OL Organic Letters

Letter

Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Iron-Catalyzed Cross-Coupling of Functionalized Benzylmanganese Halides with Alkenyl Iodides, Bromides, and Triflates

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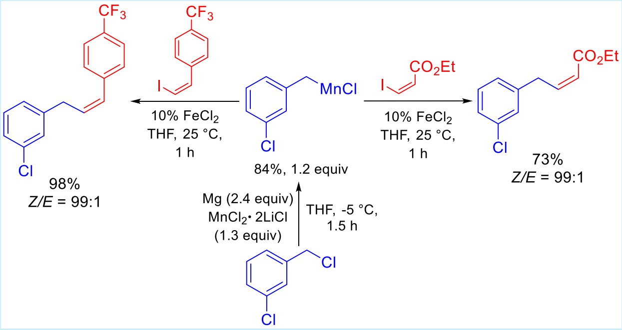
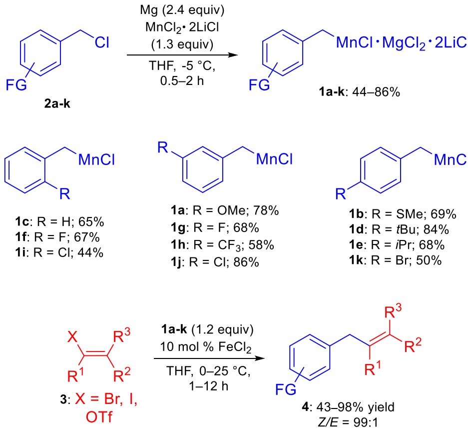
Supporting Information

ABSTRACT: Various substituted benzylic manganese chlorides were prepared by insertion of magnesium turnings in the presence of $MnCl_2 \cdot 2LiCl$ in THF at −5 °C within 2 h. These benzylic manganese reagents underwent smooth cross-couplings with various functionalized alkenyl iodides, bromides, and triflates or iodoacrylates in the presence of 10 mol % $FeCl_2$ at 25 °C for 1−12 h. Mechanistic studies showed that benzylic manganese halides produced, in the presence of $FeCl_2$, a very reactive iron *ate* complex.



Transition-metal catalyzed cross-couplings are essential for forming C−C bonds with unsaturated electrophiles.[1] Although palladium- and nickel-catalyzed cross-couplings[2] are the most versatile, tolerating various functionalities on both electrophiles and nucleophiles, these metals have drawbacks including acute toxicity for nickel[3] and high prices in the case of palladium.[4] Alternative metal catalyses based on copper,[5] iron[6] and cobalt[7] have been developed. As organometallic reaction partners, organomagnesium[8] and organozinc[9] reagents have mainly been used.[10]

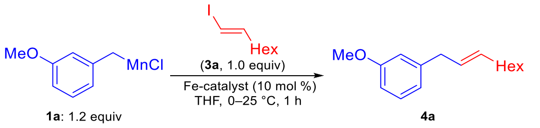
Scheme 1. Preparation of Benzylic Manganese Reagents[a] by *in Situ* Transmetalation Followed by Iron-Catalyzed Cross-Couplings with Alkenyl Iodides, Bromides, and Triflates



[a]For clarity, the magnesium salt has been omitted. Yields were determined by titration against iodine in THF.

Organomanganese reagents pioneered by Cahiez have proven to be excellent nucleophiles in various cross-coupling reactions, including those catalyzed by iron salts.[11] However, these reactions required the use of *N*-methylpyrrolidinone (NMP)[12,13] and displayed limited functional group tolerance.

Table 1. Catalyst Screening of the Reaction between the Benzylic Manganese Chloride 1a[a] and (*E*)-1-Iodooctene (3a)

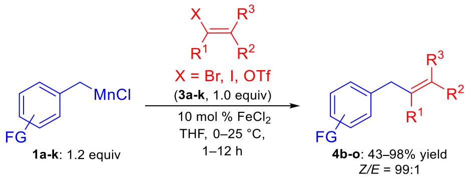


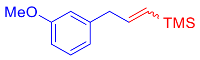
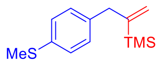
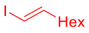
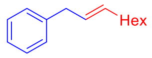
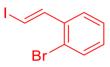
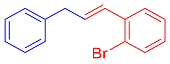
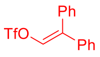
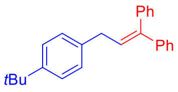
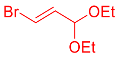
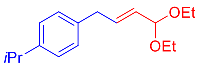
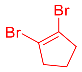
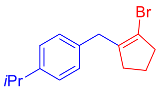
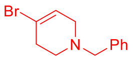
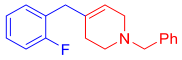
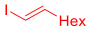
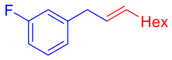
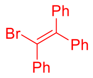
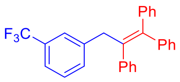
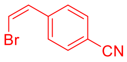
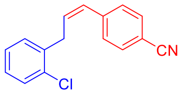
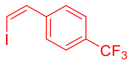
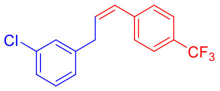
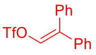
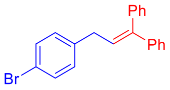
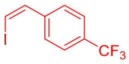
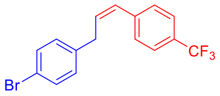
entry	catalyst (10 mol %)	yield (%)[b]
1	none	65
2	$FeBr_2$	63
3	$Fe(acac)_2$	75
4	$Fe(acac)_3$	74
5	$FeBr_3$	80
6	$FeCl_3$	96
7	$FeCl_2$ (99.5% purity)	97
8	$FeCl_2$ (99.99% purity)	98

[a]For clarity, the magnesium salt has been omitted. [b]Yield of analytically pure product.

Received: September 17, 2019

Table 2. Iron-Catalyzed Cross-Couplings of Benzylmanganese Reagents (1a–k)[a] with Alkenyl Iodides, Bromides, and Triflates (3a–k)[b]



entry	benzylic manganese reagent	electrophile	yield (%)^c
1	**1a**	 **3b**: *Z*/*E* = 10:90	 **4b**: 92 (0)^d *Z*/*E* = 6:94
2	**1b**	 **3c**	 **4c**: 92 (0)^d
3	**1c**	 **3a**: *Z*/*E* = 1:99	 **4d**: 77 (7)^d *Z*/*E* = 1:99
4	**1c**	 **3d**: *Z*/*E* = 1:99	 **4e**: 87 (52)^d *Z*/*E* = 1:99
5	**1d**	 **3e**	 **4f**: 95 (74)^d
6	**1e**	 **3f**: *Z*/*E* = 1:99	 **4g**: 79 (0)^d *Z*/*E* = 1:99
7^e	**1e**	 **3g**	 **4h**: 57 (8)^d
8	**1f**	 **3h**	 **4i**: 84 (0)^d
9	**1g**	 **3a**: *Z*/*E* = 1:99	 **4j**: 94 (0)^d *Z*/*E* = 1:99
10	**1h**	 **3i**	 **4k**: 87 (7)^d
11	**1i**	 **3j**: *Z*/*E* = 99:1	 **4l**: 98 (21)^d *Z*/*E* = 99:1
12	**1j**	 **3k**: *Z*/*E* = 99:1	 **4m**: 98 (58)^d *Z*/*E* = 99:1
13	**1k**	 **3e**	 **4n**: 43 (20)^d
14	**1k**	 **3k**: *Z*/*E* = 99:1	 **4o**: 53 (12)^d *Z*/*E* = 99:1

[a] For clarity, the magnesium salt has been omitted. [b] Reaction time: 1 h for iodides, 12 h for bromides and triflates. [c] Yield of analytically pure product. [d] In parentheses, yield obtained without catalyst. [e] For this reaction, 1.0 equiv of **1e** was used.

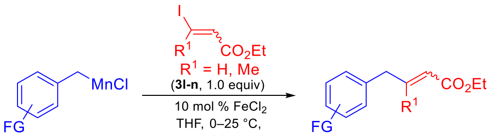
Because of the low price and low toxicity of these metals, such cross-couplings are attractive alternatives especially compared to organo-boronic esters which may have genotoxic properties.[14]

Recently, we have developed an effective preparation of functionalized benzylic manganese reagents of type **1** starting from benzylic chlorides of type **2**.[15] Herein, we report an iron-catalyzed cross-coupling of functionalized benzylic manganese reagents (**1**) with alkenyl iodides, bromides, and triflates of type **3** providing a range of polyfunctionalized alkenes of type **4** (Scheme 1).

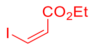
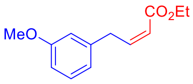
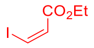
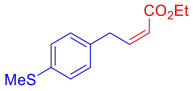
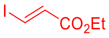
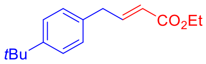
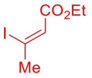
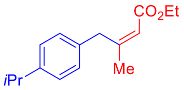
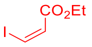
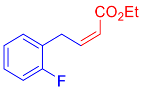
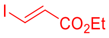
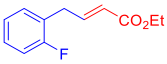
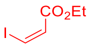
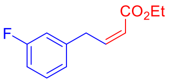
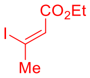
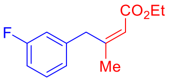
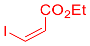
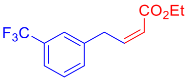
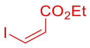
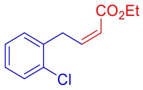
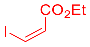
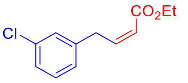
In preliminary experiments, we have prepared various benzylic organometallics derived from 3-methoxybenzyl chloride (**2a**). Thus, the benzylic manganese reagent **1a** was conveniently prepared by treating **2a** (1.0 equiv) in THF at −5 °C with magnesium turnings (2.4 equiv) and $MnCl_2{\cdot}2LiCl$ (1.3 equiv) for 1 h. Titration[16] with iodine led to a yield for **1a** of 78%. We also prepared the corresponding benzylic magnesium (**5**; 48% yield) and zinc (**6**; 42% yield) chlorides.[17]

In the absence of any iron catalyst, the cross-coupling of **1a** with (*E*)-1-iodooctene (**3a**; 25 °C, 1 h) produced the desired cross-coupling product **4a** in 65% yield (Table 1, entry 1). Under these conditions, **5** and **6** gave lower yields

Table 3. Iron-Catalyzed Cross-Couplings of Benzylmanganese Reagents (1a–b, d–j)[a] with Iodoacrylates (3l–n)



1a-b,d-j: 1.2 equiv
4p-4z: 50–98% yield
Z/E = 99:1

entry	benzylic manganese reagent	electrophile	yield (%)[b]
1	**1a**	 **3l**: *Z*/*E* = 99:1	 **4p:** 98 (73)[c] *Z*/*E* = 99:1
2	**1b**	 **3l**: *Z*/*E* = 99:1	 **4q:** 78 *Z*/*E* = 99:1
3	**1d**	 **3m**: *Z*/*E* = 1:99	 **4r:** 55 (44)[c] *Z*/*E* = 1:99
4	**1e**	 **3n**: *Z*/*E* = 99:1	 **4s:** 78, *Z*/*E* = 99:1 (60, *Z*/*E* = 44:56)[c]
5	**1f**	 **3l**: *Z*/*E* = 99:1	 **4t:** 97 *Z*/*E* = 99:1
6	**1f**	 **3m**: *Z*/*E* = 1:99	 **4u:** 66 (41)[c] *Z*/*E* = 1:99
7	**1g**	 **3l**: *Z*/*E* = 99:1	 **4v:** 71 *Z*/*E* = 99:1
8	**1g**	 **3n**: *Z*/*E* = 99:1	 **4w:** 69, *Z*/*E* = 99:1 (83, *Z*/*E* = 67:33)[c]
9	**1h**	 **3l**: *Z*/*E* = 99:1	 **4x:** 50 *Z*/*E* = 99:1
10	**1i**	 **3l**: *Z*/*E* = 99:1	 **4y:** 50 *Z*/*E* = 99:1
11	**1j**	 **3l**: *Z*/*E* = 99:1	 **4z:** 73 *Z*/*E* = 99:1

[a] For clarity reasons, the magnesium salt has been omitted. [b] Yield of analytically pure product. [c] In parentheses, yield obtained without catalyst.

(respectively, 47% and 14%). Although the cross-coupling performed with $FeBr_2$ gave a moderate yield of 63%, the use of $Fe(acac)_2$, $Fe(acac)_3$, or $FeBr_3$ afforded **4a** in 74–80% yield (entries 2–5). Using $FeCl_3$ proved to be even more effective, as the yield increased to 96% (entry 6). Our best result was obtained with $FeCl_2$ as catalyst, producing **4a** in 97% yield. Moreover, the use of 99.99% pure $FeCl_2$ similarly gave **4a** in 98% yield, showing that it is unlikely that metal impurities are responsible for this catalysis (entries 7–8).

We noticed that the reprotoxic cosolvent NMP[12,13] did not positively influence the reaction.[17] However, the amount of $FeCl_2$ could be reduced to 2.5 mol % without any significant yield decrease.[17] We also observed that the benzylic magnesium and zinc species (**5** and **6**) were less efficient reagents and reacted with **3a** in the presence of 10 mol % $FeCl_2$ (25 °C, 1 h) to give **4a** in 66–68% yield.

Furthermore, the cross-coupling of **1a** with (2-bromovinyl)-trimethylsilane (**3b**; *Z*/*E* = 10:90) gave the olefin **4b** in 92% yield with retention of stereochemistry (*Z*/*E* = 6:94) whereas the yield without iron salt was 0% (Table 2, entry 1). When the electron-rich 4-(methylthio)benzylmanganese chloride (**1b**) was mixed with (1-bromovinyl)trimethylsilane (**3c**), alkenylsilane **4c** was generated in 92% yield and no product was observed without iron catalyst (entry 2). Benzylmanganese chloride (**1c**) underwent smooth cross-couplings with **3a** and (*E*)-1-bromo-2-(2-iodovinyl)benzene (**3d**) to afford *E*-alkenes **4d** and **4e** in 77% and 87% yield. In comparison, 7% and 52% were obtained without catalyst (entries 3–4). Also, 4-(*tert*-butyl)benzylmanganese chloride (**1d**) reacted with 2,2-diphenylvinyl trifluoromethanesulfonate (**3e**) to give **4f** in 95% yield (entry 5). Very interestingly, 4-isopropylbenzylmanganese chloride (**1e**) reacted with the acid-sensitive (*E*)-1-

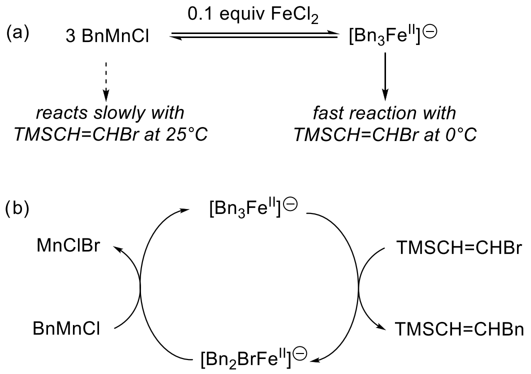


Figure 1. (a) Fast transmetalation equilibrium between BnMnCl and [Bn$_3$Fe^{II}]$^-$. (b) Proposed catalytic cycle for the benzyl-vinyl cross-coupling between BnMnCl and an aleknyl bromide under Fe-catalytic conditions.

bromo-3,3-diethoxyprop-1-ene (**3f**) and 1,2-dibromocyclopent-1-ene (**3g**, 1.0 equiv of **1e**) to provide the acetal **4g** (*Z*/*E* = 1:99) and the bromopentene derivative **4h** in 79% and 57% yield. The reaction without FeCl$_2$ gave almost no product (0–8%, entries 6–7). Electron-deficient fluorine-containing benzylmanganese reagents (**1f–1h**) also reacted with various cross-coupling partners (**3a,h–i**) producing **4i–k** in 84–94% yield (0–7% were obtained without FeCl$_2$, entries 8–10). The analogous chlorine-containing benzylmanganese species (**1i–j**) reacted with the functionalized alkenyl halides (*Z*)-4-(2-bromovinyl)benzonitrile (**3j**) and (*Z*)-1-(2-iodovinyl)-4-(trifluoromethyl)benzene (**3k**) to yield 98% of **4l** and **4m** (21% and 58% were obtained without any catalyst, entries 11–12). Finally, 4-bromobenzylmanganese chloride (**1k**) reacted with the alkenyl triflate **3e** and iodostyrene **3k**, producing the expected alkenes **4n** and **4o** in 43–53% yield (12–20% were obtained without FeCl$_2$, entries 13–14). Generally, we have observed that alkenyl bromides and electron-poor benzylmanganese reagents only gave traces of product in the absence of FeCl$_2$.

These benzylic manganese species also undergo cross-couplings with iodoacrylate derivatives (**3l–n**). Thus, the benzylic manganese chloride **1a** reacted with ethyl (*Z*)-3-iodoacrylate (**3l**) to provide the *Z*-acrylate **4p** in 98% yield (73% was obtained without catalysis). Under the same conditions, 4-(methylthio)benzylmanganese chloride (**1b**) afforded the acrylate **4q** in 78% yield (Table 3, entries 1–2). Moreover, 4-alkylated benzylic manganese chlorides **1d–e** respectively reacted with (*E*)-3-iodoacrylate (**3m**) and ethyl (*Z*)-3-iodobut-2-enoate (**3n**) to give the acrylates **4r** and **4s** in 55% and 78% yield, whereas the reactions without FeCl$_2$ gave a 44% and 60% yield (*Z*/*E* = 44:56, entries 3–4). Also, 2-fluorobenzylmanganese chloride (**1f**) reacted with both *Z* and *E* isomers of ethyl-3-iodoacrylate (**3l–m**) to yield the corresponding *Z* and *E* acrylates **4t** in 97% yield and **4u** in 66% yield (41% was obtained without catalysis, entries 5–6). The two other fluorine-containing benzylic manganese species **1g–h** also underwent smooth cross-couplings with **3l,n** to yield 50–71% of **4v–x** (**4w**: 83%, *Z*/*E* = 67:33 were obtained without FeCl$_2$; entries 7–9). The chloro-substituted benzylic manganese species **1i–j** were treated with **3l** and 10 mol % FeCl$_2$ to give the *Z*-acrylates **4y–z** in 50–73% yield (entries 10–11).[18]

Mechanistic investigations relying on low-temperature ^{1}H NMR monitoring of the reaction of benzylmanganese chloride (**1c**) and (2-bromovinyl)trimethylsilane (**3b**; *Z*/*E* = 10:90) were conducted in order to identify the catalytically active species in this benzyl-alkenyl cross-coupling reaction.[17] It was first shown that a Mn-to-Fe transmetalation of three benzyl groups per mole of iron takes place rapidly, affording the high-spin species (S = 2) [Bn$_3$Fe^{II}]$^-$, which has already been characterized by Bedford (Figure S1).[19] It was then shown that [Bn$_3$Fe^{II}]$^-$ quickly reacted with **3b** at 0 °C (with full consumption of the former in less than 10 min), whereas the reaction of BnMnCl with the electrophile proved to be much slower (Figure S2). This study then demonstrates that no reduction at a lower iron oxidation state is required to ensure a catalytic activity for this benzyl-alkenyl coupling system. Therefore, we suggest the following catalytic cycle that echoes the recent result reported by Neidig,[13] who demonstrated that the *ate* [Me$_3$Fe^{II}]$^-$ anion proved to be reactive in cross-coupling conditions with bromostyrene derivatives (Figure 1).

From a mechanistic standpoint, the nature of the activation of the C–Br bond of the electrophile remains so far unknown, as several scenarios could take place. One-electron reduction processes could occur between [Bn$_3$Fe^{II}]$^-$ and **3b**, leading to a coupling step relying on a Fe^{II}/Fe^{III} cycle with in-cage recombination of radical species, as it was suggested for the cross-coupling between various Grignard reagents and alkyl electrophiles.[20] On the other hand, formation of alkenyl C$_{sp^2}$ radicals is energetically more demanding than formation of alkyl radicals. This can open up the possibility of a cross-coupling mechanism relying on a two-electron oxidative addition of the electrophile onto the Fe^{II} species, leading to the formation of Fe^{IV} intermediates as suggested by Nakamura for the formation of biaryl systems.[21]

In summary, various electron-rich and electron-poor functionalized benzylic manganese species have been readily prepared from the corresponding benzylic chlorides by insertion of magnesium turnings in the presence of MnCl$_2$·2LiCl in THF at −5 °C within 2 h. These benzylic manganese reagents underwent smooth cross-couplings with various functionalized alkenyl iodides, bromides, and triflates or iodoacrylates in the presence of 10 mol % FeCl$_2$ at 25 °C for 1–12 h. Moreover, the reaction conditions enabled a good functional group tolerance. In particular, aryl halides are tolerated and can serve as a handle for further functionalization. Mechanistic studies showed that benzylic manganese halides produced, in the presence of FeCl$_2$, a very reactive iron(II) *ate* complex which promptly reacted with alkenyl halides. Further extensions and in-depth mechanistic studies of this activation step are currently in progress in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03292.

Full experimental details and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the CNRS, Chimie ParisTech (Paris) and LMU (Munich) in the framework of the International Associated Laboratory IrMaCar. We thank the DFG (SFB749) for financial support and Albemarle (Germany) and BASF (Ludwigshafen, Germany) for the generous gift of chemicals. G.L. also thanks the ANR research program (Project JCJC SIROCCO).

■ DEDICATION

This work is dedicated to the memory of Prof. Gérard Cahiez.

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