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Iron-Catalyzed Homo-Coupling of Simple and Functionalized Arylmagnesium Reagents

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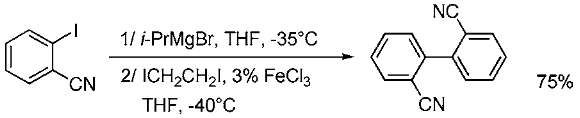
ABSTRACT



Iron-catalyzed homo-coupling of simple and functionalized arylmagnesium reagents is described. The reaction is highly chemoselective (CN, COOEt and NO_2 groups are tolerated). The procedure was used to perform intramolecular couplings. This cyclization reaction is the key step of the total synthesis of the *N*-methylcrinasiadine.

Since the beginning of the past decade we have undertaken to develop preparative iron-catalyzed coupling reactions.[1] The interest of this new area of investigation is highlighted by the increasing number of reports published in the last three years.[2] It should be noted that for large-scale preparation, iron salts such as $FeCl_3$ or $Fe(acac)_3$ are a valuable alternative to palladium and nickel complexes used as catalyst for many coupling procedures[3] because they are cheaper and much more environment-friendly. In the course of our continuing interest in this field we have recently studied the iron-catalyzed homo-coupling of aromatic Grignard reagents. A recent communication[4] in this journal prompted us to report our own results.

The homo-coupling reaction reported by Hayashi is performed in diethyl ether, at reflux, using 1.2 equiv of 1,2-dichlororethane as oxidant. For our part, we have decided to develop the reaction in THF. Indeed, diethyl ether is not convenient for large-scale application (especially at reflux). Moreover, the preparation of aromatic Grignard reagents is easier in THF, and the scope of the reaction is clearly larger in this solvent (preparation of ArMgCl from aryl chlorides, preparation of functionalized ArMgX by halogen−magnesium exchange etc.).

The results described in Table 1 show that in THF the reaction can be easily performed at room temperature in the presence of 3% $FeCl_3$ by using only a stoichiometric amount of dichloroethane as oxidant (0.6 equiv). Good yields of homo-coupling product are thus obtained. Interestingly, the reaction can be applied to heteroaromatic Grignard reagents (entry 8).

From *ortho*-substituted aryl Grignard reagents the reaction is slower. Thus, 10 min is enough to react the 3- or 4-methoxyphenylmagnesium bromides **1b** and **1c** (entries 2

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[1] (a) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 669. (b) Cahiez, G.; Marquais, S. *Tetrahedron Lett*. **1996**, *37*, 1773. (c) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199. (d) Dohle, W.; Koppe, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, *12*, 1901.

[2] (a) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (b) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (c) Quintin, J.; Frank, X. Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 3547. (d) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (e) Scheiper, B. Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (f) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (g) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.

[3] *Metal-Catalysed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-WCH: Weinheim, 1998**.** For review on aryl-aryl coupling reactions, see: (a) Stanforth, S. *Tetrahedron* **1998**, *54*, 263. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schultz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

[4] Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491.

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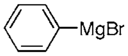
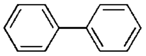
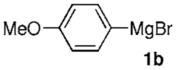
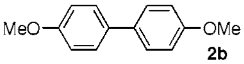
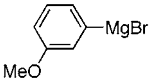
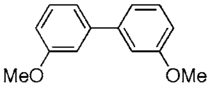
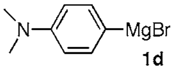
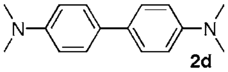
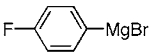
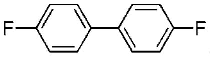
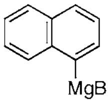
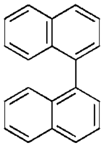
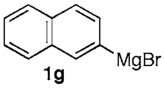
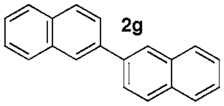
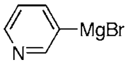
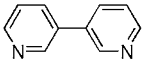
Table 1. Iron-Catalyzed Homo-Coupling of Aryl Grignard Reagents[a]

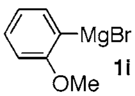
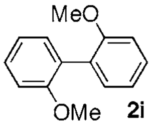
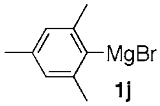
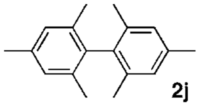
$$\underset{\mathbf{1}}{\text{Ar-MgBr}} \xrightarrow[\text{THF, rt, 10 min}]{\text{0.6 equiv ClCH}_2\text{CH}_2\text{Cl, 3\% FeCl}_3} \underset{\mathbf{2}}{\text{Ar-Ar}}$$

entry	aryl Grignard **1**	product **2**	yield[b] (%)
1	 **1a**	 **2a**	86
2	 **1b**	 **2b**	90
3	 **1c**	 **2c**	96
4	 **1d**	 **2d**	87
5	 **1e**	 **2e**	78
6	 **1f**	 **2f**	74
7	 **1g**	 **2g**	81
8	 **1h**	 **2h**	82[c]

[a] Reactions were carried out by stirring the aryl Grignard reagent (10 mmol), 1,2-dichloroethane (6 mmol), and $FeCl_3$ (0.3 mmol) in THF at room temperature for 1 h. [b] Isolated yield. [c] Isolated as the corresponding picrate. Reaction time was 4 h.

Table 2. Iron-Catalyzed Homo-Coupling of *ortho*-Substituted Aryl Grignard Reagents[a]

$$\underset{\mathbf{1}}{\text{Ar-MgBr}} \xrightarrow[\text{THF, rt, 10 min}]{\text{0.6 equiv XCH}_2\text{CH}_2\text{X, 3\% FeCl}_3} \underset{\mathbf{2}}{\text{Ar-Ar}}$$

entry	aryl Grignard **1**	product **2**	X	yield[b] (%)
1	 **1i**	 **2i**	Cl	21 (81)[c]
2			Br	73
3	 **1j**	 **2j**	Cl	5 (6)[c]
4			Br	60
5			I	61

[a] The reactions were carried out by stirring the aryl Grignard reagent (10 mmol), 1,2-dihalogenoethane (6 mmol), and $FeCl_3$ (0.3 mmol) in THF at room temperature for 10 min. [b] Isolated yield. [c] Reaction time was 4 h.

and 3), whereas the coupling of the 2-methoxyphenylmagnesium bromide **1i** lasts 4 h (81%, Table 2, entry 1). Interestingly, we found that the reaction is clearly accelerated by using 1,2-dibromo- or 1,2-diiodoethane in place of 1,2-dichloroethane as oxidant since the reaction is then completed within 10 min (entries 1 and 2).

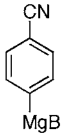
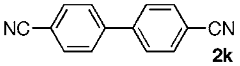
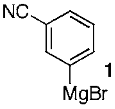
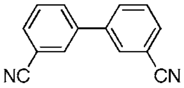
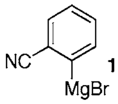
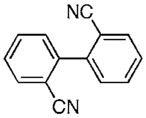
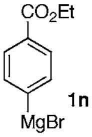
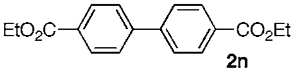
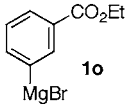
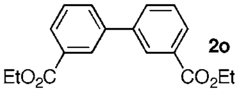
From the more hindered mesitylmagnesium bromide **1j** the reaction is still more difficult. Under standard conditions (1,2-dichloroethane), poor yields of homo-coupling product **2j** were obtained whatever the reaction time (entry 3). In this case, a dramatic improvement was observed when the reaction was performed with 1,2-dibromo- or 1,2-diiodoethane since the yield jumped from 6% to 60% (entries 4 and 5).

From a preparative point of view, the synthesis of simple symmetrical biaryls is not very challenging. Thus we have turned our attention to the preparation of highly functionalized molecules (Table 3).

Recently, in collaboration with the Knochel group we have described the preparation of functionalized aryl Grignard reagents via an iodine–magnesium exchange reaction.[5] Thus, cyanophenylmagnesium bromides and carbethoxyphenylmagnesium bromides were easily and efficiently prepared from the corresponding aryl iodide and isopropylmagnesium bromide in THF at −40 °C. Similarly, 2-nitrophenylmag-

Table 3. Iron-Catalyzed Homo-Coupling of Functionalized Aryl Grignard Reagents[a]

$$\underset{\mathbf{3}}{\text{Ar-I}} \xrightarrow[\text{-35 °C, 30 min}]{\textit{i}\text{-PrMgBr, THF}} \underset{\mathbf{1}}{\text{Ar-MgBr}} \xrightarrow[\text{3\% FeCl}_3\text{, THF, -40 °C or -35 °C to rt}]{\text{ICH}_2\text{CH}_2\text{I}} \underset{\mathbf{2}}{\text{Ar-Ar}}$$

entry	aryl Grignard **1**	product **3**	yield (%) from **1**
1	 **1k**	 **2k**	75
2	 **1l**	 **2l**	70
3	 **1m**	 **2m**	75
4	 **1n**	 **2n**	63
5	 **1o**	 **2o**	67

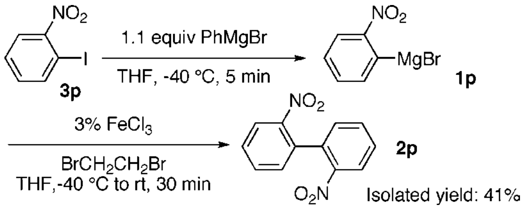
[a] Reactions were carried out by stirring the aryl Grignard reagent (10 mmol), 1,2-diodoethane (10 mmol), and $FeCl_3$ (0.3 mmol) in THF at −40 °C (entries 1−3) for 2 h or at room temperature for 1 h (entries 4 and 5). [b] Isolated yield.

nesium bromide **1p** can also be prepared from 2-iodonitrobenzene **3p** and phenylmagnesium bromide at −40 °C in THF.[6]

To develop a new way to prepare highly functionalized biaryl compounds, we have tried to apply the homo-coupling reaction conditions described herein to these functionalized aryl Grignard reagents. In fact, the main difficulty is to avoid the competitive cross-coupling reaction between the starting arylmagnesium reagent and the isopropyl iodide formed during the iodine−magnesium exchange reaction ($ArI + i\text{-}PrMgX \rightarrow ArMgX + i\text{-}PrI$). By working with 1,2-dichloroethane as oxidant, the homo-coupling occurs too slowly to be efficient,[7] especially when the reaction has to be performed below −20 °C to prevent the decomposition of the Grignard reagent. Fortunately, we have found that with 1,2-dibromo- or 1,2-diiodoethane the homo-coupling reaction occurs successfully even at −35 °C (Table 3).

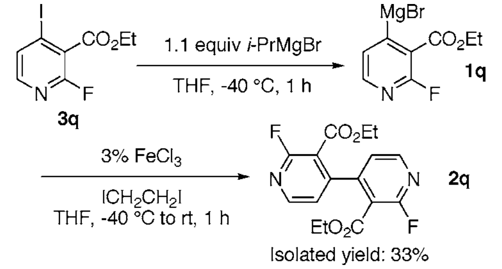
Dicyanobiphenyls **2k**−**m** (entries 1−3) as well as dicarbethoxybiphenyls **2n** and **2o** (entries 4 and 5) were thus prepared in satisfactory yields. Under similar coupling conditions, the 2,2′-dinitrobiphenyl **2p** was prepared from the corresponding Grignard reagent **1p** in 41% yield (Scheme 1). This yield is satisfactory for this very challenging example.

Scheme 1. Iron-Catalyzed Homo-Coupling of 2-Nitrophenylmagnesium Bromide



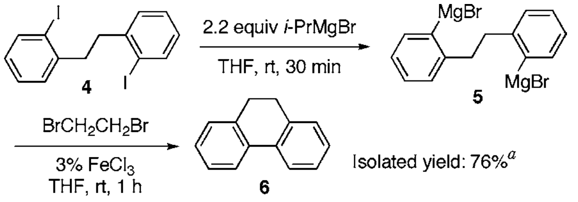
We have also applied these coupling conditions to the functionalized pyridylmagnesium bromide **1q**. The starting 2-fluoro-3-carbethoxy-4-iodopyridine **3q** was synthesized in 66% yield from 2-fluoro-3-iodopyridine according to a procedure reported by Quéguiner.[8] It was then reacted with *i*-PrMgBr at −40 °C for 1 h to give the Grignard reagent **1q**. This latter was then treated with 1,2-diiodoethane in the presence of 3% $FeCl_3$ to give the homo-coupling product **2q** in 33% overall yield (Scheme 2). All of these results show that this homo-coupling procedure is highly chemoselective.

Scheme 2. Iron-Catalyzed Homo-Coupling of 2-Fluoro-3-carbethoxy-4-pyridylmagnesium Bromide



It was tempting to try to perform intramolecular coupling reactions from di-Grignard reagents such as **5** (Scheme 3).

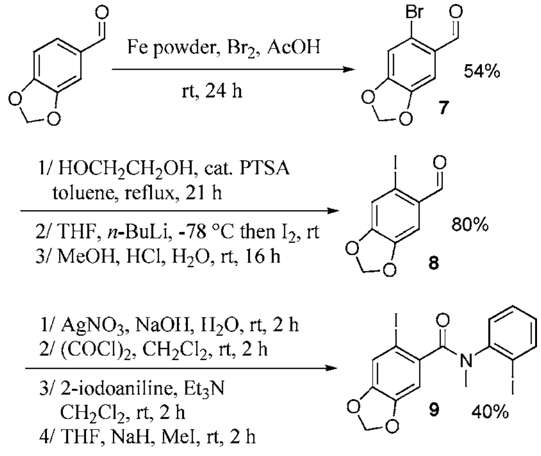
Scheme 3. Iron-Catalyzed Intramolecular Coupling Reaction



Thus the diiodo compound **4** reacted with *i*-PrMgBr at room temperature for 30 min to give **5**. Then, the treatment of the di-Grignard **5** with 1,2-dibromoethane in the presence of 3% $FeCl_3$ provided the dihydrophenanthrene **6** in 76% overall yield.

It is interesting to note that via such an intramolecular cyclization reaction it is possible to obtain a "cross-coupling" product using a "homo-coupling" reaction. This is exemplified by the following total synthesis of *N*-methylcrinasiadine, a natural product extracted from *Lapiedra martinezii* (*Amaryllidaceae*).[9] The 2,2′-diiodo-*N*-methyl-4,5-methylenedioxybenzanilide **9** was prepared in 8 steps from piperonal

Scheme 4. Preparation of 2,2′-Diiodo-*N*-methyl-4,5-methylenedioxybenzanilide **9**[10]



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(5) (a) Boymond, L.; Röttländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem, Int. Ed.* **1998**, *37*, 1701. (b) 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. For a review, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Anh Vu, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

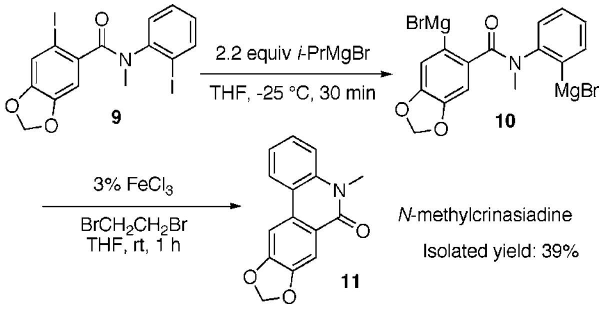
(6) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *4*, 1610.

(7) Until 40% yield of cross-coupling product between the starting aryl Grignard reagent and *i*-PrI were obtained. The iron-catalyzed cross-coupling reaction between arylmagnesium reagent and secondary alkyl halide in THF has been reported: (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (b) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. The reaction can also be performed in ether: Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.

(8) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832.

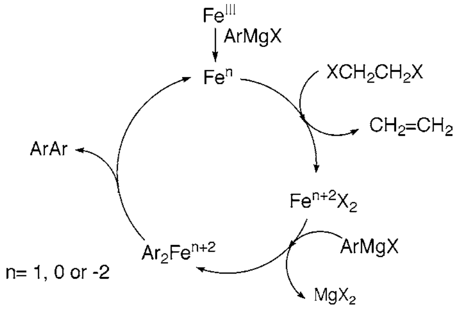
(Scheme 4). The di-Grignard reagent **10** was then prepared through iodine−magnesium exchange. Under the coupling conditions previously used, it afforded the *N*-methylcrinasiadine **11** in 39% overall yield (Scheme 5).

Scheme 5. Preparation of *N*-Methylcrinasiadine



A plausible mechanism is proposed in Scheme 6. The role of the 1,2-dihaloethane is to oxidize the iron ($Fe^{n} \rightarrow Fe^{n+2}$) after the reductive elimination step. It should be noted that the oxidation states of the iron species involved in the catalytic cycle are uncertain. A couple Fe^{I}/Fe^{III} or Fe^{0}/Fe^{II} can be proposed,[11] but a recent study[1a,b] puts forward a couple Fe^{-II}/Fe^{0}.

Scheme 6. Mechanism for the Homo-Coupling Reaction



In summary, we have developed an efficient iron-catalyzed homo-coupling reaction of aryl Grignard reagents. It should be noted that the reaction is chemoselective. Thus, various functionalized aryl and heteroarylmagnesium reagents have been used successfully to prepare polyfunctionalized biaryl and biheteroaryl compounds. Moreover, this procedure allows perfomance of intramolecular coupling reactions.

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

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(9) Suau, R.; Gomez, A. I.; Rico, R. *Phytochemistry* **1990**, *29*, 1710.

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