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Iron-Catalyzed Grignard Cross-Coupling with Alkyl Halides Possessing *β*-Hydrogens

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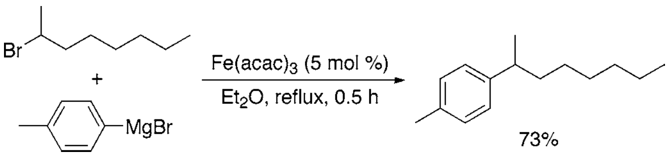
ABSTRACT



Tris(acetylacetonato)iron(III) (Fe(acac)$_3$) was found to be an efficient catalyst for the cross-coupling reaction between aryl Grignard reagents and alkyl halides possessing *β*-hydrogens. The reaction is applicable to secondary alkyl halides as well as primary ones.

Transition-metal-catalyzed Grignard cross-coupling with organic halides is one of the most powerful tools for constructing a new carbon−carbon bond.[1] During the past three decades, a wide variety of transition-metal catalysts, based mostly on nickel or palladium metal, have been demonstrated to be effective for this useful transformation. Surprisingly, much less attention has been paid to less expensive iron catalysts for Grignard cross-coupling. Since Kochi's pioneering work,[2] several reports appeared on iron-catalyzed cross-coupling,[3,4] but they are mostly concerned with the C(sp^2)−X compounds as coupling partners,[5] except one specific example where 2-bromocyclobutanone ethylene glycol ketal is the coupling partner.[6] Considering the recent growing interest in cross-coupling with alkyl halides,[7−9] it is important to develop an iron-based catalyst system for this

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[1] For a review: *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.

[2] (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Tamura, M.; Kochi. J. K. *Synthesis* **1971**, 303. (c) Tamura, M.; Kochi, J. K. *J. Organomet. Chem.* **1971**, *31*, 289. (d) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (e) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502. (f) Kwan, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 4903. (g) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351.

[3] (a) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199. (b) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53. (c) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901. (d) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449. (e) Fürstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009. (f) Fakhakh, M. A.; Franck, X.; Hocquemiller, R.; Figadère, B. *J. Organomet. Chem.* **2001**, *624*, 131. (g) Felkin, H.; Meunier, B. *J. Organomet. Chem.* **1978**, *146*, 169. (h) Walborsky, H. M.; Banks, R. B. *J. Org. Chem.* **1981**, *46*, 5074.

[4] (a) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 3547. (d) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (e) Fürstner, A.; Méndez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355. (f) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5358.

[5] Kochi reported that the reaction between alkyl Grignard reagents and alkyl halides in THF gave mainly disproportionation products alkanes and alkenes; thus, no further study for synthetic use was carried out. See ref 2a,c.

[6] Brinker, U. H.; König, L. *Chem. Ber.* **1983**, *116*, 882.

[7] Difficulty of using alkyl halide for cross-coupling has been reviewed, see: (a) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3018. (b) Luh, T.-Y.; Leung, M.-k.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187. (c) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384.

[8] (a) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945. (c) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. (d) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056. (e) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (f) Menzel, K.; Fu, G. C.; *J. Am. Chem. Soc.* **2003**, *125*, 3718. (g) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616. (h) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (i) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726. (j) Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079. (k) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (l) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82.

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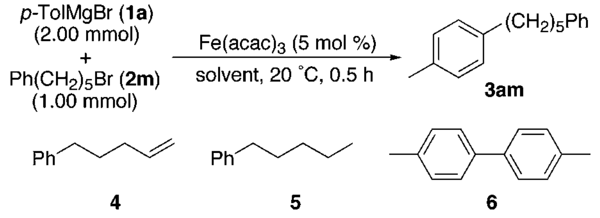
cross-coupling reaction. Here, we wish to report a new iron-catalyzed cross-coupling which provides a general method of forming a carbon−carbon bond between aryl Grignard reagents and alkyl halides.

As a first set of experiments, several reaction conditions were examined for the iron-catalyzed reaction of 5-phenyl-1-bromopentane (**2m**) with *p*-tolylmagnesium bromide (**1a**) (2.0 equiv) (Table 1). The conditions reported to be best for the cross-coupling of alkyl Grignard reagents with aryl[4a,b] and alkenyl halides[3a] did not fit in well with the present reaction of the alkyl halide. Thus, the reaction in the presence of 5 mol % of Fe(acac)$_3$ in THF/NMP (NMP = *N*-methylpyrrolidone) at 20 °C for 0.5 h gave only 25% yield of the cross-coupling product, 5-phenyl-1-*p*-tolylpentane (**3am**) (entry 1). The alkyl bromide **2m** was converted mainly into 5-phenyl-1-pentene (**4**) (25%) and 1-phenylpentane (**5**) (24%). The formation of a considerable amount of 4,4′-bitolyl (**6**) was also observed. The reaction in THF gave similar results (entry 2). Use of diethyl ether as a solvent in place of THF greatly improved the yield of the cross-coupling product **3am** (entries 3 and 4). The yield of **3am** was increased to 60% and the formation of side products **4** and **5** was suppressed to some extent. In refluxing ether, the yield of **3am** was 69%.

Table 1. Distribution of Products in the Reaction of **1a** with **2m**

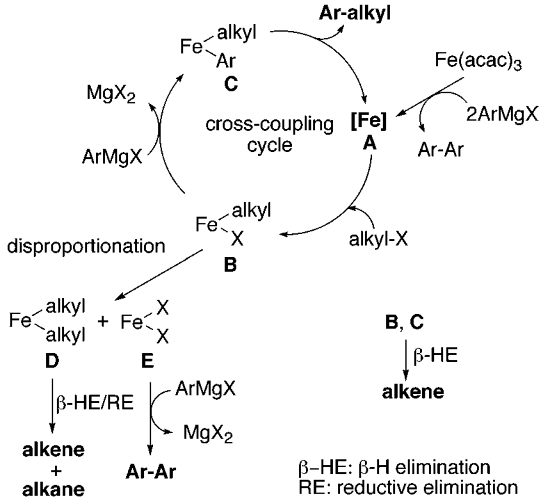


entry	solvent	product (mmol)				
		2m	**3am**	**4**[a]	**5**	**6**[b]
1	THF/NMP	0.15	0.25	0.25	0.24	0.26
2	THF	0	0.27	0.37	0.20	0.25
3	Et$_2$O	0	0.60	0.19	0.12	0.12
4[c]	Et$_2$O	0	0.69	0.18	0.09	0.08

[a] A mixture of olefinic isomers in which **4** is the major component. [b] The amount (0.05 mmol) of **6** formed at the reduction of Fe(acac)$_3$ is subtracted from the total amount of **6** after the catalytic reaction (see ref 11). [c] The reaction was carried out in refluxing Et$_2$O.

Based on the mechanism generally accepted for the cross-coupling reactions catalyzed by transition metals including iron, a catalytic cycle for the present cross-coupling is illustrated in Scheme 1. Thus, the oxidative addition of alkyl halide to a low-valent iron intermediate **A**,[10] which is generated by the reaction of Fe(acac)$_3$ with the Grignard reagent, gives alkyliron species **B**. Transmetalation of an aryl group from magnesium to iron forming diorganoiron **C** followed by reductive elimination of the cross-coupling product regenerates **A**. The formation of alkene **4**, alkane **5**, and 4,4′-bitolyl (**6**) as the side products gives us significant information on the mechanism of the present cross-coupling. Considering that 5% yield (one equivalent to Fe(acac)$_3$) of **6** is formed at the reduction of catalyst precursor Fe(acac)$_3$,[11] the molar ratio of **5** to **6** formed in the catalytic cycle is always about 1:1 regardless of the reaction conditions (see Table 1). The amount of **4** is more than that of **5** or **6**. These results can be rationalized by the disproportionation of the alkyliron halide intermediate **B** giving dialkyliron **D** and dihalide **E**, which will produce the same amount of alkene **4**, alkane **5**, and the biaryl **6**. The alkene **4** is also provided by *β*-hydrogen elimination on the intermediates **B** and **C**, resulting in the formation of more **4** than **5** or **6**.

Scheme 1. Plausible Mechanism for the Aryl−Alkyl Coupling



The present iron-catalyzed cross-coupling was applicable to octyl chloride, iodide, and tosylate under the same conditions as described above (in refluxing ether for 0.5 h), although the yields are lower than that for octyl bromide (**2n**) (entries 1−4 in Table 2). The cross-coupling of aryl Grignard reagents substituted with methoxy (**1b**) and fluoro (**1c**) with **2n** proceeded as well without troubles (entries 5 and 6). Introduction of methyl groups onto the ortho positions of the phenyl Grignard reagents resulted in somewhat lower yield of the cross-coupling products **3dn** and **3en** (entries 7 and 8). It is noteworthy that secondary alkyl bromides are good coupling partners as well as the primary alkyl bromides in this iron-catalyzed reaction. Acyclic and cyclic secondary alkyl bromides **2p** and **2q** gave the corresponding cross-coupling products in around 70% yield on reaction with the Grignard reagent **1a** (entries 10 and 11). Although the yield

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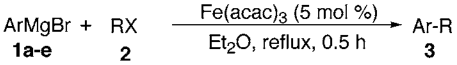
(9) (a) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (b) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646. (c) Terao, J.; Naitho, Y.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2003**, *32*, 890.

(10) In the iron-catalyzed Grignard cross-coupling, Fe(I), Fe(II), and Fe(−II) species are proposed as catalytically active species: See ref 4b and references therein.

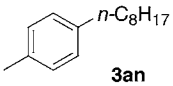
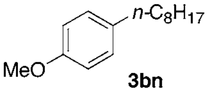
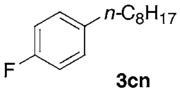
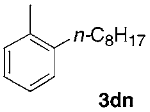
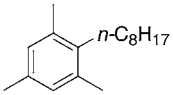
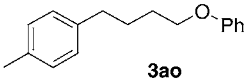
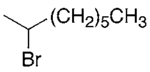
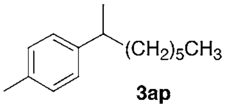
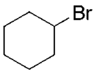
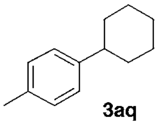
(11) On addition of an excess amount of *p*-tolylmagnesium bromide (**1a**) to Fe(acac)$_3$ in the absence of alkyl bromides in ether, the formation of 4,4′-bitolyl (**6**) in an amount equivalent to Fe(acac)$_3$ was observed.

Table 2. Iron-Catalyzed Coupling of Arylmagnesium Bromide (**1**) with Alkyl Halide (**2**)[a]



$$\underset{\textbf{1a-e}}{\text{ArMgBr}} + \underset{\textbf{2}}{\text{RX}} \xrightarrow[\text{Et}_2\text{O, reflux, 0.5 h}]{\text{Fe(acac)}_3\text{ (5 mol \%)}} \underset{\textbf{3}}{\text{Ar-R}}$$

Ar = 4-MeC_6H_4 (**1a**), 4-$MeOC_6H_4$ (**1b**), 4-FC_6H_4 (**1c**), 2-MeC_6H_4 (**1d**), 2,4,6-$Me_3C_6H_2$ (**1e**)

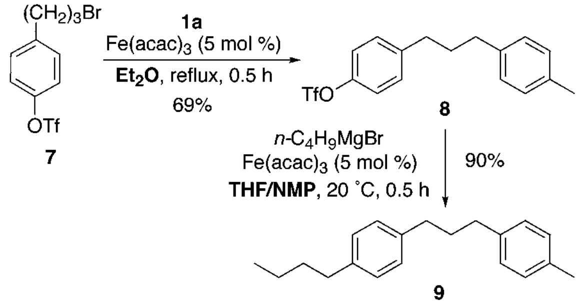
entry	ArMgBr	RX	product	yield (%)[b]
1	**1a**	n-$C_8H_{17}Br$ (**2n**)	 **3an**	70[c]
2		n-$C_8H_{17}Cl$		32[c]
3		n-$C_8H_{17}I$		60[c]
4		n-$C_8H_{17}OTs$		50[c]
5	**1b**	**2n**	 **3bn**	73
6	**1c**	**2n**	 **3cn**	60
7	**1d**	**2n**	 **3dn**	62
8	**1e**	**2n**	 **3en**	60
9	**1a**	$PhO(CH_2)_4Br$ **2o**	 **3ao**	65
10	**1a**	 **2p**	 **3ap**	73
11	**1a**	 **2q**	 **3aq**	69
12	**1a**	t-C_4H_9Br	ND[d]	0

[a] The reaction was carried out with ArMgBr (1.04 mmol), RX (0.52 mmol), and $Fe(acac)_3$ (0.026 mmol) in refluxing ether for 0.5 h. Alkyl halides were completely consumed in all entries. [b] Isolated yield. [c] Major side products are 1-octene and octane. [d] No cross-coupling product was detected by GC−MS analysis of the crude material.

is still not satisfactory, it is comparable to that obtained in the reaction with secondary alkyl bromides catalyzed by nickel complexes reported recently.[8i,k] Unfortunately, tertiary alkyl bromide did not give the cross-coupling product (entry 12).

During our studies on the cross-coupling, it was found that aryl triflates are not reactive toward iron-catalyzed cross-coupling under the present reaction conditions. It is rather surprising because Fürstner recently reported[4a,b] the cross-coupling of aryl triflates with the alkyl Grignard reagents by use of the same $Fe(acac)_3$ as a catalyst precursor. Taking advantage of this finding, a chemoselective cross-coupling was realized for the substrate **7** which possesses both aryl triflate and alkyl bromide moieties (Scheme 2). Thus, the reaction of **7** with p-tolylmagnesium bromide (**1a**) catalyzed by $Fe(acac)_3$ in refluxing ether gave 69% yield of the cross-coupling product at the alkyl bromide, leaving the triflate group intact. The triflate **8** was subjected to the iron-catalyzed cross-coupling with butylmagnesium bromide according to Fürstner's procedures[4a,b] to give a high yield of the butylated product **9**.

Scheme 2. Iron-Catalyzed Chemoselective Cross-Coupling



In summary, we have demonstrated that the cross-coupling between aryl Grignard reagents with primary and secondary alkyl bromides possessing β-hydrogens is efficiently catalyzed by $Fe(acac)_3$ in refluxing diethyl ether. The choice of the solvent is very important in this reaction, the reaction in THF or THF/NMP causing undesired side reactions.

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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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