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Cobalt-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides

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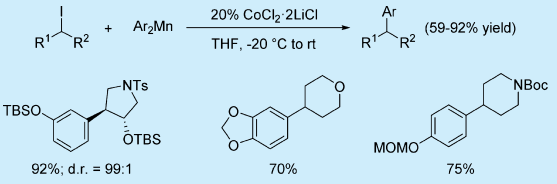
Supporting Information

ABSTRACT: A cobalt-catalyzed cross-coupling of diarylmanganese reagents with secondary alkyl iodides using the THF-soluble salt $CoCl_2$·2LiCl, which leads to the cross-coupling products in up to 92% yield, is reported. High diastereoselectivities can be reached in these cross-couplings (dr up to 99:1). Remarkably, rearrangement of secondary alkyl iodides to unbranched products was not observed in these C–C forming reactions.

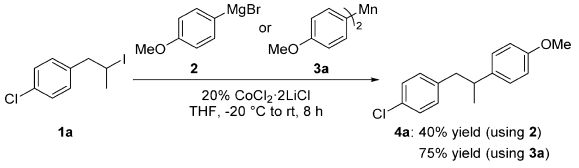


Palladium-catalyzed cross-couplings have widely been used.[1] However, cost[2] and toxicity[3] considerations led to the search of alternative transition metal catalysts for cross-coupling reactions. Especially cobalt-catalyzed transformations have shown their synthetic utility.[4] Pioneering work of Oshima,[5] Cahiez,[6] Gosmini,[7] and Cossy[8] demonstrated the broad field of applications of cobalt salt catalysis for forming new carbon–carbon bonds. Ackermann[9] and Yoshikai[10] also used cobalt complexes for direct C–H activation of various unsaturated systems. Recently, we have shown that cobalt halides are excellent catalysts for the cross-couplings between C(sp^3)–C(sp^2),[11] C(sp^3)–C(sp),[12] and C(sp^2)–C(sp^2)[13] centers using magnesium or zinc organometallics. However, these organometallic reagents are not always the best choice for performing C–C bond formations since homocouplings are often observed side-reactions.

Herein, we report a new cobalt-catalyzed cross-coupling between secondary alkyl iodides and diarylmanganese reagents catalyzed by $CoCl_2$·2LiCl and performed in the absence of any additional ligand. Thus, preliminary experiments have shown that the cross-coupling between the secondary alkyl iodide **1a** and *p*-anisylmagnesium bromide (**2**) proceeds in the presence of 20 mol% $CoCl_2$·2LiCl in THF at −20 to 25 °C (8 h) to produce the substitution product **4a** in only 40% yield due to extensive homocoupling side reactions.

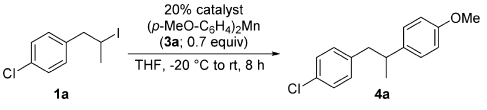
However, we found that by replacing **2** with the corresponding dianisylmanganese reagent (**3a**) prepared by the transmetalation of **2** with $MnCl_2$·2LiCl[14] (0.5 equiv), the same cross-coupling now produces **4a** in 75% isolated yield (Scheme 1). Remarkably, we did not observe rearrangement products (branched to unbranched) during these couplings.[15]

Scheme 1. Cobalt-Catalyzed Cross-Coupling Reactions of Various Metal Reagents with Alkyl Iodide 1a

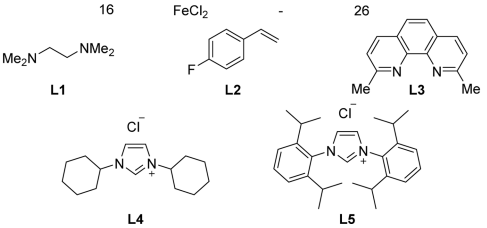


This encouraging result led us to examine the scope of this cross-coupling more extensively (Table 1). $CoCl_2$·2LiCl was the preferred catalyst since $Co(acac)_2$, $Co(acac)_3$, $CoBr_2$, and $CoCl_2$ gave inferior yields (entries 1–4). The use of 10% $CoCl_2$·2LiCl instead of 20% reduced the yield of **4a** to 64% (compare entries 5

Table 1. Reaction Condition Optimization of the Cross-Coupling of Alkyl Iodide 1a with the Manganese Reagent 3a



entry	catalyst	ligand[a]	yield (%)[b]
1	$Co(acac)_2$	-	54
2	$Co(acac)_3$	-	82
3	$CoBr_2$	-	73
4	$CoCl_2$	-	79
5	$CoCl_2$·2LiCl	-	83 (75)[c]
6	$CoCl_2$·2LiCl[d]	-	64
7	$CoCl_2$·2LiCl	L1	32
8	$CoCl_2$·2LiCl	L2	32
9	$CoCl_2$·2LiCl	L3	11
10	$CoCl_2$·2LiCl	L4	69
11	$CoCl_2$·2LiCl	L5	77
12	$PdCl_2$	-	2
13	$CuCl_2$	-	3
14	$CrCl_2$	-	3
15	$NiCl_2$	-	7
16	$FeCl_2$	-	26



[a]Using 40% of the ligand. [b]Calibrated GC-yield using undecane as internal standard. [c]Isolated yield. [d]Using 10% $CoCl_2$·2LiCl.

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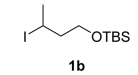
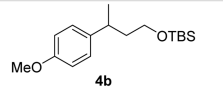
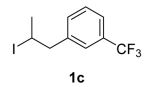
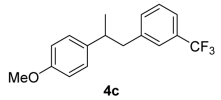
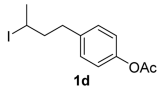
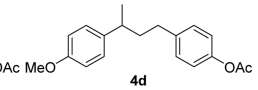
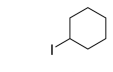
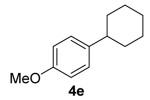
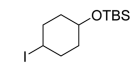
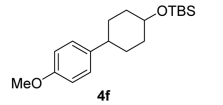
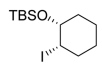
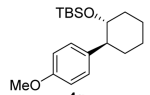
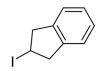
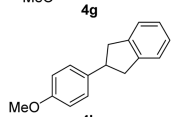
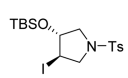
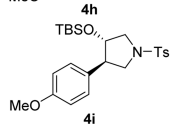
and 6). Attempts to improve the reaction by adding ligands such as TMEDA (**L1**),[16] 4-fluorostyrene (**L2**),[17] or neocuproine (**L3**)[12,18] did not improve the reaction yield (entries 7−9). Using NHC ligands **L4** or **L5** did not improve the reaction outcome (entries 10 and 11). Also alternative transition metal salts such as $PdCl_2$, $CuCl_2$, $CrCl_2$, $NiCl_2$, or $FeCl_2$ were inefficient (entries 12−16). A solvent screening showed that THF was the best solvent when compared to NMP, DMPU, DME, 1,4-dioxane, and *t*BuOMe.

These cobalt-catalyzed alkylations proved to be general, and the cross-coupling between the dianisylmanganese reagent (**3a**) and various secondary alkyl iodides has been successfully performed (Table 2).[19] Thus, various secondary alkyl iodides

Table 2. Cobalt-Catalyzed Cross-Coupling Reactions between Various Secondary Alkyl Iodides of Type 1 and the Diarylmanganese Reagent 3a

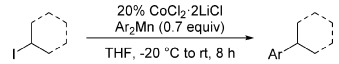
entry	electrophile	product	yield
1	 **1b**	 **4b**	73% (63%)[a]
2	 **1c**	 **4c**	77%
3	 **1d**	 **4d**	75%
4	 **1e**	 **4e**	84% (81%)[a]
5	 **1f**	 **4f**	75%[b]
6	 **1g**	 **4g**	83% dr = 99:1
7	 **1h**	 **4h**	70%
8	 **1i**	 **4i**	59% dr = 95:5

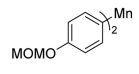
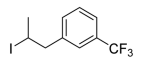
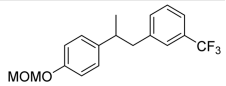
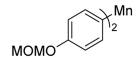
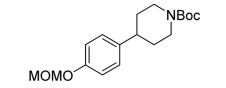
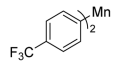
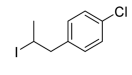
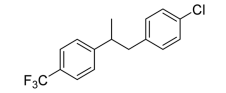
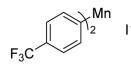
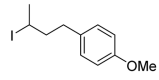
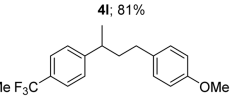
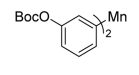
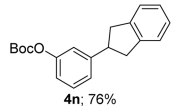
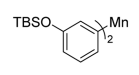
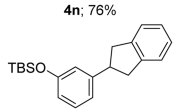
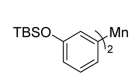
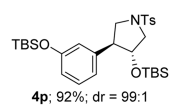
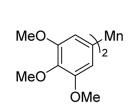
[a]20% $CoCl_2$ was used instead of $CoCl_2$·2LiCl. [b]dr ca. 70:30.

bearing a range of various functional groups (OTBS, CF_3, OAc; **1b−d**) reacted with the dianisylmanganese reagent (**3a**) providing the expected products **4b−d** in 73−77% yield (entries 1−3). Also, various cyclohexyl iodides underwent the cross-coupling with **3a** yielding the desired arylated products **4e−g** in 75−84% yield. Additionally, this cross-coupling can also be performed with cyclopentyl iodides **1h−i**, leading to the expected products **4h** and **4i** in 59−70% yield (entries 7 and 8). When a TBSO substituent was present in position 2 to the carbon-iodide bond, excellent diastereoselectivities were observed (dr up to 99:1, see entries 6 and 8).[20]

Furthermore, a range of functionalized diarylmanganese reagents could also be readily used in this reaction (Table 3). (p-MOMO-C_6H_4)$_2$Mn (**3b**) reacted smoothly with the alkyl

Table 3. Cobalt-Catalyzed Cross-Couplings of Diaryl Manganese Reagents of Type 3 with Secondary Alkyl Iodides of Type 1



entry	manganese reagent	substrate	product; yield
1	 **3b**	 **1c**	 **4j**; 76%
2	 **3b**	 **1j**	 **4k**; 75%
3	 **3c**	 **1a**	 **4l**; 81%
4	 **3c**	 **1k**	 **4m**; 87%
5	 **3d**	 **1h**	 **4n**; 76%
6	 **3e**	 **1h**	 **4o**; 74%
7	 **3e**	 **1i**	 **4p**; 92%; dr = 99:1
8	 **3f**	**1e**	**4q**; 80% (48%)[a]
9	**3f**	**1b**	**4r**; 60% (19%)[a]
10	**3g**	**1l**	**4s**; 66%
11	**3g**	**1m**	**4t**; 70%
12	**3h**	**1h**	**4u**; 63%
13	**3h**	**1i**	**4v**; 82%; dr = 99:1

[a]20% $CoCl_2$ was used instead of $CoCl_2$·2LiCl.

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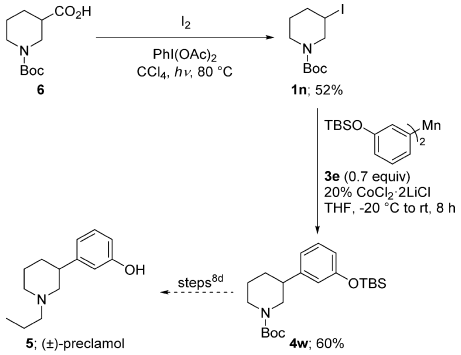
iodides **1c** and **1j**, leading to the arylated products **4j–k** in 75–76% yield (entries 1 and 2). The coupling of the electron-poor manganese reagent **3c** with **1a** or **1k** afforded the cross-coupling products **4l–m** in 81–87% yield (entries 3 and 4). Interestingly, the manganese reagents bearing an OBoc (**3d**) or an OTBS group (**3e**) were well tolerated, and the cross-coupling with **1h** and **1i** (dr = 99:1) led to the desired products **4n–p** in 74–92% yield (entries 5–7). Moreover, the electron-rich diarylmanganese reagent **3f** was readily coupled with the cyclic alkyl iodides **1e** and **1b** to provide the corresponding arylated products **4q–r** in 60–80% yield. The cross-coupling of **1l** or **1m** with the di(1,3-benzodioxol-5-yl) manganese reagent (**3g**) afforded the arylated compounds **4s–t** in 66–70% yield (entries 10 and 11). Also, the di(4-methoxy-3,5-dimethylphenyl)manganese reagent (**3h**) was successfully coupled with **1h** and **1i** (dr = 99:1), leading to the desired products **4u–v** in 63–82% yield (entries 12 and 13). For the diarylmanganese reagents **3e** and **3h** using the protected heterocyclic iodohydrine **1i** (dr = 99:1), we also observed excellent diastereoselectivities (dr = 99:1, see entries 7 and 13).

In order to demonstrate the synthetic utility of this method, we prepared the protected iodopiperidine **1n**, which is a key intermediate for the synthesis of (±)-preclamol (**5**). Thus, the commercially available carboxylic acid **6** was converted into the iodide **1n** according to the procedure of Boto and co-workers (Scheme 2).[8d,21] The cobalt-catalyzed cross-coupling with the

Scheme 2. Formal Synthesis of (±)-Preclamol (5)



diarylmanganese reagent **3e** furnished the desired product **4w** in 60% yield.

In summary, we have reported a new cobalt-catalyzed cross-coupling of polyfunctional diarylmanganese reagents with secondary alkyl iodides using the highly soluble cobalt salt $CoCl_2$·2LiCl in the absence of any additional ligand. Remarkably, no rearrangement of the secondary alkyl group is observed. Also, this cross-coupling was applied to the preparation of a key intermediate for the synthesis of (±)-preclamol. Further extension of this method as well as mechanistic studies are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03349.

Full experimental details; ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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