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Cobalt-Catalyzed *ortho*-Alkylation of Secondary Benzamide with Alkyl Chloride through Directed C−H Bond Activation

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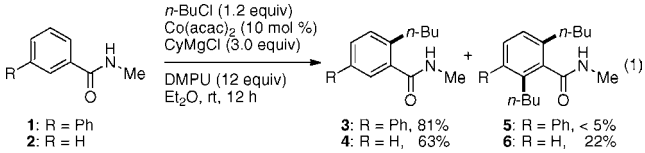
Abstract: Coupling of an alkyl chloride with a secondary benzamide derivative at the *ortho*-position can be achieved in good to excellent yield in the presence of a cobalt catalyst and cyclohexylmagnesium chloride in diethyl ether at room temperature. Cyclohexylmagnesium chloride formally acts to remove hydrogen atoms from the amide nitrogen and from the *ortho*-position and to generate the active cobalt species.

C−H bond activation of an aromatic compound leading to regioselective formation of an aryl−aryl bond has received considerable attention; however the corresponding alkyl−aryl bond formation has met only with limited success.[1] Furthermore, despite potential use in medicinal and materials research, C−H bond activation next to an amide group has been scarcely investigated,[2] and to the best of our knowledge the alkylation of simpe benzamide has not been reported.[3] The reported methods typically require precious metal catalysts and harsh reaction conditions, which led us to study iron catalysis,[4,5] especially C−H bond activation,[6] and now we disclose a new cobalt-catalyzed[7] C−H bond activation.[8,9] We report here that a cobalt-catalyzed coupling of a secondary benzamide with an alkyl chloride in the presence of cyclohexylmagnesium chloride (CyMgCl) takes place at room temperature to afford an *ortho*-alkylated benzamide in good to excellent yields.

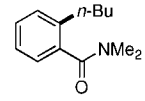
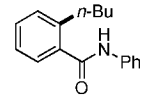
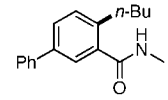
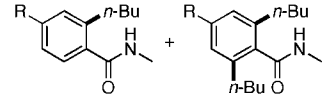
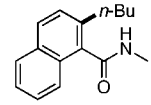
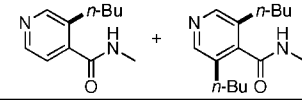
The butylation of *N*-methyl-3-phenylbenzamide (**1**) with *n*-BuCl shown in eq 1 is representative. **1** (0.50 mmol), $Co(acac)_2$ (10 mol %), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 12 equiv), and *n*-BuCl (1.2 equiv) were placed in a Schlenk tube, followed by dropwise addition of a diethyl ether solution of CyMgCl (2.0 mol/L, 0.75 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h and afforded selectively a 6-butylated product **3** in 81% isolated yield, accompanied by a dibutylated product **5** (<5%) as detected by ^{1}H NMR. Thus, the *meta*-phenyl group in **1** controlled the alkylation to selectively occur on the less hindered position. When an unsubstituted *N*-methylbenzamide **2** was used as a substrate, a monoalkylated product **4** and a dialkylated product **6** were isolated in 63% and 22% yield, respectively. Thus, the combined yield based on **2** was 85% and that based on *n*-BuCl was 89%.



The optimum conditions for the reaction of **2** with *n*-BuCl (1.2 equiv) call for the use of 3 equiv of CyMgCl, DMPU (12 equiv to **2**), and a catalytic amount of $Co(acac)_2$ (10 mol %) in diethyl ether at room temperature. A 2 equiv amount of CyMgCl is formally necessary to deprotonate the amide nitrogen and to remove the *ortho*-hydrogen atom,[10] and a slight excess of CyMgCl was used to reduce Co(II)[7] and also to compensate for side reactions such as homocoupling and β-hydride elimination. All reagents are mandatory for the success of the reaction. No conversion occurred in the absence of either CyMgCl or DMPU.[11] *n*-BuBr gave a much lower yield than *n*-BuCl (see Supporting Information). $Co(acac)_3$ and $CoCl_2$ performed as efficiently as $Co(acac)_2$, suggesting that they are converted into the same catalytic species under the reaction conditions. The reaction did not proceed at all in the absence of the cobalt catalyst. $Ni(acac)_2$ gave **4** in low yield, while $PdCl_2(PPh_3)_2$, $Cu(OTf)_2$, and $Fe(acac)_3$, among others, did not give any desired product and the starting material was mostly recovered.

Table 1 summarizes the scope of the aromatic substrates. A tertiary amide (entry 1) did not afford any alkylated products and

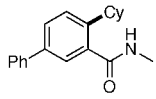
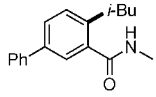
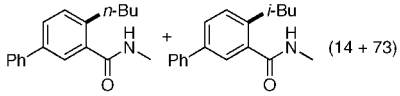
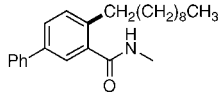
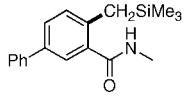
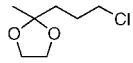
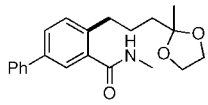
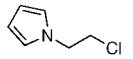
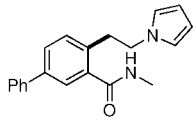
Table 1. Cobalt-Catalyzed *ortho*-Butylation of Benzamides and Congeners with Butyl Chloride[a]

entry	product	yield (%)[b]
1		0
2[c]		35
3		81
4		63 + 22 (R = H)
5[d]		(71 + 14) (R = H)
6		45 + 33 (R = OMe)
7[d]		< 5 + 88 (R = F)
8		64
9[d]		< 5 + 79

[a] The reaction was performed under the conditions shown in eq 1. See the Supporting Information for details. The newly formed C−C bond is shown in bold. [b] Isolated yield. The values in parentheses refer to the ^{1}H NMR yield. Most of the starting material was recovered when the yield was low. [c] 20 mol % of catalyst was used. [d] 2.5 equiv of *n*-BuCl, 4.0 equiv of cyclopentylmagnesium chloride, and 18 equiv of DMPU were used.

10.1021/ja1099853

Table 2. Cobalt-Catalyzed *ortho*-Alkylation of *N*-Methyl-3-Phenylbenzamide with Various Alkyl Chlorides[a]

entry	R–Cl	product	yield (%)[b]
1	CyCl		(15)
2	*t*-BuCl		83
3[c]	*n*-BuCl + *t*-BuCl		(14 + 73)
4	$CH_3(CH_2)_8CH_2Cl$		68
5	Me_3SiCH_2Cl		42
6			64
7[d]			59

[a] The reaction was performed under the conditions shown in eq 1. See the Supporting Information for details. The newly formed C−C bond is shown in bold. [b] Isolated yield. The values in parentheses refer to the ^{1}H NMR yield. [c] 1.2 equiv of each alkyl chloride was used. [d] 2.0 equiv of the alkyl chloride was used.

resulted largely in the recovery of the starting material, indicating that a deprotonated amide acts as a directing group. *N*-Phenylamide gave the butylated product in low yield (entry 2), together with the recovery of the starting material. The alkylation of the anilide ring[12] was not observed. The selective 6-butylation of the 3-phenyl substrate (*vide supra*, entry 3) suggests steric control. The reaction tolerates the presence of MeO and F groups (entries 6 and 7). In contrast to its R = H counterpart **2**, which predominantly gave the monobutylated product **4** (entries 4 and 5), 4-fluorobenzamide tends to give the dibutylated product, and the use of excess BuCl (2.5 equiv) and of cyclopentylmagnesium chloride (4.0 equiv) gave the dibutyl compound in 88% yield (entry 7). 1-Naphthylamide (entry 8) and *N*-methylisonicotinamide[2e] (entry 9) also serve as a substrate of this reaction. The latter selectively undergoes dibutylation reaction (entry 9), similarly to the 4-fluoro substrate.

Table 2 summarizes the scope of the alkylating reagent. The reactions gave a monoalkylated product accompanied by a trace or undetectable amount of the dialkylated product. The use of cyclohexyl chloride (in combination with CyMgCl) resulted largely in the recovery of the starting amide (entry 1). The reaction of *t*-BuCl gave an isobutylated product (entry 2) suggesting β-elimination rearrangement of a σ-cobalt intermediate[13] or intermediacy of a π-complex.[14] A competition experiment using an equimolar mixture of *n*-BuCl and *t*-BuCl (entry 3) gave predominantly the product from *t*-BuCl (i.e., the isobutylated product), suggesting a radical-like activation of the alkyl chloride. Alkyl chlorides bearing trimethylsilyl, acetal, and pyrrole groups (entries 5−7) smoothly took part in the reaction to give the desired compound, suggesting considerable synthetic potential for this method.

In summary, we have developed a cobalt-catalyzed directed activation of an *ortho* C−H bond of a secondary benzamide, which results in regioselective coupling with an alkyl chloride. This reaction represents a rare example of the cobalt-catalyzed introduction of a saturated hydrocarbon group directly to an aromatic group through C−H bond activation, especially to a benzamide substrate. An intricate reaction mechanism yet to be investigated allowed us to couple the benzamide and the primary alkyl chloride directly without preparing the corresponding alkyl anion separately.[15] The mild reaction conditions and the use of an inexpensive ligand, DMPU, are additional attractive features. Benzamide is a functional group of established importance, and the present alkylation method will be useful in various fields including medicinal and organoelectronics applications. Finally, this finding will contribute to the expansion of the repertoire of cobalt catalysis that has received considerable attention in recent years.[7]

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Supporting Information Available: Experimental procedures and data of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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