OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

Cp*Co(III)/MPAA-Catalyzed Enantioselective Amidation of Ferrocenes Directed by Thioamides under Mild Conditions

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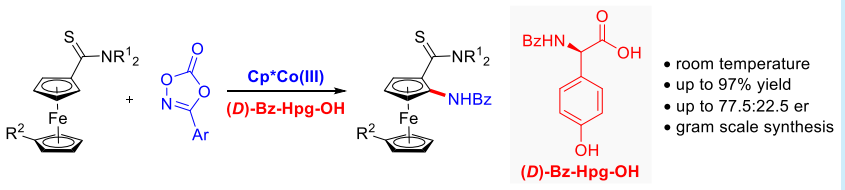
Supporting Information



ABSTRACT: Cp*Cobalt(III)-catalyzed enantioselective C−H amidation of ferrocenes using monoprotected amino acids (MPAAs) as chiral ligands was developed. The reaction was performed under mild conditions in high yields (up to 97%) with moderate enantioselectivity (up to 77.5:22.5 er), providing a promising strategy to create planar chirality via base-metal-catalyzed enantioselective C−H activation.

In recent decades, chelation-assisted C−H functionalization catalyzed by group 9 transition metals (Co, Rh, Ir) has become a powerful synthetic strategy to access functionalized organic molecules, owing to the diverse reactivity, robustness, and functionality tolerance of these catalysts.[1] Meanwhile, the development of the asymmetric versions is a significant topic in C−H activation and has received tremendous attention.[2] In general, most transition-metal-catalyzed C−H activation steps are proposed to proceed via a carboxylate-assisted concerted metalation−deprotonation (CMD) mechanism wherein the presence of a catalytic amount of carboxylate proved essential.[3] Thus, one may argue that the use of chiral carboxylic acid (CCA) may be a promising strategy for asymmetric C−H activation and formation of a chiral cyclometal intermediate. Major breakthroughs were achieved by Yu and co-workers, who disclosed that monoprotected α-amino acids (MPAAs) could serve as efficient chiral ligands in Pd(II)-catalyzed enantioselective C−H activation.[4a,b] MPAAs have been identified as a type of privileged chiral ligand for the stereoinduction as well as rate acceleration.[3c,4] Later, chiral phosphoric acids were also developed for the Pd-catalyzed enantioselective C−H activation.[5]

However, the application of these MPAA type bidentate κ^2 ligands to group 9 metals is not straightforward, since Pd(II) adopts a square-plannar geometry while Cp*M(III) (M = Co, Rh, Ir) adopts a pseudo-octahedral geometry and lacks a vacant coordination site for an external chiral ligand. Thereby, enantioselective C−H activation catalyzed by group 9 transition metals generally relies on the use of chiral (pseudo) C_2 symmetric Cp^x ligands that precoordinated with metal catalysts.[6−11] However, the precisely designed Cp^x ligand requires multiple steps to be synthesized and then must be precoordinated with the metal catalyst.[12] Thus, the development of an asymmetric strategy using achiral metal catalysts and chiral ligands is in high demand, yet challenging. In this context, Matsunaga and Yoshino[13] as well as Ackermann[14] reported the achiral Cp*M(III) (M = Rh or Co)-catalyzed enantioselective alkylation of 2-phenylpyridines and indole derivatives using (peseudo) C_2-symmetric chiral disulfonate and carboxylic acid, respectively. In 2015, Chang and co-workers reported the Cp*Ir(III)-catalyzed enantioselective amidation of phosphine oxides using dipivaloyl L-tartaric acid as a source of chiral information in moderate er value (66:34 er) (Scheme 1A).[15] In 2018, Matsunaga and Yoshino designed axially chiral monocarboxylic acid based on the binaphthyl backbone and realized the Cp*Rh(III)-catalyzed asymmetric C−H alkylation of diarylmethanamines with diazomalonates in high enantioselectivities (up to 98.5:1.5 er) (Scheme 1B).[16] While this work was in progress, Matsunaga and Yoshino reported the Cp*Co(III)-catalyzed enantioselective C(sp^3)−H amidation with up to 94:6 er (Scheme 1C).[17] Notably, previous work developed to date focused on the construction of point chirality and mostly rely on precious transition metals. As part of our endeavors in transition-metal-catalyzed asymmetric C−H activation,[5d,18] we present herein a Cp*Co(III)/MPAA-catalyzed amidation of ferrocenes to construct plannar chirality.[19,20] After recrystallization, the amidation product could be obtained in high enantiopurity (>99% ee).

Received: February 8, 2019

DOI: 10.1021/acs.orglett.9b00511
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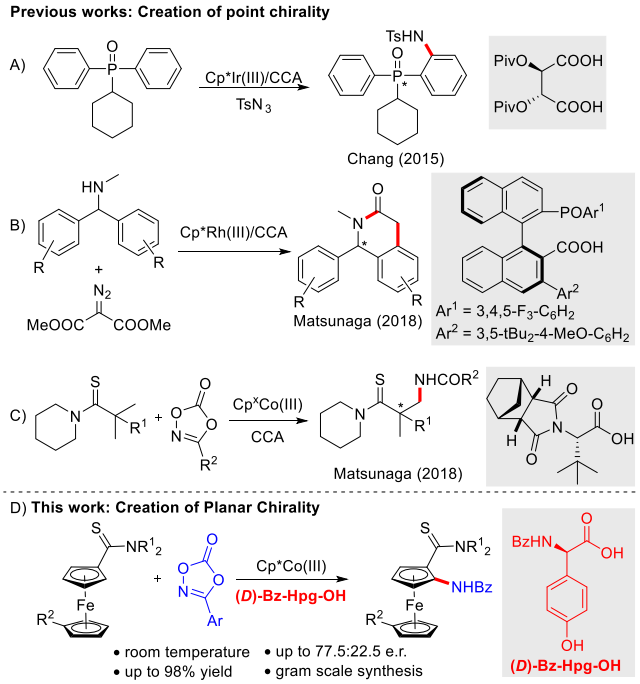
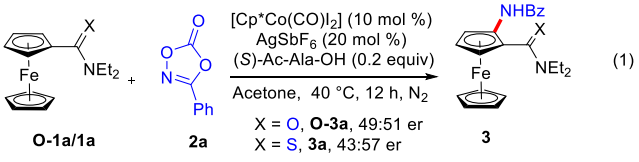
Scheme 1. Achiral Cp^{x}M(III)/CCA-Catalyzed Enantioselective C−H Activation



We suspected that this protocol would open intriguing opportunities for the use of MPAAs in enantioselective C−H functionalization catalyzed by metal catalysts other than palladium.

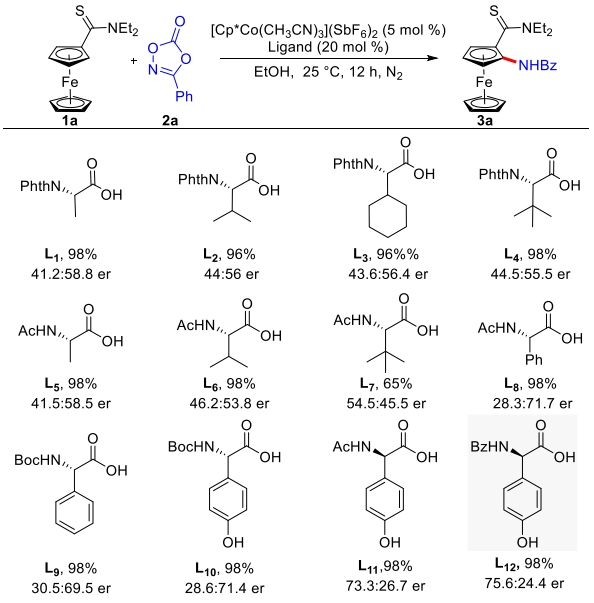
Recently, we reported an amide-directed Co(III)-catalyzed C−H amidation of ferrocenes with dioxazolones.[21,22] We found that the choice of a bulky carboxylic acid, such as PivOH, could significantly enhance the reactivity. However, the reaction of **O-1a** in the presence of various CCAs, including MPAAs and phthaloyl-protected AAs, only gave trace-level enantioselectivity (eq 1, (*S*)-Ac-Ala-OH, 49:51 er).



We reasoned that the proper choice of directing groups (DGs) might be important for the asymmetric version, considering the subtle coordination environment around the metal center provided by the DGs and chiral ligands. Consistent with this hypothesis, the amidation of thioamide **1a** gave **3a** with promising enantioselectivity (43:57 er). The amidation reaction proceeded smoothly even at room temperature; however, a strong background reaction was observed in the absence of any acid additive (47%, Table S1, entry 3). These results encouraged us to further screen solvents to inhibit the background reaction. Fortunately, significant ligand acceleration was observed when EtOH was used as solvent. Only a trace of **3a** was observed in the absence of AdCOOH, while the addition of AdCOOH dramatically improved the yield to 98% (Table S1, entries 11 and 12). The accelerating effect was further confirmed by the H/D exchange experiment (eq S1).

Various CCA ligands were then investigated (Scheme 2). Phthaloyl protected AAs have been used in combination with

Scheme 2. Ligand Optimization[a,b,c]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.2 equiv), [Cp*Co(CH$_3$CN)$_3$](SbF$_6$)$_2$ (0.05 equiv), Ligand (0.2 equiv) in EtOH (2.0 mL) at 25 °C for 12 h. [b]Yield was determined by ^{1}H NMR using dibromomethane as internal standard. [c]The er values were determined by HPLC analysis on a chiral stationary phase.

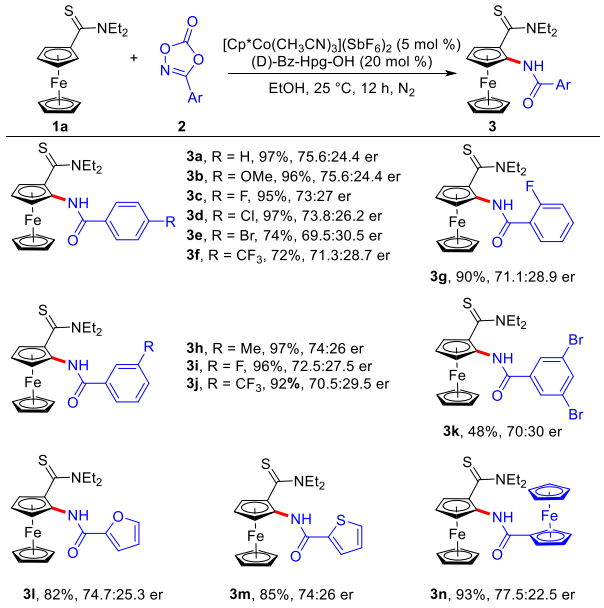
chiral Cp^{x}M(III) to enable the asymmetric transformation of C−H bonds.[10,14a] Thus, several Phth-protected AAs with varying bulkiness of side chain was first evaluated and nearly quantitative yields were obtained (**L$_1$**−**L$_4$**). However, the best enantioselectivity obtained using this type of CCA was only 41.2:58.8 with (*S*)-Phth-Ala-OH (**L$_1$**) as the ligand. The enantiocontrol decreased as the bulkiness of the side chains increased (**L$_1$**−**L$_4$**). A similar trend was observed when using the acetyl protected AAs as chiral ligands (**L$_5$**−**L$_8$**). Intriguingly, the opposite enantiomer was formed preferentially when using (*S*)-Ac-Tle-OH (**L$_7$**), bearing a sterically more bulky side chain, as the ligand. The replacement of the side chain with a phenyl group led to a significantly elevated enantioselectivity (**L$_8$**, 28.3:71.7 er). Changing the protecting group from acetyl to Boc was detrimental to the er (**L$_9$**, 30.5:69.5), while the adoption of D-*p*-hydroxylphenylglycine (Hpg) and using benzoyl as the protecting group finally enhanced the er to 75.6:24.4 (**L$_{12}$**). Further elaboration of the Hpg-type ligand, including Hpg-derived dipeptides (Table S2), and Hpg bearing other protecting groups (Table S3), proved fruitless at this point.

With the optimal conditions in hand, the scope of dioxazolones was examined first (Scheme 3). Dioxazolones bearing both electron-rich (e.g., OMe, Me) and electron-deficient substituents (e.g., F, Cl, Br, CF$_3$) on the phenyl ring were all compatible with this reaction, affording the desired amidation products in high yields and moderate er values (**3a**−**3k**). Besides, heteroarenes, including furan (**2l**) and thiophene (**2m**), were also well tolerated. Ferrocene-derived dioxazolone **2n** also reacted smoothly to give **3n** in high yield and moderate er (93%, 77.5:22.5 er).

The scope of ferrocene derivatives was also examined (Scheme 4). Various tertiary thioamides were well tolerated and delivered the products in high yield and moderate er (**3o**−**3t**). In addition, ferrocenes with substituents at the cyclo-

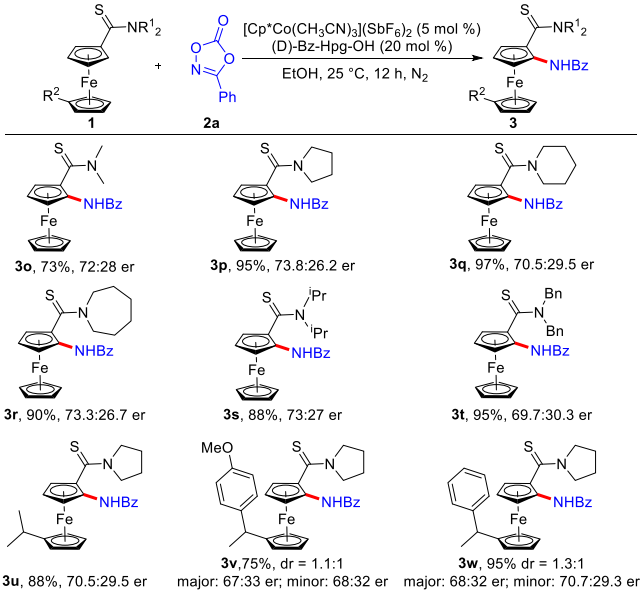
DOI: 10.1021/acs.orglett.9b00511
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of Various Dioxazolones[a,b,c]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (1.2 equiv), $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ (0.05 equiv), Ligand (0.2 equiv) in 2 mL of EtOH at 25 °C for 12 h. [b]Isolated yield. [c]The er values were determined by HPLC analysis on a chiral stationary phase.

Scheme 4. Scope of Ferrocenes[a,b,c]

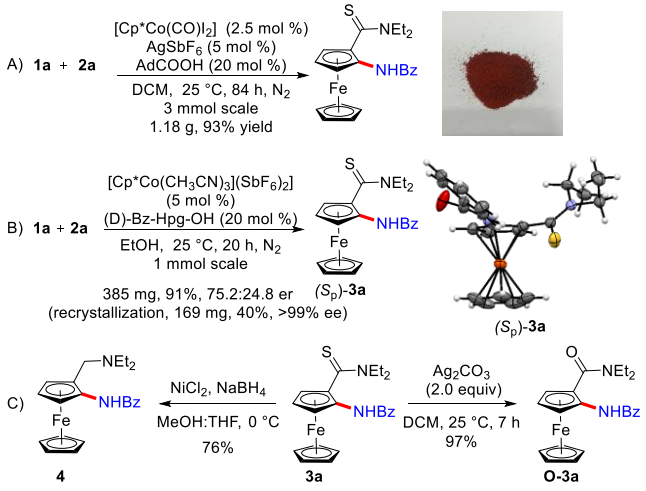


[a]Reaction conditions: **1** (0.1 mmol), **2a** (1.2 equiv), $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ (0.05 equiv), Ligand (0.2 equiv) in EtOH (2.0 mL) at 25 °C for 12 h. [b]Isolated yield. [c]The er values were determined by HPLC analysis on a chiral stationary phase.

pentadiene ring also reacted smoothly to give the desired products (**3u**−**3w**). It is worth noting that thioamides show better reactivity than their amide analogues (72−97% vs 22−90% yield).[21a]

To demonstrate the robustness and potential applications, the gram-scale synthesis was conducted. The racemic reaction could be conducted in 3 mmol scale using 2.5 mol % Co(III) catalyst (Scheme 5A, 1.18 g, 93%). The enantioselective

Scheme 5. Gram-Scale Synthesis and Derivations



version could be conducted in a 1.0 mmol scale without erosion in yield and er value (Scheme 5B, 91%, 75.2:24.8 er). Notably, after recrystallization, **3a** could be obtained in 40% overall yield with excellent optical purity (>99% ee). The absolute configuration of **3a** was assigned to be *Sp* by X-ray crystallography (CCDC 1900254). **3a** was readily converted to amide **O-3a** and amine **4** by treatment with Ag_2CO_3 and $NiCl_2/NaBH_4$, respectively (Scheme 5C).

In conclusion, we have developed a Cp*Co(III)/MPAA catalytic system for the enantioenriched amidation of ferrocenes. The reaction proceeded at room temperature, and promising stereocontrol was achieved. Further design and exploration of chiral carboxylic acids for asymmetric C−H activation is underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

and X-ray for compound **3a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00511.

Experimental details and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1900254 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.9b00511
Org. Lett. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

Financial support from the NSFC (21772170, 21572201) and the Fundamental Research Funds for the Central Universities (2018XZZX001-02) is gratefully acknowledged.

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DOI: 10.1021/acs.orglett.9b00511
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DOI: 10.1021/acs.orglett.9b00511
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