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Cobalt-Catalyzed Carbonylation of C(sp^2)−H Bonds with Azodicarboxylate as the Carbonyl Source

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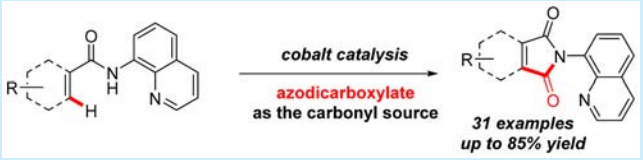
Supporting Information

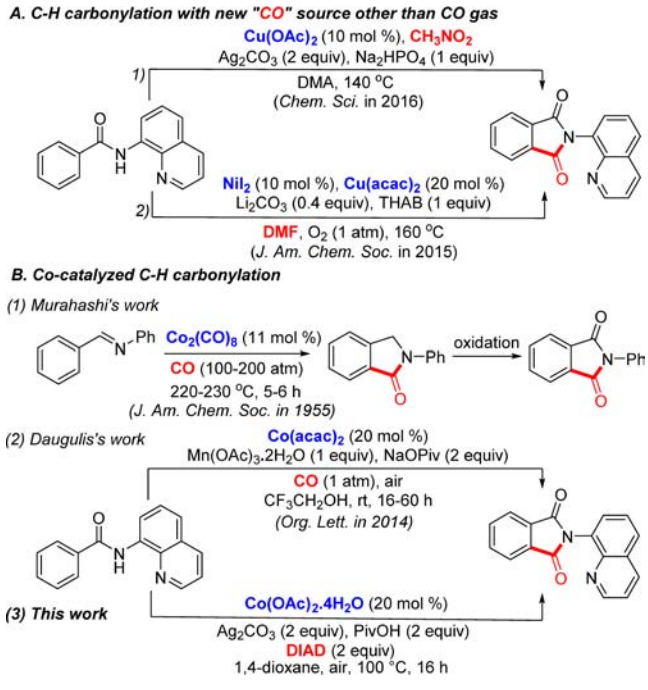
ABSTRACT: A novel and efficient approach for the C(sp^2)−H bond carbonylation of benzamides has been developed using stable and inexpensive $Co(OAc)_2·4H_2O$ as the catalyst and the commercially available and easily handling azodicarboxylates as the nontoxic carbonyl source. A broad range of substrates bearing diverse functional groups were tolerated. This is the first example where cobalt-catalyzed C(sp^2)−H bond carbonylation occurs with azodicarboxylate as the carbonyl source.



Transition-metal-catalyzed C−H activation and functionalization have continued to bring more effective and untraditional strategies for the synthesis of many biologically active compounds, natural products, and structure-diversified libraries.[1] Among these strategies, transition-metal-catalyzed C−H carbonylation has attracted considerable interest due to the wide presence of carbonyl groups in organic and medicinal chemistry.[2] Using carbon monoxide (CO) as the most widely used and direct carbonyl source, introduction of a carbonyl group into aromatic rings to construct phthalimide motifs by a C−H activation strategy has been well developed by Chatani[3a] and Rovis groups,[3b] respectively. Unfortunately, both of the methods used the second-row precious transition metals as the catalyst and toxic CO gas as the carbonyl source at high pressure and high temperature. Therefore, alternative strategies using the much abundant and cheap first-row transition metals, such as Cu, Co, and Ni, and an environmentally benign carbonyl source are highly desired. Recently, an elegant improvement was reported by the Ge and Li groups, who disclosed a site-selective carbonylation of unactivated C(sp^3)−H and C(sp^2)−H bonds by using $Cu(OAc)_2$ as the catalyst and nitromethane as the carbonyl source in 140 °C (Scheme 1A(1)).[4a] Meanwhile, the Ge group further found that the same carbonylation reaction could be realized through NiI_2/Cu(acac)$_2$ synergistic catalysis at 160 °C with the solvent DMF as a new carbonyl source (Scheme 1A(2)).[4b]

Encouraged by these pioneering studies, we decided to develop alternative cost-effective, environmentally benign, and more practical carbonylation strategies by using the easily accessible cobalt catalysts.[5] As a matter of fact, Co-catalyzed direct carbonylation for construction of phthalimide motifs remains a barely exploited topic, and only two approaches have been reported so far. The first example of Co-catalyzed carbonylation of a C(sp^2)−H bond was unraveled in 1955 by

Scheme 1. Transition-Metal-Catalyzed Carbonylation of C(sp^2)−H Bonds



Murahashi (Scheme 1B(1)), who reported that *N*-phenylphthalimide could be synthesized by direct carbonylation of *N*-aryl aldmines using $Co_2(CO)_8$ as the catalyst and CO as the carbonyl source at 100−200 atm and 220−230 °C.[6a] The

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second example of Co-catalyzed carbonylation of a C(sp^2)−H bond was reported in 2014 by Daugulis (Scheme 1B(2));[6b] they found that carbonylation of benzamides could be realized at room temperature by using 8-aminoquinoline as the bidentate directing group, $Co(acac)_2$ as the catalyst, $Mn(OAc)_3{\cdot}2H_2O$ as the Co-catalyst, and CO (1 atm) as the carbonyl source. However, in both cases, the use of toxic CO gas limited their further application. In this report, we develop a cobalt salt ($Co(OAc)_2{\cdot}4H_2O$)-catalyzed carbonylation of C(sp^2)−H bonds with azodicarboxylates as a new carbonyl source, thus allowing for the convenient formation of a library of functionalized phthalimides in a more environmentally friendly, safe, economic, and practical manner (Scheme 1B(3)).

Our initial objective using $Co(OAc)_2{\cdot}4H_2O$ and diisopropyl azodicarboxylate (DIAD) was to introducing a hydrazine functionality at the *ortho*-site of benzamides for further transformation through the Co-catalyzed C−H activation process with 8-aminoqinoline as the bidentate directing group. However, we found that treating *N*-(quinolin-8-yl)-benzamide (**1a**, 1.0 equiv) and DIAD (**2a**, 2.0 equiv), with $Co(OAc)_2{\cdot}4H_2O$ (20 mol %) as the catalyst and Ag_2CO_3 (2.0 equiv) as the oxidant in 1,4-dioxane (100 °C), did not give the expected product; instead, the *ortho*-carbonylative cyclization product **3a** was unexpectedly obtained in 66% yield. In view of the limited success in Co-catalyzed C−H carbonylation and the novelty of using DIAD as the nontoxic carbonyl source, we decided to turn our current protocol into a new Co-catalyzed C−H carbonylation process. Therefore, optimization of the reaction conditions was first conducted and the results are summarized in Table 1. The screening of various commercially available cobalt catalysts revealed that $Co(OAc)_2{\cdot}4H_2O$ was the optimal catalyst (entries 1−3). Among the examined bases, Na_2CO_3 was found to be the best choice, and Cs_2CO_3 did not promote the reaction at all (entries 4−6). It was of note that acidic additives exerted a positive influence on the reaction, especially PivOH that exhibited higher efficiency than basic additives (entries 7−8). Other solvents such as toluene and DCE were also examined, and neither delivered better efficacy than 1,4-dioxane (entries 9−10). Additional silver salts (AgOAc, Ag_2O) were tested as well, as the oxidant and the effects were no better than in the case of Ag_2CO_3 (entries 7, 11−12). Using oxone as the oxidant, product **3a** was obtained but in a lower yield (62%, entry 13). In addition, reducing the loading of PivOH to 1 equiv slightly decreased the yield (entry 14). Further screening of the reaction at higher or lower temperature led to no improvement (entries 7, 15−16). It has to be mentioned that replacement of DIAD with DMF or $MeNO_3$ as the carbonyl source as reported by Ge[4] did not promote the reaction at all.

With the optimized catalytic reaction conditions in hand, we subsequently explored the substrate scope with respect to diverse carboxamide substrates to test the generality and limitations of the reaction. As illustrated in Scheme 2, all the reactions went through smoothly and the carbonylation products **3** were obtained in moderate to good yields (up to 85%). Aromatic amides bearing a variety of *para*-substituents that are either electron-donating (Me, MeO, ^{t}Bu) or electron-withdrawing (acetyl, halide) showed good compatibility, and the corresponding products **3b−i** were obtained in 61−85% yields. Lower yields were observed in the cases of 4-nitro- and 4-cyano-substituted benzamide substrates (42% for **3j**, 22% for **3k**), likely due to the poor solubility of both substrates and products. Gratifyingly, halides such as F-, Cl-, and Br- were well tolerated under the standard reaction conditions, thus providing possible access for further functional transformations. Similarly, carbonylation of benzamides bearing an *ortho*-substituent occurred as well and the corresponding products **3l−o** were obtained in 59−71% yields. Moreover, disubstituted benzamides also showed the same good reactivity as monosubstituted ones. 1-Naphenyl- and 1,3-benzodioxolo-carboxamides were converted to corresponding products **3p** and **3q** in 68% and 49% yields, respectively. 3,5- or 2,4- or 2,5-disubstituted benzamides also went through the reaction very well and provided the corresponding products **3r−t** in 61−78% yields. For *meta*-substituted benzamides, it was found that the reactions occurred at both *ortho*-positions, but the less hindered *ortho*-position was favored (**3b** vs **3l**, **3f** vs **3n**, **3g** vs **3o**). Notably, 2- or 3-phenyl substituted acrylamides (cinnamamides) and 2,3-diphenylacrylamide also went through the C−H carbonylation and the corresponding products **3u−v** were obtained in 37−78% yields. More appealingly, the heteroaromatic substrate (isonicotinamide) took part in the carbonylation as well providing product **3w**, although the yield was relatively lower (35%).

Meanwhile, we were delighted to find that the reaction was not restricted to DIAD. As shown in Scheme 3, other commercially available azodicarboxylates **2b−d** were also suitable as the carbonyl source, and phthalimide **3a** was obtained in 64−82% yields.

To gain insights into the reaction mechanism, some additional experiments were conducted (Scheme 4). First, the

Table 1. Optimization of the Reaction Conditions[a]

entry	[Co] catalyst	oxidant	additive	solvent	yield (%)[b]
1	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	–	1,4-dioxane	66
2	$Co(acac)_2$	Ag_2CO_3	–	1,4-dioxane	36
3	$Co(acac)_3$	Ag_2CO_3	–	1,4-dioxane	trace
4	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	Na_2CO_3	1,4-dioxane	86
5	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	K_2CO_3	1,4-dioxane	10
6	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	Cs_2CO_3	1,4-dioxane	0
7	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	PivOH	1,4-dioxane	88
8	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	AcOH	1,4-dioxane	70
9	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	PivOH	toluene	47
10	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	PivOH	DCE	18
11	$Co(OAc)_2{\cdot}4H_2O$	AgOAc	PivOH	1,4-dioxane	78
12	$Co(OAc)_2{\cdot}4H_2O$	Ag_2O	PivOH	1,4-dioxane	83
13	$Co(OAc)_2{\cdot}4H_2O$	Oxone	PivOH	1,4-dioxane	62
14[c]	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	PivOH	1,4-dioxane	79
15[d]	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	PivOH	1,4-dioxane	76
16[e]	$Co(OAc)_2{\cdot}4H_2O$	Ag_2CO_3	PivOH	1,4-dioxane	69

[a]Reactions were carried out by using **1a** (0.1 mmol), **2a** (0.2 mmol), cobalt catalyst (0.02 mmol), oxidant (0.2 mmol), additive (0.2 mmol), solvent (1 mL), 100 °C, air, 16 h. PivOH = pivalic acid. [b]Isolated yield. [c]PivOH (1 equiv). [d]At 110 °C. [e]At 90 °C.

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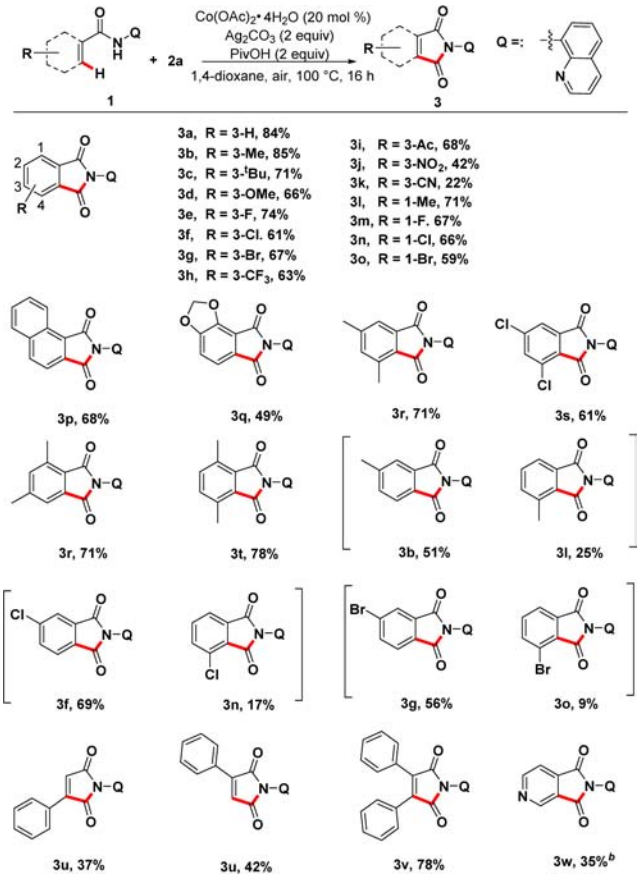
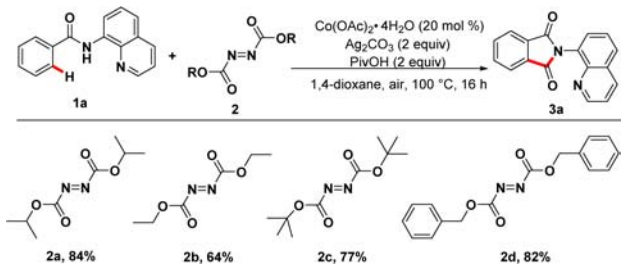
Scheme 2. Scope of Carboxamide Amides[a]



[a]Reactions were carried out by using **1a** (0.2 mmol), **2a** (0.4 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.04 mmol, 20 mol %), Ag_2CO_3 (0.4 mmol), PivOH (0.4 mmol), 1,4-dioxane (2 mL), 100 °C, air, 16 h. [b]**2a** (0.8 mmol), 32 h.

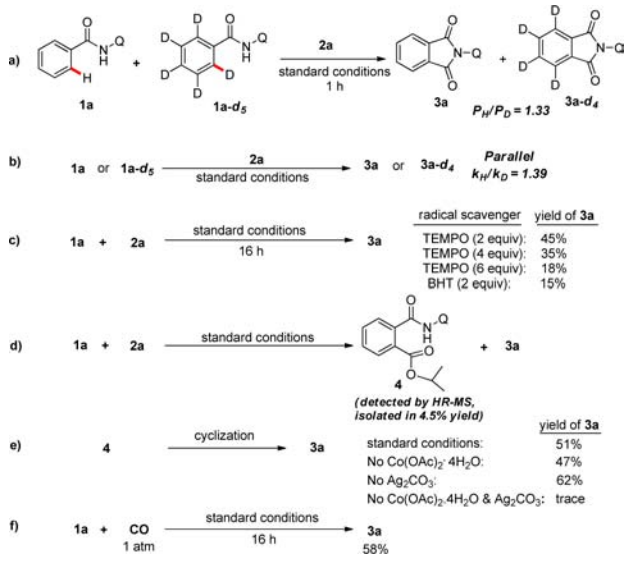
Scheme 3. Scope of Azodicarboxylates[a]



[a]Reactions were run at the standard conditions on 0.2 mmol scale.

intermolecular competition experiment gave a kinetic isotopic effect (KIE) of P_H/P_D = 1.33 (Scheme 4a). The k_H/k_D value of 1.39 was obtained by two parallel reactions using substrates **1a** and **1a**-d_5, indicating that the C−H bond cleavage probably occurred in the rate-determining step (Scheme 4b).[7] Second, we found that radical scavengers, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), significantly suppressed the reaction (Scheme 4c), indicating that a single electron transfer (SET) process might be involved in the reaction. According to the literature,[8] DIAD can release the esteric radical, which might act as the active carbonylation species in our C−H carbonylation reaction. Indeed, a careful examination of the reaction mixture led to the

Scheme 4. Mechanistic Studies



identification of intermediate **4** by HRMS, which was then isolated in 4.5% yield and confirmed by comparison with synthetic samples (Scheme 4d; also see Supporting Information). Meanwhile, reaction of intermediate **4** under the standard conditions afforded product **3a** in 51% yield (Scheme 4e). These results supported that ester **4** is likely the key intermediate. In the meantime, we also conducted control experiments to investigate the transformation of **4** to **3a**. It was found that either $Co(OAc)_2{\cdot}4H_2O$ or Ag_2CO_3 could promote the cyclization reaction, whereas nearly no product was detected without any metal. On the basis of this result, we inferred that metal salts might act as Lewis acid catalysts in the intramolecular *N*-nucleophilic cyclization process (Scheme 4e).

In addition,[9] we also investigated the probability of an alternative mechanism involving production of CO gas by DIAD. Indeed, we determined[10] the extrusion of CO from the reaction system after 3 h (see Supporting Information). Further, product **3a** was obtained in 58% yield under the standard conditions using CO gas instead of DIAD (Scheme 4f) as the carbonyl source. Collectively, the mechanism of our current protocol may involve both the esteric radical and CO insertion processes.

Based on the experiments above and the literature reports on Co catalysis,[5g,h] a proposed mechanism for the current cobalt-catalyzed C(sp^2)−H carbonylation is shown in Scheme 5. Initially, Co(II) salt is oxidized to Co(III) species, which then coordinates with benzamide **1a** followed by the C(sp^2)−H bond cobaltation to form intermediate **B**. Thermal decomposition of DIAD produces the esteric radical that would then attack the intermediate **B** to generate the intermediate **C** (path a).[8] The Co(IV) species **C** subsequently undergoes the reductive elimination to generate the esterification product **4** and release the Co(II) species. The generated Co(II) species is reoxidized to Co(III) species by silver salts to complete the catalytic cycle. The ester **4** subsequently undergoes an *in situ* intramolecular *N*-nucleophilic cyclization to afford phthalimide **3a**, along with elimination of isopropanol.[11] Alternatively, the CO might be generated from the esteric radical (path b),[6b,8a] which then inserts the C−Co bond of the intermediate **B** to afford the species **D**. Product **3** can be obtained via a reductive

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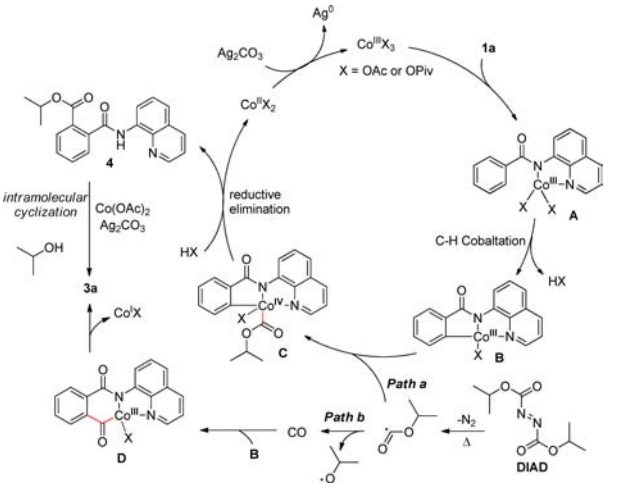
Scheme 5. Proposed Reaction Mechanism



elimination process. The Co(I) species can be reoxidated to Co(III) to reactivate the catalytic cycle.

In summary, we have established an efficient and convenient approach for the C(sp^2)−H bond carbonylation of benzamides using stable and inexpensive $Co(OAc)_2{\cdot}4H_2O$ as the catalyst and the commercially available and easily handling azodicarboxylates as the novel and nontoxic carbonyl source. The transformation exhibited a broad substrate scope with high functional group compatibility. To the best of our knowledge, the current approach not only represents the first example where azodicarboxylates was used as the carbonyl source but also is among the limited examples of cobalt-catalyzed C−H bond carbonylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03111.

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

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Notes

The authors declare no competing financial interest.

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