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Copper-Mediated Cross-Coupling of Functionalized Arylmagnesium Reagents with Functionalized Alkyl and Benzylic Halides

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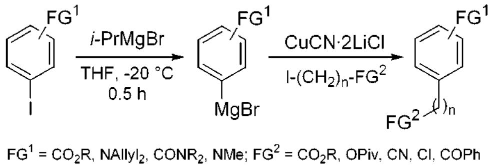
ABSTRACT



Functionalized arylmagnesium halides, prepared via an iodine–magnesium exchange, undergo a smooth cross-coupling reaction with functionalized primary alkyl iodides and benzylic bromides in the presence of CuCN·2LiCl, either in stoichiometric (with trimethyl phosphite as an additive) or catalytic quantities.

Transition metal catalyzed cross-coupling reactions are an important method for forming new carbon−carbon bonds.[1] Recently, we have reported a general preparation of highly functionalized arylmagnesium halides using an iodine−magnesium exchange reaction.[2] Herein, we wish to report a procedure allowing a Cu(I)-mediated cross-coupling of functionalized arylmagnesium bromides of type **1** with various functionalized alkyl iodides of type **2**.[3] Although several Cu(I)-catalyzed cross-coupling reactions between unfunctionalized arylmagnesium reagents and alkyl halides are known,[4] in most cases the reaction proceeds only at temperatures higher than 0 °C, implying that organomagnesium species bearing sensitive functional groups, such as a cyano group or an ester function, cannot be used. However, we have discovered that functionalized arylmagnesium compounds **1**, which are obtained from the corresponding aryl iodides **3** by reaction with *i*-PrMgBr[5] in THF[6] (−20 °C, 0.5−1 h), undergo a smooth transmetalation with CuCN·2LiCl[7] at −20 °C, leading to the corresponding arylcopper reagents. Furthermore, by performing this transmetalation in the presence of trimethyl phosphite, the resulting aryl-

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[1] (a) Diederich, F., Stang, P. J., Eds. *Metal-catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (b) Tamao, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.2, p 435.

[2] (a) Rottländer, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 767. (b) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618. (c) Delacroix, T.; Bérillon, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 8108. (d) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 477. (e) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481. (f) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339.

[3] For Cu(I)-catalyzed cross-coupling between functionalized zinc reagents and alkyl iodides, see: Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 4781.

[4] (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) Novak, J.; Salemink, C. A. *Synthesis* **1983**, 597. (c) Onuma, K.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2582. (d) Normant, J. F.; Villieras, J.; Scott, F. *Tetrahedron Lett.* **1977**, *18*, 3263. (e) Friedman, L.; Shani, A. *J. Am. Chem. Soc.* **1974**, *96*, 7101. (f) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82. (g) Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, *17*, 3225. (h) Leder, J.; Fujioka, H.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 1463.

[5] The commercially available isopropylmagnesium chloride (either as a solution in THF or diethyl ether) is equally suitable for the halogen−magnesium exchange.

[6] Addition of DMPU or NMP as a cosolvent offers no significant improvement in the rate or yield of the exchange or cross-coupling. When diethyl ether is used as solvent, addition to any reactive functional group (e.g., ester) is observed instead of I−Mg exchange.

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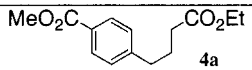
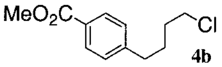
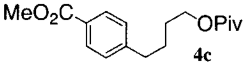
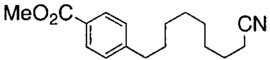
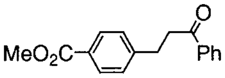
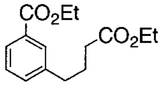
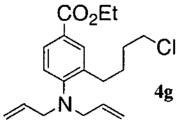
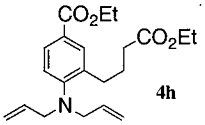
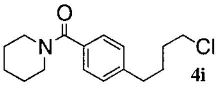
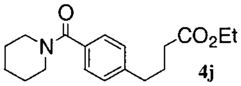
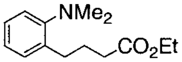
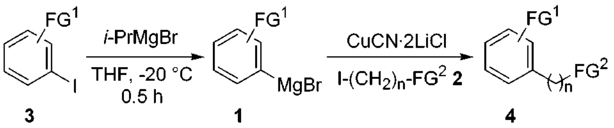
Table 1. Copper(I)-Mediated Cross-Coupling between Functionalized Arylmagnesium Derivatives **1** and Functionalized Alkyl Iodides **2**, Leading to Polyfunctional Arylated Products of Type **4**

entry	FG^1-ArMgBr FG^1	FG^2-$(CH_2)_n$-I (n, FG^2)	method[a]	product of type 4	yield(%)[b]
1	1a (*p*-CO_2Me)	2a (3, CO_2Et)	A	 4a	75
2	1a (*p*-CO_2Me)	2a (3, CO_2Et)	B	4a	60
3	1a (*p*-CO_2Me)	2b (4, Cl)	A	 4b	81
4	1a (*p*-CO_2Me)	2b (4, Cl)	B	4b	63
5	1a (*p*-CO_2Me)	2c (4, OPiv)	A	 4c	89
6	1a (*p*-CO_2Me)	2c (4, OPiv)	B	4c	57
7	1a (*p*-CO_2Me)	2d (8, CN)	A	 4d	81
8	1a (*p*-CO_2Me)	2d (8, CN)	B	4d	55
9	1b (*p*-CO_2Et)	2e (2, COPh)	A	 4e	56
10	1c (*m*-CO_2Et)	2a (3, CO_2Et)	A	 4f	71
11	1d (*o*-$N(C_3H_7)_2$ *m*-CO_2Et)	2b (4, Cl)	A	 4g	69
12	1d (*o*-$N(C_3H_7)_2$ *m*-CO_2Et)	2a (3, CO_2Et)	A	 4h	65
13	1e (*p*-$CON(CH_2)_5$)	2b (4, Cl)	A	 4i	69
14	1e (*p*-$CON(CH_2)_5$)	2a (3, CO_2Et)	A	 4j	63
15	1f (*o*-NMe_2)	2a (3, CO_2Et)	A	 4k	73

[a] Method A: CuCN·2LiCl (1 equiv), $P(OMe)_3$ (1.9 equiv), 20 °C, 2−8 h. Method B: CuCN·2LiCl (0.2 equiv), −5 °C, 20−24 h. [b] Isolated yield of analytically pure product.

copper species are stable at 20 °C; in the absence of this additive, extensive formation of homocoupling products (biphenyls) is observed. Thus, under these developed conditions, various primary alkyl iodides[8] undergo the expected cross-couplings within a few hours at room temperature (method A; Scheme 1, Table 1). It was observed that the presence of electron-withdrawing substituents, such as an ester or amide group, on the aryl moiety considerably reduces their reactivity toward most electrophiles compared with the corresponding unfunctionalized arylmagnesium species. Nonetheless, various arylmagnesium compounds bearing an ester function have been used successfully (Table 1, entries 1−12). The alkyl iodide can also bear functionality such as an ester (Table 1, entries 1, 2, 5, 6, 10, 12, 14, and 15), a nitrile (Table 1, entries 7 and 8), a chloride (Table 1, entries 4, 6,

Scheme 1



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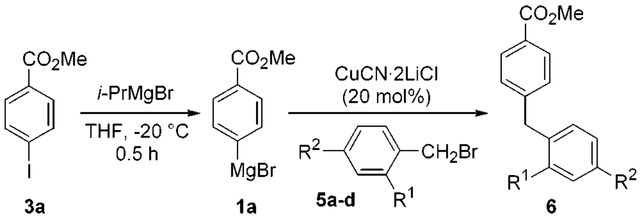
(7) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(8) Alkyl tosylates do not undergo the reaction.

Scheme 2



6a: $R^1 = R^2 = H$; 72%; **6b**: $R^1 = CF_3$, $R^2 = H$; 71%
6c: $R^1 = H$, $R^2 = Br$; 61%; **6d**: $R^1 = R^2 = F$; 67%

12, and 14) or even a keto group (Table 1, entry 9). In all cases, the desired cross-coupling products are obtained in good to excellent yields (56−89%). Nitrogen functionalities, such as an amide or a tertiary amine, are also well tolerated, both in the organomagnesium reagent and in the alkyl iodide (Table 1, entries 11−15).

We have also found that this cross-coupling can be mediated by substoichiometric quantities of Cu(I).[9] In particular, using 20 mol % of CuCN•2LiCl, good yields (55−63%) of cross-coupled products are obtained after reaction at −5 °C for 24 h (Table 1, entries 2, 4, 6, and 8). Additionally, the use of this low-temperature substoichiometric protocol results in greatly decreased quantities of homocoupling products, thus obviating the need for the trimethyl phosphite additive. $Cu(OAc)_2$ has also been used for the cross-coupling of unfunctionalized aryl Grignard reagents with unfunctionalized alkyl iodides,[10] and this led us to evaluate this copper source. However, $Cu(OAc)_2$ and Cu(OAc) were both inferior to CuCN•2LiCl.[11] The catalytic CuCN-mediated cross-coupling procedure can also be applied to functionalized benzylic bromides such as **5a**−**d**, affording the desired benzhydryl derivatives **6a**−**d** in 61−72% yields (Scheme 2).[12]

In summary, we have developed a method allowing the Cu(I)-catalyzed cross-coupling of functionalized arylmagnesium compounds with alkyl iodides. Extensions of these methods are currently underway in our laboratory.

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Supporting Information Available: All analytical data for compounds of Table 1 and Schemes 1 and 2 and procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] In the absence of any Cu species, the reaction proceeds in very low yield. For example, the cross-coupling between **1a** and **2a** gave product **4a** in only 6% yield after 72 h at −5 °C.

[10] Masada, H.; Yasunishi, Y.; Kikuchi, N. *Nippon Kagaku Kaishi* **1995**, *10*, 844.

[11] In the cross-coupling of magnesium reagent **1a** and alkyl iodide **2a** using $Cu(OAc)_2$ (20 mol %), the expected product **4a** was formed in only 20% yield (compared with 60% with CuCN•2LiCl). When Cu(OAc) (20 mol %) was employed as the catalyst, arylmagnesium species **1a** and iodide **2c** were coupled to give **4c** in 46% yield (compared with 57% using CuCN•2LiCl).

[12] **Typical procedure: preparation of methyl 4-(4-chlorobutyl)-benzoate (4b):** A dry 10 mL Schlenk flask was charged with methyl 4-iodobenzoate (650 mg, 2.481 mmol, 1 equiv) and the flask evacuated then filled with argon and this process repeated a further two times. Dry THF (2.5 mL) was added, and the solution was cooled to −25 °C in a dry ice/2-propanol bath; then isopropylmagnesium bromide (1.6 mL, 1.6 M in THF, 2.560 mmol, 1.03 equiv) was added slowly over 5 min, keeping the temperature below −20 °C. On completion of the addition, the reaction mixture was stirred at −20 °C for 30 min. A solution of CuCN•2LiCl (0.5 mL, 1 M in THF, 0.500 mmol, 0.2 equiv) was then added, followed by 1-chloro-4-iodobutane (440 mg, 2.014 mmol, 0.8 equiv), and the flask placed in a cryostatically controlled cooling bath at −5 °C. Stirring was continued for 24 h; then the reaction was quenched by the addition of a 9:1 solution of saturated NH_4Cl(aq) and 25% NH_3(aq) (3 mL) and poured into water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed with water (20 mL) and dried over Na_2SO_4. The solvents were removed in vacuo, and the residue was purified by flash chromatography (1:1 pentane/CH_2Cl_2) to give 288 mg of a colorless oil (63% yield).