\text{Pd}^0 \text{ or } \text{Pd}^{II}\ (\text{Cu}^I)} \text{R–C}{\equiv}\text{CR'}$$

In this scheme, R may represent an aryl, hetaryl, (cyclo-)olefinic group or an allenic system. As to the nature of R' there are practically no limitations. In the case of acetylene itself, the product is a disubstituted acetylene RC≡CR. By far most of the couplings are performed under the joint catalytic action of a palladium complex and a copper(I) halide, while the solvent is usually an amine, which also serves to bind the hydrogen halide eliminated.

A useful variant is the reaction of metallic derivatives of acetylenes (R'C≡C–ZnCl [6] or R'C≡C–MgX [7]) with sp^2-halides (R–Hlg) (see Chapter 11):

$$\text{R–Hlg} + \text{M–C}{\equiv}\text{CR'} \xrightarrow{\text{Pd}^0 \text{ or } \text{Pd}^{II}} \text{R–C}{\equiv}\text{CR'} \qquad \text{M} = \text{ZnCl, MgX}$$

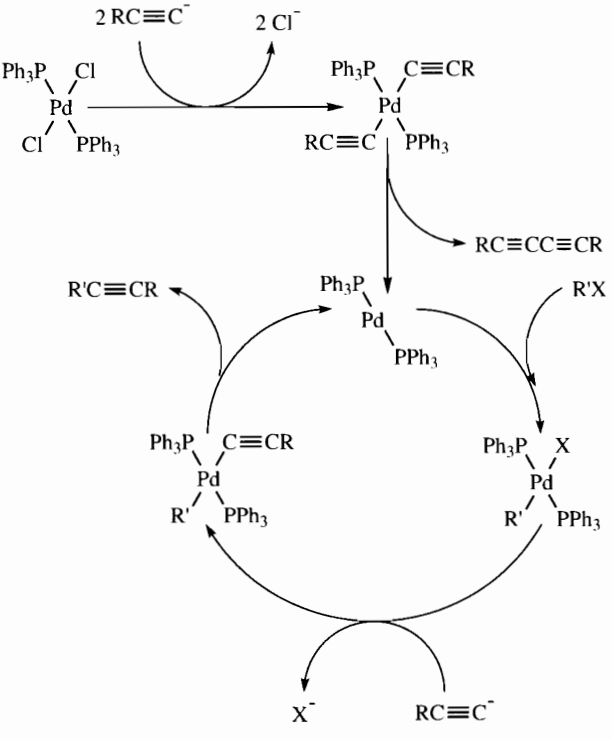
The preliminary communications on these catalytic methods were followed by a large number of papers. A number of selected procedures are described in a book by Heck [8] while reviews have been published by Kalinin [9] and Rossi et al. [10].

References (Sect. 10.1)

1. Sonogashira K, Tohda Y, Hagihara N (1975) Tetrahedron Lett 4467
2. Dieck HA, Heck RF (1975) J Organometal Chem 93, 259
3. Cassar L (1975) J Organometal Chem 93, 253
4. Stephens RD, Castro CE (1963) J Org Chem 28, 3313; Sladkov AM, Yu Ukhin L, Korshak VV (1963) Izv Akad Nauk, Ser Khim 2213; Bull Acad Sci USSR, Div Chem Sci (Engl Transl) (1963) 2043

5. Burdon J, Coe PL, March CR, Tatlow JC (1967) J Chem Soc, Chem Commun 1259
6. King AO, Negishi E, Villani FJ, Jr, Silveira A, Jr (1978) J Org Chem 43, 358
7. Dang HP, Linstrumelle G (1978) Tetrahedron Lett 191; Hopf H, Theurig M (1994) Angew Chem, Int Ed (engl) 33, 1099
8. Heck RF (1985) Palladium Reagents in Organic Synthesis, Acad Press, London
9. Kalinin VN (1992) Synthesis 413
10. Rossi R, Carpita A, Bellina F (1995) Org Prep and Proced Int 27, 127
11. Vasilevsky SF, Slabuka PA, Izyumov EG, Shvartsberg MS, Kotlyarevsky IL (1979) Izv Akad Nauk, Ser Khim 851; Bull Acad Sci USSR, Div. Chem Sci (Engl Transl) (1979) 795

10.2 Mechanistic Considerations



The most commonly used procedures for the catalytic cross-couplings involve reaction of the free acetylene with an olefinic or (het)aryl halide in the presence of a palladium compound (usually $Pd(PPh_3)_4$ or $PdCl_2{\cdot}2PPh_3$) and a copper halide (usually CuBr or CuI) using an aliphatic or cycloaliphatic amine as solvent. Sonogashira et al. [1] suggested the initial formation of bis(triphenylphosphane)dialkynylpalladium(II), which decomposes into bis(triphenylphosphane)palladium(0) and the "dimeric" acetylene (cf. also Dieck and Heck [2]). The coordinatively unsaturated Pd species and the olefinic or aryl halide form the oxidative addition product, which undergoes nucleophilic attack by

the acetylide anion. Reductive elimination subsequently affords the disubstituted acetylene and $Pd(PPh_3)_2$.

Cassar [3] proposed that in the case of using tetrakis(triphenylphosphane)palladium(0) the oxidative addition product is formed first, after which the pathway of nucleophilic substitution, reductive elimination, etc. is followed:

$$R'X + Pd(PPh_3)_4 \longrightarrow R'PdX{\cdot}2PPh_3 + 2\,PPh_3$$

Detailed mechanisms are not yet available. The global representation is supported by the following observations:

(a) Addition of a relatively large excess (more than two equivalents with respect to the amount of Pd-catalyst) of triphenylphosphane causes the reaction to slow down or to stop (suppressing the substitution of phosphane ligands by other organic groups) [4].
(b) In piperidine, pyrrolidine and diisopropylamine the reaction proceeds markedly faster than in more weakly basic amines such as diethylamine (less easy formation of acetylide in the latter solvent) [1,5].

While it has been noticed [1,5] that copper(I) halide considerably facilitates the couplings in amines, it is not known at what stage it intervenes in the reaction. A likely assumption is that a copper alkynylide is formed, which reacts with the oxidative adduct $(Ph_3P)_2Pd(X)R'$ to give $(Ph_3P)_2Pd(R')(C{\equiv}CR)$. In this respect, a comparison may be made with the Pd^0-catalyzed reactions of alkynylzinc chlorides with vinylic or (het)aryl halides [6].

References (Sect. 10.2)

1. Sonogashira K, Tohda Y, Hagihara N (1975) Tetrahedron Lett 4467
2. Dieck HA, Heck RF (1975) J Organometal Chem 93, 259
3. Cassar L (1975) J Organometal Chem 93, 253
4. Observation by the authors
5. Alami M, Ferri F, Linstrumelle G (1993) Tetrahedron Lett 6403
6. A.O. King, E. Negishi, F.J. Villani, Jr., A. Silveira, Jr., J. Org. Chem. (1978) 43, 358

10.3 Scope and Limitations

From the various papers dealing with Pd(Cu)-catalyzed cross-couplings of acetylenes with sp^2-halides (cf. the reviews [1]) it may be concluded that this reaction has a very broad scope. There are only a few limitations. 1,3-Diynes (and more unsaturated systems) are thermally unstable and prone to decomposition reactions. Therefore, good results can be expected only if their reaction partners are sp^2-iodides, or bromides such as vinyl bromide and 2-bromopyridine, compounds which are sufficiently reactive at temperatures in the range of 20 to 50 °C. The coupling reactions first seemed to be restricted to activated chlorides, such as 1,1- or 1,2-dichloroethene [2–4] and a compound with the system –C(Cl)=N– [5], but Alami and Linstrumelle [6] recently showed that even vinylic chlorides RCH=CHCl smoothly react at room temperature in the presence of copper(I)iodide and the weakly ligated palladium compounds

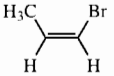
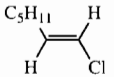
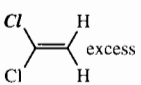
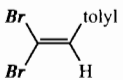
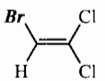
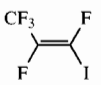
$PdCl_2 \cdot (CH_3C{\equiv}N)_2$ and $PdCl_2 \cdot (PhC{\equiv}N)_2$. In these couplings the relatively strongly basic piperidine was used as a solvent. Strikingly, the more commonly used complexes $Pd(PPh_3)_4$ and $PdCl_2 \cdot (PPh_3)_2$ were found to be much less efficient catalysts in couplings with olefinic chlorides; on the other hand, for cross-couplings with olefinic iodides $Pd(PPh_3)_4$ turned out to be the most efficient catalyst.

In Table 8 a number of procedures from literature illustrate the synthetic potential of the coupling methods.

References (Sect. 10.3)

1. Kalinin VN (1992) Synthesis 413; Rossi R, Carpita A, Bellina F (1995) Org Prep and Proced Int 27, 127
2. Ratovelomanana V, Linstrumelle G (1985) Tetrahedron Lett 315
3. Guillerm D, Linstrumelle G (1981) Tetrahedron Lett 315
4. Ratovelomanana V, Hammoud A, Linstrumelle G (1987) Tetrahedron Lett 1649
5. Austin WB, Bilow N, Kelleghan WJ, Lau KSY (1981) J Org Chem 46, 2280
6. Alami M, Linstrumelle G (1991) Tetrahedron Lett 6109

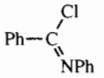
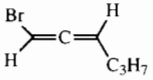
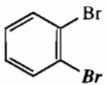
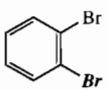
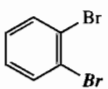
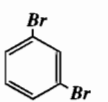
Table 8. Selected Pd/Cu catalyzed couplings between acetylenes and sp^2-halides[a]

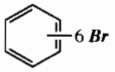
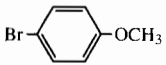
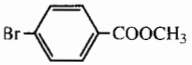
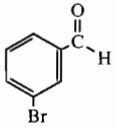
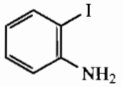
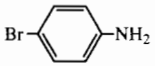
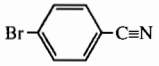
Acetylene **R**-C≡CH	sp^2-halide	Scale mmol	Solvent	Catalyst(s) in (mol %) or in mg	Reaction conditions	Literature[b]
$HOCH_2$		70	Et_2NH	$Pd(PPh_3)_4$, (1.3) CuI, (0.6)	25°C, 18 h yield moderate	T (1982) 631
C_5H_{11} excess		–	Piperidine	$PdCl_2{\cdot}(CH_3C{\equiv}N)_2$ (5) CuI (10)	20°C, 1 h	TL (1991) 6109
$HO(CH_2)_2$	*E*-ICH=CHC_5H_{11}	1	Pyrrolidine	$Pd(PPh_3)_4$, 58	20°C, 15 min	TL (1993) 6403
H	*E*-BrCH=CHPh	20	Et_2NH	$PdCl_2{\cdot}(PPh_3)_2$, (0.5) CuI, (1.0)	20°C, 6 h; only di-substituted acetylene	TL (1975) 4467
$HOCH_2$	*E*-BrCH=CHPh	40	Et_2NH	$PdCl_2{\cdot}(PPh_3)_2$, (0.13) CuI, (0.25)	20°C, 3h	TL (1975) 4467
$AcO(CH_2)_2$		50	$BuNH_2$ C_6H_6	$Pd(PPh_3)_4$, (5) CuI (5)	25°C, 6 h	TL (1987) 1649
Me_3Si		–	$CH_3C{\equiv}N$	$PdCl_2{\cdot}(PPh_3)_2$ (5)	100°C, 14 h	JACS (1990) 9330
Ar		42	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 123 PPh_3, 110 CuI, 57	reflux, 4 h	S (1990) 125
C_5H_{11}		20	Et_3N	$PdCl_2{\cdot}(PPh_2)_2$, 700 CuI, 190	20°C, 6 h	TL (1990) 1369

[a] Yield generally satisfactory. For the sake of clarity, halogens that are (selectively) substituted, are printed in bold italic.

[b] Abbreviations: CPB.Jpn = Chem. Pharm. Bull., (Jpn); JACS = J. Am. Chem. Soc; JOC = J. Org. Chem.; S = Synthesis; SC = Synthetic Communications; T = Tetrahedron; TL = Tetrahedron Lett.

Table 8. (Continued)

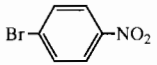
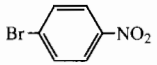
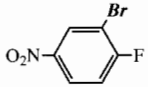
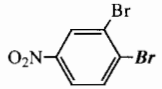
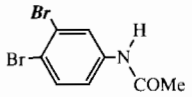
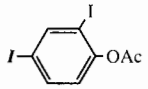
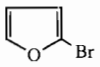
Acetylene R-C≡CH	sp^2-halide	Scale mmol	Solvent	Catalyst(s) in (mol %) or in mg	Reaction conditions	Literature
Me_3Si		100	Et_3N	$Pd(OAc)_2$, 100 PPh_3, 200	80°C, 2 h	JOC (1981) 2280
		11.2	Et_2NH	$Pd(PPh_3)_4$, 150 CuI, 50	20°C, 2.5 h	S (1983) 32
H		10	Et_2NH	$PdCl_2{\cdot}(PPh_3)_2$, (1) CuI, (0.5)	20°C, 6 h only disubstitution (PhC≡CPh)	TL (1975) 4467
EtSCH=CH-		300	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 1500 PPh_3, 2000 CuBr, 1000	Reflux, 1 h	TL (1992) 4229
$HOCH_2$ 1.5 eq		5	$C_3H_7NH_2$	$Pd(PPh_3)_4$, (2) without Cu-catalyst!	Reflux, 5 h	TL (1987) 5981
Me_3Si excess		50	Et_3N	$Pd(PPh_3)_4$, 2300 CuI, 760	70°C, 7 h	T (1988) 6337
		40	Et_3N	$Pd(PPh_3)_4$, 1840 CuI, 610	60°C, 5 h	T (1988) 6337
Me_3Si excess		48	$(i\text{-}Pr)_2NH$	$PdCl_2{\cdot}(PhC{\equiv}N)_2$, (5) Ph_3P, (10) $Cu(OAc)_2$, (5)	Reflux, ~3 h	JOC (1988) 2489

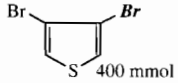
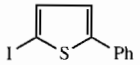
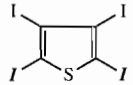
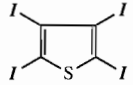
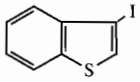
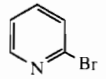
Me_3Si		–	Et_3N	$PdCl_2 \cdot (PPh_3)_2$ CuI	100°C, 72 h	JACS (1986) 3150
Me_3Si		100	Et_3N	$Pd(OAc)_2$, 100 Ph_3P, 500 CuI, 100	80°C, 16 h	JOC (1981) 2280
$n\text{-}C_5H_{11}$		3.6	Et_3N	$Pd(PPh_3)_4$, (2) CuBr, (3)	90°C, 105 min	JOC (1989) 4453
Me_3Si		100	Et_3N	PdAc, 200 Ph_3P, 400 without Cu-catalyst!	100°C, 4.5 h	JOC (1981) 2280
Me_3Si		580	Et_3N	$Pd(OAc)_2$, 1500 Ph_3P, 3000 without Cu-catalyst!	Reflux, 4 h	JOC (1981) 2280
Me_3Si		13.7	Et_2NH, DMF	$Pd(PPh_3)_4$, 78 CuI, 27	20°C, 6 h	TL (1989) 2581
$n\text{-}C_5H_{11}$		3.6	Et_3N	$Pd(PPh_3)_4$, (2) CuBr, (3)	90°C, 8 h	JOC (1989) 4453
$n\text{-}C_5H_{11}$		3.6	Et_3N	$Pd(PPh_3)_4$, (2) CuBr, (3)	90°C, 10 min or 20°C, 9 h	JOC (1989) 4453

[a] Yield generally satisfactory. For the sake of clarity, halogens that are (selectively) substituted, are printed in bold italic.

[b] Abbreviations: CPB.Jpn = Chem. Pharm. Bull., (Jpn); JACS = J. Am. Chem. Soc; JOC = J. Org. Chem.; S = Synthesis; SC = Synthetic Communications; T = Tetrahedron; TL = Tetrahedron Lett.

Table 8. (Continued)

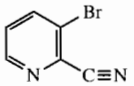
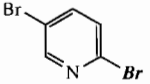
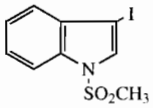
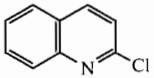
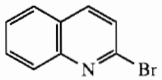
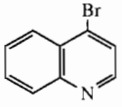
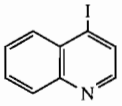
Acetylene R-C≡CH	sp^2-halide	Scale mmol	Solvent	Catalyst(s) in (mol %) or in mg	Reaction conditions	Literature
n-C_5H_{11}		3.6	Et_3N	$Pd(PPh_3)_4$, (2) CuBr, (3)	90°C, <3 min or 20°C, 6 h	JOC (1989) 4453
Me_3Si		10	Et_2NH	$PdCl_2{\cdot}(PPh_3)_2$, 140 CuI, 10	20°C, 4 h	S (1980) 627
Me_3Si		100	Et_3N	$Pd(OAc)_2$, 500 Ph_3P, 1000 without Cu-catalyst	100°C, 24 h	JOC (1981) 2280
n-C_5H_{11}		3.6	Et_3N	$Pd(PPh_3)_4$, 83 CuBr, 31	Reflux, 5 h	JOC (1989) 4453
n-C_5H_{11}		3.6	Et_3N	$Pd(PPh_3)_4$, 83 CuBr, 31	Reflux, 10 min or 20°C, 5 h	JOC (1989) 4453
n-C_5H_{11}		3.6	Et_3N	$Pd(PPh_3)_4$, 83 CuBr, 31	Reflux, 6 h	JOC (1989) 4453
Me_3Si		–	Et_3N	$Pd(PPh_3)_4$ (5) CuI (20)	20°C, 14 h	TL (1994) 6993
EtSCH=CH-		300	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 1500 PPh_3, 2000 CuBr, 1000	Reflux, 1 h	TL (1992) 4229

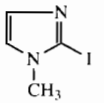
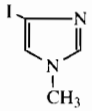
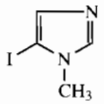
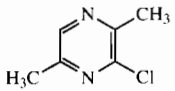
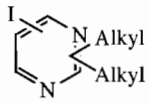
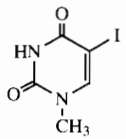
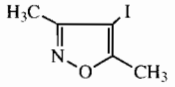
Me_3Si		200	Piperidine	$PdCl_2{\cdot}(PPh_2)_2$, 600 CuI, 100 PPh_3, 100	~100°C, ~1 h	SC (1990) 1889
EtSCH=CH-		300	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 1500 PPh_3, 2000 CuBr, 1000	Reflux, 1 h	TL (1992) 4229
Me_3Si	 400 mmol	200	Et_2NH	$PdCl_2{\cdot}(PPh_2)_2$, 500 CuI, 150 PPh_3, 200	Reflux, 7 h	SC (1990) 2275
CH_3 excess		24.5	C_6H_6, H_2O	$Pd(PPh_3)_4$, 1000 CuI, 250 $Et_3(PhCH_2)NCl$, NaOH	20°C, 7 h	T (1985) 621
Me_3Si		1.45	$(i\text{-Pr})_2NH$	$PdCl_2{\cdot}(PhC{\equiv}N)_2$, 27 PPh_3, 37 CuI, 14	0°C, 1 h + 20°C, 12 h + reflux, 1 h	JOC (1988) 2489
Me_3Si excess		3	(*i*-Pr)2NH	$PdCl_2{\cdot}(PhC{\equiv}N)_2$, 108 PPh_3, 146 CuI, 54	20°C, 3 h + reflux	JOC (1988) 2489
$SiMe_3$ Ph Bu CH_2OH		2	Et_3N DMF	$PdCl_2{\cdot}(PPh_3)_2$, 64 CuI, 32	25°C	CPB.Jpn (1988) 2248
H		20	Et_2NH	$PdCl_2{\cdot}(PPh_3)_2$, (0.5) CuI, (1)	20°C, 6 h only 2-py C≡C-2-py	TL (1975) 4467

[a] Yield generally satisfactory. For the sake of clarity, halogens that are (selectively) substituted, are printed in bold italic.

[b] Abbreviations: CPB.Jpn = Chem. Pharm. Bull., (Jpn); JACS = J. Am. Chem. Soc; JOC = J. Org. Chem.; S = Synthesis; SC = Synthetic Communications; T = Tetrahedron; TL = Tetrahedron Lett.

Table 8. (Continued)

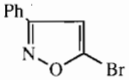
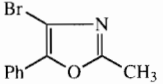
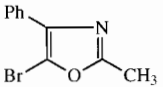
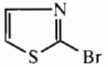
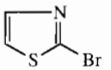
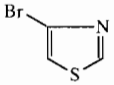
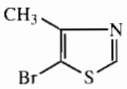
Acetylene R-C≡CH	sp^2-halide	Scale mmol	Solvent	Catalyst(s) in (mol %) or in mg	Reaction conditions	Literature
C_5H_{11}		3.6	Et_3N	$Pd(PPh_3)_4$, (2) CuBr, (3)	90°C, 20 min or 20°C, 3 h	JOC (1989) 4453
Ph		10	Et_3N	$PdCl_2{\cdot}(PPh_2)_2$, 160 CuI, 80	120°C, 4-6 h	CPB.Jpn (1988) 1890
Me_3Si		63	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 1000 CuI, 270	0°C, 1 h + 20°C, 1 h	JOC (1988) 386
$SiMe_3$ Ph Bu CH_2OH		2	Et_3N DMF	$PdCl_2{\cdot}(PPh_3)_2$, 64 CuI, 32	25°C	CPB.Jpn (1988) 2248
Me_3Si		10	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 200 CuI, 100	80°C, 14 h	S (1983) 312
Me_3Si		10	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 200 CuI, 100	70°C, 3 h	S (1983) 312
Me_3Si		10	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 200 CuI, 100	70°C, 15 h	S (1983) 312
Me_3Si		10	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 200 CuI, 100	20°C, 22h	S (1983) 312

Ph		10	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 280 CuI, 150	90°C, 7 h low yield	CPB.Jpn (1987) 823
Ph		10	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 280 CuI, 150	90°C, 8 h low yield	CPB.Jpn (1987) 823
Ph		10	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 280 CuI, 150	90°C, 7 h low yield	CPB.Jpn (1987) 823
n-Bu $HOCH_2$		2	DMF	$Pd(PPh_3)_2$, 116 KOAc, 294	100°C, 2 h	CPB.Jpn (1986) 1447
Alkyl		10	Et_3N	$PdCl_2{\cdot}(PPh_2)_2$, 100 CuI, 50	20°C, "several" h	CPB.Jpn (1981) 3843
n-Bu excess		5	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 25 CuI, 25	50°C, 2 h	JOC (1983) 1854
Ph		22	Et_3N	$PdCl_2{\cdot}(PPh_3)_2$, 400 CuI, 200	Reflux, 10 h	CPB.Jpn (1981) 3543

[a] Yield generally satisfactory. For the sake of clarity, halogens that are (selectively) substituted, are printed in bold italic.

[b] Abbreviations: CPB.Jpn = Chem. Pharm. Bull., (Jpn); JACS = J. Am. Chem. Soc; JOC = J. Org. Chem.; S = Synthesis; SC = Synthetic Communications; T = Tetrahedron; TL = Tetrahedron Lett.

Table 8. (Continued)

Acetylene R-C≡CH	sp^2-halide	Scale mmol	Solvent	Catalyst(s) in (mol %) or in mg	Reaction conditions	Literature
Ph		5	Et_3N	$PdCl_2 \cdot (PPh_3)_2$, 80 CuI, 40	**Reflux**, 18 h	CPB.Jpn (1981) 3543
Ph		10	Et_3N	$PdCl_2 \cdot (PPh_3)_2$, 280 CuI, 150	90°C, 15 h	CPB.Jpn (1987) 823
Ph		10	Et_3N	$PdCl_2 \cdot (PPh_3)_2$, 280 CuI, 150	90°C, 4 h	CPB.Jpn (1987) 823
Me_3Si		30	$(i\text{-Pr})_2NH$	$PdCl_2 \cdot (PhC{\equiv}N)_2$, (5) PPh_3, (10) $Cu(OAc)_2$, (5)	45°C good yield	JOC (1988) 2489
Ph		10	Et_3N	$PdCl_2 \cdot (PPh_3)_2$, 280 CuI, 150	90°C, 3 h low yield	CPB.Jpn (1987) 823
Ph		10	Et_3N	$PdCl_2 \cdot (PPh_3)_2$, 280 CuI, 150	80°C, 3 h good yield	CPB.Jpn (1987) 823
Ph		10	Et_3N	$PdCl_2 \cdot (PPh_3)_2$, 280 CuI, 150	80°C, 14 h good yield	CPB.Jpn (1987) 823

[a] Yield generally satisfactory. For the sake of clarity, halogens that are (selectively) substituted, are printed in bold italic.

[b] Abbreviations: CPB.Jpn = Chem. Pharm. Bull., (Jpn); JACS = J. Am. Chem. Soc; JOC = J. Org. Chem.; S = Synthesis; SC = Synthetic Communications; T = Tetrahedron; TL = Tetrahedron Lett.

10.4 Relative Rates of Coupling

As expected, aryl chlorides have been shown to be considerably less reactive than the corresponding bromides and iodides. The difference in reactivity between *p*-chloro- and *p*-bromobenzonitrile, for example, is of the order of 400 times [1]. In general, vinylic halides react more readily than aryl halides, while in hetaryl halides the halogen atom is substituted by an acetylenic group faster than in the analogous aryl halides [2, 4]. A halogen in the α-position of a heteroatom is considerably more reactive than a more remote halogen atom [3]. Already in one of the first papers on Pd-catalyzed cross-couplings with acetylenes the influence of substituents in the aryl halide on the reactivity of the halogen atom is mentioned [1]. Singh and Just [4] measured relative rates of a number of *para*-substituted aryl halides in the catalyzed reaction with 1-heptyne in triethylamine at room temperature and at elevated temperatures. Electron-donating substituents such as OCH_3 and NH_2 make substitution less easy, whereas C≡N and CH=O groups facilitate the couplings. Austin et al. came to the same conclusion [5]. In our experiments *p*-bromoanisole and *p*-bromo-*N,N*-dimethylaniline reacted less easily than did bromobenzene [2]. The relative rates are more or less parallel to those observed with oxidative additions of $Pd(PPh_3)_4$ to aryl halides. Dieck and Heck [6] noticed that alkylacetylenes are less reactive than phenylacetylene. However, such differences will be leveled out when using more strongly basic amines such as piperidine, and when the reactions are carried out at elevated temperatures. Alkyl substituents on the double bond retard the reactions with acetylenes. Thus, whereas vinyl bromide reacts under very mild conditions, substitution of bromine in $(CH_3)_2C{=}CHBr$ requires heating at 70 °C or higher temperatures [2].

We found that 3-bromofuran and 3-bromothiophene react rather sluggishly. 3-Bromopyridine, however, showed a high reactivity, comparable with that of the 2-isomer [2].

References (Sect. 10.4)

1. Cassar L (1975) J Organometal Chem 93, 253
2. Observations by the authors
3. Tilley JW, Zawoiski S (1988) J Org Chem 53, 386
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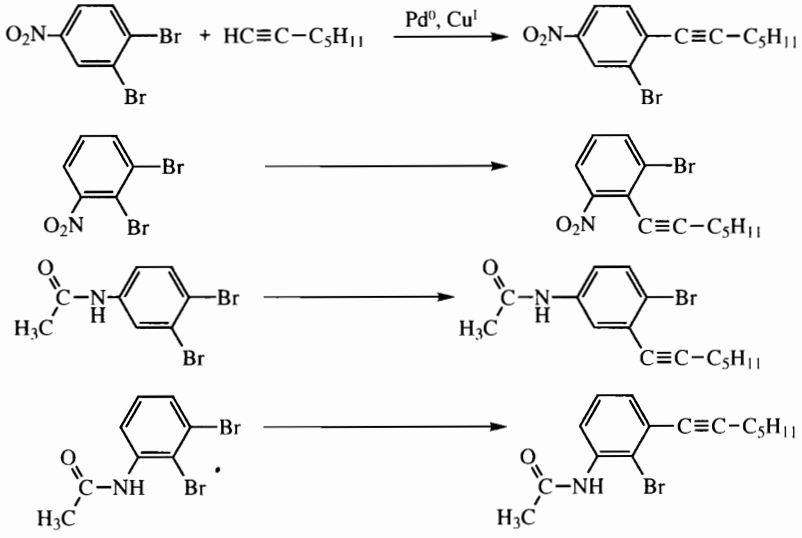
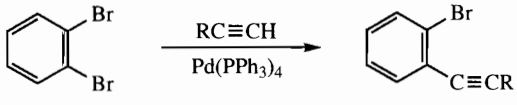
10.5 Regiochemistry and Stereochemistry

Highly selective substitution of 2-bromine in 2,3-dibromofuran [1], 2,3-dibromothiophene [1] and 2,5-dibromopyridine [2] has been observed. Reaction of tetraiodothiophene with two equivalents of trimethylsilylacetylene in diisopropylamine led to specific displacement of the 2- and 5-iodine atoms [3]. If 1,2-dibromo-4-nitro- and 1,2-dibromo-3-nitrobenzene and one equivalent of an alkyne are allowed to interact in the presence of Pd(0) and Cu(I), the bromine atom in the *para*- and *ortho*-positions is displaced much faster than the *meta*-bromine atom, so that mono-alkynylation prod-

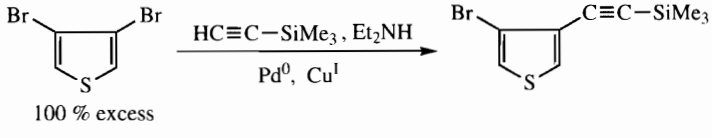
ucts can be obtained in excellent yields. In similar reactions with the analogous dibromoacetamidobenzenes the *meta*-bromine atom was substituted slowly, but specifically [4].



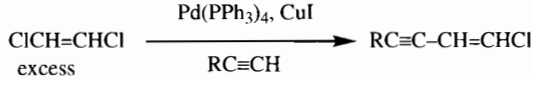
Successful mono-displacements in 1,2-dibromobenzene have been reported by Just and Singh [5].



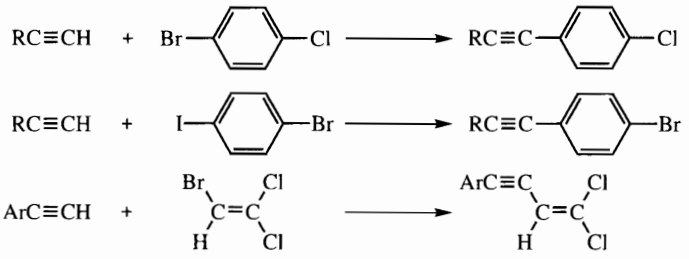
The coupling reactions were carried out in *n*-propylamine, *t*-butylamine or diethylamine, the only catalyst being $Pd(PPh_3)_4$. Di-substitution could be effected by using more acetylene and refluxing for longer times. Using Cu(I) as a co-catalyst the reaction times for di-substitution were much shorter. We could effect a satisfactory monosubstitution in 3,4-dibromothiophene and in the 2,5-isomer by using a 100 mol% (or more) excess of the dibromides [1].



Using a large excess of 1,2-dichloroethene Linstrumelle et al. [6] succeeded in displacing only one of the chlorine atoms by an alkynyl group. The reaction was reported to proceed with retention of configuration (cf. also [7] for this aspect) (according to a personal communication from G. Linstrumelle, the excess of dichloroethene can be diminished considerably).



The reactivity differences between the halogens are sufficiently large to allow a regiospecific performance of the following types of reactions [1, 8]:



Bates and Gabel [9] reported that in the acetate and *t*-butoxycarbonyl derivatives of 2,4-diiodophenol the *p*-iodine atom was selectively displaced by an acetylenic group in the Pd^0/Cu^I-catalyzed coupling with acetylenes in triethylamine at room temperature.

References (Sect. 10.5)

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10.6 Synthetic Applications of the Cross-Coupling Reactions with Acetylenes

The well-recognized versatility of the acetylenic group in synthetic transformations together with its generally successful coupling to sp^2-carbon atoms in aliphatic and (hetero)aromatic systems under mild conditions gives rise to several useful synthetic applications.

10.6.1 Simple Applications of the Cross-Coupling

In continuation of the preliminary communications by Hagihara, Heck, Cassar, Negishi et al. [1–4] several papers with well-described experimental conditions for the Pd- or Pd–Cu-catalyzed cross-couplings have appeared. Some of them are directed to the synthesis of alkynes with a terminal acetylenic function. The usual strategy to couple the halogen compound with trimethylsilylacetylene or 2-methyl-3-butyn-2-ol,

followed by base-catalyzed removal of the Me_3Si-group or elimination of acetone [5–11]:

$$RX + H{-}C{\equiv}CSiMe_3 \longrightarrow R{-}C{\equiv}CSiMe_3 \xrightarrow{\text{base}} RC{\equiv}CH$$

$$RX + H{-}C{\equiv}CC(CH_3)_2(OH) \longrightarrow R{-}C{\equiv}C{-}C(CH_3)_2OH \xrightarrow{\text{base}} RC{\equiv}CH + (CH_3)_2C{=}O$$

In the synthesis of 1,3-diynylamines, a Pd–Cu-catalyzed cross-coupling was the first step [12]:

$$ArC{\equiv}CH + BrCH{=}CCl_2 \longrightarrow ArC{\equiv}C{-}CH{=}CCl_2 \xrightarrow{R_2NLi} [ArC{\equiv}C{-}C{\equiv}CCl] \longrightarrow ArC{\equiv}C{-}C{\equiv}CNR_2$$

A number of *Z*-enynes RCH=CHC≡CH, in which R represents an aryl or hetaryl group, have been prepared through the following sequence of reactions [13]:

$$HC{\equiv}CCH{=}CHSC_2H_5 + RBr\ (\text{or RI}) \xrightarrow[Et_3N]{Pd^{II},\ Ph_3P,\ CuBr} R{-}C{\equiv}CCH{=}CHSC_2H_5 \xrightarrow[EtOH]{Zn\ (\text{activ.})}$$

$$\longrightarrow Z\text{-}R{-}CH{=}\dot{C}H{-}CH{=}CHSC_2H_5 \xrightarrow[2.\ H_2O]{1.\ NaNH_2,\ \text{liq } NH_3} Z\text{-}R{-}CH{=}CH{-}C{\equiv}CH$$

Although, in general, the fully catalytic method [1–3] seems more practical than the zinc halide method [4] (see Chapter 11), the latter may have distinct advantages when gaseous acetylenes are to be coupled.

Bromoallenes and acetylenes couple under very mild conditions [14]:

$$R^1R^2C{=}C{=}CHBr + H{-}C{\equiv}CR^3 \xrightarrow[Et_2NH,\ 20\ ^\circ C]{Pd^0,\ Cu^I} R^1R^2C{=}C{=}CH{-}C{\equiv}CR^3$$

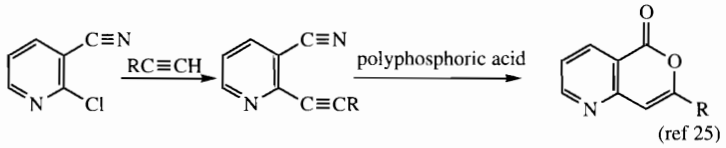
A number of 5-iodo-1-methyluracil and 5-iodouracil nucleosides [15], haloisoxazoles [16], 2-amino-3-cyano-5-bromopyrazine [17], 6- and 2-halo-9-phenyl-9*H*-purines [18], halo-1,3-azoles [19] and 2-,4- and 5-iodopyrimidines, 2,4-diiodo- and 2,6-diiodopyrimidines [20], 3-iodoindoles and 3-iodobenzo[*b*]-thiophene [21], have been coupled with acetylenes in the presence Pd or Pd–Cu-catalysts.

10.6.2 Synthesis of Structurally Interesting Acetylenic Compounds

Applying the Pd/Cu-catalyzed cross-coupling method with trimethylsilylacetylene in combination with base-catalyzed removal of the trimethylsilyl group, a variety of di- and polyethynylarenes and -hetarenes have been synthesized [22]. Other types of polyethynylaromatics, used as intermediates in the construction of polycylic aromatic compounds, have been obtained analogously [23, 24]. In addition to the KOH-alcohol method, potassium fluoride and 18-crown-6 were used for the removal of the trimethylsilyl group.

10.6.3 Coupling Followed by Cyclization

Cyclic vicinal dihalides and cyclic halogen compounds having a reactive functional group in the vicinal position have been used for the synthesis of condensed bicyclic compounds. In these syntheses the first step is the Pd or Pd/Cu-catalyzed introduction of an acetylenic function. Some examples are given below:



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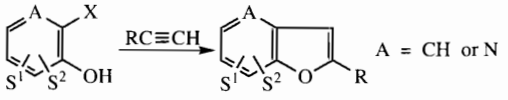

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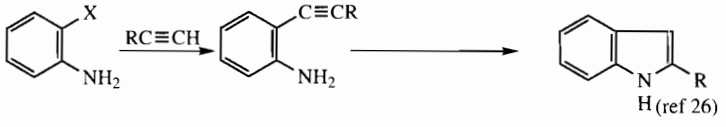

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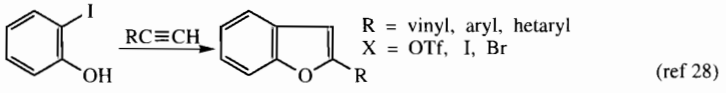

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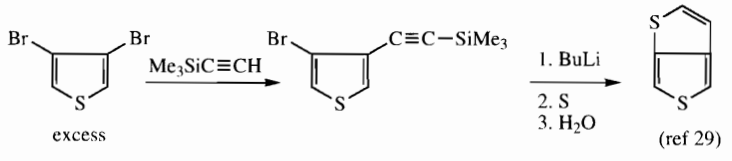

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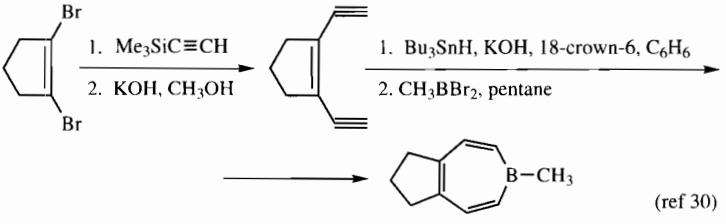
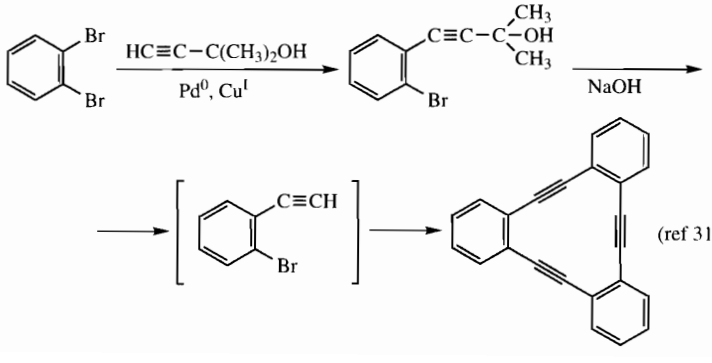


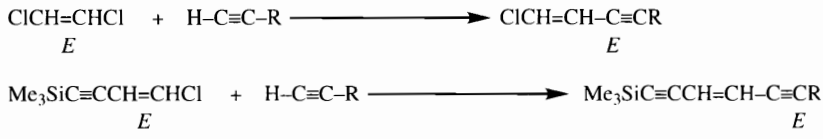
(ref 30)



(ref 31)

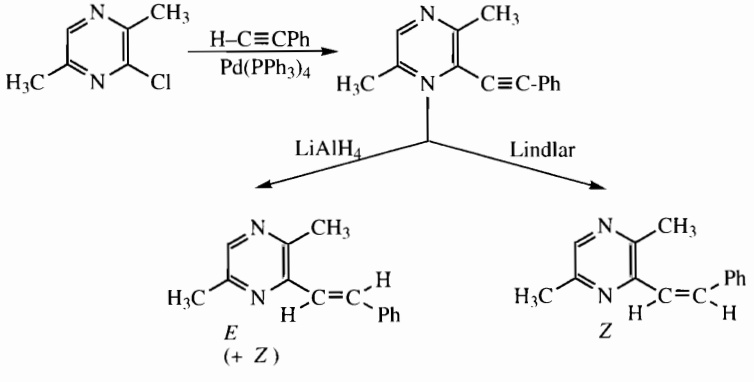
10.6.4 Synthesis of Biologically Interesting Compounds

An important step in the syntheses of leukotriene derivatives and of the isomer (methyl punicate) of the feeding deterrent of the boll-weevil on cotton, published by Linstrumelle et al. [32–35] is the Pd/Cu-catalyzed displacement of one chlorine in *E*-dichloroethene or in a *E*-chloroenyne by an acetylenic function. These reactions proceed with retention of configuration of the double bond.

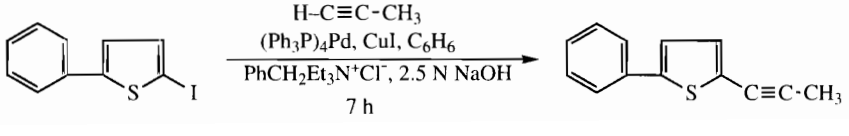


In their synthesis of leukotriene B_4 Nicalaou et al. [36] performed a Pd/Cu catalyzed coupling of an acetylenic intermediate with an *E*-olefinic bromide, while in the synthesis of a novel antitumor agent by Just and O'Connor [37] such a catalyzed cross-coupling was carried out with a *Z*-alkenyl bromide. The high yields obtained in Pd/Cu-catalyzed cross-couplings with acetylenes performed in syntheses of a number of other structurally complicated pharmaceutically interesting compounds [38–40] show that the conditions of the couplings are compatible with a diversity of functional groups.

Ohta et al. [41] applied the Pd-catalyzed coupling to synthesize two compounds which have been isolated from the Argentine ant:



Rossi et al. [42–44] performed Pd/Cu-catalyzed cross-couplings of free acetylenes with 1-bromo- and 1-iodoalkenes and 2-iodothiophene in diethylamine or with alkynylzinc chloride in the presence of $Pd(PPh_3)_4$ in the syntheses of some odoriferous compounds from plants and insect pheromones. In addition to the usual procedures for these catalytic couplings, the Italian investigators successfully carried out reactions under phase-transfer conditions [43, 44], *e.g.*:



10.6.5 Special Methods

Rossi et al. [43–45] reported procedures for the coupling of a number of olefinic and (het)aryl halides with acetylenes under phase-transfer conditions:

$$R'Hlg + HC{\equiv}CR \xrightarrow[PhCH_2N^+Et_3Cl^-]{Pd(PPh_3)_4,\ CuI,\ NaOH} R'{-}C{\equiv}CR$$

Generally, the reaction times are very long. Several of the couplings mentioned can be carried out much more quickly and with good yields under the "conventional" coupling conditions at room temperature or by heating at slightly elevated temperatures.

Russian investigators [46] communicated the reaction of phenylacetylene with *p*-iodonitrobenzene in tetrahydrofuran in the presence of solid sodium hydroxide, $PdIPh(PPh_3)_2$ and 18-crown-6. Whereas this coupling proceeded excellently, other aryl iodides such as iodobenzene gave less good results. Recently, successful cross-couplings between some iodoarenes and propargyl alcohol in the presence of water were reported by the same group. The ligand in the Pd-catalyst was a triarylphosphane in which one of the aryl groups was sulfonated [48].

French chemists [47] prepared a water-soluble catalyst in situ from palladium acetate and *meta*-sulfonated triphenylphosphane, with which successful couplings with a number of sp^2-iodides and acetylenes were carried out in a mixture of acetonitrile and water.

In his coupling method, proposed already in 1975 [3] Cassar used sodium methoxide–dimethylformamide as the base–solvent combination instead of the generally used amines. The latter method may be generally preferred, however, because of the milder conditions:

$$R'X + H{-}C{\equiv}CR + NaOCH_3 \longrightarrow R'{-}C{\equiv}CR + NaX + CH_3OH$$

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10.7 Practical Aspects of the Coupling Reactions

10.7.1 Performance of the Reactions and Isolation of the Products

As to the experimental skill most of the Pd or Pd/Cu-catalyzed couplings are not very demanding. In the usual procedures, the desired amounts of catalysts and additives are added to a mixture of the acetylene, the sp^2-halide and an amine (sometimes with a co-solvent). The mixture is stirred under inert gas (oxygen may cause "dimerization" of the acetylene or other reactions) at room temperature or with heating "until GLC or TLC indicates complete conversion". Temperature control during performance of the reaction is only necessary in the case of very fast reactions and volatile halides such as

vinyl bromide and in the case of gaseous acetylenes. The progress of the reaction can be qualitatively followed from the suspended amine salt (thickness of the salt layer after temporarily stopping the stirrer). Another way, applicable in the cases of volatile acetylenes such as trimethylsilylacetylene (b.p. ~52 °C at atmospheric pressure), provided that the amine is much less volatile, is to observe the temperature in the reaction mixture if the reflux is held constant. If no further increase of the temperature is observed, the conversion is (nearly) finished. We often observed that during heating the mixtures up to reflux the solution turned brown in the beginning, but became light-yellow at somewhat higher temperature. Especially in sluggishly proceeding reactions or in reactions with propargyl alcohol the brown colour may become more intensive and sometimes the reaction mixture may become black due to the formation of metallic palladium. If the latter stage has been reached, the conversion has stopped. In some cases this decomposition could be prevented by adding a *limited* amount of triphenylphosphane at the moment a brown colour begins to develop (Pd "in statu nascendi"). We therefore advise keeping triphenylphosphane ready before starting the reaction. The amount (in weight) should not exceed half the amount of $Pd(PPh_3)_4$ or be the same as the amount of $PdCl_2(PPh_3)_2$. At higher concentrations of triphenylphosphane the reaction is slowed down or may even stop. Very often, however, an additional amount of triphenylphosphane is added already at the beginning if bivalent palladium is used. In some cases, metallic palladium was formed upon addition of the Pd-and Cu-catalysts. This seemed to be caused by reaction of the Pd-compound with the copper salt when the rates of their dissolution were too low due to slight solubilities in the amine (especially diisopropylamine) or to insufficient powdering (or coagulation of the particles) of the catalysts. The following practical advice may be useful. The sp^2-halide is first warmed for a short time at 40–60 °C with $Pd(PPh_3)_4$ or the mixture of $PdCl_2(PPh_3)_2$ and PPh_3 without or with a very small amount of the amine until dissolution is complete (partial formation of the oxidative addition complex), then the amine and the acetylene are added and finally the copper salt. The latter is preferably added in a *dissolved* form: 200 mg of Cu(I)halide on 1 g of anhydrous lithium bromide in ~5 ml of THF. In general, this order of charging the reaction flask with reagents, solvents and catalysts gives satisfactory results.

After cooling the reaction mixture to room temperature, either a "dry" or an aqueous work-up may be carried out. In the first case a sufficient amount of ether or (if the product ist sufficiently soluble) pentane or hexane (or both together with ether) is added. Subsequently the amine salt is filtered off on a sintered-glass funnel (G1, with suction) and rinsed well with the organic solvent. Complete conversions should yield nearly the theoretically expected amount of dried salt. The filtrate is concentrated under reduced pressure and the residue subjected to a flash distillation at a very low pressure, using a short column. If there is a great risk of decomposition of the product under the influence of the Pd and Cu-remnants (the bulk of the Pd-catalyst has already been precipitated during the addition of the organic solvent), the crude product is dissolved in an organic solvent and the solution filtered through a short column of alumina or silica gel in order to remove traces of the catalysts. Purification by crystallization or distillation may then follow.

In the aqueous working-up procedure, water and pentane or ether are added successively, followed by extraction, washing with water, drying and evaporation of the

solvents under reduced pressure. The isolation of the product is carried out as described above.

In general, distillation of products from catalyzed cross-coupling reactions involves the risk of decomposition under the influence of the catalyst remnants, particularly in the case of reactions of olefinic halides with propargyl alcohol or in the case of acetylenes with a conjugated system of double or triple bonds (e.g. 1,3-diynes). The distillation should therefore be carried out using short columns and with amounts not exceeding ~5 gram.

10.7.2 Choice of the Solvent and Catalysts for Coupling Reactions

The most frequently used solvents are diethylamine, triethylamine and piperidine. The volatile diethylamine is applied in reactions that proceed readily at room temperature or slightly elevated temperatures. Linstrumelle et al. [1] found that at room temperature couplings in the absence of copper salts are much faster in piperidine or pyrrolidine than in more weakly basic amines such as diethylamine or triethylamine. Similar differences were found when a copper halide was used as a co-catalyst. They may be explained if it is assumed that the active form of the acetylene in the reaction is the acetylide. In the more strongly basic amines the latter is formed more easily. Couplings with less reactive sp^2-halides such as 3-bromothiophene, *p*-bromoanisole and *p*-bromo-*N,N*-dimethylaminobenzene can be sucessfully carried out in a short time at temperatures in the range 110–115 °C, using piperidine as the solvent. An additional advantage is the higher attainable temperature with this solvent [2]. In their di- and poly-alkynylation reactions with aryl and hetaryl di- and poly-halides, Neenan and Whitesides [3] used diisopropylamine as a solvent. An explanation for this choice of solvent is not given. Using diisopropylamine we obtained better results in the reaction of 1,3-dibromobenzene with two equivalents of trimethylsilylacetylene than in piperidine. Whereas the reaction of 1-bromocyclooctene with propargyl alcohol in triethylamine gave rise to the formation of an intractable mixture, a satisfactory result was obtained when diisopropylamine was applied (see experimental part of this chapter).

The most commonly used catalytic system is a combination of a palladium catalyst and copper(I) bromide or iodide, as proposed by Hagihara [4]. The Pd-catalyst may be either $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$, in the latter case often combined with two molar equivalents of additional triphenylphosphane. In general, there is no or little difference in activity between the two variants (see catalytic cycle, Sect. 10.2).

Although in some procedures carried out at elevated temperatures, the copper salt is omitted (see Table 8), this does not seem to have special advantages. We also found that at temperatures above 60 °C the reaction proceeded much faster in the presence of copper halide. Singh and Just [5] found a molar ratio for $Pd(PPh_3)_4$: CuBr of 2 : 3 to be optimal for their reactions at room temperature.

References (Sect. 10.7.2)

1. Alami M, Ferri F, Linstrumelle G (1993) Tetrahedron Lett 6403
2. Brandsma L, van den Heuvel HGM (1990) Synth Commun 20, 1889

3. Neenan TX, Whitesides GM (1988) J Org Chem 53, 2489
4. Sonogashira K, Tohda Y, Hagihara N (1975) Tetrahedron Lett 4467
5. Singh R, Just G (1989) J Org Chem 54

10.8 Experimental Section[1]

General note: All reactions were carried out under nitrogen

10.8.1 Pd/Cu-Catalyzed Cross Couplings of Acetylenic Compounds with Aliphatic sp^2-Halides Using Diethylamine as a Solvent

Although a variety of aliphatic secondary and tertiary amines may be used as a solvent and scavenger of the hydrogen halide, diethylamine is preferred for couplings that proceed very readily. This amine is easily removed after completion of the reaction either in a dry work-up after filtration, or by adding a lot of water, in which it dissolves completely. The dry work-up is recommended if the product is soluble in water to some extent.

10.8.1.1 4-Penten-2-yn-1-ol

$$H_2C{=}CHBr + HC{\equiv}CCH_2OH + Et_2NH \xrightarrow[CuI \text{ or } CuBr,\ Pd(PPh_3)_4]{Et_2NH,\ Et_2O} H_2C{=}CH{-}C{\equiv}C{-}CH_2OH + Et_2NH{\cdot}HBr\downarrow$$

Scale: 0.20 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a combination of thermometer and reflux condenser (or a so-called cold finger, filled with dry ice and acetone).

Procedure: Diethylamine (100 ml), propargyl alcohol (0.20 mol, 11.2 g, freshly distilled under a pressure of ~200 mmHg) and finely powdered copper(I) bromide (0.3 g) or copper(I) iodide (0.5 g) were successively placed in the flask. After stirring for 15 min at 20–25 °C, a suspension of 0.5 g of $Pd(PPh_3)_4$ (see Note 1) in 10–20 ml of diethyl ether was added in one portion. Subsequently, a mixture of 0.30 mol (32.0 g, excess) of vinyl bromide (see Note 2) and 50 ml of dry ether (cooled initially at −10 °C) was added in 5 equal portions over 45 min. After introducing the first portion, the temperature gradually rose to 35–40 °C, while salt began to separate from the solution. During the further additions the temperature of the suspension was maintained

1 With the collaboration of Mr. H.G.M. van den Heuvel

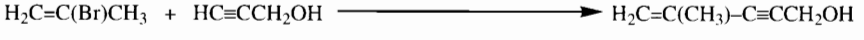
(occasional cooling or warming) between 40 and 45 °C. Since the suspension became rather thick, ~75 ml of ether was added gradually. After an additional hour (a gentle reflux was maintained) the suspension was cooled to 20 °C and then filtered on sintered glass. The salt was rinsed well with dry ether. Upon cooling to −20 °C a small amount of salt was precipitated from the ethereal solution. The supernatant solution was decanted from the salt (the latter was rinsed with a small portion of ether) and subsequently concentrated under reduced pressure (temperature heating bath not higher than 30 °C). The remaining yellow brown liquid was subjected to flash distillation at <1 mmHg through a 20-cm Vigreux column and the distillate was collected in a single receiver cooled in a bath at < −40 °C (see Note 3). Redistillation at water-aspirator pressure gave the enyne alcohol (b.p. 67 °C/15 mmHg, n^{20}_D 1.4974) in at least 80% yield.

Notes:

1. Using smaller amounts of $Pd(PPh_3)_4$ and CuBr or CuI, the reaction presumably will also proceed smoothly.
2. A quick test for the presence of non-volatile compounds (polymer) is to allow 1 ml of vinyl bromide to evaporate (b.p. ~15 °C) on a watch glass. If no residue remains, no distillative purification is necessary.
3. Under these mild conditions (temperature of the heating bath not higher than ~35 °C) the risk of decomposition of the compound under the influence of the catalysts is small. If, however, the reaction is carried out on a larger scale and more catalyst is needed, it is advisable to precipitate the greater part of the catalysts. This may be done by adding a relatively large amount of a mixture of pentane and ether (ratio >5) to the reaction mixture.

The performances of the procedures described below are closely similar to the procedure for the coupling of propargyl alcohol with vinyl bromide and will therefore be described more briefly.

10.8.1.2 4-Methyl-4-penten-2-yn-1-ol



Diethylamine (150 ml), 0.20 mol (11.2 g) of propargyl alcohol, 0.5 g of $Pd(PPh_3)_4$, 0.5 g of CuI or 0.3 g of CuBr were placed in the flask. After heating to 40–45 °C, the bromide (0.25 mol, excess) was added portionwise over 30 min. The temperature of the suspension was maintained between 45 and 50 °C (occasional warming). After an additional 1 h of heating under reflux (small amounts of ether may be added to facilitate stirring), the salt was filtered off on sintered glass and rinsed with dry ether. The dark brown solution was concentrated under reduced pressure and the remaining liquid subjected to a flash distillation at <0.5 mmHg and collected in a strongly cooled single receiver, while keeping the temperature of the heating bath below 50 °C. Redistillation of the distillate through a 20-cm Vigreux column gave the enyne alcohol, b.p. 75 °C/15 mmHg, n^{20}_D 1.4873, in ~80% yield.

10.8.1.3 1-Nonen-3-yne

$$H_2C{=}CHBr + HC{\equiv}CC_5H_{11} \longrightarrow H_2C{=}CH{-}C{\equiv}CC_5H_{11}$$

The procedure for this coupling was similar to that of the preceding experiments. After termination of the reaction, ice water (300 ml) was added and three extractions with pentane were carried out. During this operation most of the Pd-catalyst was precipitated. The combined extracts were washed with cold 2 M hydrochloric acid. After drying over $MgSO_4$, the solvent was distilled off under atmospheric pressure through a 40-cm Vigreux column. Distillation of the remaining liquid gave the product (b.p. 45 °C/15 mmHg, n^{20}_D 1.4582) in >80% yield.

10.8.1.4 2-Methyl-6-trimethylsilylhexa-2,3-dien-5-yne

$$(CH_3)_2C{=}C{=}CHBr + HC{\equiv}CSiMe_3 \longrightarrow (CH_3)_2C{=}C{=}CH{-}C{\equiv}CSiMe_3$$

The acetylene (0.12 mol) and bromoallene (0.10 mol) reacted smoothly at ~30 °C. During the reaction ~50 ml of ether was added to facilitate stirring. The reaction was finished half an hour after the addition of the bromoallene. The product (b.p. ~55 °C/0.5 mmHg, n^{20}_D 1.4942) was obtained in ~75% yield after an aqueous work-up. Relatively much pentane was added to precipitate the catalyst.

Bromopropadiene $H_2C{=}C{=}CHBr$ and $Me_3SiC{\equiv}CH$ did not give the expected product. Presumably, diethylamine and bromoallene reacted to give diethyl propargylamine.

10.8.1.5 6-Ethoxy-2-methylhex-5-en-3-yn-2-ol

$$C_2H_5OCH{=}CHBr + HC{\equiv}CC(OH)(CH_3)_2 \longrightarrow C_2H_5OCH{=}CH{-}C{\equiv}CC(OH)(CH_3)_2$$

To a mixture of 50 ml of diethylamine and 0.10 mol (8.4 g) of 2-methyl-3-butyn-2-ol were added successively 250 mg of copper(I) iodide and 300 mg of $Pd(PPh_3)_4$. Subsequently, 0.06 mol (9.3 g) of the bromoether (*E/Z* ~20:80) was added at room temperature to the clear solution. The mixture was warmed to 40 °C, after which the reaction started. Another amount of 0.05 mol of the bromo compound was added over ~15 min. After the exothermic reaction had subsided, the mixture was heated for 1 h under reflux. The salt was filtered off on sintered glass and rinsed with ether. The amount of dry salt was 14.2 g (theoretical amount 15.4 g). The ethereal solution was washed with a saturated aqueous solution of ammonium chloride and dried over $MgSO_4$. After concentration of the solution under reduced pressure, the remaining liquid was subjected to distillation at <1 mmHg to give the product [b.p. ~75 °C (*E/Z* ~0.7)] in 81% yield.

From the reaction of *propargyl alcohol* with $BrCH{=}CHOC_2H_5$ under similar conditions the coupling product could not be isolated. During attempted distillation decomposition occurred.

10.8.1.6 6-Ethoxyhex-5-en-3-yn-2-ol

$$C_2H_5OCH{=}CHBr + HC{\equiv}CCH(CH_3)OH \longrightarrow C_2H_5OCH{=}CH{-}C{\equiv}CCH(CH_3)OH$$

Following the same procedure as described for $HC{\equiv}CC(CH_3)_2OH$ and using a 50% molar excess of $BrCH{=}CHOC_2H_5$, the product, b.p. ~80 °C/1 mmHg, was obtained in 78% yield. The *E/Z*-ratio of the product was higher than that of the starting compound. Possibly, the *Z* to *E* conversion is promoted by the catalysts during the work-up or the distillation.

10.8.1.7 2,5-Dimethylhex-5-en-3-yn-2-ol

$$H_2C{=}C(Br)CH_3 + HC{\equiv}CC(CH_3)_2OH \longrightarrow H_2C{=}C(CH_3){-}C{\equiv}CC(CH_3)_2OH$$

Using a 50% molar excess of the bromide (0.15 mol), the reaction under the influence of CuI (200 mg) and $Pd(PPh_3)_4$ (250 mg) started at room temperature. After heating for an additional half hour at 45-50 °C, the product was isolated as described in the preceding experiment. The enyne alcohol (b.p. ~40 °C/ 1 mmHg, n^{20}_D 1.4692) was isolated in 80% yield.

If the copper salt was omitted, the reaction proceeded only after warming at ~50 °C.

10.8.1.8 2,6-Dimethylhep-5-en-3-yn-2-ol

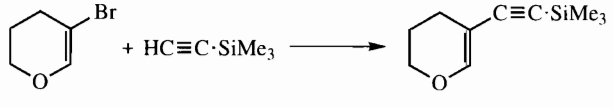
$$(CH_3)_2C{=}CHBr + HC{\equiv}CC(CH_3)_2OH \longrightarrow (CH_3)_2C{=}CH{-}C{\equiv}CC(CH_3)_2OH$$

To a mixture of 50 ml of diethylamine, 0.10 mol (8.4 g) of the acetylenic alcohol and 0.15 mol (20.3 g) of isobutenyl bromide were successively added 250 mg of $Pd(PPh_3)_4$ and 200 mg of copper(I) iodide. The mixture was heated for 1 h under reflux and then cooled to room temperature. After filtering the salt on sintered glass and rinsing it with pentane, the filtrate was cooled to –20 °C. The clear liquid was decanted from the precipitate (salt) and concentrated under reduced pressure. Flash distillation (b.p. ~40 °C/0.3 mmHg) afforded the product (n^{20}_D 1.482) in 86% yield.

In the case of *propargyl alcohol* the reaction proceeded sluggishly, while the solution became very dark because of the formation of Pd.

10.8.1.9 5-Trimethylsilylethynyl-2,3-dihydro-4H-pyran

(Cf. also the exp. in Sect. 10.8.6.7)



To 35 ml of diethylamine were added 100 mg of copper(I) iodide, 150 mg of triphenylphosphane and 400 mg of $PdCl_2(PPh_3)_2$. After addition of 0.10 mol (16.3 g) of bro-

modihydropyran a brown to yellow solution gradually formed. Upon subsequent addition of trimethylsilylacetylene (0.12 mol, 12.1 g) the solution became almost colourless. The mixture was heated for 4 h under reflux and then cooled to room temperature. Pentane, (150 ml) and water (200 ml) were successively added. The aqueous layer was extracted twice with pentane. The organic solution was washed with water, dried over anhydrous potassium carbonate and concentrated under reduced pressure. Careful distillation of the remaining liquid afforded the expected product, b.p. 105 °C/15 mmHg, n^{20}_D 1.4986, in 78% yield.

^{1}H-NMR spectrum (CCl_4): 6.6 (m, 1H); 3.72-3.97 (t, 2H); 1.5-2.2 (m, 4H) ppm.

10.8.1.10 6-Chloro-2-methylhex-5-en-3-yn-2-ol

$$ClCH{=}CHCl + HC{\equiv}CC(CH_3)_2OH \longrightarrow ClCH{=}CH{-}C{\equiv}CC(CH_3)_2OH$$

Diethylamine (50 ml), 2-methyl-3-butyn-2-ol (0.10 mol, 8.4 g) and *E*-dichloroethene (0.50 mol, 48.5 g, large excess) were mixed. To the stirred mixture were added 200 mg of $PdCl_2(PPh_3)_2$ and 100 mg of copper(I) iodide and the suspension was heated to 40 °C. The mixture first became clear then salt appeared. The red-brown mixture was heated under reflux for 2 h, then it was cooled to room temperature and 100 ml of pentane or hexane was added. The salt was filtered off on sintered glass and rinsed with pentane or hexane. After concentration of the solution under reduced pressure, the remaining liquid was distilled through a 20-cm Vigreux column to give the product, b.p. ~55 °C/0.5 mmHg, n^{20}_D 1.5090, in ~80% yield.

An attempt to distill the crude product from the coupling of *propargyl alcohol* resulted in a vigorous explosion.

10.8.1.11 1-Chlorodec-1-en-3-yne

$$ClCH{=}CHCl + HC{\equiv}CC_6H_{13} \longrightarrow ClCH{=}CH{-}C{\equiv}CC_6H_{13}$$

To a mixture of 50 ml of diethylamine, 0.10 mol (11.0 g) 1-octyne and 50 g (large excess) of *E*-dichloroethene were added 450 mg of $Pd(PPh_3)_4$ and 450 mg of copper(I) iodide. After warming to ~30 °C, the reaction started and a few min later salt was formed.The mixture was kept under reflux for 1.5 h, then the salt was filtered off on sintered glass and rinsed with ether or pentane. The dark solution was concentrated under reduced pressure and the residue dissolved in 40 ml of pentane. Flash chromatography on neutral Al_2O_3 followed by evaporation of the solvent and distillation gave the enyne, b.p. ~60 °C/6 mmHg, n^{20}_D 1.4857, in 80% yield.

^{1}H-NMR spectrum (CCl_4): 6.38 (d, J = 13.5 Hz, 1H); 5.83 (dt, J = 13.5 Hz, 1 H) ppm.

10.8.1.12 2-Chlorooct-1-en-3-yne

$$Cl_2C{=}CH_2 + HC{\equiv}CC_4H_9 \longrightarrow H_2C{=}C(Cl){-}C{\equiv}CC_4H_9$$

The amounts of solvents and reagents, and the performance were the same as in the preceding exp. As catalysts $PdCl_2(PPh_3)_2$ (600 mg) and CuI (450 mg) were used. In view of the relatively high volatility of the product, the greater part of the solvents was distilled off at normal pressure (bath temperature not higher than 75 °C). The product, b.p. 57 °C/15 mmHg, was obtained in 70% yield.

^{1}H-NMR spectrum (CCl_4): 5.47 (d, 2H); 2.28 (t, 2H) ppm.

10.8.1.13 Other Cross Couplings, Using Similar Conditions

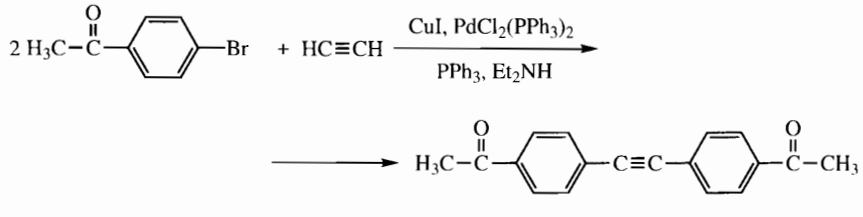
Linstrumelle and coworkers (Tetrahedron Lett. (1994) 3543 and personal communication) followed the procedure described below for preparing *Z*-ClCH=CH-C≡CCH_2OH, *Z*-ClCH=CH-C≡$CCH_2OC_2H_5$, *Z*-ClCH=CH-C≡$C(CH_2)_2OH$, *Z*-ClCH=CH-C≡$CCH_2N(CH_3)_2$, *Z*-ClCH=CH-C≡CPh, *p*-NO_2-C_6H_4-C≡$C(CH_2)_2OH$, *p*-NO_2-C_6H_4C≡CCH_2OH, *p*-NO_2-C_6H_4C≡C-$C(CH_3)_2OH$ and several other derivatives with a conjugated system of unsaturated units.

To a stirred solution of $Pd(PPh_3)_4$ (1.164 g, 1 mmol), *Z*-1,2-dichloroethene (3.917 g, 40.4 mmol), *n*-butylamine (2.93 g, 40.1 mmol) and propargyl alcohol (1.142 g, 20.4 mmol) in benzene (35 ml) was added CuI (388 mg, 2.05 mmol). The reaction was slightly exothermic. After keeping the mixture for 4 h at ~20 °C, a saturated aqueous solution of ammonium chloride was added, followed by dilute hydrochloric acid (just enough to neutralize the excess of *n*-butylamine). The product was isolated in 70% yield by chromatography of the extract over silicagel (elution with pentane-diethyl ether 6:4).

10.8.2 Pd/Cu-Catalyzed Couplings of Acetylene with Aryl and Hetaryl Halides

Note: Before adding the catalysts the mixture was perfused with acetylene.

10.8.2.1 1,2-Bis(4-acetylphenyl)ethyne

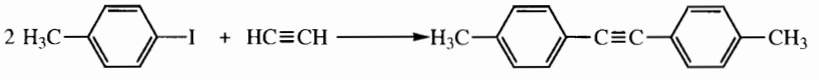


Scale: 0.05 molar.

Apparatus: 500-ml round-bottomed, three-necked flask (vertical necks), equipped with a gas inlet tube, an efficient mechanical stirrer and a reflux condenser.

Procedure: Diethylamine (100 ml) and 0.05 mol (10.0 g) of *p*-bromoacetophenone were placed in the flask and acetylene was passed (~0.5 l/min) through the stirred mixture during 10 min, then 100 mg of $PdCl_2 \cdot 2PPh_3$, 200 mg of triphenylphosphane and 100 mg of copper(I) iodide (finely powdered) were successively introduced. The mixture was heated under gentle reflux during 30 min, while continuing the flow of acetylene at a rate of ~200 ml/min. TLC then indicated complete conversion. After an additional 1 h the mixture was cooled to room temperature, water was added and the product was extracted with ether. The ethereal solution was washed with water and filtered through SiO_2. After evaporation of the ether under reduced pressure the almost pure product (88% yield) remained. Recrystallization from benzene gave the pure product m.p. 195-96 °C, in 80% yield.

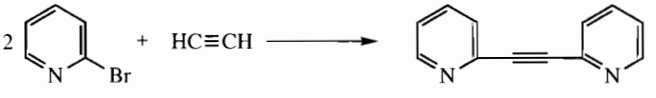
10.8.2.2 Bis(4-methylphenyl)ethyne



Reaction time 3 h.

The pure product, m.p. 140–41 °C (after crystallization from C_6H_6) was obtained in 90% yield.

10.8.2.3 Di(2-pyridyl)ethyne

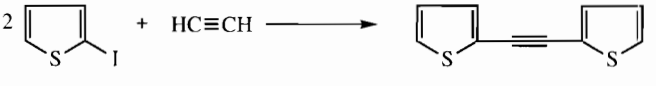


Reaction time 2 h.

The yield of the disubstituted acetylene, m.p. 71–72 °C (crystallization from hexane) was 80%.

3-Bromopyridine reacted very sluggishly.

10.8.2.4 Di(2-thienyl)ethyne

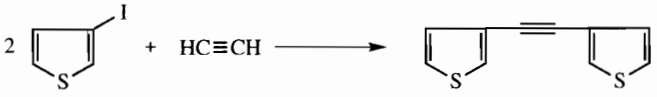


Reaction time 2 h.

The m.p. of the product after crystallization from pentane was 100-101 °C, the yield 83%.

2-Bromothiophene reacted sluggishly.

10.8.2.5 Di(3-thienyl)ethyne



Reaction time 4 h.

The m.p. of the product after crystallization from hexane was 95–96 °C, yield 89%.

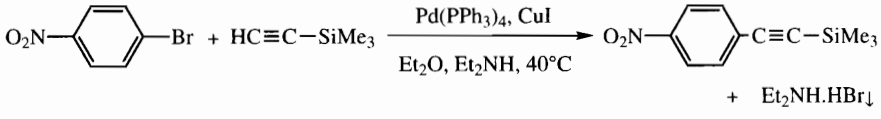
10.8.2.6 Bis(1-methylimidazol-2-yl)ethyne

From 0.05 mol (10.4 g) of 2-iodo-1-methylimidazole, 200 mg of $PdCl_2{\cdot}(PPh_3)_2$, 100 mg of copper(I) iodide and 180 mg of triphenylphosphane in 60 ml of triethylamine the disubstituted acetylene, m.p. 98–99 °C (after crystallization from a benzene-hexane mixture), was obtained in 80% yield. The time of introduction of acetylene at 55 °C was 1.5 h.

10.8.3 Pd/Cu-Catalyzed Couplings of Acetylenic Compounds with Aryl and Hetaryl Halides Using Diethylamine as a Solvent

Note: All reactions were carried out under inert gas.

10.8.3.1 1-Nitro-4-(trimethylsilylethynyl)benzene



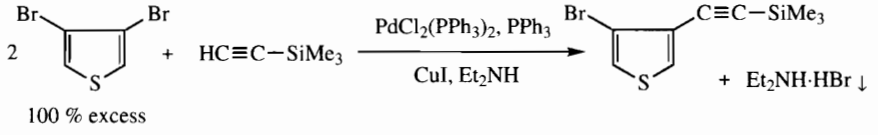
Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a nitrogen inlet, an efficient mechanical stirrer and a combination of a reflux condenser and a thermometer.

Procedure: 1-Bromo-4-nitrobenzene (0.10 mol, 20.2 g), diethylamine (120 ml) and trimethylsilylacetylene (0.12 mol, 12.1 g) were placed in the flask. To the mixture were added with stirring $Pd(PPh_3)_4$ (1.0 g) (or $PdCl_2(PPh_3)_2$, 0.8 g) and copper(I) iodide (0.5 g) or copper(I) bromide (0.4 g). The mixture was stirred for 1 h at 35 to 40 °C, after which 200 ml of a 1:1 mixture of ether and pentane was added at room temperature.

The salt was filtered off on sintered glass and rinsed well with the ether-pentane mixture. The solution was washed with water in order to remove traces of salt, then dried over $MgSO_4$ and concentrated under reduced pressure. The product (brown crystals) obtained in an excellent yield, was purified by flash chromatography on neutral Al_2O_3 and subsequently crystallized from a 2:1 mixture of pentane and ether (m.p. 95–97 °C).

10.8.3.2 3-Bromo-4-trimethylsilylethynylthiophene



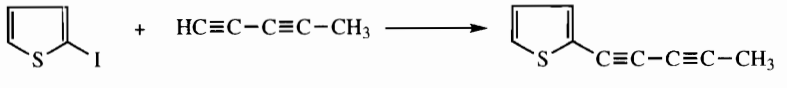
Scale: 0.10 molar ($Me_3SiC{\equiv}CH$).

Apparatus: Same as in preceding exp., 250-ml flask.

Procedure: 3,4-Dibromothiophene (0.20 mol, 48.8 g, corresponding to 100% excess) was gently stirred for 35 min with 500 mg of $PdCl_2(PPh_3)_2$ and 200 mg of triphenylphosphane, then 30 g of diethylamine and 0.10 mol (9.8 g) of trimethylsilylacetylene were successively added. To this mixture was added 150 mg of copper(I) iodide. After 3 h (vigorous reflux, gentle stirring) the temperature (~80 °C) of the mixture did no longer rise. Water (50 ml) and 100 ml of a 1:1 mixture of ether and pentane were added, after which the product was extracted. The combined organic solutions (most of the catalyst had been precipitated) were washed with a dilute aqueous solution of ammonia and ammonium chloride, dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The remaining liquid was subjected to flash distillation through a short column at the lowest possible pressure. Careful redistillation of the contents of the receiver through a 30-cm Vigreux column gave [after a forerun with almost 100% recovery of the excess of 3,4-dibromothiophene (b.p. up to 110 °C/12 mmHg)] the coupling product (b.p. 125-132 °C/12 mmHg) in ~75% yield.

In piperidine (at temperatures between 100 and 110 °C) the reaction proceeded much faster, but poor results were obtained.

10.8.3.3 2-(Penta-1,3-diynyl)thiophene



Scale: 0.05 molar.

Apparatus: Same as in preceding exp., 250-ml flask.

Procedure: To a solution of 0.05 mol (10.4 g) of 2-iodothiophene and 4 g (0.06 mol) of 1,3-pentadiyne in 80 ml of triethylamine were added at room temperature 200 mg of

$PdCl_2(PPh_3)_2$, 100 mg of finely powdered copper(I) iodide, and 200 mg of triphenylphosphane. The mixture was stirred for 1 h at 40 °C, then the salt was filtered off on a sintered-glass funnel and rinsed well with pentane. After drying, almost the theoretical amount of salt was obtained. The filtrate was concentrated in vacuo, diluted with 50 ml of pentane and the resulting solution was filtered through a 3 cm thick layer of neutral Al_2O_3. Concentration of the solution under reduced pressure, followed by distillation through a short Vigreux column gave the coupling product (b.p. 85 °C/0.5 mmHg, n^{20}_D 1.675) in ~90% yield.

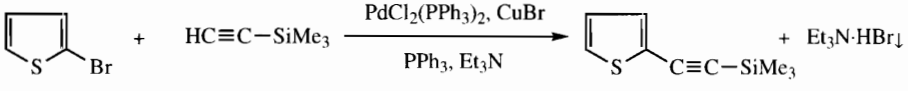
^{1}H-NMR spectrum (CCl_4): 7.14–7.29 (m, 2H); 6.87–6.99 (m, 1 H); 1.97 (s, 3H) ppm.

2-Bromothiophene and *2-bromofuran* gave much intractable material.

10.8.4 Pd/Cu-Catalyzed Couplings of Acetylenic Compounds with Aryl and Hetaryl Halide Using Triethylamine as a Solvent

Note: All reactions were performed under inert gas.

10.8.4.1 2-(Trimethylsilylethynyl)thiophene

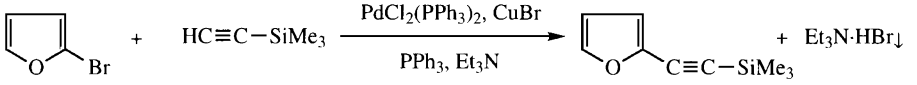


Scale: 0.30 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a combination of nitrogen inlet and thermometer, an efficient mechanical stirrer and a reflux condenser.

Procedure: In the flask was placed a mixture of 0.30 mol (48.9 g) of 2-bromothiophene, 200 ml of triethylamine, 450 mg of $PdCl_2(PPh_3)_2$ and 450 mg of triphenylphosphane. After adding 0.30 mol (30 g) of trimethylsilylacetylene, 0.35 g of finely powdered copper(I) bromide was introduced (a better alternative is to add a solution of 0.35 g Cu(I)Br and 2 g of anhydrous lithium bromide in 15 ml of THF). The mixture was heated under gentle reflux for 2 h, during which period its temperature rose to a maximum of 90–95 °C. After cooling to room temperature, 300 ml of water was added and four extractions with pentane were carried out (part of the catalyst was precipitated). The combined extracts were washed several times with water in order to remove the greater part of the triethylamine. After drying over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. Careful redistillation of the remaining liquid through a 30-cm Vigreux column gave the product (b.p. 85 °C/15 mmHg, n^{22}_D 1.5375) in ~75% yield.

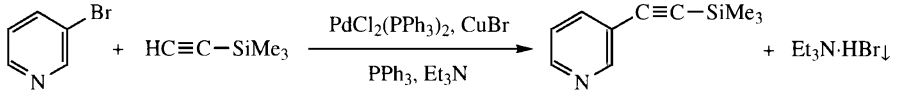
10.8.4.2 2-(Trimethylsilylethynyl)furan



2-Bromofuran (0.40 mol, 59 g), triethylamine (250 ml), $PdCl_2(PPh_3)_2$ (700 mg), PPh_3 (500mg), finely powdered CuBr (400 mg) and trimethylsilylacetylene (0.40 mol, 40 g) were used. After 1 h of refluxing the work-up was carried out. The product (b.p. 78 °C/15 mmHg, n^{21}_D 1.5009) was isolated in 74% yield.

^{1}H-NMR spectrum (CCl_4): 7.27 (d, 1H); 6.53 (m, 1H); 6.30 (m, 1H) ppm.

10.8.4.3 3-(Trimethylsilylethynyl)pyridine



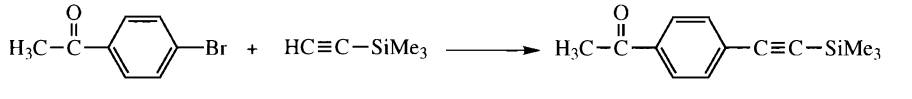
3-Bromopyridine (0.30 mol, 47.4 g), 0.35 mol (35 g) of trimethylsilylacetylene, 250 ml of triethylamine, 800 mg of $PdCl_2(PPh_3)_2$, 600 mg of PPh_3 and 400 mg of CuBr were used. After 1 h refluxing the work-up was carried out. The product, b.p. 105 °C/15 mmHg, was isolated in 94% yield.

^{1}H-NMR spectrum (CCl_4): 8.5 (broadened s, 1H); 8.42 (d, 1H); 8.36–8.42 (m, 1H); 7.42–7.63 (m, 1H) ppm.

10.8.4.4 3-(4-Nitrophenyl)prop-2-yn-1-ol

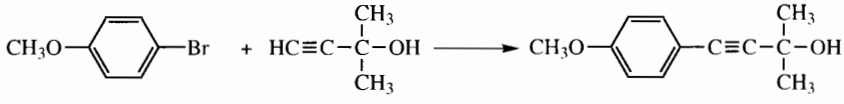
A mixture of 0.05 mol (10.2 g) of 1-bromo-4-nitrobenzene, 0.08 mol (4.5 g) of propargyl alcohol, 10 ml of triethylamine, 20 ml of benzene, 200 mg of $PdCl_2(PPh_3)_2$, 200 mg of CuI and 200 mg of Ph_3P was heated under reflux for 2 h. After cooling to room temperature the salt was filtered off on sintered glass and rinsed well with ether. The amount of dried salt was ~90% of the theoretically expected value. The organic solution was concentrated under reduced pressure and the residue dissolved in 50 ml of ether. The ethereal solution was subjected to flash chromatography on neutral Al_2O_3. Evaporation of the ether gave the product in ~95% yield. Recrystallization from carbon tetrachloride gave 85% of pure product (m.p. 95–96 °C).

10.8.4.5 4-(Trimethylsilylethynyl)acetophenone



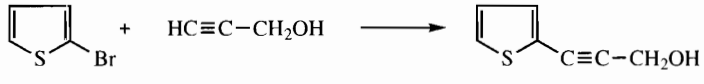
Using a procedure similar to the preceding one, a mixture of 0.20 mol (39.3 g) *p*-bromoacetophenone , 50 ml of triethylamine, 0.23 mol (23 g) of trimethylsilylacetylene, 600 mg of $PdCl_2(PPh_3)_2$, 300 mg of CuI and 400 mg of PPh_3 was heated for 3 h at 80–85 °C. After purification by filtration through neutral Al_2O_3, the product was distilled through a very short column to give the pure coupling product, b.p. ~115 °C/0.5 mmHg, n^{20}_D 1.548, in 85% yield.

10.8.4.6 2-Methyl-4-(4-methoxyphenyl)but-3-yn-2-ol



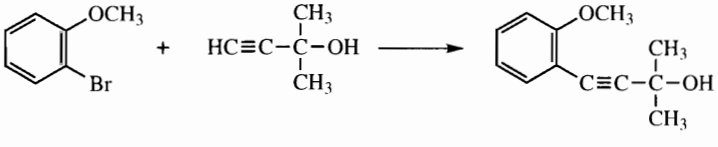
A mixture of 0.20 mol (37.5 g) of *p*-bromoanisole, 0.25 mol (21.0 g) of 2-methyl-3-butyn-2-ol, 100 ml of triethylamine, 600 mg of $PdCl_2(PPh_3)_2$, 300 mg of CuI and 400 mg of PPh_3 was heated at 85–90 °C for 4.5 h. The salt was filtered off on sintered glass and rinsed with ether. The dried salt weighed 31 g (36 g corresponds to 100% yield). After removal of the solvents under reduced pressure, the residue was diluted with 100 ml of ether and the solution filtered through a 4 cm thick layer of neutral Al_2O_3 on a sintered-glass funnel. Evaporation of the ether, followed by crystallization from pentane gave the pure product, m.p. 49–50 °C, in 63% yield.

10.8.4.7 3-(2-Thienyl)prop-2-yn-1-ol



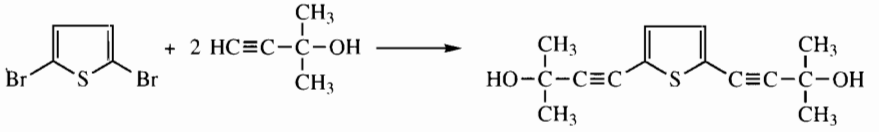
A mixture of 0.10 mol (16.3 g) of 2-bromothiophene. 0.12 mol (7.0 g) of propargyl alcohol, 40 ml of benzene, 15 ml of triethylamine, 350 mg of $PdCl_2(PPh_3)_2$ 200 mg of copper(I) iodide and 300 mg of triphenylphosphane was heated for 3 h at 75 °C. After a work-up as described in the preceding exp., the coupling product (b.p. ~100 °C/0.5 mmHg, n^{20}_D 1.6175) was obtained in 80% yield.

10.8.4.8 2-Methyl-4-(2-methoxyphenyl)but-3-yn-2-ol



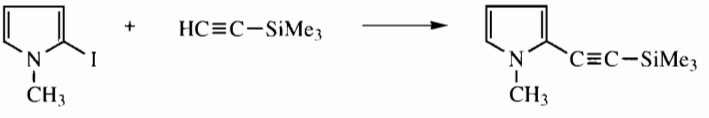
A mixture of 0.22 of *o*-bromoanisole (42 g), 0.3 mol (25.2 g) of 2-methyl-3-butyn-2-ol, 100 ml of triethylamine, 400 mg of $PdCl_2(PPh_3)_2$, 300 mg of triphenylphosphane and 200 mg of powdered copper(I)bromide was heated for 4 h at 75 to 80 °C. Following the procedures described in the preceding exps., the coupling product (b.p. ~135 °C/0.4 mmHg, n^{20}_D 1.557) was obtained in 75% yield.

10.8.4.9 4,4'-(Thiophene-2,5-diyl)di-(2-methylbut-3-yn-2-ol)



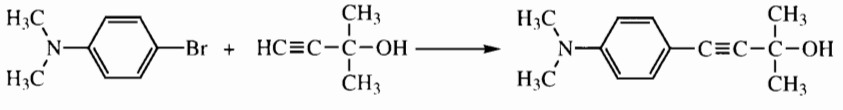
A mixture of 0.10 mol (24.6 g) of 2,5-dibromothiophene, 0.25 mol (20.8 g) of 2-methyl-3-butyn-2-ol, 100 ml of triethylamine, 300 mg of $PdCl_2(PPh_3)_2$, 200 mg of powdered copper(I) bromide and 400 mg of triphenylphosphane was heated for 2.5 h at 80 °C. The dry work-up, described above, gave 35 g of salt (~100%) and 24.2 g (89%) of coupling product (m.p. 135–136 °C, after crystallization from a benzene-hexane mixture).

10.8.4.10 1-Methyl-2(trimethylsilylethynyl)pyrrole



A mixture of 0.25 mol (52.0 g) of 2-iodo-1-methylpyrrole, 0.30 mol (30 g) of trimethylsilylacetylene, 100 ml of triethylamine, 600 mg of $PdCl_2(PPh_3)_2$ and 250 mg of powdered copper(I) bromide was heated for 3 h at 70–75 °C. After cooling to room temperature, 100 ml of water and 150 ml of pentane were added. After washing repeatedly with water in order to remove the greater part of the triethylamine, the organic solution was dried over anhydrous $MgSO_4$ and subsequently concentrated under reduced pressure. Distillation of the remaining liquid through a 30-cm Vigreux column afforded the coupling product (b.p. 82 °C/15 mmHg, $n^{20}{}_D$ 1.526) in 79% yield.

10.8.4.11 4-(4-Dimethylaminophenyl)-2-methylbut-3-yn-2-ol

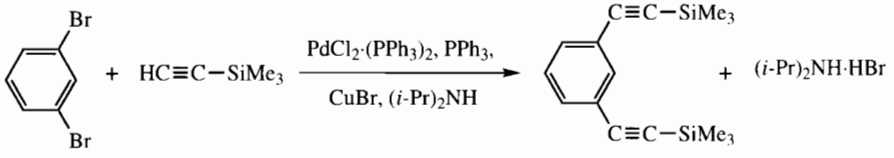


A mixture of 0.10 mol (20 g) of *p*-bromo-*N*,*N*-dimethylaniline, 0.12 mol (10.2 g) of 2-methyl-3-butyn-2-ol, 100 ml of triethylamine, 300 mg of $PdCl_2(PPh_3)_2$ and 150 mg of copper(I) iodide was heated for 7 h at 90 °C. After cooling to room temperature the product (m.p. 88–89 °C, after crystallization from a 1:1 mixture of diethyl ether and pentane) was obtained in 73% yield by the dry work-up described above for the coupling with *p*-bromoanisole (Sect. 10.8.4.6).

10.8.5 Pd/Cu-Catalyzed Couplings of Acetylenic Compounds Using Diisopropylamine as Solvent

Note: All reactions were carried out under inert gas.

10.8.5.1 1,3-Bis(trimethylsilylethynyl)benzene



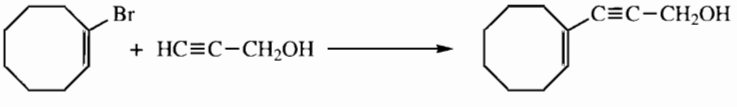
Scale: 0.05 molar (1,3-dibromobenzene).

Apparatus: 500-ml round-bottomed, three-necked flask equipped with a nitrogen inlet-thermometer combination, an efficient mechanical stirrer and a reflux condenser.

Procedure: (Cf. T.X. Xeenan, G.M. Whitesides, J. Org. Chem. (1988) 53, 2488.) 1,3-Dibromobenzene (0.05 mol, 12.8 g), 500 mg $PdCl_2(PPh_3)_2$, and 800 mg of triphenylphosphane were placed in the flask. The mixture was warmed to 30–35 °C under swirling until much of the solid had dissolved, then 75 ml of diisopropylamine, 0.12 mol (12 g) of trimethylsilylacetylene and a solution of 400 mg of copper(I) bromide and 1.5 g of anhydrous lithium bromide in 10 ml of THF were successively added and the mixture was brought to reflux. A thick suspension was formed very soon. After ~1 h the temperature in the flask did not rise further: maximum value between 80 and 85 °C. After an additional half hour the mixture (light-brown) was cooled to room temperature and 150 ml of pentane and 200 ml of water were successively added. The aqueous layer was extracted three times with pentane. The combined organic solutions were washed four times with water and then once with 2 M cold hydrochloric acid. After drying over anhydrous $MgSO_4$, the solution was concentrated under reduced pressure to give the solid, almost pure product, in essentially quantitative yield.

Note: When piperidine was used as the solvent, the yield was ~25% lower.

10.8.5.2 3-(Cyclooct-1-enyl)prop-2-yn-1-ol



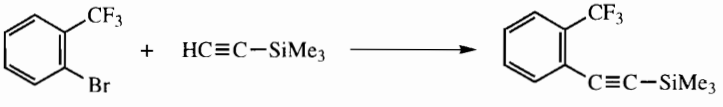
A mixture of 1-bromocyclooctene (0.10 mol, 19.0 g), 400 mg of triphenylphosphane and 200 mg of $PdCl_2(PPh_3)_2$ was warmed for 30 min at 30 °C with occasional swirling (or stirring), then 100 ml of diisopropylamine, 6.0 g (0.1 mol + slight excess) of

propargyl alcohol and a solution of 250 mg of copper(I) bromide and 1.5 g of anhydrous lithium bromide in 10 ml of THF were added. The mixture was brought to reflux. After 2 h the suspension was cooled to room temperature, and a mixture of 100 ml of ether and 100 ml of pentane was added, followed by 300 ml of water. After vigorous shaking and separation of the layers, the aqueous layer was extracted twice with the ether-pentane mixture. The combined organic solutions were washed with water and dried over anhydrous $MgSO_4$. The liquid remaining after concentration of the solution in vacuo was subjected to distillation through a very short column. The coupling product (b.p. ~115 °C/0.5 mmHg, n^{21}_D 1.536) was obtained in ~60% yield. There was a lot of brown viscous residue.

^{1}H-NMR spectrum (CCl_4): 5.98 (t, 1H); 4.28 (s, 2H) ppm.

In the case of triethylamine as solvent a black slurry was deposited on the bottom of the flask and the reaction stopped.

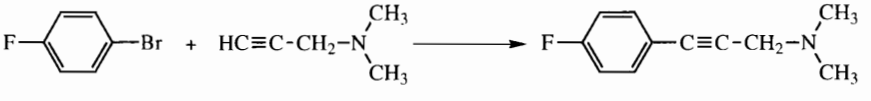
10.8.5.3 1-Trifluoromethyl-2-(trimethylsilylethynyl)benzene



Scale: 0.10 molar.

$HC{\equiv}CSiMe_3$ was used in 30% molar excess. The amounts of the catalysts were the same as in the preceding exp.; 75 ml of diisopropylamine was used. After refluxing for 4 h, the product was isolated: b.p. 100 °C/15 mmHg, yield 95%.

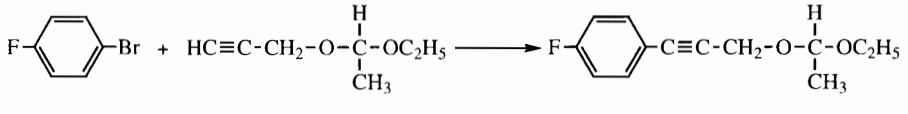
10.8.5.4 3-(4-Fluorophenyl)-N,N-dimethylprop-2-yn-1-amine



Scale: 0.1 molar.

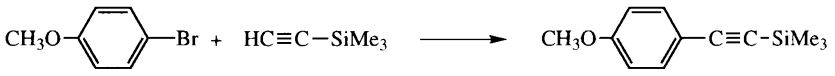
The amounts of catalysts and solvent were the same as in the preceding exps. After refluxing for 3.5 h, the product was isolated: b.p. ~95 °C/15 mmHg, n^{20}_D 1.506, yield 90%.

10.8.5.5 1-{3-(1-Ethoxyethoxy)prop-1-ynyl}-4-fluorobenzene



Procedure: As described above. The product (b.p. ~110 °C/0.5 mmHg, was isolated in ~85% yield.

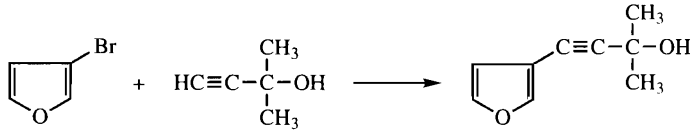
10.8.5.6 1-Methoxy-4-(trimethylsilylethynyl)benzene



The amounts of catalysts and solvent were the same as in the preceding exps. After 7 h of refluxing, the product (b.p. 125 °C/15 mmHg, n^{20}_D 1.5418) was isolated in 75% yield.

Poor results were obtained from the reactions of *HC≡CCH$_2$OH* with *1-bromo-4-methoxybenzene* and *1-bromo-4-fluorobenzene* in diisopropylamine. In an early stage of the reactions metallic Pd was formed, after which the conversion was very slow.

10.8.5.7 4-(3-Furyl)-2-methylbut-3-yn-2-ol



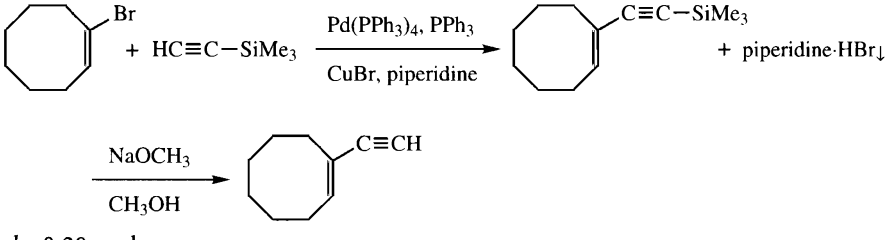
A mixture of 0.20 mol (29.5 g) of 3-bromofuran, 100 ml of diisopropylamine, 20 ml of piperidine, 0.25 mol (21 g) of 2-methyl-3-butyn-2-ol, 1.5 g of $PdCl_2(PPh_3)_2$, 200 mg of triphenylphosphane and 200 mg of copper(I) bromide (dissolved together with 1 g of anhydrous lithium bromide in 7 ml of THF) was heated under reflux for 5 h. After a work-up with pentane and water, the organic solution was dried over anhydrous magnesium sulfate and subsequently concentrated in vacuo. The remaining liquid was dissolved in ether and the solution filtered through a short (3–4 cm) layer of neutral Al_2O_3. The coupling product (b.p. ~80 °C/0.5 mmHg) was obtained in 77% yield.

^{1}H-NMR-spectrum (CCl_4): 7.50 (1H); 7.30 (1H) and 6.36 (1H) ppm.

10.8.6 Pd/Cu-Catalyzed Couplings with Acetylenic Compounds, Using Piperidine as a Solvent

Note: All reactions were carried out under inert gas.

10.8.6.1 1-Ethynylcyclooctene



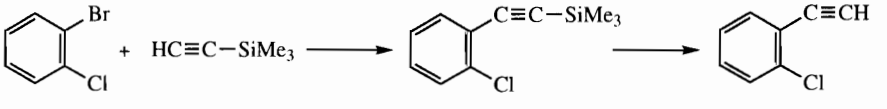
Scale: 0.20 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, a reflux condenser and a mechanical stirrer.

Procedure: 1-Bromocyclooctene (0.20 mol, 38 g), $Pd(PPh_3)_4$ (600 mg) and triphenylphosphane (300 mg) were placed in the flask. After swirling for a few min, 90 g of piperidine, 0.24 mol (24 g) of trimethylsilylacetylene and a solution consisting of 300 mg of copper(I) bromide and 1.0 g of anhydrous lithium bromide in 10 ml of THF were added. The mixture was brought to reflux while stirring at a moderate rate. After ~5 min (during which a constant rather strong reflux was maintained by gradually increasing the bath temperature) the temperature (initially ~90 °C) had risen to 110 °C. After an additional 15 min the mixture was cooled to room temperature, and pentane (100 ml) and water (200 ml) were added to the salt mass. The aqueous layer was extracted three times with small portions of pentane. The combined organic solutions were washed twice with cold 2 M hydrochloric acid and subsequently dried over anhydrous $MgSO_4$. The liquid remaining after concentration of the solution under reduced pressure was diluted with 30 ml of methanol in which 2 g of potassium hydroxide had been dissolved. The solution was heated for 15 min at 50 °C. Water (100 ml) was added, after which three extractions with 50-ml portions of pentane were carried out. The dried extracts ($MgSO_4$) were concentrated under reduced pressure and 1-ethynylcyclooctene (b.p. 75 °C/15 mmHg, n^{22}_D 1.5065) was obtained in 80% yield.

^{1}H-NMR spectrum (CCl_4): 6.08 (t, 1H); 2.60 (s, 1H) ppm.

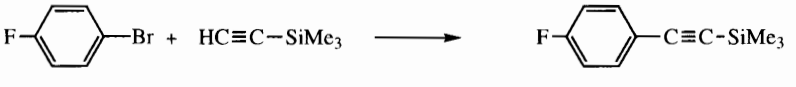
10.8.6.2 2-Chloro-1-ethynylbenzene



Scale: The amounts of catalysts and solvent were the same as in the preceding exp.

The coupling proceeded more slowly: after 40 min of refluxing the reaction mixture was worked-up. The crude coupling product was converted into the free acetylene (b.p. 70 °C/15 mmHg, n^{23}_D 1.5683) overall yield 78%.

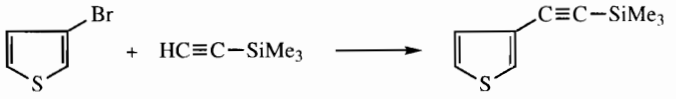
10.8.6.3 4-Fluoro-1-(trimethylsilylethynyl)benzene



Scale: The amounts of catalysts and solvent were the same as in the preceding exp.

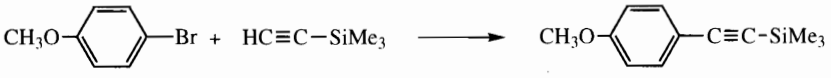
After 30 min refluxing the reaction mixture was worked-up to give the coupling product (b.p. 95 °C/15 mmHg, n^{21}_D 1.5091).

10.8.6.4 3-(Trimethylsilylethynyl)thiophene



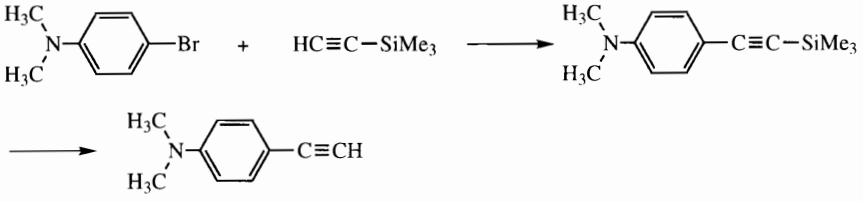
This coupling, carried out as described above gave the product (b.p. 97 °C/15 mmHg, n^{21}_D 1.5422) in 88% yield.

10.8.6.5 1-Methoxy-4-(trimethylsilylethynyl)benzene



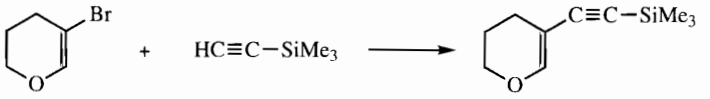
A mixture of 75 g of piperidine, 0.12 mol (12 g) of trimethylsilylacetylene, 0.10 mol (18.7 g) of *p*-bromoanisole, 300 mg of finely powdered copper(I) iodide, 300 mg of $PdCl_2 \cdot 2PPh_3$ and 500 mg of triphenylphosphane was heated for 2 h under reflux. The usual work-up afforded the product (b.p. 125 °C/15 mmHg, n^{20}_D 1.5418) in 76% yield.

10.8.6.6 4-N,N-Dimethylamino-1-ethynylbenzene



A mixture of 75 g of piperidine, 0.10 mol of *p*-bromo-*N,N*-dimethylaniline, 0.14 mol (14 g) of trimethylsilylacetylene, 400 mg of finely powdered copper(I) iodide, 500 mg of $PdCl_2(PPh_3)_2$ and 1 g of triphenylphosphane was heated under reflux for 2 h. After the usual work-up the crude, undistilled product (containing PPh_3) was obtained in almost quantitative yield. After adding 50 ml of ether, the solution was subjected to flash chromatography on neutral Al_2O_3. The resulting, almost clear, solution was concentrated under reduced pressure, after which 40 ml of methanol (in which 2 g of KOH had been dissolved), were added. The solution was heated for 15 min at 50 °C, then 200 ml of water was added and the product was extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated in vacuo to give the fairly pure (~95%) free acetylene as a solid in ~85% overall yield.

10.8.6.7 5-(Trimethylsilylethynyl)-2,3-dihydro-4H-pyran (compare also the exp. in Sect. 10.8.1.9)

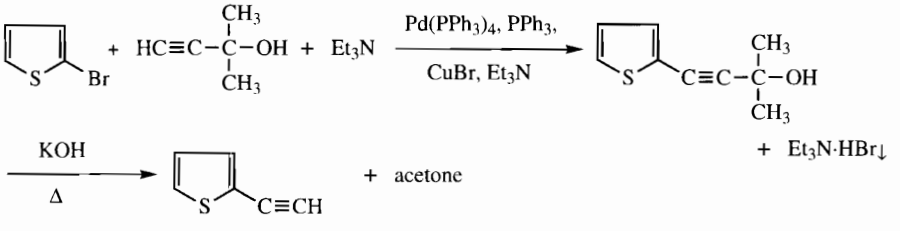


Scale: 0.10 molar; amounts of catalysts: 150 mg $Pd(PPh_3)_4$, 120 mg of CuI, 120 mg PPh_3, 40 g of piperidine. Refluxing time 30 min. Yield of product 82 % (b.p. 100 °C/15 mmHg, $n^{21}{}_D$ 1.4990).

10.8.7 Preparation of 2-Ethynylarenes and -hetarenes by Pd/Cu-Catalyzed Cross Coupling of Bromoarenes or -hetarenes with 2-Methyl-3-butyn-2-ol and Subsequent KOH-Catalyzed Elimination of Acetone

Note: All reactions were carried out under inert gas.

10.8.7.1 4-(2-Thienyl)-2-methylbut-3-yn-2-ol and 2-Ethynylthiophene



Scale: 0.20 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, a mechanical stirrer and a reflux condenser.

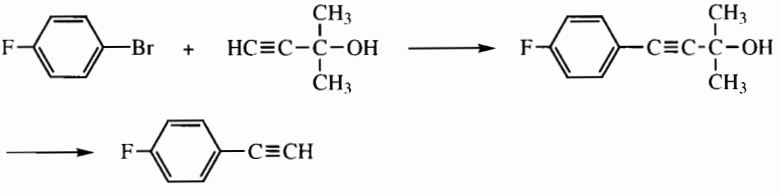
Preparation:

(a) 4-(2-Thienyl)-2-methylbut-3-yn-2-ol: 2-Bromothiophene (0.20 mol, 32.6 g)was gently stirred at room temperature with 200 mg of $Pd(PPh_3)_4$ and 200 mg of triphenylphosphane. After 30 min the acetylenic alcohol (0.22 mol, 18.5 g), triethylamine (100 ml) and a solution consisting of 100 mg of copper(I) bromide and 0.5 g of anhydrous lithium bromide in 10 ml of THF were added. After gentle refluxing for 40 min, the mixture was cooled to room temperature and water (200 ml) and pentane (100 ml) were added. The aqueous layer was extracted four times with pentane. The combined organic solutions were repeatedly washed with water in order to remove most of the triethylamine. After drying over anhydrous $MgSO_4$, the pentane was removed under reduced pressure. The remaining liquid was almost pure coupling product, yield ~95%. Distillation through a very short column gave the product as a somewhat viscous oil (b.p. ~100 °C/0.2 mmHg) in ~85% yield.

(b) 2-Ethynylthiophene: The coupling product was transferred into a 1-l round-bottomed flask and 50 ml of paraffin oil and 2 g of powdered potassium hydroxide were added. The flask was equipped for a vacuum distillation (30-cm Vigreux column, condenser and single receiver cooled at –75 °C). The flask was gradually heated to ~200 °C (strong foaming). The volatile products, 2-ethynylthiophene and acetone were collected in the cold receiver. Careful redistillation afforded pure 1-ethynylthiophene (b.p. 38 °C/15 mmHg, n^{20}_D 1.5826) in 82% overall yield.

^{1}H-NMR (CCl_4): 6.7–7.2 (m, 3H); 3.20 (s, 1H) ppm.

10.8.7.2 4-(4-Fluorophenyl)-2-methylbut-3-yn-2-ol and 1-Ethynyl-4-fluorobenzene



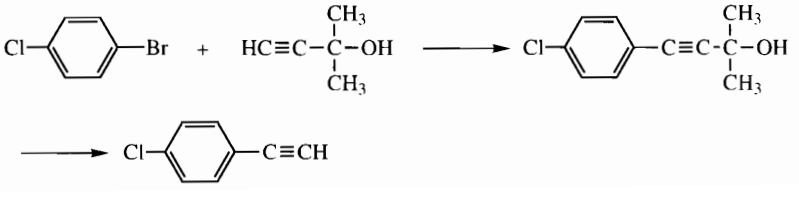
(a) 4-(4-Fluorophenyl)-2-methylbut-3-yn-2-ol: This experiment was carried out with 0.20 mol of 1-bromo-4-fluorobenzene, using 0.25 mol (21 g) 2-methyl-3-butyn-2-ol, 400 mg of $Pd(PPh_3)_4$, 400 mg of Ph_3P, 250 mg of CuBr (as a solution in THF, together with 1 g of anhydrous LiBr) and 100 ml of triethylamine. Upon heating, the mixture became light-brown and somewhat later light-yellow. At a later stage, during reflux, the brown colour returned. After 3.5 h of refluxing the mixture was worked up to give the coupling product (b.p. ~110 °C/0.5 mmHg) in ~90% yield.

(b) 1-Ethynyl-4-fluorobenzene: Treatment of the coupling product with NaOH (see Note) in paraffin oil as described for 2-ethynylthiophene (see exp. in Sect. 10.8.7.1) gave 1-Ethynyl-4-fluorobenzene (b.p. 39 °C/15 mmHg) in 70% overall yield. The compound solidified while standing at room temperature.

^{1}H-NMR spectrum (CCl_4): 7.35–7.50 (m, 2H); 6.85–7.05 (m, 2H); 2.91 (s, 1H) ppm.

Note: With NaOH, the risk of a subsequent displacement of fluorine by OH under the forcing conditions of the elimination seems less than in the case of KOH.

10.8.7.3 4-(4-Chlorophenyl)-2-methylbut-3-yn-2-ol and 4-Chloro-1-ethynylbenzene

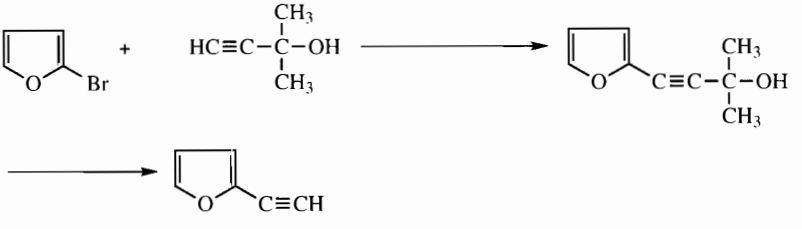


(a) 4-(4-Chlorophenyl)-2-methylbut-3-yn-2-ol: 1-Bromo-4-chlorobenzene (0.25 mol, 43.4 g, see Note) and 40 ml of triethylamine were warmed at 30 °C until the solid had dissolved, then 400 mg of $Pd(PPh_3)_4$ and 200 mg of triphenylphosphane were added. After 15 min, 2-methyl-3-butyn-2-ol (0.20 mol, 16.8 g) and a solution of 200 mg of copper(I) bromide (dissolved together with 1.5 g of anhydrous lithium bromide in 10 ml of THF) were sucessively added. The mixture was heated under reflux until the ratio (GLC) of *p*-bromochlorobenzene and product had become minimal (1.5 h). For the work-up see above. The product (b.p. ~110 °C/0.5 mmHg) was obtained in 90% yield (the first fraction, 1-bromo-4-chlorobenzene, was collected separately using an air condenser).

(b) 1-Ethynyl-4-chlorobenzene: Elimination of acetone from the coupling product with NaOH or KOH in paraffin oil gave 1-ethynyl-4-chlorobenzene (b.p. 80 °C/ 15 mmHg, as a solid (an air condenser was used) in 80% overall yield.

Note: An excess of 1-bromo-4-chlorobenzene was used to reduce the risk of subsequent displacement of chlorine in the desired coupling product.

10.8.7.4 4-(2-Furyl)-2-methylbut-3-yn-2-ol and 2-Ethynylfuran



(a) 4-(2-Furyl)-2-methylbut-3-yn-2-ol: 2-Bromofuran (0.30 mol, 45 g) was stirred for 15 min at room temperature with 300 mg of $Pd(PPh_3)_4$, then 90 ml of triethylamine and 0.4 mol (33.6 g, excess) of the 2-methyl-3-butyn-2-ol were added, followed by 200 mg of triphenylphosphane and a solution of 200 mg of copper(I) bromide (dissolved together with 1.5 g of anhydrous lithium bromide in 15 ml of THF). While the mixture was being heated, the initial brown colour gradually changed to light-yellow. At a later stage, the mixture turned brown again. After stirring for 1 h at 85–93 °C (temperature of the mixture), the work-up as described in the exp. in Sect. 10.8.7.1 was carried out. The coupling product (b.p. ~90 °C/0.3 mmHg, n^{22}_D 1.5210) was obtained in 84% yield.

(b) 2-Ethynylfuran: The coupling product was mixed with 50 ml of paraffin oil in a 1-l flask and 2 g of powdered KOH was added. The flask was equipped for a vacuum distillation: 30-cm Vigreux column, condenser and single receiver cooled in a bath at ~–75 °C. During strong heating, a mixture of ethynylfuran and acetone condensed in the receiver. It was washed several times in a small dropping funnel with 10 ml-portions of cold (0 °C) 2 M hydrochloric acid in order to remove acetone (washing with water appeared to be less effective), then dried over 5 g of anhydrous potassium car-

bonate in a 500-ml round-bottomed flask. Flash distillation from the flask (single receiver cooled at −75 °C) gave 2-ethynylfuran (b.p. <25 °C/15 mmHg, in ~70% yield.

^{1}H-NMR spectrum (CCl_4): 7.23 (d, 1H); 6.50 (d, 1H); 6.25 (d, 1H); 3.18 (s, 1H) ppm.

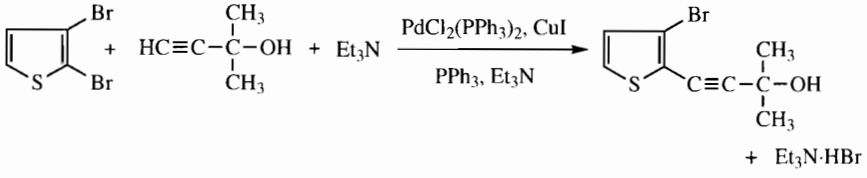
10.8.8 Pd/Cu-Catalyzed Mono-Substitutions with Aryl or Hetaryl Dibromides

Notes:

(a) All reactions were carried out under inert gas.

(b) See also the reaction of 3,4-dibromothiophene with $HC{\equiv}CSiMe_3$ (exp. in Sect. 10.8.3.2).

10.8.8.1 4-(3-Bromothienyl)-2-methylbut-3-yn-2-ol



Scale: 0.07 molar (2,3-dibromothiophene).

Apparatus: 250-ml three-necked, round-bottomed flask, equipped with a combination of gas inlet and thermometer, a mechanical stirrer and a reflux condenser.

Procedure: In the flask were placed 0.07 mol (16.8 g) of 2,3-dibromothiophene, 50 ml of triethylamine and 0.07 mol (5.9 g) of 2-methyl-3-butyn-2-ol, then 200 mg of $PdCl_2{\cdot}2PPh_3$ and 100 mg of triphenylphosphane were introduced. The mixture was stirred for ~15 min at 35 °C, after which a solution of 100 mg of copper(I) bromide and 500 mg of anhydrous lithium bromide in 5 ml of THF was added. The mixture was stirred for 2 h at 55 to 60 °C, and then for 1 h at 80 °C. After cooling to room temperature, the mixture was diluted with 150 ml of pentane and then poured into water. The aqueous layer was extracted four times with ether. The combined organic solutions were dried over potassium carbonate and subsequently concentrated under reduced pressure. The remaining oil was dissolved in 100 ml of ether and the solution filtered through a 3-cm thick layer of neutral Al_2O_3 on a sintered-glass funnel. After evaporation of the ether, the product was distilled (b.p. ~120 °C/0.5 mmHg) through a short Vigreux column. The distillate, which solidified after standing at room temperature, was pure mono-substituted product, yield 72%, m.p. 41–42 °C.

Reaction of *2,5-dibromothiophene with 2-methyl-3-butyn-2-ol* under similar conditions gave only satisfactorily yields of mono-substitution product if a 100 to 200 mol% excess of the dibromo compound was used. Most of the excess could be recovered by distillation.

10.8.8.2 3-Bromo-2-(trimethylsilylethynyl)furan

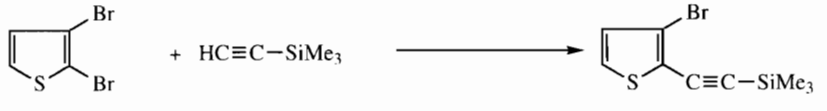
Scale: 0.05 molar.

Apparatus: Same as for the exp in Sect. 10.8.8.1.

Procedure: A mixture of 0.05 mol (11.3 g) of 2,3-dibromofuran, 0.05 mol (5.0 g) of trimethylsilylacetylene, 70 ml of triethylamine and 150 mg of $Pd(PPh_3)_4$ was heated for 15 min at 75 °C. Only a small amount of salt was formed. The suspension was cooled again to room temperature and a solution of 70 mg of copper(I) bromide and 500 mg of anhydrous lithium bromide in 5 ml of THF was added. The mixture was then heated for 1.5 h under constant reflux. After cooling to room temperature, 100 ml of pentane and 50 ml of water were added. The aqueous layer was extracted twice with pentane. The organic solution was dried over potassium carbonate and subsequent concentrated under reduced pressure. The remaining brown residue was subjected to flash distillation (pressure <0.5 mmHg) and the distillate collected in a single, strongly cooled receiver. Careful redistillation through a 20-cm Vigreux column gave, after a small first fraction of 2,3-dibromofuran, the product (b.p. ~100 °C/15 mmHg, n^{20}_D 1.526) in 60% yield. There was a dark-brown viscous residue.

^{1}H-NMR spectrum (CCl_4): 7.25 (d, 1H); 6.39 (d, 1H) ppm.

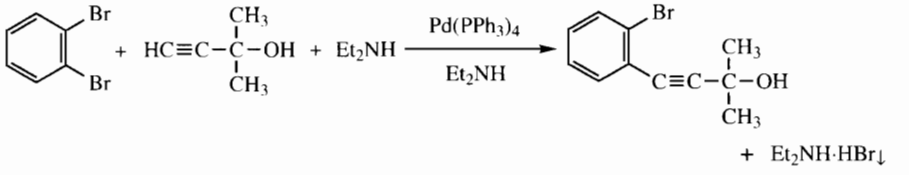
10.8.8.3 3-Bromo-2-(trimethylsilylethynyl)thiophene



Scale, *apparatus*, and *procedure* were similar to the exp in Sect. 10.8.8.1.
Instead of triethylamine, diisopropylamine was used as a solvent, the refluxing period was 2 h. The product (b.p. ~125 °C/15 mmHg) was obtained in 50% yield. The more volatile fraction contained much $Me_3SiC{\equiv}CC{\equiv}CSiMe_3$.

^{1}H-NMR spectrum (CCl_4): 6.88 (d, 1H); 7.06 (d, 1H) ppm.

10.8.8.4 4-(2-Bromophenyl)-2-methylbut-3-yn-2-ol



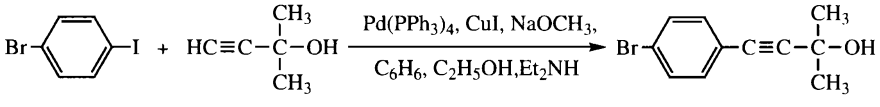
Scale and *apparatus:* Same as for the exp in Sect. 10.8.8.1.

Procedure: A mixture of 0.05 mol (12 g) of 1,2-dibromobenzene, 100 ml of diethylamine, 0.07 mol (5.9 g) of 2-methyl-3-butyn-2-ol and 300 mg of $Pd(PPh_3)_4$ was heated under reflux for 14 h. After cooling to room temperature the mixture was worked-up with pentane and water. After removal of the solvent under reduced pressure, the residue was dissolved in 100 ml of ether and the solution filtered through a 3 cm thick layer of neutral Al_2O_3. Distillation through a short column gave, after a first fraction of 1,2-dibromobenzene, the product (b.p. ~115 °C/0.4 mmHg) in 55% yield.

10.8.9 Preparation of Disubstituted Acetylenes by Pd/Cu-Catalyzed Reactions with Aryl and Hetaryl Iodides in the Presence of an Amine and Sodium Methoxide

Note: All reactions were carried out under inert gas.

10.8.9.1 4-(4-Bromophenyl)-2-methylbut-3-yn-2-ol

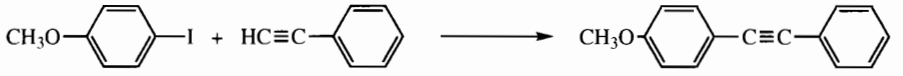


Scale: 0.02 molar.

Apparatus: 250-ml round-bottomed, three-necked flask, equipped with a nitrogen inlet, a thermometer and an outlet; magnetic stirring.

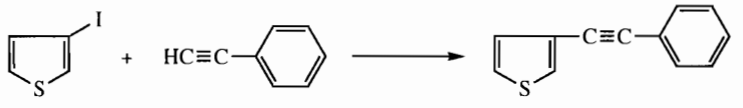
Procedure: In the flask was prepared a solution of 0.02 mol (5.6 g) of 1-bromo-4-iodobenzene in 10 ml of benzene, 10 ml of diethylamine and 10 ml of ethanol. Subsequently 1.4 g of sodium methoxide (or the same amount of $NaOCH_3$ as a very concentrated solution in methanol), 400 mg of $Pd(PPh_3)_4$ and 100 mg of powdered copper(I) iodide were introduced. Upon addition of 0.03 mol (~1.8 g) of propargyl alcohol the temperature rose to 40–45 °C. After half an hour, GLC showed that the reaction was complete. The mixture was diluted with ether, after which water was added. The organic layer was extracted five times with ether. The combined extracts were dried over anhydrous $MgSO_4$ and subsequently filtered through SiO_2. Concentration of the solution under reduced pressure followed by distillation afforded the coupling product (b.p. ~90 °C/0.5 mmHg, n^{21}_D 1.584) in 70% yield (yield of rather pure product before distillation ~90%).

10.8.9.2 1-(4-Methoxyphenyl)-2-phenylethyne



The operations were similar to those described above in the exp. of Sect. 10.8.9.1. The product (m.p. 63–64 °C, after crystallization from pentane) was obtained in 75% yield.

10.8.9.3 3-(Phenylethynyl)thiophene



The procedure was similar to those of the preceding experiments. The disubstituted acetylene (m.p. 48–49 °C) was obtained in 65% yield.

11 Nickel- and Palladium-Catalyzed Cross-Coupling Reactions with Organometallic Intermediates

11.1 Introduction

In 1972 Kumada [1] and Corriu [2] reported the cross-coupling of olefinic and aryl halides with alkyl- and arylmagnesium halides in the presence of nickel compounds, such as dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) ($NiCl_2$·dppe) and nickel acetylacetonate ($Ni(acac)_2$). Somewhat later coupling reactions were carried out with other organometallic compounds under the influence of various nickel and palladium catalysts. The cross-couplings may be represented by the following general scheme:

$$R\text{–}M + R'L \xrightarrow{\text{“Ni” or “Pd”}} R\text{–}R' + ML$$

In the organometallic compound R–M the metal M may be an alkali metal (mostly Li), –MgX, –ZnX, or a group containing boron, tin, aluminum, zirconium or copper. By far most of the couplings have been carried out with olefinic, aryl and hetaryl compounds in which the leaving group L is a *halogen*. In some cases, triflates have been used.

A number of reviews on nickel- and palladium-catalyzed cross-couplings have appeared in journals and books [3–12].

In this chapter a number of cross-couplings with relatively simple, cheap and readily available organometallic reagents and substrates are illustrated with experimental procedures carried out in our laboratory. Organometallic reagents such as tin and boron compounds have proved their usefulness in the syntheses of compounds containing functional groups (CN, COOR, etc.) that are not compatible with organolithium or -magnesium compounds. Cross-couplings with boron and tin compounds are especially useful in syntheses of structurally complicated molecules. Since it would involve considerable effort to synthesize the required reagents and substrates, these cross-couplings have been illustrated only with procedures for the preparation of structurally simple compounds.

References (Sect. 11.1)

1. Tamao K, Sumitami K, Kumada M (1972) J Am Chem Soc 94, 4372
2. Corriu RJP, Masse JP (1972) J Chem Soc, Chem Comm 144
3. Kalinin VN (1992) Synthesis 413 (couplings with heterocyclic compounds)
4. Negishi E (1982) Acc Chem Res 15, 340 (mainly organozinc and -aluminum compounds)

5. Negishi E, Takahashi T, Akiyoshi K (1988) In: Catalysis of Organic Reactions (eds. Rylander PN, Greenfeld H, Augustine RL) Chemical Industries Series, vol 33, Marcel Dekker, New York, p 381 (general aspects of Ni- and Pd-catalyzed couplings)
6. Heck RF (1985) Palladium Reagents in Organic Synthesis, Acad. Press, New York (selected procedures with Pd-catalysts, taken from literature)
7. Stille JK (1985) Pure Appl Chem 57, 1771; Angew. Chem. (1986) 98, 504; Int Ed (Engl.) (1986) 25, 508 (Pd-catalyzed synthesis with organotin compounds)
8. Kumada M (1980) Pure Appl Chem 52, 669 (review of his research)
9. Suzuki A (1982) Acc Chem Res 15, 178; Suzuki A (1991) Pure and Appl Chem 63, 419 (Pd-catalyzed syntheses with organoboron compounds)
10. Martin AR, Yang Y (1993) Acta Chem Scand 47, 221 (Pd-catalyzed cross-couplings of organoboronic acids)
11. Miyaura N, Suzuki A (1995) Chem Revs 95, 2457-2483 (Pd-catalyzed cross-couplings of organoboron compounds)
12. Mitchell TN (1992) Synthesis 803-815 (in part Stille-couplings); see also Mitchell TN, (1986) J Organometal Chem 304, 1

11.2 Possibilities of Connecting Organic Groups by Transition Metal Catalysis

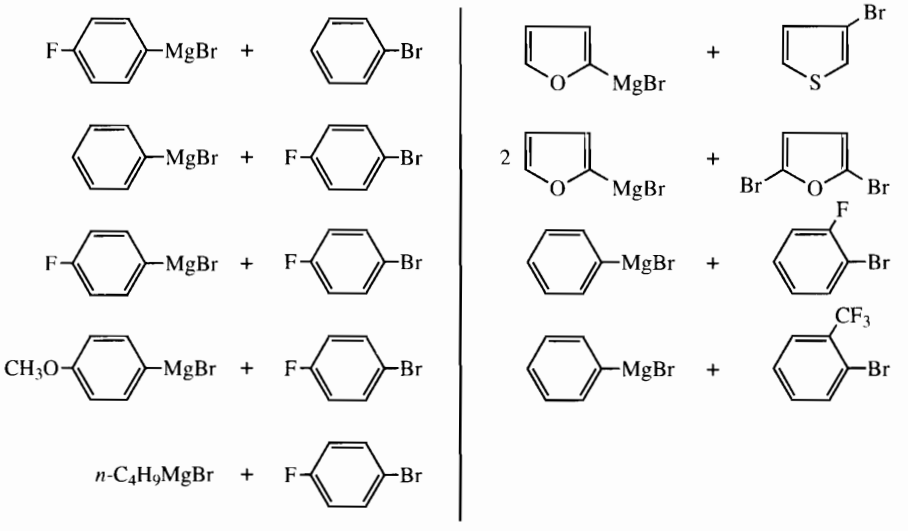
Applying nickel- and palladium-catalyzed cross-couplings a considerable number of combinations of organic groups can be realized. If copper catalysis (see Chapter 7) is included, many additional possibilities are achievable. Table 9 (adapted from Negishi et al., see Sect. 11.1, Ref. 5) summarizes the various possibilities. They are exemplified with literature references. Copper-catalyzed couplings are extensively described in Chapters 3-7. Pd-catalyzed allylations of stabilized enolates, reviewed by B.M. Trost (Acc. Chem. Res. (1980) 13, 385) are not included in Table 9.

11.3 Catalysts and Ligands

(See also Sect. 11.10.)

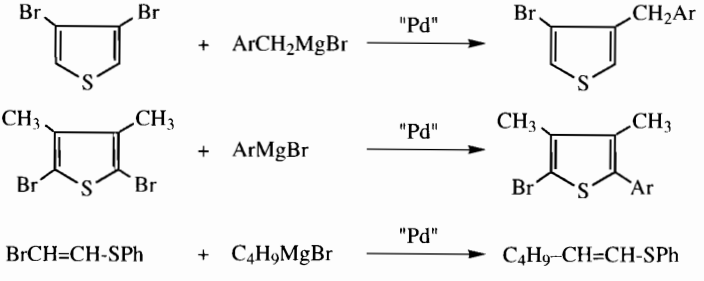
An impressive number of cross-couplings with structurally simple organometallic compounds and substrates have been successfully achieved using nickel complexes as catalysts. Many of these reactions are also possible with palladium catalysts. Nickel catalysts are more reactive and therefore less selective. For example, a nitro group is not compatible with Ni-phospane catalysts (due to redox reactions), whereas under the influence of Pd-catalysts in many cases good results are obtained. Negishi et al. [1] isolated the expected product from the Pd-catalyzed reaction of *o*-tolylzinc chloride and *p*-bromonitrobenzene in a good yield. Under similar conditions, the reaction in the presence of the analogous nickel catalyst did not give any of the cross-coupling product. With a Pd-catalyst (generated in situ from $PdCl_2 \cdot (PPh_3)_2$ and diisobutylaluminum hydride (DIBAH)) the reactions of alkynylzinc chlorides (RC≡CZnCl) with aryl and alkenyl halides gave significantly higher yields than did the nickel-catalyzed reactions [2, 3]. Whereas nickel-catalyzed alkenyl-alkenyl cross-couplings showed some stereochemical scrambling, excellent retention of the configurations of the dou-

ble bonds was obtained when using Pd-catalysts [3]. We obtained good results in many aryl-aryl and hetaryl-hetaryl couplings catalyzed by $NiCl_2$·bis(1,3-diphenylphosphino)propane, but the following combinations unexpectedly proceeded unsatisfactorily (many amorphous products), incomplete conversion, homo-coupling, etc.):



Using $PdCl_2$·bis(1,4-diphenylphosphino)butane or, in the reactions with C_4H_9MgBr, $PdCl_2$· bis(1,1'-di-phenylphosphino)ferrocene gave good results under similar conditions.

Application of palladium catalysts allows selective displacements in 1,2-disubstituted (hetero)-aromatic and vinylic compounds, for example [4, 5]:



In Pd-catalyzed cross-couplings involving alkenyl and aryl halides the iodides and bromides participate readily. Nickel complexes are capable of catalyzing reactions with a number of chlorides (Sect. 11.1, Ref. 5).

In nearly all of the nickel and palladium pre-catalysts used in cross-couplings with organometallic intermediates, Ni and Pd are ligated by mono- or bidentate phosphanes. Beletskaya et al. [6] compared $PdCl_2$·$(PPh_3)_2$ with the "ligandless" $PdCl_2$·$(CH_3CN)_2$ in the reactions of phenylmagnesium bromide and triphenylaluminum with *p*-iodoanisole and found the latter complex much less selective.

Of the monodentate ligands triphenylphosphane has appeared the most effective one [7, 8]. It is used in the combinations $NiCl_2$·$(PPh_3)_2$, $Ni(PPh_3)_4$, $PdCl_2$·$(PPh_3)_2$ and

$Pd(PPh_3)_4$. The zerovalent-nickel complex $Ni(PPh_3)_4$ is usually generated in situ by reduction of $NiCl_2 \cdot (PPh_3)_2$ or $Ni(acac)_2$ with ethylmagnesium bromide (e.g. [9]) or diisobutylaluminum hydride (e.g. [10]) in the presence of an additional amount of triphenylphosphane. The latter is omitted when zerovalent Pd is generated from $PdCl_2 \cdot (PPh_3)_2$ and the aluminum hydride (e.g. [10]). The reaction of ester enolates, e.g. $LiCH_2COO\text{-}t\text{-}C_4H_9$, with aryl and alkenyl halides has been performed in the presence of Ni^0, generated from nickel(II) bromide and *n*-butyllithium [11]. It should be noted that no coupling product was obtained when the nickel catalyst was generated in the presence of triphenylphosphane or when $Ni(PPh_3)_4$ was used.

In many cases, bidentate phosphanes gave better results than monodentate phosphanes. The reason for this is that the organic groups introduced by oxidative addition and transmetallation have to be in the *cis*-position for an easy reductive elimination. This condition is automatically met in the case of a bidentate phosphane. Many cross-couplings have been succesfully achieved with $NiCl_2$·1,3-bis(diphenylphosphino)propane ($NiCl_2 \cdot$dppp) [8]. We found $NiCl_2 \cdot$dppp much more active than $NiCl_2 \cdot (PPh_3)_2$ in the coupling of 2-thienylmagnesium bromide with 2-bromopyridine. In reactions involving sterically hindered Grignard reagents (e.g. mesitylmagnesium bromide) $NiCl_2 \cdot (PPh_3)_2$ works better than $NiCl_2 \cdot$dppp [7].

Of the various nickel-bidentate complexes $NiCl_2 \cdot$dppp has been reported to be the most efficient one in the reaction of chlorobenzene with *n*-butylmagnesium bromide [8].

In the $Pd(PPh_3)_4$-catalyzed coupling of *o*-bromofluorobenzene with *p*-fluorophenylmagnesium bromide we found much homo-coupled product; using $PdCl_2 \cdot$dppb or $PdCl_2 \cdot$dppf the reaction proceeded considerably faster, while the amount of the (undesired) homo-product was ~5% only [12].

Whereas Grignard reagents prepared from primary alkyl halides couple in a satisfactory manner with vinylic and aryl halides, the Ni-catalyzed reaction of secondary and tertiary-alkyl Grignard compounds can be accompanied by alkyl group isomerization from secondary and tertiary to primary and secondary, respectively, and by reduction of the aryl halide to the arene (see Sect. 11.9, side reactions). The isomerization occurs to a considerable extent with $NiCl_2 \cdot (PPh_3)_2$ and $NiCl_2 \cdot Me_2P(CH_2)_2PMe_2$, but is almost negligible if the ligands of nickel are $Ph_2PCH_2CH_2PPh_2$, $Ph_2P(CH_2)_3PPh_2$ and 1,1'-bis(diphenylphosphino)ferrocene. Reduction is influenced in the same way [8].

Satisfactory yields in the reaction between bromobenzene and $H_2C{=}CHCH_2MgBr$ or $CH_3CH{=}CH\text{-}MgBr$ have been obtained only with $NiCl_2 \cdot Me_2P(CH_2)_2PMe_2$ [8].

Kumada et al. found $Ni(acac)_2$ more active than nickel-phosphane complexes in the reactions of Grignard reagents with silyl enol ethers, $RCH{=}CH\text{-}O\text{-}SiR'_3$. In many cases, isomerizations to the most stable alkene occurred with $Ni(acac)_2$ [13].

Whereas with $NiCl_2 \cdot$dppp successful substitution of SCH_3 in 2-methylthiobenzothiazole by phenyl or primary alkyl could be achieved in reactions with Grignard reagents, isopropylmagnesium bromide and cyclohexylmagnesium bromide reacted very sluggishly. However, $NiCl_2 \cdot$dppe proved to be a very efficient catalyst [14].

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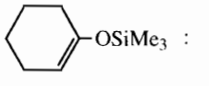
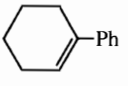
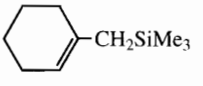
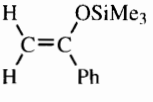
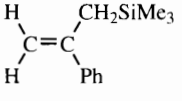
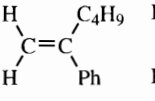
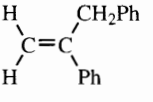
11.4 Leaving Groups

The most commonly used leaving groups are (in the order of decreasing reactivity) I, OTfl (trifluorosulfonate), Br and Cl. Chlorides react less easily in palladium-catalyzed reactions, but are often useful substrates in reactions under the influence of nickel complexes. The readily available trimethylsilyl enol ethers [1] react with Grignard reagents under the catalytic influence of $Ni(acac)_2$, $NiCl_2$·dppf and $NiCl_2(PPh_3)_2$ to give the cross-coupling products in fair to good yields [2].

$$R^1R^2C{=}C(R^3)OSiMe_3 + R^4MgX \xrightarrow{\text{"Ni"}} R^1R^2C{=}CR^3R^4$$

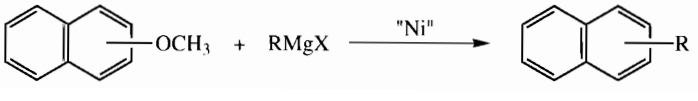
Examples of products obtained by this method are:

from  :



from  :




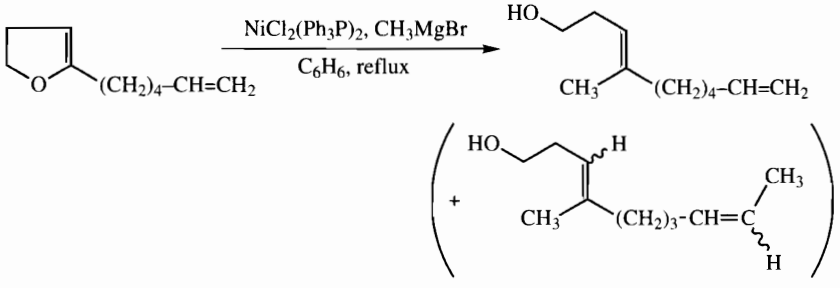
Application of the $Ni(acac)_2$ method led in some (other) reactions to $Z \rightarrow E$-isomerization of the product, but this subsequent reaction could be avoided by using $NiCl_2$·dppf. Other enol ethers and some methoxyarenes react with Grignard reagents in the presence of nickel complexes to give mixtures of the substitution (= coupling) and reduction product in good yields [3–7]. The reactions with the olefinic ethers proceed with retention of the stereochemistry, provided that subsequent isomerization reactions induced by the nickel catalyst are avoided by a careful work up [5].

$$\begin{matrix} R'CH{=}CH{-}OR'' \\ E \\ Z \end{matrix} + RMgX \xrightarrow{\text{"Ni"}} \begin{matrix} R'CH{=}CHR \\ E \\ Z \end{matrix} \quad (+\ R'CH{=}CH_2)\ \text{reduction product}$$



The reduction products are formed if the group R of RMgX possesses a β-hydrogen atom. This side reaction occurs to a lesser extent if $NiCl_2$·1,2-bis(diphenylphosphino)propane ($NiCl_2$·dppp) is used instead of $NiCl_2$·$(PPh_3)_2$ [5, 6]. These coupling reactions have been usefully applied in the synthesis of homoallylic alcohols from cyclic enol ethers [5, 6], e.g.:

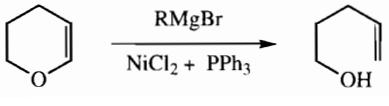
Preparation of E-4-Methyldeca-3,9-dien-1-ol:



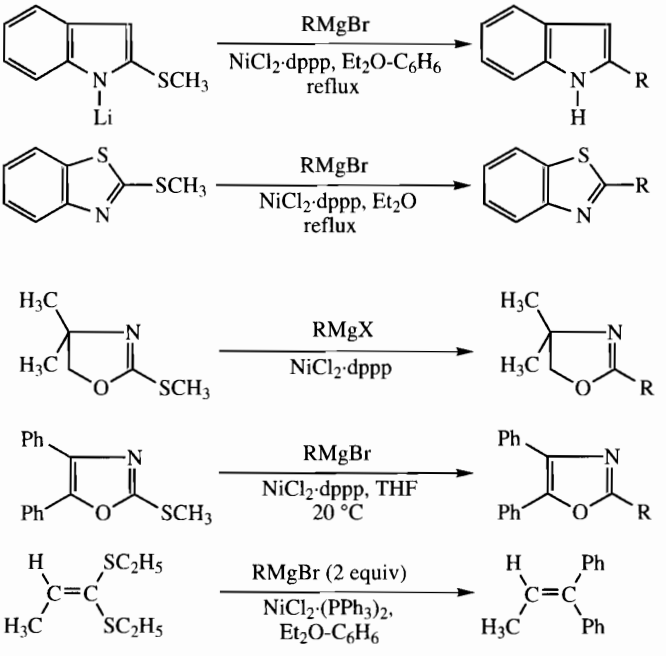
To bis(triphenylphosphane)nickel(II)chloride (6.85 g, 10.5 mmol) in dry benzene (150 ml) under argon at room temperature was added dropwise methylmagnesium bromide (17 ml, 3 M solution in diethyl ether, 51 mmol) (generation of the Ni^0-catalyst). After stirring for 15 min at room temperature more methylmagnesium bromide (70 ml of 3 M solution, 210 mmol) was added before most of solvent was removed in vacuo by rotary evaporation. The residue was suspended in benzene (200 ml) and 2,3-dihydro-5-(hex-5-enyl)furan (15.9 g, 105 mmol, see scheme above) in benzene (20 ml) was added. The mixture was refluxed for 45 min, cooled to 0 °C and quenched by pouring as a slow stream into a vigorously stirred saturated aqueous ammonium chloride solution (350 ml) at 0 °C. Stirring was continued for 20 min before the organic layer was separated and the aqueous phase extracted with diethyl ether (4 times). The combined organic layers were dried ($MgSO_4$), the solvent removed and the residue chromatographed on silica (diethyl ether : light petroleum, 1 : 3 to 1 : 1 as eluent) to remove the biphenyl impurity. Kugelrohr distillation (200 °C/14 mmHg) gave the alcohol (16.8 g, 96% yield) as a colourless oil. Gas chromatography (6% OV 101 on chromosorb, 150 °C) indicated that the product was >99% *E*-isomer.

If during the aqueous quench the stirring was inefficient, substantial amounts of the isomeric products (see scheme above) were formed in which the C-3 – C-4 double bond had isomerized and the terminal alkene had rearranged itself into the chain (*E*- and *Z*-isomers). When the quench was performed by slowly adding water, the isomeric products accounted for >80% of the reaction mixture.

This ring opening reaction mentioned above is one of the crucial steps in a synthesis of zoapatanol [8]. Analogous useful syntheses with dihydropyran derivatives have been carried out [4]. The formation of reduction products from dihydropyran is especially favoured if isopropyl- or cyclohexylmagnesium halide in combination with a 1:1 mixture of $NiCl_2$ and PPh_3 is used:



The methylthio group in 2-methylthioindole [9], 4-methylthiopyridine [9], 2-methylthiobenzothiazole [10, 17], 2-methylthiooxazolines [11], 2-methylthiooxazoles [12], and 1-alkylthio- or 1,1-bisalkylthioalkenes [13, 14] has been replaced by the group R in a Grignard reagent, using nickel complexes as pre-catalysts, e.g.:



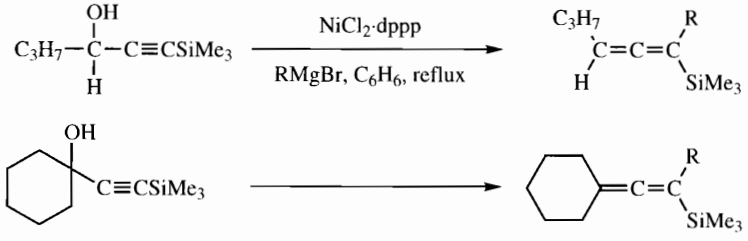
The reaction of 2-methylthiooxazolines was also readily achieved under the catalytic influence of $PdCl_2$·1,1'-bis(diphenylphosphino)ferrocene ($PdCl_2$·dppf) [11]. As in the case of ethers, the substitution (cross-coupling) may be accompanied by reductive removal of the SCH_3 group. This reaction is promoted by using Grignard compounds containing β-hydrogen atoms, particularly isopropyl- and cyclohexylmagnesium halide, and monodentate nickel, especially the 1 : 1 mixture of $NiCl_2$ and triphenylphosphane. For example, *p*-(*t*-butyl)thioanisole (*p*-$Bu^tC_6H_4SCH_3$) was converted into *t*-butylbenzene with high yields [7, 9].

2-Butyl-4,5-diphenyloxazole [12]: To a stirred solution of 2-methylthio-4,5-diphenyloxazole (1.0 g, 3.745 mmol) in THF (40 ml) are added a solution of butylmagnesium chloride (5 mmol) in ether and 1,2-bis(diphenylphosphino)-ethanenickel(II)chloride (50 mg, 0.0947 mmol, 2.5 mol%). After 18 h the reaction mixture is quenched by pouring onto saturated aqueous ammonium chloride (50 ml). After the usual work-up, the crude product is purified by flash chromatography over silica gel using petroleum ether / diethyl ether (9/1) as eluent. Yield 1.0 g (3.6 mmol, 96%), b.p. 128–130 °C/0.1 torr.

Using the same catalyst ($NiCl_2$·dppe) we succeeded in preparing *n*-alkyl-, phenyl-, isopropyl- and cyclohexylbenzoxazole and the corresponding benzothiazoles in good yields by heating mixtures of 2-methylthiobenzoxazole or 2-methylthiobenzothiazole

and Grignard compounds in diethyl ether under reflux (cf. scheme above). With $NiCl_2$·dppp the couplings with isopropyl- and cyclohexylmagnesium halides proceeded very inefficiently [17].

Interestingly, trimethylsilyl-protected secondary and tertiary acetylenic alcohols (primary alcohols gave complicated product mixtures) reacted with methyl- and arylmagnesium halides in the presence of $NiCl_2$·dppp to give allenes by 1,3-substitition [14].



With arylmagnesium halides the reactions were much faster than with methylmagnesium halide.

Analogous reactions with allylic alcohols are described by Felkin at al [15].

Furan, thiophene, selenophene and tellurophene have been reported to undergo ring opening (with the formation of 1,3-dienes) with Grignard reagents in the presence of $NiCl_2(PPh_3)_2$ or $NiCl_2$·dppp [16].

Kumada et al. [18] reported the successful cross-coupling of aryl phosphates ($ArOP(O)(OEt)_2$, easily obtainable from the phenol and $ClP(O)(OEt)_2$) with Grignard and aluminum reagents in the presence of $Ni(acac)_2$, $NiCl_2(PPh_3)_2$ or $NiCl_2$·dppp. Aryl phosphates are less reactive than the analogous bromides and iodides.

Julia et al. [19] used *t*-butylsulfonyl as leaving group in the reaction of methyl- and phenylmagnesium halide with olefinic sulfones (>C=C(R)–SO_2–*t*-Bu) catalyzed by $Ni(acac)_2$.

Gais and Bülow [20] described the $NiCl_2$·dppp-catalyzed cross-coupling of a chiral sulfoximine (with the structure system C=CH–SO(Ph)=NMe) with organozinc reagents $Zn(CH_2SiMe_2X)_2$ (X = CH_3 or *i*-C_3H_7). This reaction required the assistance of magnesium bromide.

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11.5 Couplings with Organolithium Compounds

Although organolithium compounds are in many cases readily available by deprotonation or halogen–metal exchange reactions [1, 2], their use in transition metal-catalyzed cross-couplings is subject to limitations connected with their high reactivity towards some functional groups. If the reaction partner (as in most cases) is a halide, dehydrohalogenation (with olefinic halides) or halogen–lithium exchange (and subsequent transition metal-catalyzed homo-coupling [9]) with olefinic and (het)aryl halides may occur. Nevertheless, some successful couplings with organolithium compounds have been reported. In these reactions only palladium catalysts can be used. Organolithium compounds RLi may give palladates Li_2PdR_4 with the palladium intermediates, $R'Pd(PPh_3)_2Hlg$ formed by oxidative addition of Pd^0 to the organic halide R'Hlg, thus retarding the desired reductive elimination that yields the cross-coupling product RR'. In cross-coupling reactions with organozinc halides, which proceed much better, this retardation was not observed [8].

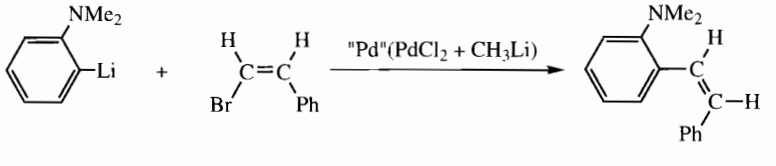
Lithiated allenic hydrocarbons and ethers couple with iodobenzene and *E*- or *Z*-1-iodooctene in the presence of tetrakis(triphenylphosphane)palladium or zerovalent palladium, generated in situ from $PdCl_2$, triphenylphosphane and diisobutylaluminum hydride (DIBAH) to give substituted allenes or allenic ethers in good yields [3].

$$R^1R^2C{=}C{=}CHLi \xrightarrow{R^3I,\ \text{"Pd"}} RR'C{=}C{=}CHR^3 \quad (R^3 = \text{Ph, } E\text{- or } Z\text{-}C_6H_{13}CH{=}CH\text{–})$$

$$H_2C{=}C{=}C(Li)OCH_3 \xrightarrow{PhI} H_2C{=}C{=}C(Ph)OCH_3$$

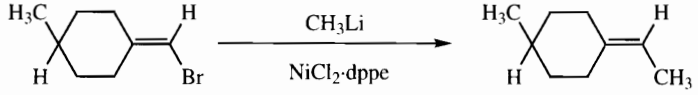
$$LiCH{=}C{=}C(C_4H_9)OCH_3 \xrightarrow{PhI} PhCH{=}C{=}C(C_4H_9)OCH_3$$

In analogous procedures, alkyllithium, 2-furyl- and 2-thienyllithium and 2-lithiodimethylaminobenzene were reacted with *Z*- or *E*-β-bromostyrene or *p*-iodotoluene. As in the case of the lithiated allenes, the couplings proceeded with retention of the *E*- or *Z*-configuration [4].



A serious practical drawback of these procedures is the need to apply inversed-order addition, especially in the case of the thermally unstable lithiated allenes, whose solutions have to be maintained at very low temperatures during the period of addition. If the solutions are too concentrated, dehydrobromination of the bromoalkene may occur as a side reaction.

Walborski et al. [5] described the following reaction with $NiCl_2$·1,2-bis(diphenylphosphino)ethane ($NiCl_2$·dppe):



Lithiated esters $LiC(R^1)(R^2)COOR^3$ (R^1 and R^2 = H, CH_3 or Ph) and the lithiated crotonic ester $LiCH_2CH{=}CHCOOC_2H_5$ have been found to react with iodobenzene and olefinic bromides to give C-functionalized derivatives [6] (cf. [7]). The catalyst was generated from nickel(II) bromide and *n*-butyllithium at low temperatures. Unexpectedly, no reaction occurred if tributylphosphane or tri-phenylphosphane was added before or after the reaction of $NiBr_2$ with *n*-butyllithium. Tetrakis(tri-phenylphosphane)nickel(0) was inactive in the reaction of $LiCH_2COO\textit{t}\text{-}C_4H_9$ with $CH_3CH{=}CHBr$.

$$LiC(R^1)(R^2)COOR^3 \xrightarrow[\text{“Ni”, THF, 20 °C}]{\text{RI or RBr}} RC(R^1)(R^2)COOR^3$$

$R^1 = R^2 = H$ or CH_3

$R^1 = H$, $R^2 = CH_3$ or Ph

$R^3 = \textit{t}\text{-}C_4H_9$ or C_2H_5

R = Ph, $CH_3CH{=}CH{-}$, $H_2C{=}C(CH_3){-}$

$$LiCH_2CH{=}CHCOOC_2H_5 \xrightarrow{CH_3CH{=}CHBr} CH_3CH{=}CHCH_2CH{=}CHCOOC_2H_5$$

The reactions with $CH_3CH{=}CHBr$ proceeded with retention of the stereochemistry. Optimal yields (varying from moderate to good) were obtained only when using stochiometrical amounts of nickel bromide.

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11.6 Couplings with Organomagnesium and Organozinc Halides

An impressive number of cross-couplings with organomagnesium halides and substrates lacking reactive functional groups have been reported. They are treated together with the reactions of organozinc derivatives, because the methods (directly from the metals and an organic halide or from an organolithium compound and the metal halide) of preparing organomagnesium and organozinc halides are similar.

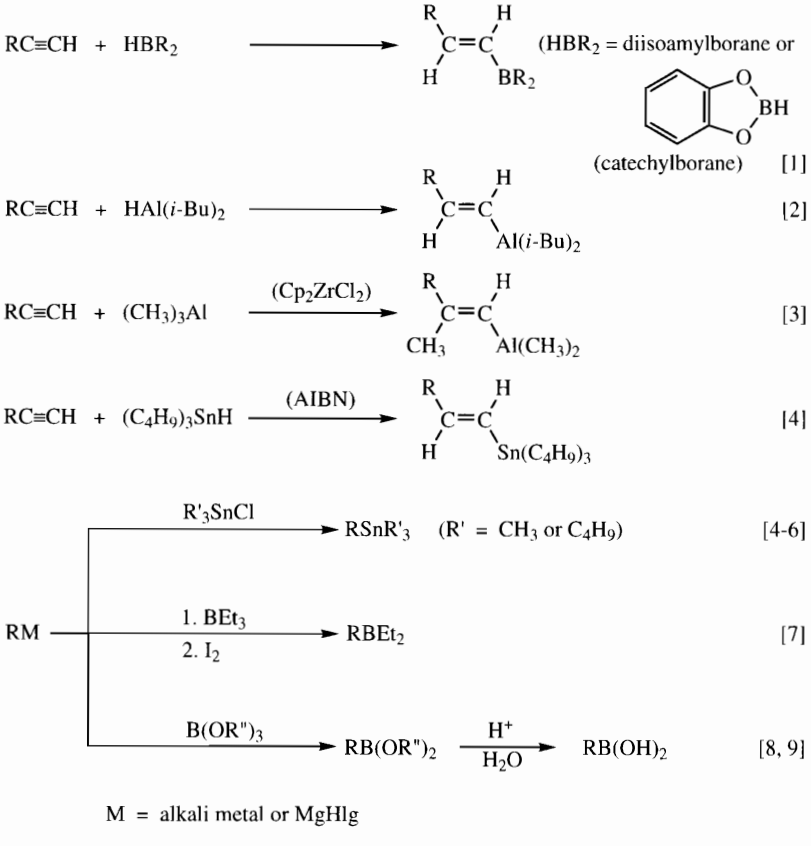
Organozinc intermediates have the advantage that they are compatible with functional groups (NO_2, C≡N, CO, COOR) that easily interact with organomagnesium compounds, but also in many couplings with substrates lacking such functionalities better results have been obtained with organozinc compounds. Transfer of the organic group from RM to the transition metal in exchange for the leaving group (halide, triflate, etc) is more efficient for organozinc than for organomagnesium compounds.

For the substitution of ether or thioether groups in alkenylic, aromatic or heteroaromatic ethers or sulfides organo*magnesium* compounds (in combination with a nickel catalyst) seem to be required.

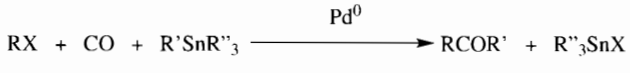
The transition-metal-catalyzed cross-couplings with organomagnesium and organozinc compounds allow derivatizations of heterocyclic compounds that are unachievable by other methods: for example, the introduction of a saturated-alkyl chain at the 3-position of thiophene by reacting 3-lithiothiophene with an alkyl halide or tosylate requires conditions (temperature) under which ring opening can occur. Moreover, the alkyl halide will experience serious competition from the butyl bromide that is formed during the generation of 3-thienyllithium from 3-bromothiophene and *n*-butyllithium. Alkylation of nitrogen-containing heterocycles (pyridines, azoles) by classical procedures is difficult because of the low stability of their alkali metal derivatives. In the Tables 9–20, cross-couplings with the various organomagnesium and organozinc compounds are summarized. The lists are illustrative rather than exhaustive, as some important papers may have been overlooked and from a number of publications only representative examples of reactions have been selected.

11.7 Cross-Couplings with Organoaluminum, Organoboron and Organotin Compounds

The principal methods for the preparation of aluminum, boron and tin compounds used in transition metal-catalyzed cross-couplings are depicted in the general schemes below:



The ready accessibility of stereo-defined alkenylaluminum, -boron and -tin compounds constitutes a significant extension of the scope of transition-metal-catalyzed cross-couplings. The versatility of tin derivatives in these couplings has been increased through the possibility of combining the coupling with the introduction of a carbonyl group when the reaction is carried out in an atmosphere of carbon monoxide [4, 10].



Reactive functional groups such CN, NO_2, CH=O, COOR are tolerateRd in couplings with organotin and -boron intermediates. Cross-couplings with aluminum, boron and tin

compounds are extensively used in synthesis of natural products and in the construction of bi- and tricyclic aromatic and heteroaromatic compounds (e.g. [6, 9, 11–18]).

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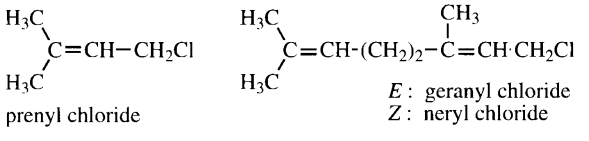
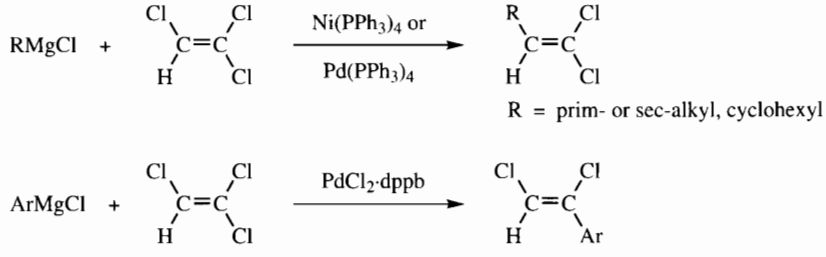
11.8 Regiochemical and Stereochemical Aspects

The palladium-catalyzed reaction of alkenylalanes and arylzinc halides with γ,γ-unsubstituted, γ,γ,-disubstituted and γ-monosubstituted allylic electrophiles has been investigated by Negishi and coworkers [1, 2]. In all cases there is a strong preference for coupling at the primary carbon atom of the allylic substrates. Thus, prenyl chloride, geranyl and neryl chloride or acetate reacted with very high regio- and stereoselectivity. Although the selectivity in the coupling of *E*-2-methyl-1-octenyl-dimethylalane with *E*-crotyl acetate was as high as 80% [2] (10% of *E,Z*-$C_6H_{13}(CH_3)CH{=}CH\text{-}CH_2CH{=}CHCH_3$ and 10% of *E*-$C_6H_{13}C(CH_3){=}CH\text{-}CH_2CH(CH_3)CH{=}CH_2$), this result is not satisfactory, since the products cannot be easily separated. Stille et al. obtained similar results in Pd-catalyzed cross-couplings of allylic substrates with organotin compounds [3] (cf. [4]):

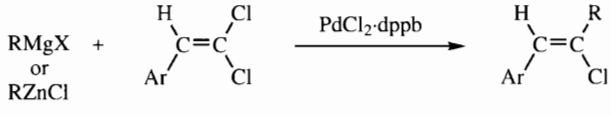


Couplings with allylic tin compounds occur with transposition with respect to the tin compound. French investigators [5] reported the reaction of propargylic halides with alkyl- and arylmagnesium halide RMgX proceeding under the influence of $Pd(PPh_3)_4$. As in the copper halide-catalyzed reaction allenes were formed. Elsevier et al. [6] found that the Pd-catalyzed reaction of phenylzinc chloride with optically pure propargylic substrates R(–)-HC≡C–CH(Ph)X (X = OAc, CF_3COO, $CH_3S(O)O$) proceeded with ~80% anti-stereoselectivity to give R(–)-PhCH=C=CHPh as the predominant product. Similar or higher stereoselectivities were found in reactions of PhZnCl with propargylic esters HC≡C-C(R^1)(R^2)X in which C(R^1)(R^2) represents ring D of a stereoid.

The Ni- or Pd-catalyzed reactions of alkyl-(or cyclohexyl)magnesium halide [7] and aryl-(or hetaryl)magnesium halides [8] with trichloroethene remarkably show opposite regiochemistry:



In 1,1-dichloroalkenes the chlorine atom in the trans position of the substituent is specifically substituted [8]:



Reactions of organoaluminum, -boron and -tin derivatives with alkenyl halides (or triflates) generally proceed with retention of the double bond geometry in both reaction partners [9–11]. Pd-catalysts give a better stereoselectivity even than do Ni-complexes in couplings with alkenylalanes [9]. Whereas in Ni- and Pd-catalyzed couplings with alkenyl halides RCH=CH–Hlg their stereo-structure is retained in the product [12] (an exception is $BrCH=CHOC_2H_5$ [13]; cf., however [14]), a non-specific coupling was observed between alkenylic Grignard reagents RCH=CHMgBr and aryl halides under the influence of $NiCl_2$·1,2-bis(dimethylphosphino)ethane ($NiCl_2$·dmpe) [15]. The loss of stereochemistry has been explained by Kumada et al. [15]. Using $Pd(PPh_3)_4$ as a catalyst, Dang and Linstrumelle [16] found complete retention of configuration in reactions of olefinic iodides with alkenylmagnesium halide. Reactions of organotin and -aluminum compounds and allylic or benzylic halides have been found to proceed with inversion at the allylic or benzylic carbon atom: this is a result of retention during the reductive elimination and inversion during the oxidative addition step [17–20].

A number of research groups have carried out cross-couplings between racemic Grignard reagents and alkenyl halides under the influence of nickel or palladium catalysts containing chiral ligands [21], e.g.:

$$PhCH(CH_3)MgCl + BrCH{=}CH_2 \xrightarrow{\text{chiral catalyst}} PhC^*H(CH_3)CH{=}CH_2$$

In many cases modest enantiomeric excesses were obtained. The highest chiral induction (80–90% e,e) was achieved with β-aminoalkyl phosphanes as ligands.

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11.9 Mechanism and Side Reactions

The following general scheme (Fig.1) may serve as a working hypothesis for nickel- and palladium-catalyzed cross-couplings [1].

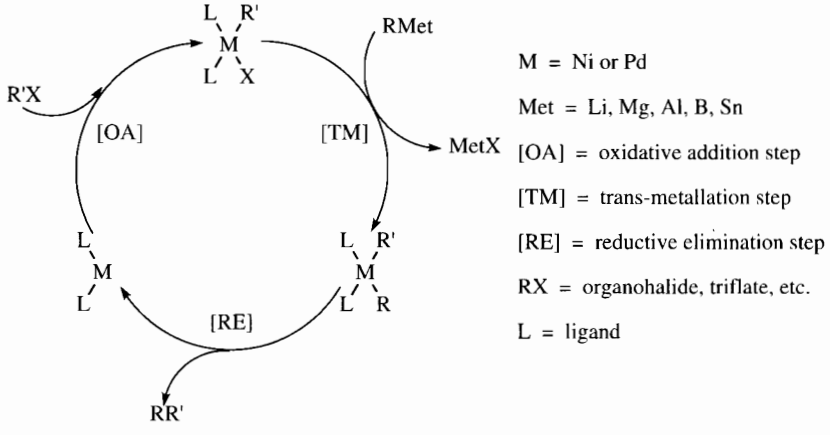


Fig. 1

The actual catalyst in this cycle, the zerovalent species ML_2 may be generated in the following reaction of the pre-catalyst with the organometal derivative RMet [2]:

In this reaction the homo-coupled product RR is formed in an amount corresponding to the quantity of pre-catalyst used. In some cases this may cause problems with the purification of the desired product, especially when the amount of catalyst is relatively large (in small-scale reactions). Other methods for generating the catalytic species are treatment of the dihalogeno-metal complex with diisobutylaluminum hydride [4] in the presence of at least two equivalents of (mono-dentate) ligand (e.g. Ph_3P) or with methylmagnesium halide (e.g. [3]). In many Pd-catalyzed reactions, however, $Pd(PPh_3)_4$ is used. It can enter into the cyclus by dissociation into $Pd(PPh_3)_2$ and PPh_3, followed by oxidative addition of R'X.

It is assumed on the basis of experimental evidence that the trans-metallation (TM) step in many Pd-catalyzed cross-couplings is rate-determining [4]. For some other Pd- and Ni-catalyzed reactions alternative mechanisms have been proposed [4–7].

Cross-couplings can be accompanied to a higher or lesser extent by homo-coupling, reductive elimination and isomerization, in the latter case either *Z* to *E*, or *sec*- or *tert*-alkyl to *prim*- or *sec*-alkyl, respectively.

One of the most pronounced examples of cross-homo scrambling is the Pd-catalyzed reaction of alkynylmetals RC≡CM (M = Mg, Al, Zn, Sn, etc.) with R'C≡CX (X = Cl, Br, I). A nearly statistical mixture of RC≡CC≡CR, RC≡CC≡CR' and R'C≡CC≡CR' is formed in high yield [8] (cf., however [8a]). Homo-coupling was found to be most serious with organolithium compounds compared to the organomagnesium and

-zinc halides in their Pd^0-catalyzed reaction with *E*-1-iodooctene. The organozinc halide gave only a few percent of homo products. The extent to which these side products are formed may greatly depend upon small variations in the structures of the organometallic partner and the organohalide. Whereas the $NiCl_2$·dppp-catalyzed reaction of Grignard compounds with 3-bromothiophene in diethyl ether gives 3-alkylthiophenes in excellent yields [9], under similar conditions very low yields of 2-alkylthiophenes are obtained [10]. Reactions with organolithium compounds with organo-halides can lead to halogen-lithium exchange. This reaction does not require the aid of the transition metal catalyst. The homo-products are formed in a catalyzed cross-coupling.

$$\text{RLi} + \text{R'Hlg} \rightleftharpoons \text{RHlg} + \text{R'Li}$$

$$\text{RLi} + \text{RHlg} \xrightarrow{\text{"Ni" or "Pd"}} \text{RR}$$

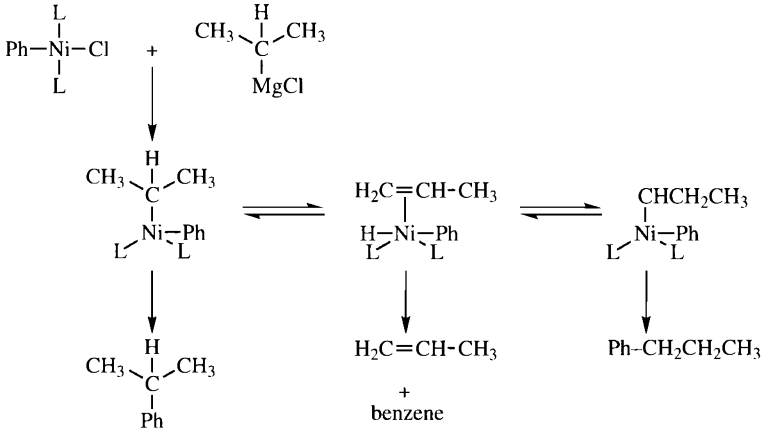
$$\text{R'Li} + \text{R'Hlg} \xrightarrow{\text{"Ni" or "Pd"}} \text{R'R'}$$

$$\text{RLi} + \text{R'Hlg} \xrightarrow{\text{"Ni" or "Pd"}} \text{RR'}$$

We found that the $NiCl_2$·dppp-catalyzed reaction of *iso*-propylmagnesium bromide with 2-bromothiophene gives significant (good yield) amounts of 2,2'-bithienyl, presumably as a result of halogen–metal exchange and subsequent reaction of 2-thienylmagnesium bromide with 2-bromothiophene. We also showed that the exchange reaction can proceed in the absence of a transition metal catalyst.

Another possibility for the formation of homo-coupling products is some kind of radical process. Little is known, however, about the mechanisms by which homo-coupled products are formed.

The isomerization of secondary or tertiary alkyl groups to primary or secondary alkyl groups respectively, often observed in Ni-catalyzed reactions of aryl halides with secondary or primary alkyl groups, has been explained by Kumada with the following scheme [12]:



In this scheme, a hydrido(olefin) nickel intermediate equilibrates with two σ-alkylnickel compounds. This σ–π conversion is facilitated by an increase in electron densi-

ty on the nickel caused by electron donation from the ligands. The hydride complex partly decomposes to propene and benzene.

The reaction of homoallyl bromide $H_2C{=}CHCH_2CH_2Br$ with phenylmagnesium bromide in the presence of $NiCl_2$·dppp gave only traces of the cross-coupling product $H_2C{=}CHCH_2CH_2Ph$, the main products being the isomers $H_2C{=}CHCH(CH_3)Ph$ and $CH_3CH{=}CHCH_2Ph$, formed by a similar mechanism [12]. The secondary to primary isomerization can be largely prevented by using $PdCl_2$·dppf as catalyst [13]. Negishi et al. reported clean palladium-catalyzed cross-couplings with homoallyl- ($H_2C{=}CHCH_2CH_2-$), homopropargyl- ($RC{\equiv}CCH_2CH_2-$) and homobenzyl- ($PhCH_2CH_2-$)-zinc halides [14,15].

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11.10 Practical Aspects of Transition-Metal-Catalyzed Couplings

Reactions between Grignard compounds and organic halides catalyzed by nickel complexes are usually carried out by gradually adding an ethereal solution of the Grignard derivative to a solution of the organic halide in ether or THF, containing a catalytic amount of the nickel precatalyst. First a few ml of the Grignard solution are added at room temperature, or a somewhat lower temperature, in order to generate the actual Ni^0-catalyst. If the ligand is bidentate (e.g. 1,3-bis(diphenylphosphino)-

propane), no additives are used. In the case of monodentate complexes (e.g. $NiCl_2 \cdot (PPh_3)_2$) this generation is carried out in the presence of two equivalents of triphenylphosphane. After the generation of the catalytic system (requiring a few minutes, visible from a distinct change in colour) the remaining Grignard solution is added over a certain period. Since successful Ni-catalyzed reactions usually are very fast, the reaction is visible from a strong heating effect that causes reflux of the ether. In order to be sure that the reaction is complete, a small amount of Ni precatalyst may be added after the reaction has subsided and the solution has been heated under reflux for an additional period. If there is no temperature response to this addition of precatalyst, the reaction may be considered to be complete (as GLC monitoring will also show). Vinyl chloride and bromide react very readily, and in view of their high volatility, the reaction should be carried out at temperatures that are lower than the boiling point of diethyl ether. Too fast addition of the Grignard solution may result in a vigorous reaction, and part of the halide may evaporate from the solution.

Some Grignard compounds are slightly soluble in ether or DMF (e.g. 1-naphthylmagnesium bromide), making experimentation difficult. A suitable solvent, e.g. benzene, should then be added to achieve dissolution of the Grignard compound.

The work-up is best carried out by cautiously pouring the reaction mixture (often a dark brown solution or suspension) into an aqueous solution of ammonium chloride. Due to the formation of decomposition products, some problems may be encountered during the separation of the layers. In reactions with thiophene derivatives, we often noticed the smell of hydrogen sulfide during the hydrolyzing procedure. Apparently, cleavage of the ring can occur. If the product is stable towards acids, a small amount of dilute acid may be added in order to achieve a smoother separation of the layers. Traces of nickel compounds can be removed by flash chromatography on alumina or silica gel prior to carrying out distillative purification or crystallization. In these cases, distillation or crystallization is often not necessary and the pure product is obtained after removal of the solvent under reduced pressure.

Palladium-catalyzed cross-couplings with RMgBr or RZnCl usually proceed much less vigorously, making prolonged refluxing often necessary. Using diethyl ether, the attainable temperature range is limited, but with THF as solvent or as cosolvent the temperature can rise to a level on which the reaction proceeds at an acceptable rate. In the case of reactions performed on a modest (i.e. 20.2 molar) scale all reagents can be combined, prior to heating the mixture. The work-up is similar to that applied in Ni-catalyzed reactions.

If a Ni-catalyzed reaction gives unsatisfactory results (much homo-coupling product or intractable material), the general advice that can be given is to try the reaction with a Pd-catalyst. If $Pd(PPh_3)_4$ does not work or the result is not satisfactory (e.g. homo-coupling), variants, notably $PdCl_2 \cdot$dppb or $PdCl_2 \cdot$dppf may be tried. A general, more or less empirical rule is that these catalysts can work more selectively than $Pd(PPh_3)_4$ in couplings with organomagnesium and -zinc intermediates.

Palladium-catalyzed couplings with organoboronic acids, $RB(OH)_2$, and organotrialkyltin derivatives, $RSnMe_3$ or $RSnBu_3$, are in most cases simply performable. The organometallic compound, substrate, catalyst and additive are added together in a suitable solvent and the mixture is heated "until GLC or TLC monitoring has indicated complete conversion". In many cases, the reaction times mentioned in literature

procedures can be shortened considerably by using less solvent. Especially in reactions with boronic acids completion of the reaction is visible from the black colour of colloidal metallic palladium. In some cases, reaction times can be shortened by using a suitable solvent (e.g. DMF in reactions of stannanes) or cosolvent (DME in reactions with boronic acids, which require the assistance of aqueous alkali carbonate).

The most commonly used catalyst for couplings with organoboron and -tin intermediates is $Pd(PPh_3)_4$, but there are several examples of couplings in which the pre-catalyst does not work satisfactorily. As there is not yet a profound understanding of the mechanism, the method of trial and error [8] has to be followed in order to find the most satisfactory combination of pre-catalyst [e.g. $PdCl_2$·dppb, $Pd(OAc)_2$, $PdCl_2$·dppf, $PdCl_2$·$(CH_3CN)_2$, $Pd_2(dba)_3$·$CHCl_3$], solvent (e.g. DMF) and additive (e.g. triethylamine in the case of couplings with boronic acids, and CuO or Ag_2O in Stille-couplings with 2-pyridylstannanes [9]). For the use of other, more successful catalyst-solvent-additive systems in couplings with certain boronates see [1-4]. Especially the so-called ligandless palladium [2,5] in pre-catalysts, such as $Pd(OAc)_2$ and $Pd_2(dba)_3$·$CHCl_3$, has been shown to give better results than the traditional $Pd(PPh_3)_4$ in some cross-couplings with boronates. Triphenylphosphane even seems to inhibit the coupling [2].

A detailed study of the influence of various ligands on cross-couplings with organostannanes in the presence of $Pd_2(dba)_3$·$CHCl_3$ showed large rate accelerations with tri(2-furyl)phosphane and tri-phenylarsane [6] (cf. also [7] for the use of trifurylphosphane).

The extent of homo-coupling in a particular cross-coupling reaction, in general, cannot be predicted by analogical reasoning: for example, whereas 2-furanboronic acid and 2-bromothiophene gave relatively much bifuryl and bithienyl in the $PdCl_2$·dppb-catalyzed reaction, bifuryl was found in much smaller amounts, when 2-bromothiophene was replaced by 4-bromofluorobenzene, while 4,4'-difluorobiphenyl was not detected at all [15].

In palladium-catalyzed ($Pd(PPh_3)_4$ or $PdCl_2$·dppb) couplings of boronic acids with *p*-bromo-*N,N*-dimethylaniline, metallic palladium was formed at an early stage. A more complete conversion could be achieved, however, when the catalyst was added in portions over a certain period [15].

For the isolation of products from reactions with tin derivatives a number of techniques are mentioned in the literature. The crucial problem in all cases is the separation of the desired product from the side product trialkyltin halide. If the scale is very small (1 mmol or less), the reaction mixture may be subjected to column chromatography (Al_2O_3 or SiO_2) [10]. Tri*methyl*tin halides can be removed by aqueous hydrolysis [13]. Unfortunately, the use of trimethyltin derivatives for coupling reactions is limited because of the very high price of the starting reagent trimethyltin chloride. For this reason, the requisite organotin derivatives are mostly prepared with the much cheaper tri*butyl*tin chloride. The tributyltin halide formed as a side product in the cross-coupling can be "neutralized" by addition of an aqueous solution of potassium fluoride, affording the polymeric tributyltin fluoride [11]. A satisfactory separation of the organic and aqueous phase in the slurry may be effected by filtering through a thin (~1 cm) layer of celite on a sintered glass filter. Remnants of tributyltin fluoride should be removable by flash chromatography on Al_2O_3 or SiO_2. However, in

some cases we did not succeed in obtaining "tin-free" products in this way. Others [14] also noticed the sometimes difficult work-up, especially when working on a larger scale.

If the product contains an azomethine function (in derivatives of pyridine or thiazole), treatment of the reaction mixture with dilute hydrochloric acid (cf. [12]) proves to be an effective and quick way to of separating the product from tributyltin bromide. The product is obtained in a pure state by making the acid layer alkaline with an excess of potassium hydroxide.

References (Sect. 11.10)

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15. Observations in the author's laboratory

11.11 Experimental Section[1]

In this section Ni- and Pd-catalyzed cross-couplings between organometallic reagents and organohalides are illustrated with several experimental procedures carried out at the laboratory in Utrecht. As may be noticed, the couplings with Grignard compounds and organozinc halides are represented by relatively many examples. However, most of the coupling reactions that are successful with the combinations of Ni-catalyst and organomagnesium halides and of organozinc halides and Pd-catalyst also give good or even better results when carried out with organoboron- or -tin compounds under the influence of Pd-catalysts. The advantage of many organomagnesium and -zinc halides is their easy preparation, either from the organohalide and metal or by addition of magnesium- or zinc halide to a solution of organolithium derivatives. Organoboron and -tin derivatives have to be prepared in a seperate step and isolated.

In our procedures with organomagnesium and -zinc compounds the complexes $NiCl_2$·dppp, $PdCl_2$·dppb and $PdCl_2$·dppf serve as catalysts. This choice is based upon the general experience that these catalysts work better and more selectively than $NiCl_2(PPh_3)_2$ or $Ni(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ in these cross-coupling reactions. In a few

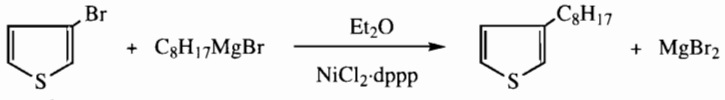
1 With collaboration of Mr. T.H.A. Peters, Dr. H. Hoorn and Mr. F.H. Beyer

cases we showed that the catalysts with bidentate ligands give the best results, but possibly in some other procedures the other catalysts can be successfully used.

The large number of cross-couplings between relatively simple organometallic compounds and organohalides represented in the tables and exemplified with experimental procedures might suggest a very broad scope. Yet there are several reactions that do not proceed satisfactorily. It is, in general, not possible to predict these.

11.11.1 Nickel-Catalyzed Cross-Couplings with Alkylmagnesium Halides

11.11.1.1 3-*n*-Octylthiophene



Scale: 0.05 molar.

Apparatus: 500-ml round-bottomed, three-necked flask equipped with a nitrogen inlet-thermometer combination, a dropping funnel and a reflux condenser; magnetic stirring.

The preparation of pure 3-alkylthiophenes by reaction of 3-lithiothiophene with alkylation reagents is very difficult, since *n*-butyl bromide, formed in the generation of 3-lithiothiophene from 3-bromothiophene and *n*-butyllithium, competes with the alkylation reagents. Alkylations with *sec*-alkyl and *cyclo*-hexyl halides generally give very low yields.

Procedure: After flushing with nitrogen, 40 ml of ether, 0.3 g of $NiCl_2$·dppp and 0.05 mol (8.2 g) of 3-bromothiophene were placed in the flask. About 4 ml of a solution of ~0.6 mol of *n*-octylmagnesium bromide (prepared from 0.7 mol of *n*-octyl bromide) in 65 ml of ether were added at 15 °C. After stirring for 15 min at 15 to 20 °C, the remaining solution of $C_8H_{17}MgBr$ was added dropwise over 30 min at 25 to 30 °C. The dark brown solution was then heated under reflux for an additional half hour. After cooling to 20 °C, the reaction mixture was cautiously poured into 200 ml of 2 M aqueous hydrochloric acid. The aqueous layer was extracted once with pentane. After drying the organic solution over anhydrous $MgSO_4$, the solvent was removed under reduced pressure and the remaining liquid distilled through a 20-cm Vigreux column. 3-*n*-Octylthiophene, b.p. ~130 °C/15 mmHg, n^{20}_D 1.485, was obtained in 90% yield.

^{1}H-NMR spectrum (CCl_4): 7.0–7.15 (m, 1H); 6.65–6.8 (m, 2H); 2.58 (t, 2H) ppm.

11.11.1.2 3-Cyclohexylthiophene

B.p. 110 °C/15 mmHg. It was prepared in ~85% yield from *c*-$C_6H_{11}MgCl$ and 3-bromothiophene. The reaction with this Grignard reagent proceeded more smoothly than the coupling with *n*-octylmagnesium bromide.

11.11.1.3 3-Benzylthiophene

B.p. 130 °C/15 mmHg, n^{20}_D 1.592. It was prepared in ~80% yield from $PhCH_2MgCl$ and 3-bromothiophene.

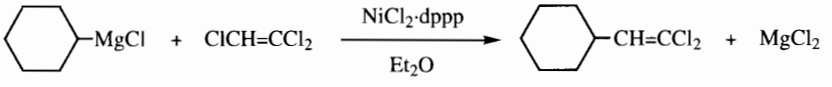
^{1}H-NMR spectrum (CCl_4): 7.0–7.3 (m, 6H); 6.85 (d, 2H); 3.96 (s, 2H) ppm.

Following a procedure similar to the one described above, *2-bromo-(or 2-chloro)thiophene* gives low yields, even when Pd-catalysts and 2-thienylzinc halides were used. The main product was bithienyl, formed by halogen–metal exchange and subsequent cross-coupling of 2-thienylmagnesium or -zinc halide with still unconverted 2-bromothiophene.

The $NiCl_2$·dppp-catalyzed reactions of *alkylmagnesium halides* (including *c*-$C_6H_{11}MgCl$) with *2-bromofuran* and *bromobenzene* were found to proceed successfully.

The reaction of *1-bromo-4-fluorobenzene* with *n*-C_4H_9MgBr in Et_2O in the presence of $NiCl_2$·dppp gave mainly the homo-coupled product *pp'*-difluorobiphenyl. Under similar conditions, *1-methoxy-4-bromobenzene* and *n*-C_4H_9MgBr gave in a high yield *p*-C_4H_9-$C_6H_4OCH_3$, while with *c*-$C_6H_{11}MgCl$ bromine was substituted by the cyclohexyl group. The homo-coupled products were present in traces only.

11.11.1.4 (2,2-Dichlorovinyl)cyclohexane



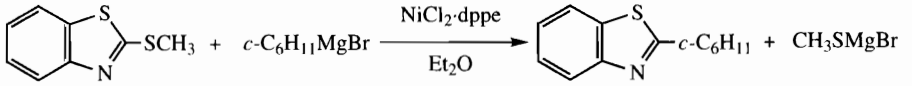
Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and a reflux condenser.

Procedure: (Cf. Ratovelomanana, c.s., Tetrahedron Lett. (1985) 2575 and Minato, c.s., J. Am. Chem. Soc. (1987) 109, 1257.) After flushing the flask with nitrogen, it was charged with 50 g of trichloroethene (large excess) 80 ml of dry ether and 0.5 of $NiCl_2$·dppp. A solution of 0.10 mol of cyclohexylmagnesium chloride in ~80 ml of ether was added at a rate such that a gentle reflux of the ether could be maintained (~30 min). A white suspension was formed. After an additional half hour of refluxing, the suspension was poured into 250 ml of 2 M hydrochloric acid. The aqueous phase was extracted twice with ether. The organic solution was dried over anhydrous $MgSO_4$. Distillation gave the product (b.p. 82 °C/15 mmHg, n^{21}_D 1.4939) in an excellent yield.

^{1}H-NMR spectrum (CCl_4): 5.65 (d) ppm.

11.11.1.5 2-Cyclohexylbenzothiazole



Scale: 50 mmolar.

Apparatus: 250-ml round-bottomed, two-necked flask, equipped with a nitrogen inlet and a reflux condenser; magnetic stirring.

Procedure: (Cf. Takei et al., Chem. Lett. (1979) 1447.) After perfusing the flask with nitrogen, it was charged with 50 ml of diethyl ether, 50 mmol (9.1 g) of 2-methylthiobenzothiazole and 1.2 g of $NiCl_2$·dppe. To the orange suspension was added (by syringe) a solution of 60 mmol of *c*-hexylmagnesium chloride in 120 ml of ether. The orange suspension turned yellow and heat was evolved. After refluxing for 2 h, GLC indicated complete conversion of the starting compound. The solution was cooled to room temperature and subsequently poured into a solution of 20 g of ammonium chloride in 100 ml of water and 50 ml of 1 M aqueous hydrochloric acid. After three extractions with ether, the combined organic solutions were dried over anhydrous K_2CO_3. Distillation through a very short column afforded the substitution product (b.p. ~150 °C/0.5 mmHg) in 73% yield (see Note).

^{1}H-NMR spectrum ($CDCl_3$): 7.98 (d, J = 8.1 Hz, 1H); 7.84 (d, 1 H, J = 7.8 Hz); 7.44 (dd, 1 H); 7.33 (dd, 1H); 3.13 (m, 1H) ppm.

Note: The ether containing some methanethiol was distilled off at atmospheric pressure.

Using $NiCl_2$·dppe a smooth reaction with *isopropylmagnesium bromide* was effected, giving the substitution product in a good yield. With $NiCl_2$·dppp the reactions with *c*-$C_6H_{11}MgBr$ and $(CH_3)_2CHMgBr$ proceeded sluggishly and the expected products were obtained in low yields. *n*-C_4H_9MgBr and PhMgBr, however, reacted satisfactorily under the influence of $NiCl_2$·dppp. *2-Methylthiobenzoxazole* or *4-methyl-2-methylthiothiazole* and the Grignard compounds gave good yields of the substitution products, when $NiCl_2$·dppe was used.

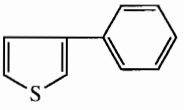
11.11.2 Nickel-Catalyzed Cross-Couplings with Aryl- and Hetarylmagnesium Halides

$$RMgX + R'Br \xrightarrow[NiCl_2\cdot dppp]{Et_2O} RR' \quad (R \text{ and } R' = \text{aryl or hetaryl})$$

Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a nitrogen inlet-dropping funnel combination, a thermometer and a reflux condenser. Magnetic stirring. For starting compounds see Chapter 2, for the catalyst Chapter 1.

11.11.2.1 3-Phenylthiophene



After perfusing the flask with nitrogen, 16.3 g (0.10 mol) of 3-bromothiophene and 100 ml of dry diethyl ether were placed in the flask. $NiCl_2$·dppp (0.5 g) was introduced, followed by 4 ml of a solution of 0.12 mol of phenylmagnesium bromide in 75 ml of diethyl ether. The red suspension soon changed into a yellowish brown solution. After stirring for 10 min at 15–20 °C, dropwise addition of the Grignard solution was started. The rate of addition (over ~15 min) was adjusted such that the ether refluxed gently. When, after completion of the addition, spontaneous refluxing had stopped, an additional amount of 0.2–0.3 g of catalyst was added and the dark red-brown solution was heated for a short period (~30 min) under reflux until GLC indicated complete disappearance of 3-bromothiophene. The reaction mixture was cooled to between 0 and 10 °C and then cautiously poured into a solution of 25 g of ammonium chloride in 150 ml of water (see Note 1). After vigorous shaking and extraction of the aqueous layer with one or two small portions of pentane, the organic solution was dried over anhydrous $MgSO_4$, followed by filtration through a short (~5 cm) column of neutral Al_2O_3 (see Note 2). Concentration of the filtrate gave 3-phenylthiophene as a white powder in an excellent yield (purity by GLC ~96%). Crystallization from an ether/pentane mixture (1 : 3) gave a purer sample.

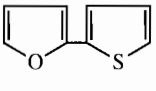
^{1}H-NMR spectrum ($CDCl_3$, 300 MHz): 7.61 (m, 2H); 7.40 (m, 6H) ppm.

Notes:

1. If the product is stable towards acid and does not dissolve into the acidic solution (as do pyridine derivatives!), a small amount of dilute hydrochloric acid may be added to facilitate separation of the layers.
2. Since the product is stable, effective purification can also be performed by distillation in vacuo (b.p. ~130 °C/15 mmHg), using a short column and and air condenser.

The following compounds were prepared by an essentially similar procedure. Yields were generally higher than 70%.

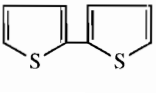
11.11.2.2 2-(2-Thienyl)furan



B.p. 100 °C/15 mmHg, liquid compound, from 2-bromofuran and a 10% molar excess of 2-thienyl-MgBr.

^{1}H-NMR spectrum (CCl_4): 6.85–7.30 (m, 4H); 6.25–6.45 (m, 2H) ppm.

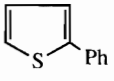
11.11.2.3 2,2'-Bithienyl



B.p. 125 °C/15 mmHg, light-yellow solid, from 2-bromothiophene and a 10% molar excess of 2-thienyl-MgBr.

^{1}H-NMR spectrum (CCl_4): 6.8–7.1 (m) ppm.

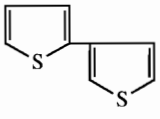
11.11.2.4 2-Phenylthiophene



Solid, b.p. ~120 °C/15 mmHg, from 2-bromothiophene and 20% molar excess of phenyl-MgBr. Additional refluxing for 2 h with two extra small portions of catalyst was necessary.

^{1}H-NMR spectrum ($CDCl_3$, 300 MHz): 7.65 (m, 2H); 7.34 (m, 5H); 7.10 (dd, 1H) ppm.

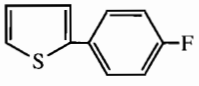
11.11.2.5 2,3'-Bithienyl



White solid after filtration through neutral Al_2O_3, from 3-bromothiophene and 15% molar excess of 2-thienyl-MgBr. Two additional portions of 0.2 g of $NiCl_2$·dppp had to be introduced at 30–35 °C in order to effect complete conversion.

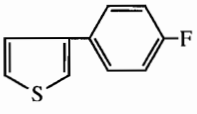
^{1}H-NMR spectrum (CCl_4):7.0–7.4 (m) ppm.

11.11.2.6 2-(4-Fluorophenyl)thiophene



Solid, b.p. 120 °C/15 mmHg, from 1-bromo-4-fluorobenzene and 15% molar excess of 2-thienyl-MgBr.

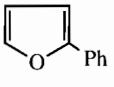
11.11.2.7 3-(4-Fluorophenyl)thiophene



Solid, m.p. 81–82 °C, from 3-bromothiophene and 10% molar excess of *p*-fluorophenylmagnesium bromide.

^{1}H-NMR spectrum (CCl_4): 7.4–7.6 (m, 2H); 6.9–7.2 (m, 5H) ppm.

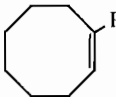
11.11.2.8 2-Phenylfuran



Liquid, b.p. 100 °C/15 mmHg, n^{20}_D 1.598, from 2-bromofuran and 15% molar excess of phenylmagnesium bromide.

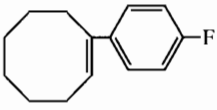
^{1}H-NMR spectrum (CCl_4): 7.6 (m, 2H); 7.2 (m, 4H); 6.5 (m, 1H); 6.3 (m, 1H) ppm

11.11.2.9 1-Phenylcyclooctene



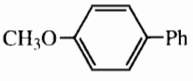
B.p. ~130 °C/15 mmHg, (purity ~90%), from 1-bromocyclooctene and 20% molar excess of phenylmagnesium bromide.

11.11.2.10 1-(4-Fluorophenyl)cyclooctene



Liquid, b.p. ~140 °C/15 mmHg, n^{20}_D 1.544, from 1-bromocyclooctene and 20% molar excess of *p*-fluorophenyl-MgBr. This reaction proceeded rather slowly and the reaction mixture had to be refluxed for 4 h in order to achieve completion.

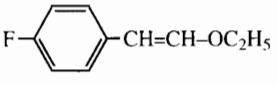
11.11.2.11 4-Methoxybiphenyl



Solid, from *p*-methoxybromobenzene and 25% molar excess of phenylmagnesium bromide. After 1 h reflux THF (50 ml) was added and heating was continued for an additional 3 h, with intermediate addition of two extra 0.2 g portions of catalyst.

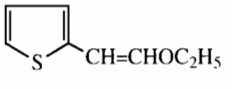
^{1}H-NMR spectrum (CCl_4): 7.1–7.5 (m, 7H); 6.8 (d, 2H); 3.58 (s, 3H) ppm.

11.11.2.12 1-(2-Ethoxyvinyl)-4-fluorobenzene



B.p. 100 °C/15 mmHg (*E/Z* mixture), from BrCH=$CHOC_2H_5$ (>90% *Z*) and 20 molar excess of *p*-fluorophenylmagnesium bromide. Two hours of refluxing were necessary.

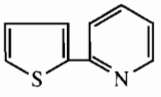
11.11.2.13 2-(2-Ethoxyvinyl)thiophene



B.p. 100 °C/15 mmHg (20/80 *E/Z* mixture), from BrCH=$CHOC_2H_5$ (>90% *Z*) and 20% molar excess of 2-thienylmagnesium bromide. In diethyl ether the reaction did not proceed very smoothly. THF (50 ml) was added and the mixture heated for 3 h under reflux.

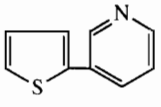
^{1}H-NMR spectrum (CCl_4): 7.05–6.55 (m, 3H); 5.77–6.05 (4 signals, 2H); 5.45 (d, 1H); 3.5–3.9 (2q, 2H); 1.1–1.3 (t, 3H) ppm.

11.11.2.14 2-(2-Thienyl)pyridine



Solid, b.p. 140 °C/15 mmHg, from 2-bromopyridine and 10% molar excess of 2-thienylmagnesium bromide. In diethyl ether with $NiCl_2{\cdot}(PPh_3)_2$ (instead of $NiCl_2{\cdot}$dppp), the reaction was very slow.

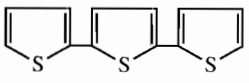
11.11.2.15 3-(2-Thienyl)pyridine



Liquid, b.p. 140 °C/15 mmHg, from 3-bromopyridine and 10% molar excess of 2-thienyl-MgBr. During the addition of the Grignard reagent a thick suspension was formed. THF (80 ml) was added and the mixture was heated for 4 h under reflux.

^{1}H-NMR spectrum (CCl_4): 8.77 (d, 1H); 8.34 (m, 1H); 7.55–7.74 (m, 1H); 6.23–6.88 (m, 4H) ppm.

11.11.2.16 2,2':5'2"-Terthiophene

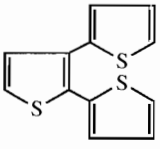


Yellow solid, m.p. 95 °C, from 2,5-dibromothiophene and 30% molar excess of 2-thienyl-MgBr (scale 0.025 molar). After addition of the Grignard reagent (at 30–35 °C), 40 ml of THF was added and the mixture was heated for 1 h under reflux, with intermediate addition of three 0.1 g portions of $NiCl_2$·dppp.

The reaction with $NiCl_2$·$(PPh_3)_2$ gave much intractable material and the yield of terthienyl was much lower.

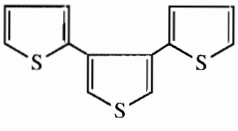
^{1}H-NMR spectrum (CCl_4): 6.9–7.3 (m)ppm.

11.11.2.17 2,3':2'2"-Terthiophene



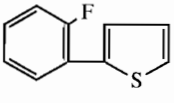
Light-yellow solid, b.p. ~120 °C/0.03 mmHg, from 2,3-dibromothiophene and 2 equivalents of 2-thienyl-MgBr (+ 20% molar excess).

11.11.2.18 2,3':4',2"-Terthiophene



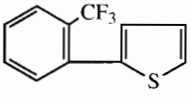
Light-yellow solid, b.p. ~125 °C/0.5 mmHg, from 3,4-dibromothiophene and 2 equivalents (+ 20% molar excess) of 2-thienyl-MgBr.

11.11.2.19 2-(2-Fluorophenyl)thiophene



Liquid, b.p. 123 °C/15 mmHg, from 2-thienyl-MgBr (10% molar excess) and 1-bromo-2-fluorobenzene.

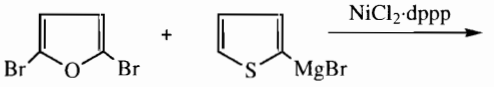
11.11.2.20 2-(2-Trifluoromethylphenyl)thiophene



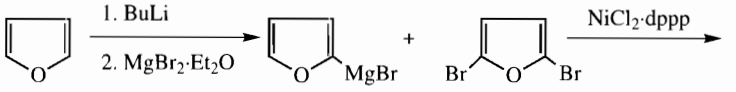
Liquid, b.p. 110 °C/15 mmHg, from 1-bromo-2-trifluoromethylbenzene and 20% molar excess of 2-thienyl-MgBr.

^{1}H-NMR spectrum (CCl_4): 7.6–7.8 (m, 1H); 7.2–7.4 (m, 4H); 6.8–7.1 (m, 2H) ppm.

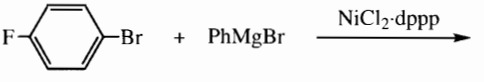
11.11.2.21 Unsatisfactory Results



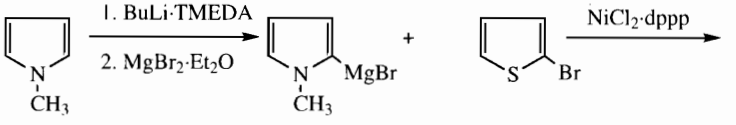
(a) The reaction proceeded sluggishly. More than one product was formed.



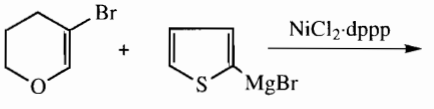
(b) An intractable product was formed. $PdCl_2$·dppb gave an excellent result (cf. exp. 11.11.3.15).



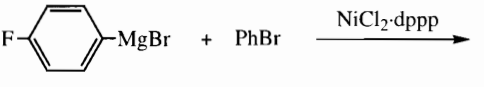
(c) Much insoluble material was formed. The desired product was present in small amounts only. $PdCl_2$·dppb gave an excellent result.



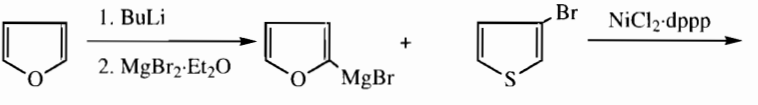
(d) The reaction proceeded sluggishly, in spite of several additions of extra $NiCl_2$·dppp. An intractable product mixture was obtained. The reaction of 1-methyl-2-pyrryl–ZnCl with 2-bromothiophene with $PdCl_2$·dppf proceeded successfully.



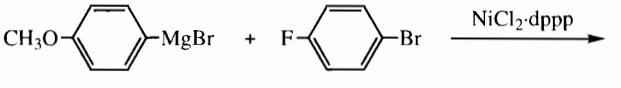
(e) Very sluggish reaction.



(f) The main product was a solid insoluble in organic solvents.



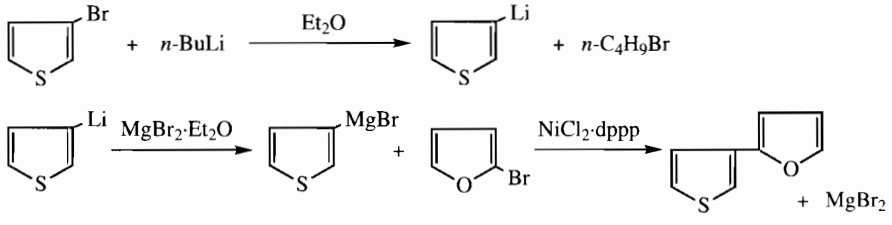
(g) Much intractable, solid material was formed. The desired product was present in small amounts only.



(h) Much intractable, solid material was formed. $PdCl_2$·dppb gave an excellent result.

(i) Rather slow reaction. Conversion incomplete after 5 h reflux.

11.11.2.22 2-(3-Thienyl)furan



Scale: 0.10 molar.

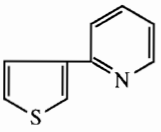
Apparatus: 500-ml round-bottomed, three-necked flask equipped with a combination of dropping funnel and nitrogen inlet, a mechanical stirrer and a combination of outlet and thermometer for the preparation of 3-thienyllithium. For the cross-coupling, the outlet-thermometer combination was replaced with a reflux condenser. For starting compounds and reagents see Chapter 1 and 2.

Procedure: After perfusing the flask with nitrogen, a solution of 0.12 mol of *n*-BuLi in 75 ml of hexane (see Note) and 50 ml of dry diethyl ether were placed in the flask. 3-Bromothiophene (16.3 g, 0.10 mol) was added over 10 min with cooling at −30 to −20 °C. After an additional 15 min (at −20 °C) a solution of 0.12 mol of $MgBr_2$·etherate was added over a few min with cooling of −40 to −20 °C. $NiCl_2$·dppp (0.3 g) was then added at −30 °C, followed by 0.10 mol of 2-bromofuran. The temperature of the two-layers system was allowed to rise gradually over 30 min until refluxing started (the outlet-thermometer combination was replaced by the reflux condenser). When the reaction had subsided, an additional portion of ~0.3 g of catalyst was added and the reaction mixture was heated for half an hour under reflux. After cooling to room temperature, the mixture was poured into 200 ml of an aqueous solution of 20 g of ammonium chloride. After vigorous shaking (some dilute hydrochloric acid may be added to facilitate separation of the layers), the aqueous phase was extracted twice with pentane. The organic solution was dried over anhydrous $MgSO_4$ and then filtered through a short column (~5 cm) of neutral Al_2O_3. Removal of the solvent under reduced pressure followed by distillation (air condenser) through a short column gave the product (b.p. ~100 °C/15 mmHg) in ~65% yield. While standing at room temperature it became solid.

^{1}H-NMR spectrum (CCl_4): 7.0–7.35 (m, 4 H); 6.30 (m, 2 H) ppm.

Note: The use of an excess of *n*-BuLi gives *n*-BuMgBr, which will react with 2-bromofuran to give 2-*n*-butylfuran. This is much more volatile than the desired product, however.

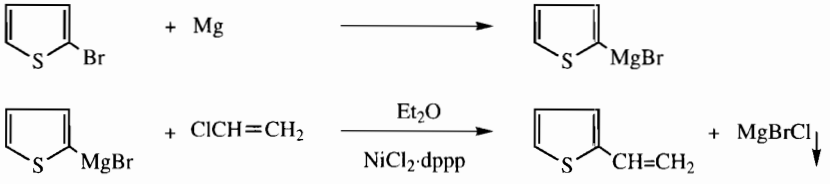
11.11.2.23 2-(3-Thienyl)pyridine



Liquid, b.p. 135 °C/15 mmHg, was obtained in ~60% yield by a similar procedure to 2-bromopyridine and 3-thienylmagnesium bromide.

^{1}H-NMR spectrum (CCl_4): 6.8–7.8 (well-resolved multiplet, 6H); 6.50 (m, 1 H) ppm.

11.11.2.24 2-Vinylthiophene



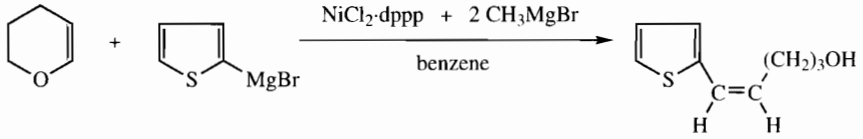
Scale: 0.40 molar.

Apparatus: 1-l round-bottomed, three-necked flask equipped with a combination of a nitrogen inlet and a dropping funnel, a gas-tight mechanical stirrer and a combination of an outlet and a thermometer.

Procedure: Vinyl chloride (35 g, ~0.6 mol), condensed in a cold trap (–70°C) was dissolved in 200 ml of cold (–5 °C) diethyl ether, and 0.4 g of $NiCl_2$·dppp was introduced. Subsequently 4 ml of a ~2 molar ethereal solution of 2-thienylmagnesium bromide (prepared in the usual way from magnesium and 2-bromothiophene) was added. After 10 min 0.40 mol of this solution was added portionwise over 30 min while keeping the temperature between 0 and 10 °C. A salt slurry was formed gradually. After the addition the mixture was stirred for an additional half hour at 15 °C, then 0.3 g of $NiCl_2$·dppp was added. When this addition did not result in an increase of the temperature, the mixture was cautiously poured into a solution of 100 g of ammonium chloride in 300 ml of water. After shaking and separation of the layers, the aqueous phase was extracted once with 40 ml of pentane. After drying the solution over anhydrous $MgSO_4$ and adding 0.5 g of Ionox 330 (polymerization inhibitor), the solvent was distilled off at atmospheric pressure through a 30-cm Vigreux column. Distillation in vacuo gave 2-vinylthiophene (b.p. ~35 °C/15 mmHg) in 90% yield. There were 3 g of crystalline residue (bithienyl). The compound should be stored at –20 °C in the presence of a trace of Ionox 330.

^{1}H-NMR spectrum (CCl_4): 6.55–7.10 (various signals, 4H); 5.4 (d, 1H); 5.04 (d, 1H) ppm.

11.11.2.25 *Z*-5-(2-Thienyl)pent-4-en-1-ol



Scale: 0.15 molar.

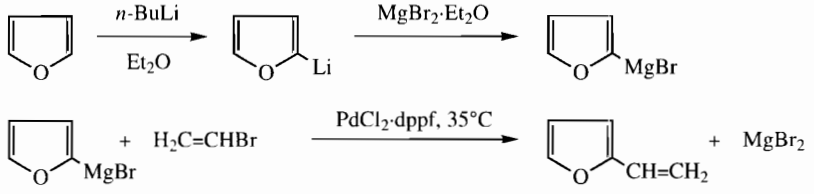
Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a thermometer-gas inlet combination, a mechanical stirrer and a reflux condenser; the requisite solution of CH_3MgBr was prepared in a separate small flask under magnetic stirring.

Procedure: (Cf. Wadman et al., J. Chem. Soc., Chem. Comm. (1987) 241 and Wenkert et al., J. Org. Chem. (1984) 49, 4894.) A solution of ~0.15 mol of 2-thienylmagnesium bromide in ~100 ml of ether was prepared in the usual way in a separate flask from 0.17 mol of 2-bromothiophene. Most of the ether was removed under reduced pressure (bath temperature ~30 °C), after which 130 ml of benzene was added. In a separate flask a solution of ~0.02 mol of methylmagnesium bromide in 15 ml of ether was added to a suspension of 1.6 g (~3 mmol) of $NiCl_2$·dppp in 20 ml of benzene at room temperature. After 15 min the yellowish brown solution was added to the solution of 2-thienylmagnesium bromide in benzene, followed by 0.20 mol (16.8 g, excess) of freshly distilled dihydropyran. The mixture was heated under reflux for 2 h under nitrogen and then added by syringe to a vigorously stirred solution of 30 g of ammonium chloride in 150 ml of water. After two extractions with ether and drying over anhydrous $MgSO_4$, the dark-brown organic solution was concentrated under reduced pressure. The remaining viscous brown oil was dissolved in 100 ml of ether and the solution filtered twice through a short column (~5 cm) of silica gel. Concentration of the filtrate in vacuo, followed by distillation through a short column gave the product, b.p. ~115 °C/0.7 mmHg, in 65% yield.

^{1}H-NMR spectrum (CCl_4): 7.0–7.15 (m, 1H); 6.75 (d, 2H); 6.37 (d, 1H, J = 12 Hz); 5.25–5.58 (dt, 1H, J = 12 Hz); 3.45 (t, 2H); 2.35 (q, 2H); 1.66 (q, 2H) ppm.

11.11.3 Palladium-Catalyzed Cross-Couplings with Grignard Compounds and Organozinc Halides

11.11.3.1 2-Vinylfuran



Scale: 0.40 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel combined with a nitrogen inlet, a gas-tight mechanical stirrer and a reflux condenser filled with a mixture of dry ice and acetone (cold finger). The condenser was connected via a plastic tube with a cold trap (–70 °C).

Procedure: After flushing the flask with nitrogen, a solution of 0.40 mol of *n*-butyllithium in ~260 ml of hexane was placed in the flask and the hexane was completely (see Note 1) removed by evacuation (temperature of the heating bath ~30 °C, towards the end of this operation 60 °C). The remaining viscous liquid was diluted with 100 ml (see Note 1) of cold (~–20 °C) ether. The flask was equipped for the procedure and 45 g (large excess) of freshly distilled furan was introduced. After about half an hour a gentle reflux started (before this stage much butane escaped from the solution). The mixture (white suspension) was warmed under reflux for an additional 1 h and subsequently cooled to ~0 °C. Magnesium bromide etherate (0.45 mol, see Chapter 1) was added over 15 min with vigorous stirring and cooling in a bath of ice and ice water. The resulting mixture was brought at ~20 °C, after which 0.7 g of $PdCl_2$·dppf (see Chapter 1) and 64 g (0.6 mol) of cold vinyl bromide (–10 °C) were added. Refluxing started after a short period (occasional cooling may be necessary). After 1.5 to 2 h the spontaneous refluxing had ceased. The contents of the cold trap were returned to the reaction mixture and the gently stirred mixture was heated for an additional 1.5 h under reflux. The reaction mixture was cautiously poured into a stirred solution of 100 g of ammonium chloride in 250 ml of water cooled in a bath with ice water. The layers were separated as completely as possible (see Note 2) and the aqueous phase was extracted three times with 30-ml portions of pentane. After drying the organic solution over anhydrous $MgSO_4$, the greater part of the solvent was slowly distilled off at atmospheric pressure using a 40-cm Widmer column (bath temperature not higher than 110 °C). The remaining liquid was carefully distilled through a shorter Widmer column to give 2-vinylfuran (b.p. 95–100 °C/760 mmHg) in ~75% yield. There was practically no residue. The compound should be stored at ~–20 °C in the presence of a trace of Ionox 330 (polymerization inhibitor).

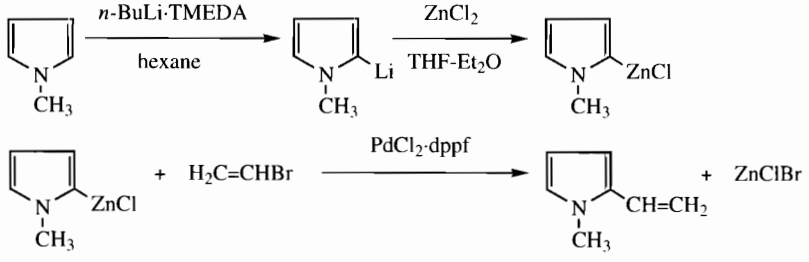
^{1}H-NMR spectrum (CCl_4): 7.25 (d, 1H); 6.15–6.60 (m, 3H); 5.60 (dd, 1H); 5.10 (dd, 1H) ppm.

Notes:

1. The product has a b.p. that is only ~30 °C higher than that of hexane. In order to avoid time-consuming fractional distillation, the amounts of solvents are kept limited.
2. Some problems may be encountered during the separation of the layers, due to the presence of some slurry (presumably formed from the catalyst) between the layers.

The use of vinyl chloride (slow reaction) in combination with $NiCl_2$·dppp gave several unidentified products. Using $PdCl_2$·dppf or $PdCl_2$·dppb, a clean product was obtained from the reaction with vinyl chloride. However, the reaction was very slow.

11.11.3.2 1-Methyl-2-vinylpyrrole



Scale: 0.20 molar.

Apparatus: 1-l round-bottomed, three-necked flask equipped with a combination of a nitrogen inlet and a thermometer, a gas-tight mechanical stirrer and a reflux condenser connected to a trap cooled at −70 °C.

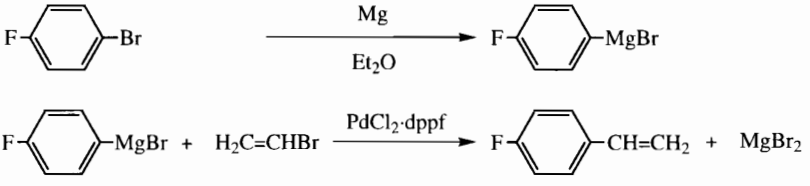
Procedure: A solution of 0.20 mol of *n*-butyllithium in ~130 ml of hexane was placed in the flask, which had been previously flushed with nitrogen. Freshly distilled *N*-methylpyrrole (0.22 mol, 17.8 g) was added in one portion, followed by 0.22 mol (25.5 g) of TMEDA (dried by shaking with machine-powdered potassium hydroxide and subsequent distillation in a partial vacuum). After the exothermic reaction had subsided, the mixture was heated under reflux for 20 min and subsequently cooled to 0 °C. A solution of 0.20 mol (27.3 g) of anhydrous zinc chloride (the commercial anhydrous salt was dried by azeotropic removal of water with toluene) in 120 ml of THF was added over a few min, while keeping the temperature of the suspension between 20 and 30 °C. $PdCl_2$·dppf (1.0 g) was introduced, after which 26.7 g (0.25 mol) of precooled (−10 °C) vinyl bromide was added in one portion. After bringing the temperature to 30 °C, an exothermic reaction started, during which the temperature was allowed to rise gradually (occasional cooling) to above 50 °C. After the reaction had subsided and the temperature had dropped to ~45 °C, the vinyl bromide (if any) which had condensed in the cold trap was returned to the reaction mixtuire and the mixture was heated for an additional 45 min at 50 °C. The clear solution was cooled to room temperature and then cautiously poured into a solution of 100 g of ammonium chloride in 250 ml of water. The aqueous layer was extracted twice with small portions of pentane. After drying the combined organic solutions over anhydrous magnesium

sulfate and addition of 0.5 g of Ionox 330 (polymerization inhibitor), the greater part of the solvents was distilled off at atmospheric pressure (nitrogen atmosphere) through a 30-cm Vigreux column (bath temperature 2110 °C). After cooling to below 40 °C, the remaining liquid was carefully distilled in vacuo to give 1-methyl-2-vinylpyrrole, b.p. 60 °C/15 mmHg, n^{20}_D 1.552, in ~70% yield. There was practically no residue (see Note). The compound should be stored at–20 °C in the presence of a trace of Ionox 330.

^{1}H-NMR spectrum (CCl_4): 6.15–6.50 (m, 3H); 5.35 (m, 1H); 5.3 (DD, 1H); 4.85 (dd, 1H); 3.37 (s, 3H) ppm.

Note: When $PdCl_2$·dppb was used as catalyst, the yield was 10% lower and some solid (possibly the bipyrryl derivative) remained after distillation.

11.11.3.3 4-Fluorostyrene



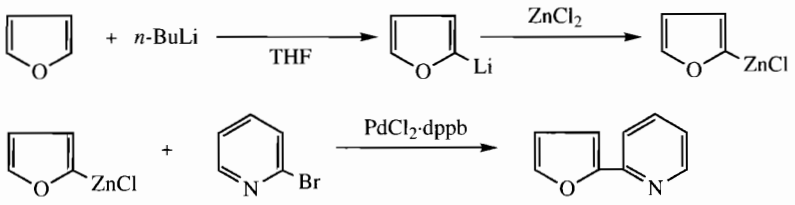
Scale: 0.30 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet, a gas-tight mechanical stirrer and a reflux condenser, connected to a cold trap (–70 °C).

Procedure (see Note.) A solution of ~0.30 mol of 4-fluorophenylmagnesium bromide in ~200 ml of diethyl ether was prepared from 0.35 mol of 4-fluorobromobenzene and a 20% molar excess of magnesium. After flushing with nitrogen, this solution was transferred into the reaction flask. At 10 °C, 0.4 mol (43 g) of cold (–10 °C) vinyl bromide was added, followed by 0.5 g of $PdCl_2$·dppf. After some heating the ether started to reflux. After several minutes (30 or longer), the reaction had subsided and the spontaneous refluxing had stopped. The contents (if any) of the cold trap were returned into the flask and an additional 10 g of vinyl bromide was added. The mixture was heated under reflux for a further half hour, then cooled to room temperature and cautiously poured into a solution of 100 g of ammonium chloride in 300 ml of water. The product was isolated as described for 2-vinylthiophene (see Sect. 11.11.2.24). 4-Fluorstyrene (b.p. ~35 °C/15 mmHg, n^{19}_D 1.5147) was obtained in 85% yield. The compound should be stored at –20 °C in the presence of a small amount of the polymerization inhibitor Ionox-330.

Note: Possibly, the combinations vinyl *chloride*–$NiCl_2$·dppp (inverse addition!) and vinyl *bromide*–$PdCl_2$·dppb will also give good results.

11.11.3.4 2-(2-Furyl)pyridine

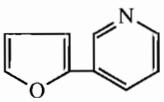


Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a thermometer-nitrogen inlet combination, a mechanical stirrer and an outlet; for the coupling, the latter was replaced with a reflux condenser.

Procedure: After perfusing the flask with nitrogen, a solution of 0.12 mol of *n*-BuLi in ~75 ml of hexane and 75 ml of THF were introduced with cooling below 0 °C. Freshly distilled furan (0.15 mol, 10 g) was added in one portion at 0 °C, after which the temperature was allowed to rise. After 30 min the solution was cooled to −30 °C and a solution of 18 g of anhydrous zinc chloride (traces of water had been removed azeotropically with toluene) in 50 g of THF was added with vigorous stirring (without external cooling). 2-Bromopyridine (0.10 mol, 16 g) and $PdCl_2$·dppb (0.7 g, see Chapter 1) were added at 30–35 °C and the outlet was quickly replaced with the reflux condenser. After some minutes a vigorous reflux started. After the exothermic reaction had subsided, the mixture (two-phase system) was heated for an additional period (~1.5 h) under reflux. When GLC monitoring had indicated completion, the reaction mixture was cooled to 20 °C and then poured into 200 ml of an aqueous solution of 25 g of ammonium chloride containing some ammonia. After shaking and separation of the layers, three extractions with ether were carried out. The combined organic solutions were dried over anhydrous K_2CO_3 and the solvent removed in vacuo. The residue was dissolved in 50 ml of ether and the solution was filtered through a layer of 5 cm of neutral Al_2O_3 in order to remove the catalyst. Distillation gave the product (purity ~97% by GLC, b.p. 105 °C/15 mmHg) in 84% yield.

11.11.3.5 3-(2-Furyl)pyridine



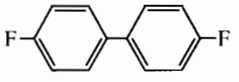
B.p. 110 °C/15 mmHg, was obtained in 70% yield from 2-furylzinc chloride and 3-bromopyridine (cf. 11.11.3.4).

11.11.3.6 3-Phenylpyridine

A solution of 0.12 mol of *n*-BuLi in 75 ml of hexane was added over a few min to a solution of 0.12 mol of bromobenzene in 50 ml of THF, while keeping the temperature between −70 and −80 °C. After 15 min (at

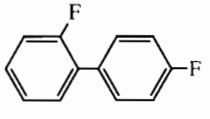
~–75 °C) a solution of 0.12 mol of anhydrous $ZnCl_2$ (for removal of water see above) in 50 ml of THF was added with vigorous stirring and cooling below –50 °C. After this addition 0.10 mol (16 g) of 3-bromopyridine and 0.8 g of $PdCl_2$·dppb were introduced. The mixture was warmed to 40 °C, after which a vigorous reaction started (the outlet was replaced with a reflux condenser, see above). Within 45 min the conversion was complete and GLC analysis indicated a ratio of 12 : 86 for the homo-coupled product biphenyl and the desired product. Using $Pd(PPh_3)_4$, this ratio was ~10 : 90, while $PdCl_2$·dppf (very smooth reaction) gave ~6 : 92 (only ~2% 3,3'-bipyridyl). In all cases pure 3-phenylpyridine could be isolated in high yields by treating the crude product with a slight excess of dilute hydrochloric acid, removing biphenyl by extraction with pentane and treating the acidic phase with KOH.

11.11.3.7 4,4'-Difluorobiphenyl



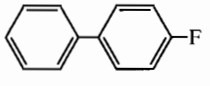
Solid, was obtained in an excellent yield by heating a mixture of *p*-F-C_6H_4MgBr (0.12 mol in ~80 ml of THF) and *p*-FC_6H_4Br with $PdCl_2$·dppb for 1.5 h under reflux. There were no by-products. With $NiCl_2$·dppp, mainly amorphous insoluble material was formed.

11.11.3.8 2,4'-Difluorobiphenyl



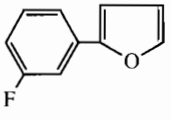
This was obtained in a high yield from *o*-F-C_6H_4Br and *p*-F-C_6H_4MgBr (20 mol % excess) in THF and $PdCl_2$·dppb. There was ~6% of a homo-coupled product (structure not determined). $PdCl_2$·dppf gave a similar result, but the reaction in the presence of $Pd(PPh_3)_4$ proceeded sluggishly, while considerable amounts of homo-coupled products were detected by GLC.

11.11.3.9 4-Fluorobiphenyl



M.p. ~70 °C, was obtained in excellent yield and purity from PhMgBr (20 mol % excess) and *p*-F-C_6H_4Br in THF, using $PdCl_2$·dppb as a catalyst.

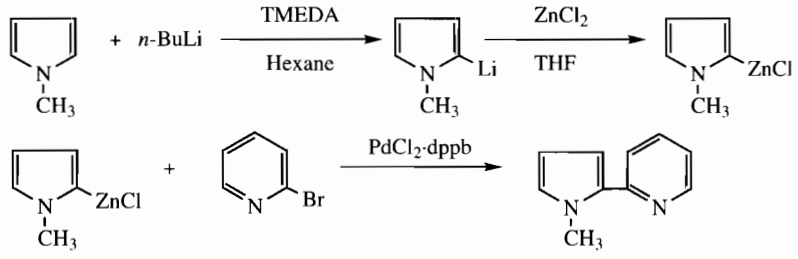
11.11.3.10 2(3-Fluorophenyl)furan



B.p. 105 °C/15 mmHg, was obtained in a high yield from *m*-bromofluorobenzene and 2-furylzinc chloride, with $PdCl_2$·dppb as a catalyst.

The $PdCl_2$·dppb-catalyzed reaction of *2-furylzinc chloride* with *m-nitrobromobenzene* gave considerable amounts of bifuryl. Also when using $PdCl_2$·dppf much of this homo-coupled product was formed.

11.11.3.11 2-(1-Methyl-2-pyrrolyl)pyridine



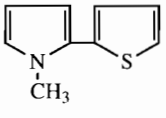
Scale: 0.10 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, a mechanical stirrer and a reflux condenser.

Procedure: After perfusing the flask with nitrogen, it was charged with a solution of 0.12 mol of *n*-BuLi in ~75 ml of hexane and 0.12 mol (14 g) of TMEDA (dried over powdered KOH and subsequently filtered). Freshly distilled *N*-methylpyrrole (0.12 mol, 9.6 g) was added at room temperature and the solution was heated under gentle reflux for 20 min. After cooling to 20 °C, 40 ml of THF was added, followed by a solution of 18 g of anhydrous zinc chloride (traces of water had been removed azeotropically with toluene) in 50 ml of THF. During this addition the mixture was vigorously stirred and the temperature kept below 20 °C. 2-Bromopyridine (0.10 mol, 16 g) and $PdCl_2$·dppb (1.2 g) were then added at room temperature and the mixture was heated under reflux for 2.5 h (complete conversion, by GLC). The reaction mixture was then poured into a solution of 30 g of ammonium chloride in 200 ml of water containing some ammonia. After shaking, separation of the layers and extraction of the aqueous phase four times with diethyl ether, the combined solutions were dried over anhydrous K_2CO_3. Concentration in vacuo, followed by distillation afforded the product (liquid, b.p. 135 °C/15 mmHg) in ~80% yield.

^{1}H-NMR spectrum (CCl_4): 8.39–8.54 (m, 1H); 7.37–7.53 (m, 2H); 6.76–6.90 (m, 1H); 6.44–6.61 (m, 2H); 5.96–6.12 (m, 1H); 3.94 (s, 3H) ppm.

11.11.3.12 1-Methyl-2-(2-thienyl)pyrrole

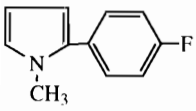


B.p. 125 °C/15 mmHg, was obtained in 70% yield by a similar procedure from 2-(1-methylpyrrolyl)zinc chloride and 2-bromothiophene after a refluxing period of 6 h, using $PdCl_2$·dppf (1.1 g) as a catalyst. The product had a purity of ~95%. With $PdCl_2$·dppb, the amount of contamination (presumably homo-coupled products) was much higher (~15%).

^{1}H-NMR spectrum (CCl_4): 6.7–7.0 (m, 3H); 6.40 (m, 1H); 6.14 (m, 1H); 5.95 (m, 1H); 3.44 (s, 3H) ppm.

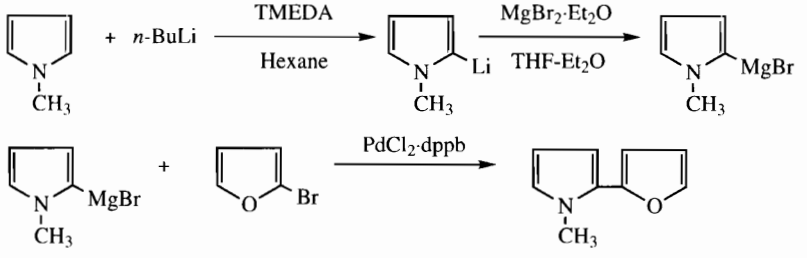
3-Bromothiophene and *2-(1-methylpyrrolyl)zinc chloride* reacted in the presence of $PdCl_2$·dppb (7 h reflux) to give a mixture of the desired compound and homo-coupling products (~12%).

11.11.3.13 2-(4-Fluorophenyl)-1-methylpyrrole



B.p. 135 °C/15 mmHg (solid), was obtained in an excellent yield from 2-(1-methylpyrrolyl)zinc chloride and *p*-bromofluorobenzene after 6 h of refluxing with $PdCl_2$·dppb (1 g on 0.10 molar scale). The amount of (assumed) homo-coupling products was ~4%.

11.11.3.14 2-(2-Furyl)-1-methylpyrrole



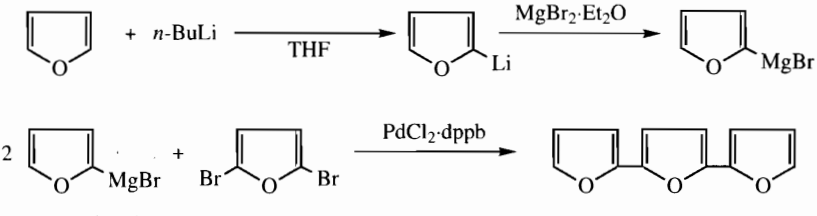
Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask equipped with a thermometer-nitrogen inlet combination, a mechanical stirrer and an outlet; for the cross-coupling, the outlet was replaced with a reflux condenser.

Procedure: 1-Methylpyrrole (0.12 mol) was lithiated as described in the preceding experiment 11.11.3.11. After addition (at ~0 °C) of 80 ml of THF and then 0.12 mol of $MgBr_2$·Et_2O (see Chapter 1) (at 0–20 °C) 1.0 g of $PdCl_2$·dppb was introduced, followed by 0.10 mol (14.7 g) of 2-bromofuran. The outlet was replaced with the reflux condenser and the two-phase system was heated for 2 h under reflux. After cooling to 20 °C, the mixture was poured into 250 ml of a solution of 30 g of ammonium chloride. After extraction with ether (three times), the organic solution was dried over anhydrous $MgSO_4$ and subsequently concentrated under reduced pressure. The residue was dissolved in 50 ml of diethyl ether and the solution filtered through neutral Al_2O_3 (5 cm layer). The product (liquid) was obtained in 75% yield by distillation (b.p. ~100 °C/12 mmHg). The purity was ~97%.

^{1}H-NMR spectrum (CCl_4): 7.28 (d, 1H); 5.95–6.40 (m, 5H); 3.58 (s, 3H) ppm.

11.11.3.15 2,2':5',2"-Terfuran



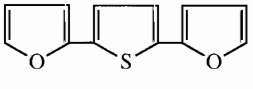
Scale: 0.05 molar (2,5-dibromofuran).

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a thermometer-nitrogen inlet combination, a mechanical stirrer and an outlet; for the coupling reaction the outlet was replaced with a reflux condenser.

Procedure: After perfusing the flask with nitrogen, a solution of 0.12 mol of *n*-BuLi in ~75 ml of hexane and 50 ml of THF were introduced with cooling below 0 °C, followed by freshly distilled furan (0.15 mol, 10 g). The temperature was allowed to rise to 20 °C. After 30 min 0.15 mol of $MgBr_2 \cdot Et_2O$ (see Chapter 1) was added with vigorous stirring and cooling between 10 and 20 °C. 2,5-Dibromofuran (0.05 mol, 11.3 g) and $PdCl_2$·dppb (0.6 g) were introduced successively, after which the outlet was replaced with the condenser. The mixture (two-phase system) was heated under reflux for 2·5 h, then cooled to 20 °C and cautiously poured into a solution of 30 g of ammonium chloride in 200 ml of water. After shaking and separation of the layers, two extractions with pentane were carried out. The solution was dried over anhydrous $MgSO_4$ and subsequently concentrated in vacuo. After removal of the solvents under reduced pressure, the residue was dissolved in 50 ml of diethyl ether and the solution filtered through a 5-cm column of neutral Al_2O_3. 2,2':5',2"-Terfuran (b.p. ~140 °C/15 mmHg, air condenser), was obtained as a solid in an excellent yield.

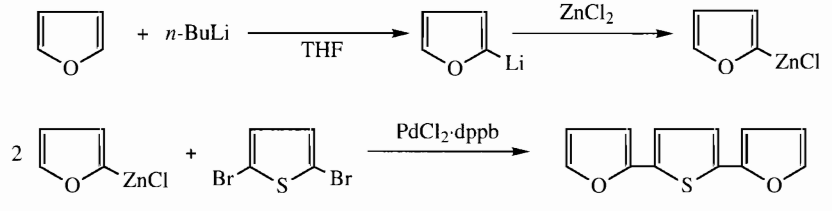
^{1}H-NMR spectrum (CCl_4): 7.35 (s, broadened); 6.55 (s, broadened); 6.3 (m, 2H) ppm.

11.11.3.16 Thiophene-2,5-diyl-2,2'-difuran



This was obtained as a solid in ~60% yield by a similar procedure from 2,5-dibromothiophene and 2-furylmagnesium bromide. The product was not completely pure, however (for another method, see the next exp.).

11.11.3.17 Thiophene-2,5-diyl-2,2'-difuran



Scale: 0.05 molar (2,5-dibromothiophene).

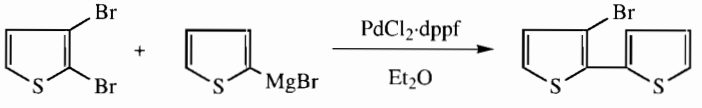
Apparatus: See preceding experiments.

Procedure: After perfusing the flask with nitrogen, a solution of 0.12 mol of *n*-BuLi in ~75 ml of hexane was added. THF (40 ml) was added at 0 °C, followed by 0.15 mol (10 g) of freshly distilled furan. The temperature was allowed to rise to ~20 °C. After 30 min the solution was cooled to below –40 °C (formation of a suspension) and a solution of 18 g of anhydrous zinc chloride (traces of water had been removed azeotrop-

ically with toluene) in 60 ml of THF was added with vigorous stirring and some external cooling. A two-phase system was formed. Subsequently 0.05 mol (12.2 g) of 2,5-dibromothiophene and 0.8 g of $PdCl_2$·dppb were added at 20 °C. The outlet was replaced with the reflux condenser and the mixture was heated for 2 h under reflux. After cooling to 20 °C, the dark brown reaction mixture was cautiously poured into a solution of 30 g of ammonium chloride in 200 ml of water containing some ammonia. The aqueous phase was extracted twice with diethyl ether. The combined organic solutions were dried over anhydrous $MgSO_4$ and subsequently concentrated under reduced pressure. The dark residue was dissolved in 50 ml of ether and the solution filtered through a column (5 cm) of neutral Al_2O_3. Removal of the ether in vacuo followed by distillation (b.p. 115–120 °C/0.5 mmHg, air condenser) gave the pure product as a solid in an excellent yield.

^{1}H-NMR spectrum (CCl_4): 7.25 (d, 2H); 7.0 (s, 2H); 6.3 (m, 4H).

11.11.3.18 3-Bromo-2-(2-thienyl)thiophene (Selective Substitution of the 2-Bromine Atom in 2,3-Dibromothiophene)



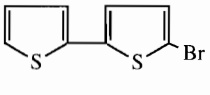
Scale: 0.10 molar (2,3-dibromothiophene).

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a dropping funnel-nitrogen inlet combination, a mechanical stirrer and an outlet.

Procedure: After replacing the air in the flask by nitrogen, 0.10 mol (24.5 g) of 2,3-dibromothiophene, 150 ml of diethyl ether and 1.0 g of $PdCl_2$·dppf were added successively. A solution of 0.10 mol of 2-thienylmagnesium bromide in 80 ml of diethyl ether (prepared in the usual way from 2-bromo-thiophene and magnesium) was added dropwise over 30 min, while keeping the temperature between 25 and 30 °C. After stirring the reaction mixture for an additional half hour, it was poured into 300 ml of cold (0 °C) 2 M hydrochloric acid. The aqueous layer was extracted twice with diethyl ether. After drying over anhydrous $MgSO_4$, the ethereal solution was filtered through a short (5 cm) column of neutral Al_2O_3. Distillation afforded the desired coupling product (b.p. ~110 °C/0.5 mmHg, n^{20}_D 1.697) in ~80% yield.

^{1}H-NMR spectrum (CCl_4): 6.8–7.3 (m) ppm.

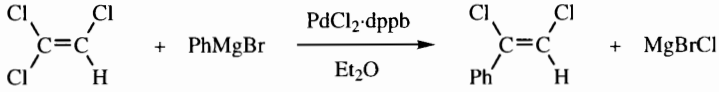
11.11.3.19 2-Bromo-5-(2-thienyl)thiophene



B.p. ~110 °C/0.5 mmHg (solid), was obtained in ~50% yield from 2,5-dibromothiophene (15 mol % excess) and 2-thienylmagnesium bromide by a similar procedure. There was a considerable high-boiling residue, solidifying upon cooling: terthienyl. Using 100 mol % excess of 2,5-dibromothiophene, 2-bromo-dithienyl was obtained in ~70% yield after fractional distillation. Even under these conditions terthienyl was formed.

11.11.4 Palladium-Catalyzed Reaction of Arylmagnesium Bromides with Trichloroethene

11.11.4.1 1,2-Dichlorovinylbenzene



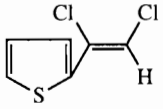
Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a combination of dropping funnel and nitrogen inlet, a mechanical stirrer and a reflux condenser.

Procedure: (Cf. Minato et al., J. Am. Chem. Soc. (1987), 109, 1257.) A mixture of 40 g of trichloroethene (large excess), 40 ml of dry ether and 0.5 g of $PdCl_2$·dppb was placed in the flask. After replacing the air by nitrogen, 10 ml of a solution of 0.10 mol of phenyl-magnesium bromide in 80 ml of ether was added. The temperature rose gradually and a gentle reflux started. The remaining 70 ml of Grignard solution was added over half an hour. The resulting suspension was heated under reflux for an additional 2 h. After cooling to 20 °C, the reaction mixture was poured into 250 ml of 2 M hydrochloric acid (the catalyst may give rise to some problems with the separation of the layers). The aqueous phase was extracted four times with pentane. The combined organic solutions were filtered through a 5-cm column of neutral Al_2O_3. The product, b.p. 106 °C/15 mmHg, was obtained in an excellent yield.

^{1}H-NMR spectrum (CCl_4): 6.57 (s) ppm.

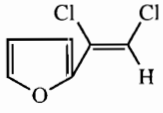
11.11.4.2 2-(1,2-Dichlorovinyl)thiophene



B.p. 108 °C/15 mmHg, was obtained in an excellent yield from 2-thienylMgBr and trichloroethene.

^{1}H-NMR spectrum (CCl_4): 6.50 (s) ppm.

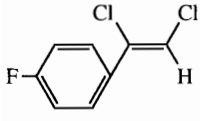
11.11.4.3 2-(1,2-Dichlorovinyl)furan



B.p. 75 °C/15 mmHg, was obtained in ~70% yield from 2-furylmagnesium bromide and trichloroethene (2-furylMgBr was prepared from 2-furyllithium and $MgBr_2$·Et_2O as described in exp. 11.3.15 (procedure for Terfuran). The compound is unstable at room temperature (development of a green colour).

^{1}H-NMR spectrum (CCl_4): 6.80 (s).

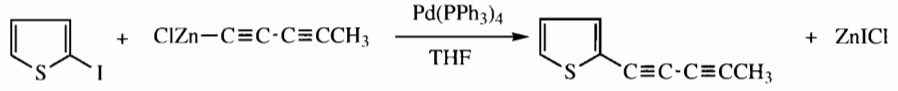
11.11.4.4 1-(1,2-Dichlorovinyl)-4-fluorobenzene



B.p. 100 °C/12 mmHg, was obtained in an excellent yield from *p*-F-C_6H_4MgBr and trichloroethene.

11.11.5 Palladium-Catalyzed Couplings with Alkynylzinc Halides

11.11.5.1 2-(1,3-Pentadiynyl)thiophene



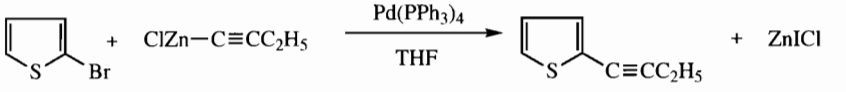
Scale: 0.10 molar.

Apparatus: 500-ml round bottomed, three-necked flask, equipped with a nitrogen inlet-dropping funnel combination, a stirrer and a thermometer-outlet combination.

After perfusing with nitrogen, a mixture of 0.10 mol (6.4 g) of 1,3-pentadiyne and 40 ml of THF was placed in the flask. A solution of 0.10 mol of *n*-butyllithium in 63 ml of hexane was added dropwise over 15 min, while keeping the temperature of the mixture below −30 °C (occasional cooling in a bath with liquid nitrogen permits a quick addition). Subsequently, a solution of 0.11 mol of anhydrous zinc chloride (traces of water had been azeotropically removed with toluene) in 40 ml of THF was added over a few min at −10 to +5 °C. $Pd(PPh_3)_4$ (1 g) was introduced, followed by (in one portion, at ~0 °C) 0.10 mol (21 g) of 2-iodothiophene. The temperature rose gradually to ~30 °C. The conversion was terminated by warming the mixture for an additional 45 min at 35 °C. Pentane (300 ml) was then added, followed by 150 ml of a saturated aqueous solution of ammonium chloride (most of the Pd-catalyst deposited as a slurry on the wall of the flask). The aqueous layer was extracted twice with small portions of pentane. The combined organic solutions were washed five times with 200-ml portions of water in order to remove as much as possible of the THF and were subsequently dried over $MgSO_4$. After filtering the solution through a 3 cm thick layer of neutral Al_2O_3 on a sintered-glass funnel, the solvent was removed under reduced pressure. Distillation of the remaining liquid through a 20-cm Vigreux column gave the coupling product (b.p. ~70 °C/0.5 mmHg) in ~85% yield.

Note: Attempts to couple free 1,3-pentadiyne with 2-bromothiophene or 2-bromofuran in the presence of $Pd(PPh_3)_4$ and CuI gave mainly intractable material.

11.11.5.2 2-(1-Butynyl)thiophene

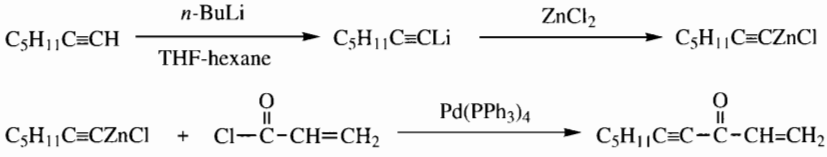


Scale and *apparatus* same as in the preceding exp.

Procedure: A solution of 0.10 mol of $C_2H_5C{\equiv}CZnCl$ in THF and hexane was prepared as described in the preceding exp. $Pd(PPh_3)_4$ (1 g) and 0.10 mol (16.3 g) of 2-bromothiophene were added at room temperature, after which the mixture was heated for 3 h under reflux. After a work-up similar to that described in the preceding exp., the coupling product (b.p. 80 °C/12 mmHg, $n^{22}{}_D$ 1.5734) was isolated in 85% yield.

Several *other heteroaromatic iodides and bromides* were successfully coupled with alkynylzinc chlorides. Aryl halides are less reactive. In the case of gaseous acetylenes ($CH_3C{\equiv}CH$, $C_2H_5C{\equiv}CH$, $H_2C{=}CHC{\equiv}CH$) the zinc chloride method is preferred over the Pd-Cu-catalyzed coupling of the free acetylenes (see Chapter 10), which usually requires heating at temperatures in the region of 80 °C.

11.11.5.3 Dec-1-en-4-yn-3-one



Scale: 0.10 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a nitrogen inlet-dropping funnel combination, a mechanical stirrer and a thermometer-outlet combination.

Procedure: After perfusing the flask with nitrogen, a mixture of 0.11 mol (10.6 g) of 1-heptyne and 60 ml of THF was added. A solution of 0.11 mol of *n*-BuLi in ~70 ml of hexane was added over 15 min, while cooling below 0 °C. Subsequently, a solution of 0.11 mol (15 g) of anhydrous zinc chloride (traces of water had been removed azeotropically with toluene) in 50 ml of THF was added over a few min with vigorous stirring and cooling between 0 and 10 °C. $Pd(PPh_3)_4$ (0.7 g) was introduced, after which freshly distilled acryloyl chloride (0.10 mol, 9.0 g) diluted with 20 ml of ether was added dropwise over a few min, while keeping the temperature between 0 and 5 °C. After an additional 10 min (at 5–10 °C, see Note 1) 300 ml of pentane was added and the reaction mixture was poured into 150 ml of a saturated aqueous solution of ammonium chloride. After vigorous shaking and separation of the layers, the aqueous layer was extracted once with 100 ml of pentane. The combined organic solutions were washed 4 times with 50 ml portions of a saturated aqueous ammonium chloride solution and subsequently dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the light-brown oil (see Note 2) was distilled through a short column (the bath temperature should be as low as possible) giving the ketone (b.p. ~60 °C/0.5 mmHg, n^{20}_D 1.4710) in ~70% yield.

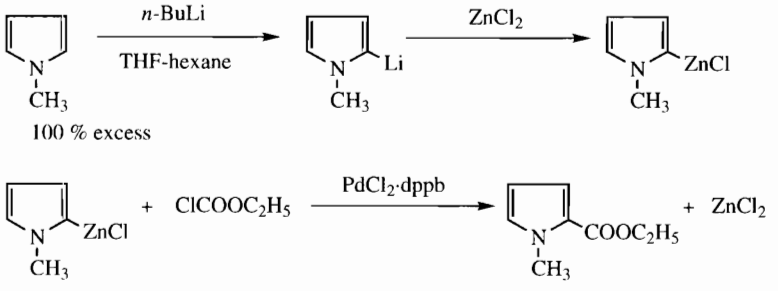
Notes:
1. Short reaction times seem to be essential for obtaining optimal yields.
2. In general, flash chromatography on neutral Al_2O_3 for removing the last traces of catalyst is advised.

11.11.5.4 1-Phenylbut-2-yn-1-one

The reaction of $C_2H_5C{\equiv}CZnCl$ with $C_6H_5C(=O)Cl$ (at 10–15 °C) gave *$C_2H_5C{\equiv}CC(=O)C_6H_5$* (b.p. ~90 °C/0.5 mmHg, n^{20}_D 1.5570) in 83% yield.

11.11.6 Palladium-Catalyzed Reaction of Aryl- and Hetarylzinc Halides with Ethyl Chloroformate

11.11.6.1 Ethyl-1-methylpyrrole-2-carboxylate (1-Methylpyrrole-2-carboxylic Acid Ethyl Ester)



Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a nitrogen inlet-thermometer combination, a mechanical stirrer and an outlet; the latter was later replaced with a reflux condenser.

Procedure: After perfusing the flask with nitrogen, 70 ml of THF was added, followed (at 0 °C) by a solution of 0.10 mol of *n*-BuLi in ~65 ml of hexane. Freshly distilled *N*-methylpyrrole (0.20 mol, 16 g) was added in one portion, after which the solution was kept for 1.5 h at 35 °C (see Note 1). A solution of 0.15 mol (20 g) of anhydrous zinc chloride (traces of water had been removed azeotropically with toluene) in 70 ml of THF was then added with vigorous stirring and cooling betwen 20 and 30 °C. Freshly distilled ethyl chloroformate (0.11 mol, 11 g) was added at room temperature, followed by 0.6 g of $PdCl_2$·dppb (see Note 2). The clear brown solution was heated under reflux for 30 min and then hydrolyzed with 100 ml of a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted twice with ether. After drying the combined organic solutions, the solvent was removed in vacuo and the remaining liquid distilled. The ester, b.p. ~75 °C/2 mmHg, n^{20}_D 1.5056, was obtained in 64% yield.

^{1}H-NMR spectrum ($CDCl_3$): 6.92 (m, 1H); 6.69 (m, 1H); 6.05 (m, 1H); 4.22 (q, 2H); 3.84 (s, 3H).

Notes:

1. If the lithiation is carried out with *n*-BuLi.TMEDA in hexane, only a slight excess of *N*-methylpyrrole has to be used. However, TMEDA reacts very easily with chloroformates.

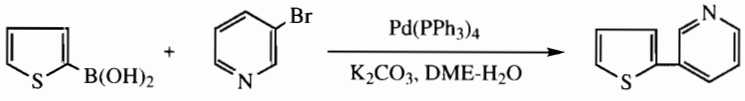
2. The use of $PdCl_2 \cdot (PPh_3)_2$, in general, gives rise to the formation of homo-coupled products.

A number of *aryl and hetaryl carboxylates* were prepared in a similar way from the lithium derivatives, $ZnCl_2$ and $ClCOOC_2H_5$. Yields were generally high, but starting from *2- or 3-bromopyridine (Br–Li exchange)* and *N-methylimidazole* (*n*-BuLi, THF-hexane) the esters were not obtained because of a very easy reaction of the azomethine-N with the chloroformate (formation of a thick suspension).

11.11.7 Palladium-Catalyzed Cross-Couplings with Boronic Acids

Note: An atmosphere of inert gas is not necessary.

11.11.7.1 3-(2-Thienyl)pyridine



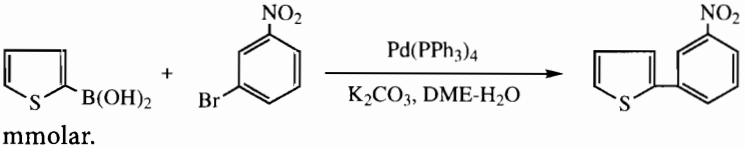
Scale: 30 mmolar.

Apparatus: 250-ml round-bottomed flask and reflux condenser; magnetic stirring (no inert gas was used).

Procedure: 3-Bromopyridine (30 mmol, 5.0 g), 1,2-dimethoxyethane (20 ml), water (10 ml), anhydrous potassium carbonate (30 mmol, 4.5 g), $Pd(PPh_3)_4$ (0.3 g) and 2-thiopheneboronic acid (33 mmol, 4.5 g, Chapter 1) were placed in the flask. The vigorously stirred mixture was heated under reflux. Within 45 min GLC indicated complete conversion, while the solution had become black by the formation of metallic palladium. The DME was removed on the rotary evaporator, after which three extractions with ether were carried out. The combined ethereal solutions were extracted twice with 40-ml portions of 2 M aqueous hydrochloric acid. The combined acidic layers were treated with a solution of 25 g of potassium hydroxide in 50 ml of water under cooling in ice. The product was isolated by extraction with ether (three times), drying the ethereal solution over anhydrous K_2CO_3 and removing the ether under reduced pressure. Pure (>97%) thienylpyridine was obtained in an excellent yield.

^{1}H-NMR spectrum (CCl_4): 8.83 (d, 1H); 8.42 (m, 1H); 7.68 (m, 1H); 6.9–7.3(m, 4H) ppm.

11.11.7.2 2-(3-Nitrophenyl)thiophene



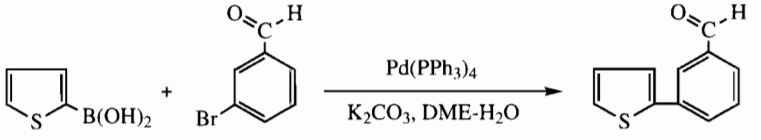
Scale: 30 mmolar.

Apparatus: Same as in the exp. Sect. 11.11.7.1.

Procedure: 1-Bromo-3-nitrobenzene (20 mmol, 4.04 g), 1,2-dimethoxyethane (20 ml), water (10 ml), anhydrous potassium carbonate (30 mmol, 4.5 g), $Pd(PPh_3)_4$ (0.3 g) and 2-thiopheneboronic acid (33 mmol, 4.5 g, see Chapter 1) were placed in the flask. The vigorously stirred mixture was heated under reflux. GLC monitoring and formation of metallic Pd showed the reaction to be complete within half an hour. DME was removed on the rotary evaporator. After addition of 50 ml of water, the mixture was extracted five times with a 3 : 1 mixture of ether and THF. The combined organic solutions were dried over anhydrous $MgSO_4$ and subsequently filtered through a column (~5 cm) of neutral Al_2O_3 in order to remove the palladium. After removal of the solvent, the pure (>97% by GLC) product (yield ~80%) remained as a brown solid. Further purification may be carried out by crystallization from diethyl ether.

^{1}H-NMR spectrum (CCl_4): 8.4 (m, 1H); 8.1 (m, 1H); 7.8 (m, 1h), 7.0–7.6 (m, 4H) ppm.

11.11.7.3 3-(2-Thienyl)benzaldehyde



This reaction was carried out under nitrogen. After a reaction time of ~45 min the mixture was extracted with diethyl ether. The crude product (purity by GLC .97%) was obtained as a liquid in practically quantitative yield by a procedure similar to the preceding exp. 11.11.7.2.

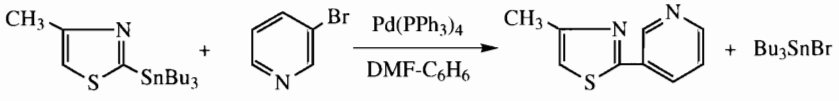
^{1}H-NMR spectrum (CCl_4): 9.95 (s, 1H); 7.90 (d, 1H); 6.9–7.8 (m, 5H) ppm.

11.11.7.4 Other Cross-Couplings with Boronic Acids

The $Pd(PPh_3)_4$-catalyzed couplings between 2-furanboronic acid and 2-bromothiophene or 3-bromopyridine proceeded much more slowly than those with 2-thiopheneboronic acid and *p*-fluorophenylboronic acid. Smooth couplings with furanboronic acids (W.J. Thompson, J. Gaudino, J. Org. Chem. (1984), 49, 5237) with $Pd(OAc)_2$ and P(*o*-tolyl)$_3$ have been effected in DMF at 100 °C, using triethylamine instead of alkali carbonate. Using $PdCl_2$·dppf and $PdCl_2$·dppb, we could achieve fast couplings between 2-furanboronic acid and 2-bromothiophene or 4-bromofluorobenzene in DME-water-K_2CO_3. In the reaction with 2-bromothiophene, however, appreciable amounts of the homo-products bifuryl and trithienyl were formed. In the case of 1-bromo-4-fluorobenzene (catalyst $PdCl_2$·dppb) a small amount of bifuryl (but no 4,4'-difluorobiphenyl) was formed in a very smooth reaction. Also the reaction between 2-furanboronic acid and 3-bromopyridine under the influence of $PdCl_2$·dppb (K_2CO_3–H_2O–DME) was finished within 1 hour. The "ligandless" catalyst $PdCl_2$·$(CH_3CN)_2$ (cf. T.I. Wallow, B.M. Novak, J. Org. Chem. (1994), 59, 5034) initially worked very well in this coupling, but the reaction stopped at a stage of ~50% conversion; addition of more of the catalyst had no result.

11.11.8 Palladium-Catalyzed Cross-Couplings with Tin Derivatives

11.11.8.1 3-(4-Methylthiazol-2-yl)pyridine



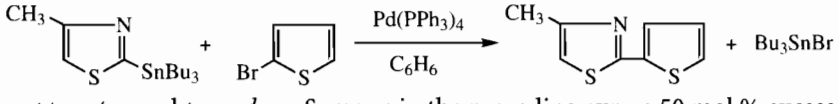
Scale: 30 mmolar.

Apparatus: 250-ml round-bottomed flask and reflux condenser; magnetic stirring; an atmosphere of inert gas is not necessary.

Procedure: 2-Tributylstannyl-4-methylthiazole (30 mmol, 11.6 g, see Chapter 1), 3-bromopyridine (35 mmol, 5.5 g), DMF (12 g), benzene (7 g) and $Pd(PPh_3)_4$ (0.4 g) were placed in the flask. The vigorously stirred mixture was heated under reflux. After ~5 h GLC indicated complete conversion. The benzene and DMF were distilled off in vacuo and the brown residue was extracted twice with ether. The ethereal solution was extracted four times with 15 ml portions of 5 M aqueous hydrochloric acid. The combined acidic solutions were made alkaline by portionwise addition of 25 g of potassium hydroxide under cooling in ice water, after which three extractions with ether were carried out. After drying the ethereal solution over anhydrous K_2CO_3 and concentration in vacuo (bath temperature ~45 °C), there remained 4.4 g of solid material (purity by GLC >96%), corresponding to a yield of 83%.

^{1}H-NMR spectrum (CCl_4): 9.07 (d, 1H); 8.80 (dt, 1H); 8.50 (dd, 1H); 7.20–7.35 two d, 1H); 6.82 (s, 1H); 2.48 (s, 3H).

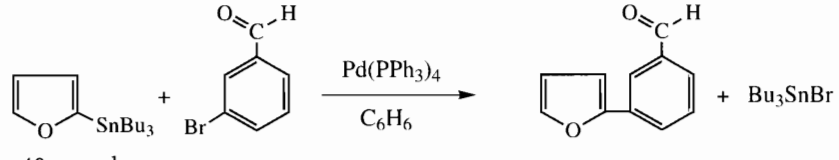
11.11.8.2 2-(4-Methylthiazol-2-yl)thiophene



Scale, *apparatus* and *procedure*: Same as in the preceding exp.: a 50 mol % excess of 2-bromothiophene was used; the only solvent was benzene. After 20 hours, GLC indicated complete conversion. After a work-up similar to that described in the preceding exp., the pure liquid product was obtained in 80% yield.

^{1}H-NMR spectrum (CCl_4): 7.2–7.4 (m, 2H); 6.8–7.0 (m, 1H); 6.62 (broadened s, 1H); 2.38 (broadened s, 3H) ppm.

11.11.8.3 3-(2-Furyl)benzaldehyde



Scale: 40 mmolar.

Apparatus: Same as in preceding exp.; the reaction was carried out under inert gas.

Procedure: 1-Bromo-3-nitrobenzene (40 mmol, 8.1 g), tributylstannylfuran (40 mmol, 14.3 g, Chapter 1), benzene (25 g) and $Pd(PPh_3)_4$ (1 g) were placed in the flask and the mixture was heated under reflux. After ~5 h the conversion was complete. After cooling to room temperature, 150 ml of a 3 : 1 mixture of ether and THF was added, whereupon the dark (metallic Pd) solution was added over a few min (by syringe) to a vigorously stirred solution of 30 g of potassium fluoride in 100 ml of water. After vigorous stirring for half an hour at ~30 °C, the dark slurry was filtered (with gentle suction) through a 1 cm thick layer of Celite on a glass filter. The Celite was thoroughly rinsed with the ether–THF mixture. The aqueous layer of the filtrate was extracted twice with small portions of the ether–THF mixture. The organic solution was dried over anhydrous $MgSO_4$ and then concentrated to a volume of ~150 ml. This solution was filtered through a column of ~5 cm of neutral Al_2O_3. Concentration of the light-brown filtrate under reduced pressure gave the reasonably pure product in 84% yield. The product can be further purified by crystallization from diethyl ether.

^{1}H-NMR spectrum (CCl_4): 8.33 (m, 1H); 7.7-8.0 (m, 2H); 7.4–7.5 (m, 2H); 6.70 (m, 1H); 6.37 (m, 1H) ppm.

11.11.8.4 Other Coupling Reactions with Organotin Derivatives

The Pd-catalyzed reaction between $H_2C{=}C(OC_2H_5)SnBu_3$ and 2-bromothiophene in benzene proceeded very slowly. Using a DMF–benzene mixture, however the reaction was finished (GLC) after 2 h at 100 °C. At the end the solution had become black because of the formation of metallic palladium.

Also the cross-coupling between 1-methyl-2-tributylstannylpyrrole and *m*-bromobenzaldehyde proceeded very smoothly in DMF (100 °C) as the only solvent (formation of metallic Pd after 1.5 h, complete conversion, according to GLC). The product could not be obtained in a pure state, some tin-containing contamination being present, even after repeated filtration through neutral Al_2O_3.

Abbreviations of literature references in Tables 9-20:

AAC = L. Brandsma, H.D. Verkruijsse, Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier, Amsterdam (1981); AC = Angew. Chem.; AC.IntEd = Angew. Chem., Int. Ed.; AK = Arkiv. Kemi; AL = Author's laboratory; Ann. Chim = Annales de Chimie; BCS.Jpn = Bull. Chem. Soc. Japan; BSC.Fr = Bull. Soc. Chim. France; CA = Chem. Abstr.; CB = Chem. Ber.; CC = J. Chem. Soc., Chem. Comm.; Ch. Acetylenes = Chemistry of Acetylenes, H.G. Viehe (ed.), Marcel Dekker, New York (1969); ChScr = Chemica Scripta; CL = Chem. Lett; CPB.Jpn = Chem. Pharm. Bull., (Jpn); CR = Compt. Rend.; H = Heterocycles; HCA = Helv. Chim. Acta; HW= Houben-Weyl; JACS = J. Am. Chem. Soc.; JCS = J. Chem. Soc.; JCS, (P. I) = J. Chem. Soc., (Perkin I); JHC = J. Heterocycl. Chem.; JMC = J. Mol. Catal.; JOC = J. Org. Chem.; JOM = J. Organometal. Chem.; LAC = Lieb. Ann. Chem.; NJC = New. J. Chem.; OOP = Org. Prep. and Proc., Int.; OS = Organic Syntheses; OS, ..., C... = Organic Syntheses, Collective Volume; PAC = Pure and Appl. Chem.; PrAcCh = L. Brandsma, Preparative Acetylenic Chemistry, Elsevier, Amsterdam (1988); RTC = Recl. Trav. Chim., Pays-Bas; S= Synthesis; SC = Synthetic Communications; SL= Synlett; T = Tetrahedron; TL = Tetrahedron Lett.

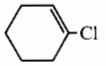
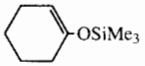
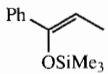
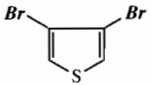
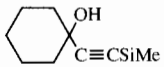
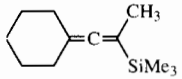
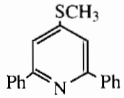
Table 9

Couplings of organometallic intermediates with R(C=O)Hal and ClCOOR (see Negishi et al., Tetrahedron Lett. (1983) 24 5181) and other special coupling reactions, e.g. with homoallylic, propargylic and homobenzyliczinc halides (see Negishi et al., J. Am. Chem. Soc. (1980) 102, 3298, J. Org. Chem. (1980) 45, 5223 and Negishi et al., Tetrahedron Lett. (1983) 3823) are not included.

Table 9. Examples of Cu, Pd and Ni catalyzed cross-couplings with organometallic reagents

R'L→ ↓ RM	C=C–L	(Het)aryl–L	C≡C–L	C=C–C–L	C≡C–C–L C=C=C–L	(Cyclo)alkyl–L	Ar–C–L
C=C–M	Pd TL (1978) 191	Ni PAC (1980) 669	Pd TL (1979) 3437	Pd OS, C7, 245	Pd TL (1981) 1451	Cu TL (1976) 3225	Pd TL (1981) 2715 JACS (1979) 4992
(Het)aryl–M	Pd OS, C7, 172	Ni, Pd T (1985) 1919	Ni PAC (1980) 669	Pd T (1990) 2623	Cu AAC (1981)	Ni S (1987) 40 TL (1991) 189	Pd T (1990) 2623
C≡C–M	Ni JOC (1984) 4733 Pd JACS (1986) 4685; (1987), 2138	Pd JOC (1978) 358	Pd SC (1991) 977	Cu PrAcCh (1988)	Cu PrAcCh (1988)	Uncatalyzed with primary RHlg	
C=C–C–M		Ni PAC (1980) 669 JHC (1973) 243 Pd JOC (1992) 678		Cu S (1978) 528 Pd JOM (1983) 250, 551		Cu TL (1978) 4069	
C≡C–C–M ↔ C=C=C–M	Pd S (1982) 738	Pd JOM (1982) 224, 399			Pd TL (1981) 1451		
(Cyclo)alkyl–M	Ni, Pd TL (1978) 191 TL (1985) 2575	Ni JOC (1984) 478 OS, C6, 407	Ni CB (1990) 1495	Cu JACS (1990) 6615 Pd JOC (1983) 4098 (enolates)	Cu AAC (1981)	Cu JACS (1974) 7101 TL (1979) 1503 Ni TL (1991) 189 Pd TL (1986) 6013	Cu S (1977) 316 Pd JACS (1979) 4992
(Het)aryl-C–M	Ni, Pd TL (1981) 2715 JOC (1983) 2195	Pd TL (1980) 845		Cu TL (1982) 3115	Cu RTC (1974) 183		Pd JACS (1979) 4992

Table 10. Cross-couplings with sp^3-magnesium halides and zinc halides

RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
CH_3MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 3–20 h		OS (1988) C6, 407
CH_3MgBr		Et_2O	$Ni(acac)_2$	20°C, 20 h		TL (1980) 3915
CH_3MgBr		C_6H_6	$NiCl_2$·$(PPh_3)_2$	100°C, 3–5 h		TL (1980) 3915
CH_3MgBr		Et_2O	$Pd(PPh_3)_4$	Reflux, 20 h	Reaction not complete only mono in 24 % yield	TL (1980) 845
CH_3MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 20 h		T (1982) 3347
CH_3MgBr		Et_2O-C_6H_6	$NiCl_2$·dppp	Reflux, 48 h	Product: 	JOC (1985) 1122
CH_3MgBr		C_6H_6	$NiCl_2$·$(PPh_3)_2$	Reflux, 20 h	Products: $CH_3CH{=}CH\text{-}(CH_2)_3OH$ $E + Z$	JOC (1984) 4894
CH_3MgBr		C_6H_6	$NiCl_2$·$(PPh_3)_2$	80°C, 12 h		JOC (1985) 1125

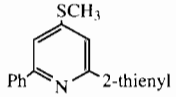
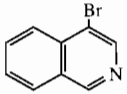
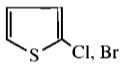
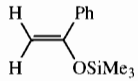
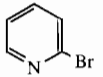
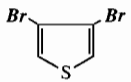
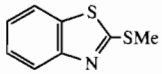
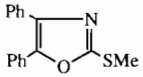
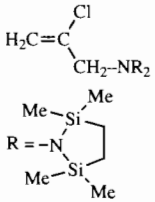
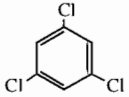
CH_3MgBr		C_6H_6	$NiCl_2{\cdot}(PPh_3)_2$	80°C, 12 h	Low yield	JOC (1985) 1125
CH_3MgBr		Et_2O	$NiCl_2{\cdot}$dppp	Reflux, 20 h		T (1982) 3347
$CH_3(CH_2)_nMgBr$						
n = 1	RCH=CHI (*E* or *Z*)	C_6H_6-THF	$Pd(PPh_3)_4$	20°C, –	Retention of configuration	TL (1978) 191
n = 3		Et_2O	$NiCl_2{\cdot}$dppp	Reflux, – Reflux, 2 h	(Cl) low yield (Br) mainly thiophene	AL T (1982) 3347
n = 3 (MgCl)		C_6H_6	$NiCl_2{\cdot}$dppf	Reflux, 3–5 h	Fair yield	TL (1980) 3915
n = 3		Et_2O	$NiCl_2{\cdot}$dppp	20°C, 2 h + reflux, 6 h		OS (1988) C6, 407
n = 3		Et_2O	$PdCl_2{\cdot}$dppb	Reflux, 20 h	Mono 76 % di 5 %	TL (1980) 845
n = 3		Et_2O	$NiCl_2{\cdot}$dppp	Reflux, –	20°C, 2.5 h	OS (1988) C6, 407 T (1982) 3347
n = 3		Et_2O	$NiCl_2{\cdot}$dppp	Reflux, 16 h		T (1982) 3347

Table 10. (Continued)

RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
$CH_3(CH_2)_n$-MgBr						
n = 3		Et_2O	$NiCl_2$·dppp	20°C, 2.5 h	Moderate yield	T (1982) 3347
n = 3		Et_2O	$NiCl_2$·dppp	Reflux, 8 h		CL (1979) 1447
n = 3 (MgCl)		THF-Et_2O	$NiCl_2$·dppe	20°C, 16 h		S (1984) 1047
$CH_3(CH_2)_n$-MgBr						
n = 3		Et_2O	$NiCl_2$·dppp	20°C, 16 h		JOC (1987) 678
n > 3		Et_2O	$NiCl_2$·dppp	25–30°C, 0.5 h + reflux, 0.5 h; 20°C, 16 h + reflux, 1 h		AL; NJC (1992) 1009
n > 3		Et_2O	$NiCl_2$·dppe	25°C, ~16 h + reflux, 2 h		JOC (1984) 478

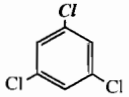
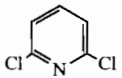
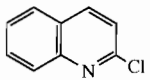
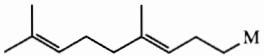
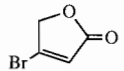
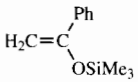
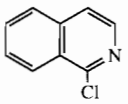
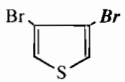
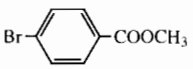
n > 3		THF	Ni(acac)2	–20°C !, 6 h	Fair yields	JOC (1984) 478
n > 3 (R-MgCl)	Cl_2C=CHCl	Et_2O-C_6H_6	$Pd(PPh_3)_4$	20°C, 6 h		TL (1985) 2575
n > 3 (R-MgCl)	*E*-ClCH=CHCl	Et_2O-C_6H_6	$Ni(PPh_3)_4$	10°C, 0,5 h + 20°C, 2,5 h	Retention of configuration	AL; TL (1981) 315
n > 3 $CH_3(CH_2)_n$-MgBr	***Br***CH=CHOEt	Et_2O or THF	$NiCl_2$·dppp	20 or 45°C, 16 h	Stereochemistry lost	CL (1976) 1237
n = 7 (MgCl)	H_2C=CHCl	Et_2O + C_6H_6 + THF	$NiCl_2$·dppe	20°C, 20 h		JACS (1972) 4374
$(CH_3)_3C$-MgCl	*E*-PhCH=CHBr	Et_2O	$NiCl_2$·dppf	35°C, 11 h	Pd-catalysts are less reactive and less selective	CL (1980) 767
$BrMg(CH_2)_{10}MgBr$		THF	$NiCl_2$·dppp	20 or 40°C, ≤20 h	33 % yield of meta-cyclophane	JACS (1975) 4405
c-C6H_{11}-MgCl	Cl_2C=CH***Cl***	Et_2O-C_6H_6	$Pd(PPh_3)_4$	20°C, 6 h		TL (1985) 2575
c-C6H_{11}-MgCl		THF	$PhPdI(PPh_3)_2$	Reflux, 0.5 h	Fair yield	JOM (1976) 118, 349
c-C_6H_{11}-MgBr	*n*-C_6H_{13}I	THF	$PdCl_2$·dppf	Reflux, 16 h		TL (1986) 6013
c-C_6H_{11}-MgBr		THF	$PdCl_2$·dppf	Reflux, 16 h	Fair yield	TL (1986) 6013

Table 10. (Continued)

RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
$H_2C{=}CHCH_2$-MgCl		Et_2O	$NiCl_2{\cdot}(PPh_3)_2$	20°C, 24 h		JHC (1973) 243
		THF	$PdCl_2{\cdot}(PPh3)_2$ + 2 DIBAH	20°C, 16 h		JOC (1980) 5223
M=ZnCl (JOC); ZnBr (PAC)		THF	$Pd(PPh_3)_4$	20°C, 16 h		PAC (1981) 2333
$PhCH_2MgCl$		C_6H_6	$NiCl_2(PPh_3)_2$	100°C, 3–5 h		TL (1980) 3915
$PhCH_2MgCl$		Et_2O	$NiCl_2(PPh_3)_2$	20°C, 24 h		JHC (1975) 443
$PhCH_2MgCl$		Et_2O	$NiCl_2{\cdot}dppp$	20°C, 21 h		T (1982) 3347
$PhCH_2ZnBr$		THF	$Pd(PPh_3)_4$	50°C, 16 h	68 % mono-substitution 12 % di-substitution	TL (1980) 845
$PhCH_2ZnBr$		THF	$Pd(PPh_3)_4$	50°C, 20 h	52 % mono-substitution 6 % di-substitution	TL (1980) 845
$PhCH_2ZnBr$		THF-Et_2O	$Ni(acac)_2$ + Ph_3P + DIBAH	~25°C, 1–2 h		JOC (1977) 1821

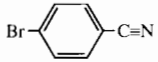
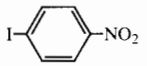
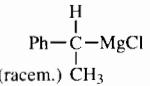
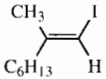
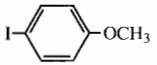
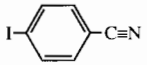
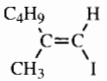
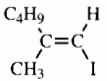
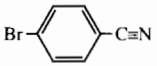
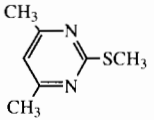
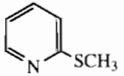
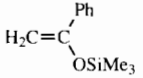
$PhCH_2ZnBr$		$THF\text{-}Et_2O$	$Ni(acac)_2$ + 4 Ph_3P + DIBAH	~25°C, 1–2 h		JOC (1977) 1821
$PhCH_2ZnBr$		$THF\text{-}Et_2O$	$PdCl_2{\cdot}(PPh_3)_2$ + 2 DIBAH	~25°C, 1–2 h		JOC (1977) 1821
		Et_2O	$NiCl_2{\cdot}$(–)Norphos	First, < 0, – then 20°C, 2 h	(S)-3-Phenyl-1-butene, 95 % chemical yield, 67 % optical yield	JOM (1981) 209, C1
$PhCH_2CH_2ZnCl$		THF	$Pd(PPh_3)_4$	25°C, 3 h		TL (1983) 3823
$PhCH_2CH_2ZnCl$		THF	$Pd(PPh_3)_4$ or $Ni(PPh_3)_4$	25°C, 3 h		TL (1983) 3823
$EtOOCCH_2ZnBr$	PhBr	$CH_2(OCH_3)_2$ + HMPT	$Ni(PPh_3)_4$	45°C, 3 h		JOM (1979) 177, 273
$EtOOCCH_2ZnBr$		$CH_2(OCH_3)_2$ + HMPT	$Ni(PPh_3)_4$	45°C, 3 h		JOM (1979) 177, 273
$EtOOCCH_2ZnBr$		$CH_2(OCH_3)_2$ + HMPT	$Ni(PPh_3)_4$	45°C, 3 h		JOM (1979) 177, 273
$EtOOCCH_2ZnBr$	PhCH=CHBr *E* and *Z*	$CH_2(OCH_3)_2$ + HMPT + Et_2O	$Pd(PPh_3)_4$	Reflux, 3 h		JOM (1981) 209, 109
$R(CH_2)nZnI$ n = 2,3 R = COOEt		$CH_3C(O)NMe_2$ + C_6H_6	$PdCl_2{\cdot}(PPh_3)_2$	70°C, 12 h (n = 2) 20°C, 0.5 h (n = 3)		S (1988) 485
$R(CH_2)_3ZnI$ R = COOEt		$CH_3C(O)NMe_2$ + C_6H_6	$PdCl_2{\cdot}(PPh_3)_2$	20°C, 1 h		S (1988) 485

Table 10. (Continued)

RM	Electrophile	Solvent	Catalyst	Reaction conditions Remarks	Literature
$Me_3SiC{\equiv}C(CH_2)_2ZnCl$		THF-Et_2O	$Pd(PPh_3)_4$	20–25°C, 2 h	JACS (1980) 3298
$H_2C{=}CH(CH_2)_2ZnCl$		THF-Et_2O	$Pd(PPh_3)_4$	20–25°C, 16 h	JACS (1980) 3298
$H_2C{=}CH(CH_2)_2ZnCl$		THF	$Pd(PPh_3)_4$ or $Ni(PPh_3)_4$	25°C, 3 h	TL (1983) 3823
$Ph(CH_2)_3MgBr$	C_2H_5I	THF	$PdCl_2$·dppf + 2 DIBAH	21°C, 16 h	TL (1986) 6013
$Ph(CH_2)_3MgBr$		Et_2O	$NiCl_2$·dppp	Reflux, 8 h	CL (1979) 1447
$Ph(CH_2)_3MgBr$		Et_2O	$NiCl_2$·dppp	2 h reflux, 8 h	CL (1979) 1447
Me_3SiCH_2MgCl		Et_2O	$Ni(acac)_2$	Reflux, 3–6 h	TL (1980) 3915
$ArO(CH_2)_nMgBr$		Et_2O	$NiCl_2$·dppp	Reflux, 12–15 h	AC (1990) 419

Yields are satisfactory, unless indicated otherwise; for the sake of clarity, in some cases the leaving group (mostly halogen) that is selectively substituted is printed in bold-italic.

Table 11. Cross-coupling reactions with olefinic and allenic metal reagents

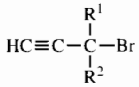
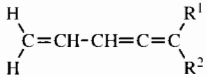
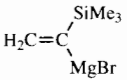
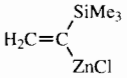
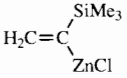
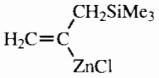
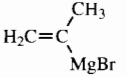
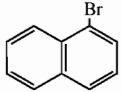
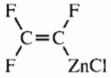
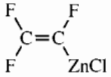
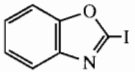
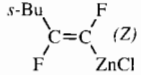
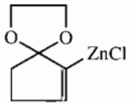
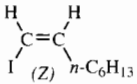
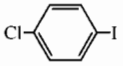
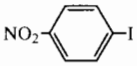
RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
$H_2C{=}CHMgBr$	$C_6H_{13}CH{=}CHI$ *E* or *Z*	THF-C_6H_6	$Pd(PPh_3)_4$	20°C, 1–2 h	Retention of stereochemistry	TL (1978) 191
$H_2C{=}CHZnCl$		THF or THF-Et_2O	$Pd(PPh_3)_4$	–, –	Products are: 	TL (1981) 1451
E-$CH_3CH{=}CHMgBr$	E-$C_6H_{13}CH{=}CHI$	THF-C_6H_6	$Pd(PPh_3)_4$	20°C, 2 h	Retention of stereochemistry	TL (1978) 191
		THF	$PdCl_2$·dppb	Reflux, 19 h	Some homo-coupling ~60 % yield of product	TL (1984) 83
		THF	$PdCl_2$·dppb	Reflux, 17 h		TL (1984) 83
		THF	$PdCl_2$·dppb	Reflux, 2 h		TL (1984) 83
		THF	$PdCl_2$·dppb	Reflux, 2 h		TL (1984) 83
		–	$NiCl_2$·dmpe	–	$NiCl_2$·dppp is inactive	PAC (1980) 669

Table 11. (Continued)

RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
		THF-Et_2O	$Pd(PPh_3)_4$	20°C, –		TL (1985) 3999
		THF-Et_2O	$Pd(PPh_3)_4$	20°C, –		TL (1985) 3999
		THF-Et_2O	$Pd(PPh_3)_4$	20°C, –	Retention of stereochemistry	TL (1985) 3999
		THF	$Pd(PPh_3)_4$	22°C, 2h	Retention of stereochemistry	CL (1987) 1007
t-BuCH=C=CH-M M = -ZnCl or MgCl	*n*-C_4H_9CH=CHI *E* or *Z*	THF	$Pd(PPh_3)_4$	35–50°C, 1–2 h	Retention of stereochemistry	JOM (1982) 224, 399
t-BuCH=C=CH-M M = -ZnCl		THF-HMPT	$Pd(PPh_3)_4$	25°C, 1 h		JOM (1982) 224, 399
t-BuCH=C=CH-M M = -ZnCl		THF-HMPT	$Pd(PPh_3)_4$	25°C, 1 h		JOM (1982) 224, 399
n-BuCH=C=CH-M M = -Li		THF-toluene	$PdCl_2$+ PPh_3 + DIBAH	20°C, 1 h		S (1982) 738

Yields are satisfactory, unless indicated otherwise; for the sake of clarity, in some cases the leaving group (mostly halogen) that is selectively substituted is printed in bold-italic.

Table 12. Cross-coupling reactions with alkynylmagnesium and alkynylzinc halides

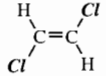
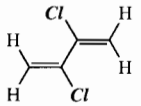
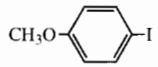
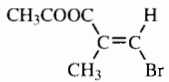
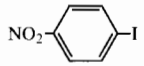
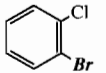
RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
$(Me)_3SiC{\equiv}CMgBr$		THF-Et_2O	$NiCl_2$·dppp	20°C, 12 h		JOC (1984) 4733
$(Me)_3SiC{\equiv}CMgBr$		THF	$NiCl_2$·dppp	−78 → 0°C, 2 h + 20°C, 6 h		AC.Int (1994) 1099
$HC{\equiv}CZnCl$	$C_4H_9CH{=}CHI$	THF	$Pd(PPh_3)_4$	25°C, –		CC (1977), 683
$HC{\equiv}CZnCl$ (100 % excess)		THF	$Pd(PPh_3)_4$	20°C, 1 h	With $HC{\equiv}CMgBr$ lower yields	JOC (1978) 358
$C_4H_9C{\equiv}CZnCl$		THF	$Pd(PPh_3)_4$	25°C, –		CC (1977) 683
n-$C_5H_{11}C{\equiv}CZnCl$		THF	$PdCl_2{\cdot}2PPh_3$ + DIBAH	20°C, 3 h		JOC (1978) 358
$Me_3SiC{\equiv}CZnCl$		THF	$Pd(PPh_3)_4$	30°C, 2–3 h		PrAcCh, 215
$Me_3SiC{\equiv}CZnCl$		THF	$Pd(PPh_3)_4$	30°C, 3 h		PrAcCh, 215
$CH_3(C{\equiv}C)_2ZnCl$		THF	$Pd(PPh_3)_4$	30°C, 2–3 h		PrAcCh, 215

Table 12. (Continued)

RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
$Me_3SiC{\equiv}CZnCl$		THF	$Pd(PPh_3)_4$	Reflux, 2–3 h		PrAcCh, 216
$Me_3SiC{\equiv}CZnCl$		THF	$Pd(PPh_3)_4$	Reflux, >4 h		PrAcCh, 216
n-$C_5H_{11}C{\equiv}CZnCl$	BrCH=CH***Br*** *E* + *Z* large excess	THF	$Pd(PPh_3)_4$	−50°C, 1 h + −20°C, 4 h + 0°, 12 h	only E reacts 58 % monoalkynylation 17 % dialkynylation	T (1987) 4591

Yields are satisfactory, unless indicated otherwise; for the sake of clarity, in some cases the leaving group (mostly halogen) that is selectively substituted is printed in bold-italic.

Table 13. Cross-couplings with 2-furylmagnesium and 2-furylzinc halides

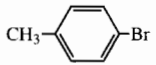
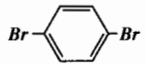
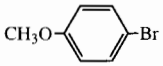
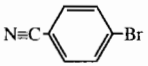
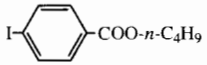
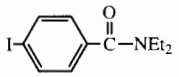
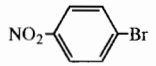
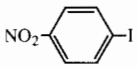
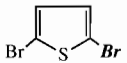
 M	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
ZnCl	$BrCH_2C{\equiv}N$	THF	*c*-$C_6H_{11}PPh_2$ + $Ni(acac)_2$	55°C, 0.5 h	moderate yield	S (1987) 40
ZnCl		THF	$Pd(PPh_3)_4$	20°C, –		OS (1993) C8, 430
ZnCl		THF	$Pd(PPh_3)_4$	50°C, 24 h	high yield $NiCl_2{\cdot}(PPh_3)_2$ gives a low yield	S (1987) 51
ZnCl		THF	$Pd(PPh_3)_4$	50°C, 24 h		S (1987) 51
ZnCl		THF	$Pd(PPh_3)_4$	50°C, 24 h		S (1987) 51
ZnCl		THF	$Pd(PPh_3)_4$	20°C, 24 h		JOM (1990) 390, 389
ZnCl		THF	$Pd(PPh_3)_4$	20°C, 2 h		JOM (1990) 390, 389
ZnCl		THF	$Pd(PPh_3)_4$	20°C, 2 h		JOM (1990) 390, 389
ZnCl		THF	$Pd(PPh_3)_4$	50°C, 24 h		S (1987) 51

Table 13. (Continued)

 M	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
ZnCl		THF	Pd(PPh3)4	20°C, 2 h		JOM (1990) 390, 389
ZnCl		THF	PdCl2·dppf	0°C, 0.5 h + 20°C, 15 h	Some disubstitution	T (1985) 1919

Yields are satisfactory, unless indicated otherwise; for the sake of clarity, in some cases the leaving group (mostly halogen) that is selectively substituted is printed in bold-italic.

Table 14. Cross-couplings with 3-thienyl- and 3-furylmagnesium or corresponding zinc halide

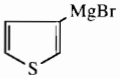
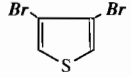
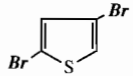
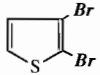
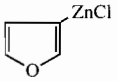
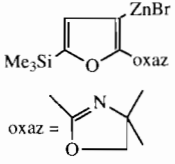
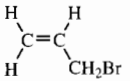
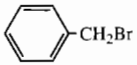
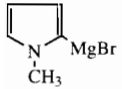
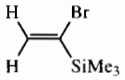
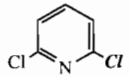
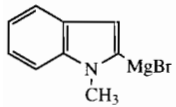
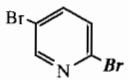
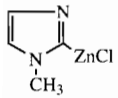
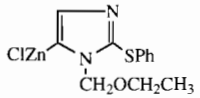
RMgBr or RZnCl(Br)	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
		Et_2O	$NiCl_2$·dppp	Reflux, 16 h		H (1986) 2261
MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 20 h		H (1986) 2261
MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 20 h		H (1986) 2261
MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 48 h	Reasonable yield	H (1986) 2261
MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 48 h		H (1986) 2261
		THF	$Pd(PPh_3)_4$	20°C, –		OS (1993) C8, 430
		THF	$Pd(PPh_3)_4$	Reflux, 16 h		T (1990) 2623

Table 14. (Continued)

RMgBr or RZnCl(Br)	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
RZnBr		THF	$Pd(PPh_3)_4$	Reflux, 16 h		T (1990) 2623
RZnBr		THF	$Pd(PPh_3)_4$	Reflux, 16 h		T (1990) 2623

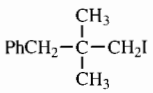
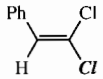
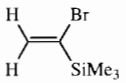
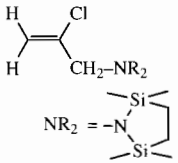
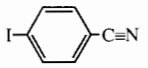
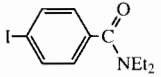
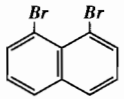
Yields are satisfactory, unless indicated otherwise; for the sake of clarity, in some cases the leaving group (mostly halogen) that is selectively substituted is printed in bold-italic.

Table 15. Cross-couplings with metallated *N*-heterocycles

RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
		THF	$PdCl_2$·dppb	Reflux, 1 h		TL (1984) 83
MgBr		THF	$PdCl_2$·dppb	–, –		CC (1984) 511
ZnCl		THF	$PdCl_2$·dppb	20°C, 22 h		TL (1981) 5319
		THF	$PdCl_2$·dppb	–, –		CC (1984) 511
		THF	$Pd(PPh_3)_4$	Reflux, 4 h	200 % excess $ZnCl_2$ required	TL (1988) 5013
		THF	$Pd(PPh_3)_4$	Reflux, 4 h		TL (1988) 5013

Yields are satisfactory, unless indicated otherwise; for the sake of clarity, in some cases the leaving group (mostly halogen) that is selectively substituted is printed in bold-italic.

Table 16. Cross-couplings with 2-thienylmagnesium and 2-thienylzinc halides

	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
MgBr		Et_2O	$NiCl_2$·dppf	Reflux, 12–20 h	Also homo-coupling	TL (1991) 189
MgBr		Et_2O	$PdCl_2$·dppb	Reflux, 2 h		JACS (1987) 1257
MgBr		Et_2O	$PdCl_2$·dppb	Reflux, 2 h		TL (1984) 83
MgBr	BrCH=CHOEt	Et_2O or THF	$NiCl_2$·dppp	10–50°C, 16 h		CL (1976) 1237
MgBr		Et_2O	$NiCl_2$·dppp	23°C, 1 h		JOC (1987) 678
MgBr		THF	$Pd(PPh_3)_4$	20°C, 2 h		JOM (1990), 390, 389
MgBr		THF	$Pd(PPh_3)_4$	20°C, 2 h		JOM (1990) 390, 389
MgBr		Et_2O	$NiCl_2$·dppp	–, –	36 % di- and 30 % mono-substitution	TL (1992) 7553

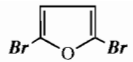
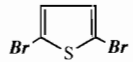
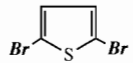
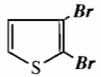
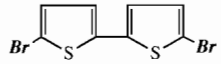
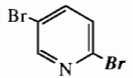
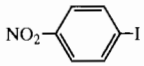
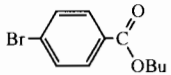
MgBr		Et_2O	$PdCl_2$·dppf	20°C, 2.5 h	T (1985) 1919
MgBr		Et_2O	$NiCl_2$·dppe	Reflux, 5 h	T (1985) 1919
MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 3 h	T (1982) 3347
MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 20 h	T (1982) 3347
MgBr		Et_2O-THF	$NiCl_2$·dppp	60°C, 15 h	T (1982) 3347
MgBr		Et_2O-THF	$NiCl_2$·dppe	Reflux, 5 h	T (1985) 1919
MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 12 h	H (1986) 2261
MgBr		Et_2O	$NiCl_2$·dppp	Reflux, 3 h	T (1982) 3347
MgBr		Et_2O	$PdCl_2$·dppb	20°C, 5 h	CC (1984) 511
MgI		Et_2O	$NiCl_2$·dppe	Reflux, 3 h	T(1984) 2773

Table 16. (Continued)

	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
ZnCl	$BrCH_2C{\equiv}N$	THF	$Ni(acac)_2$ + $c\text{-}C_6H_{11}PPh_2$	55°C, 0.5 h	Fair yield	S (1987) 40
ZnCl		THF	$Pd(PPh_3)_4$	–, –		TL (1987) 5213
ZnCl		THF	$Pd(PPh_3)_4$	20°C, 2 h		JOM (1990) 390, 389
ZnCl		THF	$Pd(PPh_3)_4$	20°C, 24 h		JOM (1990) 390, 389

Yields are satisfactory, unless indicated otherwise; for the sake of clarity, in some cases the leaving group (mostly halogen) that is selectively substituted is printed in bold-italic.

Table 17. Cross-couplings with arylmagnesium and arylzinc halides

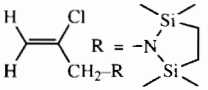
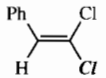
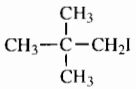
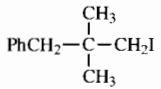
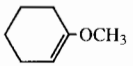
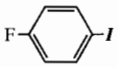
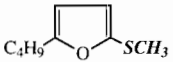
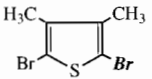
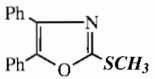
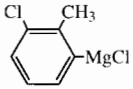
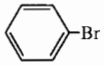
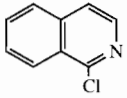
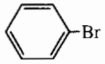
RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
PhMgBr		Et_2O	$NiCl_2$·dppp	20°C, 16 h		JOC (1987) 678
PhMgBr		Et_2O	$NiCl_2$·dppe	Reflux, 20 h		JACS (1972) 4374
PhMgBr		Et_2O	$PdCl_2$·dppb	Reflux, 2 h		JACS (1987) 1257
PhMgBr		Et_2O	$NiCl_2$·dppf	Reflux, 12–20 h		TL (1991) 189
PhMgBr		Et_2O	$NiCl_2$·dppf	Reflux, 12–20 h	5 % homo-coupling	TL (1991) 189
PhMgBr	(*Z*)-C_2H_5CH=CH-$OSiMe_3$	C_6H_6	$NiCl_2$·$(PPh_3)_2$	Reflux, 3–5 h	8/92 (*E*/*Z*)	TL (1980) 3915
	(*E*)-C_2H_5CH=CH-$OSiMe_3$	C_6H_6	$NiCl_2$·$(PPh_3)_2$	Reflux, 3–5 h	100 (*E*)	TL (1980) 3915
PhMgBr		C_6H_6	$NiCl_2$·$(PPh_3)_2$	Reflux, 15–48 h		JACS (1979) 2246
PhMgBr		Et_2O	$PdCl_2$·dppb	Reflux, 20 h	Little di-substitution product	TL (1980) 845
PhMgBr		THF	$Pd(PPh_3)_4$ or $Pd(Ph)I·(PPh_3)_2$	Reflux, 0.5 h		JOM (1976) 118, 349

Table 17. (Continued)

RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
PhMgBr		Et_2O	$NiCl_2$·dppe	20°C, 16 h		JOC (1982) 1590
PhMgBr		Et_2O	$NiCl_2$·dppe	20°C, 16 h		JOC (1982) 1590
PhMgBr		THF	$Pd(PPh_3)_4$	50°C, 20 h	72 % mono-substitution product	TL (1980) 845
PhMgBr		THF	$NiCl_2$·dppe	20°C, 16 h		S (1984) 1047
p-F-C_6H_4MgBr		THF	$PhPdI·(PPh_3)_2$	Reflux, 0.5 h		JOM (1976) 118, 349
p-H_3C-C_6H_4MgBr	HC≡CC(Me)$_2$Cl	THF	$PdCl_2$ + PPh_3 + DIBAH	25°C, 1 h	Product is p-H_3C-C_6H_4CH=C=CMe_2	TL (1980) 5019
		THF	$NiCl_2$	50–55°C, –	No ligand!	S (1990) 147
p-F_3C-C_6H_4MgBr		THF	$NiCl_2$·dppp	20°C, 16 h		JHC (1980) 1289
p-CH_3O-C_6H_4MgBr	PhCH_2C(CH_3)$_2$CH_2I	Et_2O	$NiCl_2$·dppf	Reflux, 12–20 h	5 % homo-coupling	TL (1991) 189
o-CH_3O-C_6H_4MgBr		THF	$Pd(PPh_3)_4$	65°C, –		T (1986) 2111

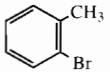
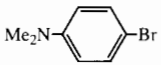
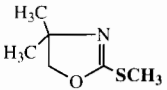
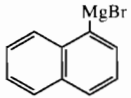
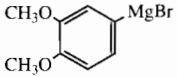
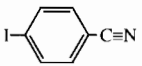
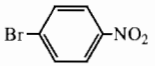
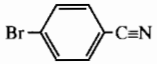
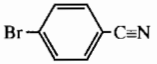
o-CH_3O-C_6H_4MgBr		THF	$Pd(PPh_3)_4$	65°C, –	Very slow reaction low yield	T (1986) 2111
o-CH_3O-C_6H_4MgBr		THF	$Pd(PPh_3)_4$	65°C, 4 h		T (1986) 2111
p-CH_3O-C_6H_4MgBr		Et_2O	$PdCl_2$·dppf	25°C, 1–3 h		JOC (1981) 5402
	H_2C=CHCl	Et_2O + C_6H_6 + THF	$NiCl_2$·dppe	20°C, 20 h		JACS (1972) 4374
	$BrCH$=$CHOC_2H_5$	Et_2O or THF	$NiCl_2$·dppp	20 or 40–50°C, 16 h	Non-stereospecific	CL (1976) 1237
p-CH_3 SC_6H_4MgBr		THF	$Pd(PPh_3)_4$	20°C, 2 h		JOM (1990) 390, 389
PhZnCl		THF	$Pd(PPh_3)_4$	20°C, –		OS (1993) C8, 430
PhZnCl		THF	$Pd(PPh_3)_4$	20°C, –		OS (1993) C8, 430
PhZnCl		THF	$Pd(PPh_3)_4$	20°C, –	No reaction !	OS (1993) C8, 430
p-CH_3O-C_6H_4ZnCl		THF	$Pd(PPh_3)_4$	20°C, 12 h		JOM (1990) 390, 389

Table 17. (Continued)

RM	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
p-CH_3O-C_6H_4ZnCl		THF	$Pd(PPh_3)_4$	20°C, 24 h		JOM (1990) 390, 389
p-Me_2N-C_6H_4ZnCl		THF	$Pd(PPh_3)_4$	20°C, 12 h		JOM (1990) 390, 389

Yields are satisfactory, unless indicated otherwise; for the sake of clarity, in some cases the leaving group (mostly halogen) that is selectively substituted is printed in bold-italic.

Table 18. Cross-couplings with organoaluminum compounds

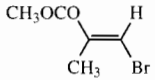
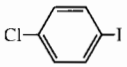
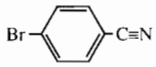
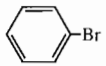
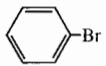
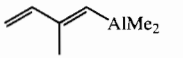
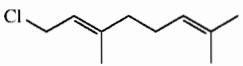
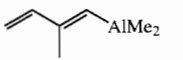
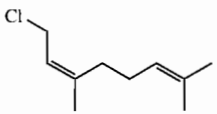
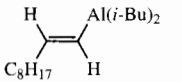
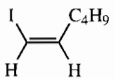
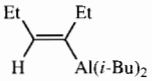
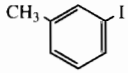
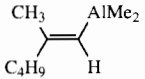
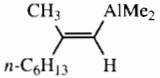
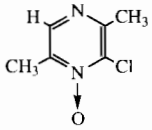
Al Compound	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
E-$C_4H_9CH{=}CHAl(i\text{-}Bu)_2$	*E*-*t*-$C_4H_9CH{=}CHI$	THF-hexane	$PdCl_2{\cdot}(PPh_3)_2$ + 2 DIBAH	25°C, –	Good yield	JACS (1976) 6729
E-$C_4H_9CH{=}CHAl(i\text{-}Bu)_2$	*E*-*t*-$C_4H_9CH{=}CHI$	Et_2O-hexane	$Ni(acac)_2$ + 4 PPh_3 + 2 DIBAH	25°C, –	Fair yield + homo-coupling: 8 % (C14), 6 % (C12)	JACS (1976) 6729
E-$C_4H_9CH{=}CHAl(i\text{-}Bu)_2$		THF-hexane	$PdCl_2{\cdot}(PPh_3)_2$ + 2 DIBAH	Reflux, 0.25 h		JACS (1976) 6729
E-$C_4H_9CH{=}CHAl(i\text{-}Bu)_2$		THF-hexane	$Ni(acac)_2$ + 4 PPh_3 + DIBAH	25°C, 6 h		JACS (1987) 2393
E-$C_4H_9CH{=}CHAl(i\text{-}Bu)_2$		THF-hexane	$Ni(acac)_2$ + 4 PPh_3 + DIBAH	25°C, 1 h		JACS (1987) 2393
E-$C_4H_9CH{=}CHAl(i\text{-}Bu)_2$	*E*-$C_4H_9CH{=}CHI$	THF or Et_2O	$Ni(acac)_2$ + 4 PPh_3 + DIBAH	25°C, –	Low yield	JACS (1987) 2393
E-$C_5H_{11}CH{=}CHAl(i\text{-}Bu)_2$	*E*-$C_4H_9CH{=}CHI$	Et_2O-hexane	$PdCl_2{\cdot}(PPh_3)_2$ + 2 DIBAH	25°C, –		JACS (1976) 6729
E-$C_5H_{11}CH{=}CHAl(i\text{-}Bu)_2$	*E*-$C_4H_9CH{=}CHI$	Et_2O-hexane	$Ni(acac)_2$ + 4 PPh_3 + 2 DIBAH	25°C, –	Good yield +homo-coupling: 15 % (C14), 2 % (C12)	JACS (1976) 6729
E-$C_5H_{11}CH{=}CHAl(i\text{-}Bu)_2$ 100 % excess		THF-hexane	$Ni(acac)_2$ + 4 PPh_3 + DIBAH	50°C, 3 h		JACS (1987) 2393
E-$C_5H_{11}CH{=}CHAl(i\text{-}Bu)_2$ 100 % excess		THF-hexane	$Pd(PPh_3)_4$	Reflux, 24		JACS (1987) 2393

Table 18. (Continued)

Al Compound	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
		THF	$Pd(PPh_3)_4$	25°C, 6 h		OS (1990) C7, 245
		THF	$Pd(PPh_3)_4$	–, –		JACS (1981) 2882
		THF	$Pd(PPh_3)_4$ + 1 eq. $ZnCl_2$	25°C, 6 h		OS (1988) 66, 60
		THF	$Pd(PPh_3)_4$ + $ZnCl_2$	25°C, 1 h	High yield (without $ZnCl_2$ no product)	JACS (1978) 2254
$AlPh_3$	*E*-$CH_3CH{=}CHCH_2OAc$	THF	$Pd(PPh_3)_4$	25°C, 3 h	E/Z mixture of 1,1- and 1,3-substitution products	TL (1981) 3737
	Geranyl acetate Neryl acetate	THF	$Pd(PPh_3)_4$	25°C, 1 h	only 1,1-substitution products; retention of configuration	TL (1981) 3737
		THF	$Pd(PPh_3)_4$	25°C, 5 h		H (1982) 117
Me_3Al		dioxane, hexane	$Pd(PPh_3)_4$	Reflux, 2 h		H (1985) 133

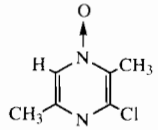
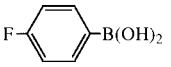
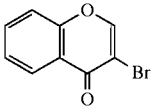
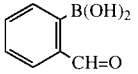
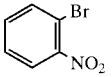
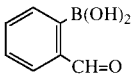
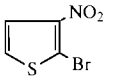
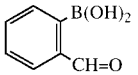
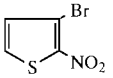
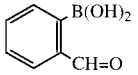
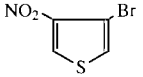
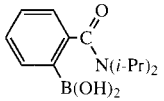
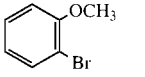
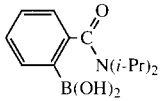
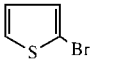
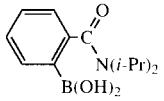
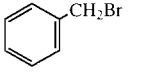
Me_3Al		Dioxane, $Pd(PPh_3)_4$ hexane	Reflux, 2 h	H (1985) 133

Table 19. Cross-couplings with organoboron compounds

Boron Compound	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
		H_2O, C_6H_6	$Pd(PPh_3)_4$ + 2 Na_2CO_3	Reflux, 6 h		BCS.Jpn (1988) 3008
		DME, H_2O	$Pd(PPh_3)_4$ + $NaHCO_3$	Reflux, 1 h		ChScr (1986) 26, 383
		DME, H_2O	$Pd(PPh_3)_4$ + $NaHCO_3$	Reflux, 1 h	Only bis-(3-nitro-2-thienyl)sulfide in low yield	ChScr (1986) 26, 383
		DME, H_2O	$Pd(PPh_3)_4$ + $NaHCO_3$	Reflux, 1 h	Moderate yield	ChScr (1986) 26, 383
		DME, H_2O	$Pd(PPh_3)_4$ + $NaHCO_3$	Reflux, 1 h		ChScr (1986) 26, 383
		Toluene, H_2O	$Pd(PPh_3)_4$ + Na_2CO_3	Reflux, 6–12 h		TL (1985) 5997
		Toluene, H_2O	$Pd(PPh_3)_4$ + Na_2CO_3	Reflux, 6–12 h		TL (1985) 5997
		Toluene, H_2O	$Pd(PPh_3)_4$ + Na_2CO_3	Reflux, 6–12 h		TL (1985) 5997

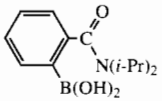
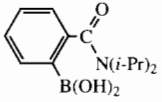
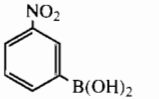
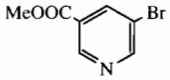
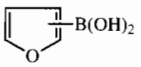
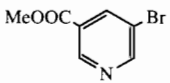
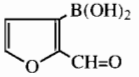
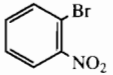
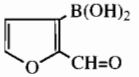
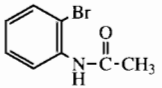
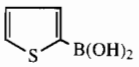
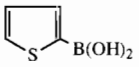
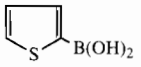
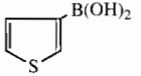
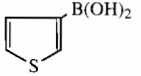
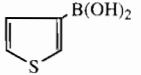
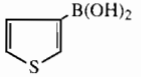
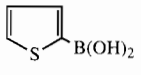
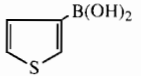
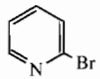
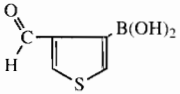
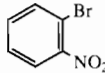
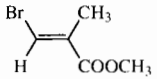
		Toluene, H_2O	$Pd(PPh_3)_4$ + Na_2CO_3	Reflux, 6–12 h		TL (1985) 5997
		Toluene, H_2O	$Pd(PPh_3)_4$ + Na_2CO_3	Reflux, 6–12 h		TL (1985) 5997
		Toluene, CH_3OH, H_2O	$Pd(PPh_3)_4$ + Na_2CO_3	80°C, 6 h		JOC (1984) 5237
		DMF, Et_3N	$Pd(OAc)2$ +	100°C, 2–3 h		JOC (1984) 5237
		DME, H_2O	$Pd(PPh_3)_4$ + $NaHCO_3$	Reflux, 1 h		SC (1989) 1001
		DMF, Et_3N	$Pd(PPh_3)_4$	100°C, 4 h	Product is furo[2,3,c]quinoline	SC (1989) 1001
		C_6H_6 H_2O	$Pd(PPh_3)_4$ + 1 Na_2CO_3	Reflux, 24 h	Yield moderate	ChScr (1984) 23, 120
		C_6H_6 H_2O	$Pd(PPh_3)_4$ + 2 Na_2CO_3	Reflux, –	Complete hydrolysis of boronic acid	ChScr (1984) 23, 120

Table 19. (Continued)

Boron Compound	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
		DME H_2O	$Pd(PPh_3)_4$ + 1 Na_2CO_3	Reflux, 0.5 h	Good yield	ChScr (1984) 23, 120
		DME H_2O	$Pd(PPh_3)_4$ + 1 Na_2CO_3	Reflux, 0.5 h		ChScr (1984) 23, 120
		C_6H_6 H_2O	$Pd(PPh_3)_4$ + 2 Na_2CO_3	Reflux, 7 h		ChScr (1984) 23, 120
		C_6H_6 H_2O	$Pd(PPh_3)_4$ + 1 Na_2CO_3	Reflux, 20 h		ChScr (1984) 23, 120
		THF H_2O	$Pd(PPh_3)_4$ + 1 Na_2CO_3	Reflux, 2 h		ChScr (1984) 23, 120
		DME H_2O	$Pd(PPh_3)_4$ + 1 or 2 Na_2CO_3	Reflux, 16 h	Yield moderate	ChScr (1984) 24, 5
		DME H_2O	$Pd(PPh_3)_4$ 1 or 2 Na_2CO_3	Reflux, 16 h		ChScr (1984) 24, 5
		DME H_2O	$Pd(PPh_3)_4$ $NaHCO_3$	Reflux, 1 h		ChScr (1986) 26, 383
Z-C_4H_9CH=CHB(O-*i*-Pr)$_2$		CH_3OH	$Pd(OAc)_2$ PPh_3 2 K_2CO_3	Reflux, 5 h	Retention of configuration	BSC.Jpn, (1989) 3892

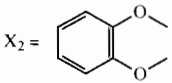
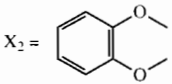
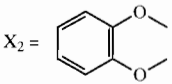
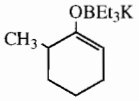
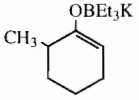
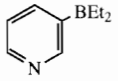
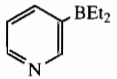
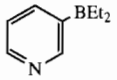
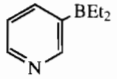
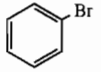
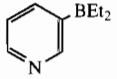
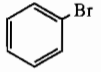
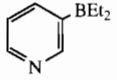
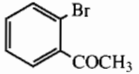
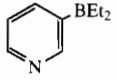
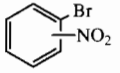
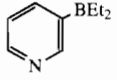
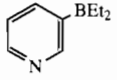
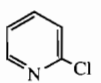
E-$C_4H_9CH{=}CHBX_2$ 	*Z*-BrCH=CHCOOEt	C_2H_5OH H_2O	$Pd(OAc)_2$ dppf 2 K_2CO_3	25°C, 24 h	Retention of configuration	BSC.Jpn (1989) 3892
E-$C_6H_{13}CH{=}CHBX_2$ 	*E*-BrCH=CHCOOEt	C_2H_5OH H_2O	$Pd(OAc)_2$ PPh_3 2 Na_2CO_3	Reflux, 4 h	Retention of configuration	BSC.Jpn (1989) 3892
E-$C_6H_{13}CH{=}CHBX_2$ 	*Z*-$C_6H_{13}CH{=}CHBr$	C_6H_6 C_2H_5OH H_2O	$Pd(PPh_3)_4$ 2 $NaOC_2H_5$	Reflux, 2 h	Mixture of *E/Z* and *E/E*	TL (1979) 3437
	E-$C_6H_{13}CH{=}CHBr$			Reflux, 2 h	Good yield, only *E/E*	
	$H_2C{=}C(Cl)CH_2\mathit{Cl}$	THF	$Pd(PPh_3)_4$	25°C, 12 h		JOC (1983) 2427
	$H_2C{=}C(Cl)CH_2\mathit{Cl}$	THF	$Pd(PPh_3)_4$	25°C, 12 h		JOC (1983) 2427
	R-CH=CHCH$_2$OAc (geranylacetaat)	THF	$Pd(PPh_3)_4$	25°C, 24 h	Regiospecific; retention of configuration	JOC (1982) 3188
	*Z*-EtOCH=CHBr	THF	$Pd(PPh_3)_4$, KOH, Bu_4NBr	Reflux, 1 h		H (1984) 2475

Table 19. (Continued)

Boron Compound	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 1 h		H (1984) 2475
	*E*-PhCH=CHBr	THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 1 h		H (1984) 2475
		C_6H_6 C_2H_5OH	$Pd(PPh_3)_4$ $NaOC_2H_5$	Reflux, 1 h		H (1984) 265
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 1 h	Compare: S, (1984), 936 for reaction times	H (1984) 265
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 3 h	Compare: S, (1984), 936 for reaction times	H (1984) 265
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 3 h (2-NO_2) Reflux, 2 h (3-NO_2)	Compare: S, (1984) 936 for reaction times	H (1984) 265
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 8 h	Compare: H, (1984), 265 for reaction times	S (1984) 936
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 8 h	Compare: H, (1984), 265 for reaction times	S (1984) 936

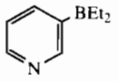
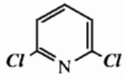
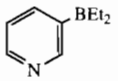
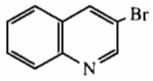
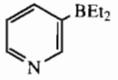
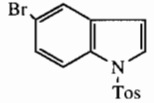
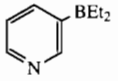
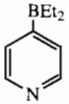
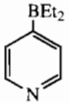
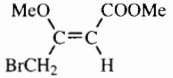
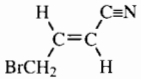
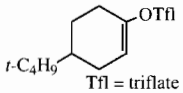
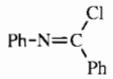
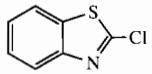
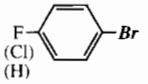
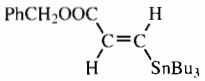
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 8 h	Moderate yield	S (1984) 936
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 8 h	Compare: H, (1984), 265 for reaction times	S (1984) 936
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 8 h	Moderate yield	S (1984) 936
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 8 h	Moderate yield	S (1984) 936
		THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 2.5 h		H (1984) 2475
	*E*-PhCH=CHBr	THF	$Pd(PPh_3)_4$ KOH Bu_4NBr	Reflux, 4 h		H (1984) 2475

Table 20. Cross-couplings with organotin compounds

Tin Compound	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
$H_2C{=}CHSnBu_3$		$CHCl_3$	PhCH2PdCl $(PPh_3)_2$	65°C, 48 h	Fair yield	JACS (1984) 4833
$H_2C{=}CHSnBu_3$		$CHCl_3$	PhCH2PdCl $(PPh_3)_2$	65°C, 48 h	Reasonable yield	JACS (1984) 4833
$H_2C{=}CHSnBu_3$	 Tfl = triflate	THF 2 eq LiCl	$Pd(PPh_3)_4$	Reflux, 17 h	Aqueous work-up, filtration through SiO_2	JACS (1984) 4630
$H_2C{=}CHCH_2SnBu_3$		C_6H_6	$PdCl_2$ $(PPh_3)_2$	120°C, 10 h	Bu_3SnCl removed with KF in H_2O Product is: PhN=CPh(R) R = CH=CHMe	BCS.Jpn (1986) 677
$CH_3CH{=}CHSnBu_3$		Xylene	$PdCl_2$ $(PPh_3)_2$	120°C, 20 h	Bu_3SnCl removed with KF in H_2O	BCS.Jpn (1986) 677
$H_2C{=}CHCH(OEt)\text{-}SnBu_3$		THF	$Pd(PPh_3)_4$			CL (1977) 301
		THF	$Pd(dba)_2$ 2 PPh_3	50°C, 24–48 h		JACS (1984) 4833

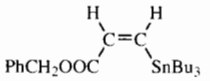
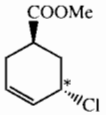
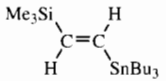
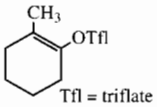
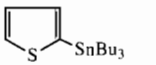
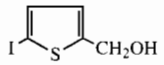
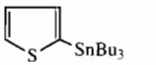
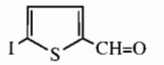
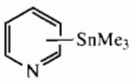
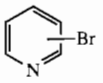
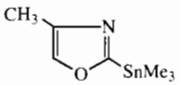
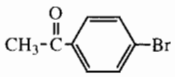
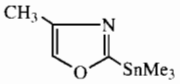
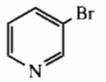
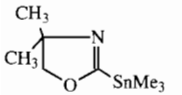
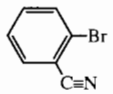
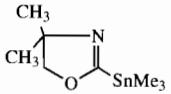
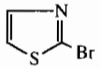
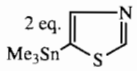
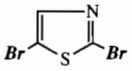
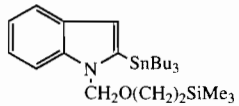
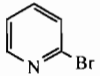
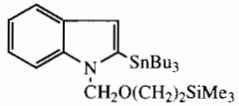
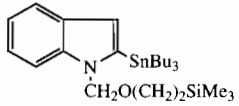
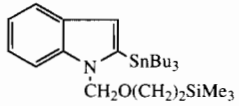
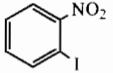
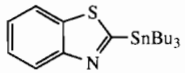
		THF	$Pd(dba)_2$ 2 PPh_3	50°C, 24–48 h	Inversion of configuration at C*	JACS (1984) 4833
		THF	$Pd(PPh_3)_4$ 2 eq LiCl	Reflux, 100 h	Aqueous work-up, filtration through SiO_2	JACS (1984) 4630
		THF	$PdCl_2$ $(PPh_3)_2$	60°C, 16 h	Dry work-up prep. TLC	SC (1989) 307
		THF	$PdCl_2$ $(PPh_3)_2$	60°C, 16 h		SC (1989) 307
		Xylene	$Pd(PPh_3)_4$	Reflux, 12 h	Extraction with HCl-H_20	S (1986) 564
		C_6H_6	$Pd(PPh_3)_4$	80°C, 12 h	Dry work-up, chromatographic purification	S (1987) 693
		C_6H_6	$Pd(PPh_3)_4$	80°C, 24 h	Dry work-up, chromatographic purification	S (1987) 693
		C_6H_6	$Pd(PPh_3)_4$	80°C, 20 h	Dry work-up, chromatographic purification	S (1987) 693

Table 20. (Continued)

Tin Compound	Electrophile	Solvent	Catalyst	Reaction conditions	Remarks	Literature
		C_6H_6	$Pd(PPh_3)_4$	80°C, 24 h	Dry work-up, chromatographic purification	S (1987) 693
		C_6H_6	$Pd(PPh_3)_4$	Reflux, 48 h	Dry work-up, chromatographic purification	S (1987) 185
		DMF	$Pd(PPh_3)_4$	110°C, 72 h	Chromatography (SiO_2) after aq. work-up	HCA (1993) 2356
	$PhCH_2Br$	THF	$Pd_2(dba)_3$ $(2\text{-Furyl})_3P$	60°C, 3 h	Chromatography (SiO_2) after aq. work-up	HCA (1993) 2356
	Geranyl bromide	THF	$Pd_2(dba)_3$ $(2\text{-Furyl})_3P$	60°C, 76 h	Good yield	HCA (1993) 2356
		DMF	$Pd(PPh_3)_4$	110°C, 72 h	Yield only 12 %	HCA (1993) 2356
		DMF	$Pd(PPh_3)_4$	110°C, 6 h	Chromatography (SiO_2) after aq. work-up	HCA (1993) 2356
	PhBr	Xylene	$PdCl_2$ $(PPh_3)_2$	120°C, 20 h	Fair yield	BCS. Jpn (1986) 677

Index of Reaction Types[1]

[1] Excluded the transition metal-catalyzed reactions in Chaps. 3–11

Index of Experimental Procedures

Chapter 5 (p. 70) Cu-Catalyzed Oxidative Couplings of Acetylenes

$$RC{\equiv}CH \xrightarrow[\text{additive(s)}]{O_2,\ \text{solvent}} RC{\equiv}C\text{–}C{\equiv}CR$$

R	Solvent	Additive	Page
Et	pyridine	DBU	78
Me_3Si	DMF	pyridine	80
Me_3Si	acetone	TMEDA	75[a]
t-Bu	pyridine	DBU	79
Ph	acetone	TMEDA	75
Ph	pyridine	–	78
2-Furyl	acetone	TMEDA	75
2-Furyl	pyridine	–	78
2-Thienyl	acetone	TMEDA	75
2-Pyridyl	pyridine	–	78
3-Pyridyl	pyridine	–	78
2-(1-Me-pyrryl)	pyridine	DBU	79
CH_3OCH_2	acetone	TMEDA	72
Et_2NCH_2	pyridine	–	78
$(EtO)_2CH$	DMF	TMEDA	76
$(EtO)_2CH$	acetone	TMEDA	75[a]
$EtSCH_2$	DMF	TMEDA	76
$EtSCH_2$	acetone	TMEDA	75[a]
H_2NCH_2	H_2O	HCl, NH_4Cl	80[a]
$NH_2C(CH_3)_2$	H_2O	HCl, NH_4Cl	80
$CH_3OCH{=}CH$	acetone	TMEDA	74
t-BuC≡C	pyridine	–	78
$HOCH_2$	acetone	TMEDA	75
$HOCH_2$	H_2O	NH_4Cl	71
$HOCH(CH_3)$	acetone	TMEDA	73
$HOC(CH_3)_2$	acetone	TMEDA	73
$HOCH_2CH_2$	acetone	TMEDA	74
$HO(CH_2)_4$	pyridine	–	77

[a] Failure or less successful
[b] Disubstitution of halogen
[c] Monosubstitution of halogen: indicated in ***bold italic.***
[d] Only the symmetrically substituted acetylene R'C≡CR' formed

Abbreviations: TMEDA = *N,N,N',N'*-Tetramethylethylene diamine
DBU = 1,8-Diazabicyclo[5,4,0]undec-7-ene
NMP = *N*-Methylpyrrolidinone

Chapter 6 (p. 85) Copper-Catalyzed Alkoxy-Dehalogenation

$$RHlg + NaOR' \xrightarrow[\text{additive(s)}]{CuBr} ROR'$$

RHlg (R)	NaOR' (R')	Solvent	Page
2-Br-thiophene	CH_3	CH_3OH	99
3-Br-thiophene	CH_3	CH_3OH-NMP	100
3-Br-pyridine	CH_3	CH_3OH	100
2,5-Di-Br-thiophene	CH_3	CH_3OH	101[b]
3,4-Di-Br-thiophene	CH_3	CH_3OH	101[b]
1-Br-cyclooctene	CH_3	CH_3OH-DMF	101
2-Br-thiophene	C_2H_5	C_2H_5OH	102
3-Br-thiophene	C_2H_5	CH_3OH-DMF	102
3-Br-thiophene	$CH(CH_3)_2$	i-C_3H_7OH-DMF	102
2-Br-furan	$CH_2CH_2NMe_2$	$Me_2NCH_2CH_2OH$	102
3-Br-furan	$CH_2CH_2NMe_2$	$Me_2NCH_2CH_2OH$	103[a]
2-Br-thiophene	$CH_2CH_2NMe_2$	$Me_2NCH_2CH_2OH$	103
1-Br-cyclooctene	$CH_2CH_2NMe_2$	$Me_2NCH_2CH_2OH$	103
2-Br-thiophene	CH_2CH_2OMe	$MeOCH_2CH_2OH$	103
1,4-Di-Br-benzene	F_3CCH_2	NMP	104[b]
1,4-Di-Br-benzene	F_3CCH_2	F_3CCH_2OH	104[b]

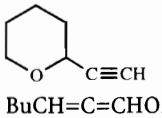
For footnotes see p. 316.

Chapter 7 (p. 107) Copper(I)Bromide Catalyzed Cross-Couplings and Substitution

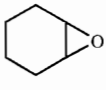
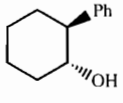
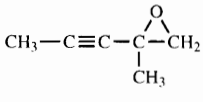
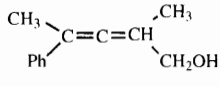
$$RMgHlg + R'L \xrightarrow{CuBr} RR'$$

$$R''C{\equiv}CH + R'L \xrightarrow{CuBr} R''C{\equiv}C{-}R'$$

L = Halogen, OTs, OAlkyl
R' = $(CH_2)_n$, C=C–C, C=C=C or C≡C–C

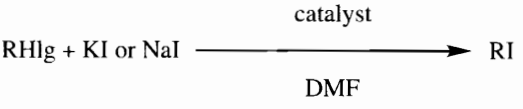
Grignard Compound or Nucleophile	Substrate	Product	Page
EtMgBr		$EtCH{=}C{=}CH(CH_2)_4OH$	129
BuMgBr	$BuCH{=}C{=}CHOMe$	$Bu_2CHC{\equiv}CH$	129
BuMgCl	$HC{\equiv}C\text{-}CH(OEt)_2$	$BuCH{=}C{=}CHOEt$	127
BuMgBr	$H_2C{=}CH\text{-}CH(OEt)_2$	$BuCH_2CH{=}CHOEt$	126

Chapter 7 (continued)

Grignard Compound or Nucleophile	Substrate	Product	Page
t-BuMgCl	$Br(CH_2)_4)Br$	*t*-$Bu(CH_2)_4$*t*-Bu	118
t-BuMgCl	$Br(CH_2)_4OR$ (R=$CH(CH_3)OEt$)	*t*-$Bu(CH_2)_4OR$	119
t-BuMgCl	$Br(CH_2)_4Cl$	*t*-$Bu(CH_2)_4Cl$	120
t-BuMgCl	2-ThienylCH_2CH_2OTs	2-ThienylCH_2CH_2*t*-Bu	121
t-BuMgCl	$PhCH_2Cl$	$PhCH_2$*t*-Bu	122
t-BuMgCl	$HC{\equiv}CCH_2Cl$	*t*-$BuCH{=}C{=}CH_2$	123
t-BuMgCl	*t*-$BuC{\equiv}CCH_2OTs$	(*t*-$Bu)_2C{=}C{=}CH_2$	125
t-BuMgCl	$H_2C{=}CHCH(OEt)_2$	*t*-$BuCH_2CH{=}CHOEt$	126
t-BuMgCl	$HC{\equiv}CCH(OEt)_2$	*t*-$BuCH{=}C{=}CHOEt$	127
c-PentylMgCl	$H_2C{=}C{=}CHOCH_3$	*c*-$PentCH_2C{\equiv}CH$	129
c-HexylMgCl	$HC{\equiv}CCH_2OCH_3$	*c*-$HexCH{=}C{=}CH_2$	128
RMgX	$HC{\equiv}CCH_2Cl$	$RCH{=}C{=}CH_2$	128
c-HexylMgBr	$Br(CH_2)_nBr$	*c*-$Hex(CH_2)_nBr$	120
ArylMgX	$Br(CH_2)_nBr$	Aryl$(CH_2)_nBr$	120
PhMgBr	2-ThienylCH_2CH_2OTs	2-ThienylCH_2CH_2Ph	121
p-$F(C_6H_4)MgBr$	$PhCH_2Cl$	*p*-$F(C_6H_4)CH_2Ph$	122
p-$CH_3O(C_6H_4)MgBr$	$PhCH_2Cl$	*p*-$CH_3O(C_6H_4)CH_2Ph$	122
2-ThienylMgBr	2-ThienylCH_2CH_2OTs	2-ThienylCH_2CH_2-2-thienyl + 2-Thienyl-CH_2CH_2Br	121[a]
ArylMgBr	$PhCH_2Cl$	ArylCH_2Ph	122
PhMgBr			127
PhMgBr			128
2-ThienylMgBr	$H_2C{=}C{=}CHOCH_3$	–	129[a]
$C_6H_{13}C{\equiv}CMgBr$	$H_2C{=}CHCH_2Br$	$C_6H_{13}C{\equiv}CCH_2CH{=}CH_2$	124
$C_6H_{13}C{\equiv}CMgBr$	$HC{\equiv}CCH_2Br$	$C_6H_{13}C{\equiv}CCH_2C{\equiv}CH$	124
$HOCH_2C{\equiv}CH$	$HC{\equiv}CCH_2Cl$	$H_2C{=}C{=}CHC{\equiv}CCH_2OH$	124
$HOCMe_2C{\equiv}CH$	$HC{\equiv}CCH_2Cl$	$H_2C{=}C{=}CHC{\equiv}CCMe_2OH$	124

For footnotes see p. 316.

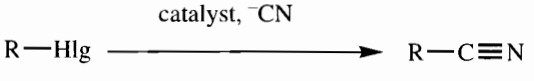
Chapter 8 (p. 141) Nickel-Catalyzed Conversion of Chlorides or Bromides into Iodides



Halogenide RHlg	Catalytic system	Page
1-Br-cyclooctene	$NiBr_2$-Bu_3P	145
4-Br-benzaldehyde	$NiBr_2$-Bu_3P	146
3-Br-benzaldehyde	$NiBr_2$-Bu_3P	146
4-Br-acetophenone	$NiBr_2$-Bu_3P	146
4-Br-benzonitrile	$NiBr_2$-Bu_3P	146
1-chlorocyclohexene	$NiBr_2$-Zn	146
1-chlorocyclohexene	$Ni(COD)_2$	147
PhCH=CHCl	$Ni(COD)_2$	147
$C_8H_{17}CH$=CHCl	$Ni(COD)_2$	147
$C_3H_7C\equiv C$-CH=CHCl	$Ni(COD)_2$	147
3-Br-5,6-dihydropyran	$Ni(COD)_2$	147
3-Br-quinoline	$Ni(COD)_2$	147

For footnotes see p. 316.

Chapter 9 (p. 149) Nickel-Catalyzed Cyano-Dehalogenation



Halogenide	Catalyst	Solvent	Page
3-bromothiophene	Naphth-$NiCl(PPh_3)_2$	EtOH	171
2-bromothiophene	Naphth-$NiCl(PPh_3)_2$	EtOH	171[a]
2,5-dibromothiophene	Naphth-$NiCl(PPh_3)_2$	EtOH	172[a]
3,4-dibromothiophene	Naphth-$NiCl(PPh_3)_2$	EtOH	172[a]
2-bromofuran	Naphth-$NiCl(PPh_3)_2$	EtOH	172[a]
3-bromofuran	Naphth-$NiCl(PPh_3)_2$	EtOH	172[a]
3-bromopyridine	Naphth-$NiCl(PPh_3)_2$	EtOH	172
3-bromoquinoline	Naphth-$NiCl(PPh_3)_2$	EtOH	172
1-bromocyclohexene	Naphth-$NiCl(PPh_3)_2$	EtOH	172
1-chlorocyclohexene	Naphth-$NiCl(PPh_3)_2$	EtOH	172
1-bromocyclooctene	Naphth-$NiCl(PPh_3)_2$	EtOH	172
1-bromocyclooctene	$NiCl_2$dppf + Zn	DMF	176
1-chlorocyclohexene	$NiCl_2$dppf + Zn	DMF	176

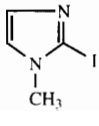
Chapter 9 (continued)

Halogenide	Catalyst	Solvent	Page
$C_5H_{11}CH{=}CHCl$	$NiCl_2dppf + Zn$	DMF	176
o-Br-C_6H_4-CH_3	Naphth-$NiCl(PPh_3)_2$	EtOH	173
p-Br-C_6H_4-CH_3	Naphth-$NiCl(PPh_3)_2$	EtOH	173
p-Br-C_6H_4-F	Naphth-$NiCl(PPh_3)_2$	EtOH	173
m-Br-C_6H_4-F	Naphth-$NiCl(PPh_3)_2$	EtOH	173
1-Br-naphthalene	Naphth-$NiCl(PPh_3)_2$	EtOH	173
2-Br-naphthalene	Naphth-$NiCl(PPh_3)_2$	EtOH	173
o-Br-C_6H_4-OCH_3	Naphth-$NiCl(PPh_3)_2$	EtOH	173
m-Br-C_6H_4-OCH_3	Naphth-$NiCl(PPh_3)_2$	EtOH	173
p-Br-C_6H_4-OCH_3	Naphth-$NiCl(PPh_3)_2$	EtOH	173
p-CH_3CO-C_6H_4-Br	Naphth-$NiCl(PPh_3)_2$	EtOH	173
p-Cl-C_6H_4-Br	Naphth-$NiCl(PPh_3)_2$	EtOH	173[b]
m-Cl-C_6H_4-Br	Naphth-$NiCl(PPh_3)_2$	EtOH	173[b]
p-F_3C-C_6H_4-Cl	$NiBr_2(PPh_3)_2$, Ph_3P, Zn	THF	175
p-CH_3CO-C_6H_4-Cl	$NiBr_2(PPh_3)_2$, Ph_3P, Zn	THF	175
p-CH_3CO-C_6H_4-Cl	$NiBr_2(PPh_3)_2$, Ph_3P, Zn	CH_3CN	176
p-CH_3CO-C_6H_4-Cl	$NiBr_2dppf + Zn$	THF	176
2-chlorothiophene	$NiCl_2dppf + Zn$	THF	176
1-chlorocycloheptene	$NiCl_2dppf + Zn$	THF	176

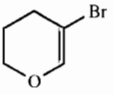
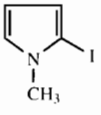
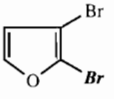
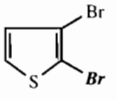
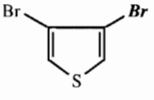
For footnotes see p. 316.

Chapter 10 (p. 179) Pd/Cu-Catalyzed Cross-Couplings with Acetylenes

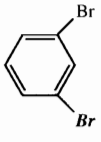
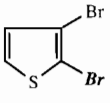
$$RC{\equiv}CH + HlgR' \xrightarrow{Pd^0 \text{ or } Pd^{II},\ CuHlg} RC{\equiv}CR'$$

R in RC≡CH	R'Hlg	Page
H	*p*-$CH_3C_6H_4$-I	207[d]
H	*p*-$CH_3COC_6H_4$-I	206[d]
H	2-Br-pyridine	207[d]
H	3-Br-pyridine	207[a,d]
H	2-I-thiophene	207[d]
H	2-Br-thiophene	207[a,d]
H	3-I-thiophene	208[d]
H		208[d]

Chapter 10 (continued)

R in RC≡CH	R'Hlg	Page
C_4H_9	$H_2C{=}CCl_2$	206[c]
C_5H_{11}	$H_2C{=}CHBr$	203
C_6H_{13}	ClCH=CHCl	205[c]
Me_3Si	$Me_2C{=}C{=}CHBr$	203
Me_3Si	$H_2C{=}C{=}CHBr$	203[a]
Me_3Si	1-Br-cyclooctene	216
Me_3Si		204, 211
Me_3Si	2-Br-furan	211
Me_3Si	2-Br-thiophene	210
Me_3Si	3-Br-thiophene	218
Me_3Si	3-Br-pyridine	211
Me_3Si		213
Me_3Si		223[c]
Me_3Si		223[c]
Me_3Si	 (100% excess)	209[c]
Me_3Si	*m*-diBr-benzene	214[b]
Me_3Si	*p*-$NO_2(C_6H_4)$Br	208
Me_3Si	*p*-$CH_3O(C_6H_4)$Br	216, 218
Me_3Si	*o*-$Cl(C_6H_4)$***Br***	217[c]
Me_3Si	*p*-$Cl(C_6H_4)$***Br***	217[c]
Me_3Si	*p*-$Me_2N(C_6H_4)$Br	218
Me_3Si	*p*-$CH_3CO(C_6H_4)$Br	211
Me_3Si	*o*-$F_3C(C_6H_4)$Br	215
Ph	3-I-thiophene	225
Ph	*p*-$CH_3O(C_6H_4)$I	225
$HOCH_2$	$H_2C{=}CHBr$	201
$HOCH_2$	$H_2C{=}C(CH_3)Br$	202

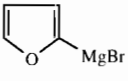
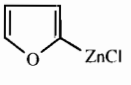
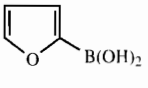
Chapter 10 (continued)

R in RC≡CH	R'Hlg	Page
$HOCH_2$	*p*-$NO_2(C_6H_4)Br$	202
$HOCH_2$	1-Br-cyclooctene	214
$HOCH_2$	2-Br-thiophene	212
$HOCH(CH_3)$	EtOCH=CHBr	204
$HOC(CH_3)_2$	EtOCH=CHBr	203
$HOC(CH_3)_2$	$H_2C=C(CH_3)Br$	204
$HOC(CH_3)_2$	$Me_2C=CHBr$	204
$HOC(CH_3)_2$	ClCH=CHCl	205[c]
$HOC(CH_3)_2$	2-Br-furan	221
$HOC(CH_3)_2$	3-Br-furan	216
$HOC(CH_3)_2$	2-Br-thiophene	219
$HOC(CH_3)_2$	2,5-DiBr-thiophene	213[b]
$HOC(CH_3)_2$	*p*-$CH_3O(C_6H_4)Br$	212
$HOC(CH_3)_2$	*o*-$CH_3O(C_6H_4)Br$	212
$HOC(CH_3)_2$	*p*-$Me_2N(C_6H_4)Br$	213
$HOC(CH_3)_2$	*p*-$F(C_6H_4)Br$	220
$HOC(CH_3)_2$	*p*-$Cl(C_6H_4)Br$	220
$HOC(CH_3)_2$		223[c]
$HOC(CH_3)_2$		222[c]
$HOC(CH_3)_2$	*p*-$Br(C_6H_4)I$	224[c]
Me_2NCH_2	*p*-$F(C_6H_4)Br$	215
$ROCH_2$ ($R = CH(CH_3)OEt$)	*p*-$F(C_6H_4)Br$	215
$CH_3C≡C$	2-I-thiophene	209

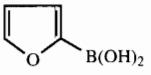
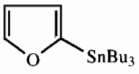
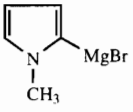
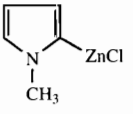
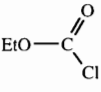
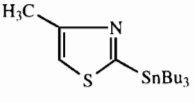
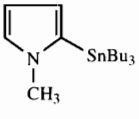
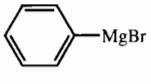
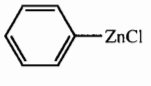
For footnotes see p. 316.

Chapter 11 (p. 227) Ni- and Pd-Catalyzed Cross-Couplings with Organometallic Reagents

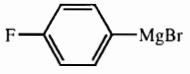
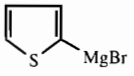
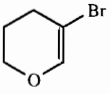
$$RM + R'L \xrightarrow{\text{Ni- or Pd catalyst}} R\text{–}R'$$

Organometallation Reagent	Substrate	Catalyst	Page
n-BuMgBr	*p*-F(C_6H_4)Br	Ni^{II}dppp	249[a]
n-BuMgBr	*p*-$CH_3O(C_6H_4)$Br	Ni^{II}dppp	249
n-BuMgBr	2-CH_3S-benzothiazole	Ni^{II}dppe	249
i-PrMgCl	2-CH_3S-benzothiazole	Ni^{II}dppe	249
c-C_6H_{11}MgCl	2-CH_3S-benzothiazole	Ni^{II}dppe	249
c-C_6H_{11}MgCl	3-Br-thiophene	Ni^{II}dppp	248
c-C_6H_{11}MgCl	2-Br-furan	Ni^{II}dppp	249
c-C_6H_{11}MgCl	2-Br-thiophene	Ni^{II}dppp	249
c-C_6H_{11}MgCl	PhBr	Ni^{II}dppp	249
c-C_6H_{11}MgCl	*p*-$CH_3O(C_6H_4)$Br	Ni^{II}dppp	249
c-C_6H_{11}MgCl	***Cl***CH=CCl_2	Ni^{II}dppp	249[c]
C_8H_{17}MgBr	3-Br-thiophene	Ni^{II}dppp	248
RMgX	2-Br-furan	Ni^{II}dppp	249
RMgX	PhBr	Ni^{II}dppp	249
$PhCH_2MgCl$	3-Br-thiophene	Ni^{II}dppp	249
EtC≡CZnCl	2-Br-thiophene	$Pd(PPh_3)_4$	269
EtC≡CZnCl	PhC(=O)Cl	$Pd(PPh_3)_4$	271
$C_5H_{11}C$≡CZnCl	H_2C=CHC(=O)Cl	$Pd(PPh_3)_4$	270
CH_3C≡CC≡CZnCl	2-I-thiophene	$Pd(PPh_3)_4$	269
	Preparation of	–	266
	H_2C=CHBr	Pd^{II}dppf	259
	ClCH=CCl(***Cl***)	Pd^{II}dppb	268
	3-Br-thiophene	Pd^{II}dppp	266[a]
	2,5-DiBr-thiophene	Pd^{II}dppb	266[a]
	2,5-DiBr-furan	Pd^{II}dppb	265[b]
	Preparation of	–	262, 266
	2,5-DiBr-thiophene	Pd^{II}dppb	266[b]
	2-Br-pyridine	Pd^{II}dppb	262
	3-Br-pyridine	Pd^{II}dppb	262
	m-F(C_6H_4)Br	Pd^{II}dppb	263
	m-$NO_2(C_6H_4)$Br	Pd^{II}dppb or Pd^{II}dppf	263[a]
	Preparation of	–	14
	2-Br-thiophene	Pd^{II}dppb or Pd^{II}dppf	273
	3-Br-pyridine	Pd^{II}dppb	273

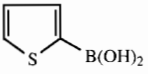
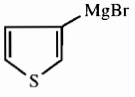
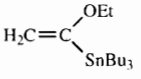
Chapter 11 (continued)

Organometallation Reagent	Substrate	Catalyst	Page
	*p*-F(C_6H_4)Br	Pd^{II}dppb	273
	Preparation of	–	15
	m-CH=O(C_6H_4)Br	$Pd(PPh_3)_4$	274
	Preparation of	–	265
	2-Br-furan	Pd^{II}dppb	264
	Preparation of	–	264
		Pd^{II}dppb	271
	2-Br-thiophene	Pd^{II}dppb	264[a]
	3-Br-thiophene	Pd^{II}dppb	264
	2-Br-pyridine	Pd^{II}dppb	264
	p-F(C_6H_4)Br	Pd^{II}dppb	265
	Preparation of	–	16
	2-Br-thiophene	$Pd(PPh_3)_4$	274
	3-Br-pyridine	$Pd(PPh_3)_4$	274
	Preparation of	–	15
	ClCH=CCl(***Cl***)	Pd^{II}dppb	268
	Br-cyclooctene	Ni^{II}dppp	252
	2-Br-thiophene	Ni^{II}dppp	252
	3-Br-thiophene	Ni^{II}dppp	251
	p-CH_3O(C_6H_4)Br	Ni^{II}dppp	253
	p-F(C_6H_4)Br	Ni^{II}dppp	255[a]
	p-F(C_6H_4)Br	Pd^{II}dppb	263
	o-F_3C(C_6H_4)Br	Ni^{II}dppp	255[a]
	2-CH_3S-benzothiazole	Ni^{II}dppp or Ni^{II}dppe	249
	Preparation of	–	262
	3-Br-pyridine	Pd^{II}dppb	262
	3-Br-pyridine	Pd^{II}dppf	262
	3-Br-pyridine	$Pd(PPh_3)_4$	262[a]

Chapter 11 (continued)

Organometallation Reagent	Substrate	Catalyst	Page
	H_2C=CHBr	Pd^{II}dppf	261
	ClCH=CCl(***Cl***)	Pd^{II}dppb	268[c]
	EtOCH=CHBr	Ni^{II}dppp	253
	1-Br-cyclooctene	Ni^{II}dppp	253
	PhBr	Ni^{II}dppp	255[a]
	o-F(C_6H_4)Br	Pd^{II}dppf	263
	p-F(C_6H_4)Br	Pd^{II}dppf	263
	2-Br-thiophene	Ni^{II}dppp	252
	Preparation of	–	257
	H_2C=CHCl	Ni^{II}dppp	257
	ClCH=CCl(***Cl***)	Pd^{II}dppb	268[c]
	1-Br-cyclooctene	Ni^{II}dppp	255[a]
	EtOCH=CHBr	Ni^{II}dppp	253
		Ni^{II}dppp	255[a]
		Ni^{II}dppp	258
	(product: *Z*-2-Th-CH=CH(CH_3)OH)		
	2-Br-furan	Ni^{II}dppp	251
	2-Br-pyridine	Ni^{II}dppp	253
	2-Br-pyridine	$Pd(PPh_3)_4$	253[a]
	3-Br-pyridine	Ni^{II}dppp	253
	2,5-DiBr-furan	Ni^{II}dppp	255[a]
	2-Br-thiophene	Ni^{II}dppp	251
	3-Br-thiophene	Ni^{II}dppp	252
	2,5-DiBr-thiophene	Ni^{II}dppp	254[b]
	3,4-DiBr-thiophene	Ni^{II}dppp	254[b]
	2,3-DiBr-thiophene	Ni^{II}dppp	254[b]
	2,5-DiBr-thiophene	Pd^{II}dppf	254[c]
	2,3-DiBr-thiophene	Pd^{II}dppp	254[c]
	o-F(C_6H_4)Br	Ni^{II}dppp	254
	p-F(C_6H_4)Br	Ni^{II}dppp	252
	o-F_3C(C_6H_4)Br	Ni^{II}dppp	254

Chapter 11 (continued)

Organometallation Reagent	Substrate	Catalyst	Page
	Preparation of	–	13
	3-Br-pyridine	$Pd(PPh_3)_4$	272
	m-$NO_2(C_6H_4)Br$	$Pd(PPh_3)_4$	272
	m-$CH{=}O(C_6H_4)Br$	$Pd(PPh_3)_4$	273
	Preparation of	–	256
	2-Br-furan	Ni^{II}dppp	256
	2-Br-pyridine	Ni^{II}dppp	257
	Preparation of	–	17
	2-Br-thiophene	$Pd(PPh_3)_4$	275

For footnotes see p. 316.

Complementary Subject Index

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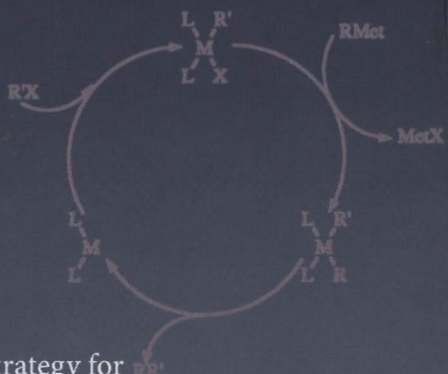

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