(58-80% yield)

Iron-Catalyzed Cross-Coupling of Benzylic Manganese Chlorides with Aryl and Heteroaryl Halides

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Received: 30.07.2015 Accepted after revision: 02.10.2015 Published online: 22.10.2015 DOI: 10.1055/s-0035-1560812; Art ID: st-2015-b0593-I

Abstract The use of FeCl₂ (10 mol%) allows a convenient iron-catalyzed cross-coupling reaction of benzylic manganese(II) chlorides with various aryl and heteroaryl chlorides, bromides and iodides leading to polyfunctionalized diaryl- and arylheteroarylmethane derivatives.

Key words manganese, iron, magnesium, benzylic organometallics, cross-coupling

Iron-catalyzed cross-coupling reactions are an important method for the formation of carbon-carbon bonds, as it allows to replace palladium or nickel catalysts by inexpensive iron salts.¹ The low toxicity and excellent catalytic activity of various iron complexes has been extensively investigated.^{2,3} The cross-coupling of benzylic organometallics with aryl and heteroaryl halides has attracted our attention since the resulting diarylmethane derivatives are present in many natural products and pharmacologically active compounds.⁴ Benzylic organometallics of Mg,⁵ In,⁶ Al,⁷ and Zn⁸ are readily available. The corresponding zinc reagents are especially attractive, since they are compatible with numerous functionalities and can be prepared in high yields.⁸ However, their moderate reactivity in iron-catalyzed crosscouplings led us to search for alternative benzylic organometallics. We have reported that benzylic manganese reagents can be prepared by the direct insertion of manganese metal into benzylic halides in the presence of InCl₃ and PbCl₂ (2.5 mol%).⁹ Recently, we have shown that the use of catalytic amounts of toxic lead salts can be avoided by treating various benzylic chlorides with magnesium turnings in the presence of MnCl₂·2LiCl at 0 °C in THF.¹⁰ The resulting benzylic manganese(II) chlorides react with various electrophiles such as enones, acid chlorides and allylic halides in the absence of any additional transition metal cata-



lyst.^{10,11} Since functionalized benzylic magnesium reagents are difficult to prepare and that benzylic zinc reagents do not readily transmetalate to iron, we envisioned that a metal with intermediate electronegativity, such as manganese, would be well suited for iron-catalyzed cross-couplings. Herein, we wish to report that these benzylic manganese(II) compounds undergo smooth iron-catalyzed cross-couplings with a variety of aryl and heteroaryl halides in good yields. Preliminary cross-coupling experiments of benzylmanganese chloride (**1a**), prepared from benzyl chloride (**2a**),¹⁰ with 4-iodoanisole (**3a**) show that neither an uncatalyzed nor a chromium(II) chloride¹² catalyzed reaction lead to a significant amount of coupling product **4** within 16 hours at 25 °C in THF (Table 1, entries 1 and 2).

The use of cobalt(II) salts,¹³ such as $CoCl_2$ and $Co(acac)_2$, gave better but still moderate yields (Table 1, entries 3 and 4). However, iron(II) and iron(III) salts displayed the best catalytic activity (Table 1, entries 5–10) and especially FeCl₂ (10 mol%) proved to be the most efficient catalyst (Table 1, entry 10).¹⁴

With these optimized conditions in hand, we studied the reaction scope of the cross-coupling between various benzylic manganese(II) chlorides (1a-f) with a broad range of aryl and heteroaryl halides. Thus, the benzylic manganese(II) reagent (1b) reacted with ethyl 5-bromofuran-2carboxylate (3b) at 0 °C within three hours leading to the desired product 5 in 70% yield (Scheme 1, eq. 1). Also the benzylic manganese(II) chloride (1c) underwent a smooth iron-catalyzed cross-coupling with ethyl 2-chloronicotinate (3c) affording the benzylated pyridine 6 within two hours in 65% yield (Scheme 1, eq. 2). However, under our conditions, standard aryl chlorides did not react.

The reaction conditions used for these cross-couplings could be extended to various other functionalized unsaturated halides. Thus, the cross-coupling of benzylmanga-

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 Table 1
 Screening of Catalysts for the Palladium-Free Cross-Coupling of Benzylic Manganese(II) Chloride (1a) with 4-Iodoanisole (3a)

la la	MnCl 3a catalyst (10 mol%) THF, 0-25 °C, 16 h	→ C OMe
Entry	Catalyst	Yield of 4 (%) ^a
1	no catalyst	0
2	CrCl ₂	0
3	Co(acac) ₂	32
4	CoCl ₂	36
5	Fe(OTf) ₃	50
6	FeBr ₃	53
7	Fe(acac) ₃	69
8	Fe(acac) ₂	72
9	FeBr ₂	77
10	FeCl ₂	84 (79) ^b

^a Determined by GC analysis with tetradecane as an internal standard. ^b Isolated yield of pure product.

nese(II) chloride (**1a**) with 4-bromobenzonitrile (**7a**) and ethyl 4-iodobenzoate (**7b**) proceeded within three hours at 25 °C and furnished the corresponding products **8a** and **8b** in 75% and 76% yield, respectively (Table 2, entries 1 and 2). Using an aryl bromide bearing moderately electron-donating substituents, such as 5-bromo-1,2,3-trimethoxybenzene (**7c**), led to the arene **8c** within 24 hours in 58% yield (Table 2, entry 3).¹⁵ Also 2-bromobenzophenone (**7d**) underwent the cross-coupling smoothly with the benzylman-



Scheme 1 First examples for iron-catalyzed cross-coupling reactions of the benzylic manganese(II) reagents 1b and 1c with heteroaryl halides 3b and 3c

ganese(II) chloride (1a) yielding the ketone 8d in 66% yield (Table 2, entry 4). Furthermore, 3-(trifluoromethyl)benzylmanganese(II) chloride (1c) reacted with 5-bromo-2-iodopyridine (7e) affording the substituted N-heterocycle 8e in 70% yield (Table 2, entry 5). Similarly, the functionalized benzylmanganese(II) reagents (1c and 1d) reacted with ketone 7d leading to the desired diarylmethane derivatives 8f and 8g in 75% and 80% yield, respectively (Table 2, entries 6 and 7). Additionally, the electron-rich 4-methoxybenzylmanganese(II) chloride (1d) cross-coupled with 1-iodo-4-(trifluoromethoxy)benzene (7f) giving 8h in 61% yield (Table 2, entry 8). The cross-couplings of the benzylmanganese(II) chloride (1e) with 2-bromobenzophenone (7d) or ethyl 3-iodobenzoate (7g) led to the desired products 8i and 8i in 79% and 79% vield, respectively (Table 2, entries 9 and 10). Finally, the reactions of 2-chlorobenzylmanganese(II) chloride (1f) with the ortho-substituted ester 7h and the functionalized pyridine **7i** proceeded within two hours at 0 °C affording the functionalized arenes 8k and 8l in 68% and 70% yield, respectively (Table 2, entries 11 and 12). These reactions display a remarkable functional group tolerance, since esters, nitriles and ketones are compatible with the mild reaction conditions of this Fe-catalyzed cross-coupling. Furthermore, very little amounts of homocoupling (<15%) of the benzylic manganese reagents were observed, allowing us to use almost stoichiometric ratios of reagents (1.1 equiv of benzylic manganese reagent was sufficient).

In summary, we have reported a convenient iron-catalyzed cross-coupling procedure of benzylic manganese(II) chlorides with a range of functionalized aryl and heteroaryl chlorides, bromides and iodides, producing polyfunctionalized diaryl- or arylheteroarylmethane derivatives.¹⁶ This method tolerates a range of functional groups, such as esters, nitriles or ketones and proceeds smoothly at room temperature within 2 to 24 hours. Further investigations towards the synthesis and applications of various benzylic organometallics are currently under way in our laboratories.

Acknowledgment

This work was supported by the CNRS and Chimie ParisTech (Paris, France), as well as by the Ludwig-Maximilians-University (Munich, Germany) in the framework of the International Associated Laboratory IrMaCaR between the research groups of P. Knochel and G. Cahiez. We also thank BASF SE (Ludwigshafen, Germany) and Rockwood Lithium GmbH (Hoechst, Germany) for the generous gift of chemicals.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560812.



$\ensuremath{\mathbb{C}}$ Georg Thieme Verlag Stuttgart \cdot New York — Synlett 2016, 27, 471–476

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Table 2 (continued)



^a Reaction conditions: 1.1 equiv of benzylic manganese reagent was used.

^b Isolated yield of pure product.

^c Less than 15% of homocoupling of the manganese reagent was observed.

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- (16) General Procedure for the Preparation of Benzylic Manganese(II) Chlorides (1a–f): A dry and argon-flushed Schlenk tube, equipped with a magnetic stirring bar and a rubber septum, was charged with magnesium (0.18 g, 7.20 mmol, 2.40 equiv), followed by freshly distilled THF (3.0 mL) or MTBE (1.9 mL) and a solution of MnCl₂·2LiCl (3.8 mL, 3.80 mmol, 1.25 equiv, 1.0 M in THF). The mixture was cooled to 0 °C, the benzyl chloride (3.0 mmol, 1.0 equiv) was added at once and maintained at 0 °C until complete conversion of the starting material was observed. The completion of the metalation was monitored by GC analysis of hydrolyzed and iodolyzed aliquots. When the

oxidative insertion was complete, the solution of benzylic manganese(II) chloride was separated from the resulting salts via a syringe equipped with a filter and transferred to another predried and argon-flushed Schlenk tube, before being titrated with iodine.

General Procedure for the Iron-Catalyzed Cross-Coupling of Benzylic Manganese(II) Chlorides 1a-f with Electrophiles: A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a rubber septum, was charged with FeCl₂ (10 mol%, 99.5% pure), the corresponding electrophile (1.0 equiv) and freshly distilled THF. Thereupon, the benzylic manganese(II) chloride solution (1.05-1.10 equiv) was added dropwise at 0 °C. After the addition was complete, the reaction mixture was stirred for a given time at the prior adjusted temperature and then allowed to warm to r.t. The reaction completion was monitored by GC analysis of the quenched aliquots. A saturated aqueous solution of NH4Cl was added and the aqueous layer was extracted three times with Et_2O or EtOAc (3 × 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification of the crude products by flash column chromatography afforded the desired products.

Ethyl 5-(3-Fluorobenzyl)furan-2-carboxylate (5): To a solution of FeCl₂ (12.7 mg, 0.10 mmol, 0.10 equiv) and ethyl 5-bromofuran-2-carboxylate (3b; 220 mg, 1.0 mmol, 1.0 equiv) in THF (1.0 mL) the benzylic manganese(II) chloride solution (1b, 4.0 mL, 0.26 M, 1.05mmol, 1.05 equiv) was added dropwise at 0 °C. Then, the reaction mixture was stirred for 2 h at 0 °C and allowed to warm to r.t. A saturated aqueous solution of NH₄Cl was added and the aqueous layer was extracted three times with Et_2O (3 × 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. Finally the crude product was purified by flash column chromatography (SiO₂, *i*-hexane-Et₂O, 99:1, R_f 0.11) leading to the desired product 5 (174 mg, 0.70 mmol, 70%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.20–7.24 (m, 1 H), 7.05 (d, J = 3.4 Hz, 1 H), 6.98 (dd, J = 8.0, 1.3 Hz, 1 H), 6.90 (m, 2 H), 6.06 (dt, J = 3.4, 0.8 Hz, 1 H), 4.31 (q, J = 7.1 Hz, 2 H), 3.99 (s, 2 H), 1.32 (t, I = 7.1 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 163.0$ (d, ¹ $I_{C-F} =$ 245 Hz), 158.9, 158.6, 144.1, 139.3 (d, ${}^{3}J_{C-F}$ = 7.0 Hz), 130.2 (d, ${}^{3}J_{C-F}$ = 8.0 Hz), 124.6 (d, ${}^{4}J_{C-F}$ = 3.0 Hz), 119.0, 115.9 (d, ${}^{2}J_{C-F}$ = 22 Hz), 113.9 (d, ${}^{2}I_{C-F}$ = 20 Hz), 109.2, 60.9, 34.5, 14.5. ${}^{19}F$ NMR (376 MHz, $CDCl_3$): $\delta = -113.0$. IR (ATR): 3128, 2983, 2361, 1713, 1616, 1591, 1519, 1488, 1448, 1383, 1368, 1297, 1251, 1205, 1173, 1126, 1075, 1016, 970, 944, 912, 866, 789, 760, 731, 681 cm⁻¹. MS (EI, 70 eV): *m*/*z* (%) = 249 (10), 248 (67), 220 (10), 219 (23), 203 (42), 176 (17), 175 (100), 147 (16), 146 (40), 127 (10). HRMS (EI, 70 eV): *m*/*z* calcd for C₁₄H₁₃FO₃: 248.0849; found: 248.0845

Ethyl 2-[3-(Trifluoromethyl)benzyl]nicotinate (6): To a solution of FeCl₂ (12.7 mg, 0.10 mmol) and ethyl 2-chloronicotinate (**3c**; 186 mg, 1.0 mmol, 1.0 equiv) in THF (1.0 mL) the benzylic manganese(II) chloride solution (**1c**, 3.3 mL, 0.34 M, 1.1 mmol, 1.1 equiv) was added dropwise at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and allowed to warm to r.t. A saturated aqueous solution of NH₄Cl was added and the aqueous layer was extracted three times with Et₂O (3 × 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (SiO₂, *i*-hexane–Et₂O, 8:2, *R*_f 0.17) afforded the desired product **6** (200 mg, 0.65 mmol, 65%) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃): δ = 8.62 (dd, *J* = 4.8, 1.8 Hz, 1 H), 8.13 (dd, *J* = 7.9, 1.8 Hz, 1 H), 7.49 (s, 1

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H), 7.40–7.17 (m, 4 H), 4.56 (s, 2 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.4, 160.4, 152.2, 140.7, 138.9, 132.6 (q, ${}^{4}J_{C-F}$ = 2.4 Hz), 130.6 (q, ${}^{2}J_{C-F}$ = 32 Hz), 128.7, 126.2, 125.9 (q, ${}^{3}J_{C-F}$ = 3.8 Hz), 124.4 (q, ${}^{1}J_{C-F}$ = 271 Hz), 123.1 (q, ${}^{3}J_{C-F}$ = 3.9 Hz), 121.7, 61.7, 42.2, 14.2. ¹⁹F NMR (376 MHz, CDCl₃): δ = -62.5. IR (ATR): 3049, 2985, 2363, 1720, 1583, 1570, 1448, 1438, 1368, 1328, 1300, 1259, 1190, 1161,

1118, 1094, 1073, 1057, 1017, 917, 862, 822, 793, 782, 747, 734, 701, 676, 660 cm⁻¹. MS (EI, 70 eV): m/z (%) = 310 (18), 309 (83), 308 (92), 290 (12), 281 (54), 264 (52), 263 (59), 262 (13), 237 (16), 236 (100), 235 (59), 234 (65), 216 (18), 167 (31), 139 (11). HRMS (EI, 70 eV): m/z calcd for C₁₆H₁₄F₃NO: 309.0977; found: 309.0966.