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Cp*Co^{III}-catalyzed C–H Functionalization and Asymmetric Reactions Using External Chiral Sources

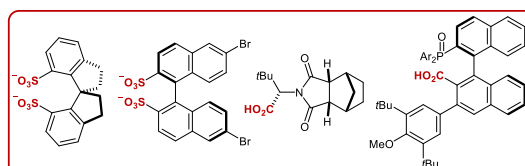
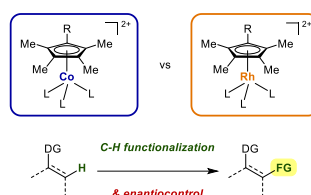
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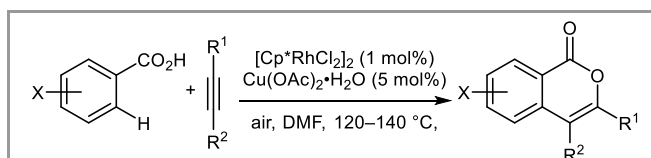
Abstract This account describes Cp*Co^{III}-catalyzed C–H functionalization reactions developed in our group between 2013 and 2018. Cp*Co^{III} catalysts not only serve as inexpensive alternatives to Cp*Rh^{III} catalysts but also exhibit unique reactivity and selectivity in several transformations. In the latter part of this review, we introduce catalytic asymmetric C–H functionalization reactions using achiral Rh^{III} or Co^{III} catalysts with chiral disulfonates or carboxylic acids as external chiral sources.

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Key words C–H functionalization, C–H activation, cobalt, rhodium, asymmetric catalysis,

a reactive organometallic intermediate, which is further coupled to other reagents leading to the incorporation of functional groups. Such transition metal-catalyzed C–H activation strategies have been intensively investigated as they enable the chemo- and site-selective functionalization of specific C–H bonds, especially in the presence of coordinating directing groups.¹

In 2007, Satoh, Miura, and co-workers reported Cp*Rh^{III}-catalyzed (Cp* = pentamethylcyclopentadienyl) oxidative annulation of benzoic acids with alkynes (Scheme 1).⁴ This seminal piece of work and the huge number of subsequent studies revealed a remarkable reactivity, generality, robustness, and functional-group compatibility of the Cp*Rh^{III} catalyst.⁵ Indeed, over the past decade, Cp*Rh^{III} has become one of the most popular and successful catalysts for C–H functionalization reactions.



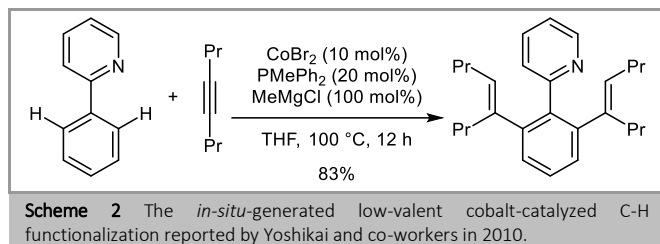
Scheme 1 Seminal work on the Cp*Rh^{III}-catalyzed C–H functionalization by Satoh, Miura, and co-workers in 2007: oxidative annulation of benzoic acids and alkynes.

1. Introduction and Overview

The direct catalytic transformation of ubiquitous but chemically inert carbon–hydrogen bonds in organic compounds, the so-called C–H functionalization reactions,¹ enables the atom-² and step-economical³ construction of complex molecules. Therefore, C–H functionalization methods have attracted increasing attention in various fields of chemical sciences, including medicinal chemistry, chemical biology, and material sciences, in which the concise synthesis of functional molecules is mandatory. Transition metal catalysts are able to cleave a C–H bond to form

The use of inexpensive and earth-abundant first-row transition metal catalysts is another current trend in the area of C–H functionalization reactions.⁶ Thus, cobalt represents a highly attractive alternative to rhodium and iridium, both of which exhibit high catalytic activity in various C–H functionalization reactions. Although several C–H functionalization reactions were sporadically reported in the 20th century,⁷ a major breakthrough was only achieved in 2010 by Yoshikai and co-workers,⁸ who reported an *in-situ*-generated low-valent cobalt catalyst from the reduction of Co^{II} with an organometallic reagent that effectively activated inert C–H bonds (Scheme 2). This *in-situ* reduction

system has significantly broadened the scope of cobalt-catalyzed C–H functionalization reactions.⁹



In this context, we began to investigate Cp*Co^{III}-catalyzed C–H functionalization reactions in 2013.¹⁰ Between 2013 and 2018, we discovered that Cp*Co^{III} catalysts exhibit not only similar catalytic activity to Cp*Rh^{III} catalysts but also unique reactivity and selectivity. The first part of this account describes our own work on such Cp*Co^{III} catalysts, focusing on their unique reactivity and the differences relative to Cp*Rh^{III} catalysts. Since publishing our initial findings, other research groups have also reported a variety of transformations using such Cp*Co^{III} catalysts. In addition, the combination of simpler cobalt precursors and bidentate directing groups has also appeared as a powerful methodology for C–H functionalization reactions, pioneered by Daugulis and co-workers.¹¹ These examples are not fully covered in this article, but several reviews on the subject are now available.^{12,13}

In contrast to the tremendous blooming of general Cp*Rh^{III}-, Cp*Co^{III}-, and Cp*Ir^{III}-catalyzed C–H functionalization reactions, only a limited number of enantioselective transformations have been reported to date.¹⁴ This is clearly due to the presence of a Cp* ligand and the lack of coordination sites during the catalytic cycle. Figure 1 shows a representative cycle for Cp*M^{III} catalysis in the presence of a carboxylate base (M = Co, Rh, Ir). Coordination of the directing group of a substrate (**I** to **II**) and subsequent C–H activation via carboxylate-assisted concerted metalation-deprotonation (CMD; internal CMD **III** or external CMD **III'**)¹⁵ affords metallacycle intermediate **IV**. In most cases, another substrate, electrophile, or other reagent coordinates to the metal center before carbon–carbon or carbon–hetero atom bond formation proceeds to afford the product. As long as the selectivity and reaction outcome are determined kinetically, the enantio-determining step is the cleavage of the C–H bond (**III**) or the bond-formation step from **V**. Both transition state **III** and intermediate **V** are coordinatively saturated 18-electron species and therefore, external chiral ligands cannot participate in the enantio-determining step.

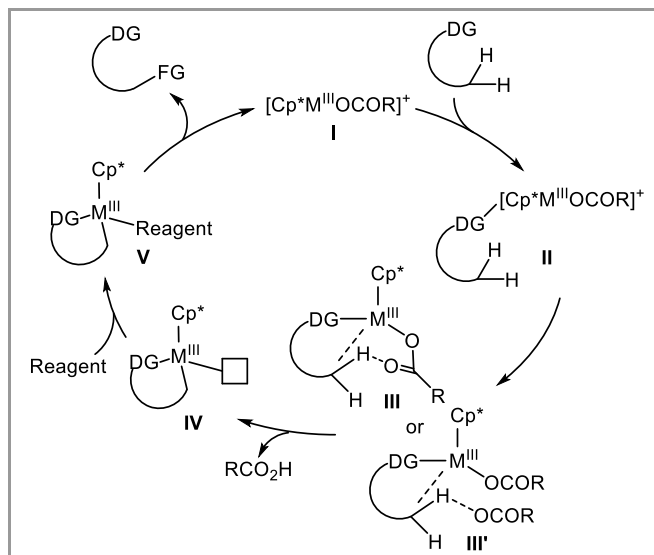


Figure 1 Representative catalytic cycle and intermediates for Cp*M^{III}-catalyzed C–H functionalization reactions (M = Co, Rh, Ir). DG = directing group. FG = functional group.

Introduction of a chiral Cp* ligand is a straightforward solution to this problem, but the development of effective and versatile Cp* ligands and Cp*M^{III} complexes remains challenging. After the groundbreaking work by Cramer and co-workers,¹⁶ several chiral Cp* ligands were reported for asymmetric C–H functionalization reactions (Figure 2).^{17,18} However, the identification and structure optimization of a chiral Cp* ligand for a specific reaction often remain an arduous task.

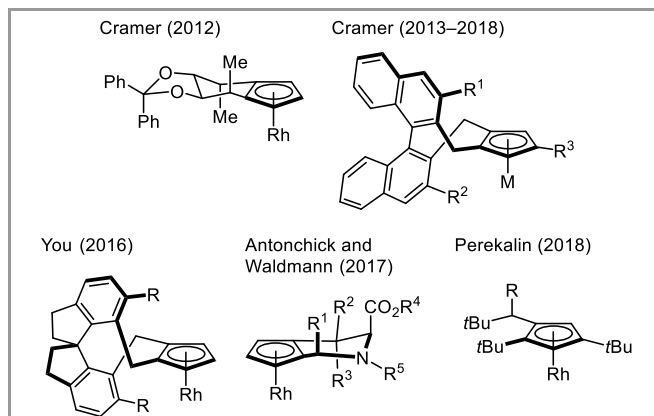


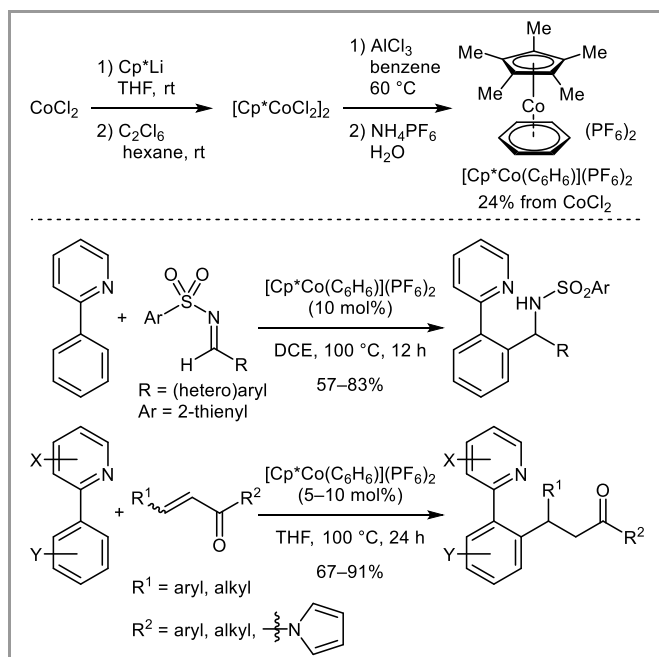
Figure 2 Chiral Cp* ligands and metal complexes used for enantioselective C–H functionalization reactions (2012–2018).

To address the aforementioned issues in enantioselective C–H functionalization reactions using high-valent group 9 metal catalysts, we recently devised Cp*Rh^{III}/chiral disulfonate and Cp*M^{III}/chiral carboxylic acid hybrid systems, demonstrating that an external chiral source may enable control over the enantioselectivity of C–H functionalization reactions. These catalytic systems are discussed in the latter part of this article.

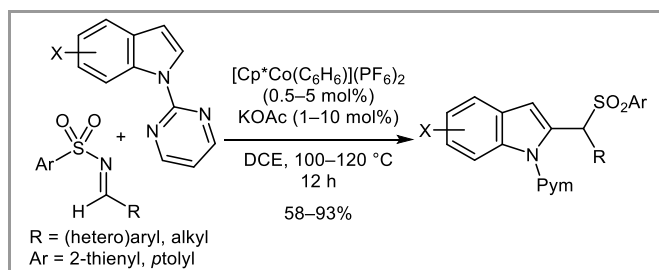
2. Cp*Co^{III}-catalyzed C-H Functionalization Reactions

2.1. C-H Addition Reactions to Polar Double Bonds

Our studies on Cp*Co^{III}-catalyzed reactions began with the finding that C-H bond addition reactions of 2-phenylpyridine derivatives to imines, enones, and α,β -unsaturated *N*-acylpyrroles proceed in the presence of catalytic amounts of [Cp*Co(C₆H₆)](PF₆)₂ (Scheme 3),^{19,20} as the arene ligand of the catalyst easily dissociates to release an active species. In control experiments using CoCl₂, CoCl₂/AgPF₆, Co(OTf)₂, Co(acac)₃, and [Cp*CoCl₂]₂, the desired product was not obtained, while [Cp*CoCl₂]₂/AgPF₆ exhibited moderate catalytic activity, indicating that a coordinatively unsaturated dicationic species is involved in the C-H functionalization reactions. The same catalyst also facilitated the C2-selective addition of indoles to imines by introducing a 2-pyrimidyl directing group at the nitrogen atom, overruling the inherent C3-selectivity of indoles toward electrophilic aromatic substitution reactions under acidic conditions (Scheme 4).²¹



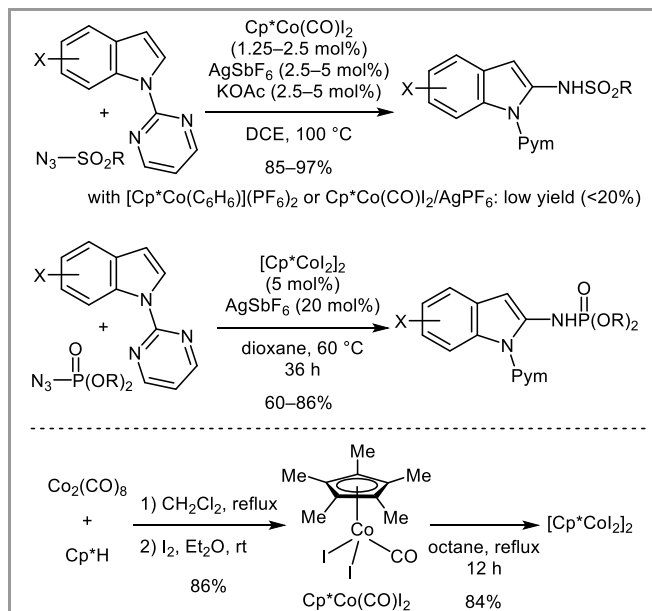
Scheme 3 C-H addition reactions to imines, enones, and α,β -unsaturated *N*-acylpyrroles catalyzed by [Cp*Co(C₆H₆)](PF₆)₂.



Scheme 4 C2-selective addition of indoles to imines via C-H activation.

2.2. Cp*Co(CO)I₂ and [Cp*CoI₂]₂ Precursors for the C2-selective C-H Amidation of Indoles

Although [Cp*Co(C₆H₆)](PF₆)₂ can be used for C-H functionalization reactions without any activating additives, such as silver salts, the synthesis from CoCl₂ and Cp*Li is low-yielding and requires tedious workup procedures due to the air-sensitive Cp*Co^{II} intermediate (Scheme 3).¹⁹ Moreover, we failed to obtain derivatives bearing a different counteranion, and we encountered drastic counteranion effects in C-H amidation reactions of indoles using organic azides (Scheme 5), in which [Cp*Co(C₆H₆)](PF₆)₂ afforded unsatisfactory results.^{22,23} We found that the combination of Cp*Co(CO)I₂ or [Cp*CoI₂]₂ with AgSbF₆ exhibited superior reactivity, although the yield significantly decreased upon changing AgSbF₆ to AgPF₆. In these reactions, the PF₆ anion is not suitable, possibly due to instability.²⁴ Since Cp*Co(CO)I₂ and [Cp*CoI₂]₂ are easily prepared in good yield and enable the investigation of counteranion effects,^{22,23,25} these precursors, combined with various silver salts, have become the most popular Cp*Co^{III} catalysts.²⁶



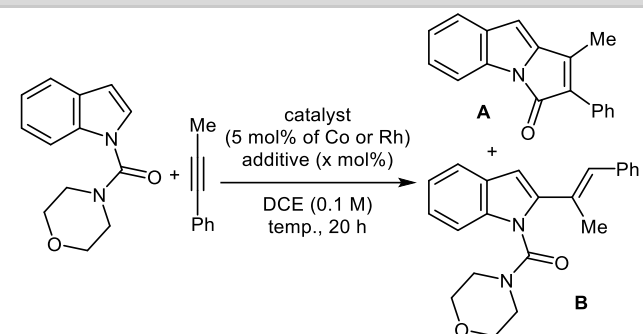
Scheme 5 C2-selective amidation of indoles using azides.

2.3. C-H Functionalization of Carbamoyl-protected Indoles Using Alkynes

We discovered the unique reactivity of the Cp*Co^{III} catalysts initially when investigating the reactions of carbamoyl-protected indoles with alkynes (Table 1).²⁷ Schipper, Fagnou, and co-workers have reported that the C-H alkenylation of carbamoyl-indoles proceeds using a Cp*Rh^{III} catalyst.²⁸ When we used [Cp*Co(C₆H₆)](PF₆)₂ as the catalyst, cyclized product **A** was obtained together with alkenylated product **B**. The product distribution depends on the reaction conditions and the substrate structure: high temperatures (120–130 °C), low concentrations (0.1 M), and the use of a morpholine-derived carbamoyl directing group maximize the yield of **A** (entries 1 and 8). In contrast, almost no cyclized product was observed when

Cp*Rh^{III} catalysts were used (entries 2–7), whilst **B** was obtained in good yield in the presence of excess pivalic acid (PivOH, entries 2 and 5).²⁸

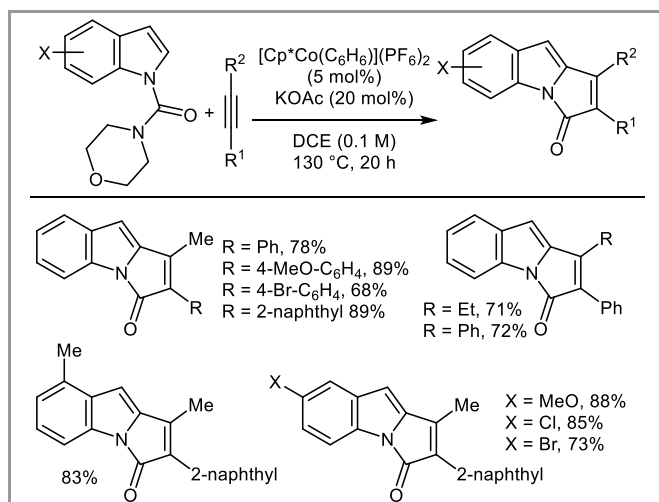
Table 1 Cobalt- and rhodium-catalyzed C–H alkenylation and annulation reactions between indoles and alkynes.



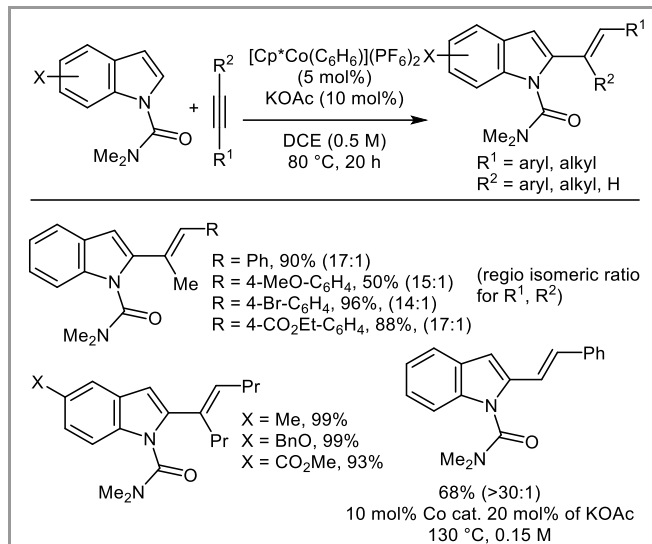
Entry	Catalyst	Additive (x mol%)	Temp. (°C)	A (%) ^a	B (%) ^a
1	[Cp*Co(C ₆ H ₆)](PF ₆) ₂	KOAc (20)	120	73	9
2	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOH (500)	120	<1	90
3	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	KOAc (20)	120	0	3
4	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	CsOPiv (20)	120	0	4
5	[Cp*RhCl ₂] ₂ /4AgPF ₆	PivOH (500)	120	0	>95
6	[Cp*RhCl ₂] ₂ /4AgPF ₆	KOAc (20)	120	0	11
7	[Cp*RhCl ₂] ₂ /4AgPF ₆	CsOPiv (20)	120	0	9
8	[Cp*Co(C ₆ H ₆)](PF ₆) ₂	KOAc (20)	130	82 (78) ^b	8

^a Determined by ¹H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. ^b Isolated yield.

Schemes 6 and 7 show representative examples of alkenylation/annulation reactions and alkenylation reactions catalyzed by [Cp*Co(C₆H₆)](PF₆)₂, respectively.²⁷ Alkynes bearing at least one aromatic substituent underwent the annulation to furnish pyrroloindolones in moderate to good yield (Scheme 6). Changing the directing group to an *N,N*-dimethylcarbamoyl group, decreasing the reaction temperature, and increasing the concentration switched the reaction in favor of alkenylation (Scheme 7). Both aromatic and aliphatic substituents were compatible for the alkynes, and even a terminal alkyne successfully provided the alkenylation product. Terminal and aliphatic alkynes did not afford the annulation product (**A**), regardless of the reaction conditions.

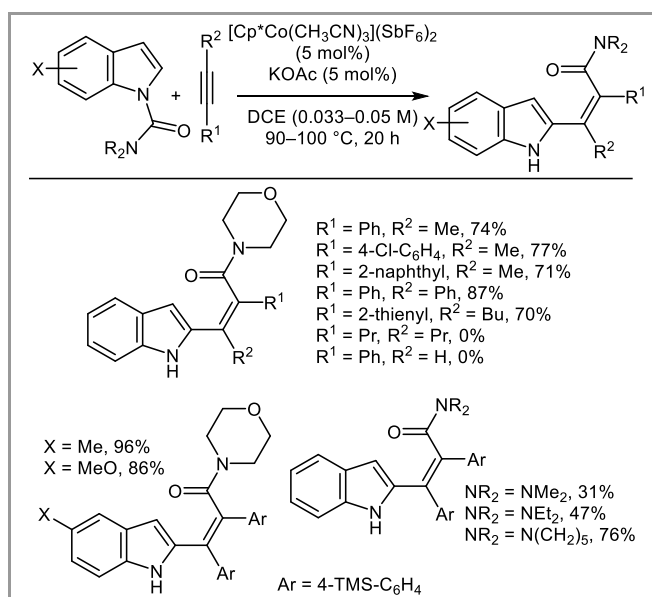


Scheme 6 Scope of the Co-catalyzed annulation of indoles and alkynes.



Scheme 7 Scope of the Co-catalyzed alkenylation of indoles with alkynes.

Further investigations of these reactions disclosed that another product was obtained under reaction conditions similar to those for the annulation reactions but at slightly lower temperature (90–100 °C) (Scheme 8).²⁹ The carbamoyl group was transferred from the nitrogen atom of the indoles to the carbon atom of the alkynes, thus furnishing tetrasubstituted alkenes with excellent *E/Z* selectivity. The scope of alkynes was similar to that of the annulation reactions (Scheme 6); terminal and aliphatic alkynes only afforded alkenylation products.



Scheme 8 Co-catalyzed alkenylation/DG migration reactions of indoles and alkynes.

Plausible reaction pathways for these three types of reactions (Schemes 6–8) are summarized in Figure 3.³⁰ C–H activation (**I**) and insertion of an alkyne would generate common intermediate **II**.³¹ A subsequent protonation of the C–Co bond would then result in alkenylation, and an intramolecular nucleophilic addition of the C–Co bond to the C=O double bond of the directing group would provide intermediate **III**. At low temperatures and high concentrations, the alkenylation pathway is dominant, probably due to fast intermolecular protonation, whereas high

temperatures and low concentrations render the intramolecular cyclization more feasible. From **III**, both annulation and DG migration are possible, and the outcome depended on subtle differences in the reaction temperature (Scheme 6 vs Scheme 8). We experimentally confirmed that the DG migration product was converted to the annulation product at 130 °C in the presence of KOAc, indicating that the annulation product is the thermodynamically favored product. Thus, the DG migration product can only be obtained as the major product by carefully controlling the reaction temperature (90–100 °C). Terminal and aliphatic alkynes do not participate in the annulation or DG migration, possibly due to the fast protonation of **II**. More importantly, using $\text{Cp}^*\text{Rh}^{\text{III}}$ catalysts exclusively provides the alkenylation product under any conditions. This critical difference can be attributed to the difference in electronegativity between Co and Rh (1.88 vs 2.28; Pauling scale); the alkenyl-cobalt intermediate (**II**) is thus more polarized and reactive toward a carbonyl group, i.e., a polar electrophile, than an alkenyl-rhodium intermediate, which is not reactive enough to generate **III**.

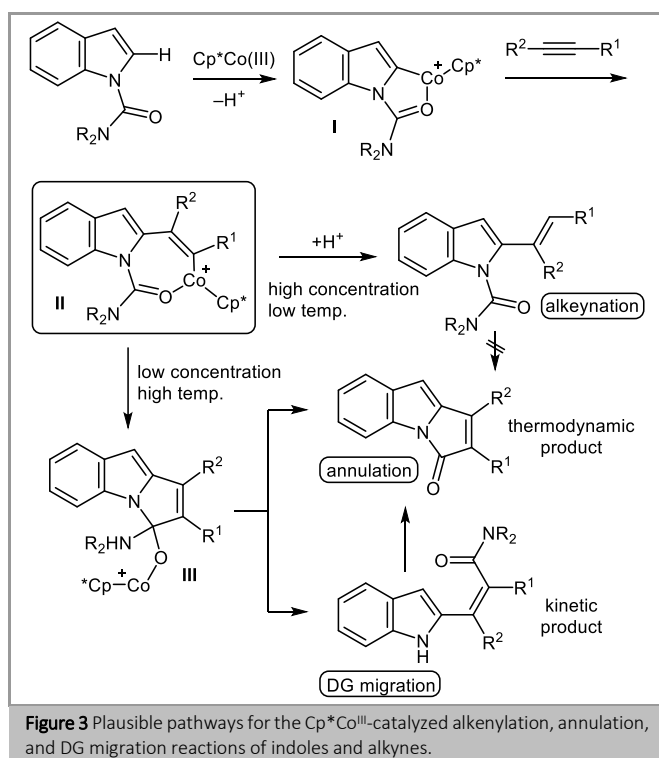
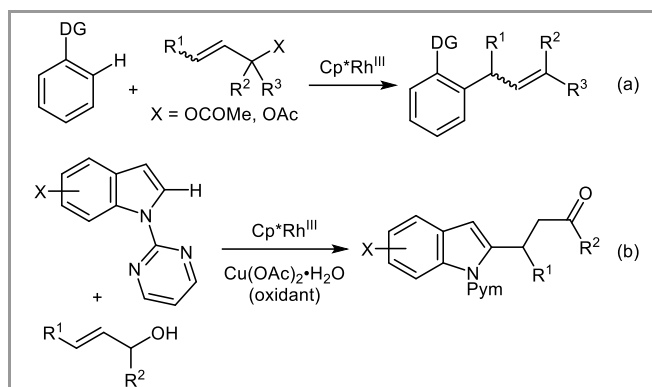


Figure 3 Plausible pathways for the $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed alkenylation, annulation, and DG migration reactions of indoles and alkynes.

2.4. C–H Allylation Using Allyl Alcohols

Allyl arenes are important synthetic intermediates in organic synthesis as the allyl moiety can be easily converted into a wide range of functional groups. C–H allylation reactions are, therefore, highly attractive transformations, and achieved using a $\text{Cp}^*\text{Rh}^{\text{III}}$ catalyst (Scheme 9a).³² In these reactions, activated allylic alcohols, such as allyl carbonates and allyl acetates, are required as coupling partners. On the other hand, Glorius and co-workers have reported that carbonyl compounds instead of allylated arenes are obtained when non-activated allyl alcohols are employed (Scheme 9b).³³



Scheme 9 $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed (a) C–H allylation using activated allylic alcohols and (b) carbonyl formation using allylic alcohols.

The different reaction pathways in these $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed reactions may be rationalized in terms of the selectivity of the β -elimination step (Figure 4). In the proposed mechanism for such C–H allylation reactions (Scheme 9a), insertion of an allyl carbonate or allyl acetate after C–H activation would afford intermediate **I**, which could undergo β -oxygen elimination via a six-membered transition state (**II**) that would finally provide the allylation product. On the other hand, the use of a non-activated allyl alcohol would render the transition state for the β -oxygen elimination an unfavorable four-membered structure (**III**). In this case, the β -hydride elimination (**IV**) would become more favorable, and the oxidative carbonyl formation would predominate.

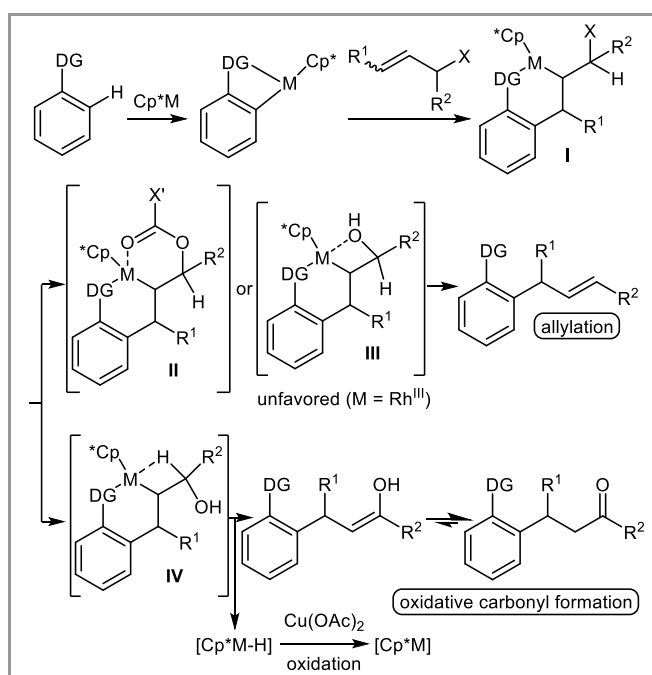
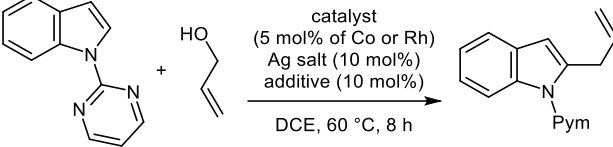


Figure 4 Selectivity of the β -elimination under $\text{Cp}^*\text{Rh}^{\text{III}}$ catalysis.

At this point, we speculated that $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed reactions would exhibit a different β -elimination selectivity given that Co^{III} is a harder acid³⁴ compared to Rh^{III} and would thus favor a β -OH elimination (Figure 4, **III**)³⁵ rather than a β -hydride elimination (**IV**), even when a non-activated allyl alcohol is used as the allylating agent. Intensive optimization studies revealed that the C2-selective C–H allylation of a pyrimidyl-protected indole with allyl alcohol proceeds in almost quantitative yield in the presence

of $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$, AgOTf , and AgOAc (Table 2, entry 1).³⁶ Under the same reaction conditions, $[\text{Cp}^*\text{RhCl}_2]_2$ instead of $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ afforded the allylation product in lower yield (entry 2). Several unidentified byproducts were observed in this $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed reaction, probably because the β -hydride elimination competes with the desired β -OH elimination and the resulting Rh-hydride species induces several side reactions in the absence of an appropriate oxidant. We briefly screened the reaction conditions using the rhodium catalyst, but the desired product was not obtained (entries 3–6). Following our report, Sundararaju and co-workers reported that reactions using quinoline *N*-oxides and allyl alcohols provide different products under $\text{Cp}^*\text{Co}^{\text{III}}$ and $\text{Cp}^*\text{Rh}^{\text{III}}$ catalysis, i.e., an allylation products with Co, and oxidative carbonyl formation products with Rh (Scheme 9b).³⁷ Our results and the following studies clearly support our hypothesis that $\text{Cp}^*\text{Co}^{\text{III}}$ catalysts selectively promote β -OH eliminations, while $\text{Cp}^*\text{Rh}^{\text{III}}$ catalysts tend to trigger β -hydride eliminations.

Table 2 $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed C–H allylation of indole with allyl alcohol and control experiments using the corresponding $\text{Cp}^*\text{Rh}^{\text{III}}$ catalyst.

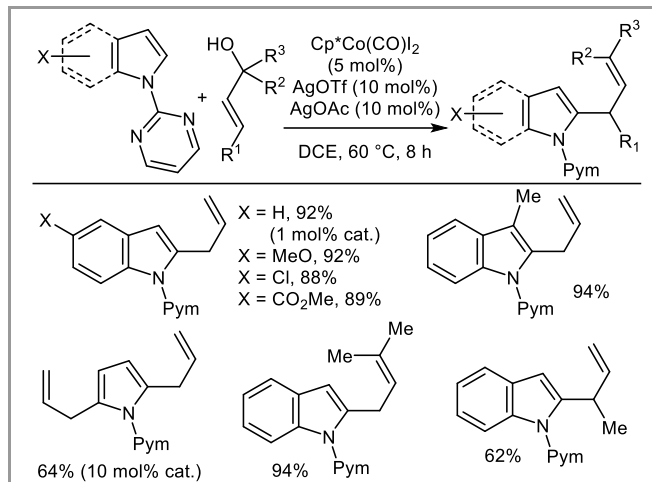


Entry	Catalyst	Ag salt	Additive	Yield (%) ^a
1	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$	AgOTf	AgOAc	99 ^b
2	$[\text{Cp}^*\text{RhCl}_2]_2$	AgOTf	AgOAc	31
3	$[\text{Cp}^*\text{RhCl}_2]_2$	AgOTf	none	0
4	$[\text{Cp}^*\text{RhCl}_2]_2$	AgSbF_6	AgOAc	0
5	$[\text{Cp}^*\text{RhCl}_2]_2$	AgSbF_6	AgOPiv	0
6	$[\text{Cp}^*\text{RhCl}_2]_2$	AgSbF_6	PivOH	trace

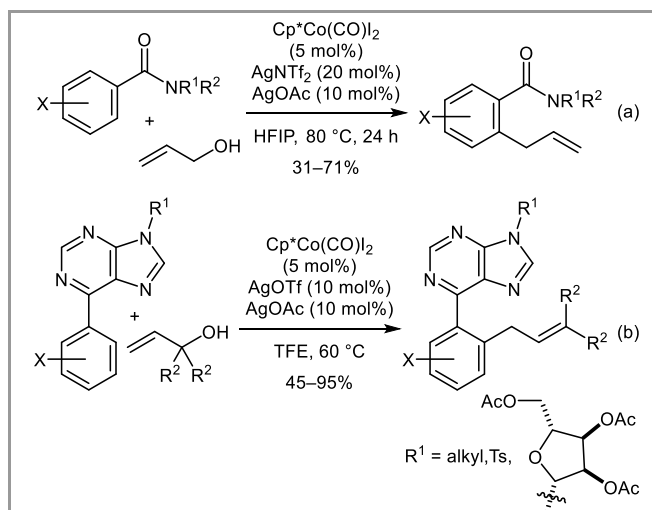
^a Determined by ^1H NMR analysis of the crude mixture using an internal standard. ^b Isolated yield.

Scheme 10 shows representative examples of C–H allylation of indole and pyrrole derivatives. Carbon–carbon bond formation selectively occurs at the γ -position of allyl alcohols, regardless of the substitution pattern, implying that the reactions proceed through an insertion/ β -OH elimination mechanism. It is worth noting that a prenyl group, which frequently appears in terpenes, was successfully introduced using 2-methylbut-3-en-2-ol.

Although the initially developed conditions (Scheme 10) resulted in unsatisfactory results with other substrates, changing the solvent to 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) or 2,2,2-trifluoroethanol (TFE) drastically improved the reactivity, expanding the scope to benzamide derivatives (Scheme 11a) and 6-arylpurines (Scheme 11b).^{38,39} We speculated that the highly polar nature, moderate acidity, and weak coordinating ability of such fluorinated alcohol solvents facilitates the generation and stabilization of certain coordinatively unsaturated cationic intermediates.



Scheme 10 $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed C–H allylation of indoles and pyrrole using allyl alcohols.



Scheme 11 $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed C–H allylation of (a) benzamide derivatives and (b) 6-arylpurines using allyl alcohols.

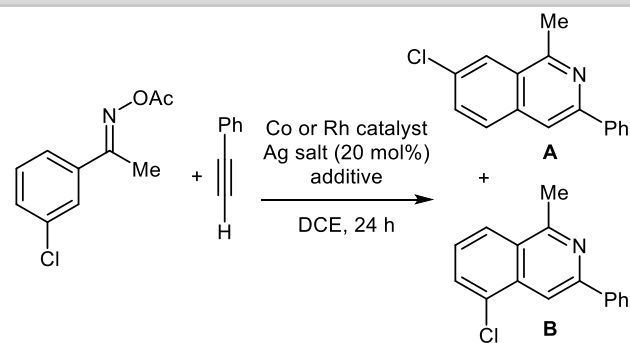
2.5. Cyclization Reactions of *O*-Acyloximes and Alkynes

Another unique feature that distinguishes $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed reactions from $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed reactions is the site-selectivity of the C–H activation on unsymmetrically substituted substrates. We discovered these significant differences during our investigations on the cyclization of *O*-acyloximes and alkynes to give isoquinoline derivatives (Table 3 and Scheme 12).^{40,41} Under the optimized conditions in the presence of a $\text{Cp}^*\text{Co}^{\text{III}}$ catalyst, a *m*-Cl-acetophenone derived *O*-acyloxime undergoes C–H activation at the less hindered position, providing isomer **A** with high selectivity (Table 3, entry 1). In contrast, the corresponding $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed reaction⁴² resulted in the formation of isomer **B** as the major product with low selectivity via a C–H activation at the *ortho*-position relative to the Cl substituent (entries 2–8). The high site-selectivity in the $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed reaction would be attributed to the steric repulsion between the Cp^* ligand and the Cl-substituent, which would render the formation of a metallacycle intermediate leading to isomer **B** unfavorable (Figure 5). In the $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed reaction, the larger size of Rh^{III} compared to that of Co^{III} and the longer Rh–C bonds relative

to the Co–C bonds would relieve such steric repulsion, thus slightly favoring isomer **B** over isomer **A** due to the higher acidity of the C–H bond *ortho* to the Cl substituent.

A similar trend in site-selectivity between Cp*Co^{III}- and Cp*Rh^{III}-catalyzed reactions was observed in the C–H alkenylation of a 3-substituted pyrrole with an alkyne (Table 4).⁴³ Selective C–H activation at the less hindered position proceeded with [Cp*Co(CH₃CN)₃](SbF₆)₂ to give isomer **A** as the major product (entry 1). When we used [Cp*Rh(CH₃CN)₃](SbF₆)₂ under otherwise identical conditions, almost no reaction occurred (entry 2). Although the alkenylation proceeded upon changing the reaction conditions to those reported by Schipper, Fagnou, and co-workers,²⁸ a non-selective C–H activation resulted in the formation of a significant amount of isomer **B** (entry 3). These differences in the site-selectivity can be rationalized in terms of the severe steric repulsion between the Cp* ligand and the substituent in the case of the Cp*Co^{III}-catalyzed reaction, as mentioned above.

Table 3 Cp*Co^{III}- and Cp*Rh^{III}-catalyzed annulation reactions of an unsymmetrically substituted *O*-acyl oxime and alkyne.



Entry	Catalyst (mol%)	Ag salt	Additive (mol%)	Temp. (°C)	Yield (%) ^a	A/B
1	Cp*Co(CO) ₂ (10)	AgSbF ₆	KOAc (20)	120	82 ^b	17:1
2 ^c	[Cp*RhCl ₂] ₂ (2.5)	none	NaOAc (30)	60	trace	n.d.
3 ^c	[Cp*RhCl ₂] ₂ (2.5)	none	CsOAc (30)	80	trace	n.d.
4	[Cp*RhCl ₂] ₂ (5)	AgSbF ₆	KOAc (20)	80	trace	n.d.
5	[Cp*RhCl ₂] ₂ (5)	AgSbF ₆	KOAc (20)	120	11	1:1.3
6	[Cp*RhCl ₂] ₂ (5)	AgSbF ₆	K ₂ CO ₃ (20)	120	9	1:1.6
7	[Cp*RhCl ₂] ₂ (5)	AgSbF ₆	CsOAc (20)	120	28	1:1.3
8	[Cp*RhCl ₂] ₂ (5)	AgSbF ₆	CsOPiv (20)	120	13	1:1.3

^a Determined by ¹H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. ^b Isolated yield. ^c MeOH was used as the solvent instead of DCE.

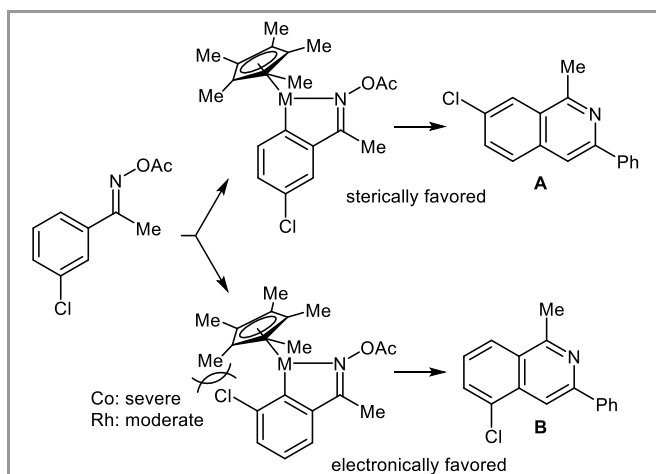
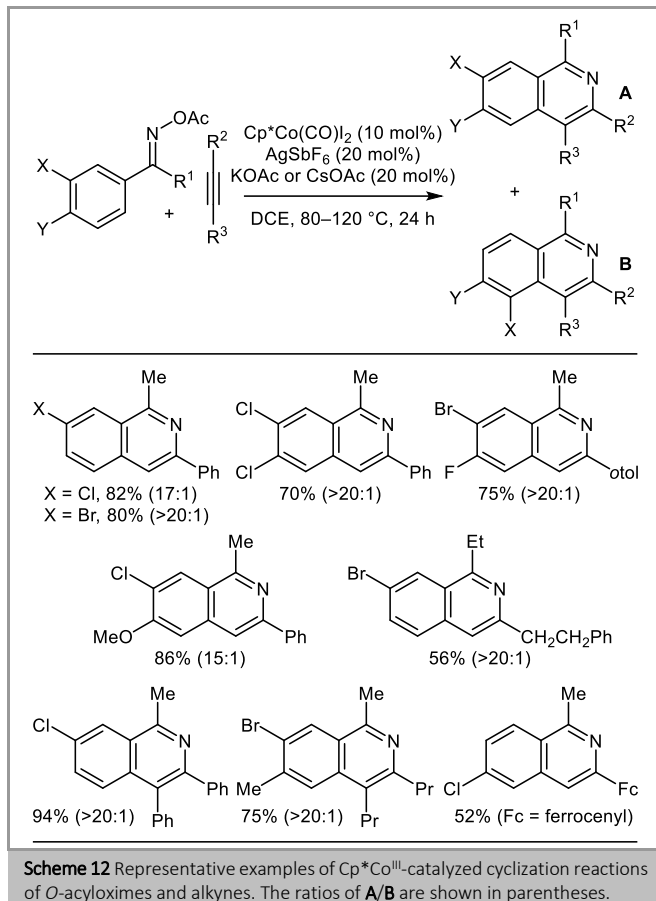
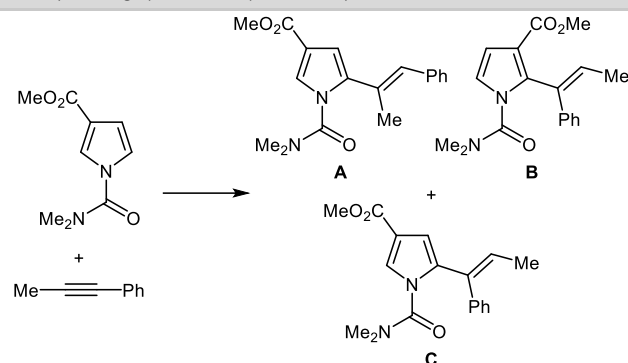


Table 4 Site-selectivity in the C–H alkenylation of a 3-substituted pyrrole with an alkyne using Cp*Co^{III} and Cp*Rh^{III} catalysts.

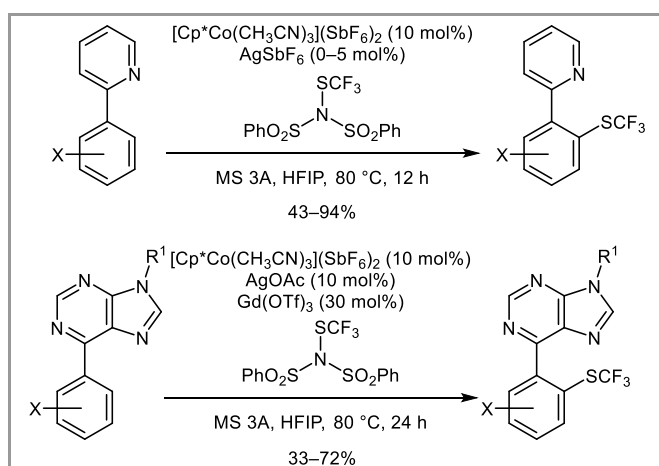


Entry	Conditions	Yield of A (%)	A/B/C ^a
1	[Cp*Co(CH ₃ CN) ₃](SbF ₆) ₂ (5 mol%) KOAc (5 mol%), PivOH (10 mol%) dioxane, 80 °C, 20 h	90 ^b	100/6/4
2	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂ (5 mol%) KOAc (5 mol%), PivOH (10 mol%) dioxane, 80 °C, 20 h	trace	n.d.
3	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂ (5 mol%) PivOH (5 equiv), DCE, 90 °C, 24 h	40 ^a	100/59/–

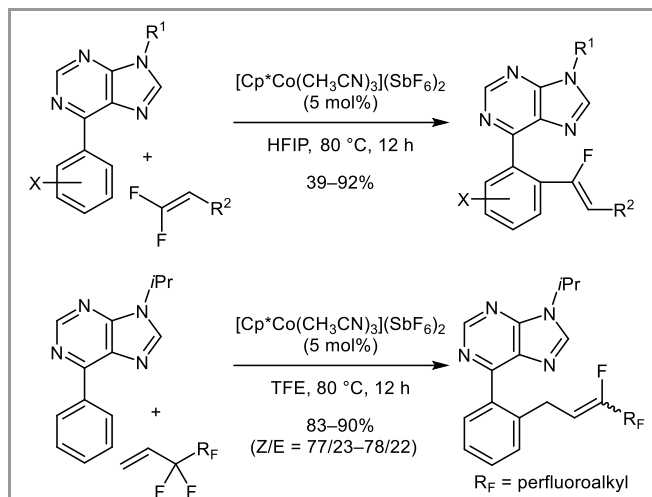
^a Determined by ¹H NMR analysis of the crude mixture. ^b Isolated yield.

2.6. Other Miscellaneous Reactions

We have also reported the introduction of fluorine-containing functional groups via C–H activation using a Cp*Co^{III} catalyst. The electrophilic trifluoromethylthiolation reagent developed by Xue, Lu, Shen, and co-workers⁴⁴ worked in combination with [Cp*Co(CH₃CN)₃](SbF₆)₂ and an additional Lewis acid to enable the trifluoromethylthiolation of a C–H bond of 2-phenylpyridines and 6-arylpurines (Scheme 13).^{45,46} The same substrates, 6-arylpurines, also reacted with fluorinated alkenes in HFIP or TFE via consecutive C–H activation, insertion, and β-F elimination steps to afford allylated or alkenylated products (Scheme 14).^{47,48}



Scheme 13 Cp*Co^{III}-catalyzed C–H trifluoromethylthiolation using electrophilic trifluoromethylthiolation reagent.



Scheme 14 Cp*Co^{III}-catalyzed C–H alkenylation and allylation using fluorinated alkenes via β-F elimination.

Amides are able to coordinate to metal centers, and thus work as effective directing groups in transition metal-catalyzed C–H functionalization reactions. We focused our attention on *N*-methoxy-*N*-methyl amides, the so-called Weinreb amides, which are highly reliable synthetic precursors for ketones and aldehydes.⁴⁹ After intensive optimization efforts, we discovered that aromatic Weinreb amides, as well as α,β-unsaturated Weinreb amides, undergo C–H allylation, alkenylation,⁵⁰ iodination, and amidation reactions (Figure 6).⁵¹ In the case of C–H amidation reactions using dioxazolones as amidation reagents,⁵² high temperatures and prolonged reaction times lead to partial cyclization of the products into 4*H*-3,1-benzoxazin-4-ones with the release of *N*-methoxy-*N*-methylamine (Scheme 15).⁵³ The cyclization is reversible, and the yield of the 4*H*-3,1-benzoxazin-4-ones was maximized upon the addition of Ac₂O to scavenge *N*-methoxy-*N*-methylamine.

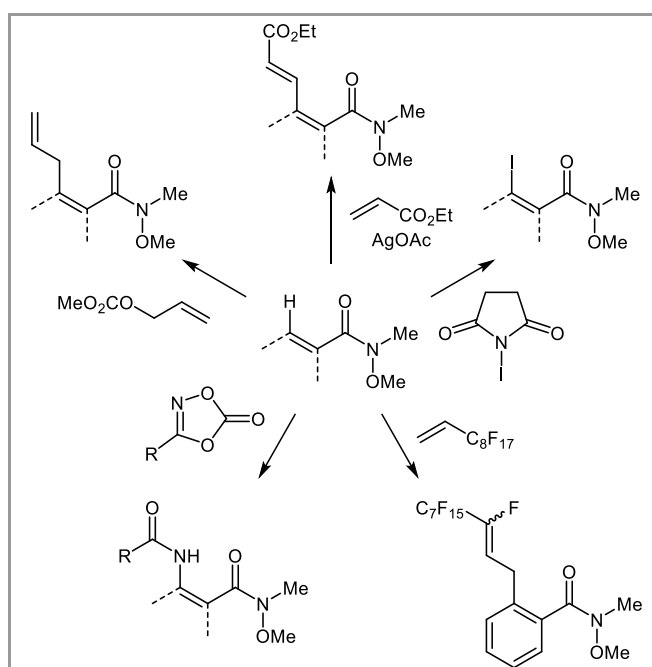
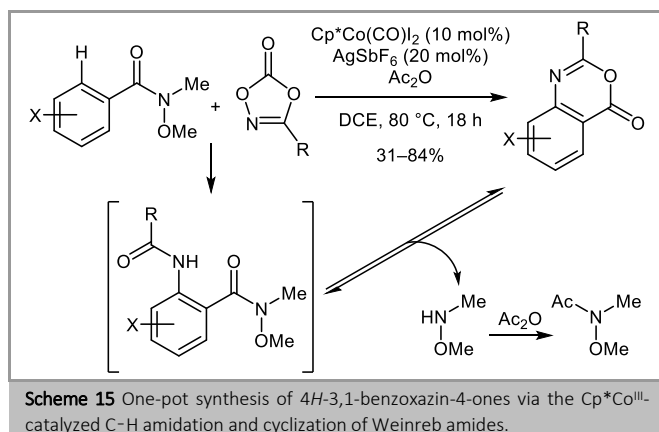


Figure 6 Cp*Co^{III}-catalyzed C–H functionalization of Weinreb amide.

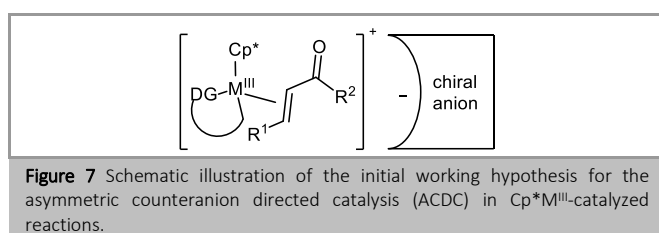


3. Enantioselective C-H Functionalization by Hybrid Catalysis

3.1. Cp*Rh^{III}/Chiral Disulfonate Catalysts for Enantioselective C-H Addition to Enones

As mentioned in the introduction, Cp*M^{III}-catalyzed asymmetric C-H functionalization reactions mostly rely on the use of elaborate chiral Cp ligands. When we started our studies on the asymmetric C-H functionalization reactions, only a few preliminary results on the use of external chiral sources had been published, and all of these reported low enantioselectivities.^{54,55}

We envisioned that chiral anions might be able to induce enantioselectivity by forming a contact ion pair without a chiral Cp ligand if a metallacycle intermediate is cationic (Figure 7). This concept, the so-called “asymmetric counteranion directed catalysis (ACDC)”,⁵⁶ has been proposed and established by List.⁵⁷ The combination of a chiral anion and a cationic transition metal catalyst was pioneered by the groups of Toste⁵⁸ and List⁵⁹ for gold and palladium catalysis, respectively.⁶⁰



We focused our attention on 1,1'-binaphthyl-2,2'-disulfonic acid (BINSA) and its dianion (BINSate) as an external source of chirality,^{61,62} speculating that the high acidity of sulfonic acid and the low coordinating ability of the sulfonate anion could lead to high reactivity of cationic Cp*M^{III} catalysts, where the coordination of anions usually inhibit the productive reaction pathways.

Cp*Rh^{III}/BINSate hybrid catalysts can be easily prepared by treating [Cp*RhCl₂]₂ with silver BINSate, which in turn is obtained from BINSA and Ag₂CO₃ (Scheme 16),⁶³ although the structure of the hybrid catalysts has not yet been fully elucidated. To test our working hypothesis, we selected a C-H addition reaction of 2-phenylpyridine to an enone as a model reaction

(Table 5). A hybrid catalyst derived from simple BINSA (X = R = H) gratifyingly afforded the target product in moderate to good enantioselectivity in various solvents (entries 1-7). The observed enantioselectivity, which was comparable in solvents of different polarity, was somewhat surprising since the structure of contact ion pairs tends to be sensitive to solvation.⁵⁸ The addition of a catalytic amount of 2-methylquinoline and MS 3A improved the enantioselectivity (entries 8 and 9). A more electron-deficient BINSate (X = Br) exhibited slightly higher selectivity (entries 10 and 12), while sterically hindered BINSate (R = Ph) was ineffective (entry 11).

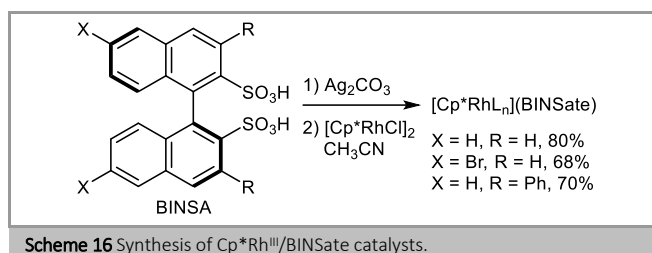


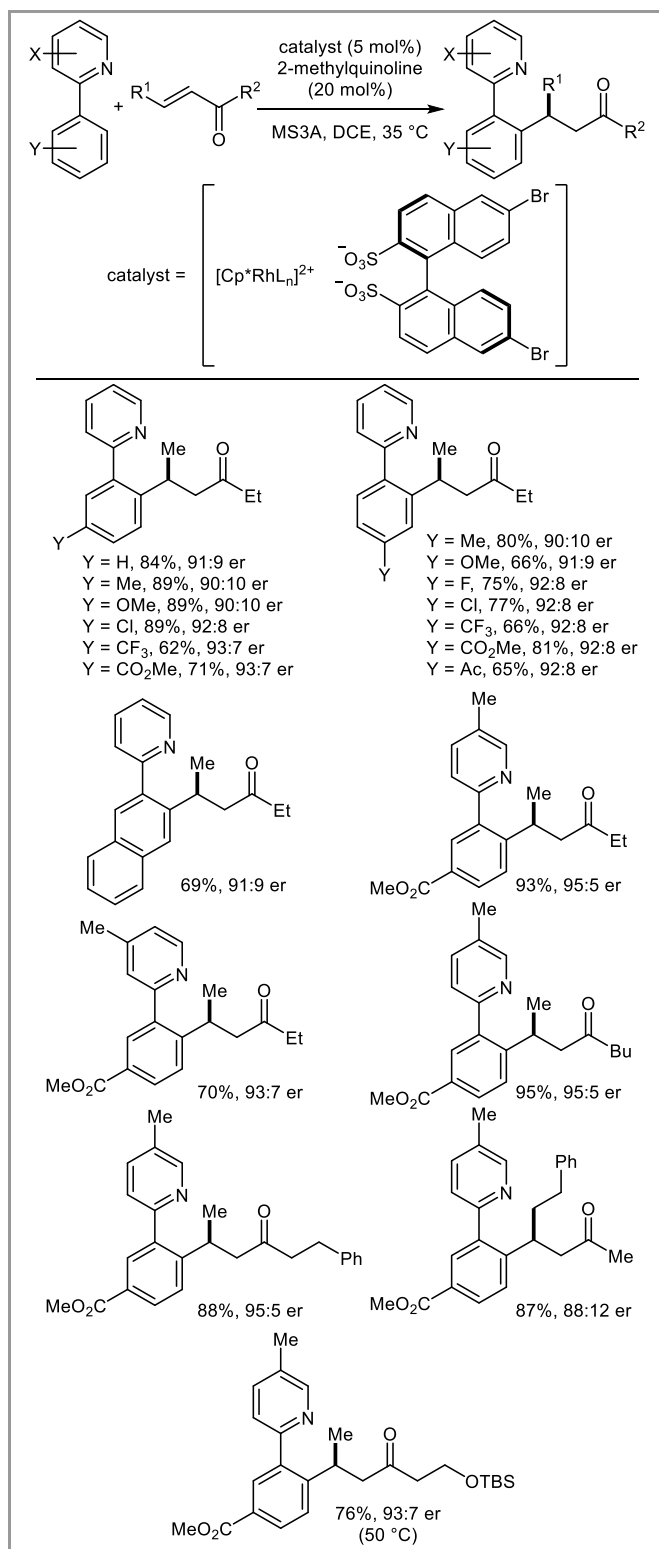
Table 5 Optimization studies on the enantioselective C-H addition reaction of 2-phenylpyridine to an enone using Cp*Rh/BINSate catalyst.^a

Entry	BINSate	Additives	Solvent	Yield (%) ^b	er
1	X = H, R = H	—	toluene	21	66:34
2	X = H, R = H	—	Et ₂ O	3	88:12
3	X = H, R = H	—	THF	79	80:20
4	X = H, R = H	—	DCM	>95	81:19
5	X = H, R = H	—	DCE	>95	81:19
6	X = H, R = H	—	acetone	>95	81:19
7	X = H, R = H	—	MeOH	12	63:37
8	X = H, R = H	2-methylquinoline (20 mol%)	DCE	86	86:14
9	X = H, R = H	2-methylquinoline (20 mol%) MS 3A	DCE	59	90:10
10	X = Br, R = H	2-methylquinoline (20 mol%) MS 3A	DCE	60	92:8
11	X = H, R = Ph	2-methylquinoline (20 mol%) MS 3A	DCE	5	46:54
12 ^c	X = Br, R = H	2-methylquinoline (20 mol%) MS 3A	DCE	84 ^d	91:9

^a Reactions were performed using 2-phenylpyridine (1.2 equiv) and enone (1.0 equiv). ^b Determined by ¹H NMR analysis of the crude mixture using dibenzyl ether as an internal standard. ^c The reaction was performed using 2-phenylpyridine (1.0 equiv) and enone (1.1 equiv) for 48 h. ^d Isolated yield.

The substrate scope of this Cp*Rh^{III}/BINSate-catalyzed enantioselective addition reaction is summarized in Scheme 17.⁶³ A variety of functionalized 2-phenylpyridines and enones afforded good enantioselectivity, demonstrating the high functional group compatibility of this catalytic system. Electron-deficient 2-phenylpyridines generally exhibited higher

selectivity than electron-rich ones, while a larger substituent at the β -position of the enone resulted in slightly decreased enantioselectivity.



Scheme 17 Substrate scope of Cp*Rh^{III}/BINSate-catalyzed enantioselective addition of 2-phenylpyridines to enones.

As shown in Figure 7, we initially considered that BINSate could work as a counteranion that enables enantioselective insertions. However, the somewhat counterintuitive solvent effects on the enantioselectivity (Table 5, entries 1–7) prompted us to consider

an alternative mechanism for the observed enantioselectivity. We speculated that BINSate could serve as a chiral proton source *in situ* and participate in the protonation (Figure 8).^{54c,64} In this scenario, the insertion of an enone is reversible, and two enantiomeric intermediates (**I** and **I'**) are generated in equilibrium, followed by selective protonation of **I** by the chiral proton source to provide the product in an enantioselective manner. A proton would be released during the C–H activation step and trapped by 2-phenylpyridine or 2-methylquinoline to give a cationic proton source. The combination of BINSate and this cation may form a mono-anionic species **II**, which could serve as a chiral proton source for enantioselective protonations. At this stage, we have not yet unequivocally determined the role of BINSate, which could serve either as a chiral counteranion or as a chiral proton source, and further studies are necessary to clarify the mechanism and stereochemical pathway affording the major enantiomer.

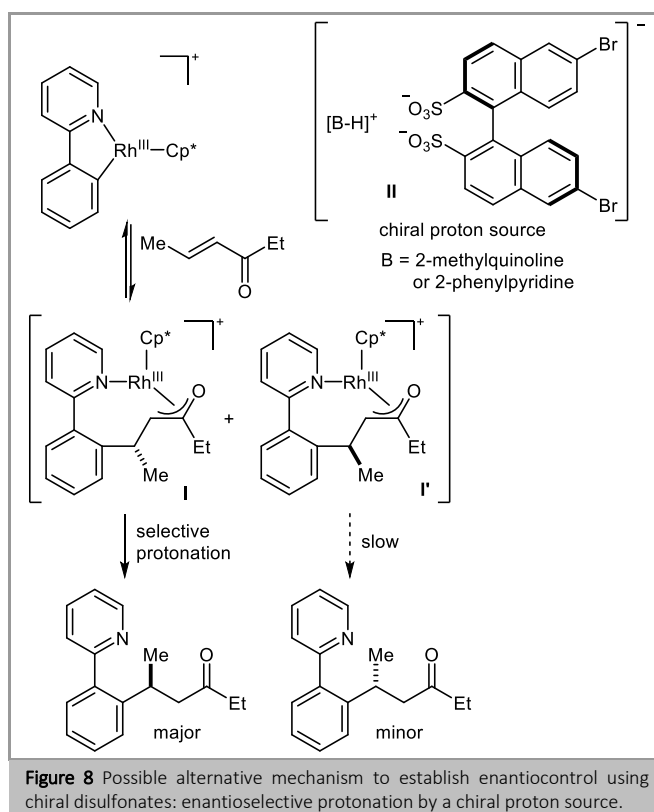
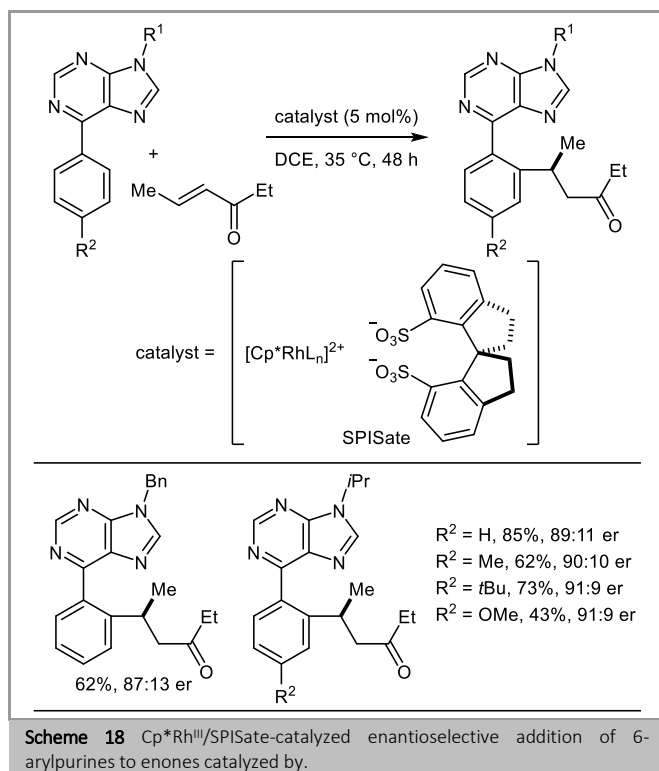


Figure 8 Possible alternative mechanism to establish enantiocontrol using chiral disulfonates: enantioselective protonation by a chiral proton source.

We also examined directing groups other than 2-pyridyl groups and found that 6-arylpurines are suitable substrates (Scheme 18).⁶³ For these substrates, a new chiral disulfonate anion bearing a spiro backbone (SPISate), which has recently been developed in our research group,⁶⁵ was more effective in terms of enantioselectivity.

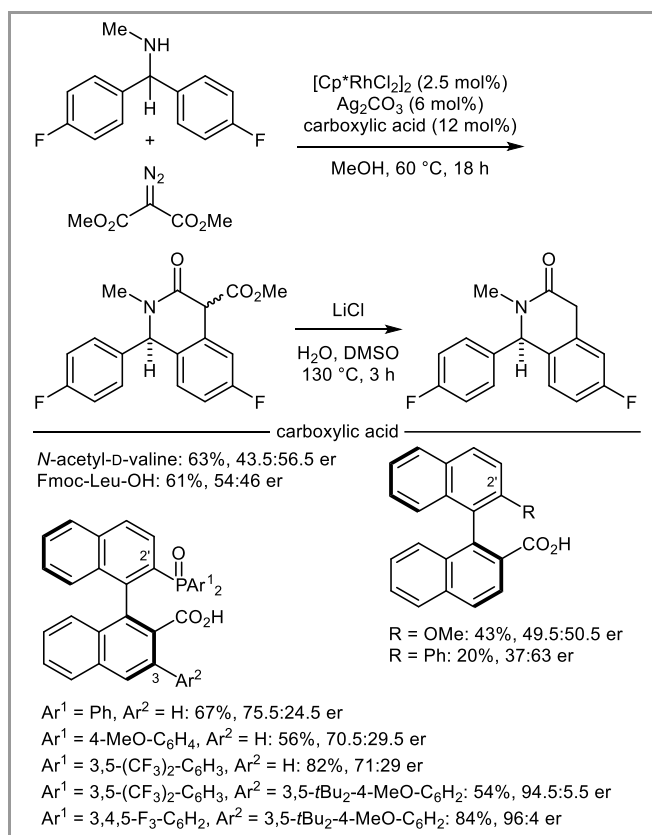


3.2. Enantioselective C–H Cleavage Using Chiral Carboxylic Acids

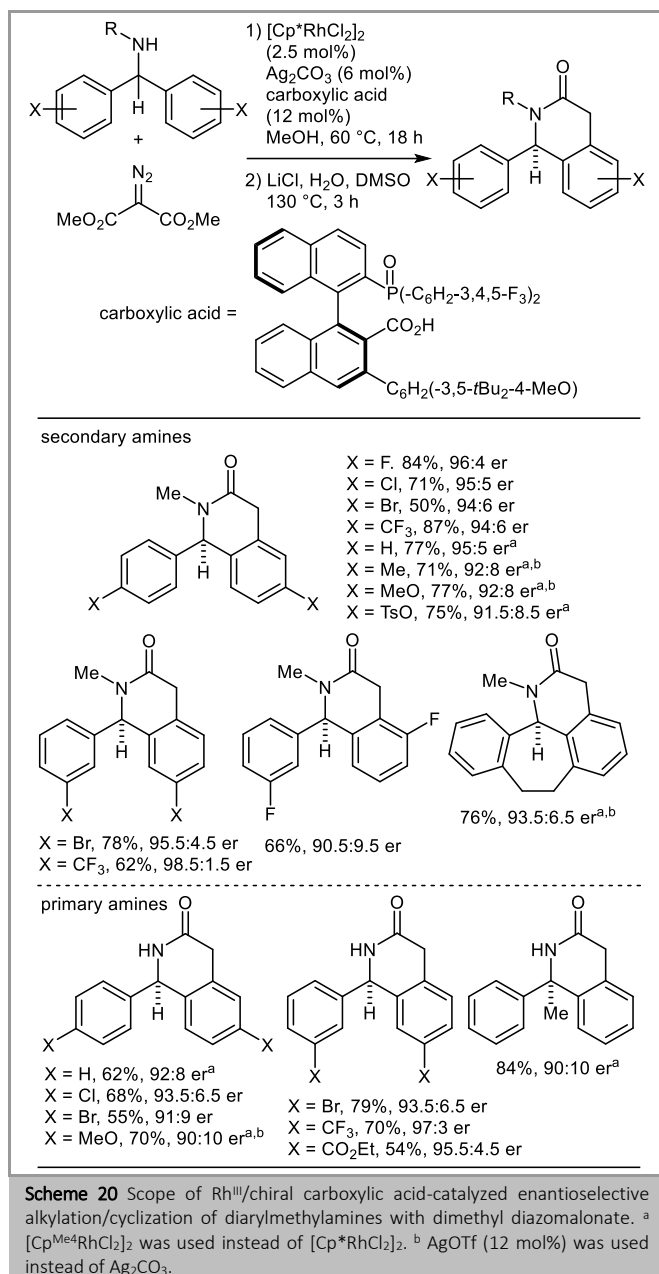
As shown in Figure 1 (II to IV), the C–H activation can be another enantio-determining step when the substrate contains enantiotopic C–H bonds. The addition of an appropriate carboxylate or related base often accelerates the C–H functionalization when using high-valent transition metals, including Co^{III}, Rh^{III}, and Ir^{III}. In such C–H functionalization reactions, the C–H activation proceeds via a carboxylate-assisted concerted metalation-deprotonation (CMD) mechanism (Figure 1, III and III'),¹⁵ in which a carboxylate works as a base to deprotonate the target C–H bond. Based on this mechanism, a chiral carboxylate should in principle enable an enantioselective C–H activation. In Pd(II) catalyst systems, Yu and co-workers have pioneered mono-protected amino acids (MPAAs) and related chiral additives for enantioselective C–H functionalization reactions.^{66,67} In contrast, chiral carboxylate-assisted CMD has been examined less for Cp^{*}M^{III} catalysts. Chang and co-workers reported that a tartaric acid derivative induced enantioselectivity in the C–H amidation reactions of prochiral phosphine oxides using a Cp^{*}Ir^{III} catalyst, but the observed enantioselectivity was below 66:34 er.^{54b} Cramer and co-workers reported chiral Cp^{*}M^{III}/chiral carboxylate cooperation systems (M = Rh, Ir) for enantioselective C–H functionalization reactions, where the presence of a chiral Cp ligand is still essential to obtain high selectivity.⁶⁸ We believe that the critical difference in Pd(II)- and Cp^{*}M^{III}-catalyzed reactions is the number of vacant coordination sites for a base; MPAAs and related bases coordinate to Pd(II) in a bidentate fashion, while only one coordination site is available for a base in case of Cp^{*}M^{III}-catalyzed reactions. Therefore, we anticipated that the discovery of a chiral carboxylic acid that is able to provide suitable chiral recognition with monodentate coordination would be crucial for

the enantioselective C–H activation using Cp^{*}M^{III}/chiral carboxylic acid hybrid catalyst systems.

We selected the C–H alkylation/cyclization reaction of a diarylmethylamine and dimethyl diazomalonate using a Cp^{*}Rh^{III} catalyst as a model reaction⁶⁹ and screened a variety of chiral carboxylic acids (Scheme 19).⁷⁰ After confirming that amino acid derivatives were not suitable, we synthesized and examined binaphthyl-based mono-carboxylic acids. Although 2'-OMe and 2'-phenyl substituted derivatives were not effective, the introduction of a phosphine oxide group at the 2'-position significantly improved the enantioselectivity. Furthermore, high enantioselectivity was achieved using a sterically hindered carboxylic acid with a 3,5-di-*tert*-butyl-4-methoxyphenyl group at the 3-position.



Subsequently, we examined the substrate scope using the optimized chiral carboxylic acid (Scheme 20).⁷⁰ Among the variety of diarylmethylamines examined, electron-deficient substrates generally afforded high enantioselectivity (up to 98.5:1.5 er). Changing the Cp^{*} ligand of the catalyst to a slightly less sterically hindered Cp^{Me4} (1,2,3,4-tetramethylcyclopentadienyl) ligand and Ag₂CO₃ to AgOTf was beneficial for electron-rich substrates in terms of the enantioselectivity. Not only *N*-methyl-substituted secondary amines but also non-protected primary amines were suitable substrates under the same reaction conditions, providing acceptable yields and enantioselectivities.



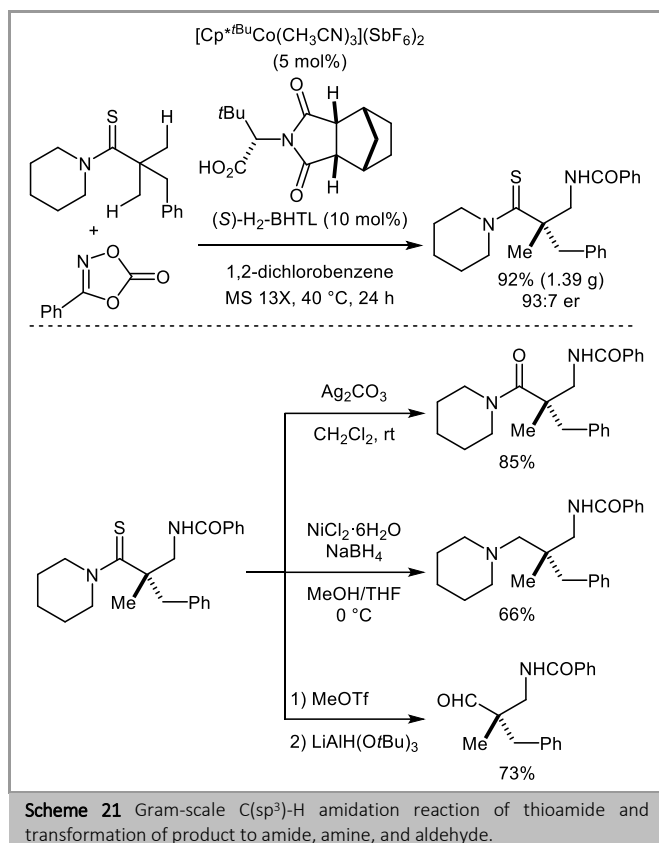
This chiral carboxylic acid-assisted enantioselective CMD approach was also viable for Co^{III}-catalyzed C(sp³)-H amidation reactions of thioamides using dioxazolones (Table 6).^{71,72} Relatively simple chiral amino acid derivatives were effective in this case, and H₂-BHTL (BHTL = (*S*)-*N*-(endo-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximido)-*tert*-leucine)⁷³ afforded the best result. The use of a sterically hindered Cp^{*t}BuCo^{III} catalyst (Cp^{*t}Bu = 1-*tert*-butyl-2,3,4,5-tetramethylcyclopentadienyl) improved the enantioselectivity compared to the standard Cp^{*}Co^{III} catalyst. Under the optimized conditions, a wide range of thioamides as well as dioxazolones afforded enantiomeric ratios better than 90:10. Sterically hindered thioamides tended to afford high selectivities (entries 7, 8, 13), whereas steric and electronic effects of dioxazolones had a negligible impact on the enantioselectivity (entries 12, 14-19). We experimentally confirmed by H/D scrambling experiments that the C-H activation step is irreversible even in the absence of a dioxazolone. The results indicated that the enantioselectivity is

completely determined at the C-H activation step, thus confirming its independence from the structure of dioxazolones.

Table 6 Co^{III}/chiral carboxylic acid-catalyzed enantioselective C(sp³)-H amidation of thioamides using dioxazolones.

Entry	Thioamide (R ¹)	Dioxazolone (R ²)	Yield (%)	er
1	Ph	Ph	82	92:8
2	<i>p</i> Cl-C ₆ H ₄	Ph	81	91:9
3	<i>p</i> Br-C ₆ H ₄	Ph	91	91:9
4	<i>p</i> CF ₃ -C ₆ H ₄	Ph	89	92:8
5	<i>p</i> MeO-C ₆ H ₄	Ph	88	92:8
6	3,5-(CF ₃) ₂ -C ₆ H ₃	Ph	81	91:9
7	2,6-Me ₂ -C ₆ H ₃	Ph	73	93:7
8	1-naphthyl	Ph	87	94:6
9	2-naphthyl	Ph	93	92:8
10	<i>i</i> Pr	Ph	50	90:10
11	cyclohexyl	Ph	76	91:9
12	Ph	<i>p</i> Cl-C ₆ H ₄	86	93:7
13	1-naphthyl	<i>p</i> Br-C ₆ H ₄	63	94:6
14	Ph	<i>p</i> MeO-C ₆ H ₄	90	92:8
15	Ph	<i>o</i> Me-C ₆ H ₄	65	91:9
16	Ph	2-furyl	96	92:8
17	Ph	2-thienyl	99	92:8
18	Ph	Me	55	92:8
19	Ph	<i>t</i> Bu	73	92:8

Since both the chiral source and the cobalt complex are easily available, we performed this asymmetric reaction on the gram-scale and successfully obtained the amidated product in good yield and enantioselectivity. The product was readily converted into the corresponding amide, amine, and aldehyde following reported procedures,^{72a,74} demonstrating the synthetic utility of the β-amino thioamide product (Scheme 21).



Scheme 21 Gram-scale C(sp³)-H amidation reaction of thioamide and transformation of product to amide, amine, and aldehyde.

4. Summary and Perspective

In summary, we have demonstrated that $\text{Cp}^*\text{Co}^{\text{III}}$ catalysts are not only a good alternative to $\text{Cp}^*\text{Rh}^{\text{III}}$ catalysts, but also exhibit unique reactivity and selectivity based on the different fundamental properties of cobalt and rhodium. Recently, our attention has been focused on the development of catalytic asymmetric reactions using CpM^{III} -type catalysts ($\text{M} = \text{Co}, \text{Rh}$) by hybridization with external chiral sources. Such external chiral sources can potentially serve as enantio-controlling elements for both C-H activation and the subsequent steps. In addition to further investigations on asymmetric reactions using achiral ligands and external chiral sources, the combination of chiral Cp ligands and external chiral sources represents a very attractive strategy, as demonstrated by pioneering work by Cramer and co-workers.⁶⁸ We expect that such hybridizations and the development of a variety of external chiral sources will expand the accessible structure space of catalysts without the need for intensive structural tuning of chiral Cp ligands, which is often non-trivial and laborious. When considering the synthesis of complex and valuable molecules, the development of enantioselective C(sp³)-H functionalization reactions is undoubtedly an urgent topic. We hope that our hybridization approach, as well as the advances in chiral Cp chemistry, will lead to the discovery of further synthetically attractive enantioselective transformation reactions of unreactive C-H bonds.

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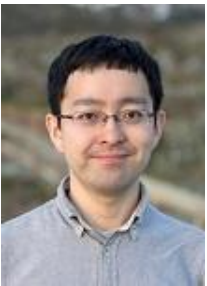
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Biosketches

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