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Iron-Catalyzed Homocoupling of Bromide Compounds

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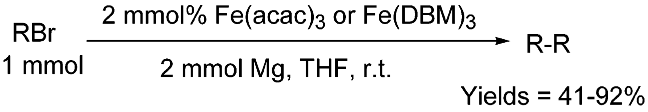

$$\underset{\text{1 mmol}}{\text{RBr}} \xrightarrow[\text{2 mmol Mg, THF, r.t.}]{\text{2 mmol\% Fe(acac)}_3 \text{ or Fe(DBM)}_3} \text{R-R}$$

Yields = 41-92%

The homocoupling of bromide compounds was successfully performed in one pot by a combination of metallic magnesium and a catalytic amount of iron salts. The binary catalytic system differentiates itself from other homocoupling reactions catalyzed by iron salts in that it requires neither the in situ preparation of Grignard reagent nor the addition of a 1,2-dihalogen compound as an oxidant. Various aromatic and alkyl bromides underwent the homocoupling smoothly affording the corresponding symmetrical hydrocarbon compounds in moderate to excellent yields.

Transition metal-catalyzed coupling reactions of halogen compounds to form carbon−carbon bonds are among the most powerful methods in organic synthesis.[1] In a few decades, this methodology evolved into a general tool for the preparation of fine chemicals, materials, and pharmaceutically active compounds both in the laboratory and on the industrial scale, and it is widely appreciated in the context of parallel synthesis and combinational chemistry.[2] Although a variety of metallic reagents can be applied in this coupling reaction, the field is largely dominated by the use of palladium and nickel complexes as the catalysts mainly because of their wide applicable scope and excellent compatibility with many functional groups.[3] However, these catalysts generally involved eco-disadvantageous ligands such as phosphine compounds so as to catalyze the coupling reaction effectively. Furthermore, most of these catalysts are expensive and/or sensitive to oxygen and moisture. Therefore, the development of a more efficient synthetic methodology to form carbon−carbon bond catalyzed with readily available, stable, and safe catalysts is still in demand. Since the pioneering work of Kochi in 1975, iron salts have emerged as a powerful and alternative catalyst used in the homo- or cross-coupling of halogen compounds and Grignard reagents.[4] Correspondingly, a large number of documents can be found concerning iron salts-catalyzed coupling reactions and their high catalytic efficiency, cheapness, and environmental friendliness made them quite impressive.[5,6] Recently, Hayashi and Cahiez group reported the homocoupling of aryl Grignard reagents catalyzed by iron trichloride in the presence of 1,2-dihalogen ethane.[7] Although their methods are better for the synthesis of symmetrical biaryls, there were three obvious drawbacks: (1) the procedure required sequential procedures; namely, Grignard reagents had to be prepared in situ before the homocoupling reaction began, (2) almost stiochiometric toxic 1,2-dihalogen ethane was used as the oxidant, and (3) no examples of alkylbromides coupling were given. Herein we wish to report a more convenient alternative method for the synthesis of several kinds of symmetrical hydrocarbons catalyzed by a combination of iron salts and metallic magnesium in one pot.

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(1) For cross-coupling, see (a) *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry; Springer: Berlin, 2002; Vol. 219. (b) *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Li, J. J., Gribble, G. W., Eds.; Elsevier: Oxford, U.K., 2000. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (d) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235. (e) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (f) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React*. **1997**, *50*, 1. (g) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 127. (h) Snieckus, V. *Pure Appl. Chem.* **1994**, *66*, 2155. (i) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, p 481. (j) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (k) Negishi, E. *Acc. Chem. Res*. **1982**, *15*, 340. (l) Kumada, M. *Pure Appl. Chem*. **1980**, *52*, 669. For self-coupling, see (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327. (c) Fanta, P. E. *Chem. Rev.* **1946**, *38*, 139; **1964**, *64*, 613; *Synthesis* **1974**, 9. (d) Goshaev, M.; Otroshchenko, O. S.; Sadykov, A. S. *Russ. Chem. Soc. Rev.* **1972**, *41*, 1046. (e) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; John Wiley: New York, 1980. (f) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655.

(2) (a) *Handbook of Combinatorial Chemistry: Drugs, Catalysts, Materials*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, Germany, **2002**. (b) Beller, M.; Zapf, A.; Mägerlein, W. *Chem. Eng. Technol*. **2001**, *24*, 575.

(3) (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1996. (c) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, U.K., 1982; Vol. 8, p 799.

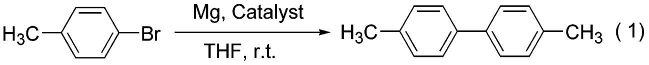
(4) (a) Kochi, J. K. *J. Organomet. Chem.* **2002**, *653*, 11. (b) Smith, R. S.; Kochi, J. K. *J. Org. Chem*. **1976**, *41*, 502. (c) Neumann, S. M.; Kochi, J. K. *J. Org. Chem*. **1975**, *40*, 599. (d) Kochi, J. K. *Acc. Chem. Res*. **1974**, *7*, 351. (f) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc*. **1971**, *93*, 1487. (g) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn*. **1971**, *44*, 3063. (h) Tamura, M.; Kochi, J. K. *Synthesis* **1971**, 303.

(5) Recent reviews: (a) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (b) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081. (c) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(6) (a) Bica, K.; Gaertner, P. *Org. Lett.* **2006**, *8*, 733. (b) Bedford, B. R.; Betham, M.; Bruce, W. D.; Danopoulos, A. A.; Frost, M. R.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104. (c) Bedford, B. R.; Bruce, W. D.; Frost, M. R.; Hird, M. *Chem. Commun.* **2005**, *4161*. (d) Bedford, B. R.; Bruce, W. D.; Frost, M. R.; Goodby, W. J.; Hird, M. *Chem. Commun.* **2004**, *2822*. (e) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (f) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. (g) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (h) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5358. (i) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373. (j) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (k) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (l) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621. (m) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (n) Cahiez, G.; Avedissian, H.; *Synthesis* **1998**, 1199. (o) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017. (p) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 513.

(7) (a) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491. (b) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943.

10.1021/jo060673l CCC: $33.50



The catalytic effect of iron, vanadium, and titanium salts on the homocoupling reaction of 4-bromotoluene was investigated in the presence of metallic magnesium (eq 1 and Table 1). It was found that no desired product was obtained with metallic magnesium in the absence of catalysts (entry 1). When a catalytic amount of $TiCl_4$, VCl_3, or VO(acac)$_2$ was added together with 2 mmol of Mg in THF, the desirable biaryl was obtained but in moderate yield (entries 3, 4, and 5). Better results came from the use of iron salts as the catalysts. For example, 5% and 2% of iron trichloride catalysis gave the biaryl in 78% and 81% isolated yield, respectively (entries 6 and 7). Compared with iron trichloride, Fe(acac)$_3$ and Fe(DBM)$_3$ gave more satisfactory results (entries 8 and 9). Several cosolvents, such as THF−ether, THF−toluene, and ether−toluene were further surveyed for the Fe(DBM)$_3$-catalyzed coupling reaction, but no improvement was observed (entries 10−12). Use of ether as a solvent resulted in lower yield also (entry 13). Considering that iron trichloride is moisture sensitive, we finally chose Fe(acac)$_3$ or Fe(DBM)$_3$ as the catalyst and THF as the solvent.

TABLE 1. The Effect of Iron, Vanadium, or Titanium Salts on the Homocoupling of 4-Bromotoluene[a]

entry	metallic salt	solvent	time (min)	yield (%)[b]
1		THF	60	0
2	3% $TiCl_4$	THF	30	65[c]
3	5% VCl_3	THF	30	62
4	3% VCl_3	THF	30	67
5	4% VO(acac)$_2$	THF	30	73[d]
6	5% $FeCl_3$	THF	30	78
7	2% $FeCl_3$	THF	30	81
8	2% Fe(acac)$_3$	THF	30	85[d]
9	2% Fe(DBM)$_3$	THF	30	88[e]
10	2% Fe(DBM)$_3$	THF−ether	60	75[f]
11	2% Fe(DBM)$_3$	THF−toluene	60	68[g]
12	2% Fe(DBM)$_3$	ether−toluene	120	45[h]
13	2% Fe(DBM)$_3$	ether	120	56

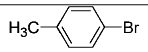
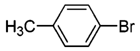
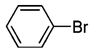
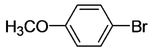
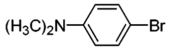
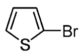
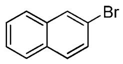
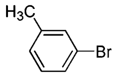
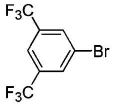
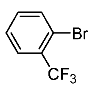
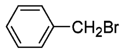
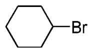
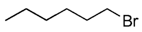
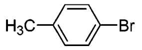
[a] 4-Bromotoluene, 1 mmol; metallic salt, see the table; metallic Mg turnings, 2 mmol; anhydrous THF, 4 mL; vigorously stirring; room temperature. [b] Isolated yields. [c] An amount of 15% 4-methylphenol was obtained. [d] Acac = acetyl acetone. [e] DBM = dibenzoyl methane. [f] A total of 3 mL of THF and 0.5 mL of ether. [g] A total of 3 mL of THF and 0.5 mL of toluene. [h] A total of 3 mL of ether and 0.5 mL of toluene.

From Table 1, the combination of Fe(acac)$_3$ or Fe(DBM)$_3$ and Mg was found to be a more efficient catalytic system to catalyze the homocoupling of 4-bromotoluene in THF; although the effect of several cosolvents, titanium, and vanadium salts was tried. To explore the scope of this catalytic coupling system, more bromide compounds were used as the substrates (eq 2 and Table 2). It should be noted that the catalytic homocoupling reaction proceeded successfully in the absence of 1,2-dichloroethane, therefore providing an extremely preferable way for the synthesis of symmetrical hydrocarbon.

$$\underset{\mathbf{1}}{\underset{1\text{ mmol}}{\text{RBr}}} \xrightarrow[\text{2 mmol Mg, THF, r.t.}]{\text{2 mmol\% Fe(acac)}_3\text{ or Fe(DBM)}_3} \underset{\mathbf{2}}{\text{R-R}} \qquad (2)$$

A variety of bromide compounds underwent the homocoupling reactions with the catalytic Fe(acac)$_3$ or Fe(DBM)$_3$/Mg system in THF at room temperature to give the corresponding symmetrical hydrocarbons in moderate to excellent yields (except entry 13). Aromatic bromides substituted with electrodonating groups such as methyl, methoxy, and *N*, *N*-dimethyl can be efficiently converted into the corresponding biaryls **2a**,**c**,**d**,**g** (entries 1, 2, 4, 5, and 8). Heteroaryl bromides such as 2-bromothiophene and *β*-bromonaphthalene also work well as the coupling substrates (entries 6 and 7). It is noteworthy that the present reaction system is tolerant of a strong electrowithdrawing group such as trifluoromethyl, and the desired products **2h** and **2i** were obtained in good yields; reductive cleavge of fluoro-carbon in the trifluoromethyl group was not observed (entries 9 and 10). Interestingly, aliphatic bromides can also undergo the self-coupling reaction though with good to reasonable yields. Benzyl bromide afforded **2j** in 79% yield (entry 11); cyclohexyl bromide afforded the **2k** in moderate yields (entry 12); and 1-bromohexane gave the dodecane **2l** in low yield (entry 13), which may result from the rapid *β*-hydro elimination as a side reaction. The present homocoupling can be readily scaled up to the reaction of 20 mmol of 4-bromotoluene using 1 mol % of the Fe(DBM)$_3$ catalyst, which gave 83% yield of **2a** (entry 14). Unfortunately, no desired product

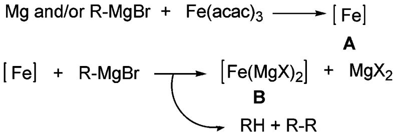
TABLE 2. Catalytic Fe(acac)$_3$ or Fe(DBM)$_3$/Mg Catalyzed the Homocoupling of Bromide Compounds[a]

Entry	Substrate **1**	2 mol% Iron catalyst	Time (min)	Product **2** and Yield (%)[b]
1		Fe(acac)$_3$	30	**2a**, 85[c]
2		Fe(DBM)$_3$	30	**2a**, 88[d]
3		Fe(DBM)$_3$	30	**2b**, 83
4		Fe(DBM)$_3$	40	**2c**, 92
5		Fe(DBM)$_3$	45	**2d**, 59
6		Fe(DBM)$_3$	30	**2e**, 81
7		Fe(DBM)$_3$	30	**2f**, 78
8		Fe(DBM)$_3$	40	**2g**, 90
9		Fe(acac)$_3$	30	**2h**, 76
10		Fe(DBM)$_3$	30	**2i**, 69
11		Fe(DBM)$_3$	30	**2j**, 79
12		Fe(DBM)$_3$	30	**2k**, 65
13		Fe(DBM)$_3$	30	**2l**, 41
14		Fe(DBM)$_3$	30	**2a**, 83[e]

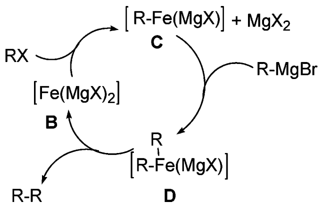
[a] Bromide compounds, 1 mmol; Fe(acac)$_3$ or Fe(DBM)$_3$, 2 mmol %; metallic Mg turnings, 2 mmol; anhydrous THF, 4 mL; vigorously stirring; room temperature. [b] Isolated yields. [c] Acac = acetyl acetonate. [d] DBM = dibenzoyl methane. [e] Reaction was carried out with 40 mmol metallic Mg turnings, 0.4 mmol Fe(DBM)$_3$, 20 mmol 4-bromotoluene, 60 mL anhydrous THF.

was obtained using chlorobenzene as the substrate under this reaction condition.

According to the reported literatures concerning iron salts catalysis,[6,7] a possible mechanism is postulated as follows (eq 3 and 4): Iron acetylacetonate was first reduced by metallic magnesium and/or Grignard reagent to form a low valent activated iron **A**.[8] Then this species reacts with Grignard reagent to generate an iron intermediate **B**, which gives a little amount of RH or R−R.[9] **B** is inserted into bromide compounds to form an iron and magnesium complex **C** which, if alkyl substituted, may undergo β-hydrogen elimination to give ethylene compounds[10] or else react with Grignard reagent to give dialkyl or diaryl substituted intermediate **D**. Reductive elimination of the homocoupling product regenerates catalytically active species **B**. Although more detailed investigation should be carried out for the mechanism of the catalytic homocoupling reaction, it can be postulated that a low-valent iron species generated by treatment with Mg or Grignard reagent is involved in the catalytic cycle.[11]



(3)



(4)

In conclusion, an efficient homocoupling reaction of bromide compounds is reported with a combination of the catalytic system $Fe(acac)_3$ or $Fe(DBM)_3$ and Mg in the absence of a 1,2-dihalogen ethane. The described here is environmentally friendly and has large-scale synthetic potential.

Experimental Section

A general procedure for the homocoupling coupling induced by the catalytic system $Fe(acac)_3/Mg$ is as follows: To a 10 mL flame-dried two-necked round-bottom flask with a suspension of 2 mmol (48 mg) of magnesium turnings and 0.02 mmol $Fe(acac)_3$ (7.0 mg) in 3 mL of anhydrous THF was added 1 mmol bromide compounds under the atmosphere of argon. The mixture was stirred at room temperature for the time indicated in Table 2. Then a little amount of silica gel (300−400 mesh) was added, and the resulting mixture evaporated to dryness. Purification was done by column chromatography on silica gel (300−400 mesh) with hexane as eluent to give the pure homocoupling products **2**.

Supporting Information Available: Experimental procedures, compound characterization data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] Bönnemann, H.; Bogdanović, B.; Brinkmann, R.; Spliethoff, B.; He, D. W. *J. Organomet. Chem.* **1993**, *451* (1−2), 23.

[9] According to Prof. H. B. Kagan's report, anhydrous THF can act as a proton source. (a) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37* (Suppl 1), 175. (b) Kagan, H. B. *New. J. Chem*. **1990**, *14*, 453.

[10] Bogdanović, B.; Schwickardi, M. *Angew. Chem., Int.* **2000**, *39*, 4610.

[11] The 2% $Fe(DBM)_3$-catalyzed coupling reaction of phenylbromide magnesium reagent with bromobenzene in a ratio of 1:1 was investigated. It gave the biphenyl in 73% yield.