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Cobalt(III)-Catalyzed C–H Bond Amidation with Isocyanates

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Abstract

The first examples of cobalt(III)-catalyzed C–H bond addition to isocyanates are described, providing a convergent strategy for arene and heteroarene amidation. Using a robust air- and moisture-stable catalyst, this transformation demonstrates broad isocyanate scope, good functional-group compatibility and has been performed on gram scale.

Abstract

In recent years, many elegant strategies employing transition-metal-catalyzed C–H bond functionalization have emerged for the synthesis of amines and nitrogen heterocycles.¹ Among the rich array of metal complexes that mediate C–H functionalization, Rh(III)-catalysts have proven to be exceptionally versatile due to their unique reactivity and high functional-group compatibility,² with additions of C(sp²)–H bonds to polarized π -bonds providing for convergent introduction of heteroatom functionality.^{3–9} In this regard, we reported direct C(sp²)–H bond addition to isocyanates as a particularly step- and atom-economic strategy for the preparation of aromatic, heterocyclic and alkenyl amides.^{6f} Direct C(sp²)–H bond additions to isocyanates have also been accomplished with Re¹⁰ and Ru¹¹ catalysts.¹² In contrast, catalytic C–H bond functionalization with earth-abundant first-row transition-metals has emerged only recently,¹³ and to our knowledge, additions to isocyanates have not been described. Herein we report the first examples of cobalt-catalyzed C–H bond amidation with isocyanates.^{14–15} This convenient benchtop procedure is effective for multiple heterocycle directing groups, shows good functional group compatibility, broad scope for aromatic and alkyl isocyanates, and is readily scalable.

For initial evaluation of Co(III)-catalyzed C–H bond additions to isocyanates, we chose 1-phenyl-1H-pyrazole (**1a**) and phenyl isocyanate (**2a**) as the coupling partners. First

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ASSOCIATED CONTENT

Supporting Information

Experimental details, gram scale synthesis, and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

developed by Kanai, Matsunaga, and co-workers for additions to sulfonyl imines^{14p} we anticipated that the cationic preformed catalyst $[\text{Cp}^*\text{Co}(\text{C}_6\text{H}_6)][\text{PF}_6]_2$ (**4a**) might also facilitate C–H bond amidation with isocyanates. Indeed, the desired reactivity was achieved when catalyst **4a** was utilized in the presence of catalytic potassium acetate at 80 °C, providing product **3a** in 74% yield (Table 1, entry 1). Given that solvent effects have been observed to play a key role in obtaining optimal yield in Ru(II)-¹¹ and Rh(III)-catalyzed C–H amidations,⁶ different solvents were evaluated. While the use of the ethereal solvents 1,4-dioxane and tetrahydrofuran (entries 1 and 2, respectively) as well as 1,2-dichloroethane (entry 3) provided comparable yields, the non-polar and non-coordinating solvent toluene resulted in a low yield (entry 4). Ultimately, the higher boiling solvent 1,4-dioxane was selected for further reaction optimization because it allowed reactions to be conducted at higher temperatures.

Performing the reaction at 120 °C rather than 80 °C moderately increased the yield (entries 1 vs 5). This reaction is amenable to benchtop set up, providing an isolated yield of 84%, identical to that achieved with glovebox setup (entry 5). Reducing the catalyst loading from 10 to 2.5 mol % did not significantly influence the reaction outcome for this substrate combination (entries 5 vs 6), although at 1 mol % of catalyst loading the yield dropped to 66% (entry 7). Using the reverse stoichiometry with **1a** as the limiting reagent provided an identical yield to that achieved under standard conditions (entries 5 vs 8), although isolation of pure product was more challenging due to byproduct formation. Conducting the reaction at a concentration of 0.5 M did not affect the reaction yield (entries 5 vs 9); however, the higher concentration of 2.0 M was selected to provide conditions that minimize solvent waste. Lowering the reaction temperature to 100 °C to operate below the boiling point of 1,4-dioxane resulted in a moderate drop in yield to 60% when 2.5 mol % of **4a** was employed (entries 6 vs 10). The non-cationic dimeric complex $[\text{Cp}^*\text{CoCl}_2]_2$ (**4b**) provided only 5% yield even at higher catalyst loading and an elevated temperature (entry 11). Operating below the solvent boiling point, a comparable yield was observed with preformed cationic catalyst **4c** relative to **4a** (entries 10 vs 12). This result indicates that for Co(III)-catalyzed C–H bond additions to isocyanates, a completely non-coordinating counterion provides no rate enhancement relative to PF_6 .¹⁶ Removal of potassium acetate dramatically reduced the yield of desired product (entry 13). Moreover, no product was observed when catalyst **4a** was excluded (entry 14), demonstrating that a Co(III)-catalyst is required for this C–H functionalization. Due to the lower cost of the PF_6 counterion, cobalt catalyst **4a** was selected for evaluating substrate scope. A catalyst loading of 10 mol % was used to achieve higher conversion for less reactive substrates (see Scheme 1). Finally, given that C–H bond amidation with isocyanates has been reported for Re, Ru, and Rh, ICP-MS analysis of Co(III)-catalyst **4a** was performed to detect the levels of several 2nd and 3rd row metals known to mediate C–H functionalization. Complex **4a** showed less than 1 ppm of Re, Ru, Rh, Ir, and Pt, and Pd at 1 ppm (see Supporting Information for details).

Substrate scope was first evaluated with a series of functionalized isocyanates **2** and *N*-aryl-1H-pyrazoles **1** (Scheme 1). For aromatic isocyanates, electron-rich (**3b**), electron-neutral (**3c**, **3e**), and electron-deficient (**3d**, **3f–h**) derivatives all coupled in high yield. Additionally, high yields were maintained when substituents were placed at the para (**3b–d**),

meta (**3e–g**), and ortho (**3h**) positions. Linear alkyl isocyanates coupled to provide the *N*-benzyl amide **3i** and *N*-hexyl amide **3j** in good yields, while a branched alkyl isocyanate gave the *N*-cyclohexyl amide **3k** in moderate yield. A higher 10 mol % catalyst loading was necessary for some of the isocyanates. For example, while a good yield was obtained when employing 2.5 mol % of catalyst **4a** in the synthesis of **3a**, a dramatically lower 19% yield of **3j** was observed at this lower loading for hexyl isocyanate.

A series of substituted *N*-aryl-1*H*-pyrazoles **1** were then evaluated and provided amide products **3** in good yields for electron-rich (**3l**, **3p**), electron-neutral (**3m–n**, **3q**), and electron-deficient (**3o**) substituents. For meta-substituted derivatives, C–H functionalization occurred exclusively at the less hindered position to give amides **3p** and **3q**, thereby demonstrating that regioselectivity can be controlled by steric effects.¹⁷ Notably, incorporation of both bromo (**3n**) and methyl ketone (**3o**) groups proceeded in good yield, highlighting the functional-group compatibility of Cp*Co(III) catalysis, which consequently enables subsequent transformations for late stage introduction of molecular complexity.

The directing group scope of this reaction was also investigated (Scheme 2). In addition to the amidation of *N*-aryl-1*H*-pyrazoles, the 2-pyridyl (**3r**) and 2-pyrimidinyl (**3s**) directing groups also provided amide products albeit in modestly diminished yields. The 2-pyrimidinyl directing group was also further successfully applied to indole functionalization (**3t**).¹⁸ Given that both 2-phenylpyrimidine and 1-(pyrimidin-2-yl)-1*H*-indole contain two potential nitrogen directing groups, we were pleased to find that only mono-amidation products **3s** and **3t** were obtained without any double addition products. We also evaluated acetanilide, which we had previously determined to be an effective substrate for Rh(III)-catalyzed isocyanate additions.^{6f} However, this substrate was not effective for Co(III)-catalyzed isocyanate addition because the KOAc additive resulted in competitive *N*-acylation rather than providing the desired C–H bond addition product **3u**.

A gram scale reaction was conducted to assess the scalability of this Co(III)-catalyzed C–H bond amidation with isocyanates (Scheme 3). Employing only 2.5 mol % of preformed catalyst **4a** and 5 mol % of KOAc under the optimized reaction conditions, pyrazole **3a** was furnished in 75% yield (1.18 g), which was a similar yield to that obtained on smaller scale.

In summary, the cationic preformed cobalt complex [Cp*Co(C₆H₆)](PF₆)₂ (**4a**) efficiently catalyzes C–H bond additions to isocyanates and represents the first example of earth-abundant metal catalysis of this type of transformation. In addition to the *N*-aryl-1*H*-pyrazole directing group, this process has been achieved with other nitrogen heterocycle directing groups. Using an air- and moisture-stable catalyst, this transformation is amenable to benchtop set up and has been performed on gram scale with low catalyst loading. The broad scope and high functional-group compatibility of this method showcases the ability of earth-abundant Cp*Co(III) catalysis to mediate practical synthetic transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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17. Reaction at the site of lower steric hindrance to provide a single regioisomer is consistent with other reports of Co(III)-catalyzed C–H bond additions to polarized π -bonds. For examples of aldehyde additions and cyanations, see refs 14g, 14b, 14h, and 14i, respectively.
18. When phenyl(pyrrolidin-1-yl)methanone was also tested as a directing group under the optimized reaction conditions, amidation was not observed. For a Ru(II)-catalyzed amidation of secondary benzamides leading to phthalimides, see ref 11a.

Figure 1.
Cobalt(III)-catalysts used for C–H functionalization.

^aConditions: isocyanate **2** (0.20 mmol), *N*-aryl-1*H*-pyrazole **1** (0.40 mmol) in 1,4-dioxane (2.0 M) at 120 °C for 20 h. ^bIsolated yields after chromatography. ^cReaction conducted using 2.5 mol % of catalyst **4a** and 5 mol % of KOAc.

Scheme 1.

Substrate Scope for Amidation of *N*-Aryl-1*H*-Pyrazoles with Isocyanates^{a,b}

^aConditions: **2a** (0.20 mmol), directing group **1** (0.40 mmol) in 1,4-dioxane (2.0 M) at 120 °C for 20 h. ^bIsolated yields after chromatography.

Scheme 2.
Directing Group Scope for C-H Bond Amidation^{a,b}

Scheme 3.
Gram Scale Synthesis of Pyrazole **3a**

Table 1

Optimization of Reaction Conditions for Co(III)-Catalyzed Amidation with Phenyl Isocyanate^a

entry	Co(III)-catalyst (mol %)	KOAc (mol %)	temp (°C)	solvent	yield (%) ^b
1	4a (10)	20	80	1,4-dioxane	74
2	4a (10)	20	80	THF	62
3	4a (10)	20	80	DCE	66
4	4a (10)	20	80	toluene	8
5	4a (10)	20	120	1,4-dioxane	84 (84) ^{c,d}
6 ^c	4a (2.5)	5	120	1,4-dioxane	80 (79) ^d
7	4a (1)	2	120	1,4-dioxane	66
8 ^e	4a (10)	20	120	1,4-dioxane	84
9 ^f	4a (10)	20	120	1,4-dioxane	84
10	4a (2.5)	5	100	1,4-dioxane	60
11	4b (5)	20	120	1,4-dioxane	5
12	4c (2.5)	5	100	1,4-dioxane	57
13	4a (10)	--	120	1,4-dioxane	7
14	--	20	120	1,4-dioxane	--

^a Conditions: **2a** (1.0 equiv), **1a** (2.0 equiv) in 1,4-dioxane (2.0 M) for 20 h.^b Determined by GC analysis relative to tetradecane as an external standard.^c Reaction run on the benchtop under nitrogen.^d Isolated yield at 0.20 mmol scale.^e Reverse stoichiometry: **2a** (2.0 equiv), **1a** (1.0 equiv).^f Reaction conducted in 1,4-dioxane (0.5 M).