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# Cobalt-Catalyzed Decarboxylative Methylation and Ethylation of Aliphatic *N*-(Acyloxy)phthalimides with Organoaluminum Reagents

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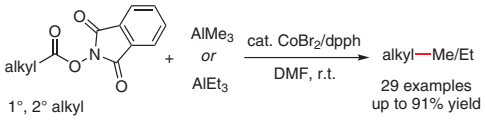


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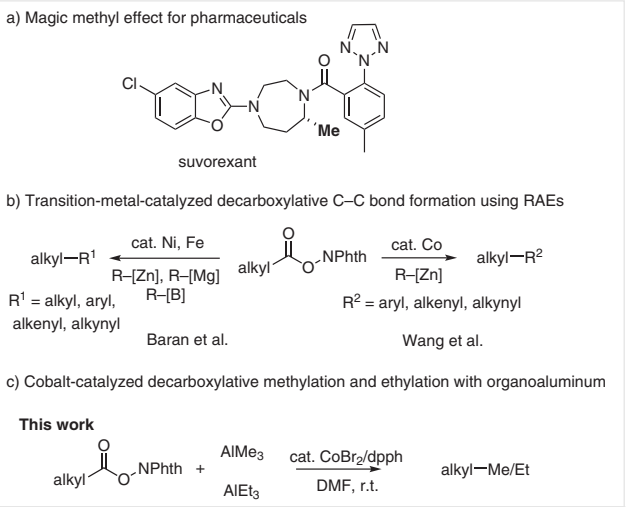
**Abstract** A cobalt-catalyzed decarboxylative methylation of aliphatic redox-active esters [*N*-(acyloxy)phthalimides; RAEs] with trimethylaluminum under mild conditions was developed, providing a method for transforming a carboxylate group into a methyl group without redox fluctuation. Primary and secondary RAEs were both amenable substrates, whereas a tertiary RAE delivered an elimination product. Triethylaluminum was also used to deliver a decarboxylative ethylation product.

**Key words** cobalt catalysis, decarboxylative methylation, ethylation, trimethylaluminum, redox-active esters

A methyl substituent can boost the potency of a bioactive molecule by regulating its interactions with its target protein.[1] The magic-methyl effect is evidenced by the drug suvorexant (Belsomra), as the installation of a methyl group on the aliphatic C-7 position leads to improved potency and pharmacokinetic properties (Scheme 1a).[2] New methods for modular installation of methyl groups on C($sp^3$) centers are therefore desirable.[3]

We previously conceived a decarboxylative methylation method using aliphatic redox-active esters (RAEs) in conjunction with mild trimethylaluminum as a reagent that can avoid redox fluctuations, unlike conventional reduction methods for transforming carboxy groups into methyl groups.[4] Related transition-metal-catalyzed decarboxylative C–C couplings[5] using RAEs[6,7] have been elegantly developed by Baran and co-workers using nickel-[8] or iron-based[9] catalysts. Wang and co-workers also reported cobalt-catalyzed alkyl–aryl, alkyl–alkenyl, and alkyl–alkynyl coupling reactions of organozinc compounds with aliphatic RAEs.[10] However, decarboxylative methylation with an easily available and mild trimethylaluminum reagent remains underdeveloped, although trimethylaluminum has been demonstrated to act as a methyl source in various C–H methylations.[11] Here, we report that cobalt(II) bromide in combination with 1,6-bis(diphenylphosphino)hexane (dpph) as a ligand catalyzes the decarboxylative methylation reaction of primary and secondary RAEs with commercial available $AlMe_3$ as a nucleophile. $AlEt_3$ is similarly an amenable reagent for installing an ethyl group smoothly. The reported work demonstrates the use of organoaluminum reagents for efficient decarboxylative alkyl–alkyl couplings under mild conditions.




**Scheme 1**

The reaction conditions after optimization are shown in Table 1 (entry 1). A mixture of the redox-active ester **1** (0.2 mmol), $AlMe_3$ (0.3 mmol), $CoBr_2$ (10 mol%), and dpph (12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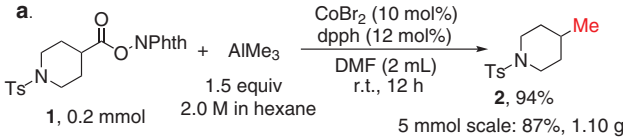
mol%) was stirred in DMF (2.0 mL) at room temperature for 12 hours. The desired decarboxylative methylation product **2** was obtained in 94% yield, as determined by $^1$H NMR analysis. The scalability of this protocol was demonstrated by a gram-scale synthesis of **2** in high yield (5 mmol scale; 87%). Changing $CoBr_2$ to other Co(II) salts resulted in significantly lower yields (Table 1, entries 2–4). The poor results using $Co(acac)_2$ and $Co(OAc)_2$ suggested that a halide anion (Cl or Br) has an essential role in achieving a high reactivity (entries 3 and 4), possibly through coordination of the halide to cobalt to form a reactive intermediate such as the cobaltate species shown below in Scheme 6. The choice of solvent is also a key for this reaction. *N*,*N*-Dimethylformamide (DMF) was found to be the optimal solvent. The yields decreased when *N*,*N*-dimethylacetamide (DMA) or *N*-methylpyrrolidone (NMP) was used instead of DMF (entries 5 and 6). Tetrahydrofuran (THF) was a poor solvent (entry 7), and no methylation product was observed when dichloroethane (DCE), acetonitrile ($CH_3CN$), toluene, acetone, or ethyl acetate (EtOAc) was used (entries 8–12). Lowering the catalyst loading to 5 mol% resulted in a decreased yield (entry 13). It was necessary to use 1.5 equivalents of $AlMe_3$ to guarantee a high conversion (entry 14), indicating that only one of the three methyl groups of $AlMe_3$ is effective in transmetalation and cross coupling. A slightly lower yield was observed when the volume of DMF was reduced to 1 mL (entry 15). An $AlMe_3$ solution in toluene also reacted well (entry 16). The cobalt salt and ligand were both essential for reactivity (entry 17). The reaction also proceeded under air with a slightly lower yield of 82% compared with that under argon. The use of $NiCl_2$ as a catalyst gave a lower yield of 54%. No methylation product was observed when $FeCl_2$ was employed.

**Table 1** Co-Catalyzed Decarboxylative Methylation under Various Conditions

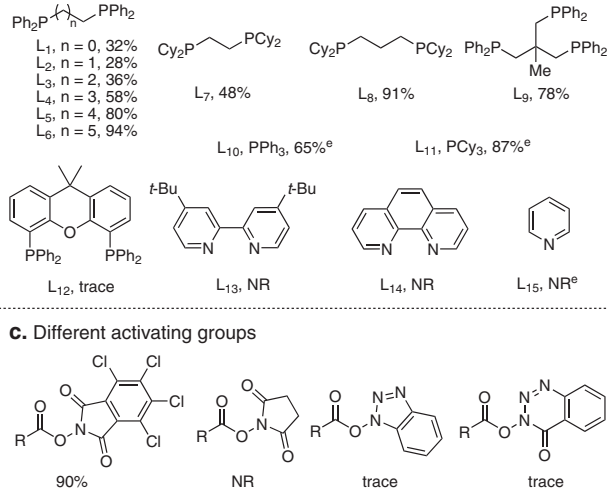



| Entry | Variation from Standard Conditions[a] | Yield[b] (%) |
|---|---|---|
| 1 | none | 94 (88)[c] |
| 2 | $CoCl_2$ instead of $CoBr_2$ | 75 |
| 3 | $Co(acac)_2$ instead of $CoBr_2$ | 18 |
| 4 | $Co(OAc)_2$ instead of $CoBr_2$ | trace |
| 5 | DMA instead of DMF | 68 |
| 6 | NMP instead of DMF | 66 |
| 7 | THF instead of DMF | 27 |
| 8 | DCE instead of DMF | NR[d] |
| 9 | MeCN instead of DMF | NR |

Table 1 (continued)

| Entry | Variation from Standard Conditions[a] | Yield[b] (%) |
|---|---|---|
| 10 | toluene instead of DMF | NR |
| 11 | acetone instead of DMF | NR |
| 12 | EtOAc instead of DMF | NR |
| 13 | $CoBr_2$ (5 mol%), dpph (6 mol%) | 62 |
| 14 | $AlMe_3$ (1.2 equiv) | 72 |
| 15 | DMF (1 mL) | 84 |
| 16 | $AlMe_3$ (1.6 M in toluene) | 88 |
| 17 | no $CoBr_2$ or dpph | NR |

**b.** Different ligands




**c.** Different activating groups

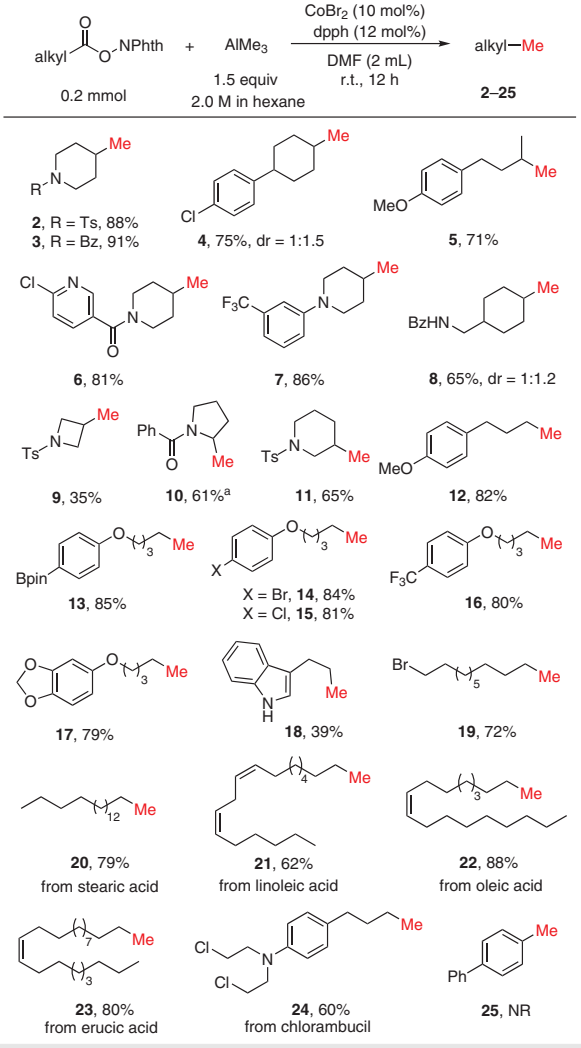



[a] Standard conditions: **1** (0.2 mmol), $AlMe_3$ (1.5 equiv), $CoBr_2$ (10 mol%), dpph (12 mol%), DMF (2 mL), r.t., 12 h, under argon.
[b] Yield determined by $^1$H NMR with diphenylmethane as an internal standard.
[c] Yield of the isolated product.
[d] NR = no reaction.
[e] Monodentate ligand (20 mol%).

A phosphine ligand was essential for the reactivity. A variety of structurally diverse ligands were examined to elucidate the ligand effect (Table 1b). Interestingly, with alkanediyl bisphosphine ligands, the yield increased as the number of methylene units between the two phosphorus atoms was increased. 1,6-Bis(diphenylphosphino)hexane (dpph) gave the highest yield among ligands $L_1$–$L_6$. 1,3-Bis(dicyclohexylphosphino)propane ($L_8$; dCypp) and tricyclohexylphosphine ($L_{11}$; $PCy_3$) were also effective ligands. Only a trace of the methylation product was detected when Xantphos ($L_{12}$) was used. Bidentate nitrogen ligands $L_{13}$ and $L_{14}$ and the monodentate nitrogen ligand $L_{15}$ were ineffective. An investigation of various activating groups (Table 1c) showed that *N*-hydroxyphthalimide and *N*-hydroxytetrachlorophthalimide were suitable for activation of carboxylic acids. RAEs derived from *N*-hydroxysuccinimide, *N*-hy-

droxybenzotriazole, or 3-hydroxybenzo[1,2,3]triazin-4(3*H*)-one did not provide the desired methylation product.

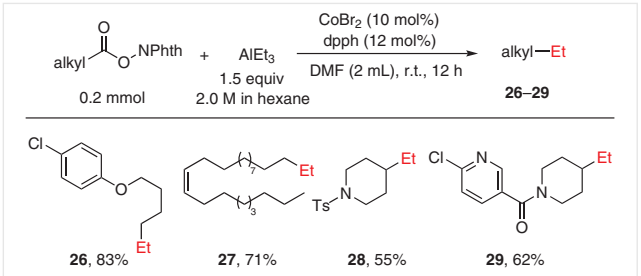
To further demonstrate the generality of this protocol, we evaluated the scope of the cobalt-catalyzed decarboxylative methylation with respect to the RAE (Scheme 2). A variety of secondary and primary RAEs were all amenable substrates, delivering the corresponding decarboxylative methylation products in moderate to high yields (35–91%). Notably, both cyclic and acyclic RAEs were well tolerated (**2**–**5**). Moreover, a methyl group was decarboxylatively introduced onto pharmaceutically relevant aliphatic structures such as substituted piperidines (**6** and **7**), a functionalized cyclohexane ring (**8**), and a strained azetidine ring (**9**). RAEs derived from an α-amino acid and a β-amino acid




**Scheme 2** Scope with respect to the RAE. *Reagents and conditions*: RAE (0.2 mmol), $AlMe_3$ (1.5 equiv), $CoBr_2$ (10 mol%), dpph (12 mol%), DMF (2 mL), r.t., 12 h, under argon. Yields of the isolated products are reported. [a] 1,1′-Bis(diphenylphosphino)ferrocene (12 mol%) was used instead of dpph at 0 °C.

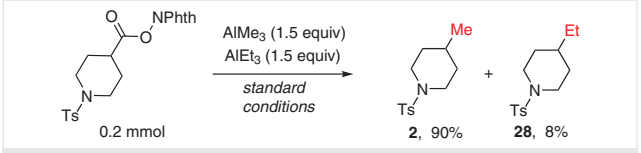
were both suitable substrates (**10** and **11**). Primary RAEs also reacted well (**12**–**19**). The reaction tolerated a variety of functional groups, including ether (**12**), aryl boronate (**13**), aryl bromide (**14**), aryl chloride (**15**), trifluoromethyl (**16**), acetal (**17**), indole (**18**), and alkyl bromide (**19**). RAEs derived from various natural products, such as stearic acid (**20**), linoleic acid (**21**), oleic acid (**22**), and erucic acid (**23**) or from the drug molecule chlorambucil (**24**) also reacted readily to yield the corresponding methylation products. Decarboxylative methylation did not proceed when an RAE derived from an aryl carboxylic acid was tested (**25**).

Apart from decarboxylative methylation, decarboxylative ethylation also proceeded smoothly with primary and secondary RAEs by using commercially available $AlEt_3$ (Scheme 3; **26**–**29**). However, $Me_2AlCl$, $Et_2AlCl$, and $(Me_3Al)_2$·DABCO were unsuccessful as coupling partners.




**Scheme 3** Decarboxylative ethylation of RAEs. *Reagents and conditions*: RAE (0.2 mmol), $AlEt_3$ (1.5 equiv), $CoBr_2$ (10 mol%), dpph (12 mol%), DMF (2 mL), r.t., 12 h, under argon. Yields of the isolated products are reported.

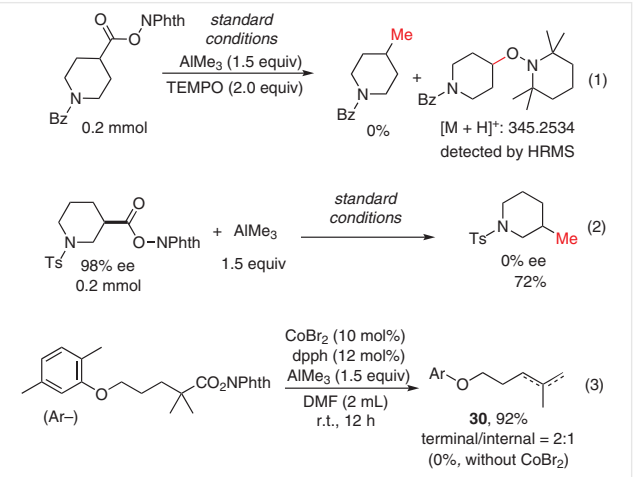
A competition experiment using equal amounts of $AlMe_3$ and $AlEt_3$ (Scheme 4) showed that methylation proceeds much faster than ethylation. The observed ratio of methylation to ethylation in the competition experiment was 11:1. This observation is possibly ascribable to a much faster transmetalation of methyl than ethyl due to its smaller steric hindrance.




**Scheme 4**

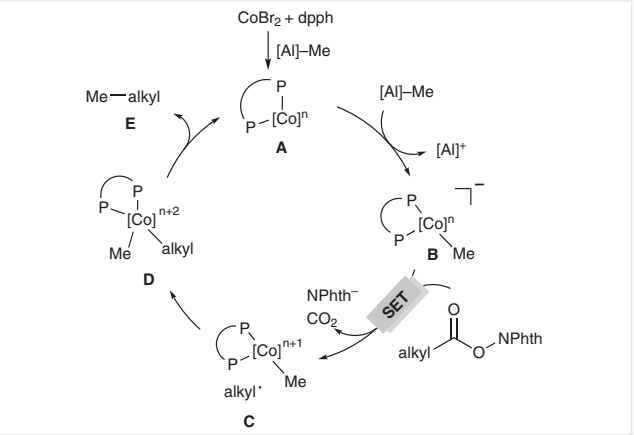
Next, experiments were conducted to gather mechanistic information. Radical-trapping experiments using TEMPO as a radical scavenger[12] showed that the reaction was suppressed completely, and a TEMPO adduct was detected by HRMS (Scheme 5, eq. 1). Furthermore, the reaction of an enantioenriched RAE with 98% optical purity led to a completely racemized methylation product (Scheme 5, eq. 2). These results are in accordance with a radical decarboxyl-

ation process. It is also worth noting that the decarboxylative elimination product **30** was obtained in high yield when a tertiary RAE was employed (Scheme 5, eq. 3).




**Scheme 5**

Based on our experimental findings and reports in the literature,[13] a catalytic cycle that accounts for the catalytic decarboxylative methylation is proposed (Scheme 6). A bisphosphine-coordinated low-valent cobalt species **A** is generated through reduction of Co(II) by the organoaluminum reagent in the presence of dpph. Species **A** undergoes transmetalation with $AlMe_3$ to generate a methylated cobalt species **B**, which is possibly an ate species. Intermediate **B** reduces the RAE through a single-electron transfer (SET) process to trigger decarboxylative fragmentation of the RAE with generation of the cobalt-bound radical species **C**. Intermediate **C** undergoes alkyl binding to form **D**. Reductive elimination on **D** delivers the methylation product and regenerates **A**.




**Scheme 6** Proposed catalytic cycle

In summary, we have developed cobalt-catalyzed decarboxylative methylation and ethylation of aliphatic RAEs with commercially available trimethylaluminum and triethylaluminum, respectively, under mild conditions,[14] providing a convenient synthetic method for the replacement of a carboxylate moiety with a methyl or an ethyl group on a primary or secondary $sp^3$-carbon center.

## Funding Information

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707946.

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(14) 4-Methyl-1-tosylpiperidine (2); Typical Procedure
Phthalimide **1** (1.0 equiv, 0.2 mmol), $CoBr_2$ (10 mol%), and dpph (12 mol%) were placed in a 10 mL transparent Schlenk tube equipped with a stirring bar. The tube was evacuated and filled with argon three times. Anhyd DMF (2.0 mL) and a 2 M solution of $AlMe_3$ in hexane (1.5 equiv) were added from a gastight syringe under argon, and the mixture was stirred at r.t. for 12 h. The reaction was then quenched with sat. aq sodium potassium tartrate solution, and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined and concentrated under vacuo. The crude product was purified by flash column chromatography [silica gel, EtOAc–PE (1:5)] to give a white solid; yield: 44.2 mg (88%); mp 83–85 °C.
$^1$H NMR (400 MHz, $CDCl_3$): d = 7.64 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 3.73 (d, *J* = 11.5 Hz, 2 H), 2.43 (s, 3 H), 2.22 (t, *J* = 10.9 Hz, 2 H), 1.67 (s, 2 H), 1.28 (dd, *J* = 12.4, 5.7 Hz, 3 H), 0.90 (d, *J* = 5.6 Hz, 3 H). $^{13}$C NMR (101 MHz, $CDCl_3$): d = 143.2, 133.3, 129.5, 127.6, 46.3, 33.3, 30.1, 21.5, 21.4.