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Citation	Organometallics, 38(20), 3921-3926 https://doi.org/10.1021/acs.organomet.9b00407
Issue Date	2019-10-28
Doc URL	https://hdl.handle.net/2115/79616
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Type	journal article
File Information	WoS_91834_Yoshino.pdf



Chiral 2-Aryl Ferrocene Carboxylic Acids for the Catalytic Asymmetric C(sp³)–H Activation of Thioamides

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ABSTRACT: Enantioselective C–H functionalization reactions using trivalent group 9 metals (Co, Rh, Ir) have been investigated mainly based on the development of well-designed chiral cyclopentadienyl (Cp) ligands. Although it has recently been demonstrated that chiral carboxylic acids combined with achiral Cp-type ligands can enable highly enantioselective C–H functionalization reactions, the structural diversity of the applied chiral acids remains limited. Here, we report that chiral 2-aryl ferrocene carboxylic acids, which are easily obtained from diastereoselective *ortho*-lithiation and Suzuki–Miyaura coupling, can serve as external chiral sources for the Cp*Co^{III}-catalyzed enantioselective C(sp³)–H amidation of α -aryl thioamides using dioxazolones.

Since the seminal work on Cp*Rh^{III} catalysis by Satoh, Miura, and co-workers in 2007,¹ trivalent group 9 metal (Co, Rh, Ir) complexes with a pentamethylcyclopentadienyl (Cp*) or other Cp-type (Cp^x) ligand have been used for a wide variety of catalytic C–H functionalization reactions in organic synthesis.^{2,3} Such Cp*M^{III} catalysts are characterized by the particularly high reactivity, functional group compatibility, and robustness. More recently, the development of catalytic asymmetric C–H functionalization reactions⁴ using these catalysts has attracted considerable attention, as controlling stereochemistry is crucial for the synthesis of complex molecules.^{5–16} Cramer and co-workers,^{5,6} as well as other groups⁷ have demonstrated that well-designed chiral Cp^x ligands and their metal complexes provide a powerful and versatile platform for asymmetric C–H functionalization reactions. Engineered protein-conjugated chiral Cp*Rh catalysts also provide efficient chiral environments, as reported by Ward, Rovis, and co-workers.⁸ Our group has focused on the combination of achiral Cp*M^{III} complexes and chiral disulfonates⁹ or chiral carboxylic acids¹⁰ as an alternative approach to enantioselective C–H functionalization reactions. Chiral carboxylic acids participate in the C–H activation step as the external chiral source in a carboxylate-assisted concerted metalation-deprotonation mechanism, leading to the selective cleavage of enantiotopic C–H bonds (Figure 1a).^{11–13} The groups of Ackermann¹⁴ and Shi¹⁵ have also reported the use of chiral carboxylic acids in enantioselective C–H functionalization reactions.¹⁶ Although these approaches using chiral carboxylic acids are attractive in terms of the accessibility of the chiral catalytic components, the diversity of the applied chiral carboxylic acids therein is still limited compared to chiral Cp ligands^{5–7,12} and bidentate ligands used in Pd^{II}-catalyzed asymmetric C–H functionalizations.^{17,18} Further development of appropriate chiral carboxylic acids is highly demanded for expanding the scope of Cp*M^{III}-catalyzed enantioselective C–H functionalization reactions.

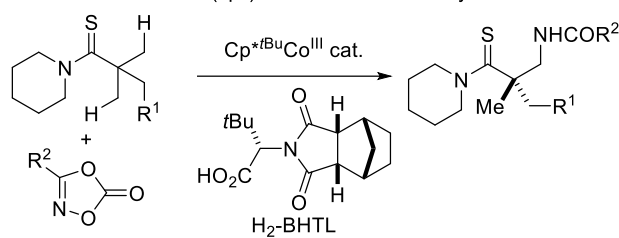
Unsymmetrically 1,2-disubstituted ferrocenes, which exhibit planar chirality, have been extensively explored in asymmetric catalysis.^{19,20} Based on their unique but readily accessible chirality, a variety of chiral ligands and organocatalysts have been developed over the past few decades (Figure 1b). We anticipated that chiral carboxylic acids with a planar chiral ferrocene backbone could serve as external chiral sources for Cp*M^{III}-catalyzed enantioselective C–H functionalization reactions, which would significantly expand catalyst diversity. Herein, we report the synthesis of chiral 2-aryl ferrocene carboxylic acids and their application to the enantioselective C(sp³)–H amidation of α -aryl thioamides using a Cp*Co^{III} catalyst (Figure 1c).^{10b,21–23} This synthetic route provides easy access to various derivatives, which is often necessary for optimization studies in asymmetric catalysis.

For the synthesis of the chiral ferrocene carboxylic acids, we initially subjected ferrocene oxazoline **1** to diastereoselective *ortho*-lithiation (Scheme S1 in Supporting Information) under previously reported conditions.²⁴ After quenching with 1,1,2,2-tetrabromoethane, bromide **2** was obtained as an almost single diastereomer. Partial hydrolysis of the oxazoline moiety, acetylation of the resulting primary amine,²⁵ and methanolysis of the ester intermediate led to the common precursor (**3**) in 76% yield over three steps. Chiral HPLC analysis of **3** indicated that an essentially pure enantiomer was obtained (99:1 er). Subsequently, we investigated cross-coupling reactions to synthesize various derivatives from **3**. Suzuki–Miyaura coupling reactions under Buchwald's conditions using SPhos²⁶ as a ligand proceeded smoothly to afford 2-aryl ferrocene carboxylic acids **4** (28–85% yield) after hydrolysis of the ester.

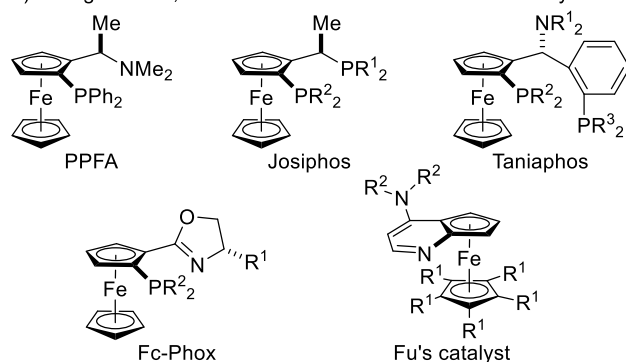
With several chiral carboxylic acids in hand (**4a–4d**), we investigated the cobalt-catalyzed enantioselective C(sp³)–H amidation reaction of α -aryl thioamide **5a** using dioxazolone **6a** (Table 1). In our previous studies (Figure 1a), only α -alkyl and α -benzyl thioamides were examined as substrates.^{10b}

a) Our previous work:

Enantioselective C(sp³)-H amidation of α -alkyl thioamides



b) Background: 1,2-disubstituted ferrocenes as chiral catalysts



c) This work: New catalyst design for α -aryl thioamides

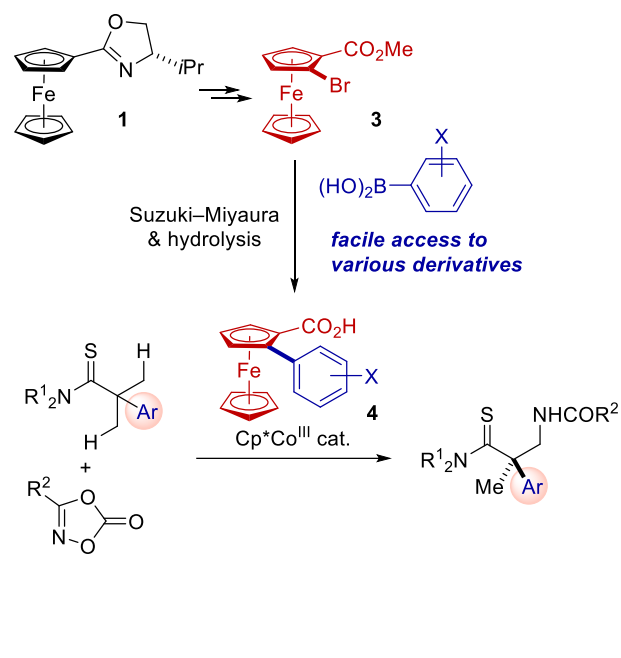
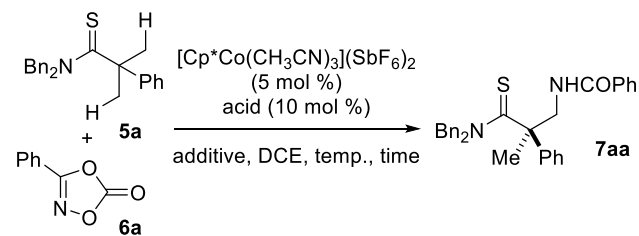


Figure 1. (a) Our previous work on enantioselective C(sp³)-H amidation of α -alkyl thioamides (b) Representative examples of chiral 1,2-disubstituted ferrocenes used in asymmetric catalysis (c) Chiral ferrocene carboxylic acids for Cp*Co^{III}-catalyzed enantioselective C(sp³)-H amidation of α -aryl thioamides (this work).

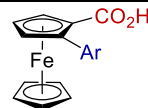
Considering the synthetic importance of this transformation to give chiral β -amino carbonyl building blocks, we decided to explore expanding the substrate scope using the newly synthesized chiral acids **4**. Our optimization studies started with screening the chiral acids **4** using [Cp*Co(CH₃CN)₃](SbF₆)₂ (entries 1–4). While **4a–4c** exhibited similar reactivity (57–62% yield) and selectivity (65:35–67:33 er), the most sterically hindered derivative (**4d**; Ar = 3,5-di-*tert*-butyl phenyl) led to higher conversion with higher enantioselectivity (84:16 er; entry 4). Since the reactivity was greatly enhanced by **4d**, lower reaction temperatures were then examined in order to improve the selectivity (entries 5–7). Although the reaction barely proceeded at 15 °C (entry 5), the addition of molecular sieves 13X (MS13X) significantly accelerated the reaction and provided a high yield with increased selectivity (entry 6). To our surprise, the reaction proceeded even at 4 °C, affording the product in 90% yield with 87:13 er after 72 h (entry 7).

The optimized reaction conditions using **4d** as the chiral source were then applied to other α -aryl thioamides **5** (Scheme 1). The electronic properties of the α -aryl group did not affect the enantioselectivity (**7aa–7ca**), albeit that the reactivity was somewhat deteriorated when a *p*Cl-phenyl-substituted substrate was used (**7ca**). 6-Methoxy-2-naphthyl-substituted thioamide (**5d**) also provided the corresponding product (**7da**) in 96% with 87:13 er. Changing the substituents at the thioamide moiety to *i*Bu groups had negligible influence on the reactivity and selectivity (**7ea**). We examined a range of dioxazolones **6** using thioamide **5a**. Aromatic, heteroaromatic, and aliphatic dioxazolones all provided the targeted products in good yield and enantioselectivity (**7ab–7af**). Steric hindrance around the dioxazolone functionality did not affect the reactions (**7ac** and **7af**). Finally, the reaction using **5a** and **6a** was carried out in 1.0 mmol scale, providing **7aa** in 92% yield with 85:15 er.

Table 1. Screening of chiral carboxylic acids **4 and optimization.^a**



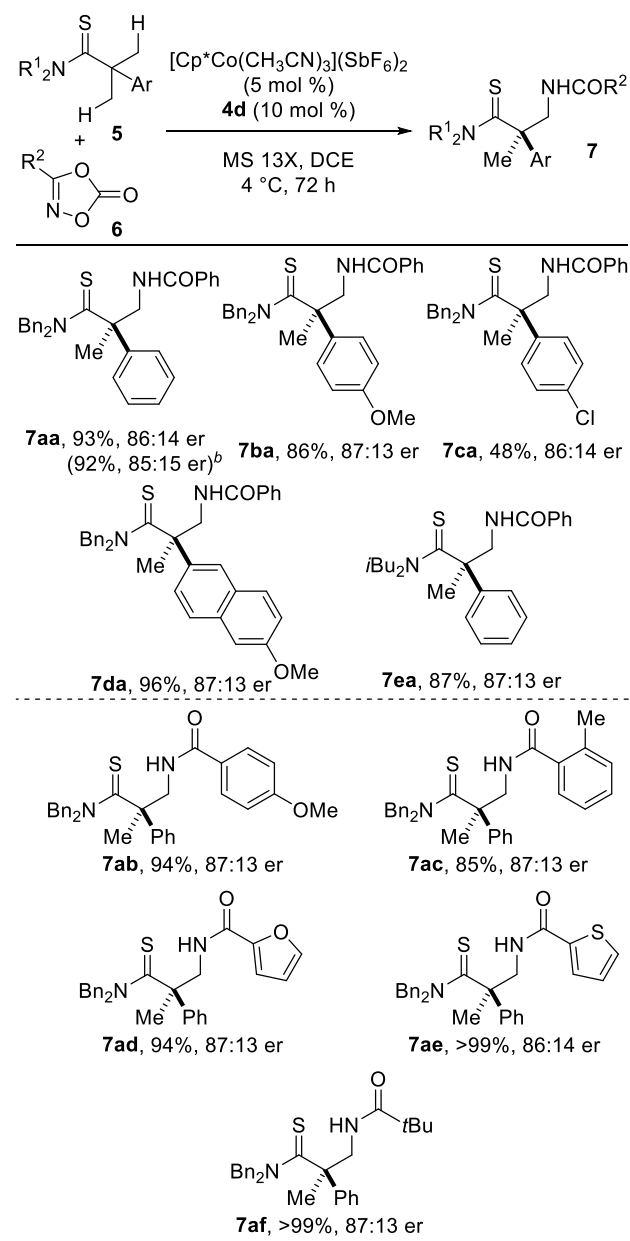
entry	acid	additive	temp. [°C]	time [h]	yield ^b [%]	er ^c
1	4a	none	30	24	59	66:34
2	4b	none	30	24	57	65:35
3	4c	none	30	24	62	67:33
4	4d	none	30	24	90	84:16
5	4d	none	15	24	5	85:15
6	4d	MS13X	15	24	90	86:14
7	4d	MS13X	4	72	90	87:13



4a, Ar = Ph
4b, Ar = 4-MeO-C₆H₄-
4c, Ar = 3,5-(CF₃)₂-C₆H₃-
4d, Ar = 3,5-(*t*Bu)₂-C₆H₃-

^aReactions were carried out using **5a** (0.050 mmol), **6a** (0.06 mmol), [Cp*Co(CH₃CN)₃](SbF₆)₂ (0.0025 mmol, 5 mol %), acid (0.005 mmol, 10 mol %), and additive (10 mg) in DCE (0.5 mL) unless otherwise noted. ^bDetermined by ¹H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard. ^cDetermined by chiral HPLC analysis. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl.

Scheme 1. Substrate scope of the enantioselective C(sp³)-H amidation of α -aryl thioamides **5 with dioxazolone **6**.^a**



^aReactions were carried out using **5** (0.20 mmol), **6** (0.24 mmol), $[\text{Cp}^*\text{Co}(\text{CH}_3\text{CN})_3](\text{SbF}_6)_2$ (0.01 mmol, 5 mol %), **4d** (0.02 mmol, 10 mol %), and MS13X (40 mg) in DCE (2 mL).
^b1.0 mmol scale.

In order to rationalize the observed enantioselectivity using **4d**, we would like to propose qualitative stereochemical models in Figure 2.²⁷ Due to the piano-stool structure of $\text{Cp}^*\text{Co}^{\text{III}}\text{L}_3$ complexes, the CoL_3 fragment constitutes a conical scaffold with concave and convex faces. The ferrocene moiety of **4d** would be aligned on the convex face to avoid the steric repulsion with the thioamide. Based on this assumption, four different transition states (TSs) for the C–H activation are possible. In **TS-(S)-1** and **TS-(R)-1**, the α -aryl group of the thioamide is located on the concave face, which would render these two TSs unfavorable. **TS-(S)-2** might be less favored than **TS-(R)-2** due to the steric repulsion between the 3,5-di-

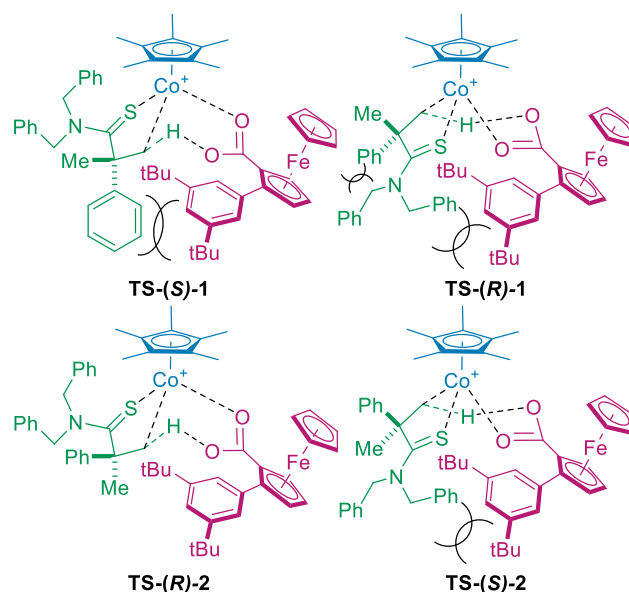


Figure 2. Stereochemical models for plausible transition states of the C–H activation to rationalize the observed enantioselectivity using chiral carboxylic acid **4d**.

tert-butyl-phenyl group of **4d** and the *N*-benzyl groups of the thioamide. Overall, **TS-(R)-2** is the most plausible transition state for the C–H activation, which selectively provides (*R*)-products.²⁸

In summary, we have synthesized several chiral 2-aryl ferrocene carboxylic acids **4**, one of which exhibited good reactivity and enantioselectivity in cobalt-catalyzed C(sp³)-H amidation reactions of α -aryl thioamides. These carboxylic acids can be easily synthesized and modified by changing the aryl substituent, which is introduced via a cross-coupling reaction in the late step of the synthesis. Investigation on catalytic enantioselective C–H functionalization using these carboxylic acids in combination with $\text{Cp}^*\text{Co}^{\text{III}}$ or $\text{Cp}^*\text{Rh}^{\text{III}}$ catalysts are currently in progress in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data of the synthesized compounds, and copies of their NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported in part by JSPS KAKENHI Grant Number JP15H05802 in Precisely Designed Catalysts with Customized Scaffolding, JP18H04637 in Hybrid Catalysis, JP17K15417, JP19K16306. S.M. is grateful for support from the Asahi Glass Foundation and the Naito Foundation.

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(28) The absolute configuration of the products was determined to be (*R*) by the X-ray analysis of **7ba** (See Supporting Information).

