Chiral Carboxylic Acid Assisted Enantioselective C–H Activation with Achiral Cp*MIII (M = Co, Rh, Ir) Catalysts

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ABSTRACT: Enantioselective C–H functionalization is a powerful tool for synthesizing chiral molecules. In the past few years, the combination of high-valent group 9 metals with achiral Cp ligands and chiral carboxylic acids (CCA) has emerged as a promising catalytic system to enable selective cleavage and functionalization of enantiotopic C–H bonds. This Perspective summarizes the background, catalyst design, and applied reactions in detail, followed by a discussion of future directions.

KEYWORDS: C–H activation, asymmetric catalysis, chiral carboxylic acid, cobalt, rhodium, iridium

1. INTRODUCTION

Direct and selective functionalization of a targeted chemically inert carbon–hydrogen bond in organic compounds can potentially enable the concise synthesis of complex natural products, biologically active compounds, functional materials, and other valuable substances from readily available sources.1 One of the most successful strategies to realize selective functionalization at a desired site is directing-group-assisted C–H activation with a transition-metal catalyst to generate reactive metallacyclic intermediates. While various transition-metal catalysts have been investigated for this strategy, trivalent group 9 metals (CoIII, RhIII, IrIII) with a pentamethylcyclopentadienyl (Cp*) or a related Cp-type ligand have attracted significant attention due to their high reactivity, good functional group tolerance, and stability (Figure 1a). Since the pioneering reports on Cp*RhIII and Cp*IrIII catalysis by Satoh and Miura in 20072 and Cp*CoIII catalysis by Matsunaga and Kanai in 2013,3 an enormous number of reactions have been developed, and many reviews have been published.4

Catalytic asymmetric organic reactions are generally achieved by introducing appropriate chiral ligands to metal-catalyzed processes. Although the difficulties associated with the synthesis of elaborate Cp-type ligands and the rotational flexibility of the Cp–metal bond make it difficult to construct an effective chiral environment around the metal center, Cramer and co-workers have presented an elegant design concept for chiral Cp* ligands,5 which has enabled a wide range of enantioselective C–H functionalization reactions (Figure 1b).6,7 In addition, their design concept has led to the further development of chiral Cp* ligands by other research groups.8,9

Chiral Cp* ligands in group 9 metal catalysis do not directly participate in bond cleavage or formation and simply construct a chiral environment around the metal center during the reaction. On the other hand, a very different strategy is commonly employed in enantioselective C–H functionalization using PdII...
Catalysts. C–H bond cleavage by high-valent electrophilic metal catalysts, including PdII and Cp*MIII, is often accelerated by carboxylate or other coordinating bases. Many mechanistic studies and quantum chemical calculations have strongly suggested that such C–H activations proceed via a base-assisted concerted mechanism (Figure 2a). Agostic interactions between a C–H bond and the electrophilic metal center weaken the C–H bond, which is deprotonated by the coordinating base to concertedly form a C–M bond. This mechanism is referred to by several different terms, such as ambiphilic metal ligand activation (AMLA), concerted metalation–deprotonation (CMD), and base-assisted internal electrophilic substitution (BIES). Although the electronic states in the transition state depend on the metal, ligand, substrate, and reaction conditions, the well-defined steric structure during the C–H bond cleavage clearly provides the opportunity to control the enantioselectivity by introducing a chiral coordinating base. In 2008, Yu and co-workers reported that mono-N-protected amino acids (MPAAs) enable the enantioselective functionalization of aromatic C–H bonds under PdII catalysis. Subsequent mechanistic studies indicated that the MPAA ligands coordinate to PdII in a bidentate manner in their dianionic form and that the amidate moiety acts as the base for C–H activation (Figure 2b, top). The combination of PdII with MPAs or related bidentate ligands has enabled various enantioselective C(sp2)–H and C(sp3)–H functionalization reactions. The bidentate coordination of the ligands to PdII can contribute to high enantioselectivity for a wide range of substrates.

On the other hand, the application of these bidentate ligands to assist C–H activation has not been successful in group 9 Cp*MIII catalysis. As Cp*MIII complexes adopt a piano-stool structure with three vacant coordination sites, the bidentate coordination of additional ligands inhibits directing-group-assisted C–H activation, for which at least two empty coordination sites are required (Figure 2b, bottom). Therefore, the ligand design for PdII, which adopts a square-planar geometry with four coordination sites, cannot be directly transferred to Cp*MIII catalysis. Ligands to assist C–H activation must coordinate to the metal in a monodentate fashion (Figure 2c), which significantly complicates the construction of an efficient chiral environment due to the conformational flexibility. Nevertheless, several types of monodentate chiral carboxylic acids (CCAs) that enabled enantioselective C–H functionalization reactions in combination with achiral Cp*MIII catalysts have recently been developed. This Perspective briefly summarizes these reports and discusses the future challenges in this area. Enantioselective C–H functionalization using achiral Cp*MIII catalysts and external chiral sources based on other strategies, including chiral acid- or anion-controlled alkylation via a selective protonation step, are not covered here.

2. SEMINAL WORK

The first enantioselective C–H functionalization via the combination of an achiral Cp*MIII catalyst and a CCA was reported by Chang in 2015 (Scheme 1). During their studies on the C–H amidation of phosphine oxides with tosyl azide using a Cp*MIII catalyst in the presence of carboxylic acid additives, the authors discovered that the pivaloyl-protected tartaric acid derivative induces enantioselectivity, although that the selectivity is not sufficient (11–32% ee). It is worth...
pointing out that this amidation reaction did not proceed in the absence of any carboxylic additive, indicating that no back-ground reaction is expected to occur without a chiral ligand. Suppressing racemic background reactions is important to achieve high enantioselectivity using this strategy.

In 2017 and 2018, Cramer demonstrated that the appropriate combination of a chiral Cp* ligand and CCA enabled highly enantioselective C−H functionalization reactions, although the CCA alone exhibited low enantioselectivity.17

3. CHIRAL BINAPHTHYL MONOCARBOXYLIC ACIDS

Several years ago, our research group began developing appropriate monodentate CCAs for enantioselective C−H functionalization using Cp*MIII catalysts. A chiral binaphthyl structure was first selected as a platform to construct a CCA catalyst library, since it is one of the most privileged and successful chiral backbones in asymmetric catalysis. Although the rational design of CCA catalysts was very challenging due to difficulties associated with fixing the conformation of the CCA, which is bound to the metal center by only a single σ-bond, we expected that an appropriate chiral environment could be achieved by intensive structure tuning. With the readily available optically active BINOL (5) as the starting material, transition-metal-catalyzed coupling technologies and carboxylate-directed C−H functionalization would enable access to various CCAs, providing different steric and electronic effects (Figure 3). While C2-symmetric binaphthyl dicarboxylic acids had been studied as chiral organocatalysts by Hashimoto and Maruoka, the investigation of such axially chiral C1-symmetric monocarboxylic acids in asymmetric catalysis was quite limited.9

As an initial model reaction to examine the CCAs, C(sp3)−H alkylation of amine 6 with diazo malonate 7 under RhIII catalysis was selected (Scheme 2). After the C−H alkylation, intramolecular amide formation would suppress the second reaction, which is potentially problematic for desymmetrization. Subsequent Krapcho decarboxylation provides a 1,4-dihydroisoquinolin-3(2H)-one derivative. Initial trials using MPAAs (9a,b) afforded the target product (8) in low enantioselectivity, implying that the MPAs could act as a monodentate ligand for CMD but failed to construct an effective chiral environment for the Cp*RhIII catalyst. While binaphthyl-type CCA 10 with a small ether group at the 2′-position afforded an almost racemic product, the more sterically hindered 11a showed promising selectivity (37:63 er). Further investigations revealed that a highly sterically crowded CCA with a phosphine oxide moiety (12e) successfully delivered the product in high enantioselectivity (96:4 er). Fine tuning of the substituents at both 2′- and 3-positions was key to enhancing the enantioselectivity. The substrate scope of this enantioselective C−H alkylation using CCA 12e is summarized in Scheme 3. It is noteworthy that nonprotected primary amines were also compatible under the optimized conditions to provide the corresponding products (8) in good to high enantioselectivity. For several substrates, replacing the Cp*RhIII catalyst with CpMe4RhIII (CpMe4 = 1,2,3,4-tetramethylcyclopentadienyl) slightly improved the enantioselectivity. As showcased by these results, the chiral

![Scheme 1. Enantioselective C−H Amidation of Phosphine Oxides 1 with Cp*IrIII/Tartaric Acid Derivatives 3](image1)

![Scheme 2. CCA Screening for Enantioselective C(sp3)−H Alkylation/Cyclization Using a Cp*RhIII Catalyst](image2)

![Figure 3. Design of chiral binaphthyl monocarboxylic acids.](image3)
environment around the metal center can be modified without changing the chiral component in the CCA-assistance strategy. The major issue remaining to be addressed in this work is the lengthy synthetic route to the phosphine oxide containing CCAs 12.

Our group also applied binaphthyl CCA 11b, which bears aryl substituents at both the 2′- and 3-positions, to methylene C(sp3)−H amidation reactions of 8-alkylquinolines 13 (Scheme 4).22,23 The use of dioxazolones 14 as the amidation reagents24 allowed the reaction to proceed at low temperatures, furnishing the corresponding products (15) in good enantioselectivity (up to 94:6 er). Various substituents at the quinoline moiety of 13 as well as at the dioxazolones 14 were well tolerated. In addition to 8-ethylquinoline, 8-propyl- and 8-pentylquinolines afforded the products with 93:7 er, albeit in somewhat diminished reactivity. Furthermore, the use of α,β-unsaturated carbonyl compounds 16 as the electrophiles instead of dioxazolones 14 led to enantioselective C−H alkylation reactions (Scheme 5).25 In these reactions, several H/D scrambling tests and the similar enantioselectivities observed with different electrophiles unambiguously indicated that the C−H bond cleavage step is an irreversible enantiodetermining step. As shown in Scheme 6, 11b and the related CCAs are readily accessible from BINOL 5. After conversion to 18 via monotosylation and subsequent triflation, Pd-catalyzed selective carbonylation provided the key intermediate 19. Two aromatic substituents could be installed by successive Ni-catalyzed Suzuki−Miyaura coupling,26 hydrolysis, and Ru-catalyzed C−H arylation.27 This modular synthetic route would be beneficial for further applications of these CCAs in which additional optimization of the CCA structure may be required.
Although the aforementioned C₁-symmetric binaphthyl CCAs are highly tunable and have been applied to several reactions, the unfixed, freely rotating dihedral angle between the two naphthyl rings can cause additional internal conformational flexibility, which, in combination with the conformational flexibility between the metal and substrate, can lead to an unfavorably large number of possible transition-state structures for C−H activation. In this context, our group more recently reported binaphthyl-based pseudo-C₂-symmetric CCAs for enantioselective C−H functionalization (Figure 4; 21). Their fixed structure and pseudo-C₂ symmetry can reduce the conformational flexibility and potentially be beneficial in recognizing the structure of some substrates. CCAs 21 were synthesized from known bromides 22 via double alkylation with a nitrile or ester and subsequent functional group transformations (Figure 4, bottom).

These pseudo-C₂-symmetric CCAs outperformed the C₁-symmetric CCA 11b and exhibited high enantioselectivity in the enantioselective C(sp³)−H amidation of 2-alkylpyridines and related heteroaromatic compounds 24 (Scheme 7). The best CCA (21a), combined with a Cp*RhCl₂ (8 mol%) or Cp*RuCl₂RhIII catalyst (Cp*RuCl₂RhIII = 1-(tert-butyl)-2,3,4,5-tetramethylcyclopentadienyl), effectively differentiated the two enantiotopic methyl groups of 24. Pyridines, isoquinoline, and benzimidazole could be used as the directing groups.

4. AMINO ACID DERIVATIVES

Amino acids are undoubtedly the most readily available and well-documented chiral carboxylic acids and are widely used for synthesizing various chiral compounds, including chiral ligands for asymmetric catalysis. Although, as explained above, MPAAs may not act as bidentate ligands for Cp*MIII catalysts, appropriately protected and/or derivatized amino acids are attractive catalyst candidates for CCA-assisted enantioselective C−H functionalization.

In 2019, our research group reported the enantioselective C(sp³)−H amidation of thioamides 26 using a Cp*RhBuCoIII catalyst and amino acid 28 (Scheme 8). Imide-protected α-amino acids were selected and screened for this reaction because such amino acids are easy to synthesize and have been studied as ligands for transition-metal catalysts, and because the sterically hindered imide moiety would provide steric bulk without coordinating to the metal center. In this study, CCA 28 was identified as the best chiral ligand, providing the products (27) in up to 94:6 er. The introduction of a sterically hindered Cp*RhBu ligand was also essential to boost the enantioselectivity. Under the optimized conditions, various α-quaternary thioamides 26 were applicable. H/D exchange experiments suggested that the C−H bond cleavage is irreversible and thus enantiodetermining. As both the cobalt catalyst and CCA 28 are readily available, a gram-scale reaction was performed (Scheme 9). Product 27 was converted into the corresponding aldehyde 29, amide 30, and amine 31, demonstrating the synthetic utility.

Shi and co-workers have demonstrated that more standard MPAAs can also be used as the chiral ligand in the Cp*CoIII-catalyzed enantioselective C(sp²)−H amidation of ferrocene derivatives to generate planar chirality (Scheme 10), although the enantioselectivity was still moderate (up to 77.5:22.5 er). Screening various MPAAs revealed that p-hydroxyphenylglycine with a benzoyl protecting group (34) exhibited the highest enantioselectivity. The use of a thioamide directing group was important to achieve this enantioselective process, and the choice of solvent (EtOH) was key to avoid the racemic background reaction. They performed the reaction on a preparative scale (1 mmol), and recrystallization of the obtained...
product furnished the optically pure product in moderate yield (Scheme 10, bottom).

Although thioamides have been demonstrated to be efficient directing groups for enantioselective C−H functionalization using group 9 metals (Schemes 9 and 10),30,32 these substrates must typically be prepared from the corresponding amides. The direct application of amides as substrates would obviously be more straightforward. In 2020, Shi and co-workers reported the enantioselective C(sp2)−H amidation of ferrocene amides 35 using an IrIII catalyst (Scheme 11).33 For this reaction, imide-protected, sterically hindered amino acids are suitable. While moderate enantioselectivity was achieved using CCA 28, which was the best for the C(sp3)−H amidation of thioamides,30 the introduction of 4-methoxyphenyl (PMP) groups at the tBu side chain further enhanced the enantioselectivity. Notably, the Pd-catalyzed C(sp3)−H arylation protocol developed by the same group34 provided straightforward access to these elaborate CCAs (37, 38). In this case, a Cp*Bu ligand was also effective to further improve the enantioselectivity. Under the optimal reaction conditions, various ferrocene amides 35 and dioxazolones 14 afforded the corresponding products 36 in high enantioselectivity (up to 97.5:2.5 er). A gram-scale reaction was also demonstrated, and recrystallization successfully provided the product with >99% ee.

He and co-workers reported the synthesis of S-chiral sulfoxides via desymmetrization and parallel kinetic resolution using an achiral IrIII catalyst and CCAs (Scheme 12).35 They identified a combination of a sterically hindered IrIII catalyst (Cp*-BuIrIII) and N-Piv-Me-Pro-OH (41) as the best catalyst to discriminate the two enantiotopic aromatic C(sp2)−H bonds of dibenzyl sulfoxides 39. In both the desymmetrization of symmetrically substituted substrates and the kinetic resolution of unsymmetrically substituted substrates, this rather simple catalytic system successfully delivered the amidation product 40 in high enantioselectivity (up to 98% ee). A wide range of functional groups, including halogens, CF3, esters, etc., were compatible. In addition, coupling with dioxazolones derived from bioactive molecules was demonstrated.
Our research group has focused on the planar chirality of 1,2-disubstituted ferrocenes as a platform for CCAs. We have developed a modular synthetic route for optically active 2-aryl-ferrocene carboxylic acids, and the synthesized CCAs were applied to the CoIII-catalyzed enantioselective C(sp3)−H amidation of thioamides (Scheme 13). Diastereoselective ortho lithiation/bromination of 43 with the aid of a chiral...
oxazoline auxiliary\(^{37}\) and the removal of the oxazoline provided ester 44 as a common intermediate. Pd-catalyzed Suzuki–Miyaura coupling and further hydrolysis allowed facile modular access to several CCAs (42\(\text{a–d}\)). Screening these CCAs revealed that 42\(\text{d}\) with a 3,5-di-tert-butylphenyl group was the most suitable, albeit there was room for improvement in terms of the enantioselectivity. Several kinds of \(\alpha\)-aryl thioamides 26 and dioxazolones 14 were tested under the optimized conditions, resulting in up to 87:13 er.

6. OUTLOOK AND FUTURE CHALLENGES

The past years have witnessed rapid progress in group 9 metal-catalyzed enantioselective C–H functionalizations using chiral carboxylic acids (CCAs). The identification of suitable metal catalyst/CCA combinations has led to moderate to high enantioselectivity for several classes of prochiral substrates. Similar to other types of asymmetric catalysis, intensive experimental screening and fine tuning of the catalysts are required to achieve high enantioselectivity. The limitations of current CCAs that have been proven to provide effective chiral environments may be an obstacle in future studies, and the design and development of new CCAs may be required. The conformational flexibility due to the forced monodentate coordination of the CCA in the transition state is also often problematic, as mentioned in the Introduction. In studies by He and co-workers (Scheme 12)\(^{35}\) and by our group (Scheme 7),\(^{28}\) the transition state structures for enantioselective C–H bond cleavage were proposed on the basis of DFT calculations. In our study, we found that several transition states with very different conformations have similar energies. In such cases, rational design to improve the enantioselectivity based on computational results and chemical intuition is a formidable challenge. To avoid this issue, additional contrivances to fix the conformation of CCAs would be necessary. In this regard, the introduction of additional interacting polar functional groups to the CCAs, \(\text{Cp}\) ligands, and directing groups might be a good solution, although the synthetic cost of the catalysts would increase to some extent. A combination with chiral \(\text{Cp}\)\(^3\) ligands would be an alternative option, as demonstrated by Cramer and co-workers.\(^{17}\)

The broad opportunity to electronically modify the metal catalysts would be an advantage of CCA-assisted enantioselective C–H functionalization. Many studies on racemic reactions have demonstrated that electronic tuning of the \(\text{Cp}\) ligands leads to higher reactivity and unique chemoselectivity or site selectivity.\(^{38}\) The hybridization of such electronically tuned \(\text{Cp}\) ligands with CCAs could also represent another future direction to realize high reactivity/unique selectivity together with enantioselectivity.

The development of enantioselective C(sp\(^3\))–H functionalization would remain a major issue for group 9 CpM\(^\text{III}\) catalysis for the next several years. The emergence of designed chiral Cp\(^4\) ligands had preceded Cp\(^8\)*/CCA catalysis, but their application to C(sp\(^3\))–H functionalization reactions was not reported until very recently.\(^{39,40}\) In contrast, the CCA-assisted
Scheme 13. Planar-Chiral Ferrocene Carboxylic Acids 42 for Enantioselective C(sp³)−H Amidation of α-Aryl Thioamides 26

**CCA Effects**

![Diagram showing CCA effects with chemical structures and reaction conditions.]

**Substrate scope under the optimized conditions**

![Diagram showing substrate scope with reaction conditions.]

The approach was quickly shown to be successful for several C(sp³)−H functionalization reactions. While the applicable substrates and directing groups remain limited, further investigation in this direction may expand the accessible chiral structures and will hopefully lead to practical applications.

While the Cp*MIII/CCA catalytic systems have successfully been applied to the construction of point and planar chirality, asymmetric synthesis of axially chiral molecules using a CCA as the sole chiral source has not yet been reported to date. As long as the C−H bond cleavage is an enantiodetermining step, the Cp*MIII/CCA catalysts can potentially produce axially chiral molecules in high enantioselectivity in principle. Therefore, when C−H activation to form a metallacycle intermediate locks a preformed chiral axis of substrates, a (dynamic) kinetic resolution can be achieved using CCA, which may be good candidates for future development.8a,42

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**Notes**

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Perspective


