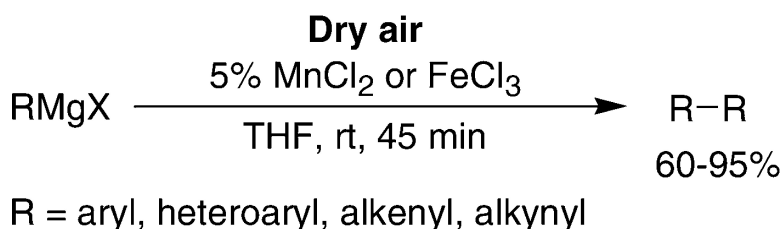Communication

Manganese- or Iron-Catalyzed Homocoupling of Grignard Reagents Using Atmospheric Oxygen as an Oxidant

Grard Cahiez, Alban Moyeux, Julien Buendia, and Christophe Duplais

$$\text{RMgX} \xrightarrow[\text{THF, rt, 45 min}]{\substack{\textbf{Dry air} \\ 5\% \text{ MnCl}_2 \text{ or FeCl}_3}} \text{R}-\text{R}$$

Dry air

5% MnCl$_2$ or FeCl$_3$

THF, rt, 45 min

R$-$R

60-95%

R = aryl, heteroaryl, alkenyl, alkynyl

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Manganese- or Iron-Catalyzed Homocoupling of Grignard Reagents Using Atmospheric Oxygen as an Oxidant

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Homocoupling reactions of aryl, alkenyl, and alkynyl Grignard reagents are an easy and efficient access to symmetrical di- or polyaromatic, olefinic, or acetylenic conjugated compounds. The potential applications of such compounds in optical materials, molecular devices, and organic conductors are well-recognized.[1] Therefore, for large-scale applications, it is interesting to develop more convenient methods with respect to environmental and economic considerations. Recently, we[2] and others[3] have demonstrated the efficiency of the iron-catalyzed homocoupling of aryl Grignard reagents using 1,2-dihalogenoethanes as an oxidant. Following that, Knochel[4] described an elegant transition-metal-free homocoupling reaction of organomagnesium compounds by direct oxidation with 3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone. However, for industrial applications, these methods are limited since they require a stoichiometric amount of organic oxidant.

In fact, the choice of the oxidant is crucial for any effective preparative method, and atmospheric oxygen is obviously the best candidate. Now, we would like to report our progress in this field. A preliminary experiment showed that excellent yield of 4,4′-dimethoxydiphenyl **1** is obtained by bubbling dry air into a solution of 4-anisylmagnesium bromide in the presence of FeCl₃ (Scheme 1). The efficiency of the iron catalysis should be underlined since, in the absence of iron salts, Grignard reagents generally react very quickly with oxygen to give various products (mainly ROH and RH) but only traces of homocoupling product.[5]

This promising result encouraged us to extend the scope of the reaction to various aryl Grignard reagents (Table 1). Thus, simple and functionalized biaryl compounds were synthesized in good yields (entries 1−5). It is noteworthy that the use of pure oxygen instead of atmospheric oxygen has no significant influence on the yields (entries 1 and 2). The conditions described above also allow the coupling of alkenyl Grignard reagents (entries 6 and 7). The corresponding conjugated dienes were obtained in moderated yields, and the reaction is stereoselective (entry 7). Unfortunately, with alkynylmagnesium halides, the reaction gave an untractable mixture of heavy products.[5] During our investigations on iron- and manganese-catalyzed cross-coupling reactions of Grignard reagents, we often noticed similar behavior between the two metals. As a consequence, we tried to perform the homocoupling of Grignard reagents under manganese catalysis.

As shown in Table 2, excellent yields of homocoupling products were obtained by using 5 mol % of MnCl₂. Various aryl and heteroaryl Grignard reagents have been used successfully (entries 1−10). The reaction is chemoselective; thus, ester, nitrile, or nitro groups are tolerated (entries 4−6 and 9). Under the same conditions, β-mono- and β,β-bisubstituted alkenyl Grignard reagents afforded the corresponding conjugated dienes in good yields. It should be noted that the coupling is highly stereoselective (entries 12 and 13). These results are interesting since MnCl₂, as FeCl₃, is a very suitable catalyst from both the economic and environmental point

Scheme 1. Iron-Catalyzed Homocoupling of Anisylmagnesium Bromide with Atmospheric Oxygen as an Oxidant
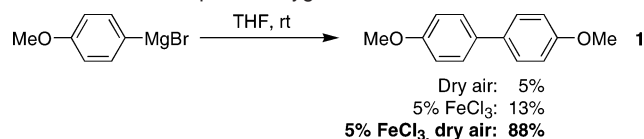

Dry air: 5%
5% FeCl₃: 13%
5% FeCl₃, dry air: 88%

Table 1. Iron-Catalyzed Homocoupling of Grignard Reagents with Atmospheric Oxygen as an Oxidant[a]

entry	RMgX	product	yield (%)[b]
1		**1**	88 (90[c])
2		**2**	85 (87[c])
3		**3**	72
4		**4**	70[d]
5		**5**	72[d]
6		**6**	60
7	E/Z = 95:5	E/E, E/Z, Z/Z = 92:6:2[e] **7**	68[f]

[a] The reaction was carried out on a 20 mmol scale. [b] Isolated yield. [c] Pure oxygen was used. [d] The reaction was performed at −20 °C. [e] The stereoselectivity was determined by GC. [f] The reaction was performed at 10 °C.

of view. As a rule, the manganese-catalyzed reaction gave better yields than the iron-catalyzed reaction, especially for the preparation of conjugated dienes.

These excellent results prompted us to try to couple hexynylmagnesium chloride again by using MnCl₂ in place of FeCl₃ as catalyst. We were very pleased to obtain 5,7-dodecadiyne **14** in 91% yield (entry 14). The reaction was successfully extended to various alkynyl Grignard reagents (entries 14−17). This should be emphasized since diynes are very important in materials sciences[1] and for the elaboration of natural products.[6]

In order to illustrate the synthetic potential of this coupling reaction in total synthesis, we decided to prepare the *N*-methylcrinasiadine **20** (Scheme 2), a natural product extracted from *Lapiedra martinezzi* (Amaryllidaceae).

The 2,2′-diiodo-*N*-methyl-4,5-methylenedioxybenzanilide **19**[7] was treated with *i*-PrMgCl to give the corresponding di-Grignard reagent via an iodine−magnesium exchange (Scheme 2). The

**Table 2.** Manganese-Catalyzed Homocoupling of Grignard Reagents with Atmospheric Oxygen as an Oxidant[a]

$$RMgX \xrightarrow[\text{THF, rt, 45 min}]{\text{Dry air, 5\% MnCl}_2\cdot\text{2LiCl}} R-R$$

entry	RMgX	product	yield (%)[b]
1	MeO—⬡—MgBr	MeO—⬡—⬡—OMe **1**	95
2	⬡—MgBr	⬡—⬡ (MeO) **2**	92
3	⬡—MgBr (OMe)	⬡—⬡ (OMe) **3**	76
4	EtO₂C—⬡—MgCl	EtO₂C—⬡—⬡—CO₂Et **4**	80[c]
5	NC—⬡—MgCl	NC—⬡—⬡—CN **5**	78[c]
6	⬡—MgCl (NO₂)	O₂N—⬡—⬡—NO₂ **8**	75[c]
7	naphthyl-MgBr	binaphthyl **9**	80
8	thienyl-MgCl	bithienyl **10**	91
9	EtO₂C—furyl—MgCl	EtO₂C—furyl—furyl—CO₂Et **11**	88[c]
10	pyridyl-MgBr	bipyridyl **12**	80
11	Bu,Bu-vinyl-MgBr	Bu,Bu-diene **6**	88
12	Ph-vinyl-MgBr, E/Z = 95:5	Ph-diene, E/E, E/Z, Z/Z = 95:3:2[d] **7**	90[e]
13	Hex-vinyl-MgBr, Z/E = 92:8	Hex-diene, Z/Z, Z/E, E/E = 90:8:2[d] **13**	92[f]
14	Bu—≡—MgCl	Bu—≡—≡—Bu **14**	91
15	Ph—≡—MgCl	Ph—≡—≡—Ph **15**	89
16	t-BuCOO—≡—MgCl	t-BuCOO—≡—≡—OOCBu-t **16**	82[e]
17	morpholino—≡—MgCl	morpholino—≡—≡—morpholino **17**	85
18	Ph-vinyl-MgCl	Ph—Ph **18**	80[g]

[a] The reaction was carried out on a 20 mmol scale. [b] Isolated yield. [c] The reaction was performed at −20 °C. [d] The stereoselectivity was determined by GC. [e] The reaction was performed at 10 °C. [f] The reaction was performed at −40 °C. [g] 15% of catalyst was used.

Scheme 2. Preparation of *N*-Methylcrinasiadine
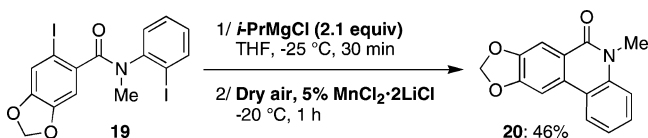
cyclization was then achieved under the coupling conditions previously reported. The *N*-methylcrinasiadine **20** was isolated in 46% yield.

A tentative mechanism is depicted in Scheme 3 for the Mn-catalyzed reaction.[8] The key step of this catalytic cycle is the conversion of the stable diorganomanganese(II) **1** to a manganese-(IV) peroxo complex **2**. This one would undergo a rapid reductive elimination to give the homocoupling product and a manganese-(II) peroxo complex **3** which would react with the Grignard reagent to give again the organomanganese **1**. With manganese and iron, the formation of peroxo complexes as catalytic intermediates is very well established for various manganese- and iron-catalyzed oxida-

Scheme 3. Tentative Mechanism for the Mn-Catalyzed Reaction
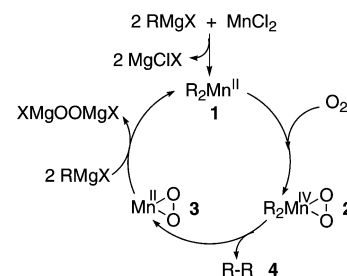
tion reactions.[9] Recently, such a complex has also been proposed as an intermediate in the palladium-catalyzed homocoupling of organoboranes.[10] It should be underlined that, in the case of the present reaction, it is necessary to have a very rapid catalytic process to avoid the direct oxidation of the Grignard reagent by oxygen. For this reason, the reductive elimination from a R₂Mn(II) species such as **1** cannot be involved since diaryl-, dialkenyl-, and dialkynylmanganese(II) compounds are generally stable at room temperature.[8,11] In fact, the best way to favor the reductive elimination is to increase the oxidation state of the metal. Thus, it is very reasonable to think that the formation of the unstable Mn-(IV) species **2** is required to achieve a very quick reductive elimination that gives **4**.[11]

In conclusion, we have developed two very efficient iron- and manganese-catalyzed procedures to couple aryl, alkenyl, and alkynyl Grignard reagents under mild conditions by using atmospheric oxygen as an oxidant. It should be noted that the reactions are chemo- and stereoselective. To the best of our knowledge, it is the first time that air has been used as an oxidant to perform such reactions with Grignard reagents. Sustainable development is now a real challenge for the chemical industry, and these economic and eco-friendly procedures constitute an interesting contribution in this field.

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