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Cobalt-Catalyzed Monoselective *Ortho*-C−H Functionalization of Carboxamides with Organoaluminum Reagent

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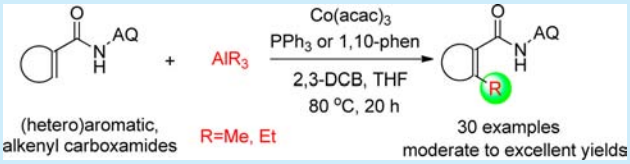
Supporting Information

ABSTRACT: A simple triphenylphosphine-ligated cobalt catalyst is reported for the direct *ortho*-C−H methylation and ethylation of aromatic, heteroaromatic, alkenyl, and even aliphatic carboxamides with inexpensive organoaluminum reagents in the presence of a cheap alkyl chloride as oxidant. This reaction shows monoselectivity in contrast with previously established C−H methylation methodologies.



There has recently emerged an intense interest in the synthetic community to use inexpensive and abundant first-row transition-metal catalysts to construct carbon−carbon bonds through direct C−H activation.[1] Among these metals, cobalt has been demonstrated as a powerful catalyst to complete such transformations[2,3] for alkylating a C−H bond with both alkyl organometallics[4] and alkyl electrophiles.[5] As pioneered by Nakamura and others, a cobalt catalyst can catalyze the *ortho*-alkylation of benzamide substrate with Grignard reagent in the presence of an oxidant.[4a,b] Considering their functional group compatibility, easy availability, and low cost, organoaluminum reagents such as trimethylaluminum can be considered as a suitable methyl donor for a C−H methylation reaction, as recently demonstrated by Nakamura et al. in iron-catalyzed C−H activation.[6] Because of the importance of C−H methylation affecting protein−ligand binding in drug discovery and pharmacology studies,[7] a call for C−H methylation methodology has recently garnered responses in the form of several methodologies by using Pd,[8] Ni,[9] Fe,[6,10] and Co[4a,11] as catalysts for the *ortho*-methylation of benzoic acid derivatives. Although developed, among these methods, for substrates possessing two accessible C−H bonds, a mixture of mono- and dimethylation products was always obtained, and monoselective C−H methylation of benzamides has not been well achieved.[6a]

To the best of our knowledge, the aluminum reagent has not been successfully applied as an alkyl donor in cobalt-catalyzed C−H functionalizations. Inspired by the recent work by Nakamura and co-workers,[6] we hypothesized that trimethylaluminum may act as a suitable methylating reagent in cobalt-catalyzed C−H methylations, and different selectivity is possibly achievable through the cooperation between cobalt and Lewis acidic aluminum and also by fine-tuning of the supporting ligand for cobalt.[12] In this work, we reported that a simple, inexpensive triphenylphosphine-ligated cobalt catalyst was able to catalyze the selective *ortho*-monomethylation of various arene, alkene, and even aliphatic carboxamides bearing an 8-aminoquinolynyl directing group[13] with trimethylaluminum in the presence of only 1.2 equiv of dichloroalkane as oxidant.[4c,14] Monomethylations were achieved with substrates possessing two accessible reaction sites tolerating various functional groups and heterocycles. Selective mono-C−H ethylation can also be achieved by using 1,10-phenanthroline as the supporting ligand to suppress undesired β-hydride elimination. This reaction provides an operationally simple and economic method to methylate and ethylate C−H bonds and is preferable, especially when monofunctionalization is required.

We commenced our experimentation by treating *N*-(quinolin-8-yl)benzamide **1a** with trimethylaluminum **2** in THF in the presence of 5 mol % of $Co(acac)_3$ and 1.2 equiv of DCB as oxidant (Table 1, entry 1). To our delight, we obained the desired monomethylation product in 39% isolated yield with monoselectivity. We considered that a ligand promotion effect as observed in similar types of iron catalysis may increase the yield of the desired product.[6] By screening various ligands (entries 2−8), we found the simplest triphenylphosphine acts as the most effective ligand for this reaction to give the desired product in 91% isolated yield. The electronic effect on the triarylphosphine ligand was studied, and the results showed that the electron-deficient ligand gave decreased yields (*p*-F, 79% compared with *p*-Me, 91%). Increasing the bulkiness of the phosphine ligand by increasing the cone angle[15] decreased the yield, demonstrating the sensitivity toward steric hindrance of this reaction ($P(o\text{-Me-Ph})_3$, PCy_3). Bipyridine (Bpy) and 1,10-phenanthroline (1,10-phen) were also suitable ligands for this reaction (entries 8 and 9). For the cobalt source, cobalt(III) showed better performance than Co(II), and $Co(acac)_3$ gave the best performance (entry 9 to entry 11). Dichloroalkane acted as a good oxidant for this reaction; among them, 2,3-dichlorobutane acted as the best oxidant (entries 13−16). Using 1 atm of air as oxidant gave a low yield (40%, entry 17). It should be noted that monomethylation was observed among all of the entries in Table 1, indicating that monoselectivity may

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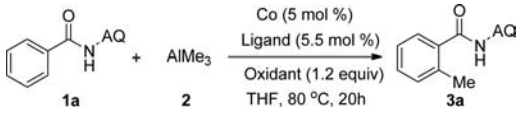
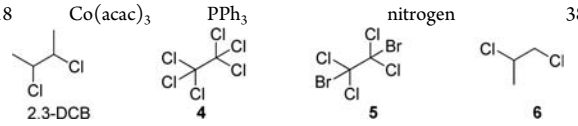
Table 1. Optimization of the Reaction Conditions[a]

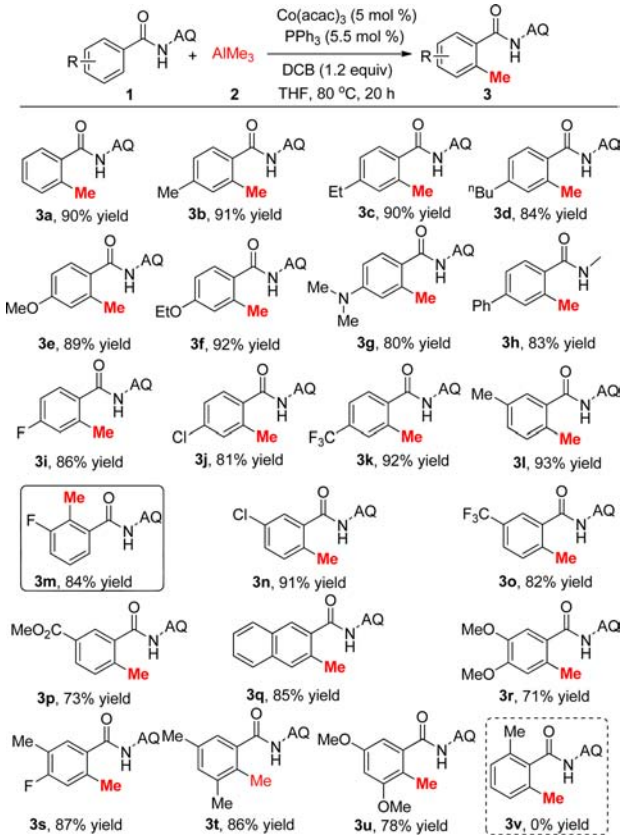


entry	Co catalyst	ligand	oxidant	yield (%)
1	$Co(acac)_3$		2,3-DCB	39
2	$Co(acac)_3$	PPh_3	2,3-DCB	91 (58)[b]
3	$Co(acac)_3$	$P(p\text{-Me-}C_6H_5)_3$	2,3-DCB	91
4	$Co(acac)_3$	$P(p\text{-F-}C_6H_5)_3$	2,3-DCB	79
5	$Co(acac)_3$	$P(o\text{-Me-}C_6H_5)_3$	2,3-DCB	80
6	$Co(acac)_3$	PCy_3	2,3-DCB	67
7	$Co(acac)_3$	1,10-Phen	2,3-DCB	90 (87)[b]
8	$Co(acac)_3$	Bpy	2,3-DCB	79
9	$Co(acac)_2$	PPh_3	2,3-DCB	63
10	$Co(OAc)_2$	PPh_3	2,3-DCB	61
11	$CoCl_2$	PPh_3	2,3-DCB	59
12	$Co(acac)_3$	PPh_3	2,3-DCB	71[c]
13	$Co(acac)_3$	PPh_3	DCE	82
14	$Co(acac)_3$	PPh_3	**4**	36
15	$Co(acac)_3$	PPh_3	**5**	11
16	$Co(acac)_3$	PPh_3	**6**	53
17	$Co(acac)_3$	PPh_3	air	40
18	$Co(acac)_3$	PPh_3	nitrogen	38



[a]Reaction conditions: **1a** (0.2 mmol), $AlMe_3$ (0.4 mmol, 2 M in toluene), Co catalysis (0.01 mmol), ligand (0.011 mmol), oxidant (0.24 mmol) in THF (0.5 mL) at 80 °C for 20 h; yields are isolated yields. [b]The value in the parentheses represents the yield when 2 mol % of catalyst was used. [c]0.3 mmol of DCB was used.

Scheme 1. Substrate Scope of *N*-Quinolylbenzamides[a]



[a]Reaction conditions: **1** (0.2 mmol), $AlMe_3$ (0.4 mmol, 2 M in toluene), $Co(acac)_3$ (0.01 mmol), PPh_3 (0.011 mmol), DCB (0.24 mmol) in THF (0.5 mL) at 80 °C for 20 h; yields are isolated yields.

originate from the Co−Al interaction with the directing group but not be affected by the ligand and oxidant used.

By testing various benzamide substrates, we found the 8-quinoline amide directing group is the most suitable directing group for this transformation. Benzamide bearing a triazolyldimethylmethyl (TAM) directing group,[16] which was developed by Ackermann, delivered the desired methylation product in lower yield (76%) compared with 8-aminoquinoline (see the SI for details).

With these optimized reaction conditions in hand, we then investigated the reaction scope (Scheme 1). We first focused on methylation of *para*-substituted benzamides in which two C−H bonds are available. The previous iron-catalyzed system reported by Nakamura et al. delivers mainly dimethylated products for these substrates,[6] but monomethylation was achieved when cobalt was used as catalyst. This reaction is also suitable for *meta*-substituted benzamide to deliver monomethylated product, but for *ortho*-substituted benzamides, such as *o*-toluamide, no reaction occurred (**3v**). The substrate limitation of refraining from use of *ortho*-substituted benzamide is accordance with the monoselectivity observed for this reaction, showing the high sensitivity toward *ortho*-steric hindrance. Although the reaction is sensitive to *ortho*-steric hindrance, it is interesting to observe that this reaction is amenable to *meta*-substitution. For 3,5-dimethylbenzamide (**1t**) and 3,5-dimethoxybenzamide (**1u**), monomethylations were still observed in high yields to give 2,3,5-trisubstituted benzamides. For 3-fluorobenzamide (**1m**), the methylation reaction occurred at the *ortho*-position of the fluoro substituent, suggesting a C−H bond of higher acidity is more reactive. This result is in accordance with the result of competition experiments in Scheme 5a. For functional group tolerance, ether (**3e**−**f**), tertiary amine (**3g**), fluoro (**3i**), chloro (**3j**), and trifluoromethyl (**3k**,**o**) were all well tolerable. Because of the mild nucleophilicity of trimethylaluminum, ester can also be well tolerated (**3p**).The reaction is not sensitive to electronic effects exerted by electron-donating and -withdrawing substituents on the arene, demonstrating that substrates possessing dimethylamino (**3g**) and trifluoromethyl (**3k**,**o**) substituents both gave good yields.

Besides arene carboxamides, heteroaromatic carboxamides were also suitable substrates (Scheme 2). Pyridine (**7**) and thiophene (**8**) carboxamides can be methylated with increased catalyst loading. Cyclohexene carboxamide (**9**) and aliphatic carboxamide (**10**) can also be successfully methylated. The reaction can be easily scaled up to gram scale as demonstrated by monomethylation of 4-(trifluoromethyl)benzamide in 87% yield on a 5 mmol scale (Scheme 3).

Ethylation was also successfully achieved by using triethylaluminum. For ethylation, triphenylphosphine gave a low yield, probably due to the undesired β-hydride elimination. By using 1,10-phenanthroline, β-hydride elimination was suppressed by saturating the coordinate site of Co (Scheme 4). Ethylation reaction shows exclusive monoselectivity, while in the previous reports mixtures of mono- and diselectivity were obtained.[6b] For higher trialkylaluminums, such tripropylalumi-

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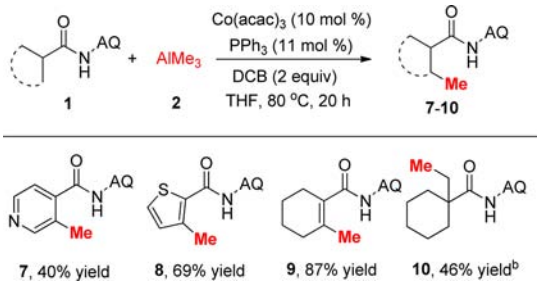
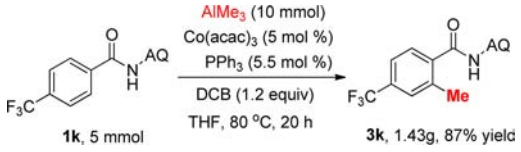
Scheme 2. Methylation of Other Types of Carboxamides.[a]

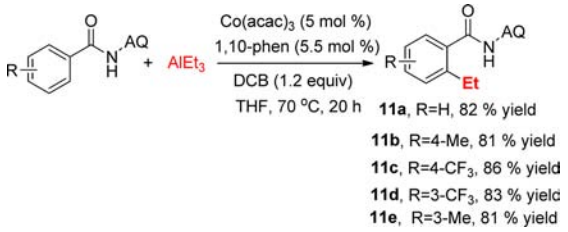


[a]Reaction conditions: **1** (0.2 mmol), $AlMe_3$ (0.4 mmol, 2 M in toluene), $Co(acac)_3$ (0.02 mmol), PPh_3 (0.022 mmol), DCB (0.24 mmol) in THF (0.5 mL) at 80 °C for 20 h; yields are isolated yields. [b]The temperature was 70 °C.

Scheme 3. Gram-Scale Synthesis



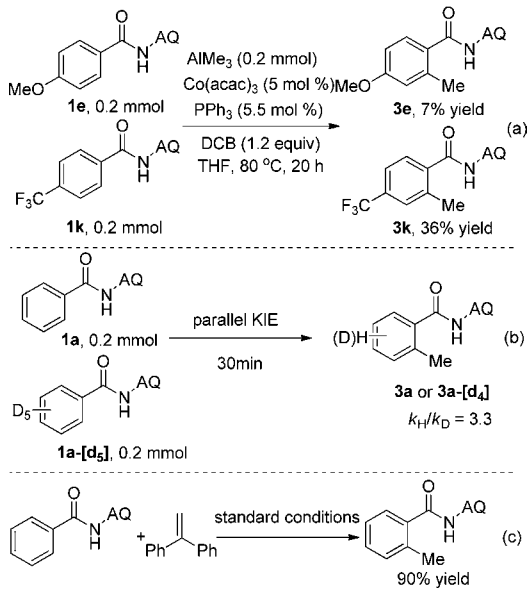
Scheme 4. Ethylation with Triethylaluminum



num and triisobutylaluminum, the reaction failed to give the desired alkylation products, probably due to steric hindrance.

Some initial experiments were carried to gain mechanistic information on this transformation (Scheme 5). First, a competition reaction using 4-OMe and 4-CF_3 substrates clearly

Scheme 5. Mechanistic Studies



shows C−H on the electron-deficient arene (more acidic) reacted faster than the one on the electron-rich arene (Scheme 5a). Second, parallel KIE experiments reveal that C−H activation is the rate determining step in this transformation (Scheme 5b; see the SI for details). Third, addition of a radical scavenger such as 1,1-diphenylethylene has no adverse effect on the reaction outcome (Scheme 5c). These initial mechanistic experiments suggest that C−H activation may proceed through a deprotonation-type mechanism by Co−Me species rather than electrophilic attack by Co(III) to activate C−H bond. The results of the radical scavenger experiments ruled out a radical pathway for C−H activation, supporting the reaction through a cobaltocycle intermediate.

Compared with other Co-catalyzed C−H activations,[3,11] although the origin of the monoselectivity of this reaction cannot be clearly revealed, we can conclude at this stage that this monoseletivity maybe ascribed to the interaction of Lewis acidic aluminum with the directing group as shown in a proposed model in Figure 1. The cobalt may coordinate with

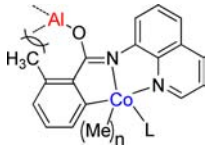


Figure 1. Rationalization of the observed selectivity for monomethylation.

the two nitrogen atoms, and aluminum may coordinate to the iminolized C−O bond to exert steric bulkiness, preventing formation of the second metallocycle.

In conclusion, we reported a simple triphenylphosphine-ligated cobalt catalyst for the direct *ortho*-C−H methylation of aromatic, heteroaromatic, alkenyl, and even aliphatic carboxamides with trimethylaluminum in the presence of a cheap alkyl chloride as oxidant. This reaction shows excellent monoselectivity, in contrast with previously established C−H methylation metholodologies. By tuning the supporting ligand for cobalt to 1,10-phenanthroline, C−H ethylation can be achieved in an excellent monoselective fashion. The method may find utility for C−H methylation and ethylation for pharmacology research, especially when monoselectivity is required.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02860.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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