Chiral Carboxylic Acid-Assisted Enantioselective C–H Activation with Achiral Cp^xM^{III} (M = Co, Rh, Ir) Catalysts.

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C–H activation, Asymmetric catalysis, Chiral carboxylic acid, Cobalt, Rhodium, Iridium

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^x 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 Article summarizes the background, catalyst design, and applied reactions in detail, followed by discussion on the future direction.

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 metallacycle intermediates. While various transition metal catalysts have been investigated for this strategy, trivalent group 9 metals (Co^{III}, Rh^{III}, Ir^{III}) 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^*Rh^{III} and Cp^*Ir^{III} catalysis by Satoh and Miura in 2007[2] and Cp^*Co^{III} catalysis by Matsunaga and Kanai in 2013,[3] an enormous number of reactions have been developed, and many review articles 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^x 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^x ligands by other research groups.[8,9]

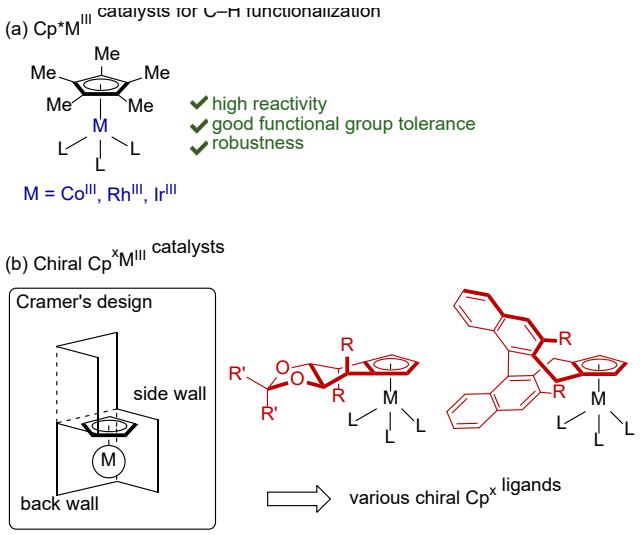


Figure 1. Group 9 Cp*M^{III} and chiral Cp^xM^{III} catalysts for C–H functionalization reactions.

Chiral Cp^x 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 Pd^{II} catalysts.[10] C–H bond cleavage by high-valent electrophilic metal catalysts, including Pd^{II} and Cp*M^{III}, is often accelerated by carboxylate or other coordinating bases.[11] Many mechanistic studies and quantum chemical calculations strongly suggested that such C–H activations proceed via a base-assisted concerted mechanism (**Figure 2a**). Agostic interactions between 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), or base-assisted internal electrophilic substitution (BIES). Although the electronic states in the transition state depend on the metal, ligand, substrate, and reaction conditions,[11d-f] 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 Pd^{II} catalysis.[12] Subsequent mechanistic studies indicated that the MPAA ligands coordinate to Pd^{II} in a bidentate manner in their dianion form and that the amidate moiety acts as the base for C–H activation (**Figure 2b**, top).[10] The combination of Pd^{II} with MPAAs or

related bidentate ligands has enabled various enantioselective C(sp^2)–H and C(sp^3)–H functionalization reactions. The bidentate coordination of the ligands to Pd^{II} can contribute to high enantioselectivity for a wide range of substrates.[10,13,14]

On the other hand, the application of these bidentate ligands to assist C–H activation has not been successful in group 9 Cp*M^{III} catalysis. As Cp*M^{III} 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 Pd^{II}, which adopts a square-planar geometry with four coordination sites, cannot be directly transferred to Cp*M^{III} 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^xM^{III} catalysts have recently been developed. This Perspective Article briefly summarizes these reports and discusses the future challenges in this area. Enantioselective C–H functionalization using achiral Cp*M^{III} catalysts and external chiral sources based on other strategies, including chiral acid- or anion-controlled alkylation via a selective protonation step,[15] are not covered here.

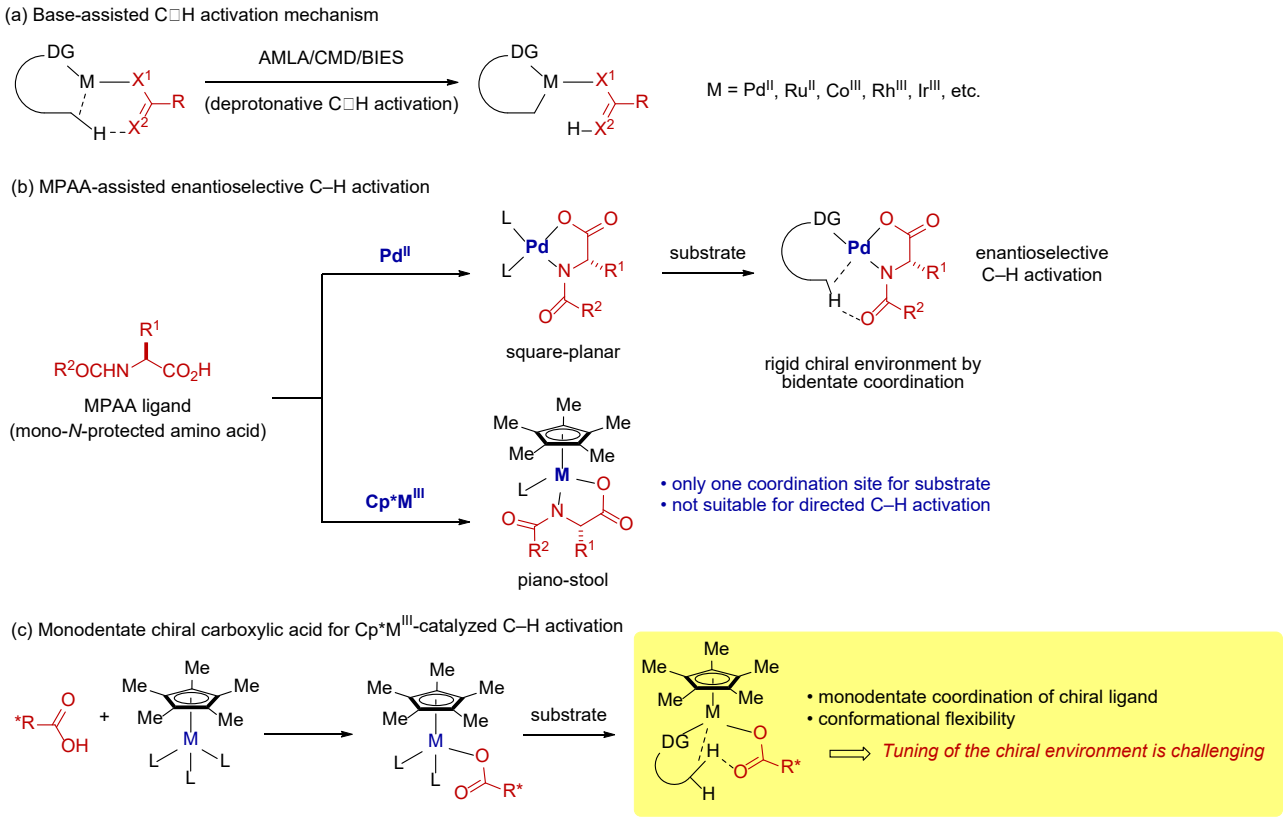
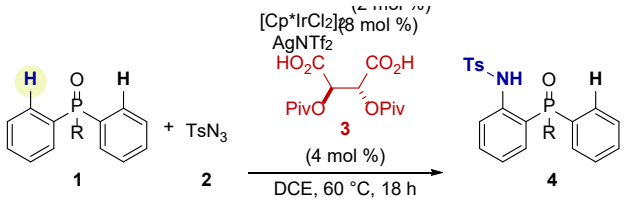


Figure 2. Chiral ligand-assisted enantioselective C–H activation using Pd^{II} or Cp^*M^{III} catalysts.

2. SEMINAL WORK

The first enantioselective C–H functionalization via the combination of an achiral Cp^*M^{III} catalyst and a CCA was reported by Chang in 2015 (**Scheme 1**).[16] During their studies on the C–H amidation of phosphine oxides **1** with tosyl azide (**2**) using a Cp^*Ir^{III} catalyst in the presence of carboxylic acid additives, the authors discovered that the pivaloyl-protected tartaric acid derivative **3** induces enantioselectivity, albeit 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 background reaction is expected to occur without a chiral ligand. Suppressing racemic background reactions is important to achieve high enantioselectivity using this strategy.

Scheme 1. Enantioselective C–H Amidation of Phosphine Oxides **1** with Cp^*Ir^{III}/Tartaric Acid Derivatives **3**.



R	Me	Bn	*t*Bu	cyclohexyl	N*i*Pr$_2$
% yield	80	91	88	84	44
% ee	11	19	27	32	31

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

3. CHIRAL BINAPHTHYL MONO CARBOXILIC ACIDS

Several years ago, our research group began developing appropriate monodentate CCAs for enantioselective C–H functionalization using Cp*M^{III} 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. Starting from readily available optically active BINOL (**5**), 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 *C*$_2$-symmetric binaphthyl dicarboxylic acids had been studied as chiral organocatalysts by Hashimoto and Maruoka,[18] the investigation of such axially chiral *C*$_1$-symmetric monocarboxylic acids in asymmetric catalysis was quite limited.[19]

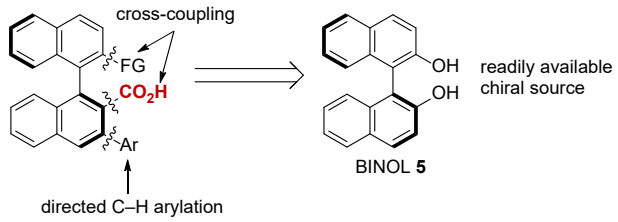
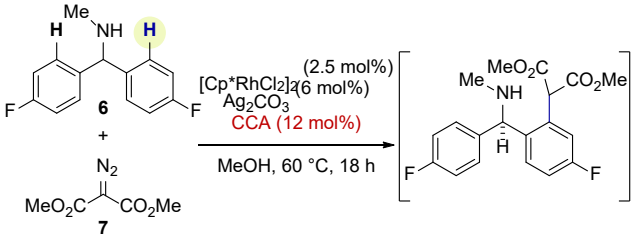
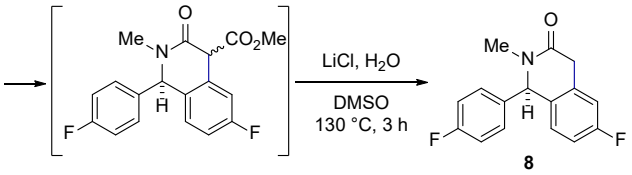


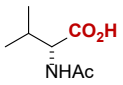
Figure 3. Design of chiral binaphthyl mono carboxylic acids.

As an initial model reaction to examine the CCAs, C(sp^2)–H alkylation of amine **6** with diazo malonate **7** under Rh^{III} catalysis was selected (**Scheme 2**).[20,21] 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(2*H*)-one derivative. Initial trials using MPAAs (**9a**, **9b**) afforded the target product (**8**) in low enantioselectivity, implying that the MPAAs could act as a monodentate ligand for CMD but failed to construct an effective chiral environment for the Cp*Rh^{III} catalyst. While binaphthyl-type CCA **11** with a small ether group at the 2′-position afforded an almost racemic product, 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 non-protected 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*Rh^{III} catalyst with $Cp^{Me4}Rh^{III}$ (Cp^{Me4} = 1,2,3,4-tetramethylcyclopentadienyl) slightly improved the enantioselectivity. As showcased by these results, the chiral 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**.

Scheme 2. CCA Screening for Enantioselective C(sp^2)–H alkylation/cyclization using a Cp*Rh^{III} catalyst.

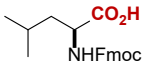






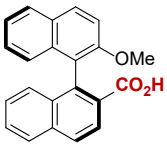
9a (*N*-Ac-D-valine)

63%, 43.5:56.5 er



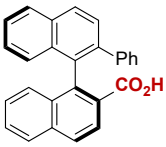
9b (*N*-Fmoc-L-leucine)

61%, 54:46 er



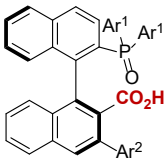
10

43%, 49.5:50.5 er



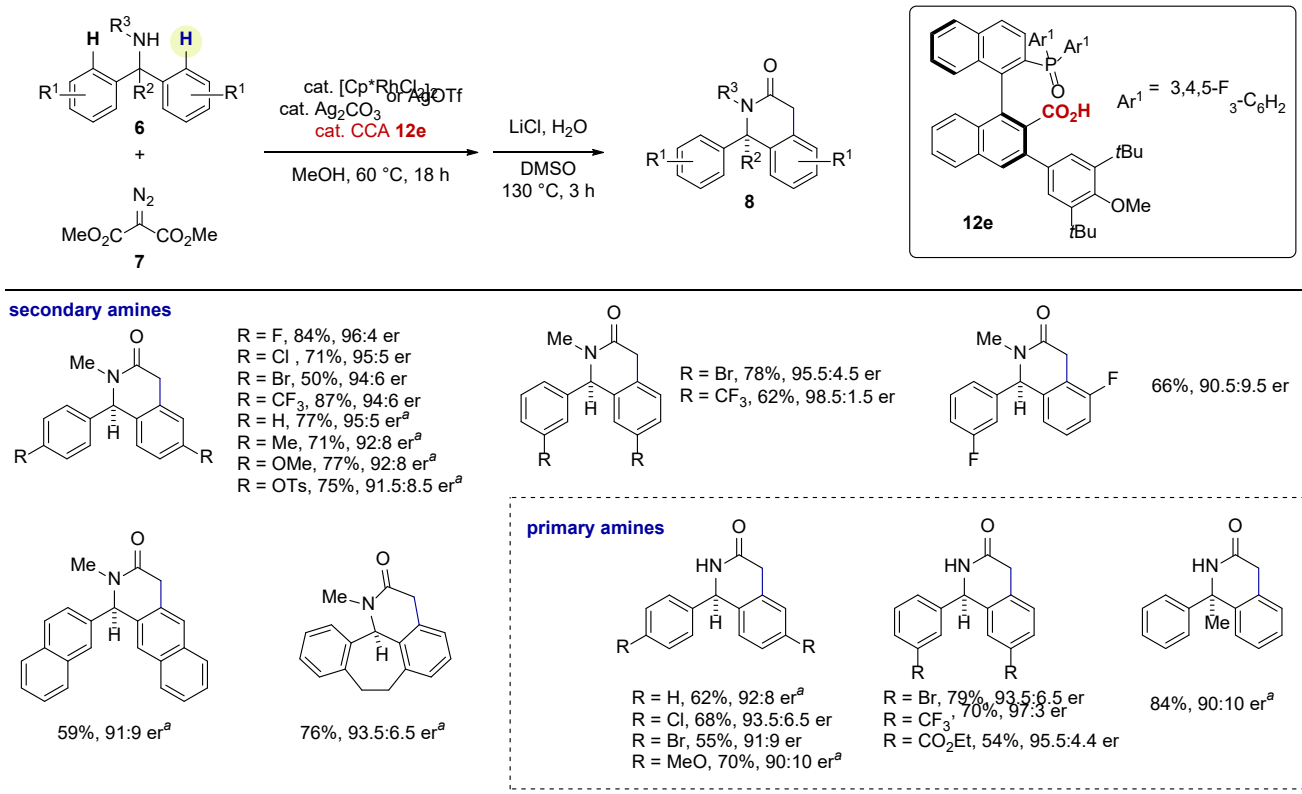
11a

20%, 37:63 er



12a: Ar^1 = Ph, Ar_2 = H, 67%, 75.5:24.5 er
12b: Ar^1 = 4-MeO-C_6H_4, Ar^2 = H, 56%, 70.5:29.5 er
12c: Ar^1 = 3,5-$(CF_3)_2$-C_6H_3, Ar^2 = H, 82%, 71:29 er
12d: Ar^1 = 3,5-$(CF_3)_2$-C_6H_3, Ar^2 = 3,5-*t*Bu$_2$-4-MeO-C_6H_2, 54%, 94.5:5.5 er
12e: Ar^1 = 3,4,5-F_3-C_6H_2, Ar^2 = 3,5-*t*Bu$_2$-4-MeO-C_6H_2, 84%, 96:4 er

Scheme 3. Scope of Enantioselective C(sp^2)–H Alkylation/Cyclization Reaction Using Rh^{III} Catalysts and CCA **12e**.

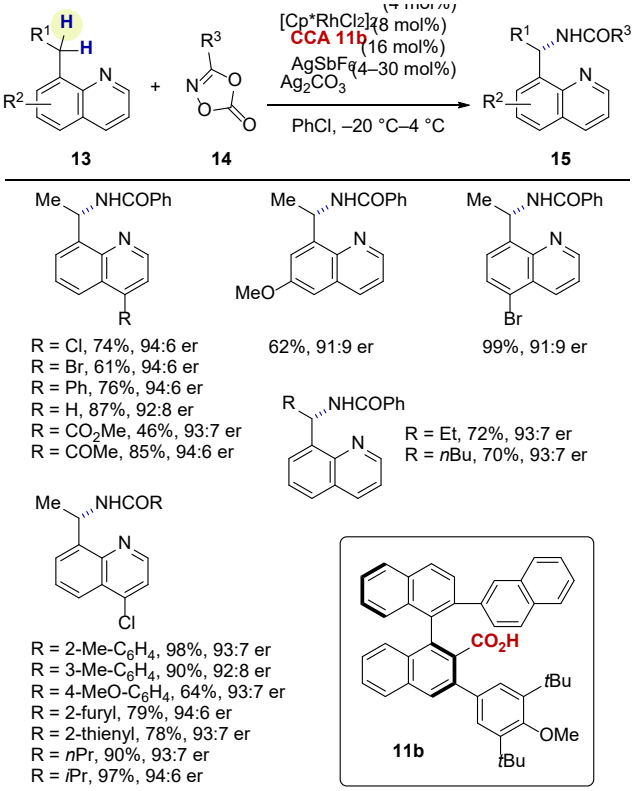


[a][$Cp^{Me4}RhCl_2$]$_2$ instead of [Cp*$RhCl_2$]$_2$

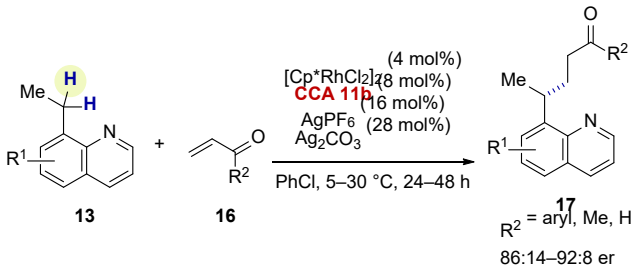
Our group also applied binaphthyl CCA **11b**, which bears aryl substituents at both the 2′- and 3-positions, to methylene C(sp^3)–H amidation reactions of 8-alkylquinolines **13** (**Scheme 4**).[22,23] The use of dioxazolones **14** as the amidation reagents[24] allowed the reaction to proceed at low 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 in the dioxazolones **14** were well tolerated. In addition to 8-ethylquinoline, 8-propyl- and 8-pentylquinoline 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 enantio-determining step. As shown in **Scheme 6**, **11b** and the related CCAs are readily accessible from BINOL **5**. After conversion to **18** via mono-tosylation 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.

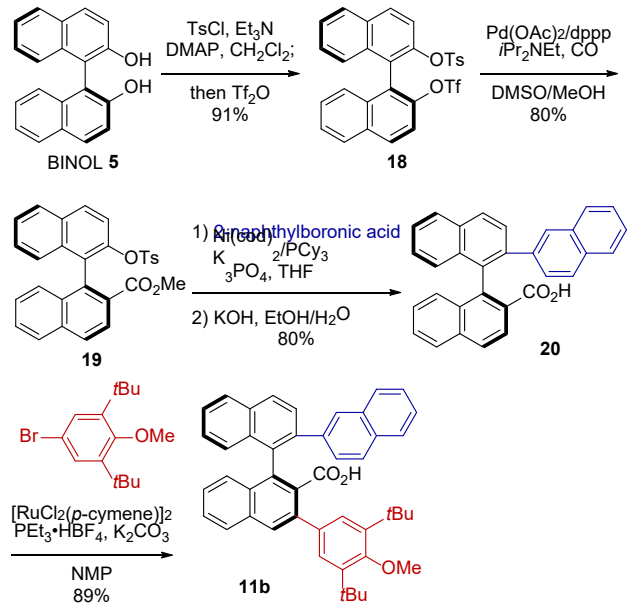
Scheme 4. Enantioselective Methylene C(sp^3)–H Amidation of 8-Alkylquinolines **13**.



Scheme 5. Enantioselective Methylene C(sp^3)–H Alkylation of 8-Ethylquinolines **13** with α,β-Unsaturated Carbonyl Compounds **16**.



Scheme 6. Concise Synthesis of CCA **11**.



Although the above-mentioned C_1-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 C_2-symmetric CCAs for enantioselective C–H functionalization (**Figure 4**; **21**).[28,29] Their fixed structure and pseudo C_2-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).

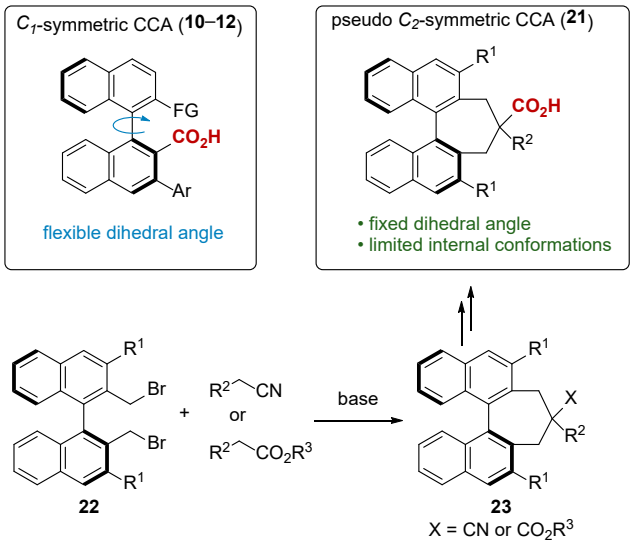
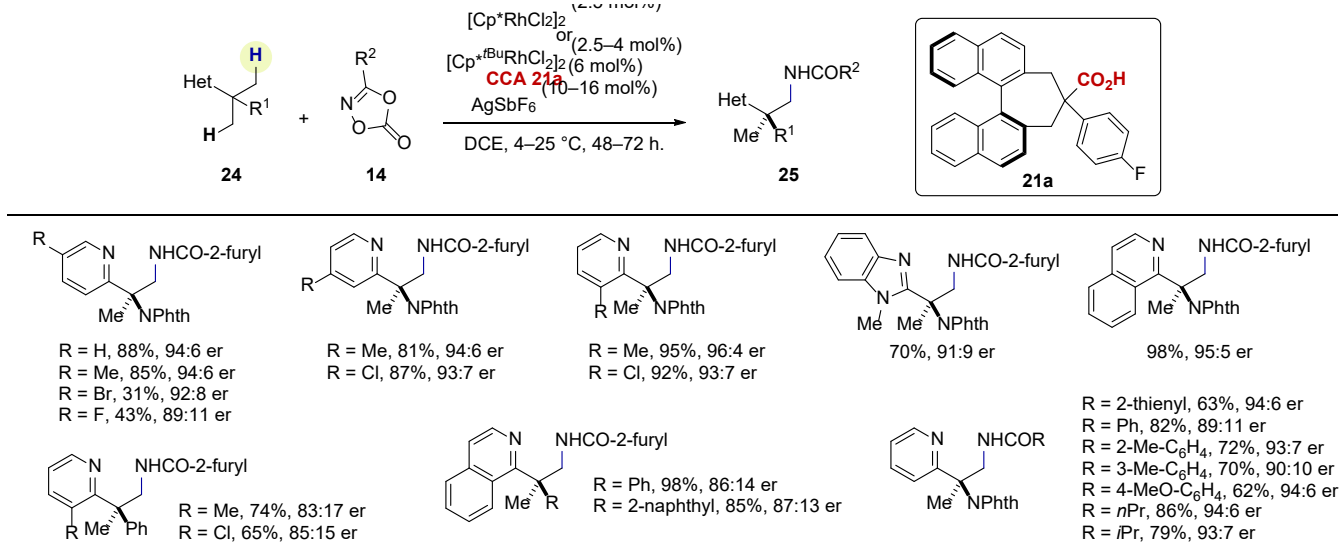


Figure 4. Comparison of C_1-symmetric and pseudo C_2-symmetric CCAs.

These pseudo C_2-symmetric CCAs outperformed C_1-symmetric CCA **11b** and exhibited high enantioselectivity in the enantioselective C(sp^3)–H amidation of 2-alkylpyridines and related hetero aromatic compounds **24** (**Scheme 7**). The best CCA (**21a**), combined with a Cp^*Rh^{III} or $Cp^{*tBu}Rh^{III}$ catalyst (Cp^{*tBu} = 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 group.

Scheme 7. Heteroaryl-directed Enantioselective C(sp^3)–H Amidation Using pseudo C_2-Symmetric CCA **21a**.

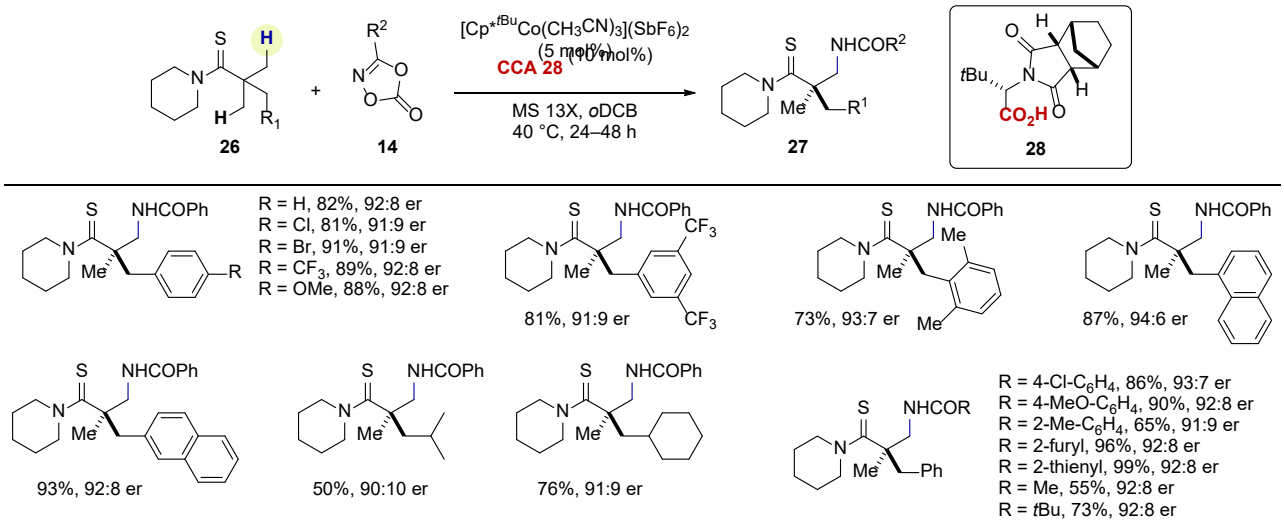


4. AMINO ACID DERIVATIVES

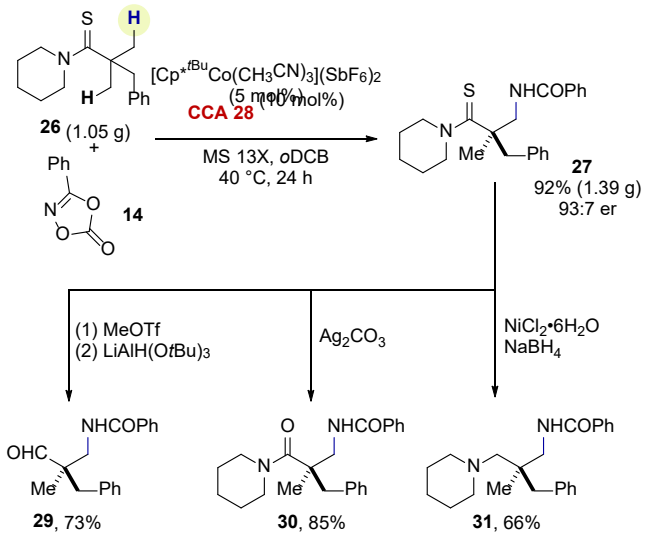
Amino acids are undoubtedly the most readily available and well-documented chiral carboxylic acids, and are widely used for synthesizing various chiral compounds including chiral ligands for asymmetric catalysis. Although, as explained above, MPAAs may not act as bidentate ligands for Cp^*M^{III} catalysts, 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(sp^3)–H amidation of thioamides **26** using a $Cp^{*t\mathrm{Bu}}Co^{III}$ catalyst and amino acid **28** (**Scheme 8**).[30,31] 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,[17] 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 $Cp^{*t\mathrm{Bu}}$ 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 enantio-determining. 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.

Scheme 8. Co^{III}-catalyzed Enantioselective C(sp^3)–H Amidation of Thioamides **26** Using Amino Acid Derivative **28**.

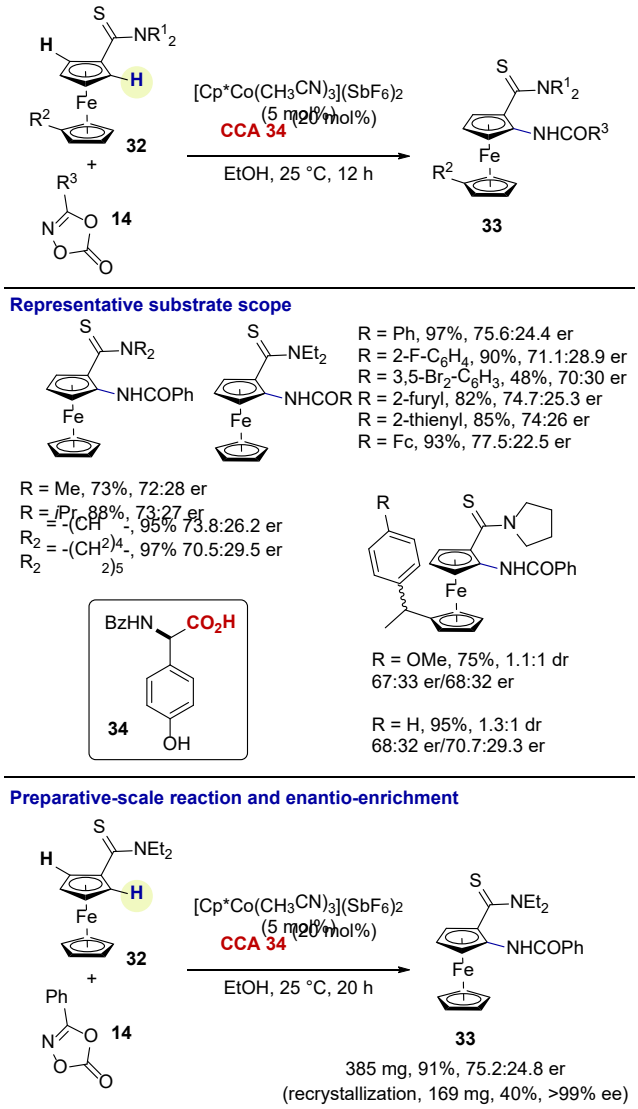


Scheme 9. Gram-scale Co^{III}-catalyzed Enantioselective C(sp^3)–H Amidation of Thioamide **26** and Subsequent Transformations.



Shi and co-workers have demonstrated that more standard MPAAs can also be used as the chiral ligand in the Cp*Co^{III}-catalyzed enantioselective C(sp^2)–H amidation of ferrocene derivatives to generate planar chirality (**Scheme 10**), although the enantioselectivity was still moderate (up to 77.5:22.5 er).[32] 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 in a preparative-scale (1 mmol), and recrystallization of the obtained product furnished the optically pure product in moderate yield (**Scheme 10**, bottom).

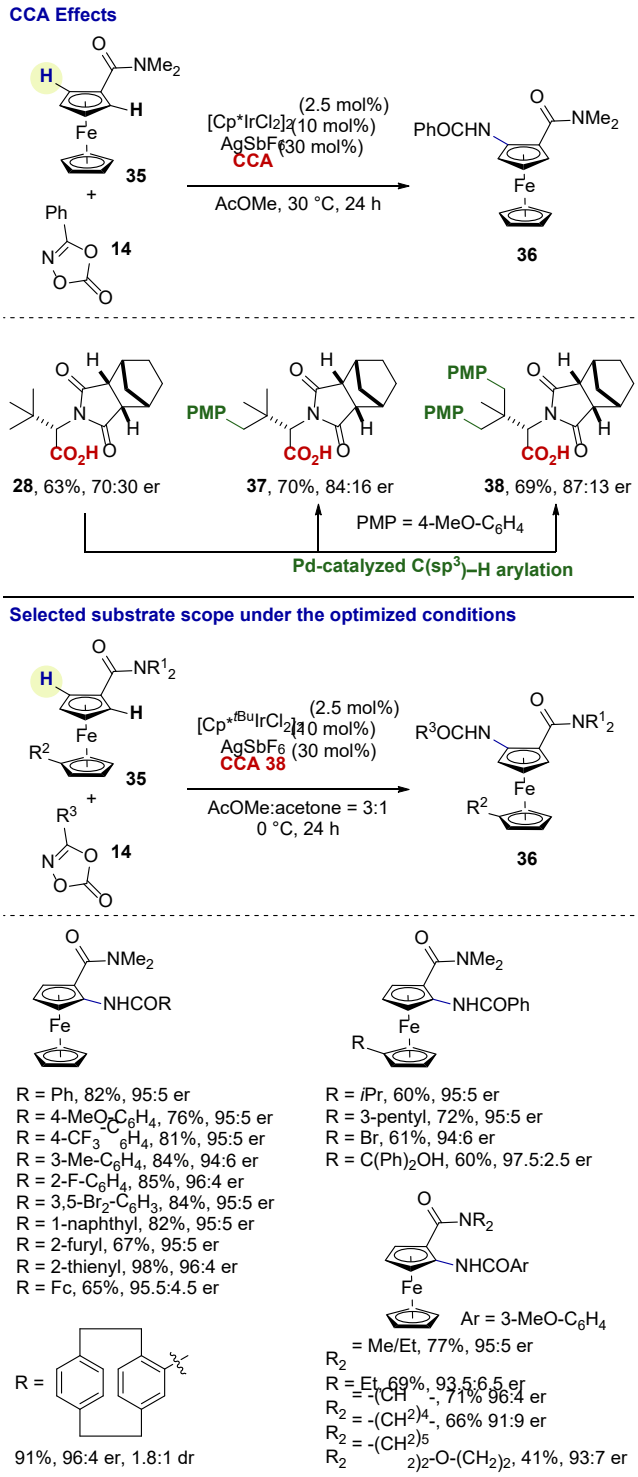
Scheme 10. Cp*Co^{III}/MPAA **34**-catalyzed Enantioselective C(sp^2)–H Amidation of Ferrocene Thioamides **33**.



Although thioamides have been demonstrated to be efficient directing groups for enantioselective C–H functionalization using group 9 metals (**Scheme 9** and **Scheme 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(sp^2)–H amidation of ferrocene amides **35** using an Ir^{III} 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(sp^3)–H amidation of thioamides,[30] the introduction of 4-methoxyphenyl (PMP) groups at the *t*Bu side chain further enhanced the enantioselectivity. Notably, the Pd-catalyzed C(sp^3)–H arylation protocol developed by the same group[34] provided straightforward access to these elaborate CCAs (**37**, **38**). In this case, a Cp*$^{t\mathrm{Bu}}$ 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.

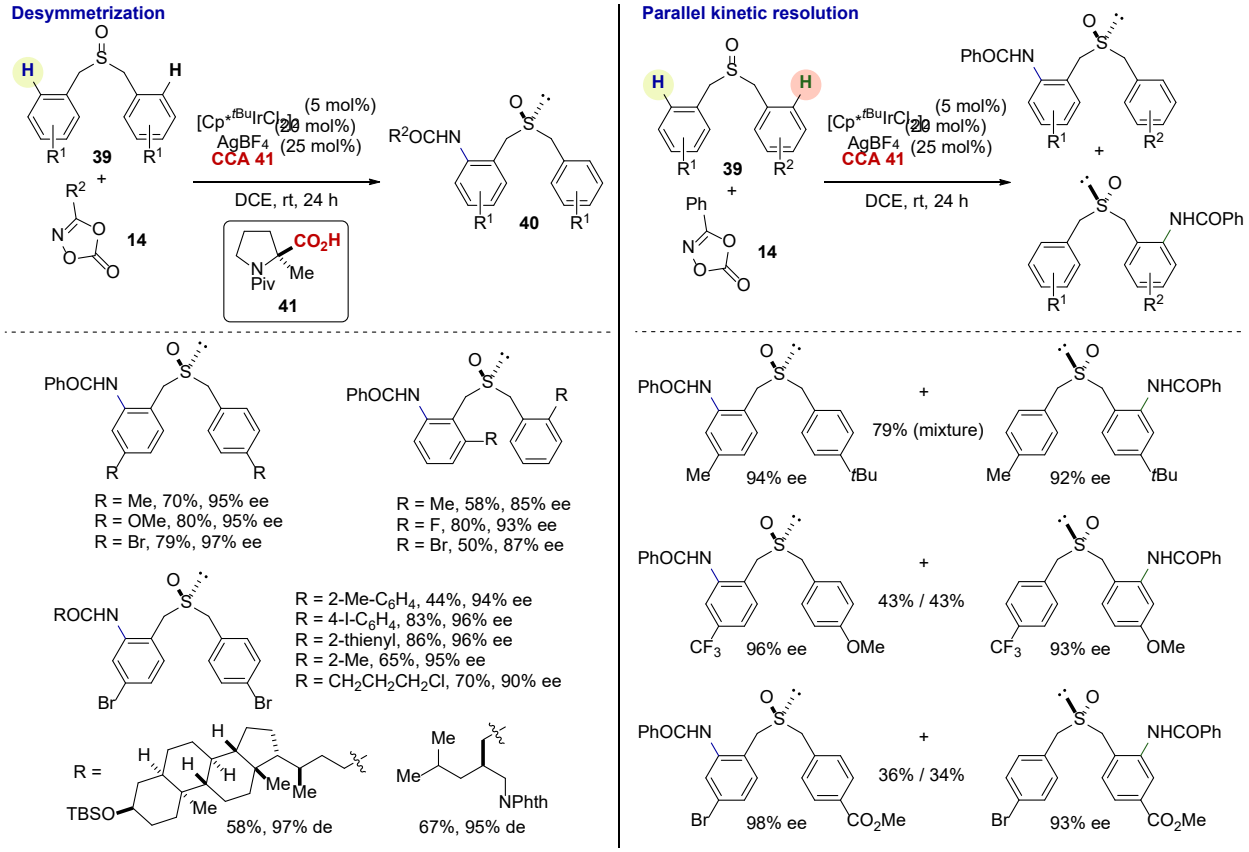
Scheme 11. Ir^{III}/CCA-catalyzed C(sp^2)–H Amidation of Ferrocene Amides **35**.



He and co-workers reported the synthesis of *S*-chiral sulfoxides via desymmetrization and parallel kinetic resolution using an achiral Ir^{III} catalyst and CCAs (**Scheme 12**).[35] They identified

a combination of a sterically hindered Ir^{III} catalyst ($Cp^{*tBu}Ir^{III}$) and *N*-Piv-Me-Pro-OH (**41**) as the best catalyst to discriminate the two enantiotopic aromatic $C(sp^2)$–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, CF_3, esters, etc. were compatible. In addition, coupling with dioxazolones derived from bioactive molecules was demonstrated.

Scheme 12. Ir^{III}/CCA-catalyzed Enantioselective C(sp^2)–H Amidation of Sulfoxides **39**: Desymmetrization and Parallel Kinetic Resolution (Representative Substrates).

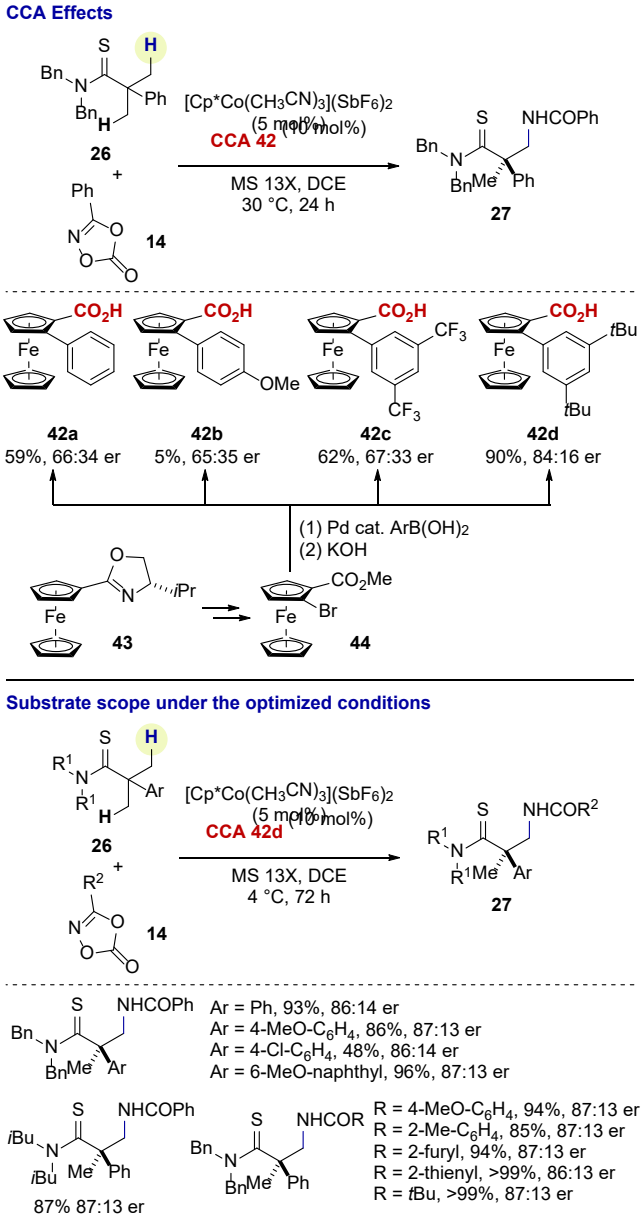


5. PLANAR-CHIRAL FERROCENE CARBOXYLIC ACIDS

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 Co^{III}-catalyzed enantioselective C(sp^3)–H amidation of thioamides (**Scheme 13**).[36] 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 (**42a**–**42d**). Screening these CCAs revealed that **42d** with a 3,5-di-*tert*-butyl-phenyl group was the most suitable, albeit with

room for improvement in terms of the enantioselectivity. Several kinds of α-aryl thioamides **26** and dioxazolones **14** were tested under the optimized conditions, resulting in up to 87:13 er.

Scheme 13. Planar-chiral Ferrocene Carboxylic Acids **42** for Enantioselective C(sp^3)–H Amidation of α-Aryl Thioamides **26**.



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 based on 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, Cp ligands, and directing groups might be a good solution, although the synthetic cost of the catalysts would increase to some extent. Combination with chiral Cp^x 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 Cp ligands leads to higher reactivity and unique chemo- or site-selectivity.[38] The hybridization of such electronically tuned 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^{III} catalysis for the next several years. The emergence of designed chiral Cp^x ligands had preceded Cp^*M^{III}/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 approach was quickly shown to be successful for several C(sp^3)–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^*M^{III}/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 enantio-determining step, the Cp^*M^{III}/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,[41] (dynamic) kinetic resolution can be achieved using CCAs, which may be good candidates for future development.[8a,42]

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Notes

The authors declare no competing financial interests.

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