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Thioamide Directed Co(III) Catalyzed Selective Amidation of C(sp^3)-H Bonds

Peng Wen Tan, Adrian M. Mak, Michael B. Sullivan, Darren J. Dixon* and Jayasree Seayad*

Abstract: A mild, oxidant-free and selective Cp*Co^{III}-catalyzed amidation of thioamides with robust dioxazolone amidating agents via C(sp^3)-H bond activation to generate the desired amidated products is reported. The method is efficient and allows for the C-H amidation of a wide range of functionalized thioamides with aryl-, heteroaryl- and alkyl- substituted dioxazolones under the Cp*Co^{III} catalyzed conditions. The observed regioselectivity towards primary C(sp^3)-H activation is supported by computational studies and the cyclometalation is proposed to proceed via an external carboxylate assisted concerted metalation/ deprotonation mechanism. The reported method is a rare example of the use of a directing group other than the commonly used pyridine/quinolone classes for Cp*Co^{III} catalyzed C(sp^3)-H functionalization and the first to exploit thioamides.

The arena of C-H functionalization has witnessed tremendous growth over the past decade.[1] The activation/functionalization of ubiquitous C-H bonds in place of traditional pre-activated functional groups is particularly attractive in terms of its directness, resource efficiency and atom economy for carbon-carbon / carbon-heteroatom bond formation. In the majority of cases, C-H bond activation/functionalization reactions employ precious metal catalyst complexes of palladium, rhodium, iridium or ruthenium, owing to their phenomenal reactivity and ease of handling and a plethora of important studies have been published.[1] However, it is not until only recently that the field has witnessed a substantial shift towards using earth-abundant first-row transition-metal catalysts as alternatives due to, among other reasons, their lower cost and toxicity.[2] Of the first row transition metals, cobalt complexes have revealed exemplary reactivity in this regard, ranging from transformations catalyzed by low-valent cobalt complexes to high-valent cobalt catalyzed C-H functionalization reactions.[3-9] Notably, high-valent Cp*Co^{III} catalysts have received significant attention due to their great stability yet outstanding reactivity[3-8], analogous to that of their Rh^{III} and Ir^{III} counterparts.[10-11] Despite the substantial amount of preceding work that has demonstrated transformations pivoting on Cp*Co^{III} catalyzed C(sp^2)-H bond activation, studies on the C(sp^3)-H activation/functionalization by Cp*Co^{III} catalysts remain limited.[8,9] This scarcity of reports prompted us to explore possible transformations that could uncover and advance the potential of cobalt catalysis for C(sp^3)-H bond activation, a process that is often beset by the poor reactivity of C(sp^3)-H bonds.[12]

Thioamides, a versatile class of building blocks derived from carboxylic acids, are known for their convenient synthetic applicability to furnish heterocyclic compounds.[13] Thioamide motifs are also used as biologically active compounds in pharmaceuticals and agrochemicals.[14] Consequently, new synthetic methods for their efficient and direct modification via C-H functionalization strategies are attractive. In 2015, Miura and co-workers demonstrated that tertiary thioamide derivatives could serve as effective directing groups (DGs) to effect Cp*Rh^{III} catalyzed *ortho* C(sp^2)-H activation/alkenylation of benzothioamides (Figure 1a).[15] Furthermore, Yu *et al.* disclosed the thioamide directed Pd^{II}-catalyzed α-C(sp^3)-H cross-coupling of cyclic amines with aryl- and heteroarylboronic acids (Figure 1b).[16] Inspired by these recent studies we envisaged that the thioamide moiety could likely serve as an efficient directing group to facilitate C(sp^3)-H activation for further transformations under Cp*Co^{III} catalyzed conditions. To this end, herein we disclose the discovery and development of a direct, selective, mild and oxidant-free Cp*Co^{III} catalyzed C(sp^3)-H activation/amidation of thioamides using readily prepared and easy-to-handle dioxazolones as amidating reagents (Figure 1c). To our knowledge this is the first example of a Cp*Co^{III} catalyzed C(sp^3)-H functionalization reaction using a thioamide as an alternative directing group to the commonly used pyridine/quinoline classes.

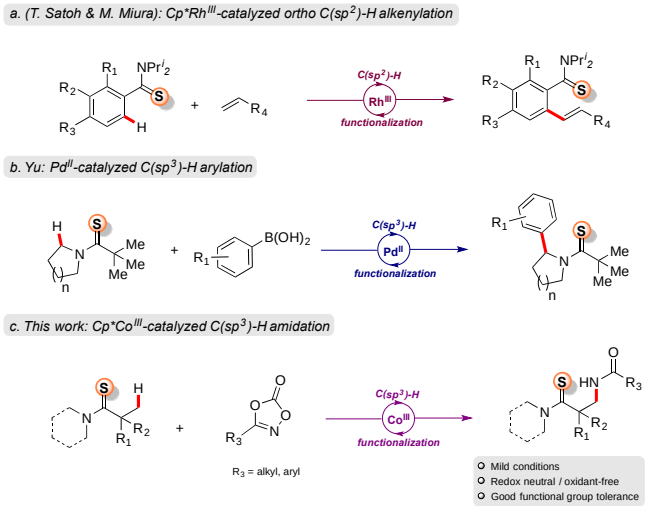

Figure 1. Thioamide directed transition metal catalyzed C(sp^3/sp^2)-H functionalization reactions.

To assess the potential of the Cp*Co^{III} catalysis for any desired C(sp^3)-H functionalization, we began a preliminary

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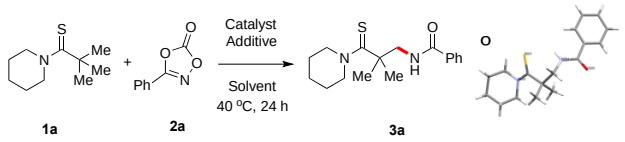
investigation using model substrates thioamide **1a** and dioxazolone **2a** (Table 1) in the presence of catalytic $[Cp^*Co(MeCN)_3][SbF_6]_2$ in dichloroethane (DCE) at 40 °C for 24h (entry 1). Encouragingly, the reaction proceeded smoothly to furnish the amidated product **3a** in 56% yield (determined by ^1H NMR by integration against an internal standard). It was noteworthy that exclusive mono amidation with selective C(sp^3)-H activation at one of the primary methyl groups of the thioamide **1a** instead of the α-methylene protons in the piperidine ring was observed. To optimize the yield of the reaction further, different carboxylic acids and their salts were evaluated as additives. Importantly, addition of 20 mol% sodium benzoate resulted in a significant increase in yield (89%, entry 4). While DCE proved to be the optimal solvent, other solvents such as trifluoroethanol, dioxane and toluene (entries 5, 6 & 7), completely suppressed reactivity and the reactions yielded trace or no product. Switching $[Cp^*Co(MeCN)_3][SbF_6]_2$ for $Cp^*Co(CO)I_2$ (entry 8) or $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (entry 9) or no transition metal catalyst at all (entry 10) led to diminished or no reactivity. While the reaction worked at room temperature with slightly lower yield (entry 12), a higher catalyst loading (entry 11) did not result in an improvement to the yield relative to entry 4. A control reaction using 2,2-dimethyl-1-(piperidin-1-yl)propan-1-one, the amide precursor of **1a**, as the substrate instead of **1a** showed no reactivity confirming the role of the thioamide as directing group for this intriguing primary C(sp^3)-H activation.

Table 1. Optimization studies on C(sp^3)- H activation/ amidation reactions of **1a** & **2a**

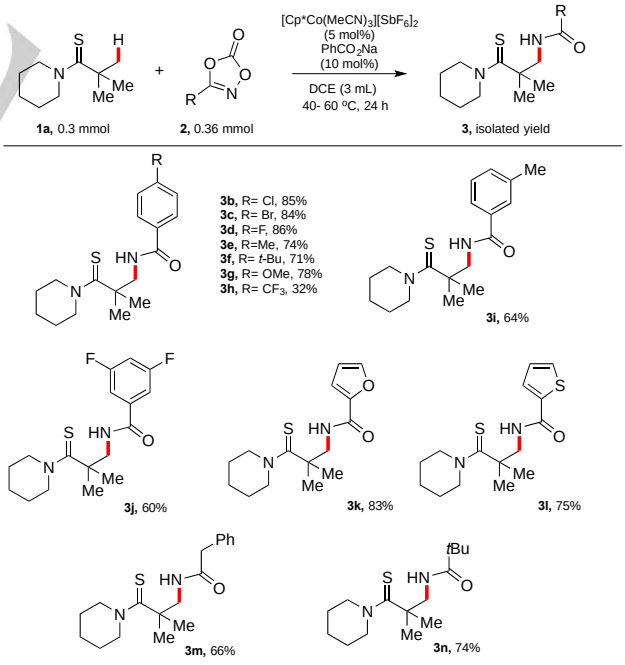


Entry [a]	Catalyst (mol%)	Solvent	Additive (mol%)	Yield[c] (%)
1	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	DCE	-	56
2	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	DCE	PivOH (20)	79
3	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	DCE	$PhCO_2H$ (20)	85
4	**$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)**	**DCE**	**$PhCO_2Na$ (20)**	**89 (86)**
5	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	TFE	$PhCO_2Na$ (20)	-
6	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	Dioxane	$PhCO_2Na$ (20)	5
7	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	Toluene	$PhCO_2Na$ (20)	-
8	$Cp^*Co(CO)I_2$ (5)	DCE	$PhCO_2Na$ (20)	-
9	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5)	DCE	$PhCO_2Na$ (20)	71
10	-	DCE	$PhCO_2Na$ (20)	-
11	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (10)	DCE	$PhCO_2Na$ (40)	85
12[b]	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	DCE	$PhCO_2Na$ (20)	71

[a] Reaction condition: **1a** (0.3 mmol), **2b** (0.36 mmol), catalyst, additive, solvent (3 mL), T= 40 °C, 24 h. [b] Reaction was carried out at RT. [c] ^1H NMR yield using CH_2Br_2 as internal standard; isolated yield in parentheses.

Having identified the optimal reaction conditions for the synthesis of **3a**, various substituted dioxazolones were then evaluated to determine their influence on the overall reactivity and to establish the reaction scope with respect to the amidating reagent (Table 2). In general, this C(sp^3)-H functionalization methodology was amenable to a range of aryl-substituted dioxazolones bearing various electron-withdrawing and electron-donating substituents, furnishing the corresponding amidated products in typically good to excellent yields. Whereas a low yield was obtained in the case of reaction with *para*-CF_3-substituted 3-phenyldioxazolones (**3h**), Cl- (**3b**) and Br- (**3c**) substituents in the *para*-position were well-tolerated delivering products that are synthetically useful for downstream transformations. Furthermore, reactions with heteroaryl-containing dioxazolone substrates proceeded smoothly under the optimized conditions to afford **3k** and **3l** in 83% and 75% yield respectively. Considering the difficulty of installing alkyl *N*-acyl amide moiety using other amidating reagents such as alkyl acyl azides,[17] it was gratifying to note that alkyl-substituted dioxazolone substrates performed well to afford **3m** and **3n** in good yields.

Table 2. C(sp^3)-H activation/amidation of thioamide **1** with various substituted dioxazolones



Subsequently, the scope of our protocol was broadened to include various thioamides derived from different cyclic or acyclic amines and carboxylic acids. As presented in Table 3,

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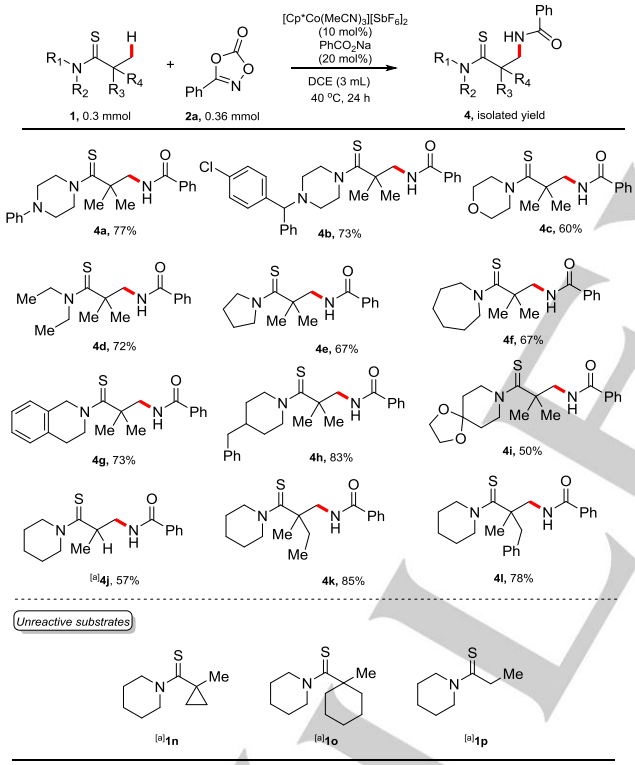
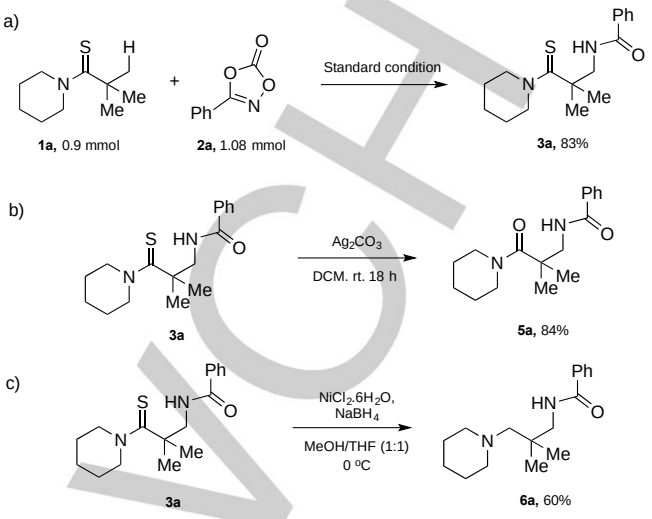
thioamide substrates containing piperazine (**4a** and **4b**) and morpholine (**4c**) scaffolds worked well to afford the desired amidated products in synthetically useful yields of 60-77%. While simple acyclic thioamide substrate (**4d**) displayed good reactivity, reactions with thioamides containing different ring sizes of azacycles (**4e** and **4f**) were also shown to be successful. 4-Substituted piperidinyl thioamides proceeded well in this transformation to generate products **4h** and **4i** in moderate to good yields. Remarkably, primary C(sp^3)-H activation was favored even in the presence of benzylic methylene protons – as showcased by reaction products **4g**, **4h** and **4l** – thus pointing towards steric factors as overriding determinants of reactivity.[18] Furthermore, isopropyl piperidinylthioamide **1k** also reacted well under these conditions to furnish **4j** in 57% yield. Unfortunately, cyclopropanethioamide **1n**, cyclohexanethioamide **1o** and propionthioamide **1p** were unreactive under the standard conditions.

Table 3: C(sp^3)-H activation/amidation of various thioamides with 3-phenyldioxazolones **2a**



[a] Reaction was carried out at 60 °C.

To investigate the efficiency and further practicality of this transformation, a three-fold scale-up of the reaction using the standard substrates **1a** and **2a** was performed (Scheme 1a). Pleasingly, negligible deviation in the obtained yield of **3a** was observed. Additionally, diversification of the amidated product to access other important functionalities was achieved through simple chemical modifications. For example conversion of thioamide **3a** to amide **5a** was efficiently carried out with Ag(I) carbonate (Scheme 1b),[19] whilst selective reduction of the thioamide using nickel boride afforded amine **6a** in 60% yield (Scheme 1c).[20]

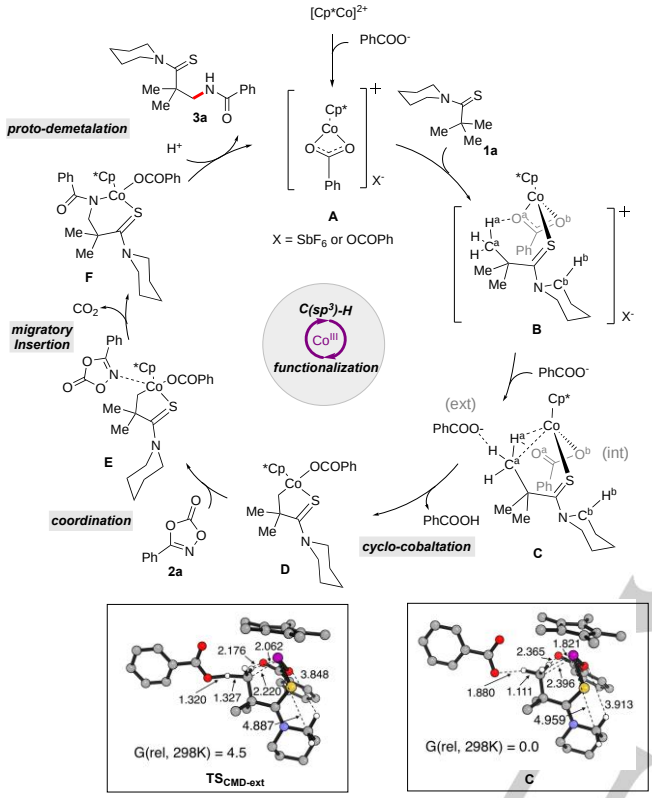


Scheme 1. a) Three-fold scale-up reaction. b) Oxidative desulfurization of thioamide **3a**. c) Reduction of thioamide **3a**.

In line with prior art[5,6] and our preliminary computational studies using *ab initio* and DFT methods implemented in Q-Chem 5.0,[21] a redox-neutral Cp^*Co^{III} catalytic cycle for the C(sp^3)-H activation/amidation of **1a** and **2a** is postulated to be in operation in this chemistry as depicted in Scheme 2. Firstly, we presumed that the first benzoate anion coordinates with $[Cp^*Co]^{2+}$ to form the intermediate, **A** in a η^2 coordination mode. Subsequent binding of **1a** to **A** to form **B** was found to be exergonic (ΔG_{298} = -117.0 kJmol^{-1}). Approach of a second external benzoate anion (ext) promotes the internal coordinated benzoate (int) converting from a η^2 to a η^1 ligand forming **C**, facilitated by an agostic interaction of H^a with Co. The regioselectivity of C(sp^3)-H activation in **1a** was then analyzed. Thus the interatomic distances of H^b—O^b (3.913 Å) and C^b—Co (4.959 Å) in intermediate **C** were calculated to be much larger than that of H^a—O^a (2.365 Å) and C^a—Co (2.396 Å) at the local minimum (see supporting information, Table S1), rendering C^b—H^b unlikely to be activated by Co. This supports the observed selective C-H amidation at the primary methyl group of the thioamide. The cyclometalation in complex **C** then leads to the intermediate **D** potentially by an external carboxylate assisted concerted metalation/ deprotonation (CMD-ext) mechanism[8a, 22]. The activation barrier for CMD-ext was determined to be lower ($\Delta G^{\ddagger}_{298}$ = 4.5 kJmol^{-1}) than the traditional intramolecular concerted metalation/deprotonation (CMD-int) ($\Delta G^{\ddagger}_{298}$ = 40.9 kJmol^{-1}) thus favoring the former. Subsequently, the coordination of intermediate **D** with dioxazolone **2a** followed by migratory insertion of the amido group results in a synchronous CO_2 extrusion to afford the amido complex **F**. Proto-demetalation of **F** would release product **3a** and concurrently regenerate active species **A** ready for further catalytic turnovers.

The absence of reactivity observed in compound **1n** and **1o** were further examined and based on our preliminary

calculations, their most stable conformations have CH_3 groups oriented away from the metal center (a dihedral of ~120° to the C=S) when coordinated to **A** (see supporting information, Figure S3). Therefore, an effective cyclo-cobaltation is less likely to occur. Further investigations on the mechanism will be discussed in detail in our subsequent work.



Scheme 2: Postulated mechanism for C(sp^3)-H activation/amidation of thioamide **1a** with dioxazolone **2a**. All bond lengths are in Ångstroms and relative free energies are in $kJmol^{-1}$ for density functional theory (DFT)-optimized structures of intermediate **C** and $TS_{CMD\text{-}ext}$.

In conclusion, we have discovered and developed a mild, efficient and selective method for C(sp^3)-H bond activation / amidation employing thioamides as the directing group, with aryl-, heteroaryl- and alkyl- substituted dioxazolones under $Co^{III}Cp^*$ catalytic conditions. Additionally, a wide range of thioamides with piperazine, morpholine, tetrahydroisoquinoline and other substituted *N*-containing heterocycles were well-tolerated. This work stands as a rare example of Cp^*Co^{III} catalyzed C(sp^3)-H functionalization using an alternative directing group to the commonly used pyridine/quinoline classes and the first using a thioamide. Computational studies support the observed regioselectivity towards primary C(sp^3)-H activation and suggest that the cyclometalation proceeds via an external carboxylate assisted concerted metalation/ deprotonation mechanism. Investigations into other synthetically relevant $Co^{III}Cp^*$ catalyzed C(sp^3)-H bond functionalization reactions directed by thioamide moieties – from ubiquitous amides, amino acids and peptides – are currently ongoing and the results will be disclosed in due course.

Experimental Section

General procedure for the synthesis of **3**: In a N_2-filled glovebox, a 8 mL reaction vial was charged with thioamide **1a** (0.30 mmol, 1 equiv), dioxazolone **2** (0.36 mmol, 1.2 equiv), PhCOONa (0.03 mmol, 4.32 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.015 mmol, 11.8 mg) in DCE (3 mL). The sealed reaction vial was then brought out of the glovebox and reaction was run under inert atmosphere at 40-60 °C. After 24 hours, the reaction mixture was cooled to room temperature and solvent was removed *in vacuo*. The crude reaction mixture was then purified and products were isolated by flash column chromatography (EtOAc/ PE = 1/9 to 2/3).

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Keywords: cobalt Cp* • C(sp^3)-H activation • amidation • thioamide • selective

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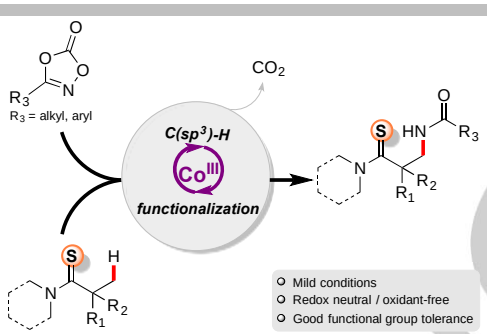
COMMUNICATION

A mild, efficient and selective method for C(sp^3)-H bond activation / amidation employing thioamides as the directing group, with aryl-, heteroaryl- and alkyl-substituted dioxazolones under $Co^{III}Cp^*$ catalytic conditions, is described.



P. W. Tan, A. M. Mak, M. B. Sullivan, D. J. Dixon and J. Seayad**

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Thioamide Directed Co(III) Catalyzed Selective Amidation of C(sp^3)-H Bonds