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Iron-Catalyzed Alkylation of Alkenyl Grignard Reagents

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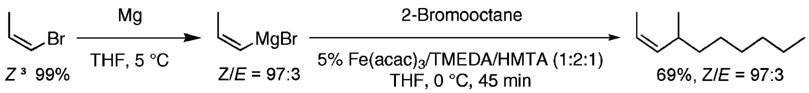
ABSTRACT



The first iron-catalyzed cross-coupling reaction between alkenyl Grignard reagents and *n*- or *s*-alkyl bromides is described. The reaction is stereoselective and takes place in the presence of 5 mol % of [Fe(acac)$_3$/TMEDA/HMTA] (1:2:1) under very mild conditions (THF, 0 °C, 45 min).

Transition-metal-catalyzed cross-coupling reactions have been extensively developed in recent years.[1] However, in spite of the considerable number of reports, some couplings are always difficult to achieve. Thus, the use of nonactivated secondary alkyl halides is often delicate because of the slow oxidative addition to transition-metal complexes and the β-hydride elimination from the intermediate organometallic species involved in the catalytic process.[2] Lately, this problem has received considerable attention; however, to the best of our knowledge, no general procedure[3] was described to couple alkenylmagnesium reagents with secondary alkyl halides. Herein, we report the first example of iron-catalyzed reaction to perform such a coupling.

The development of iron-catalyzed coupling reactions from Grignard reagents is a very challenging research area because of the considerable potential interest for large-scale applications.[1m,4,5] Actually, organomagnesium compounds are one of the most accessible and cheapest organometallics, and iron

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[2] Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749. For general reviews on cross-coupling reactions with alkyl halides, see: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (b) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (c) Càrdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384.

[3] To the best of our knowledge, only two specific cases were reported with Grignard reagents. (a) The Cu-catalyzed reaction of 1,3-butadien-2-ylmagnesium with 2-iodooctane (yield: 45%): Nunomoto, S.; Kawagami, Y.; Yamashita Y. *J. Org. Chem.* **1983**, *48*, 1912. (b) The Co-catalyzed coupling of 1-(trimethylsilyl)ethenylmagnesium bromide with various secondary alkyl bromides: Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 3093. The procedure described in this report is limited to this special Grignard reagent. Two examples of Suzuki reaction were also reported: (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

[4] For reviews on iron-mediated coupling reactions, see: (a) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

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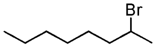
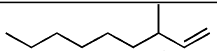
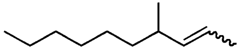
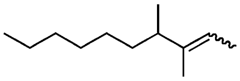
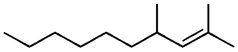
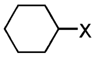
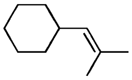
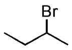
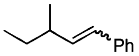
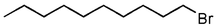
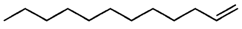
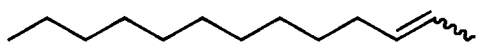
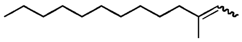
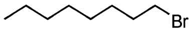
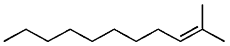
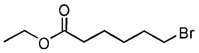
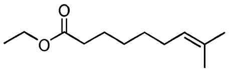
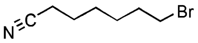
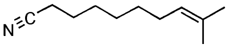
salts are cheap and environmentally benign. Recently, we have discovered two very efficient iron-based catalytic systems to react aromatic Grignard reagents with primary or secondary alkyl halides.[6] The excellent results thus obtained encouraged us to try to couple alkenyl Grignard reagents with secondary alkyl halides under similar conditions (Table 1, entries 1−8).

Table 1. Iron-Catalyzed Cross-Coupling between Alkenyl Grignard Reagent and *s*- and *n*-Alkyl Halides[a]

$$\text{AlkenylMgBr} + \text{RX} \xrightarrow[\text{0 °C, THF, 45 min}]{\text{5\% Fe(acac)}_3\text{/TMEDA/HMTA (1:2:1)}} \text{Alkenyl-R}$$

entry	alkyl halide	product	yield[b]
1			55
2	"	 *E*/*Z*: 85/15[c,d]	67
3	"	 *E*/*Z*: 85/15[c,e]	84
4	"		72
5 6 7	 X= I X=Br X= Cl		74 75 15
8		 *E*/*Z*: 76/24[c,f]	68
9			48
10	"	 *E*/*Z*: 85/15[c,d]	67
11	"	 *E*/*Z*: 86/14[c,e]	80
12			69
13			73
14			67

[a] Alkenyl Grignard reagent (37.5 mmol) was added dropwise for 45 min to a solution of alkyl halide (25 mmol), $Fe(acac)_3$ (1.25 mmol), TMEDA (2.5 mmol), and HMTA (1.25 mmol) in THF at 0 °C. [b] Isolated yield, %. [c] Alkenyl Grignards were prepared from commercial mixtures of (*Z*)- and (*E*)-alkenyl bromides. [d] MeCH═CHMgBr, *E*/*Z* = 86/14. [e] MeCH═C(Me)-MgBr, *E*/*Z* = 87/13. [f] PhCH═CHMgBr, *E*/*Z* = 78/22.

We were pleased to find that the reaction occurs in THF under mild conditions to afford satisfactory yields of coupling product by using only a reasonable excess of Grignard (1.5 equiv) in the presence of 5% $Fe(acac)_3$/HMTA/TMEDA (1:1:2).

The scope of the reaction is very large; α- or *β*-monosubstituted as well as α,*β*- or *β*,*β*-disubstituted alkenylmagnesium bromides were successfully coupled with various cyclic or acyclic secondary alkyl bromides. Secondary alkyl iodides led to similar results (entries 5 and 6), whereas the corresponding chlorides only reacted sluggishly and gave low yields (entry 7).

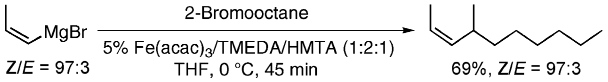
The reaction was successfully extended to primary alkyl halides (entries 9−14). Let us recall that with these substrates, the coupling can also be performed under copper,[3a,7] palladium, or nickel catalysis.[1]

Interestingly, it is possible to use functionalized substrates; thus an ester or a nitrile group is tolerated (entries 13 and 14).

It should be noted that the coupling reaction is highly stereoselective since, in all cases, the *Z*/*E* ratio of the starting alkenylmagnesium bromides is retained during the coupling (entries 2, 3, 8, 10, and 11).

It is well-known that the insertion of magnesium takes place with a partial isomerization of the double bond.[8] However, when the Grignard is carefully prepared under mild conditions the isomerization is very limited and the coupling product is obtained with a satisfactory stereomeric purity (Scheme 1).

Scheme 1



In conclusion, we have described the first iron-catalyzed cross-coupling reactions between alkenyl Grignard reagents and secondary alkyl halides. Moreover, it is also the first general metal-catalyzed procedure to perform such a coupling. The reaction can also be successfully applied to primary alkyl halides. The conditions are very mild and the coupling reaction is highly stereo- and chemoselective. In the framework of sustainable development, these results are a further step to develop less toxic and more economical catalysts.[9]

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

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(7) Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733.

(8) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286.

(9) The coupling can also be performed by using the catalytic system described by Nakamura (ref 5p) for the coupling of aryl Grignards with alkyl bromides: 5% $FeCl_3$/1.6 equiv of TMEDA (RMgX/TMEDA = 1:1). However, the yields are lower, 50% instead of 75% for the coupling of Me_2C═CHMgBr with cyclohexyl bromide (Table 1, entry 6), and the global amount of amine is clearly higher (160% instead of 15%). See the Supporting Information.