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Cross-Coupling

Manganese-Catalyzed Oxidative Cross-Coupling of Grignard Reagents with Oxygen as an Oxidant**

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Until now, only rare examples of oxidative cross-coupling reactions have been described.[1–4] Lipshutz et al.[1] and, more recently, Knochel et al.[2] showed that, at low temperature, oxidation of mixed organocuprates RR′CuLi gives the heterocoupling product R–R′ in good yield. Both reactions use a stoichiometric amount of copper. Two metal-catalyzed procedures were also reported. Lei et al.[3] coupled an alkyl zinc with an alkynyl stannane under palladium catalysis by using desyl chloride as an oxidant. Lately, we have described iron-catalyzed oxidative heterocoupling between aryl and alkyl zinc compounds by using 1,2-dibromoethane as oxidant.[4] Moreover, some interesting results involving C–H activation were recently described.[5]

In the framework of our research program to develop new iron-,[6] manganese-,[7] and cobalt-catalyzed[8] coupling procedures, we recently reported a very efficient manganese-catalyzed homocoupling reaction of Grignard reagents using atmospheric oxygen as an oxidant.[9] We noted that the reaction rate closely depends on the nature of the organic group of RMgX. In the light of these observations, we thought that it would be possible to perform an oxidative heterocoupling reaction with a mixture of two Grignard reagents RMgX and R′MgX by choosing judiciously the nature of the R and R′ groups. We now disclose the first manganese-catalyzed oxidative heterocoupling reaction of Grignard reagents.

Treating an aryl Grignard reagent with air in the presence of manganese chloride readily forms a biaryl. As a rule, coupling is rapid, but the reaction rate is highly dependent on both steric[10] and electronic[11] factors. Thus, as shown in Scheme 1, electron-poor pentafluorophenylmagnesium chloride does not give the expected homocoupling product, while hindered mesitylmagnesium bromide gives only a trace.

$$\text{ArMgX} \xrightarrow[\text{O}_2\text{, THF, 0 °C, 1 h}]{\text{20 mol\% MnCl}_2\text{•2LiCl}} \text{Ar-Ar}$$

Ar= C_6F_5: 0%
Ar= mesityl: traces
Ar= *p*-anisyl: 95%

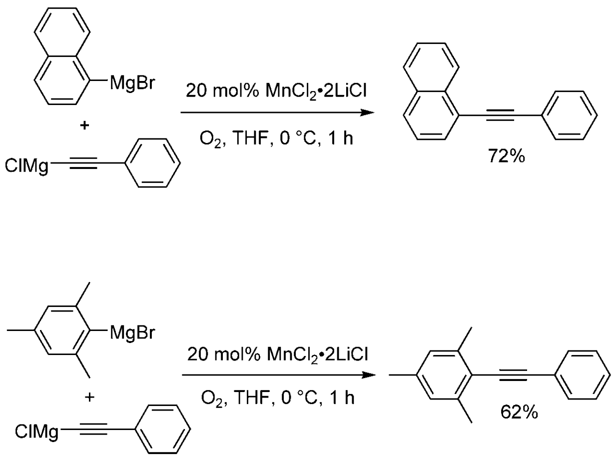
Scheme 1. Influence of electronic and steric factors on Mn-catalyzed homocoupling of aryl Grignard reagents.

Interestingly, in the case of mesitylmagnesium bromide, coupling is only prevented by steric effects, since *p*-anisylmagnesium bromide, which is less hindered, readily reacts under the same conditions (Scheme 1).

On the other hand, alkynyl magnesium halides easily couple in excellent yields under manganese catalysis. However, the reaction is less rapid than with aromatic Grignard reagents (*p*-anisylmagnesium bromide: 93% yield after 4–5 min; phenylethynylmagnesium chloride: 90% yield after 10 min). Clearly, such a difference is essentially due to electronic factors.

By considering the two examples above, we thought that it would be possible to disfavor the formation of the homocoupling products to the profit of the heterocoupling product by combining an electron-rich but sterically hindered aryl group with an alkynyl group that couples more slowly but is not bulky.

Preliminary experiments in which one equivalent of mesityl- or 1-naphthylmagnesium bromide was coupled with one equivalent of phenylethynylmagnesium chloride were consistent with our hypothesis (Scheme 2).



Scheme 2. Oxidative heterocoupling of aryl- and alkynyl Grignard reagents.

A tentative mechanism is presented in Scheme 3. The reaction of the two Grignard reagents **1** and **2** with manganese chloride can lead to a mixture of three organomanganese(II) compounds **3**, **4**, and **5** and then, after oxidation, to manganese(IV) species **6**, **7**, and **8**. The reductive elimination step mainly leads to cross-coupling product **10**, since the

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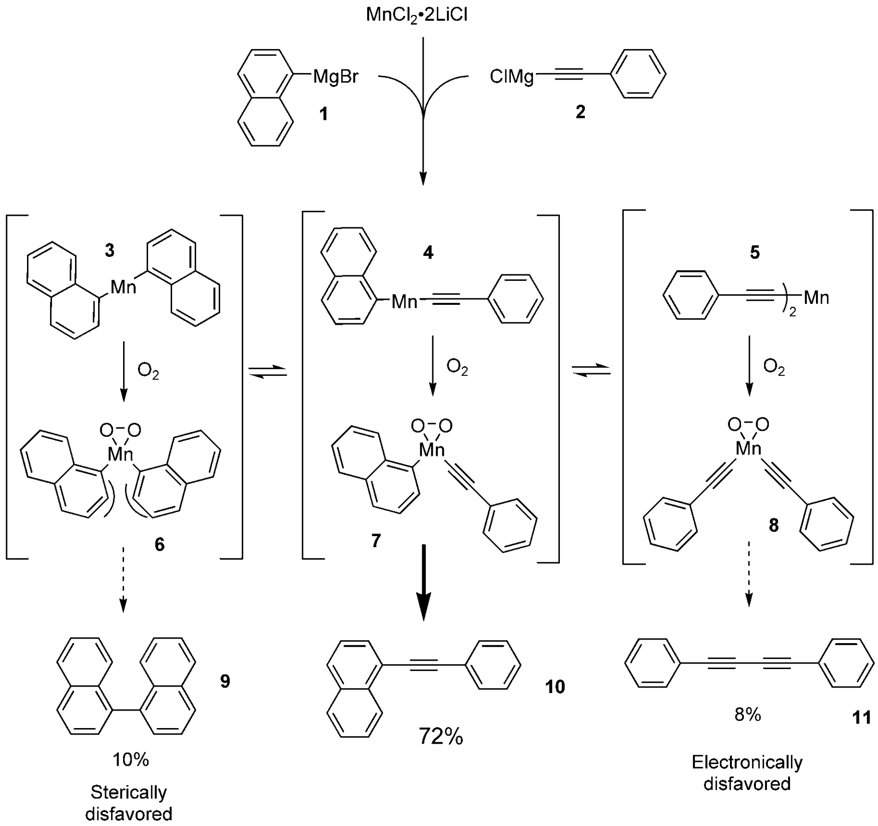


Scheme 3. Tentative mechanism for Mn-catalyzed oxidative heterocoupling.

formation of the homocoupling products is clearly disfavored for steric (**9**) or electronic reasons (**11**).

Next, we studied the reaction between Grignard reagents **2** and **12** (Figure 1). In this case, the steric factors are negligible and a statistical mixture (1:2:1) of the three coupling products **13**, **14**, and **15** was finally obtained. However, by monitoring the course of the reaction, we observed that aryl–aryl coupling clearly takes place first (Figure 1). Next, heterocoupling product **14** is formed more and more quickly as the concentration of the aromatic Grignard reagent **12** decreases. Finally, after 8–10 min, alkynyl–alkynyl coupling product **15** is obtained, since anisylmagnesium bromide **12** is completely consumed. The evolution of the reaction is fully compatible with the mechanism presented in Scheme 3.

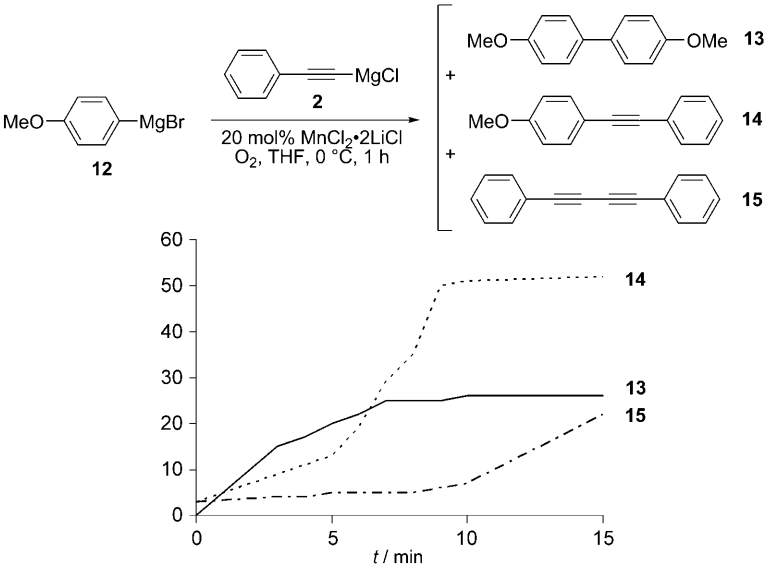


Figure 1. Manganese-catalyzed oxidative coupling of *p*-anisylmagnesium bromide and phenylethynylmagnesium chloride: Competition between homo- and heterocoupling reactions.[12]

Interestingly, we have shown that satisfactory yields of heterocoupling product **14** can be obtained by using an excess of either **2** (Table 1, entries 1–4) or **12** (Table 1, entries 1 and 5–7). By considering the final yield of **14** it seems that the influence of an excess of Grignard reagent **2** or **12** is very similar. However, in agreement with the above considerations, the course of the reaction is very different in the two cases.[13]

Under these conditions, we have prepared various aryl acetylenes in good yields (Table 2). Interestingly, functionalized aryl and alkynyl magnesium halides react successfully (Table 2, entries 4–8). The less expensive Grignard reagent was always used in excess (2.5 equiv). Note that the excess of Grignard reagent was not optimized for each example; for example, the yield of *o*-cyanodiphenylacetylene (Table 2, entry 6) only drops from 77 to 71 % by using 1.5 equiv of phenylethynylmagnesium chloride instead of 2.5 equiv.

The oxidative heterocoupling procedure was also used to synthesize biaryls (Table 3), which have numerous applications,[14] in satisfactory yields. Coupling is chemoselective, and various functionalized aryl Grignard reagents were used successfully (Table 3, entries 5–8).

The results presented in Tables 2 and 3 show that preferential formation of the heterocoupling product is not only due to a statistical effect. Indeed, when using 2.5 equiv of R^2MgX, the statistical R^1R^2/R^1R^1 ratio should be about 70/30. In fact, in most cases, the reaction takes place selectively, since the ratio is significantly higher. In accordance with the above discussion, the selectivity is very dependent on the nature of the R^1 and R^2 groups.

The procedure was extended to alkynyl–alkynyl, alkenyl–alkynyl (Scheme 4), and alkenyl–alkenyl coupling (Scheme 5). 4-Pivaloy-

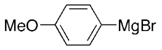
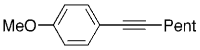
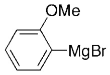
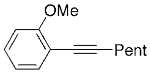
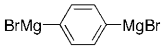
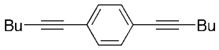
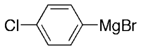
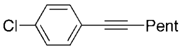
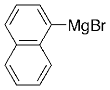
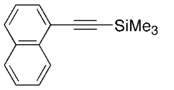
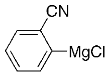
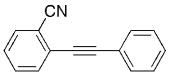
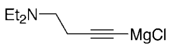
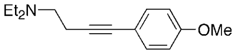
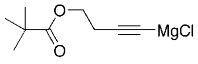
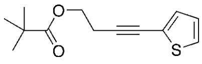
Table 1: Influence of an excess of Grignard reagent **2** or **12** on the yield of heterocoupling product **14**.[a]

Entry	Equiv of **2**	Equiv of **12**	Yield of **14** [%][b]
1	1	1	52
2	2	1	65[c]
3	2.5	1	74[c]
4	3	1	77[c]
5	1	2	63[d]
6	1	2.5	74[d]
7	1	3	77[d]

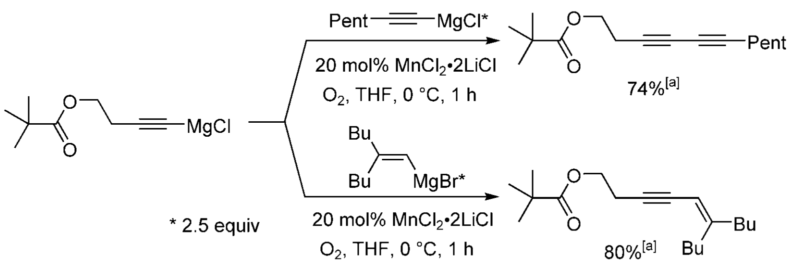
[a] The reactions were performed on a 5 mmol scale. [b] Yield was determined by GC with pentadecane as internal standard. [c] **12** is the limiting reagent. [d] **2** is the limiting reagent.

Table 2: Manganese-catalyzed oxidative cross-coupling of aryl- and alkynyl Grignard reagents.[a]

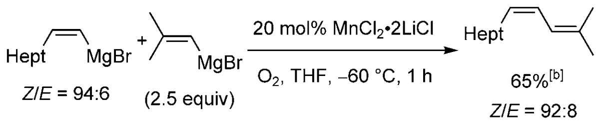
$$R^1MgX + \underset{(2.5\ \text{equiv})}{R^2MgX} \xrightarrow[\text{O}_2,\ \text{THF},\ 0\ ^\circ\text{C},\ 1\ \text{h}]{20\ \text{mol\%}\ \text{MnCl}_2\cdot 2\text{LiCl}} R^1\text{—}R^2$$

	R^1MgX	Coupling product	Yield [%][b,c]	Yield R^1R^1 [%][b,c]	R^1R^2/ R^1R^1
1			72	17	80.9/ 19.1
2			74	16	82.2/ 17.8
3			74[d]	10	88.1/ 11.9
4			81	12	87.1/ 12.9
5			89	5	94.7/ 5.3
6			77[e]	7	91.6/ 8.4
7			78	6	92.8/ 7.2
8			68	10	87.2/ 12.8

[a] The reactions were performed on a 5 mmol scale. [b] Yield of isolated product (limiting reagent: R^1MgX). [c] Yields of R^2R^2 range from 60 to 70% (limiting reagent: R^2MgX). See Table S1 in the Supporting Information. [d] 5 equiv of alkynyl magnesium reagent were used to perform the reaction. [e] Br/Mg exchange was performed with *i*PrMgCl·LiCl.



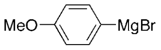
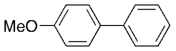
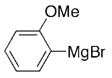
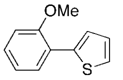
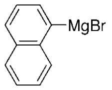
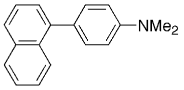
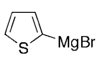
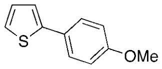
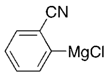
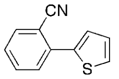
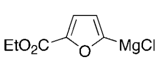
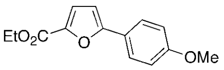
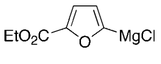
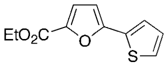
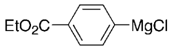
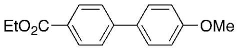
Scheme 4. Preparation of conjugated diynes and enynes by Mn-catalyzed oxidative heterocoupling reaction. [a] For selectivity, see Table S1 in the Supporting Information.



Scheme 5. Preparation of conjugated dienes by Mn-catalyzed oxidative heterocoupling.[a] [a] For the stereoselective preparation of (*Z*)-1-nonenylmagnesium bromide, see Supporting Information. [b] For selectivity, see Table S1 in the Supporting Information.

Table 3: Manganese-catalyzed oxidative cross-coupling of aryl Grignard reagents.[a]

$$Ar^1MgX + \underset{(2.5\ \text{equiv})}{Ar^2MgX} \xrightarrow[\text{O}_2,\ \text{THF},\ 0\ ^\circ\text{C},\ 1\ \text{h}]{20\ \text{mol\%}\ \text{MnCl}_2\cdot 2\text{LiCl}} Ar^1\text{—}Ar^2$$

	Ar^1MgX	Coupling product	Yield [%][b,c]	Yield Ar^1Ar^1 [%][b,c]	Ar^1Ar^2/ Ar^1Ar^1
1			80	12	87.0/ 13.0
2			76	13	85.4/ 14.6
3			68	6	91.9/ 8.1
4			65	20	76.5/ 23.5
5			81[d]	8	91.0/ 9.0
6			59[e,f]	10	85.5/ 14.5
7			69[e,f]	7	90.8/ 9.2
8			63[g]	15	80.8/ 19.2

[a] Reactions were performed on a 5 mmol scale. [b] Yield of isolated product (limiting reagent: Ar^1MgX). [c] Yields of R^2R^2 range from 60 to 70% (limiting reagent: Ar^2MgX). See Table S1 in the Supporting Information. [d] Br/Mg exchange was performed with *i*PrMgCl·LiCl. [e] The reaction was carried out at −20 °C. [f] Br/Mg exchange was performed with *i*PrMgCl. [g] I/Mg exchange was performed with $Et_2CHMgCl$.

loxy-1-butynylmagnesium chloride can be coupled chemoselectively (Scheme 4). The reaction is also highly stereoselective: (*Z*)-1-nonenylmagnesium bromide was coupled with a good retention of configuration (Scheme 5).

In conclusion, we have reported a new general procedure for the manganese-catalyzed oxidative cross-coupling of alkynyl, alkenyl, and aryl magnesium halides. To the best of our knowledge, it is the first metal-catalyzed procedure for coupling two Grignard reagents. The selectivity between hetero- and homocoupling reactions is highly dependent on the nature of the two Grignard reagents. In many cases, the outcome of the reaction is not statistical and it is possible to obtain preferentially the heterocoupling product. Alkenyl Grignard reagents couple stereoselectively, and the presence of various functional groups (ester, nitrile, etc.) is tolerated. The reaction readily takes place under mild conditions (0 °C, 1 h). The results described above pave the way to new applications of MnCl$_2$/O$_2$ as a cheap and environmental friendly catalytic system.

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Keywords: cross-coupling · Grignard reagents · manganese · oxidation · synthetic methods

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