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Cobalt(II)-Catalyzed Oxidative C−H Alkenylations: Regio- and Site-Selective Access to Isoindolin-1-one

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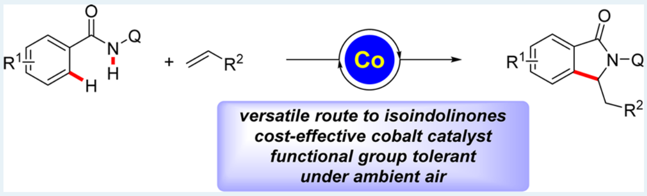
Supporting Information

ABSTRACT: Isoindolinone derivatives were prepared in a step-economical fashion by a C−H/N−H functionalization process with a catalytic system composed of $Co(OAc)_2$ and $Mn(OAc)_2$ or AgOPiv. The oxidative annulation by benzamides occurred efficiently with differently substituted electron-deficient alkenes. Mechanistic studies were indicative of a kinetically relevant, carboxylate-assisted C−H cobaltation.



KEYWORDS: *C−H activation, alkenylation, cobalt, mechanism, oxidative annulation*

Selectively substituted isoindolin-1-ones are key structural motifs found in numerous compounds of relevance to biology and medicinal chemistry.[1] Their syntheses by transition-metal catalysis largely rely on the prefunctionalization of starting materials,[2−4] which leads to undesired byproduct and waste formation. In recent years, oxidative functionalizations of otherwise unreactive C−H bonds have emerged as increasingly powerful tools for the atom-economical synthesis of decorated heterocycles.[5] Particularly, oxidative annulations of alkynes or alkenes by C−H/N−H functionalizations have proven to be useful.[6] Although the vast majority of oxidative alkene annulations was accomplished with precious 4d or 5d transition-metal complexes, the focus has recently shifted toward developing catalysts of earth-abundant first row transition metals.[7] In this context, considerable recent progress has been accomplished with versatile cobalt catalysts.[8−10] In an elegant very recent example, Daugulis and Grigorjeva reported on a cobalt-catalyzed annulation of electron-rich alkenes, regioselectively leading to six-membered heterocycles.[11] During our ongoing independent studies on cobalt-catalyzed C−H functionalization,[8,12−14] we identified a complementary oxidative coupling with electron-deficient olefins that provides expedient access to synthetically useful isoindolin-1-ones. Herein, we wish to describe the unprecedented cobalt-catalyzed oxidative annulation of electron-deficient alkenes, along with first mechanistic insights on the cobalt-catalyzed C−H/N−H functionalization process with olefins.

Our study commenced with probing various solvents for the envisioned cobalt-catalyzed oxidative alkenylation of *N*-quinolinyl (Q)-substituted[15,16] benzamide **1a** to furnish isoindolinone **3aa** (Table 1). Unfortunately, the C−H/N−H functionalization was not viable when using a representative set of common solvents, including apolar arenes (entries 1 and 2), or polar DMF, DMSO, and DMPU (entries 3−5). Likewise, DCE, 1,4-dioxane or CF_3CH_2OH proved ineffective (entries 6−8), the latter of which highlights the significant difference to transformations of electron-rich alkenes.[11] In stark contrast, more promising results were obtained with PEG 400 (entry 9), a reaction medium that we had previously exploited for palladium- and ruthenium-catalyzed C−H arylations.[17] Notably, PEG 400 was found to be advantageous as compared to glycerol or ethylene glycol (entries 10−12). Improved catalytic activities proved viable with a solvent mixture comprising of PEG 400 and CF_3CH_2OH (entry 13). Among a set of representative terminal oxidants (entries 13−16), silver(I) salts were beneficial, with optimal results being accomplished with $AgNO_3$ or AgOPiv (entries 17−24). It is noteworthy that the C−H functionalization did not occur in the absence of the cobalt catalyst, whereas additional metal acetates were not required under the optimized reaction conditions (entries 25−27). The robustness of the cost-effective cobalt(II) catalyst was reflected by a high catalytic efficacy under an ambient atmosphere of air.

With an optimized catalytic system in hand, we examined its versatility in the annulation with substituted amides **1** (Scheme 1). The most user-friendly cobalt catalyst allowed for the efficient transformation of various *para*- and sterically hindered *ortho*-substituted arenes **1**. The excellent chemoselectivity of the high-valent cobalt catalyst was illustrated by successful C−H/N−H functionalizations with substrates bearing a range of reactive electrophilic functional groups, such as chloro, bromo, iodo, cyano, or nitro substituents. Intramolecular competition experiments with *meta*-substituted benzamides **1** were largely governed by repulsive steric interactions, leading to the preferential formation of isomers **3na** and **3oa**.

Subsequently, we explored the pool of viable electron-deficient alkenes **2** (Scheme 2). Thereby, we found the cobalt catalyst to enable the C−H/N−H functionalization with differently substituted vinyl esters **2a**/**b**, ketones **2c**, or nitriles **2d**.

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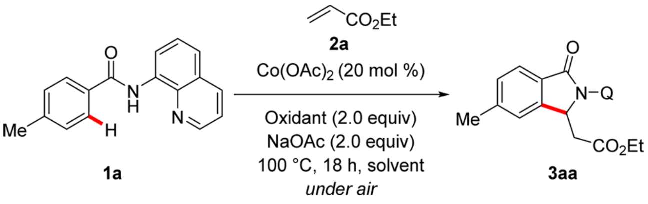
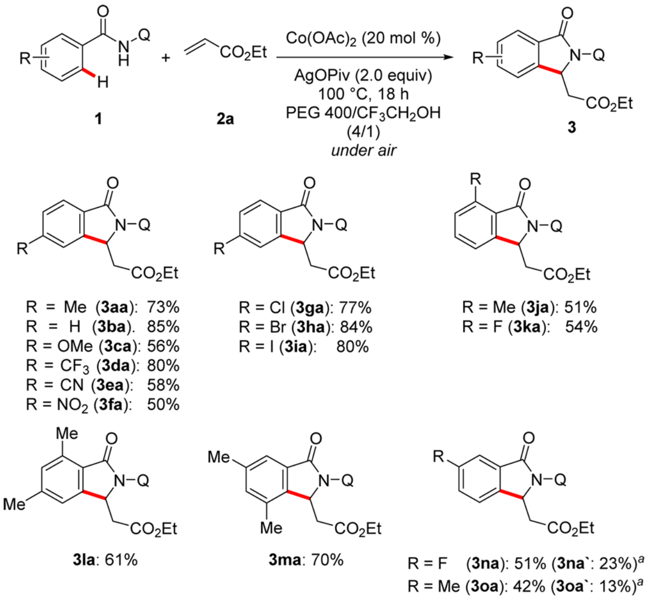
Table 1. Optimization of Cobalt-Catalyzed Isoindolinone Synthesis[a]



entry	solvent	oxidant	3aa
1	PhMe	$Mn(OAc)_2$	<5%[b]
2	PhCl	$Mn(OAc)_2$	---
3	DMF	$Mn(OAc)_2$	<5%[b]
4	DMSO	$Mn(OAc)_2$	--
5	DMPU	$Mn(OAc)_2$	<5%[b]
6	1,4-dioxane	$Mn(OAc)_2$	---
7	DCE	$Mn(OAc)_2$	---
8	CF_3CH_2OH	$Mn(OAc)_2$	<5%[b]
9	PEG 400	$Mn(OAc)_2$	37%
10	PEG 1000	$Mn(OAc)_2$	<5%[b]
11	glycerol	$Mn(OAc)_2$	---
12	ethylene glycol	$Mn(OAc)_2$	<5%[b]
13	PEG 400/CF_3CH_2OH (4:1)	$Mn(OAc)_2$	60%
14	PEG 400/CF_3CH_2OH (4:1)	$Cu(OAc)_2 \cdot H_2O$	--
15	PEG 400/CF_3CH_2OH (4:1)	$Zn(OAc)_2$	--
16	PEG 400/CF_3CH_2OH (4:1)	$PhI(OAc)_2$	<5%[b]
17	PEG 400/CF_3CH_2OH (4:1)	AgOAc	48%
18	PEG 400/CF_3CH_2OH (4:1)	Ag_2O	22%[b]
19	PEG 400/CF_3CH_2OH (4:1)	Ag_2SO_4	39%
20	PEG 400/CF_3CH_2OH (4:1)	Ag_2CO_3	47%
21	PEG 400/CF_3CH_2OH (4:1)	AgO_2CCF_3	51%
22	PEG 400/CF_3CH_2OH (4:1)	$AgNO_3$	61%
23	PEG 400/CF_3CH_2OH (4:1)	AgOPiv	65%
24[c]	PEG 400/CF_3CH_2OH (4:1)	AgOPiv	49%
25[d]	PEG 400/CF_3CH_2OH (4:1)	--	<5%[b]
26[d,e]	PEG 400/CF_3CH_2OH (4:1)	--	<5%[b]
27[d]	**PEG 400/CF_3CH_2OH (4:1)**	**AgOPiv**	**73%**

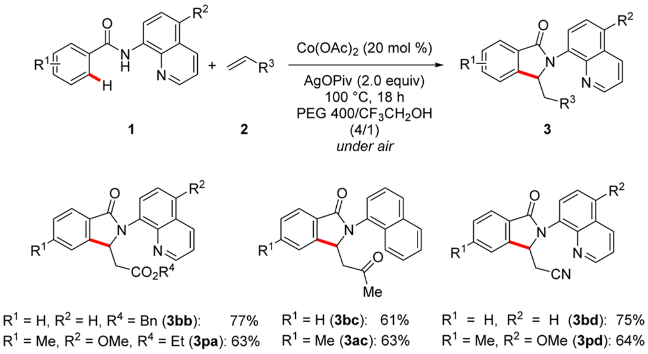
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), $Co(OAc)_2$ (20 mol %), NaOAc (2.0 equiv), solvent (2.5 mL), 100 °C, 18 h. [b]GC conversion. [c]60 °C. [d]Without NaOAc. [e]Without $Co(OAc)_2$. Q = 8-quinolinyl.

Scheme 1. Scope of Cobalt-Catalyzed Isoindolinone Synthesis

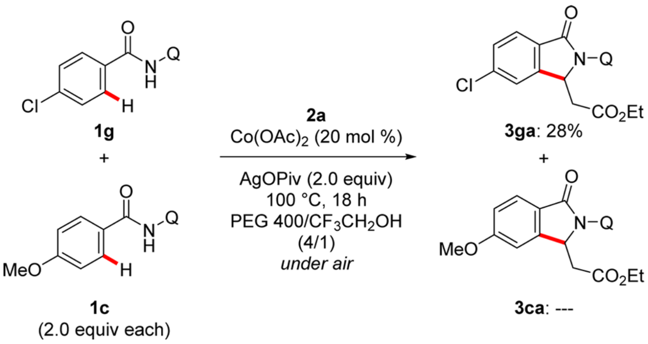


[a]Major regioisomer shown, isolated yields of minor C-2 isomers in parentheses.

Scheme 2. Cobalt-Catalyzed Annulation with Alkenes 2



Scheme 3. Competition Experiments between Amides 1



Given the unusual selectivity features of the cobalt(II) catalyst, we became intrigued by delineating its mode of action. To this end, intermolecular competition experiments between amides **1c** and **1g** were performed, which selectively delivered chloro-substituted product **3ga** as the sole product (Scheme 3).

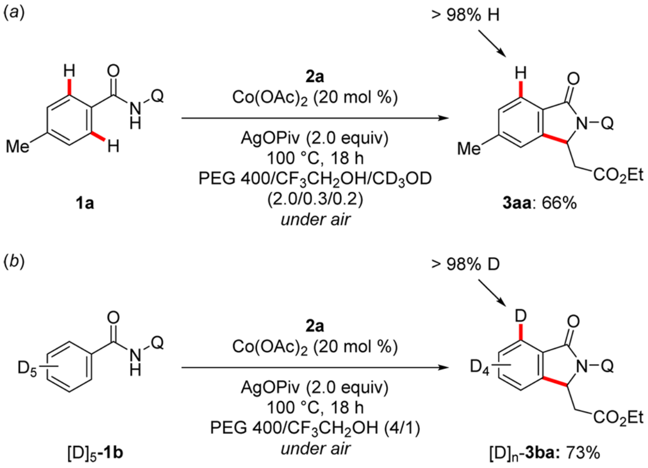
Mechanistic studies with deuterated solvent $[D_4]$-MeOH or isotopically labeled substrate $[D_5]$-**1b** indicated that a H/D scrambling was not occurring (Scheme 4). This observation is in good agreement with the C−H cobaltation being irreversible.

Cobalt-catalyzed C−H alkenylations with amide **1b** and isotopically labeled substrate $[D_5]$-**1b** revealed a considerable intermolecular kinetic isotope effect (KIE) of $k_H/k_D \approx 1.4$ (Scheme 5a), whereas the intramolecular KIE with substrate $[D_1]$-**1b** was determined to be $k_H/k_D \approx 1.6$ (Scheme 5b).

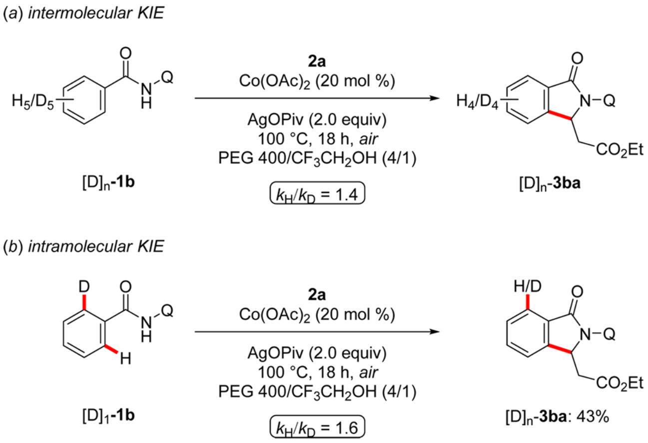
On the basis of our mechanistic studies, we propose the oxidative alkene annulation to proceed by a kinetically relevant, carboxylate-assisted[18,19] C−H cobaltation (Scheme 6), which also rationalizes the preferential functionalization of electron-deficient arenes **1** within the intermolecular competition experiments (*vide supra*). Subsequent migratory insertion of the olefin **2**, along with *β*-hydride-elimination, delivers the alkenylated benzamide **6**, which finally undergoes an intramolecular alkene hydroamidation[20] to furnish the desired isoindolinones **3**.

In summary, we have reported on the development of cobalt-catalyzed C−H/N−H functionalizations to furnish isoindolinones in an atom- and step-economical fashion. A high-valent cobalt catalyst generated in a solvent mixture consisting of PEG

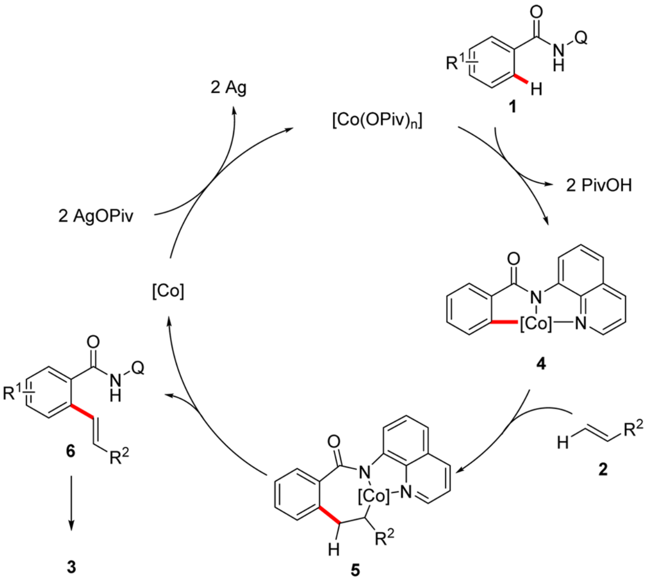
Scheme 4. Studies with Isotopically Labeled Compounds



Scheme 5. Kinetic Isotope Effect (KIE) Studies



Scheme 6. Proposed Catalytic Cycle



400 and CF_3CH_2OH allowed for the efficient oxidative annulation of electron-deficient alkenes by benzamides. The C−H functionalization occurred with ample substrate scope, using a removable bidentate auxiliary.[21] Mechanistic studies were supportive of a kinetically relevant, carboxylate-assisted C−H cobaltation.

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00322.

> Experimental procedures, characterization data, and ^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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