Direct Cobalt-Catalyzed Cross-Coupling between Aryl and Alkyl Halides

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Analytical thin-layer chromatography: TLC was performed using aluminium plates with silica gel and fluorescent indicator (Merck, 60F254). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by immersion in a staining solution of molybdatophosphoric acid in ethanol.

Column chromatography: Flash column chromatography with silica gel KMF 60 (0.040-0.063 mm). Pure cyclohexane or mixtures of cyclohexane and ethylacetate were used as solvents.

Gas chromatography with mass selective detector: Agilent 6890N Network GC-System, mass detector 5975 MS. Column: HP-5MS (30m x 0.25 mm x 0.25, 5% phenylmethylsiloxane, carrier gas: hydrogen. Standard heating procedure: 50°C (2 min), 25°C/min -> 300°C (5 min).

Chiral gas chromatography: BGB-176SE, 30x0.25mm, 0.25µm, FID detector

NMR: Proton and carbon nuclear magnetic resonance were recorded with a Bruker DPX300 (300 MHz).

IR spectroscopy: ATR technique (Thermo Nicolet 380 FT-IR). Intensity: s = strong, m = medium und w = weak.

High resolution mass spectrometry (HRMS): Mass spectra were recorded on a Finnigan MAT 900s (EI).

Cobalt(II)-chloride: Acros Organics, 97%, anhydrous, stored and weighed in a glovebox (MBraun 99.996% Stickstoff).

Solvents: THF was dried over sodium/benzophenone (reflux, freshly destilled).

Kumada-type vs. direct cross-coupling reactions

Initial experiments revealed the superiority of a direct cross-coupling protocol over conventional Kumada-type reactions with pre-formed Grignard compounds. Reactions a and b (Scheme below) exhibited incomplete conversion and a low tendency to cross-coupling. On the other hand, direct employment of both organohalides in the presence of stoichiometric
magnesium (reaction c) significantly boosted conversion and cross-coupling selectivity. The presence of large quantities of organomagnesium species is likely to hamper catalyst activity. Consistently, the cross-coupling selectivity of reactions a and b could be enhanced upon slow addition of the Grignard reagents over a period of 30-60 min. Most reported protocols of transition metal-catalyzed cross-coupling reactions with Grignard reagents require slow addition of the organometallic species in order to secure high selectivities. This entails additional operational complexity and is in opposition to a desirable energy-, time-, labour-, and cost-saving one-pot synthesis. On the other hand, slow formation of the pre-requisite organomagnesium intermediates has been observed under direct cross-coupling conditions in the presence of stoichiometric magnesium (reaction c). This results in quasi-stationary concentrations of the Grignard component which is rapidly consumed in the following cross-coupling step assuring that the concentration of reactive organomagnesium intermediates is kept to a minimum.

\[
\begin{align*}
\text{PhMgBr} + n\text{-BuBr} & \xrightarrow{11 \text{ mol\% L}} \text{Ph-Bu} + n\text{-BuBr} + \text{Ph-Ph} & (a) \\
\text{PhBr} + n\text{-BuMgBr} & \xrightarrow{11 \text{ mol\% L}} \text{Ph-Bu} + \text{Ph-Br} + \text{Ph-Ph} & (b) \\
\text{PhBr} + n\text{-BuBr} & \xrightarrow{11 \text{ mol\% L}} \text{Ph-Bu} + \text{Ph-Ph} & (c)
\end{align*}
\]

Procedure: A 10 mL flask was placed in a water bath (r.t.), charged with magnesium turnings (only in reaction c, 63 mg, 2.6 mmol), fitted with a rubber septum, and purged with argon. A solution of CoCl₂ (13 mg, 0.1 mmol, 5 mol%) and 35\textmu l Me₆-DACH in dry THF (4 mL) was added via syringe. The mixture was stirred at rt for 15 min. Then, the reaction was cooled to 0 °C, and aryl compound (Ar-Br or Ar-MgBr c=2 mmol/ml in THF, 2.0 mmol) and alkyl compound (alk-Br or alk-MgBr c=2 mmol/ml in THF, 2.0 mmol) were added. After 3 h at 0 °C, the reaction was quenched with saturated aqueous NH₄Cl (5 mL) and aqueous HCl (10%, 2 mL) and extracted with ethyl acetate (3 × 5 mL). Analyses of product and side products were performed by quantitative GC-FID.
A 10 mL flask was charged with magnesium turnings (31.5 mg, 1.3 mmol), fitted with a rubber septum, and purged with argon. A solution of CoCl$_2$ (6.5 mg, 0.05 mmol, 5 mol%), LiI (13.4 mg, 0.1 mmol) and TMEDA (0.2 mmol, 30 µl) in dry THF (6 mL) was added via syringe. The mixture was stirred at rt for 15 min. Then, the reaction was cooled to 0 °C, and arylbromide (1.2 mmol) and alkylbromide (1.0 mmol) were added. After 6 h at 0 °C, the reaction was quenched with saturated aqueous NH$_4$Cl (5 mL) and aqueous HCl (10 %, 2 mL) and extracted with ethyl acetate (3 × 5 mL). Analyses of product and side products were performed by GC-FID.

**Optimization experiments**

A 10 mL flask was charged with magnesium turnings (28 mg, 1.2 mmol), fitted with a rubber septum, and purged with argon. A solution of CoCl$_2$ (6.5 mg, 0.05 mmol, 5 mol%) and ammin additive (5 mol% or 10 mol%) in dry THF (4 mL) was added via syringe. The mixture was stirred at rt for 15 min. Then, the reaction was cooled/heated to the indicated temperature in a water or ethanol bath, and arylbromide (2.x mmol) and alkylbromide (2.y mmol) were added. After 6 h at the indicated temperature, the reaction was quenched with saturated aqueous NH$_4$Cl (5 mL) and aqueous HCl (10 %, 2 mL) and extracted with ethyl acetate (3 × 5 mL). Analyses of product and side products were performed by GC-FID.

**CoCl$_2$-effect on magnesiation of ArBr**

Unlike a recent iron-catalyzed protocol, only a slight acceleration of Grignard formation in the presence of catalytic CoCl$_2$ has been observed (see model reaction with 1-naphthylbromide). The induction period in the reaction with added CoCl$_2$ is shortened. The higher rate of magnesiation in the absence of catalyst after 40-50 min (see slope of curves) can be attributed to a temperature increase.
A 100 mL flask was placed in a water bath (r.t.), charged with magnesium turnings (243 mg, 10 mmol), fitted with a rubber septum, and purged with argon. A solution of CoCl$_2$ (65 mg, 0.5 mmol, 5 mol%) and 380µl Me$_4$DACH in dry THF (40 mL) was added via syringe. Pentadecane (10 mmol) was added as internal GC standard. The mixture was stirred at rt for 15 min. Then, the reaction was cooled to 0 °C, and tert.-butylbromide (10 mmol) and dodecylbromide (10 mmol) were added. Small samples (~50µl) were taken continuously, quenched with 0.5 ml saturated aqueous NH$_4$Cl, extracted twice with ethylacetate and analyzed by GC-FID.
A 10 mL flask was placed in a water bath (r.t.), charged with magnesium turnings (63 mg, 2.6 mmol), fitted with a rubber septum, and purged with argon. A solution of CoCl$_2$ (13 mg, 0.1 mmol, 5 mol%) and 35 µl Me$_4$DACH in dry THF (4 mL) was added via syringe. The mixture was stirred at rt for 15 min. Then, the reaction was cooled to 0 °C, and arylbromide (2.4 mmol) and alkylbromide (2.0 mmol) were added. After 6 h at 0 °C, the reaction was quenched with saturated aqueous NH$_4$Cl (5 mL) and aqueous HCl (10 %, 2 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried (Na$_2$SO$_4$), concentrated in vacuo, and subjected to flash chromatography (SiO$_2$/cyclohexane/ethyl acetate).
4-Decyl-2-fluorobiphenyl

yield: 59%

$^1$H-NMR (300 MHz, CDCl$_3$): 0.89 (3H, t), 1.28 (14H, m), 1.65 (2H, m), 2.64 (2H, t), 7.00 (2H, m), 7.28-7.60 (6H, m). $^{13}$C-NMR (75 MHz, CDCl$_3$): 14.15, 22.72, 29.30-29.65, 31.19, 31.94, 35.47 (d: 115.73, 116.02), 124.39, 127.37, 128.40, 128. 97, 130.37, 135.98, 144.64, (d: 158.03, 161.31). IR in [cm$^{-1}$]: 3032 (w), 2919 (s), 2852 (s), 1623 (m), 1580 (m), 1558 (m), 1515 (m), 1482 (s), 1464 (s), 1415 (s), 1266 (m), 1229 (m), 1172 (s), 1074 (m), 1009 (m), 948 (m), 912 (m), 867 (m), 824 (s), 763 (s).


2-Methyl-s-butylbenzene

yield: 52%

$^1$H-NMR (300 MHz, CDCl$_3$): 0.87 (3H, t, J=7.3 Hz), 1.22 (3H, d, J=9.9 Hz), 1.62 (3H, m), 2.34 (3H, s), 2.89 (1H, m), 7.04-7.23 (4H, m). $^{13}$C-NMR (75 MHz, CDCl$_3$): 12.30, 19.61, 21.18, 30.55, 36.17, 125.23, 125.36, 126.11, 130.12, 135.45, 145.87. IR in [cm$^{-1}$]: 2957 (s), 2921 (s), 2866 (m), 1486 (m), 1455 (s), 1374 (m), 755 (s), 726 (s). Retention time GC-MS: 5.08 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 148 $M^+$, 119, 115, 105, 91, 77, 65, 51. $R_f$ (Cyclohexane, SiO$_2$): 0.60


1-sec-Butyl-1-naphthale

yield: 64%
\[ ^1 \text{H-NMR (300 MHz, CDCl}_3 \text{):} \delta = 0.96 (3H, t), 1.41 (d, 3H), 1.75 (1H, m), 1.90 (1H, m), 3.55 (1H, m), 7.40-7.54 (4H, m), 7.78 (1H, d), 7.90 (1H, m), 8.15 (1H, d). \]

\[ ^13 \text{C-NMR (75 MHz, CDCl}_3 \text{):} \delta = 12.31, 21.25, 30.61, 35.33, 122.48, 123.29, 125.21, 125.62, 126.20, 127.92, 128.95, 131.83, 133.97, 143.75. \]

Retention time GC-MS: 7.64 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 184 M⁺, 165, 155, 141, 128, 115, 102, 77, 63, 51.

R\(_f\) (Cyclohexane, SiO\(_2\)): 0.50

1-Methoxy-2-(4-phenylbutan-2-yl)benzene

![Structure](image)

yield: 40%

\[ ^1 \text{H-NMR (300 MHz, CDCl}_3 \text{):} \delta = 1.20-7.06 (m, 7H, H-2,3,4,5,6,15,16), 6.88 (d, 1H, 7.5 Hz, H-14), 6.79 (d, 1H, 8.1 Hz, H-13), 4.74 (s, 3H, H-17), 3.17 (q, 1H, 7.2 Hz, H-9), 2.56-2.38 (m, 2H, H-7), 1.96-1.70 (m, 2H, H-8). 1.17 (d, 3H, 6.9 Hz, H-10). \]

\[ ^13 \text{C-NMR (75 MHz, CDCl}_3 \text{):} \delta = 157.1 (C-12), 135.5 (C-1), 125.5 (C-11), 128.4 (C-3), 128.1 (C-2), 126.8 (C-16), 126.6 (C-14), 125.5 (C-4), 120.6 (C-15), 110.5 (C-13), 55.3 (C-17), 38.9 (C-8), 34.0 (C-7), 31.8 (C-9), 21.0 (C-10). IR in [cm\(^{-1}\)]: 3061 (m), 3025 (m), 2953 (s), 2832 (m), 2358 (w), (1598 (s), 1580 (m), 1490 (s), 1455 (s), 1355 (w), 1287 (m), 1238 (s), 1179 (w), 1120 (m), 1088 (m), 1053 (m), 1029 (s), 911 (w), 796 (m), 750 (s), 697 (s). Retention time GC-MS: 8.90 min (Standard heating procedure). Chiral GC: 46.17 and 46.93 min: 50°C (2 min), 1°C/min -> 170°C. LRMS (EI, 70 eV, m/z): 240 M⁺, 135, 121, 105, 91, 77, 65, 51. R\(_f\) (Cyclohexane/Ethyl acetate: 9/1, SiO\(_2\)): 0.01

1-Cyclohexyl-4-methylbenzene

![Structure](image)

yield: 69%

\[ ^1 \text{H-NMR (300 MHz, CDCl}_3 \text{):} 1.28-1.91 (10H, m), 2.35 (3H, s), 2.50 (1H, m), 7.14 (4H, m). \]

\[ ^13 \text{C-NMR (75 MHz, CDCl}_3 \text{):} 21.01, 26.23, 27.00, 34.62, 44.20, 126.72, 129.00, 135.20, 145.18. \]


**1-Dodecyl-4-methylbenzene**

yield: 79%

$^1$H-NMR (300 MHz, CDCl$_3$): 1.00 (3H, t, J=6.9 Hz), 1.38-1.42 (18H, m), 1.73 (2H, m), 2.42 (3H, s), 2.67 (2H, t, J=7.9 Hz), 7.17 (4H, m). $^{13}$C-NMR (75 MHz, CDCl$_3$): 14.23, 21.07, 22.84, 29.51, 29.70, 29.77, 29.83, 31.80, 32.08, 35.67, 128.36, 128.99, 134.95, 139.94. Retention time GC-MS: 9.46 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 260 M$^+$, 147, 133, 118, 105, 91, 79, 77, 65, 55. HRMS (DI-EI): 260.250, calculated [M]$^+$ 260.2504. 


**1-Dodecyl-4-$	au$-butylbenzene**

yield: 53%

$^1$H-NMR (300 MHz, CDCl$_3$): 1.87 (3H, t, J=6.9 Hz), 1.20-1.29 (18H, m), 1.30 (9H, s), 1.59 (2H, m), 2.56 (2H, t, J=7.9 Hz), 7.10 (2H, d, J=8.2 Hz), 7.29 (2H, d, J=8.2 Hz). $^{13}$C-NMR (75 MHz, CDCl$_3$): 14.17, 22.75, 29.42-29.74, 31.47, 31.56, 31.98, 34.35, 34.49, 125.12, 128.05, 139.93, 148.30. IR in [cm$^{-1}$]: 2957 (m), 2927 (s), 2853 (m), 1516 (w), 1466 (m), 1363 (w), 831 (m). Retention time GC-MS: 11.91 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 302 M$^+$, 287, 207, 147, 132, 117, 105, 91, 57. R$_f$ (Cyclohexane, SiO$_2$): 0.59. EA (C$_{22}$H$_{38}$): C 86.8 H 12.6 (Calculated: C 87.3 H 12.7)

**1-Dodecynaphthalene**

yield: 68%

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 0.87$ (3H, t, J=6.8 Hz), 1.26-1.37 (18H, m), 1.72 (2H, m), 3.03 (2H, t, J=8.0 Hz), 7.26-7.68 (3H, m), 7.76 (1H, d), 7.81 (2H, m), 8.05 (1H, d). $^{13}$C-NMR (75 MHz, CDCl$_3$): 14.22, 22.80, 29.47, 29.77 (br), 29.96, 30.96, 32.03, 33.22, 123.97, 125.39, 125.60, 125.88, 126.44, 127.95, 128.80, 132.02, 133.97, 139.10. Retention time GC-MS:


**1-Cyclohexynaphthalene**

![Cyclohexynaphthalene](image)

yield: 85%

¹H-NMR (300 MHz, CDCl₃): 1.26-1.47 (1H, m), 1.47-1.70 (4H, m), 1.79-2.19 (5H, m), 3.36 (1H, m), 7.39-7.57 (4H, m), 7.76 (1H, d, J=8.2 Hz), 7.84 (1H, m), 8.05 (1H, d, J=8.2 Hz). ¹³C-NMR (75 MHz, CDCl₃): 26.62, 27.37, 34.29, 39.35, 122.33, 123.27, 125.27, 125.65, 125.73, 126.28, 129.00, 131.42, 133.99, 143.87. IR in [cm⁻¹]: 3047 (m), 2920 (s), 2828 (s), 1916 (w), 1595 (s), 1506 (s), 1447 (s), 1394 (s) 1265 (m), 987 (s), 768 (s), 728 (s). Retention time GC-MS: 9.26 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 210 M⁺, 204, 181, 167, 153, 141, 128, 115, 101, 89, 77, 67, 51. HRMS (DI-EI): 210.141, calculated [M⁺] 210.1409. Rf (Cyclohexane, SiO₂): 0.46.


**1-(2-Butyl)-4-methylbenzene**

![1-(2-Butyl)-4-methylbenzene](image)

yield: 75%

¹H-NMR (300 MHz, CDCl₃): 0.81 (3H, t, J=7.3 Hz), 1.21 (3H, d, J=7.0 Hz), 1.57 (2H, m), 2.31 (3H, s), 2.55 (1H, m), 7.08 (4H, m). ¹³C-NMR (75 MHz, CDCl₃): 12.37, 21.08, 22.05, 31.32, 41.38, 127.01, 129.03, 135.21, 144.74. Retention time GC-MS: 5.05 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 148 M⁺, 133, 119, 105, 91, 77, 65, 51. Rf (Cyclohexane, SiO₂): 0.63.
Analytical data in accordance with literature data: J. Bayardon, J. Holz, B. Schäffner, V. Andrushko, S. Verkin, A. Preets, A. Börner, Angew. Chem. 2007, 119, 6075.

1-Cyclohexyl-4-methoxybenzene

![Chemical structure](image)
yield: 65%

$^1$H-NMR (300 MHz, CDCl$_3$): 1.28-1.1.47 (5H, m), 1.74-1.88 (5H, m), 2.47 (1H, m), 3.82 (s, 3H), 6.85 (2H, d, J=8.3 Hz), 7.15 (2H, d, J=8.3 Hz). $^{13}$C-NMR (75 MHz, CDCl$_3$): 26.21, 27.16, 34.76, 43.72, 55.24, 113.67, 127.64, 140.39, 157.67. LRMS (EI, 70 eV, m/z): 190 M$^+$, 161, 147, 134, 121, 115, 108, 103, 91, 82, 77, 65, 51. IR in [cm$^{-1}$]: 3018 (w), 2920 (s), 2848 (s), 1447 (m), 1242 (s), 1034 (m), 806 (m). HRMS (DI-EI): 190.135, calculated [M]$^+$ 190.1358. R$_f$ (Cyclohexane, SiO$_2$): 0.35.


1-Cyclohexyl-2-methoxybenzene

![Chemical structure](image)
yield: 76%

$^1$H-NMR (300 MHz, CDCl$_3$): 1.29-1.86 (10H, m), 2.98 (1H, m), 3.83 (s, 3H), 7.15-7.29 (4H, m). $^{13}$C-NMR (75 MHz, CDCl$_3$): 26.47, 27.13, 33.24, 36.76, 55.38, 110.34, 120.56, 126.49, 136.26, 156.71. Retention time GC-MS: 7.56 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 190 M$^+$, 161, 147, 134, 121, 115, 108, 103, 91, 82, 77, 65, 51. IR in [cm$^{-1}$]: 3018 (w), 2924 (s), 2848 (s), 1490 (s), 1463 (s), 1237 (s), 1053 (m), 1031 (m), 749 (s). HRMS (DI-EI): 190.135, calculated [M]$^+$ 190.1358. R$_f$ (Cyclohexane, SiO$_2$): 0.35

**N,N-Dimethylamino-4-cyclohexylbenzene**

![](image)

yield: 68%

$^1$H-NMR (300 MHz, CDCl$_3$): 1.25-1.46 (5H, m), 1.72-1.85 (5H, m), 2.42 (1H, m), 2.92 (6H, s), 6.72 (2H, d, J=8.7 Hz), 7.10 (2H, d, J=8.7 Hz). $^1^3$C-NMR (75 MHz, CDCl$_3$): 26.25, 27.04, 34.73, 40.99, 43.51, 113.07, 127.31, 136.76, 148.94. Retention time GC-MS: 8.62 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 203 M$^+$, 188, 174, 160, 146, 134, 118, 103, 91, 77, 65, 51. IR in [cm$^{-1}$]: 3018 (w), 2918 (s), 2846 (s), 1612 (s), 1520 (s), 1446 (s), 1340 (s), 1162 (s), 947 (m), 811 (s). HRMS (DI-EI): 203.156, calculated [M]$^+$ 203.1674

R$_f$ (Cyclohexane, SiO$_2$): 0.08.


**1-Cyclohexyl-4-fluorobenzene**

![](image)

yield: 62%

$^1$H-NMR (300 MHz, CDCl$_3$): 1.07-1.96 (10H, m), 2.47 (1H, m), 6.96 (2H, m), 7.15 (2H, m).

$^1^3$C-NMR (75 MHz, CDCl$_3$): 26.11, 26.89, 34.67, 43.86, 114.78, 115.05, 126.66, 128.02, 128.12. IR in [cm$^{-1}$]: 2924 (m), 2851 (m), 1516 (s), 1449 (m), 1225 (m), 1158 (m), 827 (s).

Retention time GC-MS: 6.45 min (Standard heating procedure). LRMS (EI, 70 eV, m/z): 178 M$^+$, 149, 135, 122, 109, 96, 83, 77, 67, 51. R$_f$ (Cyclohexane, SiO$_2$): 0.45

**(2-Cyclohexylvinyl)benzene**

![](image)

yield: 39%

$^1$H-NMR (300 MHz, CDCl$_3$): 1.16-1.46 (5H, m) 1.67-1.90 (5H, m), 2.12 (1H, m), 6.10-6.23 (1H, m), 6.27-6.40 (1H, m), 7.16-7.37 (5H, m). $^1^3$C-NMR (75 MHz, CDCl$_3$): 26.15, 26.28,