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Cobalt-Catalyzed Decarboxylative Acetoxylation of Amino Acids and Arylacetic Acids

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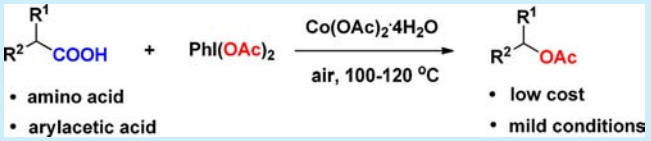
Supporting Information

ABSTRACT: The first cobalt-catalyzed decarboxylative acetoxylation reaction was accomplished. This methodology is applicable to a wide range of amino acids and arylacetic acids.

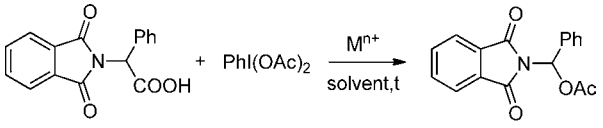


Transition-metal-catalyzed decarboxylative couplings have emerged as a versatile approach in organic synthesis.[1] This method employs inexpensive and benchtop stable carboxylic acids as substrate, without the need for preformed organometallic reagents, thus providing an attractive alternative to traditional cross-couplings. Moreover, the decarboxylative coupling strategy is likely promising for regiospecific functionalization and only provides nontoxic carbon dioxide as a byproduct.

Until now, transition-metal-catalyzed decarboxylative couplings have relied heavily on using late and noble transition metals including palladium,[2] silver,[3] and rhodium complexes.[4] Although naturally abundant first-row transition metals, such as Cu[5] and Ni,[6] have recently witnessed considerable attention, the development of a low cost, low toxicity catalyst system for decarboxylative coupling still represents a challenging task. Whereas significant progress has been made toward the decarboxylative C−C bond formations, the decarboxylative C−O couplings are rather limited.[7] Given the fact that C−O moieties are ubiquitous in both natural products and pharmaceuticals, developing efficient decarboxylative strategies for construction of a C−O bond is highly desired.[8] Herein, we report our recent efforts on cobalt-catalyzed decarboxylative acetoxylation of amino acids and arylacetic acids.[9] This method represents a new type of decarboxylative coupling reaction catalyzed by earth-abundant, inexpensive first-row transition metals.[10]

Our investigation began with the reaction of phthalimide protected phenylglycine **1a** and iodosobenzene diacetate **2** in the presence of a catalytic amount of cobalt complexes (Table 1). A screen of catalysts was first conducted with 1,2-dicholoroethane (DCE) as the solvent. The results showed that $Co(OAc)_2·4H_2O$ was the most effective catalyst for this reaction, whereas $CoCl_2·6H_2O$, $Co(acac)_2$, and CoC_2O_4 all gave lower yields (entries 1 vs 2−4); other Lewis acids such as $FeCl_3$, $Cu(OTf)_2$, and Ag_2CO_3 gave inferior results (entries 5−7). Control experiment revealed that the cobalt catalyst was essential for this transformation as only 13% yield was obtained without cobalt salts (entry 8). Further assessment of the solvent effect indicated that DCE was the best solvent for this reaction,

Table 1. Optimization of the Reaction Conditions[a]



1a **2** **3a**

entry	M^{n+}	solvent	temp (°C)	yield[b] (%)
1	$Co(OAc)_2·4H_2O$	DCE	120	86
2	$CoCl_2·6H_2O$	DCE	120	51
3	$Co(acac)_2$	DCE	120	74
4	$CoC_2O_4·2H_2O$	DCE	120	35
5	$FeCl_3$	DCE	120	14
6	$Cu(OTf)_2$	DCE	120	16
7	Ag_2CO_3	DCE	120	21
8		DCE	120	13
9	$Co(OAc)_2·4H_2O$	$CHCl_3$	120	67
10	$Co(OAc)_2·4H_2O$	Tol	120	37
11	$Co(OAc)_2·4H_2O$	dioxane	120	trace
12	$Co(OAc)_2·4H_2O$	EtOH	120	23
13	$Co(OAc)_2·4H_2O$	DCE	130	79
14	$Co(OAc)_2·4H_2O$	DCE	100	83

[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), catalyst (0.05 mmol), solvent (2 mL), 8 h. [b]Isolated yield.

providing higher yield than other commonly used solvents (entry 1 vs 9−12). Both increasing and decreasing the temperature resulted in lower yields (entries 13 and 14).

Under the optimized conditions, the substrate scope of amino acid was investigated. As shown in Figure 1, this protocol is successful with a large variety of phthalimide-protected amino acids. The electron-withdrawn group on the aromatic ring led to a slightly lower yield (**3a** vs **3b**−**e**). Compared with the substrate with *para*-substituents, those with *meta*-substituents on the aromatic ring gave better yields (**3d** vs **3b**, **3e** vs **3c**). Substrates with an alkyl substituent group were

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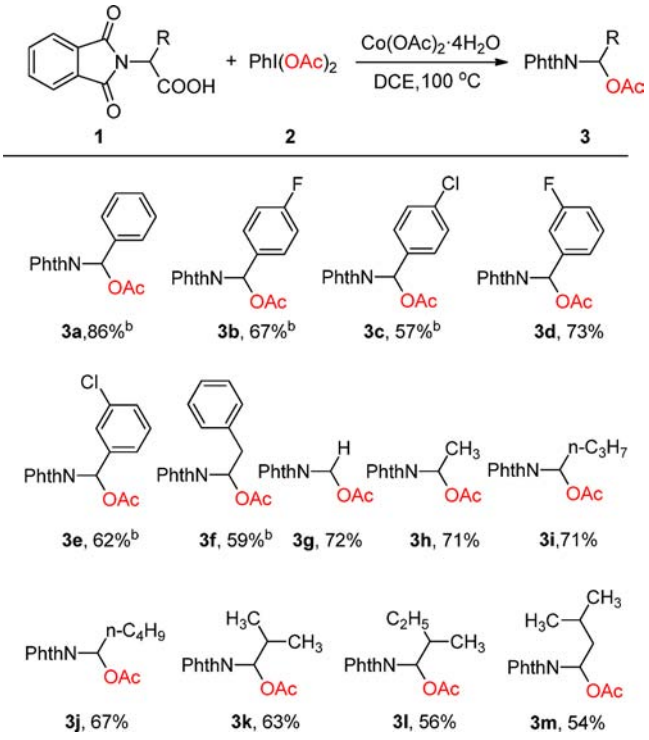


Figure 1. Substrate scope of *N*-protected amino acids. (a) Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.05 mmol), DCE (2 mL), 10 h. (b) The reaction temperature was 120 °C, 8 h.

also tolerable where the steric hindrance had a profound effect. While linear groups provided the desired products with similar level of yields, the bulky alkyl groups led to a sharp decrease of the yields (**3h**–**j** vs **3k**–**m**). Finally, *N*-phthaloylglycine was successfully employed as the substrate, giving the corresponding acetate **3g** in 72% yield.

To further establish the general utility of this transformation, we next sought to examine other types of aliphatic carboxylic acids. As shown in Figure 2, a series of primary and secondary acids were all good reaction partners with a minor modification of the standard reaction conditions. With $CoCl_2{\cdot}6H_2O$ as the

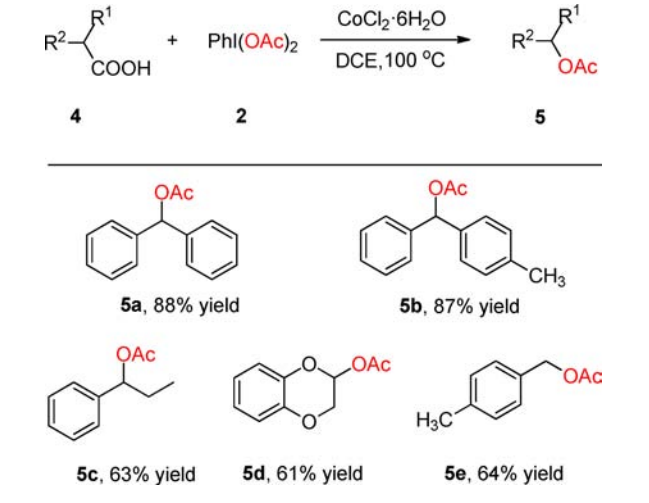
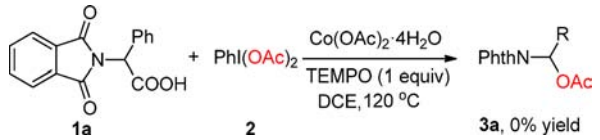


Figure 2. Substrate scope of other types of aliphatic carboxylic acids. (a) Reaction conditions: **4** (0.5 mmol), **2** (0.75 mmol), $CoCl_2{\cdot}6H_2O$ (0.05 mmol), DCE (2 mL), 10 h.

catalyst, diaryl-substituted acids could give excellent yields (**5a**,**b**); however, only moderate yield was obtained when 2-phenylbutyric acid and 1,4-benzodioxane-2-carboxylic acid were employed as the substrates (**5c**,**d**). It is noteworthy that primary carboxylic acid, such as 4-methylphenylacetic acid, was also well tolerated in this transformation, thus affording the corresponding product **5e** in 64% yield.[11] However, *n*-hexanoic acid, pivalic acid, and phenylpropionic acid were unreactive.

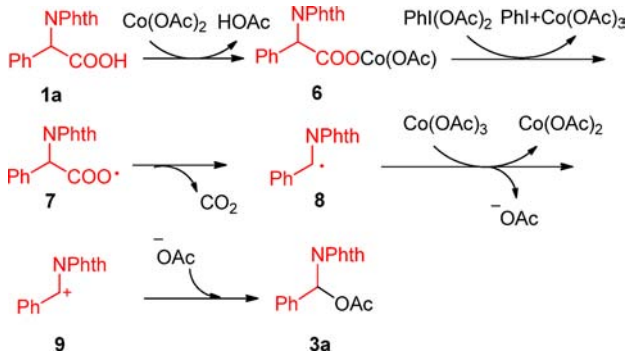
To probe the nature of this decarboxylative coupling, the radical-trapping reagent (TEMPO) was added into the reaction of **1a** and **2** (Scheme 1). It was shown that the formation of product **3a** was completely prohibited, suggesting a radical process was involved.[12]

Scheme 1. Control Experiment



On the basis of the control experiment, a plausible reaction mechanism was proposed as shown in Scheme 2. Initially,

Scheme 2. Plausible Mechanism for This Reaction



amino acid **1a** coordinated with $Co(OAc)_2$ to give cobalt carboxylate **6**, which could then be oxidized by $PhI(OAc)_2$ to form radical **7** and one molecule of $Co(OAc)_3$. Next, radical **7** could be converted into intermediate **8** with the extrusion of CO_2. Under the catalysis of $Co(OAc)_3$, radical **8** undergoes an oxidation process to give cation **9** while releasing one molecule of acetate anion. Finally, nucleophilic attack of cation **9** by acetate anion affords the desired product **3a**.

In conclusion, we have developed the first example of a cobalt-catalyzed decarboxylative C–O bond-forming reaction. The reaction is tolerable to a wide range of amino acids and arylacetic acids, giving the corresponding acetates in moderate to good yields. The ready availability and low cost of the catalyst and the mild reaction conditions render this method of practical value in the construction of C–O bonds. Efforts to expand the synthetic applications, as well as further mechanistic studies, are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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