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Iron-Catalyzed Oxidative Homo-Coupling of Aryl Grignard Reagents

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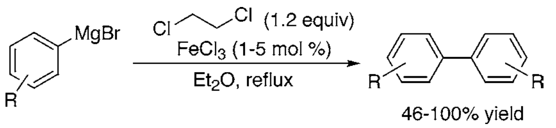
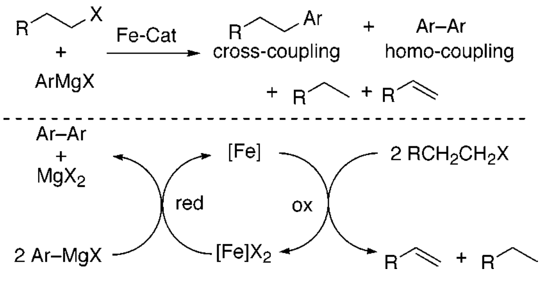
ABSTRACT



Iron-catalyzed homo-coupling of aryl Grignard reagents was successfully developed. A variety of aryl Grignard reagents were efficiently converted into the corresponding symmetrical biaryls in the presence of 1–5 mol % FeCl$_3$ and a stoichiometric amount of 1,2-dichloroethane.

Oxidative homo-coupling of aryl-metal reagents is one of the most efficient synthetic methods for the construction of a symmetrical biaryl backbone.[1] A wide variety of transition metal halides such as TiCl$_4$,[2] TlCl,[3] VO(OEt)Cl$_2$,[4] FeCl$_3$,[5] CoCl$_2$,[6] and CuCl$_2$[7] have been used as oxidants in stoichiometric amounts, and catalytic use of the metals in combination with reoxidants such as molecular oxygen and dibromoalkanes has been also examined.[8−10] Recent research interests in oxidative homo-coupling have been limited to palladium- or copper-catalyzed reactions of organoboron,[8] silicon,[9] and tin[10] reagents. In the course of our studies on the iron-catalyzed cross-coupling reaction between aryl Grignard reagents and alkyl halides possessing β-hydrogens, we found that homo-coupling of arylmagnesium reagents took place as a main side reaction, where iron is a catalyst and alkyl halides act as stoichiometric reoxidants (Scheme 1).[11] Homo-coupling as a side reaction has also been observed in the literature dealing with iron-catalyzed cross-coupling reactions.[12] However, there have been no reports on the selective homo-coupling of organometallics by iron catalysis. Herein we report an efficient and practical reaction system for the iron-catalyzed oxidative homo-coupling of Grignard reagents.

Scheme 1. Homo-Coupling of Grignard Reagents as a Side Reaction in Iron-Catalyzed Cross-Coupling



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(1) (a) *Advanced Organic Chemistry*, 4th ed.; March, J., Eds.; John Wiley & Sons: New York, 1992; pp 725−726. (b) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 219. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2000**, *56*, 9601.

(3) (a) McKillop, A.; Elsom, L. F.; Taylor, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 2423. (b) Elsom, L. F.; McKillop, A.; Taylor, E. C. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 488.

(4) (a) Ishikawa, T.; Ogawa, A.; Hirao, T. *Organometallics* **1998**, *17*, 5713. (b) Hirao, T. *Coord. Chem. Rev.* **2003**, *237*, 271.

(5) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(6) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316.

(7) Sakellarios, E.; Kyrimis, T. *Ber. Dtsch. Chem. Ges.* **1924**, *57B*, 322.

(8) (a) Rao, V. V. R.; Kumar, C. V.; Devaprabhakara, D. *J. Organomet. Chem.* **1979**, *179*, C7. (b) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33. (c) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346. (d) Smith, K. A.; Campi, E. M.; Jackson, W. R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131. (e) Koza, D. J.; Carita, E. *Synthesis* **2002**, 2183. (f) Kabalka, G. W.; Wang, L. *Tetrahedron Lett.* **2002**, *43*, 3067. (g) Klingensmith, L. M.; Leadbeater, N. E. *Tetrahedron Lett.* **2003**, *44*, 765. (h) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541. (i) Punna, S.; Díaz, D. D.; Finn, M. G. *Synlett* **2004**, 2351. See also ref 9b.

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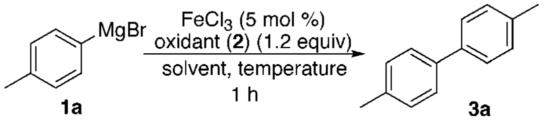
Several reaction conditions were examined for the iron-catalyzed oxidative homo-coupling of 4-methylphenylmagnesium bromide (**1a**) (Table 1). It was found that inexpensive 1,2-dichloroethane (**2a**) is an excellent oxidant for the homo-coupling, giving 4,4′-dimethylbiphenyl (**3a**) in high yields. Thus, in the presence of 5 mol % $FeCl_3$ and 1.2 equiv of **2a**, the homo-coupling of the Grignard reagent **1a** was complete in 1 h, in refluxing diethyl ether (entry 1), in THF at room temperature (entry 2), or in benzene at 40 °C (entry 3), to afford a quantitative yield of the biaryl **3a**. Use of 1,2-dibromoethane (**2b**) also gave homo-coupling product **3a** without formation of cross-coupling products, although the yield of **3a** was slightly lower (entry 5). The present oxidative homo-coupling with 1,2-dichloroethane (**2a**) can be readily scaled up to the reaction of 15.0 mmol of the Grignard reagent **1a** using 1 mol % of the $FeCl_3$ catalyst, which gave 99% yield (1.35 g) of biaryl **3a** without any byproducts (entry 6).

Table 1. Iron-Catalyzed Homo-Coupling of 4-Methylphenylmagnesium Bromide (**1a**)[a]



1a **3a**

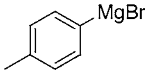
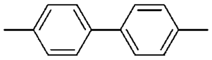
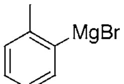
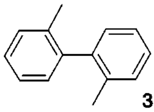
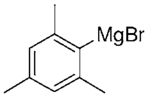
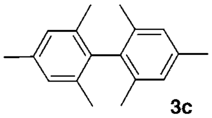
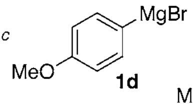
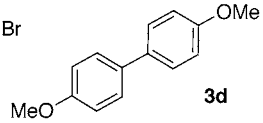
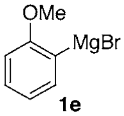
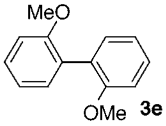
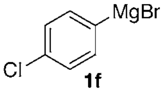
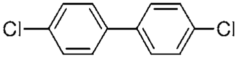
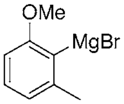
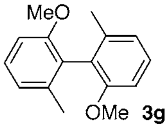
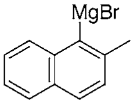
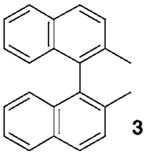
entry	solvent	temp (°C)	oxidant	yield (%)
1	Et_2O	reflux	$ClCH_2CH_2Cl$ (**2a**)	100
2	THF	rt	**2a**	96
3	benzene	40	**2a**	99
4	THF	0	**2a**	83
5	THF	0	$BrCH_2CH_2Br$ (**2b**)	75
6[b]	Et_2O	reflux	**2a**	99

[a] Reactions were carried out with 0.52 mmol of **1a**. [b] With 15.0 mmol of **1a** in the presence of 1 mol % $FeCl_3$ for 9 h. Biaryl **3a** was isolated by vacuum sublimation.

Table 2 summarizes the results obtained for the oxidative homo-coupling of other aryl Grignard reagents. Introduction of methyl groups at the ortho-positions of the aryl Grignard reagents resulted in somewhat lower yields of the homo-coupling products (entries 1−3). 4-Methoxy- and 2-methoxyphenylmagnesium bromide can be efficiently converted into the corresponding biaryls **3d** and **3e**, respectively, under similar conditions (entries 4 and 5). It is noteworthy that the present reaction system is tolerant of aryl chloride functionality (entry 6). Although sterically demanding substrates **1g** and **1h** required higher reaction temperature and/or longer reaction time, they gave the corresponding biaryls **3g** and **3h** in moderate to good yields (entries 7 and 8).

Table 2. Iron-Catalyzed Oxidative Homo-Coupling of Grignard Reagents[a]

$$\text{ArMgBr}\ \mathbf{1} \xrightarrow[\text{FeCl}_3\ (5\ \text{mol}\ \%)]{\text{ClCH}_2\text{CH}_2\text{Cl}\ (\mathbf{2a})} \text{Ar–Ar}\ \mathbf{3}$$

entry	aryl Grignard **1**	product **3**	time/h	yield/%[b]
1	 **1a**	 **3a**	1	100
2	 **1b**	 **3b**	12	81
3	 **1c**	 **3c**	12	58
4[c]	 **1d**	 **3d**	1	92
5	 **1e**	 **3e**	1	88
6	 **1f**	 **3f**	1	73
7[d]	 **1g**	 **3g**	6	46
8	 **1h**	 **3h**	12	84

[a] Unless otherwise noted, the reactions were carried out using aryl Grignard reagents (0.52 mmol), 1,2-dichloroethane (0.62 mmol), and $FeCl_3$ (0.026 mmol) in refluxing Et_2O (3 mL). [b] Isolated yield after column chromatography. [c] In THF at room temperature. [d] In benzene at 60 °C.

A proposed mechanism for the present iron-catalyzed homo-coupling is shown in Scheme 2. Oxidative addition of 1,2-dichloroethane to a low-valent iron complex **A**,[13] generated by the reaction of $FeCl_3$ with Grignard reagent, forms an alkyl iron intermediate **B**. β-Halogen elimination giving ethylene[14] and dihaloiron species **C**,[15] followed by

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(9) (a) Kang, S.-K.; Kim, T.-H.; Pyun, S.-J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 797. (b) Yamaguchi, S.; Ohno, S.; Tamao, K. *Synlett* **1997**, 1199.

(10) (a) Kanemoto, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Chem. Lett.* **1987**, 5. (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434. (c) Shirakawa, E.; Nakao, Y.; Murota, Y.; Hiyama, T. *J. Organomet. Chem.* **2003**, *670*, 132. See also ref 9b.

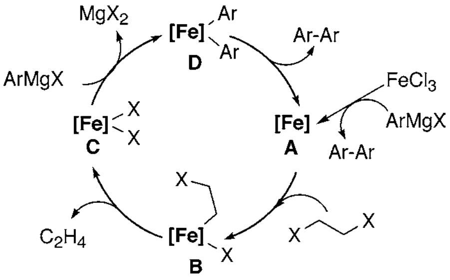
(11) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.

(12) (a) Tamura, M.; Kochi, J. K. *J. Organomet. Chem.* **1971**, *31*, 289. (b) Felkin, H.; Meunier, B. *J. Organomet. Chem.* **1978**, *146*, 169. (c) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (d) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3638.

(13) In the iron-catalyzed Grignard cross-coupling, Fe(I), Fe(II), and Fe(−II) species are proposed as catalytically active species: see ref 12c and references therein.

(14) Generation of ethylene was confirmed by trapping the evolved gas with bromine, which gave 1,2-dibromoethane. See also ref 15.

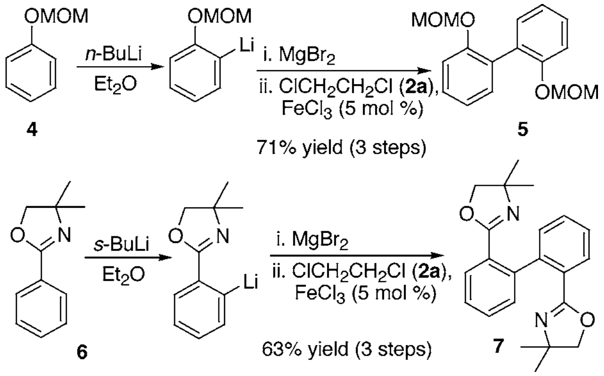
Scheme 2. Mechanism for Iron-Catalyzed Homo-Coupling



transmetalation of the aryl group from magnesium to iron, affords a diaryliron intermediate **D**. Reductive elimination of the homo-coupling product regenerates catalytically active species **A**.

Combination of the heteroatom-directed ortho-metalation technique[16] and the present homo-coupling provides a new one-pot route to 2,2′-disubstituted biaryls (Scheme 3). For example, methoxymethyl-protected phenol **4** was treated with *n*-BuLi to generate the ortho-lithiated phenol derivative.[17] Metal exchange with anhydrous magnesium bromide followed by subjection to the present homo-coupling reaction gave the corresponding biaryl **5** in 71% isolated yield. Transformation of the aryllithium to the corresponding arylmagnesium reagent is essential for the homo-coupling. Reaction of the aryllithium reagent under the same conditions resulted in only 13% yield of the biaryl.[18] The ortho-metalation and homo-coupling sequence was also successful for phenyloxazoline **6**, which gave the corresponding biaryl **7** in 63% yield.

Scheme 3. Homo-Coupling Reaction Utilizing Directed Ortho-Metalation



In summary, we have developed a new and practical reaction system for oxidative homo-coupling of Grignard reagents using $FeCl_3$ as a catalyst precursor and 1,2-dichloroethane as a reoxidant. This reaction system is applicable to the homo-coupling of various aryl Grignard reagents and is readily amenable to a large-scale synthesis of biaryl compounds.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For *β*-Cl elimination on the *β*-chloroalkyliron species, see: Boone, H. W.; Athey, P. S.; Mullins, M. J.; Philipp, D.; Muller, R.; Goddard, W. A. *J. Am. Chem. Soc.* **2002**, *124*, 8790.

(16) For a recent review on directed ortho-metalation, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(17) Rice, J. E.; Cai, Z,-W. *J. Org. Chem.* **1993**, *58*, 1415.

(18) Low yield was also observed in the homo-coupling of phenyllithium giving biphenyl (38% yield, ether reflux for 1 h).