Notes

Nickel-Mediated Cross-Coupling of Benzyl- and 2-Methyl-2-phenylpropylmagnesium Chloride with Aryl Bromides

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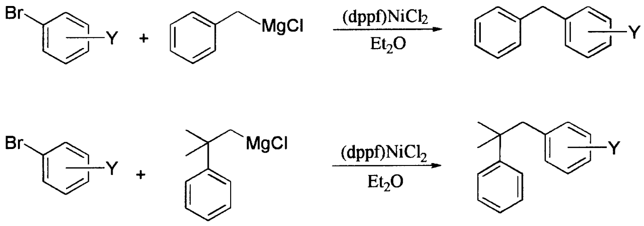
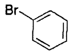
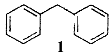
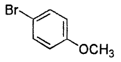
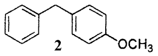
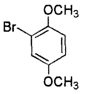
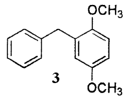
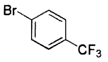
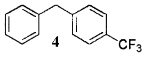
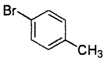
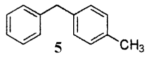
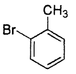
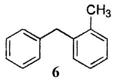
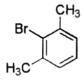
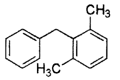
The nickel or palladium catalyzed cross-coupling reactions of organic halides or triflates with alkenes (the Heck reaction),[1] organoborons (the Suzuki reaction),[2] organotins (the Stille reaction)[3] and Grignard reagents[4,5] are powerful and widely used methods for carbon-carbon bond formation. However, it is generally known that cross-coupling reactions of alkyl organometallic compounds are difficult to conduct in good yields by comparison with aryl or vinyl organometallic compounds. A limited number of alkyl Grignard reagents, such as methyl-, several primary alkyl-, cyclopropyl-, and allylmagnesium halides, have been reported to react with aryl or vinyl halides to give the corresponding coupling products in moderate yields.[5,6] Primary alkyl Grignard reagents, regardless of the presence or the absence of β-hydrogens, were reported to couple with aryl halides most efficiently in the presence of $NiCl_2L_2$ as catalyst, with $NiCl_2(dppp)$[5,6] being most active. In contrast, secondary or tertiary alkyl Grignard reagents coupled with aryl halides in the presence of $NiCl_2(dmpe)$ or $NiCl_2(dppp)$ in low yield due to the isomerization of alkyl groups.[7]

Neopentyl compounds have been reported to display poor reactivity in most cases, and benzyl group was also less reactive than other nucleophiles in coupling reactions using transition metal.[5] We now wish to report that 2-methyl-2-phenylpropylmagnesium chloride and benzylmagnesium chloride react with various aryl bromides in the presence of catalytic $(dppf)NiCl_2$[8] to give the corresponding coupling products in good yields.



Y = H, methoxy, methyl and trifluoromethyl.

Table 1. Cross-Coupling of benzylmagnesium chloride with aryl bromides

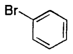
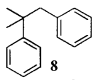
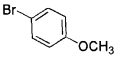
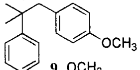
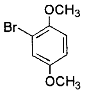
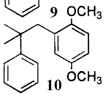
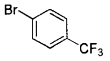
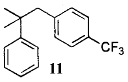
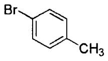
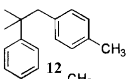
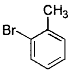
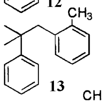
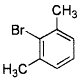
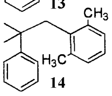
Entry	Halide	Product	Yield (%)	Reaction[b] time (hrs)
1		 1	97[a]	0.5
2		 2	84	4
3		 3	75	3
4		 4	80	2
5		 5	97[a]	5
6		 6	86[a]	35
7		 7	18[a]	30

[a] GC yield using an internal standard. [b] Time to consume 95% of starting material.

Benzylmagnesium chloride reacted with aryl bromides to give arylphenylmethanes (Table 1). Phenyl bromide coupled with benzylmagnesium chloride to give diphenylmethane (**1**) in 97% yield within 1 hour (Entry 1). Aryl bromides with electron-withdrawing substituents generally showed better reactivity toward benzyl nucleophile than those with electron-donating substituents did. 4-Trifluoromethylphenyl bromide reacted with benzylmagnesium chloride faster than 4-methylphenyl bromide did (Entry 4 and 5). 4-Methoxyphenyl bromide coupled with benzylmagnesium chloride slower than 4-trifluoromethylphenyl bromide, but faster than 4-methylphenyl bromide (Entry 2). 2,5-Dimethoxyphenyl bromide was even more reactive than 4-methoxyphenyl bromide (Entry 3), which showed that a methoxy group was an activating substituent[5] in these reactions. Steric hindrance had a dramatic effect in the reaction of 2-methylphenyl- and 2,6-dimethylphenyl bromide. While more than 95% of 4-methylphenyl bromide was consumed within 5 hours, 2-methylphenyl bromide required 35 hours to react in the same content and 2,6-dimethylphenyl bromide was too slow to be easily compared (Entry 5, 6 and 7).

Neopentylmagnesium chloride also reacted with various aryl bromides to give the corresponding coupling products (Table 2). The neopentyl nucleophile coupled with aryl bromides slower than benzyl nucleophile in most cases presumably due to the steric hindrance. Coupling of phenyl bromide with neopentylmagnesium chloride produced 2-methyl-1,2-

Table 2. Cross-Coupling of 2-methyl-2-phenylpropylmagnesium chloride with aryl bromides

Entry	Halide	Product	Yield (%)	Reaction[b] time (hrs)
1		 **8**	99[a]	2.5
2		 **9**	73	4.5
3		 **10**	70	6
4		 **11**	80	3
5		 **12**	95[a]	5
6		 **13**	59[a]	40
7		 **14**	0[a]	36

[a] GC yield using an internal standard. [b] Time to consume 95% of starting material.

diphenylpropane (**8**) almost quantitatively, although this reaction required much more time than the reaction of benzylmagnesium chloride (Entry 1). 4-Trifluoromethylphenyl- and 4-methoxyphenyl bromides reacted with neopentylmagnesium chloride faster than 4-methylphenyl bromide did, which was consistent with the case of benzylmagnesium chloride (Entry 2, 4 and 5). However, 2,5-dimethoxyphenyl bromide coupled with neopentylmagnesium chloride slower than 4-methoxyphenyl and 4-methylphenyl bromides (Entry 3). This suggested that steric hindrance was the dominating factor in the coupling of bulky neopentyl group. An *ortho*-methyl group decreased the rate and yield of the reaction considerably, and 2,6-dimethylphenyl bromide did not couple with neopentylmagnesium chloride under these conditions (Entry 6 and 7).

In summary, most of the aryl bromides coupled with neopentyl- and benzylmagnesium chloride in good yields in the presence of (dppf)NiCl$_2$. Benzylmagnesium chloride generally reacted faster than neopentylmagnesium chloride. The rate and yield of these reactions were strongly affected by the nature of substituents of aryl bromides.

Experimental Section

Reactions were monitored on a Donam DS6200 gas chromatograph equipped with 30 m × 0.25 mm cross-linked methyl silicone column. Phenyl ether was used as an internal standard to determine GC yields. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired on a Verian Gemini 2000 spectrometer using CDCl$_3$ or DMSO-d_6 as solvent and tetramethylsilane (δ 0.00) as an internal standard. IR spectra were recorded on a Nicolet Magna 750 spectrophotometer as KBr pellets. Low and high resolution GCMS were obtained on a Hewlett Packard HP 5890 (GC), HP 5970B (MSD), and JEOL JMS-AX505WA instruments respectively. The aryl bromides, benzyl magnesium chloride and 2-methyl-2-phenylpropylmagnesium chloride were obtained commercially. Et$_2$O was freshly distilled from sodium and benzophenone. (Dppf)NiCl$_2$ was prepared following literature procedures with slight modification.[9]

General procedure for coupling reaction. To a mixture of aryl halide (1.0 mmol) and (dppf)NiCl$_2$ (0.05 mmol) in Et$_2$O at rt was added alkyl Grignard reagent (3.0 mmol). The reaction mixture was stirred at reflux under nitrogen for 3-40 hours depending on the reactivity of substrates. The reaction mixture was allowed to cool to rt, diluted with Et$_2$O (20 mL) and sequentially washed with 1% aqueous HCl (30 mL × 5), water (50 mL × 2) and saturated brine (50 mL × 2). The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography and identified by GCMS, IR, ^{1}H NMR, and ^{13}C NMR data.

1-Benzyl-4-methoxybenzene (2). TLC R$_f$ 0.44 (20% Et$_2$O / hexane); Column chromatography (SiO$_2$, hexane); ^{1}H NMR (CDCl$_3$) δ 3.74 (s, 3H), 3.91 (s, 2H), 6.81 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 7.12-7.30 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 41.13, 55.36, 114.1 (2C), 126.2, 128.7(2C), 129.1(2C), 130.1 (2C), 133.5, 141.8, 158.3; IR (KBr) 1160 (strong), 1250 (strong), 1510 (strong), 2815 (medium), 2920 (medium), 3025 (medium) cm^{-1}; LRMS m/z (rel abundance) 198 (100%); HRMS calcd for C$_{14}$H$_{14}$O 198.1045, found 198.1047.

1-Benzyl-2,5-dimethoxybenzene (3). TLC R$_f$ 0.30 (20% Et$_2$O / hexane); Column chromatography (SiO$_2$, hexane); ^{1}H NMR (CDCl$_3$) δ 3.64 (s, 3H), 3.68 (s, 3H), 3.93 (s, 2H), 6.62-6.81 (m, 3H), 7.10-7.35 (m, 5H); ^{13}C NMR (CDCl$_3$) 35.6, 55.1, 55.5, 111.0, 114.3, 116.6, 125.6, 127.9 (2C), 128.7 (2C), 130.6, 140.5, 151.4, 153.3; IR (KBr) 1041 (medium), 1227 (strong), 1491 (strong), 2346 (weak), 2827 (weak) cm^{-1}; LRMS m/z (rel abundance) 228 (100%); HRMS calcd for C$_{15}$H$_{16}$O$_2$ 228.1151, found 228.1139.

1-Benzyl-4-trifluoromethylbenzene (4). TLC R$_f$ 0.59 (20% Et$_2$O / hexane); Column chromatography (SiO$_2$, hexane); ^{1}H NMR (CDCl$_3$) δ 3.97 (s, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.17-7.32 (m, 5H), 7.49 (d, J = 7.9 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 41.8, 122.8 (q, $^1J_{\text{C-F}}$ = 271 Hz), 125.6 (q, $^3J_{\text{C-F}}$ = 3.7 Hz, 2C), 126.7, 128.9 (2C), 129.0 (q, $^2J_{\text{C-F}}$ = 37.8 Hz), 129.2 (2C), 129.5 (2C), 140.3, 145.6; IR (KBr) 1018 (medium), 1122 (strong), 1314 (strong), 1438 (weak), 1513 (weak), 2951 (medium) cm^{-1}; LRMS m/z (rel abundance) 236 (88%); HRMS calcd for C$_{14}$H$_{11}$F$_3$ 236.0813, found 236.0818.

1-(2-Methyl-2-phenylpropyl)-4-methoxybenzene (9). TLC R$_f$ 0.44 (20% Et$_2$O / hexane); Column chromatography (SiO$_2$, hexane); ^{1}H NMR (CDCl$_3$) δ 1.29 (s, 6H), 2.79 (s, 2H), 3.70 (s, 3H), 6.60-6.80 (m, 4H), 7.10-7.40 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 27.6 (2C), 38.3, 49.8, 54.6, 112.5 (2C), 125.3, 125.9 (2C), 127.6(2C), 130.6, 130.9 (2C), 148.7, 157.6; IR (KBr) 1038 (weak), 1244 (strong), 1493 (medium), 1618 (weak), 2967 (medium) cm^{-1}; LRMS m/z (rel abundance) 224 (4%); HRMS calcd for C$_{17}$H$_{20}$O 240.1515, found 240.1516.

1-(2-Methyl-2-phenylpropyl)-2,5-dimethoxybenzene (10). TLC R_f 0.36 (20% Et_2O / hexane); Column chromatography (SiO_2, hexane); ^{1}H NMR (DMSO-d_6) δ 1.24 (s, 6H), 2.85 (s, 2H), 3.45 (s, 3H), 3.60 (s, 3H), 6.60-6.85 (m, 3H), 7.10-7.35 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 27.7 (2C), 38.8, 42.6, 54.8, 55.3, 111.9, 114.6, 117.2, 125.5, 126.0 (2C), 127.8 (2C), 130.6, 149.3, 152.0, 153.5; IR (KBr) 1040 (strong), 1226 (strong), 1508 (medium), 1661 (weak), 2962 (weak) cm^{-1}; LRMS m/z (rel abundance) 270 (40%); HRMS calcd for $C_{18}H_{22}O_2$ 270.1621, found 270.1623.

1-(2-Methyl-2-phenylpropyl)-4-trifluoromethylbenzene (11). TLC R_f 0.60 (20% Et_2O / hexane); Column chromatography (SiO_2, 5% EtOAc / hexane); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6H), 2.90 (s, 2H), 6.85 (d, J = 7.4 Hz, 2H), 7.23-7.32 (m, 5H), 7.36 (d, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3 (2C), 38.9, 51.1, 122.5 (q, $^1J_{C-F}$ = 267 Hz), 124.5 (q, $^3J_{C-F}$ = 3.7 Hz, 2C), 126.2, 126.4 (2C), 127.6 (q, $^2J_{C-F}$ = 55 Hz), 128.4 (2C), 130.8 (2C), 143.3, 148.4; IR (KBr) 1025 (medium), 1135 (strong), 1336 (strong), 1460 (weak), 1613 (weak), 2951 (medium) cm^{-1}; LRMS m/z (rel abundance) 278 (0.6%); HRMS calcd for $C_{17}H_{17}F_3$ 278.1283, found 278.1272.

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References

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