Low-Temperature Formation of Functionalized Grignard Reagents from Direct Oxidative Addition of Active Magnesium to Aryl Bromides

Jun-sik Lee, Raffet Velarde-Ortiz,[†] Albert Guijarro,[‡] Joshua R.Wurst,[§] and Reuben D. Rieke*

Department of Chemistry, University of Nebraska−Lincoln, Lincoln, Nebraska 68588-0304

rrieke@unlserve.unl.edu

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Introduction

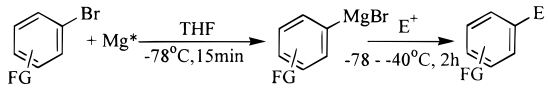
Despite being 100 years old, the Grignard reagent still plays a central role in synthetic chemistry today.[1] However, few functionalized Grignard reagents have been prepared due to the low functional group tolerance.[2] In 1998, several functionalized aromatic and vinylic Grignard reagents were prepared by iodine−magnesium exchange using an excess of diisopropylmagnesium as metalating agent at a low temperature (−40 °C). The yields were excellent to moderate after reaction with allyl bromide or benzaldehyde as electrophiles.[3] However, the thermodynamic nature of the equilibrium of exchange limits the range of substrates to arylic and vinylic halides. Moreover, the transmetalation failed to afford functionalized Grignard reagents from brominated substrates. Chromium salts can form functionalized organochromium compounds, but the chromium salts needed a catalyst for the oxidative addition step and the functionalized organochromium compounds reacted only with aldehydes so far.[4] We would like to report the use of activated magnesium (Rieke Magnesium) to prepare functionalized Grignard reagents from aryl bromides at low temperatures (−78 °C). The Grignard reagents were reacted with several electrophiles such as benzaldehyde, benzoyl chloride, or allyl iodide. The reaction of the Grignard reagents with acid chlorides yielded ketones. Because the reactions were carried out at low temperatures, we observed little or no addition to the ketones.[5] The use of the functionalized Grignard reagents represents a straightforward method to synthesize polyfunctionalized organic molecules.

Results and Discussion

In general, the low functional group tolerance of Grignard reagents precludes the use of most groups in the same molecule. However, if the oxidative addition reaction is carried out at low temperatures (−78 °C), the functionalized Grignard reagents are stable for a limited time. Functionalized Grignard reagents were successfully prepared by direct oxidative addition to aryl bromide substrates containing a nitrile, ester, or chloride group using highly active magnesium (Rieke magnesium) at low temperature (−78 °C). The oxidative addition was rapid even at this temperature and was completed in 15 min (Scheme 1). The reaction with the electrophiles (PhCHO, allyl iodide, and PhCOCl using 10% CuI) was carried out at low temperatures (−78, −40 °C) within ca. 1 h, and the yields were good to moderate (Table 1).

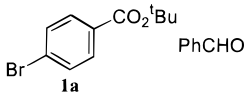
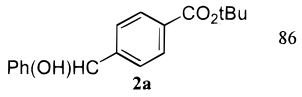
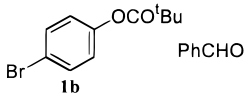
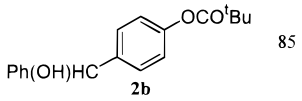
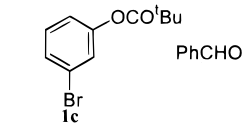
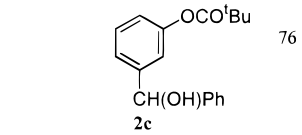
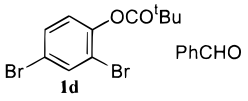
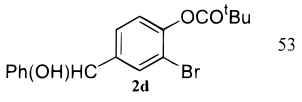
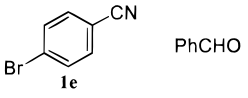
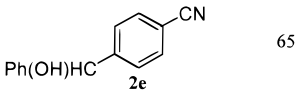
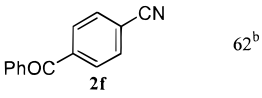
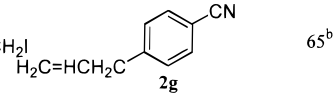
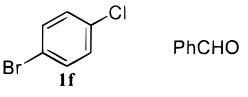
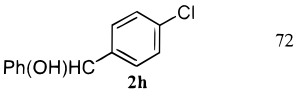
When ethyl or methyl arylcarboxylates were used, i.e., ethyl 3-bromobenzoate, the Grignard reagent did not

Scheme 1



FG = -CN, -CO_2R, -OCOR, -Cl
R = t-butyl

Table 1. Formation of Functionalized Grignard Reagents and Their Reactions with Electrophiles

Entry	Substrate	Electrophile	Product	Yield(%)[a]
1	 **1a**	PhCHO	 **2a**	86
2	 **1b**	PhCHO	 **2b**	85
3	 **1c**	PhCHO	 **2c**	76
4	 **1d**	PhCHO	 **2d**	53
5	 **1e**	PhCHO	 **2e**	65
6	**1e**	PhCOCl	 **2f**	62[b]
7	**1e**	CH_2=$CHCH_2$I	 **2g**	65[b]
8	 **1f**	PhCHO	 **2h**	72

[a] Isolated yields. [b] CuI (10 mol %, based on the substrate) was used.

[†]Present address: Department of Chemical Engineering, University of Nebraska−Lincoln, Lincoln, NE 68588.

[‡] Present address: Departamento de Quimica Organica, Universidad de Alicante, Ap. 99 E-03080, Alicante, Spain.

[§] Present address: Department of Chemistry, University of Minnesota−Morris, Morris, MN 56267.

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form at −78 °C. A possible explanation might be the coordination of the ester group to the magnesium surface, blocking the active sites of the metal and thus preventing the oxidative addition step. Raising the temperature to −50 °C permits the formation of the organomagnesium reagent. However, at the higher temperatures, more byproducts were formed, which limited the scope of the reaction. Other bidentate substrates containing groups of increased polarity, such as amides, failed to react with active magnesium at low temperature. A highly temperature-dependent equilibrium of adsorption−desorption of the functionalized group on the metal surface and active sites seems to be responsible for the capricious reactivity displayed by the halogenated substrates.

tert-Butyl arylcarboxylates proved to be good candidates for the preparation of functionalized Grignard reagents. The bulky ester group most likely prevented the coordination of the ester to the magnesium surface. The reactivity of the three isomers of the Grignard reagents also displayed important differences. Only the para-isomer gave moderate yields in the reaction with benzaldehyde. Entry 4 demonstrates that the highly reactive magnesium displays unusual selectivity in moderate yield.

The coupling reactions with the benzoyl chloride and allyl iodide required the addition of 10% CuI as catalyst to yield the corresponding ketone and allyl derivatives. In the absence of copper iodide catalyst, the above two electrophiles gave only low yields of the expected products. 1,2-Dibromoethane was used to remove the excess of magnesium when benzoyl chloride or allyl iodide was used as electrophiles (entries 6 and 7) and it did not react with the Grignard reagents under the given reaction conditions.

Finally, bromochlorobenzene is also an adequate substrate for this low-temperature chemistry (entry 8). We tested several additives, such as Me_2AlCl, LiBr, or TMSCl, on an attemp to enhance the reactivity of the resulting Grignard reagent. However, the presence of these additional Lewis acids failed to increase the yields.

When ethyl alkylcarboxylates were used, i.e., ethyl 6-bromobenzoate, some Grignard reagent was formed at −78 °C along with two major nonidentified byproducts, and some of the starting material still remained. From these data, we can conclude that simple alkyl esters are not suitable candidates for functionalized Grignard reagent preparation. Even when the functionalized Grignard reagents were made, they reacted with the ester group either in an intra- or intermolecular way. *tert*-Butyl 11-bromoundecanoate reacted with active magnesium to afford excellent yields of the corresponding Grignard reagent at −78 °C within 15 min, but the yield of reaction with the benzaldehyde was poor (∼30%).

In summary, several functionalized Grignard reagents containing an ester, nitrile, or chloride have been prepared at low temperature and their reactivities were studied. The reported procedures involving the use of highly reactive magnesium expands the well-known methodologies of Grignard reagent preparation.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz. Internal standards used in ^{1}H NMR spectra were TMS (δ 0.00) and $CDCl_3$ (δ 7.27) and in ^{13}C NMR was the center peak of $CDCl_3$ (δ 77.7). Infrared spectra were obtained using an FTIR spectrometer as neat films unless otherwise stated. GC/MS were performed by the Nebraska Center for Mass Spectrometry at the University of Nebraska—Lincoln.

All manipulations were carried out under an argon atmosphere on a dual manifold vacuum/argon system. The prepurified-grade argon was further purified by passage over a BASF R3-11 catalyst column at 150 °C, a phosphorus pentoxide column, and a column of granular potassium hydroxide. Tetrahydrofuran was distilled immediately before use from Na/K alloy under an atmosphere of argon.

Analytical thin-layer chromatography was performed on a silica gel plate (60 F_{254}). The product spots were visualized with either UV light (254 nm) or by staining a solution of phosphomolybdic acid in ethanol. Flash chromatography was performed using silica gel (230−400 mesh). Rieke magnesium (Mg*) was purchased from Rieke Metals, Inc. All other reagents were purchased from commercial suppliers and used without further purification.

Typical Procedure for the Preparation of the Corresponding Grignard Reagents. To an oven-dried 50 mL centrifuge tube, equipped with a Teflon-coated magnetic stirring bar and septum, was added, under an atmosphere of prepurified argon, Mg* (3.0 mmol) in dry THF (5 mL) via syringe. This mixture was cooled to −78 °C, and the organic substrate (1 mmol) was added dropwise with stirring via syringe. After 15 min the electrophile (1.1 mmol) was added in the same fashion at −78 °C. The temperature was increased to −40 °C for the reaction of the nitrile substrate with the benzoyl chloride and allyl iodide.

Reaction progress was monitored by gas chromatography of hydrolyzed reaction aliquots. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layers were extracted with diethyl ether three times. The organic layers were then combined, dried with $MgSO_4$, and filtered. The solvent was removed under vacuum. The crude product obtained was purified by flash chromatography.

Preparation of 1,1-Dimethylethyl 4-bromobenzoate (1a).[6] Potassium *tert*-butoxide (3.4 g, 30 mmol) in ethyl ether (30 mL) was added dropwise into a 100 mL flask containing ethyl ether (50 mL) and 4-bromobenzoyl chloride (4.5 g, 32 mmol) in an ice water bath. Almost immediately a white precipitate formed, indicating the formation of KCl salt. After 1 h of reaction, the mixture was washed with saturated $NaHCO_3$ and saturated NaCl. The organic layer was dried with $MgSO_4$ and filteredd. Removal of the solvent afforded a colorless oil (8.1 g, 95%) of **1a**: R_f = 0.72 (silica, 20% EtOAc in hexanes); IR (cm^{-1}, $CDCl_3$) 1727 (C=O), 1159 (C−O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (S, 9H), 7.54 (app d, J = 8.6 Hz, 2H), 7.85 (app d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.74, 81.84, 128.00, 131.50, 131.60, 132.03, 165.38; HREI (M)$^+$ calcd for $C_{11}H_{13}79BrO_2$ 256.0099, found $C_{11}H_{13}79BrO_2$ 256.0100.

Preparation of 4-Bromophenyl 2,2-Dimethylpropanoate (1b). Trimethylacetyl chloride (6.3 g, 52 mmol) in ethyl ether (30 mL) was added dropwise into a 100 mL flask containing ethyl ether (50 mL), triethylamine (15.2 g, 150 mmol), and 4-bromophenol (8.7 g, 50 mmol) in an ice water bath. Almost immediately a white precipitate formed, indicating the formation of triethylamine chloride salt. After 1 h of reaction, the mixture was washed with dilute HCl and saturated $NaHCO_3$. The organic layer was dried with $MgSO_4$ and filtered. Removal of the solvent afforded a white solid (8.1 g, 95%) of **1b**: mp 59−60 °C (Et_2O); R_f = 0.72 (silica, 10% EtOAc in hexanes); IR (cm^{-1}, $CDCl_3$) 1761 (C=O), 1125 (C−O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 6.96 (app d, J = 9.0, 2H), 7.49 (app d, J = 9.0, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.04, 39.06, 118.58, 123.30, 132.34, 150.12, 176.71; HREI (M)$^+$ calcd for $C_{11}H_{13}{}^{79}BrO_2$ 256.0099, found $C_{11}H_{13}{}^{79}BrO_2$ 256.0100.

Preparation of 3-Bromophenyl 2,2-Dimethylpropanoate (1c). Trimethylacetyl chloride (3.9 g, 32 mmol) in ethyl ether (30 mL) was added dropwise into a 100 mL flask containing ethyl ether (50 mL), triethylamine (12.1 g, 120 mmol), and 3-bromophenol (5.2 g, 30 mmol) in an ice water bath. Almost immediately a white precipitate formed, indicating the formation of triethylamine chloride salt. After 1 h of reaction, the mixture was washed with dilute HCl and saturated $NaHCO_3$. The

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organic layer was dried with $MgSO_4$ and filtered. Removal of the solvent afforded a colorless oil (8.3 g, 97%) of **1c**: $R_f = 0.72$ (silica, 10% EtOAc in hexanes); IR (cm^{-1}, $CDCl_3$) 1757 (C═O), 1159(C−O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 7.08−7.14 (m, 2H), 7.30−7.36 (m, 1H), 7.59−7.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.12, 39.17, 116.11, 123.63, 127.01, 128.30, 133.24, 148.35, 175.90; HREI $(M)^+$ calcd for $C_{11}H_{13}{}^{79}BrO_2$ 256.0099, found $C_{11}H_{13}{}^{79}BrO_2$ 256.0100.

Preparation of 2,4-Dibromophenyl 2,2-Dimethylpropanoate (1d). Trimethylacetyl chloride (3.9 g, 32 mmol) in ethyl ether (30 mL) was added dropwise into a 100 mL flask containing ethyl ether (50 mL), triethylamine (12.1 g, 120 mmol), and 2,4-dibromophenol (8.0 g, 30 mmol) in an ice water bath. Almost immediately a white precipitate formed, indicating the formation of triethylamine chloride salt. After 1 h of reaction, the mixture was washed with dilutr HCl and saturated $NaHCO_3$. The organic layer was dried with $MgSO_4$ and filtered. Removal of the solvent afforded a colorless oil (9.6 g, 95%) of **1d:** $R_f = 0.65$ (silica, 10% EtOAc in hexanes); IR (cm^{-1}, neat) 1755 (C═O), 1159(C−O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 6.98 (d, $J = 8.7$ Hz, 1*H*), 7.44 (dd, $J = 8.7$, 2.3 Hz, 1H), 7.75 (d, $J = 2.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.11, 39.26, 117.16, 119.13, 124.88, 131.40, 135.60, 147.68, 175.71; HREI $(M)^+$ calcd for $C_{11}H_{12}{}^{79}Br_2O_2$ 333.9204, found $C_{18}H_{20}{}^{79}Br_2O_2$ 333.9204.

1,1-Dimethylethyl 4-((hydroxyphenyl)methyl)benzoate (2a): mp 84−85 °C (EtOAc); $R_f = 0.51$ (silica, 20% EtOAc in hexanes); IR (cm^{-1}, $CDCl_3$) 3493 (OH), 1711 (C═O), 1162 (C−O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 9H), 3.06 (br s, 1H), 5.89 (s, 1H), 7.27−7.36 (m, 5H), 7.45 (app d, $J = 8.3$ Hz, 2H), 7.96 (app d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.86, 76.50, 81.74, 126.87, 127.33, 128.47, 129.28, 130.27, 131.67, 144.13, 149.06, 166.43; HREI $(M)^+$ calcd for $C_{18}H_{20}O_3$ 284.1412, found 284.1415.

4-((Hydroxyphenyl)methyl)phenyl 2,2-dimethylpropanoate (2b): $R_f = 0.48$ (silica, 20% EtOAc in hexanes); IR (cm^{-1}, $CDCl_3$) 3493 (OH), 1756 (C═O), 1140 (C−O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.89 (br s, 1H), 5.75 (s, 1H), 7.03 (app d, $J = 8.7$ Hz, 2H), 7.36 (app d, $J = 8.7$ Hz, 2H), 7.27−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.83, 39.76, 76.26, 122.09, 127.30, 128.28, 128.32, 129.18, 141.95, 144.36, 150.98, 177.90; HREI $(M)^+$ calcd for $C_{18}H_{20}O_3$ 284.1412, found 284.1409.

2,2-Dimethyl-3-((hydroxyphenyl)methyl)phenylpropionate (2c): $R_f = 0.46$ (silica, 20% EtOAc in hexanes); IR (cm^{-1}, $CDCl_3$) 3490 (OH), 1750 (C═O), 1145 (C−O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.69 (br s, 1H), 5.78 (s, 1H), 6.96−7.36 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.05, 38.98, 75.59, 119.44, 120.44, 123.75, 126.63, 127.62, 128.46, 129.26, 143.31, 145.49, 151.10, 177.10; HREI $(M)^+$ calcd for $C_{18}H_{20}O_3$ 284.1412, found 284.1414.

2,2-Dimethyl-2-bromo-4-((hydroxyphenyl)methyl)phenylpropionate (2d): $R_f = 0.42$ (silica, 20% EtOAc in hexanes); IR (cm^{-1}, neat) 3499 (OH), 1755 (C═O), 1140 (C−O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 3.08 (br s, 1H), 5.66 (s, 1H), 6.99 (d, $J = 8.3$ Hz, 1H), 7.21−7.34 (m, 6H), 7.58 (d, $J = 1.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.82, 39.92, 75.71, 116.75, 124.10, 127.23, 127.26, 128.58, 129.30, 131.91, 143.59, 143.70, 148.11, 176.97; HREI $(M)^+$ calcd for $C_{18}H_{19}79BrO_3$ 362.0518, found $C_{18}H_{19}79BrO_3$ 362.0519.

4-(Hydroxyphenyl)methyl-benzonitrile (2e):[7] ^1H NMR (300 MHz, $CDCl_3$) δ 3.13 (br s, 1H), 5.80 (s, 1H), 7.27−7.38 (m, 5H), 7.47 (app d, $J = 8.1$ Hz, 2H), 7.56 (app d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.16, 111.56, 119.56, 127.38, 127.71, 128.89, 129.52, 132.92, 143.52, 149.76.

4-Benzoyl-benzonitrile (2f):[8] ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (app t, $J = 7.5$, 2H), 7.65 (app t, $J = 7.5$, 1H), 7.79 (app d, $J = 7.5$, 2H), 7.80 (app d, $J = 8.7$, 2H), 7.88 (app d, $J = 8.7$, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.32, 118.64, 129.27, 130.69, 130.87, 132.81, 133.95, 136.93, 141.84, 195.65.

4-(2-Propenyl)-benzonitrile (2g):[9] ^1H NMR (300 MHz, $CDCl_3$) δ 3.44 (d, $J = 6.6$ Hz, 2H), 5.10 (dd, $J = 16.7$, 1.5 Hz, 1H), 5.13 (dd, $J = 10.2$, 1.5 Hz, 1H), 5.92(ddt, $J = 16.7$, 10.2, 6.6 Hz, 1H) 7.29 (app d, $J = 8.4$ Hz, 2H), 7.57 (app d, $J = 8.1$, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.67, 110.53, 117.77, 119.56, 129.95, 132.75, 136.19, 146.22.

4-Chloro-α-phenylbenzenemethanol (2h):[10] ^1H NMR (300 MHz, $CDCl_3$) δ 3.05(br s, 1H), 5.60(s, 1H), 7.16−7.30 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.17, 127.28, 128.53, 128.63, 129.28, 129.33, 133.90, 142.92, 144.10.

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