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Cobalt(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective C(sp^3)-H Amidation of Thioamides

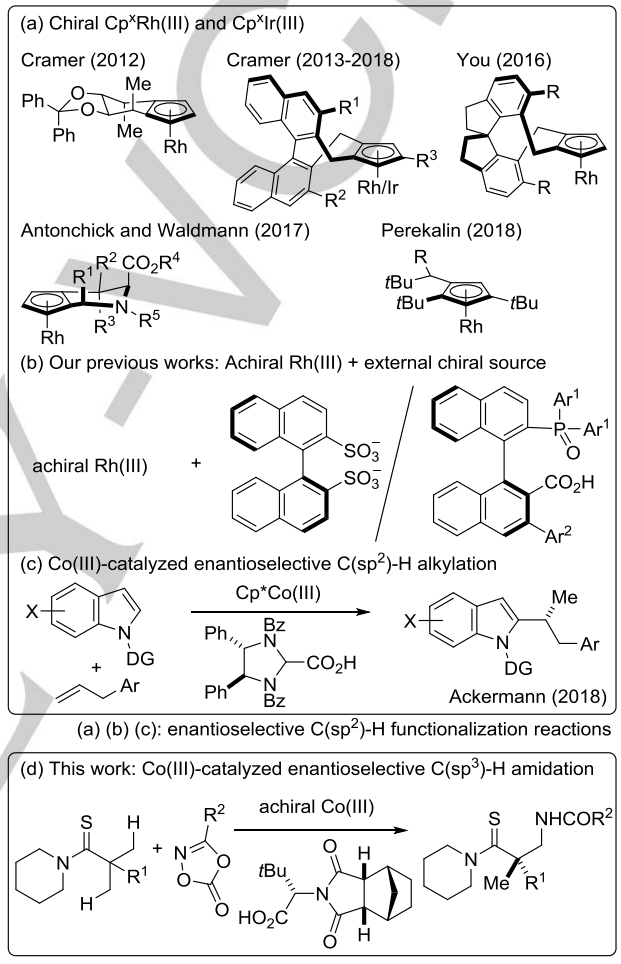
Seiya Fukagawa, Yoshimi Kato, Ryo Tanaka, Masahiro Kojima, Tatsuhiko Yoshino,* and Shigeki Matsunaga*

Abstract: Recent advances in Cp^{x}M(III) catalyses (M = Co, Rh, Ir) have enabled a variety of enantioselective C(sp^2)-H functionalization reactions, but enantioselective C(sp^3)-H functionalization is still largely unexplored. Here we describe an asymmetric C(sp^3)-H amidation of thioamides using an achiral Co(III)/chiral carboxylic acid hybrid catalytic system, providing easy and straightforward access to chiral β-amino thiocarbonyl and β-amino carbonyl building blocks with a quaternary carbon stereocenter.

Transition metal-catalyzed C-H functionalization[1] is attracting increasing attention in organic synthesis due to the potential to enable atom-[2] and step-economical[3] synthesis of functional molecules. Trivalent group 9 metals with a cyclopentadienyl-type (Cp^x) ligand exhibit remarkable catalytic performance and generality for directing group-assisted C-H activation/functionalization reactions.[4] Although catalytic control of enantioselectivity[5] under the Cp^{x}M(III) (M = Co, Rh, Ir) catalyses was a longstanding problem due to the lack of vacant coordination sites for an external chiral ligand, well-designed chiral Cp^x ligands have been developed as a powerful solution.[5a,b,6-12] After the pioneering works by Cramer's group,[6] several types of chiral Cp^x ligands and their metal complexes were synthesized and used for enantioselective C-H functionalization reactions (Scheme 1a).[7-11] We recently demonstrated that an achiral Cp^{x}Rh(III) catalyst hybridized with an external chiral source realizes enantioselective C-H functionalization reactions (Scheme 1b).[13] These previous studies on group 9 metals, however, only focused on enantioselective C(sp^2)-H functionalization reactions, and more challenging C(sp^3)-H functionalization reactions remain unexplored.[10c,14] Furthermore, Cp^{x}Co(III) catalysts were less investigated for enantioselective reactions despite their ready availability and unique properties.[4d-f,h,l,15] During the preparation of this manuscript, Ackermann and co-workers reported an enantioselective alkylation of indoles with olefins using a Cp*Co(III)/chiral carboxylic acid system, in which enantioselective protonation is a key step for the stereocontrol (Scheme 1c).[16]

Group 9 Cp*M(III),[17] Pd,[18] and other catalysts[19] were used for directed intermolecular β-C(sp^3)-H amination/amidation reactions under the assistance of carbonyl-based directing groups, providing a straightforward route to β-amino carbonyl compounds. Asymmetric variants of these reactions provide attractive methods for synthesizing related chiral building blocks, but they are scarcely studied.[20] Here we report an achiral Cp^{x}Co(III)/chiral carboxylic acid hybrid system-catalyzed C(sp^3)-H amidation of thioamides (Scheme 1d). Good enantioselectivity was achieved using a readily available ligand and carboxylic acid under mild conditions via enantioselective carboxylate-assisted concerted metalation-deprotonation (CMD).[13b,21,22]

Dixon, Seayad, and co-workers reported Cp*Co(III)-catalyzed C(sp^3)-H amidation of thioamides.[17c] Their quantum chemical calculations suggested that the C-H bond cleavage step would proceed via an external carboxylate-assisted CMD mechanism.



Scheme 1. Cp^{x}M(III)-catalyzed enantioselective C-H functionalization reactions (M = Co, Rh, Ir).

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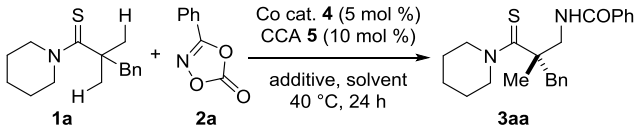
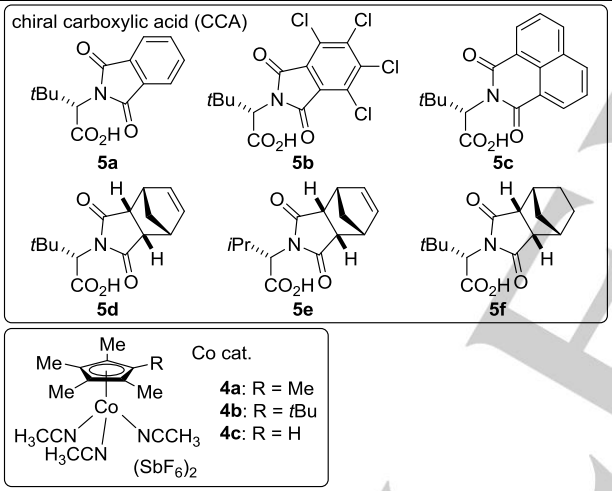
Table 1. Screening of Chiral Carboxylic Acids and Optimization of Reaction Conditions[a]



1a 2a 3aa

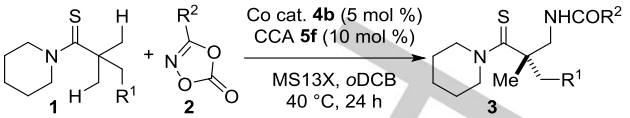
Entry	Co cat.	CCA	Solvent	Additive	Yield[b]	Er[c]
1	**4a**	**5a**	DCE	none	67%	68/32
2	**4a**	**5b**	DCE	none	47%	60/40
3	**4a**	**5c**	DCE	none	66%	75/25
4	**4a**	**5d**	DCE	none	60%	85/15
5	**4a**	**5e**	DCE	none	77%	78/22
6	**4a**	**5f**	DCE	none	93%	87/13
7	**4b**	**5f**	DCE	none	30%	90/10
8	**4c**	**5f**	DCE	none	38%	84/16
9	**4b**	**5f**	DCE	MS13X[d]	68%	90/10
10	**4b**	**5f**	PhCl	MS13X[d]	20%	89/11
11	**4b**	**5f**	*o*DCB	MS13X[d]	81%	92/8
12[e]	**4b**	**5f**	*o*DCB	MS13X[d]	82%[f]	92/8



[a] Reactions were run using **1a** (0.05 mmol), **2a** (0.06 mmol), **4** (0.0025 mmol), and **5** (0.005 mmol) in the indicated solvent (0.1 M) unless otherwise noted. [b] Determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c] Determined by chiral HPLC analysis. [d] 200 mg/mmol **1a**. [e] 0.20 mmol scale, 0.2 M. [f] Isolated yield.

Based on their results, we started our investigation with an amidation of thioamide **1a** using dioxazolone **2b** to afford **3aa**, anticipating that enantioselective CMD is possible by a chiral carboxylic acid (Table 1).[23] In this study, amino acid derivatives were selected due to their accessibility, and we found that *tert*-leucine derivatives (**5a**–**5d**)[24] were suitable for this reaction (entries 1–4). Initial screening using Cp*Co(III) catalyst **4a** revealed that (*S*)-BHTL **5d**[24b] was an efficient co-catalyst in terms of enantioselectivity (entry 4, 85/15 er). L-Valine derivative **5e** exhibited higher reactivity, but lower selectivity (entry 5). We further synthesized (*S*)-H_2-BHTL **5f**, which resulted in slightly improved selectivity and was selected as the optimal carboxylic acid (entry 6). We next examined the steric effects of Cp^{x}Co catalysts **4**. Sterically more hindered catalyst **4b** afforded higher enantioselectivity, although the reactivity significantly decreased (entry 7). Sterically less hindered **4c** decreased both the reactivity and selectivity (entry 8). After optimization studies using **4b**, we found that adding MS13X improved the reactivity without decreasing the selectivity (entry 9). Finally, screening of other halogenated solvents identified *ortho*-dichlorobenzene (*o*DCB) as the most suitable solvent (entries 10–12), and product **3aa** was obtained in 82% isolated yield with 92/8 er (entry 12).

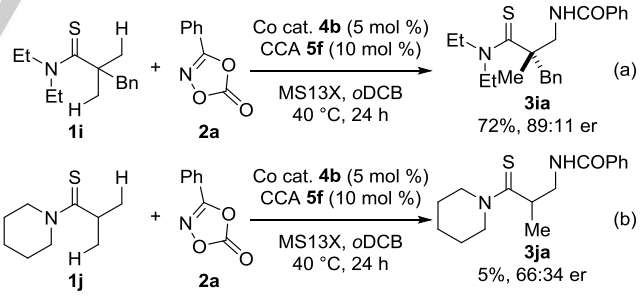
Table 2. Substrate Scope of Enantioselective Amidation of Thioamides[a]



1 2 3

Entry	R^1 (**1**)	R^2 (**2**)	**3**	Yield[b]	Er[c]
1	Ph (**1a**)	Ph (**2a**)	**3aa**	82%	92/8
2	*p*Cl-C_6H_4 (**1b**)	Ph (**2a**)	**3ba**	81%	91/9
3	*p*Br-C_6H_4 (**1c**)	Ph (**2a**)	**3ca**	91%	91/9
4	*p*CF_3-C_6H_4 (**1d**)	Ph (**2a**)	**3da**	89%	92/8
5	*p*MeO-C_6H_4 (**1e**)	Ph (**2a**)	**3ea**	88%	92/8
6	3,5-$(CF_3)_2$-C_6H_3 (**1f**)	Ph (**2a**)	**3fa**	81%	91/9
7	2,6-Me_2-C_6H_3 (**1g**)	Ph (**2a**)	**3ga**	73%	93/7
8	1-naphthyl (**1h**)	Ph (**2a**)	**3ha**	87%	94/6
9	2-naphthyl (**1i**)	Ph (**2a**)	**3ia**	93%	92/8
10[d]	*i*Pr (**1j**)	Ph (**2a**)	**3ja**	50%	90/10
11	cyclohexyl (**1k**)	Ph (**2a**)	**3ka**	76%	91/9
12	Ph (**1a**)	*p*Cl-C_6H_4 (**2b**)	**3ab**	86%	93/7
13	1-naphthyl (**1h**)	*p*Br-C_6H_4 (**2c**)	**3hc**	63%	94/6
14	Ph (**1a**)	*p*MeO-C_6H_4 (**2d**)	**3ad**	90%	92/8
15	Ph (**1a**)	*o*Me-C_6H_4 (**2e**)	**3ae**	65%	91/9
16	Ph (**1a**)	2-furyl (**2f**)	**3af**	96%	92/8
17	Ph (**1a**)	2-thienyl (**2g**)	**3ag**	99%	92/8
18	Ph (**1a**)	Me (**2h**)	**3ah**	55%	92/8
19	Ph (**1a**)	*t*Bu (**2i**)	**3ai**	73%	92/8

[a] **1** (0.20 mmol), **2** (0.24 mmol), **4b** (0.01 mmol), **5f** (0.02 mmol), and MS13X (40 mg) in *o*DCB (0.2 M) at 40 °C for 24 h unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 48 h.



1i 2a 1j 2a

Scheme 2. Scope and limitations of enantioselective amidation of thioamides. The reaction conditions are same as those in Table 2.

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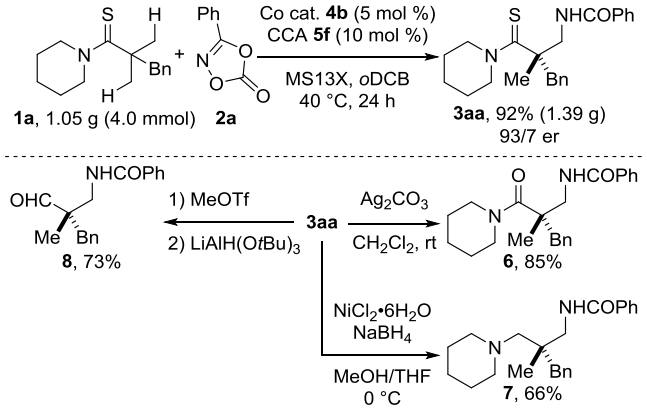
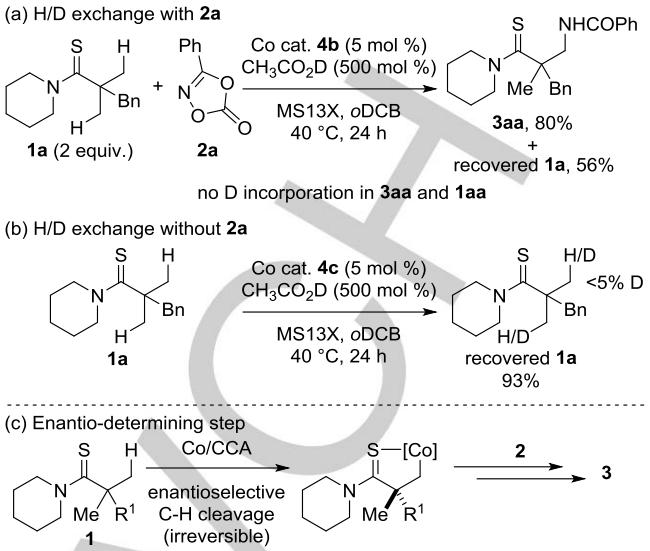


Scheme 3. Gram-scale reaction and transformation of product. See Supporting Information for the detailed reaction conditions.



Scheme 4. Reversibility of C-H activation step and enantio-determining step of C-H amidation.

The scope and limitations of the enantioselective C(sp^3)-H amidation of thioamides **1** using dioxazolones **2** are summarized in Table 2 and Scheme 2. We first investigated the scope of thioamides **1**. Thioamides bearing a various substituent at the α-position afforded the corresponding products in good yield and enantioselectivity (entries 1–11, 90/10–94/6 er). Functional groups on the aromatic moiety did not affect the reactivity or selectivity (entries 2–7). Bulkier α-substituents tended to confer slightly better enantioselectivity (entries 7 and 8). While non-cyclic thioamide **1i** also resulted in good enantioselectivity (Scheme 2a), isobutyric acid-derived thioamide **1j** exhibited very low reactivity and selectivity (Scheme 2b).[25] Next, the scope of dioxazolones **2** was examined using thioamides **1a** and **1h**. Both electron-withdrawing and electron-donating groups on **2** were well tolerated to afford 63%–90% yields and 91/9–94/6 er (entries 12–15). Even a sterically hindered dioxazolone worked efficiently as the amidation reagent (entry 15). In addition to aromatic dioxazolones, heteroaromatic and aliphatic dioxazolones afforded similarly good enantioselectivity (entries 16–19).

A gram-scale reaction using **1a** and **2a** was successfully carried out to afford **3aa** in 92% yield with 93/7 er (Scheme 3). It is worth noting that our optimized reaction conditions are feasible for scale-up because only readily available catalysts are required. Product **3aa** was readily converted to amide **6** and amine **7** by treatment with Ag_2CO_3 and $NiCl_2/NaBH_4$, respectively.[17c] Furthermore, methylation and subsequent reduction of **3aa** provided chiral β-amino aldehyde **8** in 73% yield,[26] demonstrating the utility of the enantioselective amidation products.

To confirm that the enantioselectivity is determined by enantioselective C-H bond cleavage, we checked the reversibility of the C-H activation step (Scheme 4). If this step is reversible, we cannot rule out the possibility that a chiral acid participates in the following steps and achieves the enantioselectivity. The reaction of **1a** and **2a** using an excess amount of CH_3CO_2D instead of a chiral acid proceeded to afford **3aa**, but deuterium incorporation was not observed in product **3aa** or recovered **1a** (Scheme 4a). We also confirmed that H/D exchange barely proceeded even in the absence of **2a** (Scheme 4b). These results unambiguously indicate that the C-H activation step is irreversible. Therefore, enantioselective C-H activation is a key step for the enantioselective C-H amidation.[27]

In summary, we demonstrated that the combination of achiral Co(III) complex **4b** and chiral carboxylic acid **5f** promoted asymmetric C(sp^3)-H amidation reactions of thioamides **1** using dioxazolones **2**. Good enantioselectivity was achieved with a wide range of substrates via enantioselective C(sp^3)-H activation, giving useful chiral building blocks with a quaternary carbon stereocenter. Further applications of similar hybrid catalytic systems are ongoing in our laboratory.

Acknowledgements

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Keywords: C-H activation • asymmetric catalysis • cobalt • thioamide • chiral carboxylic acid

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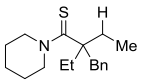

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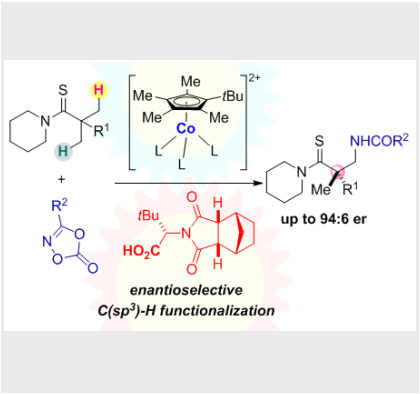
Thioamide-directed C(sp^3)-H amidation using dioxazolones proceeded in good enantioselectivity. Hybridization of a readily available cobalt catalyst and a chiral amino acid derivative opened up a straightforward route to chiral β-amino carbonyl building blocks. Irreversible and enantioselective cleavage of a C(sp^3)-H bond was achieved via chiral carboxylate-assisted concerted metalation-deprotonation.



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