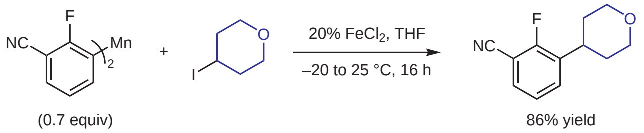
Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling Reactions of Di(hetero)arylmanganese Reagents and Primary and Secondary Alkyl Halides

Maximilian S. Hofmayer[a]
Jeffrey M. Hammann[a]
Gérard Cahiez[b]
Paul Knochel*[a]

[a] Department of Chemistry, Ludwig-Maximilians-Universität München, Butenandtstraße 5–13, Haus F, 81377 München, Germany
Paul.Knochel@cup.uni-muenchen.de
[b] Institut de Recherche de Chimie Paris, CNRS, Chimie ParisTech, 11 Rue Pierre et Marie Curie, 75005 Paris, France



20 examples
up to 88% yield

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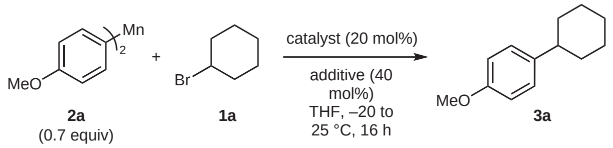
Abstract An iron-catalyzed cross-coupling between di(hetero)arylmanganese reagents and primary and secondary alkyl halides is reported. No rearrangement of secondary alkyl halides to unbranched products was observed in these C–C bond-forming reactions.

Key words iron, catalysis, cross-coupling, manganese, alkyl halides

Transition-metal-catalyzed cross-coupling reactions have found broad application, especially for the synthesis of agrochemicals and pharmaceuticals.[1] In the past, palladium and nickel complexes have frequently been used for such couplings. However, the high price[2] as well as toxicity issues[3] of these catalysts led to the search for alternative transition metals for cross-coupling reactions. Especially, iron is a cheap and environmentally benign alternative for C–C bond-forming reactions, due to its high abundance in the earth's crust. Pioneering work by Fürstner,[4] Cahiez,[5] as well as other research groups[6] demonstrated the high potential of iron salts as catalysts in coupling reactions. However, most of these reactions use magnesium organometallics as nucleophiles, which are not always the best choice due to their high nucleophilicity. In contrast, the use of organomanganese reagents enables performing coupling reactions under mild conditions.

Recently, we have demonstrated that cobalt(II) chloride is an excellent catalyst for the cross-coupling of diarylmanganese reagents with secondary alkyl halides.[7] However, some of these coupling reactions were not very efficient and gave only poor yields (Table 1, entry 1). Thus, the cross-coupling between cyclohexyl bromide (**1a**) and di(*p*-anisyl)manganese (**2a**, 0.7 equiv) using 20 mol% $CoCl_2$ gave the desired product **3a** in only 28% yield. In contrast, different iron salts proved to be more efficient and furnished **3a** in better yields (64–69%, Table 1, entries 2–4). $FeCl_2$ gave the best results. The addition of amine- (**L1, L2**), phosphine- (**L3, L4**), phenanthroline (**L5, L6**) and NHC ligands (**L7**), as well as isoquinoline (**L8**) and 4-fluorostyrene (**L9**), which were beneficial ligands in previous studies,[8] did not improve the reaction outcome (Table 1, entries 5–13). Remarkably, $CrCl_2$ and $NiBr_2$ were inefficient catalysts for this reaction (Table 1, entries 14 and 15). A solvent screening showed that THF led to the best reaction outcome compared to NMP, DME, 1,4-dioxane, and *t*BuOMe.[9] Thus, di(*p*-anisyl)manganese (**2a**) reacted in the presence of 20 mol% $FeCl_2$ in THF at –20 to 25 °C (16 h) to produce the substitution product **3a** in 69% yield (Table 1, entry 4).

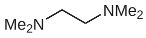
Table 1 Reaction Conditions Optimization of the Cross-Coupling of Bromocyclohexane (**1a**) with the Di(*p*-anisyl)manganese Reagent (**2a**)



Entry	Catalyst	Additive	Yield (%)[a]
1	$CoCl_2$	–	28
2	$Fe(acac)_2$	–	64
3	$Fe(acac)_3$	–	66
4	$FeCl_2$	–	69 (63[b])
5	$FeCl_2$	**L1**	64
6	$FeCl_2$	**L2**	56
7	$FeCl_2$	**L3**	66
8	$FeCl_2$	**L4**	62
9	$FeCl_2$	**L5**	62
10	$FeCl_2$	**L6**	63
11	$FeCl_2$	**L7**	58
12	$FeCl_2$	**L8**	56
13	$FeCl_2$	**L9**	54

Table 1 (continued)

Entry	Catalyst	Additive	Yield (%)[a]
14	$CrCl_2$	–	0
15	$NiBr_2$	–	5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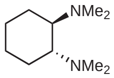
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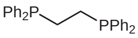
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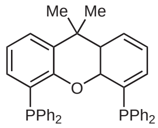
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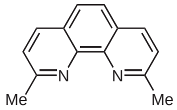
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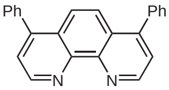
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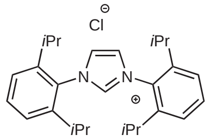
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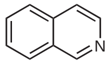
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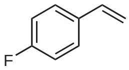
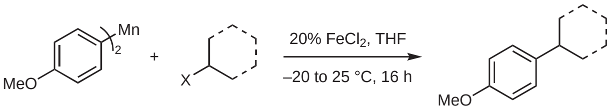

L9

[a] Calibrated GC yield using undecane as internal standard.
[b] Isolated yield.

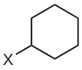
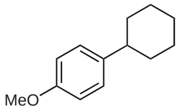
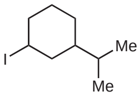
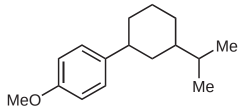
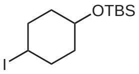
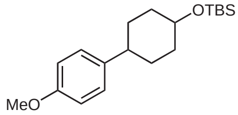
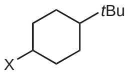
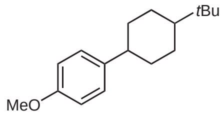
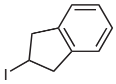
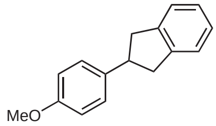
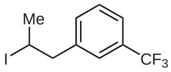
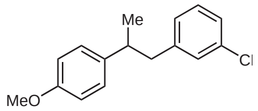
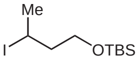
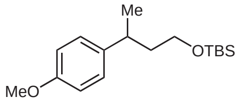
These optimized conditions proved to be general, and the cross-coupling of di(*p*-anisyl)manganese (**2a**) with various primary and secondary alkyl halides of type **1** were successfully performed (Table 2). Thus, a range of cycloalkyl halides were readily employed in this reaction. Cyclohexyl chloride (**1b**), bromide (**1a**), and iodide (**1c**) underwent the cross-coupling with **2a** to afford the desired product **3a** in 32–73% yield (Table 2, entry 1). The secondary bromides and iodides **1d–h** bearing an *i*Pr, OTBS, or a *t*Bu group were also tolerated, leading to the substitution products **3b–e** in 43–88% yield (Table 2, entries 2–5).

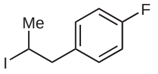
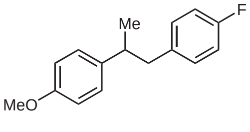
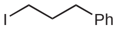
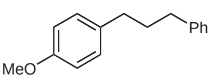
Furthermore, the functionalized acyclic secondary alkyl iodides **1i–k**, bearing a CF_3, OTBS, or a fluoro substituent, proved to be good substrates, affording the alkylated products **3f–h** in 44–58% yield (Table 2, entries 6–8). Interestingly, no rearrangement of branched secondary alkyl groups to the corresponding unbranched secondary alkyl moiety was observed. Additionally, the primary alkyl iodide (3-iodopropyl)benzene (**1l**) coupled smoothly, affording **3i** in 46% yield (Table 2, entry 9).

Table 2 Iron-Catalyzed Cross-Coupling Reactions between Various Alkyl Halides of Type **1** and the Diarylmanganese **2a** Producing Coupling Products of Type **3**



2a (0.7 equiv) **1** X = Br, I **3**

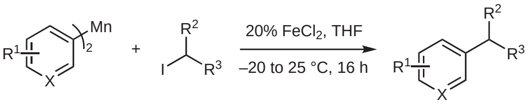
Entry	Electrophile	Product	Yield (%)
1	 **1a–c**	 **3a**	32[a] (**1b** X = Cl) 63 (**1a** X = Br) 73 (**1c** X = I)
2	 **1d**	 **3b**	51[b]
3	 **1e**	 **3c**	66[c]
4	 **1f–g** X = Br, I	 **3d**	43[d] (**1f** X = Br) 70[e] (**1g** X = I)
5	 **1h**	 **3e**	88
6	 **1i**	 **3f**	52
7	 **1j**	 **3g**	44

Entry	Electrophile	Product	Yield (%)
8	 **1k**	 **3h**	58
9	 **1l**	 **3i**	46

[a] Calibrated GC yield using undecane as internal standard.
[b] Electrophile: *cis*/*trans* ratio: 99:1; product: *cis*/*trans* ratio: 83:17.
[c] Electrophile: *cis*/*trans* ratio: 99:1; product: *cis*/*trans* ratio: 75:25.
[d] Electrophile: *cis*/*trans* ratio: 75:25; product: *cis*/*trans* ratio: 98:2.
[e] Electrophile: *cis*/*trans* ratio: 99:1; product: *cis*/*trans* ratio: 60:40.

Furthermore, a range of functionalized diarylmanganese reagents could also be used in this reaction (Table 3). $(p\text{-MOMO-C}_6\text{H}_4)_2\text{Mn}$ (**2b**) reacted smoothly with the alkyl iodides **1i** and **1m**, leading to the expected products **3j**,**k** in 46–62% yield (Table 3, entries 1 and 2). Interestingly, the diarylmanganese **2c** bearing an OBoc group was cross-coupled with **1h**, leading to the desired product **3l** in 56% yield (Table 3, entry 3). The coupling of the electron-poor diarylmanganese **2d**,**e** with the alkyl halides **1n**,**o** afforded the cross-coupling products **3m**–**o** in 48–78% yield (Table 3, entries 4–6). Also, the diarylmanganese **2f** was successfully coupled with the secondary alkyl iodide **1j**, to give the desired product **3p** in 80% yield (Table 3, entry 7). Additionally, heterocyclic diarylmanganese reagents were compatible under these conditions, leading to the expected heterocycles in good yields. Thus, the di(thiophene-3-yl)manganese (**2g**) coupled smoothly with **1p** or **1m** providing the arylated thiophenes in 82–87% yield (Table 3, entry 8). Moreover, diarylmanganese generated via directed manganation using $\text{TMP}_2\text{Mn}\cdot 2\text{MgCl}_2\cdot 4\text{LiCl}$[10] (0.7 equiv) could also be readily employed, leading to the corresponding products in 46–86% yield (Table 3, entries 9 and 10). For the coupling of the diarylmanganese **2h** an excellent diastereoselectivity in the coupling reaction was observed (dr = 99:1).

Table 3 Iron-Catalyzed Cross-Couplings of Various Diaryl- and Diheteroarylmanganese Reagents of Type **2** with Secondary Alkyl Iodides of Type **1** Leading to Products of Type **3**



2 (0.7 equiv)
X = C, N, S

1

3

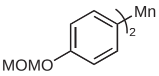
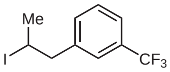
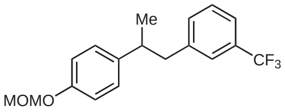
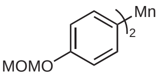
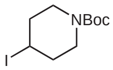
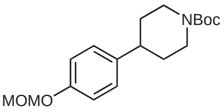
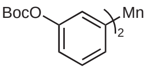
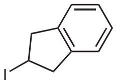
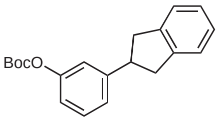
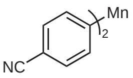
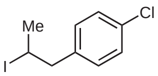
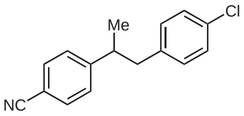
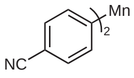
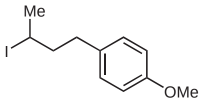
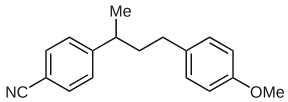
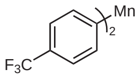
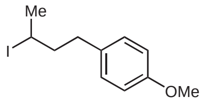
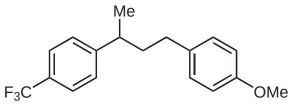
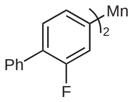
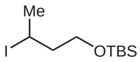
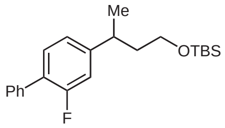
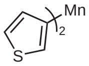
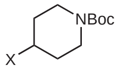
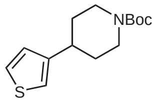
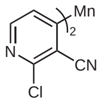
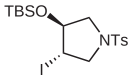
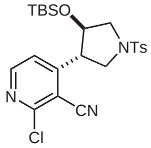
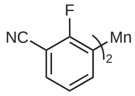
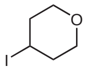
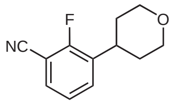
Entry	Manganese reagent	Electrophile	Product	Yield (%)
1	 **2b**	 **1i**	 **3j**	46
2	 **2b**	 **1m**	 **3k**	62
3	 **2c**	 **1h**	 **3l**	56
4	 **2d**	 **1n**	 **3m**	57

Table 3 (continued)

Entry	Manganese reagent	Electrophile	Product	Yield (%)
5	 **2d**	 **1o**	 **3n**	48
6	 **2e**	 **1o**	 **3o**	78
7	 **2f**	 **1j**	 **3p**	80
8	 **2g**	 **1p** X = Br, **1m** X = I	 **3q**	82 (using **1p**) 87 (using **1m**)
9	 **2h**	 **1q** dr = 99:1	 **3r**	46 dr = 99:1
10	 **2i**	 **1r**	 **3s**	86

In summary, we have developed an iron-catalyzed cross-coupling reaction of di(hetero)arylmanganese derivatives with secondary alkyl halides using $FeCl_2$ as a catalyst, which leads to the coupling products in up to 88% yield. High diastereoselectivities can be reached in these coupling reactions (dr up to 99:1). Remarkably, rearrangement of secondary alkyl halides to the corresponding unbranched products was not observed in these C–C forming reactions. Further investigations on this promising cross-coupling are currently under way in our laboratories.[11,12]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590891.

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(12) **Typical Procedure for the Iron-Catalyzed Cross-Coupling of Di(hetero)arylmanganese Reagents with Alkyl Halides**

A dry and argon-flushed 20 mL Schlenk tube, equipped with a stirring bar and a septum, was charged with anhydrous $FeCl_2$ (25 mg, 0.20 mmol, 20 mol%). The alkyl halide (1 mmol, 1.0 equiv) in THF (1 mL) was added, and the mixture was cooled to –20 °C. The di(hetero)arylmanganese reagent (0.7 mmol, 0.7 equiv) was added dropwise, and the mixture was allowed to warm to r.t. overnight. A sat. aq solution of NH_4Cl (5 mL) and EtOAc (5 mL) were added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and the solvents were evaporated. The residue was subjected to column chromatography purification (SiO_2; *i*-hexane/EtOAc) yielding the corresponding title compound.

1-(3-Isopropylcyclohexyl)-4-methoxybenzene (3b)

Following the typical procedure, **1d** (252 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with di(*p*-anisyl)manganese (**2a**, 0.7 mmol, 0.7 equiv) at –20 °C. The solution was allowed to warm to r.t., was stirred for 16 h, and was worked up as usual. The crude product was purified by column chromatography on silica using *i*-hexane/EtOAc (100:2) as an eluent to afford **3b** as a colorless oil (51%, 119 mg, 0.51 mmol, dr = 83:17). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.12 (m, 2 H), 6.90–6.83 (m, 2 H), 3.80 (s, 3 H), 2.48 (tt, *J* = 11.7, 3.4 Hz, 1 H), 1.95–1.81 (m, 3 H), 1.76 (dtt, *J* = 11.6, 3.4, 1.8 Hz, 1 H), 1.54–1.33 (m, 3 H), 1.33–1.21 (m, 2 H), 1.12 (dt, *J* = 12.8, 11.8 Hz, 1 H), 0.90 (dd, *J* = 6.8, 3.7 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.8, 140.5, 127.8, 113.8, 55.4, 44.6, 44.0, 38.4, 34.7, 33.2, 29.5, 27.0, 20.0, 19.9 ppm. FTIR (ATR): 2954, 2922, 2852, 1512, 1462, 1444, 1244, 1176, 1038, 824, 806 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 232 (55), 189 (78), 147 (100), 134 (68), 121 (77). HRMS (EI, 70 eV): *m/z* calcd for $[C_{16}H_{24}O]$: 232.1827; found: 232.1821.

***tert*-Butyl{3-[2-fluoro-(1,1′-biphenyl)-4-yl]butoxy}dimethylsilane (3p)**

Following the typical procedure, *tert*-butyl(3-iodobutoxy)dimethylsilane (**1j**, 314 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with **2f** (0.7 mmol, 0.7 equiv) at –20 °C. The solution was allowed to warm to r.t., was stirred for 16 h, and was worked up as usual. The crude product was purified by column chromatography on silica using *i*-hexane/EtOAc (100:4) as an eluent to afford **3p** as colorless oil (80%, 288 mg, 0.80 mmol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57–7.54 (m, 2 H), 7.46–7.42 (m, 2 H), 7.38–7.34 (m, 2 H), 7.05 (dd, *J* = 7.8, 1.7 Hz, 1 H), 7.00 (dd, *J* = 12.0, 1.7 Hz, 1 H), 3.59 (dt, *J* = 10.2, 6.2 Hz, 1 H), 3.52 (dt, *J* = 10.2, 6.7 Hz, 1 H), 2.95 (h, *J* = 7.1 Hz, 1 H), 1.82 (dt, *J* = 7.1, 6.3 Hz, 2 H), 1.29 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.03 (d, *J* = 1.5 Hz, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ =159.9 (d, *J* = 247.4 Hz), 149.3 (d, *J* = 6.7 Hz), 136.1, 130.6, 129.1, 128.5, 127.5, 126.5 (d, *J* = 13.4 Hz), 123.3, 114.7 (d, *J* = 22.6 Hz), 61.1, 41.1, 35.9, 26.1, 22.2, 18.4, –5.2 ppm. FTIR (ATR): 2956, 2928, 2856, 1484, 1472, 1462, 1418, 1254, 1098, 1076, 1010, 980, 900, 870, 832, 810, 774, 766, 724, 696 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 302 (22), 301 (100), 207 (22), 179 (77), 165 (35). HRMS (EI, 70 eV): *m*/*z* calcd for [$C_{21}H_{28}FOSi^+$]: 343.1888; found: 343.1872 [$M^+ - CH_3$].