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Cobalt(III)-Catalyzed Enantioselective C−H Functionalization: Ligand Innovation and Reaction Development

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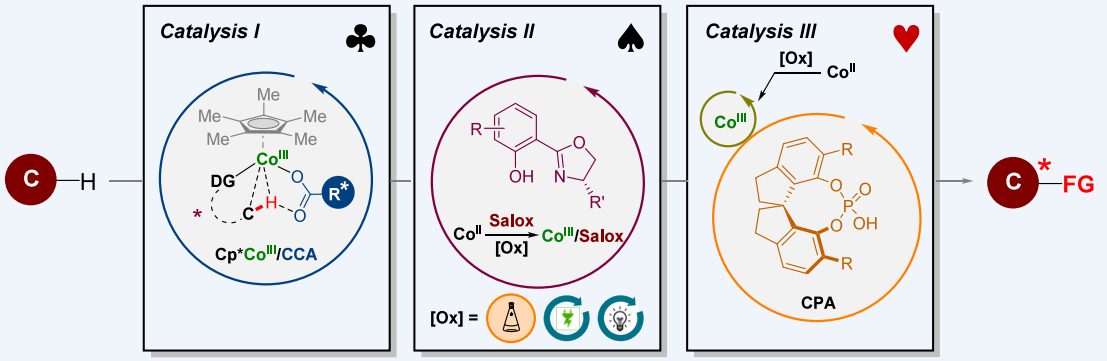

CONSPECTUS: In contrast to precious transition metals, such as palladium and rhodium, the development of novel chiral ligands for enantioselective C−H functionalizations catalyzed by earth-abundant, cost-effective, and environmentally friendly 3d metals poses substantial challenges, primarily due to the variable oxidation states, intricate coordination patterns, and limited mechanistic insights. In this Account, we summarize our research endeavors in the development of three novel types of Co(III) catalysis: pseudotetrahedral achiral Cp*Co(III)/chiral carbonyl acid (CCA) catalysis, *in situ*-generated chiral octahedral cobalt(III) via cobalt/salicyloxazoline (Salox) catalysis, and Co(II)/chiral phosphoric acid (CPA) cooperative catalysis, achieved through strategic chiral ligand design. Our initial objective was to achieve enantioselective C−H functionalization catalyzed by achiral Cp*Co(III) catalysts with external chiral ligands, aiming to circumvent the laborious preparation of chiral Cp*Co(III) complexes. To this end, we developed several CCA ligands, incorporating non-covalent interactions (NCIs) as a crucial design element. Next, to address the limitations associated with the lengthy synthesis of Cp-ligated Co(III) complexes and the difficulties of modification, we explored the concept of the *in situ* generation of Co(III) catalysis using commercially available cobalt(II) salts with tailor-made chiral ligands. This exploration led to the development of two innovative catalytic systems, namely, Co(II)/Salox catalysis and Co(II)/CCA sequential catalysis. The Co(II)/Salox catalysis emerged as a versatile strategy, demonstrating excellent enantioselectivities across a range of asymmetric C−H functionalization reactions to construct various chiral molecules with central, axial, planar, and inherent chirality. The facile synthesis in a single step, along with ease of modification, further enhances the versatility and applicability of this approach. Moreover, we successfully applied cobalt/Salox catalysis in electro- and photochemical-catalyzed enantioselective C−H functionalization, using electrons or oxygen as traceless oxidant, thereby eliminating the need for stoichiometric chemical oxidants. Through mechanistic studies and reaction developments, we elucidated the detailed ligand structure−enantioselectivity relationships in cobalt/Salox catalysis, which are expected to inform future research endeavors. Finally, the Co(II)/CPA cooperative catalysis enabled the synthesis of chiral spiro-γ-lactams through sequential C−H olefination/asymmetric [4 + 1] spirocyclization. Mechanistically, the establishment of stereochemistry occurs during the cyclization step, where the CPA ligand serves as both a neutral ligand and a chiral Brønsted acid, with stereoinduction independent of the C−H cleavage step. We anticipate that the insights and advancements detailed in this Account will inspire further innovations in ligand development and drive progress in the exploration of 3d metal-catalyzed asymmetric C−H functionalization reactions.

KEY REFERENCES

- Liu, Y.-H.; Li, P.-X.; Yao, Q.-J.; Zhang, Z.-Z.; Huang, D.-Y.; Le, M. D.; Song, H.; Liu, L.; Shi, B.-F. Cp*Co(III)/MPAA-Catalyzed Enantioselective Amidation of Ferrocenes Directed by Thioamides under Mild Conditions. *Org. Lett.* **2019**, *21*, 1895−1899.[1] *The design of chiral*

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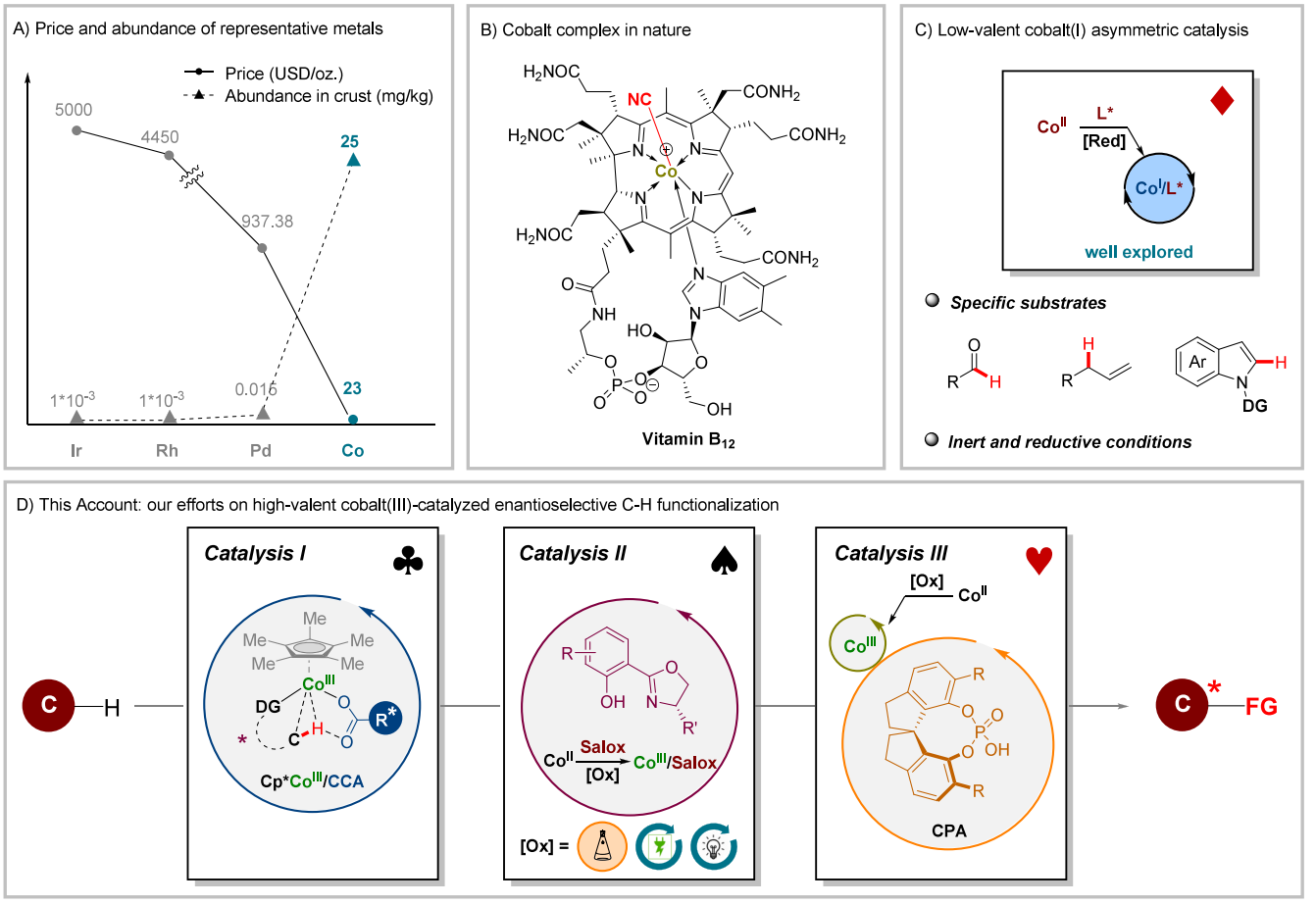
Scheme 1. Cobalt-Catalyzed Enantioselective C−H Functionalization



carboxylic acid ligands enabled the desymmetrization of ferrocenes via enantioselective C−H amidation, which is our initial investigation on cobalt(III)-catalyzed enantioselective C−H activation.

- Yao, Q.-J.; Chen, J.-H.; Song, H.; Huang, F.-R.; Shi, B.-F. Cobalt/Salox-Catalyzed Enantioselective C−H Functionalization of Arylphosphinamides. *Angew. Chem., Int. Ed.* **2022**, *61*, e202202892.[2] *The first design of salicyloxazoline (Salox) ligands for enantioselective C−H activation by enabling the in situ generation of an octahedral chiral cobalt(III) catalyst from Co(II) salts, with detailed mechanistic insights paving the way for the development of diverse reactions.*
- Yao, Q.-J.; Huang, F.-R.; Chen, J.-H.; Zhong, M.-Y.; Shi, B.-F. Enantio- and Regioselective Electrooxidative Cobalt-Catalyzed C−H/N−H Annulation with Alkenes. *Angew. Chem., Int. Ed.* **2023**, *62*, e202218533.[3] *The first example of a cobaltaelectrocatalyzed enantioselective C−H activation reaction.*
- Yuan, W.-K.; Shi, B.-F. Synthesis of Chiral Spirolactams via Sequential C−H Olefination/Asymmetric [4 + 1] Spirocyclization under a Simple Co^{II}/Chiral Spiro Phosphoric Acid Binary System. *Angew. Chem., Int. Ed.* **2021**, *60*, 23187−23192.[4] *The first example of the development of cobalt/chiral phosphoric acid (CPA) sequential catalysis for cobalt-catalyzed enantioselective C−H functionalization.*

1. INTRODUCTION

Asymmetric synthesis is a pivotal technology for the efficient assembly of chiral molecules, playing a crucial role across various applied fields, including pharmaceuticals, agriculture, and materials science. Consequently, the development of efficient asymmetric catalytic transformations remains a high priority in the scientific community. Over the past few decades, transition-metal-catalyzed enantioselective C−H functionalization has emerged as a promising strategy, as it eliminates the need for multistep synthesis to prefunctionalize starting substrates, thereby enhancing both step and atom economy.[5−10] A critical factor driving advancements in this field is the deepening of the understanding of reaction mechanisms and the innovation of chiral ligands and catalysts. The mechanistic insights and ligand innovations have led to significant progress in enantioselective C−H functionalization catalyzed by precious metal catalysts, predominantly palladium and rhodium.[6−8] However, the development of chiral ligands for earth-abundant 3d metals poses a significant challenge, primarily due to the variable oxidation states, intricate coordination patterns, and limited mechanistic insights.[10]

Cobalt, as the first and lightest element among the group 9 transition metals, offers significant advantages in catalysis. It not only has considerable reserves—over 100 times larger than the total content of platinum group metals in the geosphere (Scheme 1A)—but also serves as an essential micronutrient for mammals, exemplified by vitamin B_{12} (Scheme 1B).[11] In addition, cobalt and its complexes exhibit unique properties,

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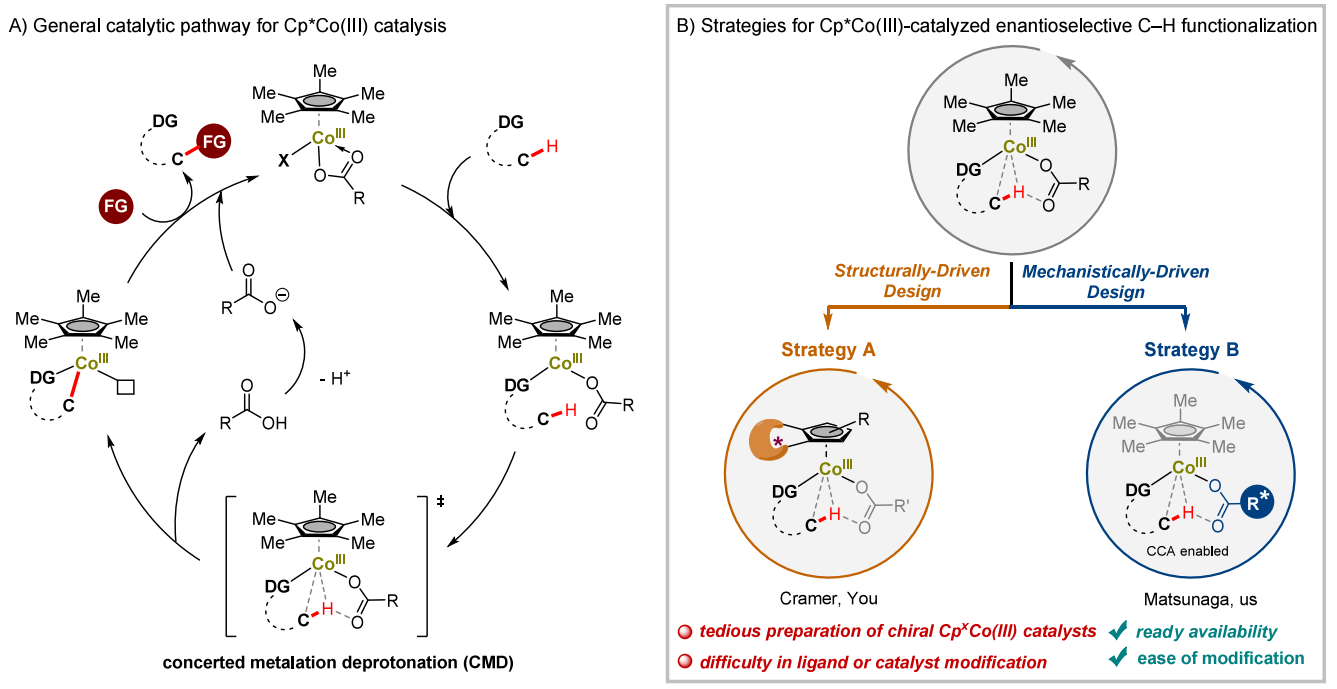
Scheme 2. Strategies for Cp*Co(III)-Catalyzed Enantioselective C−H Functionalization



such as reduced electronegativity, multiple spin states, and flexible coordination geometries, which can complement noble metal catalysts.[12]

In this context, the realization of cobalt-catalyzed enantioselective C−H activation is particularly attractive.[13,14] The catalytic modes can be mechanistically classified into two categories based on the oxidation state of the cobalt catalysts: (1) low-valent cobalt(I) asymmetric catalysis and (2) high-valent cobalt(III) asymmetric catalysis. In the first mode, low-valent cobalt(I) catalysts are generated *in situ* through the reduction of cobalt(II) species,[13,15] thereby initiating the catalytic cycle (Scheme 1C). The first mode has been well-established[16−19] since the seminal report by the Yoshikai group on the intramolecular hydroacylation of formyl C−H bonds using a cobalt/chiral diphosphine catalysis.[16] Despite the significant advancements, these methods are limited to specific substrates, such as formyl C−H bonds,[16,17] allylic C−H bonds,[18] and C2 of indoles,[19] and require inert and reductive conditions to generate cobalt(I) catalysis, complicating operational procedures.

In contrast, C−H activation employing air-stable and operationally convenient cobalt(III) has rapidly developed, featuring two main catalytic systems: (1) Cp*Co(III) catalysis (Cp* = pentamethylcyclopentadienyl), first developed by Kanai, Matsunaga, and colleagues,[20,21] and (2) active Co(III) species generated *in situ* from Co(II) salts, assisted by strongly bidentate directing groups (DGs), pioneered by Daugulis and co-workers.[22,23] Despite being developed relatively later, these catalytic systems have demonstrated versatile and sometimes unique or complementary reactivities, leading to a broad array of C−H functionalization reactions. However, the development of asymmetric versions had not achieved the same prominence as that of cobalt(I) catalysis.

With this context in mind, we posed a critical question: Is it feasible to harness the enantioselective potential of cobalt(III) and thereby unlock previously unexplored but valuable asymmetric C−H transformations? To address this under-utilization, we aimed to develop cobalt(III)-catalyzed enantioselective C−H functionalization reactions, emphasizing the innovation of chiral ligands and methodological development. This Account will detail our endeavors since 2019, which encompass achiral Cp*Co(III)/chiral carboxylic acid (CCA) catalysis (***Catalysis I***),[1,24,25] *in situ*-generated chiral octahedral cobalt(III) via cobalt/salicyloxazoline (Salox) catalysis (***Catalysis II***),[2,3,26−36] and Co(II)/chiral phosphoric acid (CPA) sequential catalysis (***Catalysis III***) (Scheme 1D).[4] We also elucidate plausible mechanisms involved in these transformations to provide valuable insights for future research directions.

2. ACHIRAL Cp*Co(III)/CCA CATALYSIS

2.1. Background and Design Philosophy

Building upon the success of Cp*Rh(III)-catalyzed C−H functionalization reactions,[37,38] Kanai, Matsunaga, and colleagues first developed a more economical alternative, cationic Cp*Co(III) catalysts, in 2013.[20] A generally accepted catalytic pathway for Cp*Co(III)-catalyzed C−H activation is shown in Scheme 2A, where a carboxylate ligand facilitates C−H metalation through a concerted metalation−deprotonation (CMD) mechanism. Two possible strategies might be feasible to enable the Co(III)-catalyzed enantioselective C−H activation, based on the structure and the mechanistic pathway. The first strategy is grounded in a structurally driven design philosophy that seeks to emulate the successes observed in chiral Cp^{x}Rh(III) catalysts, focusing on the development of Co(III) catalysts coordinated with chiral Cp^x ligands (Scheme 2B, **Strategy A**). Although the strategy appears very straightforward, it is anticipated to encounter similar challenges faced in chiral Cp^{x}Rh(III) catalysis,[5,8,39,40] such as the tedious preparation of chiral Cp^x-ligated cobalt catalysts and difficulties associated with catalyst modifications.[41−43] The second strategy is based on a mechanistically driven design (**Strategy B**). Mechanistically, it is logical to propose that employing a CCA

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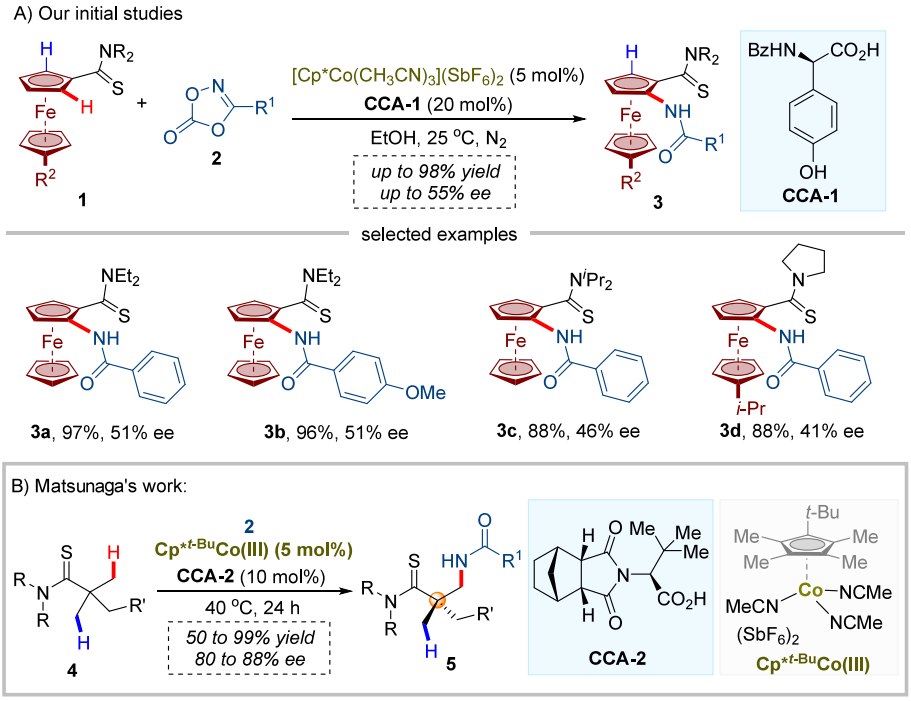
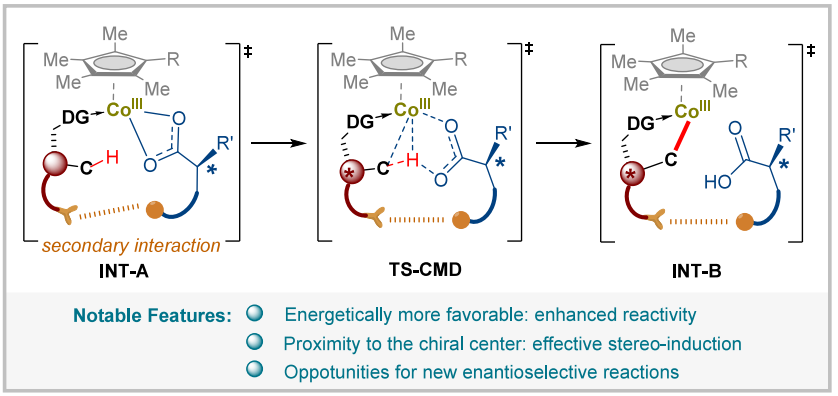
Scheme 3. Our Initial Study on Achiral Cp*Co(III)/CCA-Catalyzed Asymmetric C−H Activation



Scheme 4. Introduction of Secondary Interactions between the CCA Ligand and Substrate



could enable asymmetric C−H functionalization using achiral Cp*Co(III) as the catalyst, a strategy that has demonstrated success with other metal catalysts, such as palladium[44,45] and rhodium.[46,47] We envisioned that CCA ligands present numerous opportunities due to their ready availability and ease of modification.

2.2. Initial Development of CCA Ligands

At the outset of our research efforts in 2017, Co(III)-catalyzed enantioselective C−H activation represented an unsolved challenge. We commenced our studies on the development of proper CCA ligands for the enantioselective C−H amidation of prochiral ferrocenyl thioamides to construct planar chirality.[1] After evaluation of several CCAs, we were delighted to find that the reaction occurred smoothly to give the amidated chiral ferrocenes with moderate enantioselectivities using readily available benzoyl-protected D-*p*-hydroxyphenylglycine (**CCA-1**) as a chiral ligand (Scheme 3A). Despite the moderate enantioselectivities, this initial study proved that desymmetrization of prochiral C−H bonds could be achieved, consistent with the design philosophy (Scheme 2B, **Strategy B**). Yoshino, Matsunaga, and co-workers elegantly demonstrated that enantioselective C(sp^3)−H amidation of thioamides can be achieved (Scheme 3B).[48] In their study, a sterically more hindered achiral catalyst, Cp*$^{t\text{-Bu}}$Co(III), and a bulky CCA ligand derived from *tert*-leucine, **CCA-2**, proved to be an enabling catalytic combination.

2.3. Evolution of CCA Ligands with Non-covalent Interactions

Although these studies demonstrated the feasibility of achiral CpCo(III)/CCA catalysis, a strong desire remained to develop efficient CCA ligands with novel structural motifs. In pursuit of enhanced reactivity and enantioselectivity, we aimed to incorporate non-covalent interactions (NCIs) as a design element in the evolution of CCA ligands for several reasons (Scheme 4).[49−51] First, secondary interactions within the Cp*Co(III)/CCA−substrate intermediate (**INT-A**) could significantly lower the energy barrier associated with forming the key transition state (**TS-CMD**), thereby facilitating C−H cleavage. Second, it is reasonable to expect that these secondary interactions would draw the substrate closer to the chiral center

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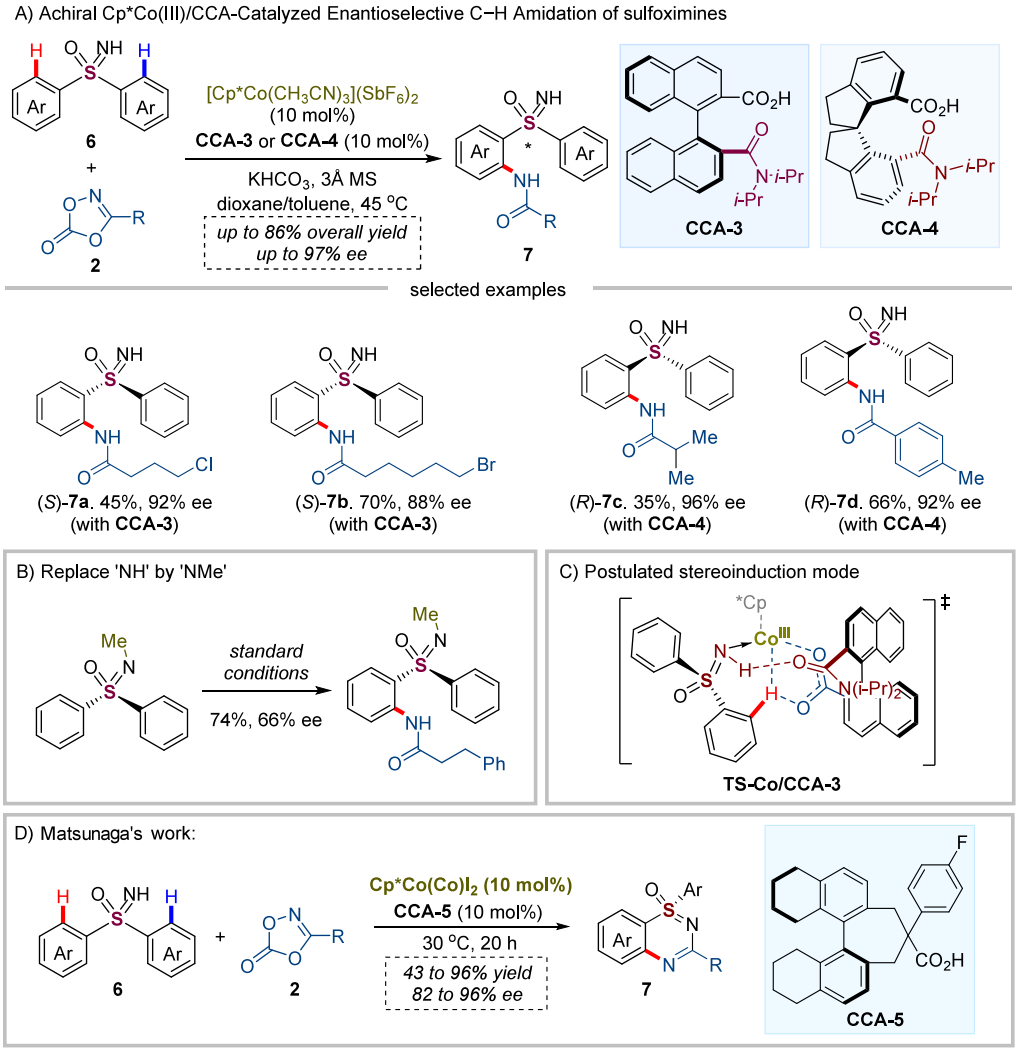
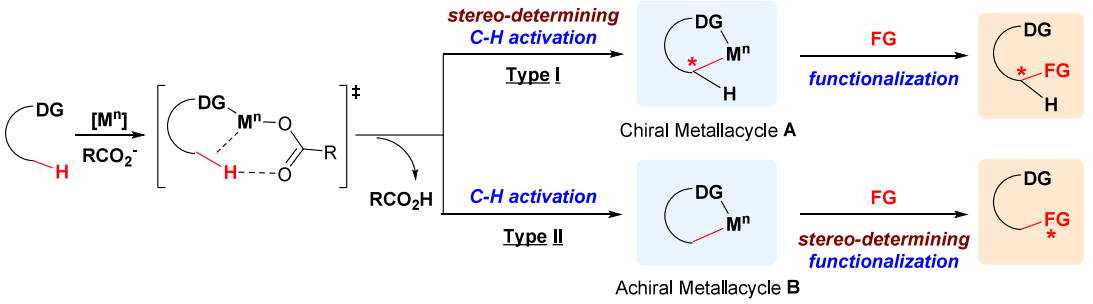
Scheme 5. Hydrogen-Bonding Interaction-Assisted Achiral Cp*Co(III)/CCA-Catalyzed Enantioselective C−H Amidation



Scheme 6. Conceptual Classification of Asymmetric C−H Functionalization Reactions



of the CCA ligand, enabling more efficient stereoinduction. Lastly, the CCA ligand could maintain non-covalent interactions in the resulting cobaltacycle after C−H metalation (**INT-B**), providing a hybrid chiral environment for subsequent functionalization and opening avenues for the development of new enantioselective reactions, where enantioselection occurs following the C−H activation step.

Building upon the rationalizations, we developed a novel type of chiral binaphthyl monocarboxylic acid featuring an axially biaryl scaffold and a tunable amide as the hydrogen-bond acceptor, which can be easily prepared from 1,1′-binaphthyl-2,2′-dicarboxylic acid. The efficacy of these CCA ligands was first demonstrated by a Ru(II)-catalyzed enantioselective C−H functionalization of sulfoximines in 2021.[52] Preliminary studies revealed that the hydrogen-bonding interaction between the NH group of the sulfoximine and the amide of CCA played a crucial role in the stereoinduction model. Inspired by these findings, we subsequently reported the hydrogen-bonding interaction-assisted achiral Cp*Co(III)-catalyzed enantioselective C−H amidation of sulfoximines with dioxazolones, using either **CCA-3** or related SPINOL-derived **CCA-4** (Scheme 5A).[24] A broad range of *S*-stereogenic sulfoximines were

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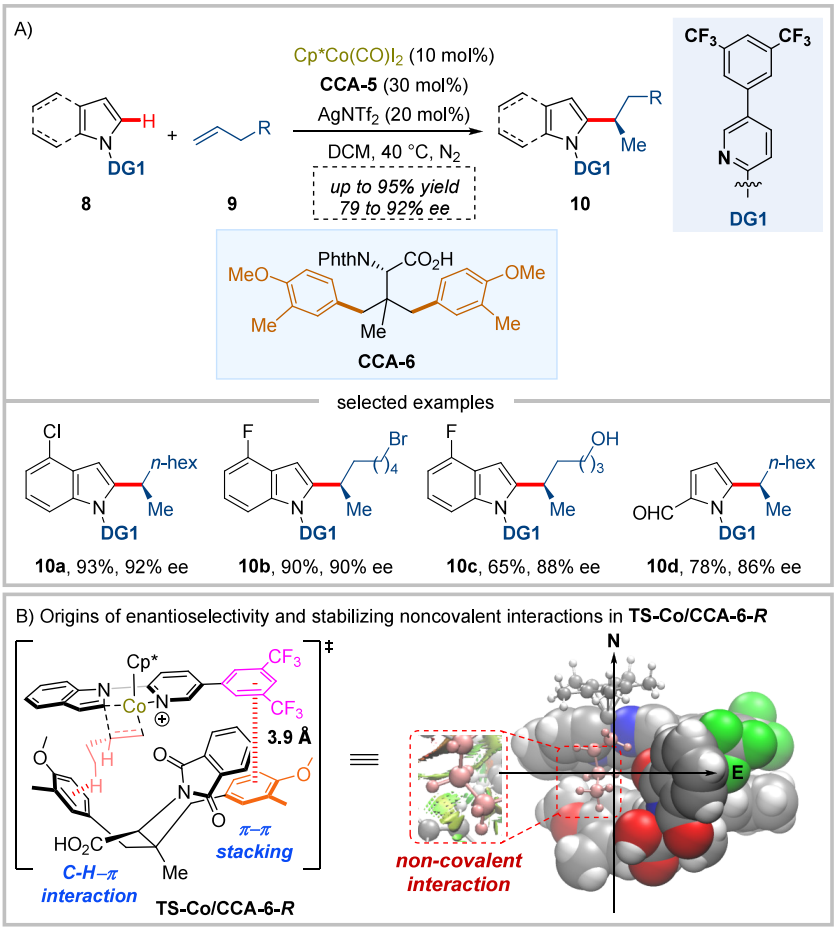
Scheme 7. Achiral Cp*Co(III)-Catalyzed Enantioselective Hydroarylation of α-Olefins via C−H Activation



obtained with good enantioselectivities (83−97% ee). A significant decrease in enantioselectivity (66% ee) was observed when the NH group of the sulfoximine was replaced with NMe, underscoring the importance of a free NH group (Scheme 5B). This stereoinduction model, which involves hydrogen bonding between the NH of the sulfoximine and the amide carbonyl group of **CCA-3** (Scheme 5C), was further supported by computational studies of analogous achiral Cp*Ir(III)/CCA catalysis.[53] Notably, Matsunaga demonstrated that the enantioselective C−H amidation/annulation of sulfoximines could also be achieved by the combination of an achiral Cp*Co(III) catalyst and a pseudo-C_2-symmetric H_8-binaphthyl CCA (Scheme 5D).[54]

From a conceptual standpoint, asymmetric C−H functionalization reactions can be classified into two general types based on the stereodetermining step (Scheme 6): (1) stereodiscrimination occurs during the C−H cleavage step, via either desymmetrization or kinetic resolution (KR), to form the chiral metallacycle **A** (**Type I**), or (2) the stereochemistry is established after the C−H activation, arising from a stereocontrolled functionalization of the resulting achiral metallacycle **B** (**Type II**). The second type typically proceeds through the asymmetric addition to unsaturated C═C or C═X (X = O, NR) bonds. We hypothesized that the introduction of NCIs in **Type II** transformations could stabilize the CCAs with the cobalt complex after C−H metalation, thereby forming a hybrid chiral environment for subsequent stereocontrolled functionalization.

Based on this hypothesis, we introduced an achiral Cp*Co(III)-catalyzed C−H activation of indoles, followed by asymmetric alkylation with α-olefins.[25] We developed a novel bulky *N*-phthaloyl-protected amino acid (**CCA-6**), which was prepared in one step from *N*-Phth-Tle-OH through a palladium(II)-catalyzed methyl C(sp^3)−H diarylation.[55] The combination of **CCA-6** and a modified pyridyl DG featuring a 3,5-bis(trifluoromethyl)phenyl at the 4-position (**DG1**) was essential for high enantioselectivity (Scheme 7A). Density functional theory (DFT) calculations revealed that $\pi-\pi$ stacking between the electron-deficient di-CF_3-substituted aryl moiety of **DG1** and the electron-rich OMe-substituted aryl scaffold of the tailored CCA ligand stabilized the cobaltacycle complex with **CCA-6**, creating a specific chiral pocket in the olefin insertion transition state. The "top wall" refers to the Cp* ligand of the Co(III) catalyst, which creates considerable steric bulk in the northern hemisphere. The substantial bulk of the phthalimide framework restricts access in the southeast quadrant, making the southwest quadrant the most accessible. In the optimized structure of **TS-Co/CCA-6**-*R*, the ethyl group of butene is positioned proximal to the electron-rich aryl group of **CCA-6**, exhibiting a C−H···π distance of 3.0 Å (Scheme 7B). DFT calculations and experimental studies suggested that alkene insertion was both the enantio- and rate-determining step. This is different from previous studies on related C−H alkylation, in which the protodemetalation step was proposed as the enantiodetermining step.[56−58]

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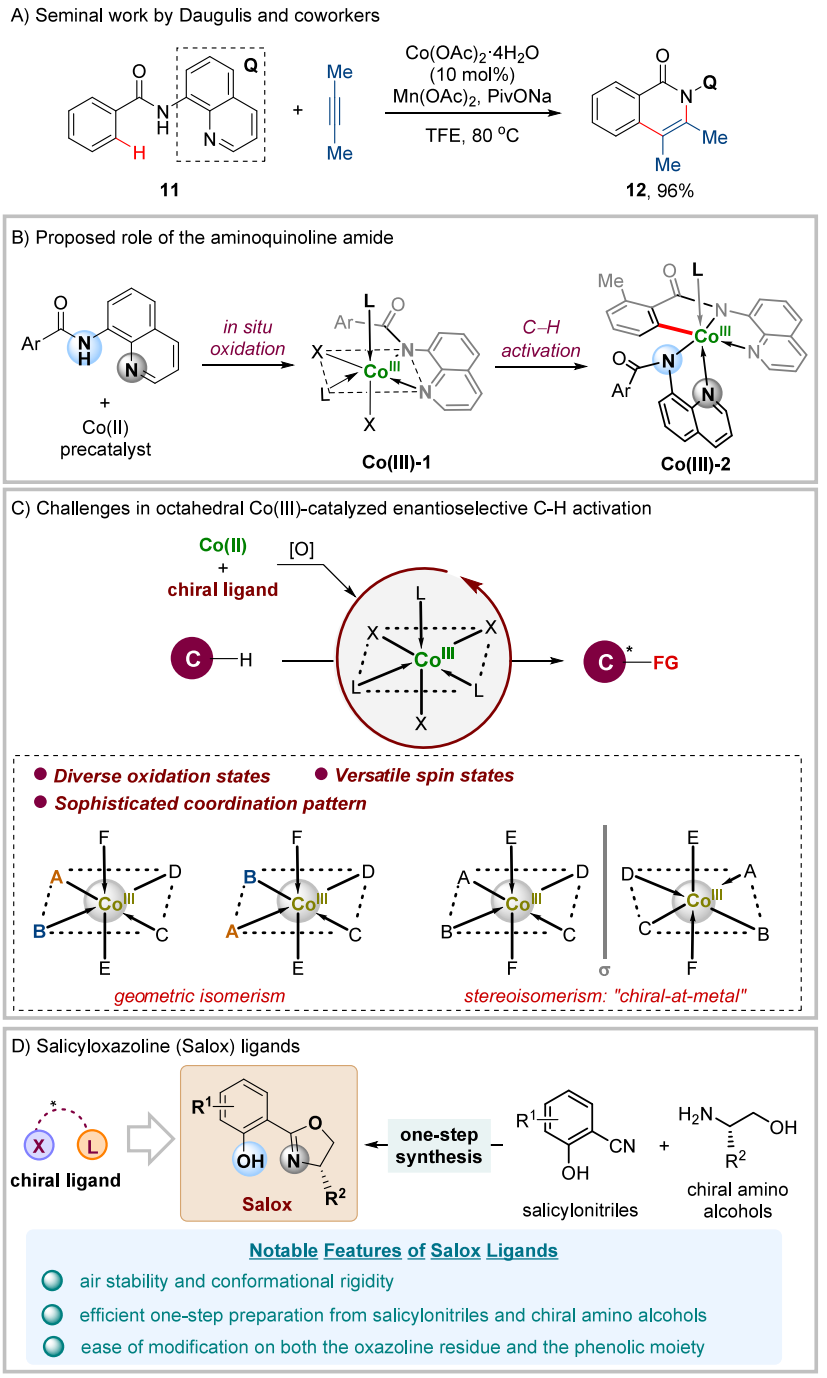
Scheme 8. Octahedral Cobalt(III)-Catalyzed C−H Activation



2.4. Perspectives

Through the examples discussed above, we successfully implemented the proposal of achiral Cp*Co(III)/CCA catalysis for asymmetric C−H activation (Scheme 2B, **Strategy B**). Despite these accomplishments, the strategies were contingent upon the precise combination of specific substrates and meticulously designed chiral ligands. Additionally, they were hindered by the use of costly half-sandwich CpCo(III) catalysts. These challenges prompted us to develop more general enantioselective C−H activation protocols utilizing commercially available and inexpensive cobalt sources.

3. COBALT/SALOX CATALYSIS

3.1. Background and Design Philosophy of Salox Ligands

In 2014, Daugulis and co-workers reported a distinctive C−H activation strategy using a Co(II) salt as a precatalyst for the oxidative C−H annulation of 8-aminoquinoline-derived benzamides with alkynes. In this approach, the active Co(III) catalyst was generated *in situ* through the oxidation of the cobalt(II) salt by oxygen and $Mn(OAc)_2$ (Scheme 8A).[22] Mechanistic studies indicated that the aminoquinoline amide acted as a monoanionic bidentate ligand (MBL) to facilitate the oxidation of the Co(II) salt to the active Co(III) catalyst **Co(III)-1**, which enabled subsequent C−H cleavage to afford pincer-type cobaltacycle **Co(III)-2** (Scheme 8B). The Co(III) species

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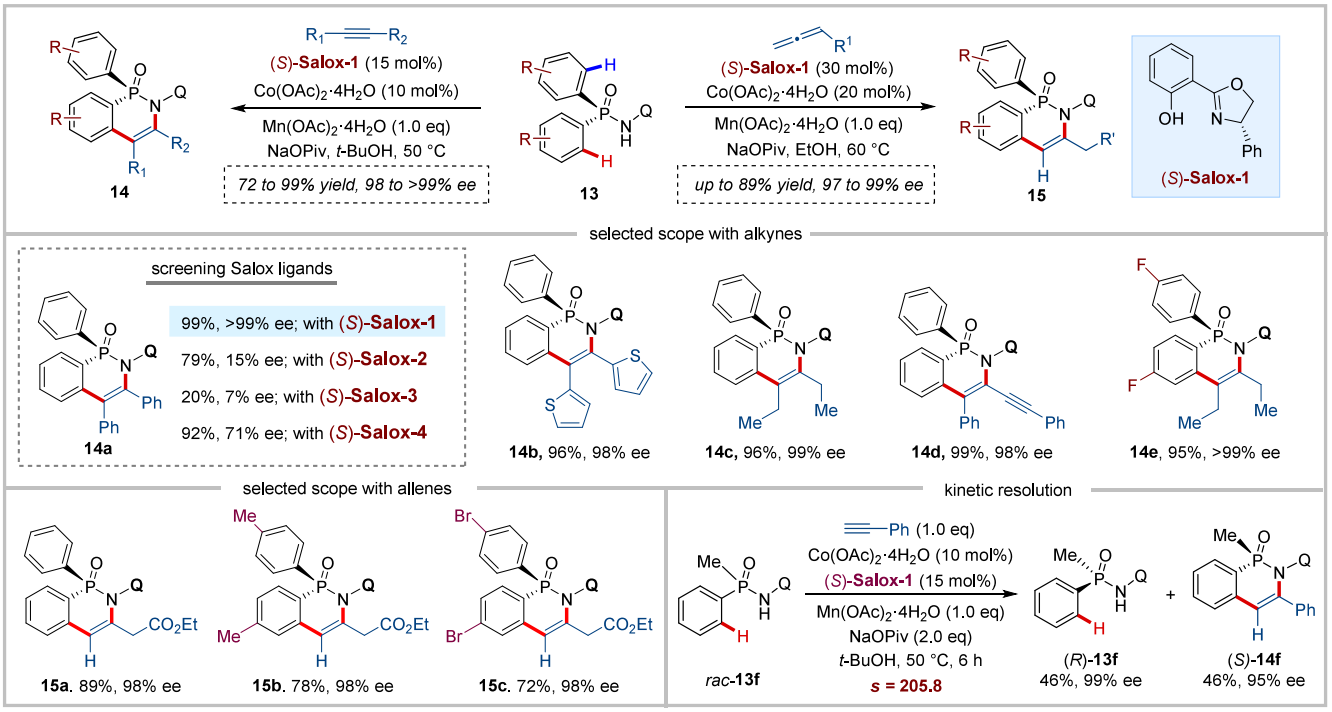
Scheme 9. Cobalt/Salox-Catalyzed Enantioselective C−H/N−H Annulation of Phosphinamides



during the reaction adopted an octahedral coordination geometry.[59] To distinguish this from half-sandwich (or pseudo-octahedral) Cp*Co(III)-catalyzed C−H activation, we define these non-CpCo(III) catalytic systems as "Octahedral Co(III)-Catalyzed C−H Activation".

This innovative protocol has enabled a range of octahedral Co(III)-catalyzed C−H functionalization reactions using Co(II) salts as precatalysts.[23,60] However, the development of octahedral Co(III)-catalyzed enantioselective C−H activation has remained elusive. The challenges are attributed to the complex reaction pathways involving various oxidation states and versatile spin states of the cobalt catalyst, as well as the intricate coordination geometries of octahedral Co(III) species, which may exhibit geometric isomerism and stereoisomerism around the cobalt center (Scheme 8C).[61,62]

We rationalized that a thoughtfully designed chiral MBL could mimic the coordination pattern of 8-aminoquinoline-derived amides, facilitating the oxidation of the Co(II) precatalyst to generate a chiral octahedral Co(III) catalyst, which may enable enantioselective C−H functionalization. Based on this rationale, we developed a new class of chiral MBLs, salicyloxazoline (Salox) ligands,[63] to achieve the first octahedral Co(III)-catalyzed enantioselective C−H activation (Scheme 8D).[2] The Salox ligands exhibit several notable features: (1) air stability and good conformational rigidity, (2) efficient one-step preparation from salicylonitriles and chiral amino alcohols, and (3) ease of modification on both the oxazoline and phenolic moieties. Due to these essential characteristics, a library of Salox ligands were synthesized, and a series of enantioselective C−H functionalization reactions were successfully achieved, resulting in the synthesis of chiral molecules featuring central, axial, planar, and inherent chirality.[2,26−36]

3.2. Enantiodetermining C−H Cleavage Reactions

Construction of Central Chirality. Our proof-of-concept study, achieved in 2022, focused on the cobalt/Salox-catalyzed enantioselective C−H/N−H annulation reaction of phosphinamides (Scheme 9).[2] Among the Salox ligands, the one derived from phenylglycinol (**Salox-1**) emerged as the optimal choice, giving a range of chiral *P*-stereogenic phosphorus products with excellent enantioselectivities (98 to >99% ee) using alkynes and allenes as coupling partners. Furthermore, the KR of unsymmetrical phosphinamide *rac*-**13a** was also feasible, achieving an *s* factor of 205.8.

To gain insight into the mechanism, a series of experiments were conducted (Scheme 10). Initially, we investigated the *in situ* generation of chiral octahedral Co(III) catalysts by oxidizing $Co(acac)_2$ with $Mn(OAc)_2{\cdot}4H_2O$ in the presence of 1.0 equiv of (*S*)-**Salox-1** in *t*-BuOH (Scheme 10A, eq 1). Two catalytically active diastereomeric complexes, Λ_{Co}-(S_C)-**Co-3** and Δ_{Co}-(S_C)-**Co-3**, containing one depronated **Salox-1** and two acetylacetone (acac) ligands, were obtained in 87% yield with 15:1 diastereoselectivity. Both diastereomers exhibited catalytic activity, with Λ_{Co}-(S_C)-**Co-3** demonstrating superior performance. The stoichiometric coordination of phosphinamide **13a** with (*S*)-**Salox-1** and $Co(acac)_2$ in the absence of NaOPiv gave the octahedral complex Δ_{Co}-(S_C)-**Co-4** without C−H bond metalation as a single diastereomer, in which the chirality at the metal center was established (Scheme 10B, eq 2). The precise assembly of substrate and Salox ligand around the cobalt center can be attributed to $\pi-\pi$ stacking between the phenyl group of the oxazoline and the quinoline moiety of the DG as well as $\pi-\pi$ stacking between one of the phenyl groups and the phenolic group of **Salox-1**. The desymmetrization of the two aryl moieties in **13** was achieved in this stage. Complex **Co-4** could successfully transform **13** to the chiral product with alkyne in the presence of NaOPiv, indicating the involvement of **Co-4** in this reaction and the necessity of NaOPiv for C−H activation (eq 3). As shown in eq 4, stereoselective self-assembly coordination around the Co(III) center via enantioselective C−H metalation provided chiral cobaltacycle *mer*-(S_C,S_P)-**Co-5** as a single diastereomer. The stoichiometric reaction with alkyne

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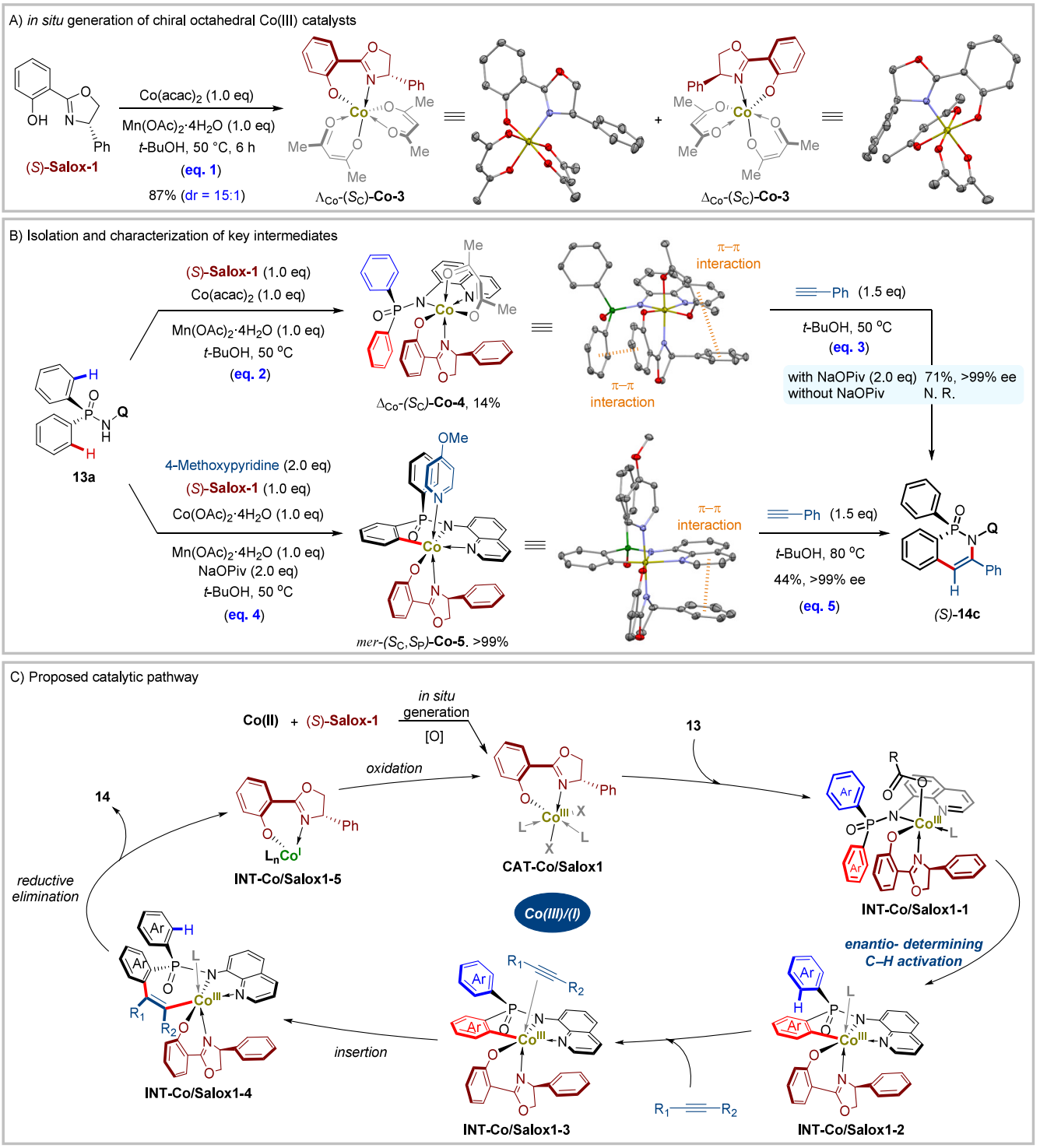
Scheme 10. Mechanistic Studies on Cobalt/Salox Catalysis



proceeded smoothly to give the product (*S*)-**14c** (eq 5), whose configuration matched with the phosphorus center in complex **Co-5**, thereby indicating the involvement of enantiodetermining C−H activation.

Based on these studies, a possible catalytic pathway was proposed (Scheme 10C). The Co(II) species coordinates with **Salox-1** and undergoes *in situ* oxidation to generate the chiral octahedral catalyst **CAT-Co/Salox1**. Ligand exchange with phosphinamide **13** gives complex **INT-Co/Salox1-1**, where the cobalt(III) chiral center is established through dual $\pi-\pi$ interactions between the substrate and Salox ligand. Subsequent enantiodetermining C−H metalation, followed by ligand exchange, delivers chiral cobaltacycle **INT-Co/Salox1-3**. Migratory insertion and reductive elimination afford the corresponding product **14** and liberate the Co(I) species, which can be reoxidized to **CAT-Co/Salox1**. Building on this study, Sundararaju and co-workers reported the enantioselective C−H annulation of phosphinamides with bromoalkynes followed by halogen exchange with carboxylates in 2024.[64]

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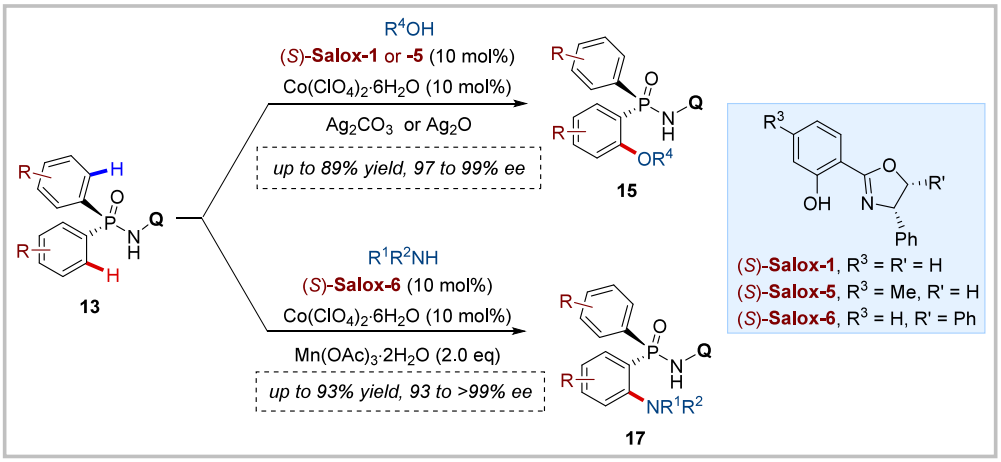
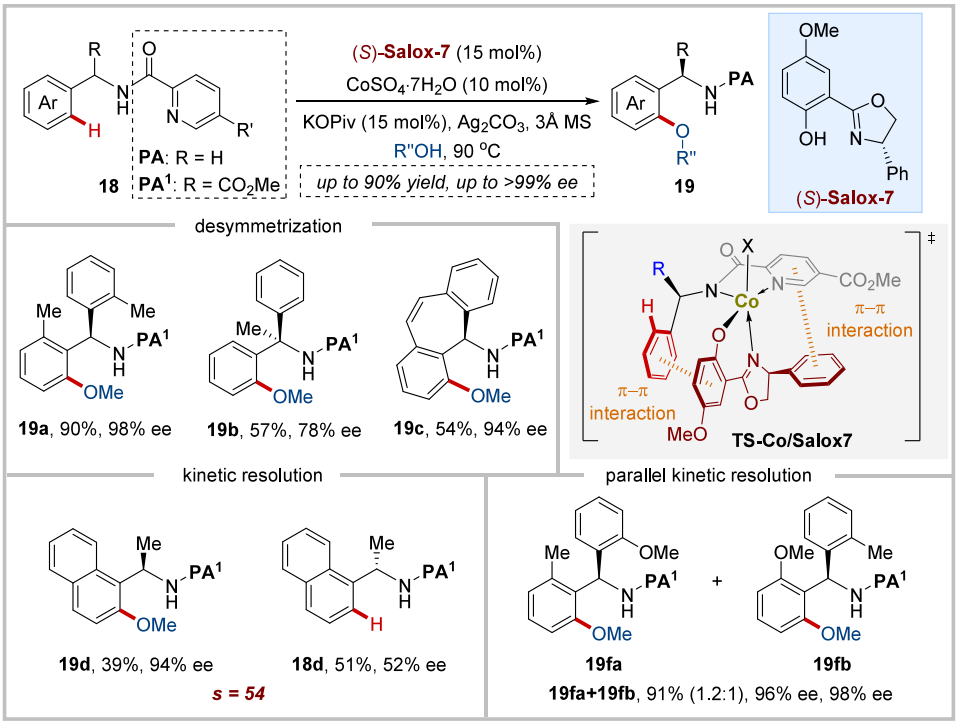
Scheme 11. Cobalt/Salox-Catalyzed Enantioselective Dehydrogenative C−H Alkoxylation and Amination



Scheme 12. Construction of Carbon Chiral Centers via Cobalt/Salox-Catalyzed Enantioselective C−H Alkoxylation



The success of cobalt/Salox catalysis and the detailed mechanistic understanding inspired us to explore additional enantioselective C−H activation reactions and expand our knowledge of ligand evolution. Shortly after this study, we achieved the first enantioselective dehydrogenative C−H alkoxylation and amination using alcohols and free amines as coupling reagents (Scheme 11).[26] Mechanistic studies revealed that in contrast to the previously mentioned enantioselective C−H/N−H annulation reaction, which proceeds through a Co(III/I) catalytic cycle, the enantioselective dehydrogenative C−H alkoxylation involves a Co(II/III/IV) manifold. Notably, we later developed an electrooxidative version of the C−H alkoxylation, and a well-defined cyclometalated cobalt(III) complex that contains MeOH as a neutral ligand was isolated under electrolysis conditions.[27]

Continuing our efforts to push the boundary of cobalt/Salox catalysis, we explored its application in the synthesis of chiral amines using picolinamides as DGs. We first developed the asymmetric synthesis of chiral α-substituted benzylamines through cobalt/Salox-catalyzed enantioselective C−H alkoxylation of picolinamides via desymmetrization, KR, and parallel KR (Scheme 12).[28] An easily removable picolinamide (**PA**) and a picolinamide bearing a methoxycarbonyl group at the 5-position of the pyridyl group (**PA^1**) were proved to be effective DGs. The electron-rich Salox ligand **Salox-7** was found to be effective in this protocol. We proposed that the $\pi-\pi$ interactions between the pyridyl group of the picolinamide and the phenyl group of the oxazoline as well as the second $\pi-\pi$ interaction between one aryl of the substrate and the phenolic skeleton of **Salox-7** facilitate precise assembly around the Co(III) center via **TS-Co/Salox7**, resulting in effective stereodiscrimination.

With the establishment of the **TS-Co/Salox7** stereoinduction model, enantioselective C−H functionalization of picolinamides was further developed with other coupling partners, including

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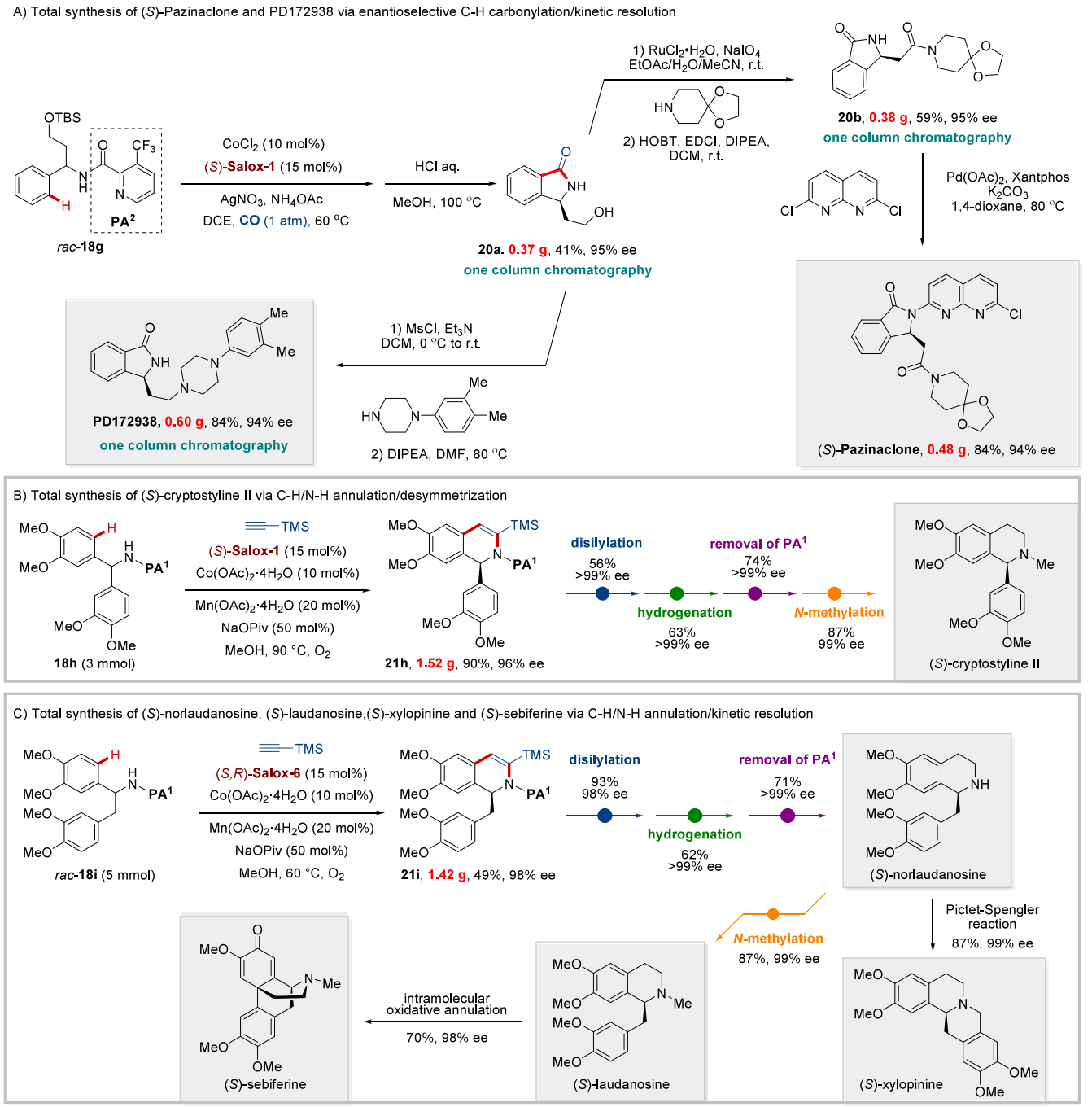
Scheme 13. Asymmetric Total Synthesis of Bioactive Molecules



C−H carbonylation using carbon monoxide to produce chiral isoindolinones[29] and C−H annulation with alkynes to synthesize C1-chiral 1,2-dihydroisoquinolines (DHIQs).[30] These newly developed methods have streamlined the asymmetric synthesis of pharmaceutical compounds such as (*S*)-PD172938 and (*S*)-pazinaclone (Scheme 13A) as well as several tetrahydroisoquinoline alkaloids, including (*S*)-crytostyline II, (*S*)-norlaudansine, (*S*)-laudanosine, (*S*)-xylopinine, and (*S*)-sebiferine (Scheme 13B,C).

Construction of Axial Chirality. In 2023, we reported the synthesis of axially chiral biaryl-2-amines through cobalt/Salox-catalyzed atoposelective C−H functionalization, utilizing **PA** as the DG and bromo-substituted Salox (**Salox-8**) as the chiral ligand (Scheme 14).[31] As shown in Scheme 14B, we hypothesized that the $\pi-\pi$ interaction between the naphthyl group of *rac*-**22** and the phenolate group of **Salox-8** plays a crucial role in the dynamic kinetic asymmetric transformation from **INT-Co/Salox8-1** to the more energetically favorable **INT-Co/Salox8-2** through the unhindered rotation of the biaryl axis. The intermediate **INT-Co/Salox8-2** then undergoes transannular C−H activation, delivering the cobaltacycle **INT-Co/Salox8-3**. The $\pi-\pi$ interaction between the phenyl ring of oxazoline and the pyridyl moiety of **PA** secures the axial chirality of the biaryl structure. Single-electron oxidation of **INT-Co/Salox8-3** with an aryl radical followed by reductive elimination affords the axially chiral biaryls in decent yields (up to 99%) with excellent enantioselectivities (up to 99% ee).

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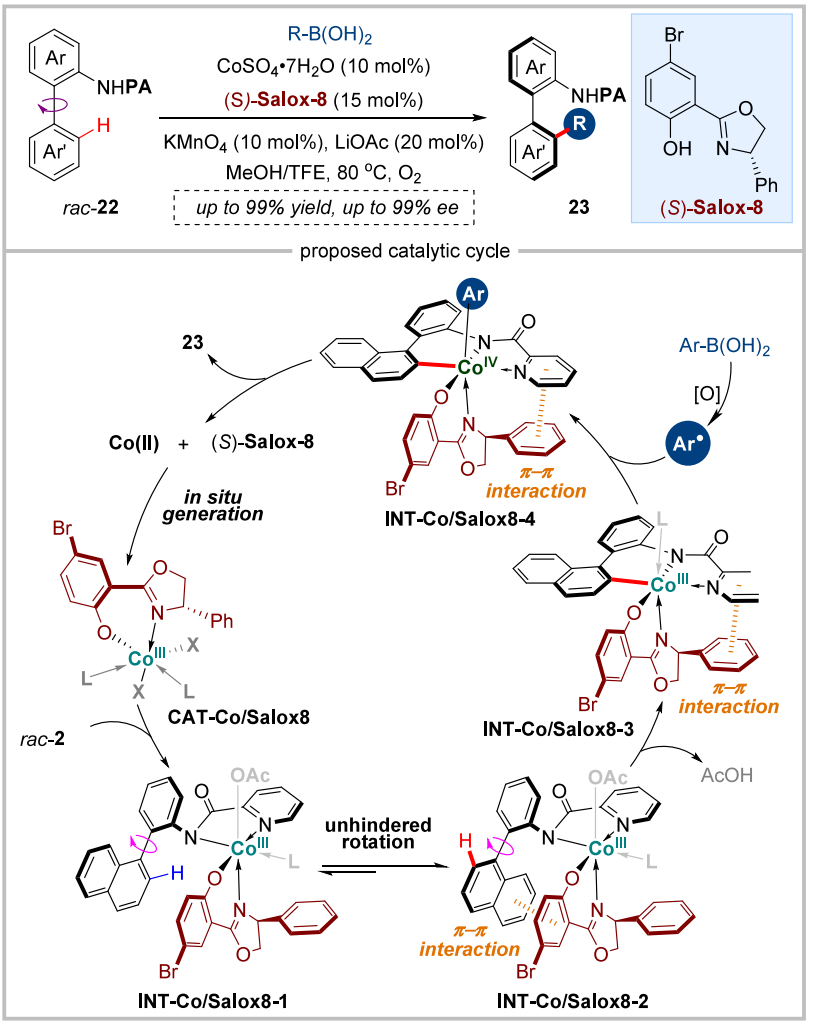
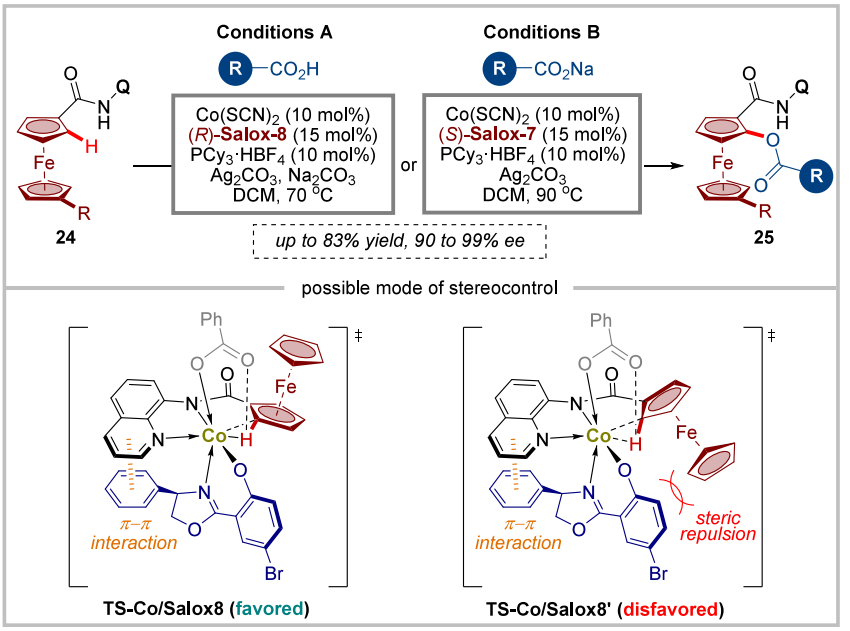
Scheme 14. Construction of Axially Chiral Biaryls through Cobalt/Salox-Catalyzed Enantioselective C−H Arylation



Scheme 15. Synthesis of Planar-Chiral Ferrocenes via Cobalt/Salox-Catalyzed Enantioselective C−H Acyloxylation



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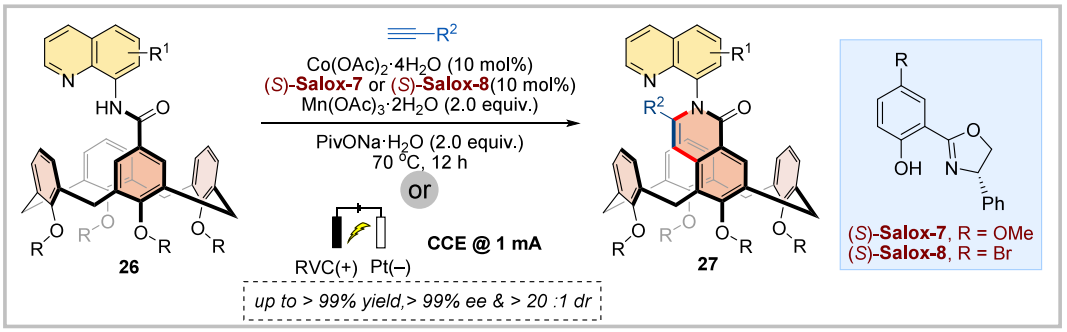
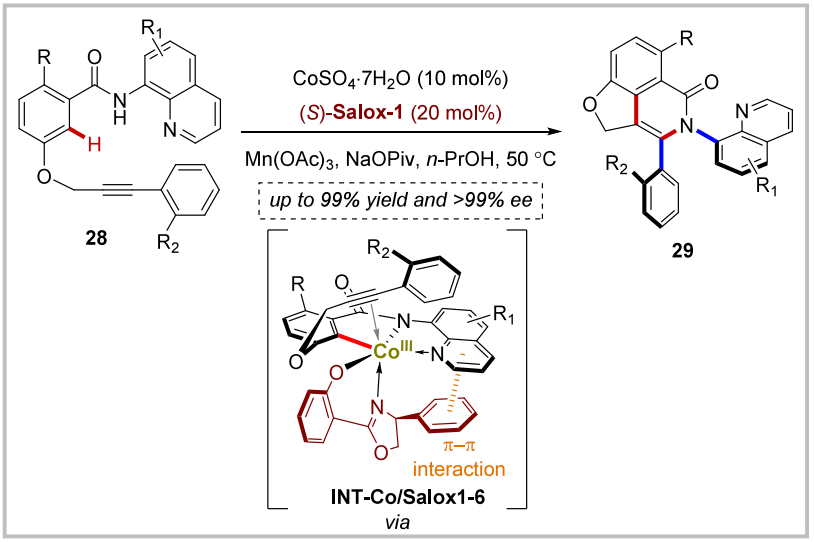
Scheme 16. Asymmetric Synthesis of Chiral Calix[4]arenes with Inherent Chirality



Scheme 17. Construction C−C and C−N Diaxial Chirality through Cobalt/Salox-Catalyzed Intramolecular Atroposelective C−H/N−H Annulation



Construction of Planar Chirality. The cobalt/Salox catalysis has also proven to be effective in constructing planar chirality. In 2024, we reported the synthesis of planar-chiral oxygen-substituted ferrocenes through cobalt/Salox-catalyzed enantioselective C−H acyloxylation with carboxylic acids or sodium carboxylates.[32] We propose that the transition state for enantioselective C−H metalation, **TS-Co/Salox8**, is significantly favored over **TS-Co/Salox8′** due to the avoidance of steric repulsion between the ferrocene skeleton and the Salox ligand (Scheme 15).

Construction of Inherent Chirality. Recently, we reported the asymmetric synthesis of calix[4]arenes that exhibit either inherent chirality or both inherent and axial chirality via cobalt/Salox-catalyzed enantioselective C−H annulation. This method provided a broad range of functionalized chiral calix[4]arenes in high yields with excellent enantio- and diastereoselectivities (up to >99% ee and >20:1 dr).[33] Furthermore, we found that electrooxidation could also be effectively utilized in this protocol, eliminating the need for sacrificial metal oxidants while giving comparable results (Scheme 16). Simultaneously, Niu and co-workers reported cobalt/Salox-catalyzed enantioselective C−H annulation to prepare inherently chiral calix[4]-arenes.[65]

3.3. Enantiodetermining Functionalization after C−H Metalation

Cobalt/Salox catalysis has achieved significant success in stereochemistry-generating C−H activation reactions (Scheme 6, **Type I**). Building on our mechanistic studies, the Salox ligand coordinates to the cobalt center as a permanent ligand, providing precise control over the coordination stereochemistry. This insight led us to envision that cobalt/Salox catalysis could offer substantial opportunities for developing reactions that involve enantiodetermining functionalization following C−H metalation (Scheme 6, **Type II**).

Construction of Atropisomers via Intramolecular C−H Activation/Annulation. Inspired by our previous work on enantioselective C−H/N−H annulation reactions,[2] we further disclosed a one-step protocol for constructing atropisomers **29** featuring vicinal C−C and C−N chiral diaxes from well-designed benzamides **28** through a cobalt/Salox-catalyzed intramolecular atroposelective C−H/N−H annulation reaction (Scheme 17).[34] We posited that intramolecular C−H metalation would lead to the formation of cobaltacycle intermediate **INT-Co/Salox1-6**, in which the $\pi-\pi$ stacking interaction between the phenyl group of the oxazoline and the quinoline moiety of the DG would ensure the precise self-assembly coordination around the Co(III) center. Meanwhile, Niu and co-workers independently introduced a similar strategy for the synthesis of C−N atropisomers through an intermolecular

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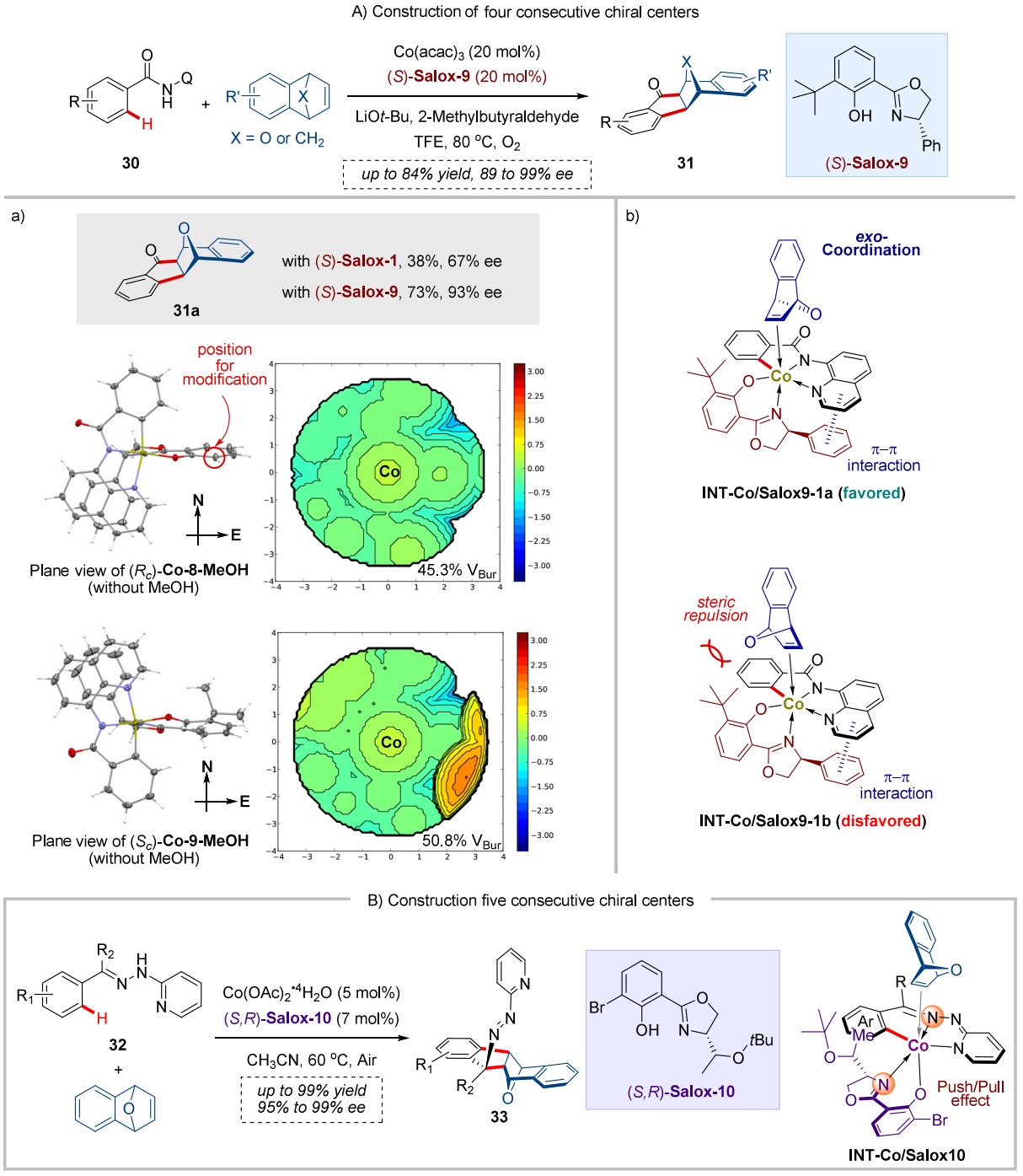
Scheme 18. Cobalt-Catalyzed Domino Transformations via Enantioselective C−H Activation/Nucleophilic [3 + 2] Annulation



atroposelective C−H annulation of benzamides with alkynes.[66] Subsequently, they further realized a series of asymmetric C−H annulation reactions for the synthesis of C−N atropisomers[67,68] and N−N atropisomers using cobalt/Salox catalysis.[69,70]

C−H Activation/Intermolecular Asymmetric Insertion. Building on the mechanistic insights into cobalt/Salox catalysis,[2] we envisioned that a well-designed Salox ligand could be employed to create a sophisticated chiral pocket in the cobaltacycle, which could effectively direct the orientation of alkene coordination and influence the facial selectivity during the migratory insertion. Such an approach could enhance the stereoselectivity of the resulting products.

In 2024, we reported a Co/Salox-catalyzed C−H activation of benzamides followed by an enantioselective nucleophilic [3 + 2] annulation reaction with *meso*-bicyclic alkenes, providing access to chiral [2.2.1]-bridged bicyclic molecules with four consecutive stereocenters in a single step (Scheme 18A).[35] A sterically hindered Salox ligand, **Salox-9**, which features a *tert*-butyl group at the *ortho* position of the phenolic ring, was crucial for the reaction (**31a**, 93% ee). In contrast, the unsubstituted ligand, **Salox-1**, resulted in only moderate enantioselectivity (67% ee). The steric map of the chiral pocket in the cobaltacycle complex (R_C)-**Co-8-MeOH**, generated from (*R*)-**Salox-1**, shows an open-wide plane for bicyclic alkene coordination, which corresponds to the unsatisfactory stereocontrol observed.

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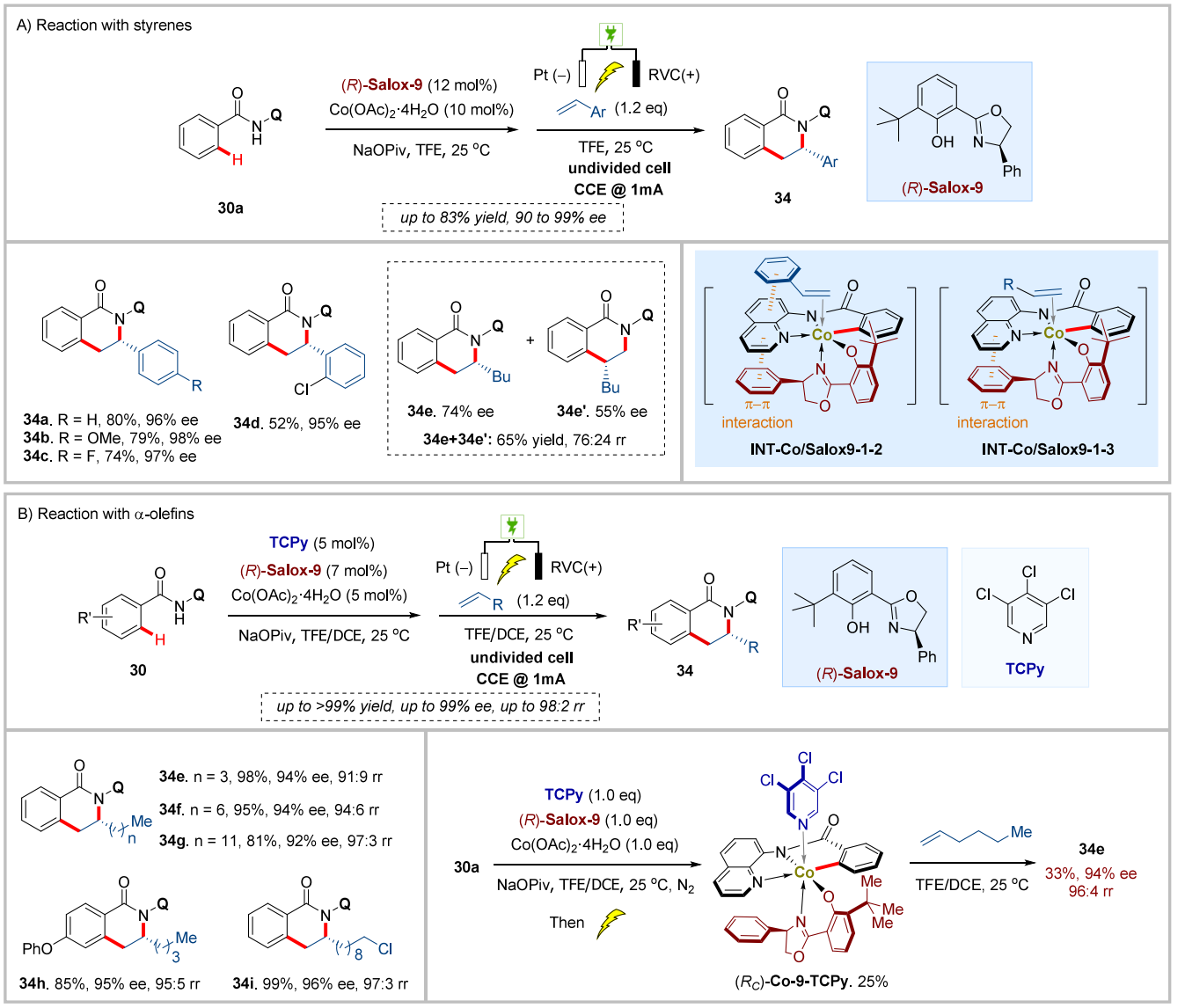
Scheme 19. Cobaltaelectrocatalyzed Enantioselective C−H/N−H Annulation Reaction with Olefins



Conversely, the map for the chiral pocket in **Salox-9** coordinated to the cobaltacycle (S_C)-**Co-9-MeOH** indicates that the bulk of the *tert*-butyl group restricts access to the eastern hemisphere. The bicyclic alkene tends to adopt a relatively favorable *exo* coordination fashion (**INT-Co/Salox9-1a**) with the chiral pocket to minimize steric repulsion (Scheme 18Ab).

We rationalized that a synergism exists between the coordination modes of the substrate and the Salox ligand around the Co(III) center, which could facilitate the design of Salox ligands for other types of substrates. To test this hypothesis, we investigated the reaction of aryl hydrazones with 7-oxabenzonorbornadiene (Scheme 18B). We rationalized that aryl hydrazones should adopt a κ^3 (X,L,X) coordination mode during the formation of a cobaltacycle. In this scenario, the N-donor of the oxazoline in the Salox ligand should adopt a *trans* coordination to the unsaturated N-donor of the hydrazone due to the "push−pull effect". The judicious modification of the residue adjacent to the nitrogen atom of the oxazoline led to the design of the sterically demanding ligand (*S*,*R*)-**Salox-10**, which provided precise control over the orientation of the coordinated alkene, as demonstrated in the proposed intermediate **INT-Co/Salox10** (Scheme 18B). With this ligand in hand, a novel class of chiral [2.2.1]-bridged bicyclic molecules containing five consecutive stereocenters were obtained with excellent enantioselectivities (95−99% ee).[35]

Asymmetric Cobaltaelectrocatalysis. Although significant achievements have been made, these reactions typically require stoichiometric metal additives or oxidants. Recently, electrochemical oxidative cross-coupling has emerged as a powerful and environmentally friendly strategy for the formation of chemical bonds. In this approach, anodic oxidation replaces the need for chemical oxidants by removing electrons from substrates or catalysts, while cathodic proton reduction releases hydrogen gas.

In 2023, we reported the first 3d metallaelectrocatalyzed asymmetric C−H activation via electrooxidative cobalt/Salox-catalyzed enantioselective C−H/N−H annulation of benzamides with alkenes.[3] (*R*)-**Salox-9** was used as the sole ligand when employing styrenes as coupling reagents, delivering the corresponding chiral products **34** with high enantioselectivities (Scheme 19A, 90−99% ee). However, unsatisfactory enantio- and regioselectivity were obtained when investigating 1-hexene

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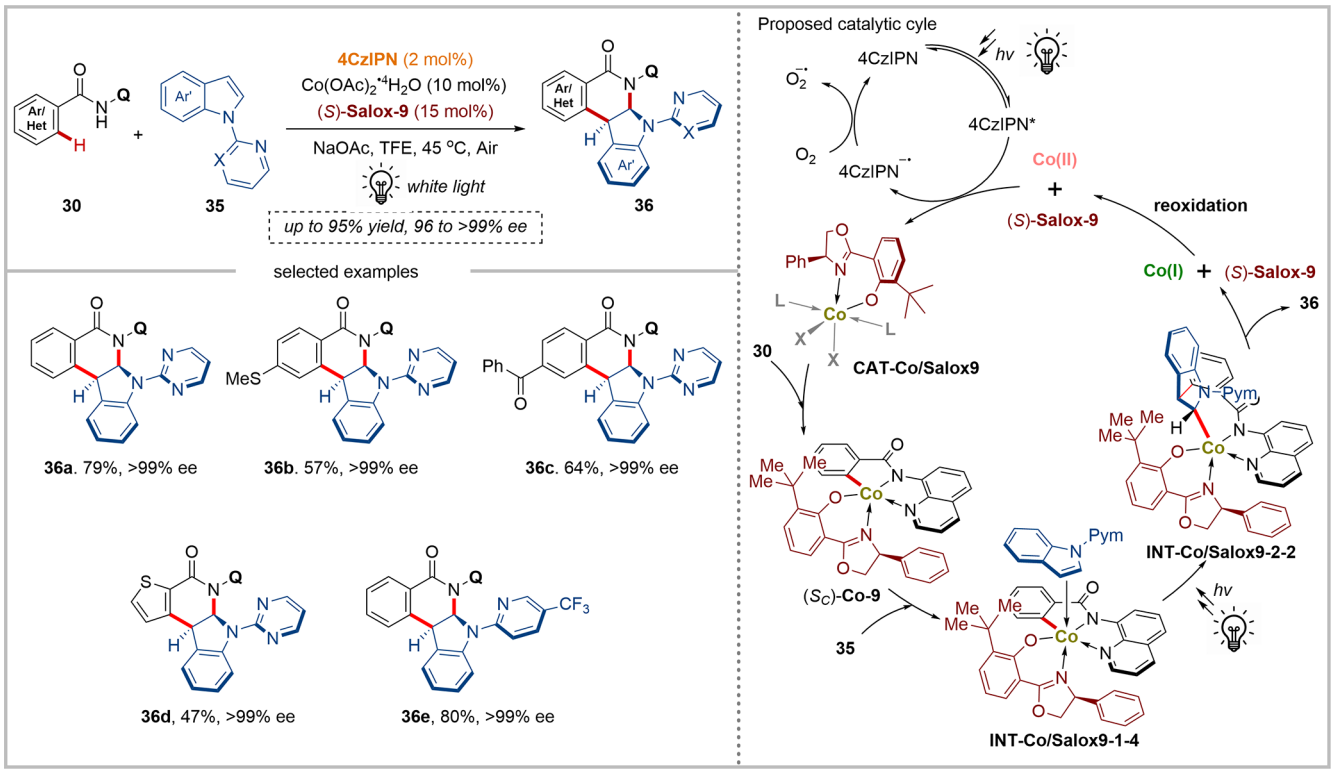
Scheme 20. Cobaltaphotoredox-Catalyzed C−H Activation/Dearomatization of Indoles



(**34e**, 70% ee; **34e′**, 55% ee; **34e**:**34e′**, 74:26 rr). We proposed that the well-defined chiral pocket in (R_C)-**Co-9** could direct the orientation of styrene through a $\pi-\pi$ stacking interaction (**INT-Co/Salox9-1-2**). In contrast, the absence of secondary interactions with 1-hexene resulted in poor enantio- and regioselectivity (**INT-Co/Salox9-1-3**).

We hypothesized that the introduction of a transient ligand could initially occupy the chiral pocket and that the subsequent ligand exchange with the α-olefin might influence the orientation of olefin coordination, leading to high enantioselectivity and regioselectivity. Based on this rationale, we introduced a dual-ligand system comprising **Salox-9** and an electron-deficient pyridine ligand, 3,4,5-trichloropyridine (**TCPy**), which facilitated the formation of products with high enantioselectivity and regioselectivity when using α-olefins (Scheme 19B, up to 99% ee and 98:2 rr). The results of the stoichiometric reaction of cobaltacycle (R_C)-**Co-9-TCPy** with 1-hexene provided strong support for the rationale.

Since our report, a series of cobaltaelectrocatalyzed enantioselective C−H activation reactions have been developed.[70−75] For example, Ackermann and co-workers merged electrosynthesis with our previously reported cobalt/Salox-catalyzed enantioselective C−H annulation of phosphinamides with alkynes[2] and alkenes,[3] dehydrogenative C−H alkoxylation,[26,27] and the Niu group's synthesis of C−N atropisomers.[65,70] The Ling group also reported the electrooxidative version of our cobalt/Salox-catalyzed enantioselective C−H annulation[2,71] and dehydrogenative C−H alkoxylation of phosphinamides.[3,73] The groups of Ackermann and Zeng reported the synthesis of atropisomers by merging electrosynthesis with cobalt/Salox catalysis.[74,75]

Asymmetric Cobaltaphotoredox Catalysis. Encouraged by our previous studies on cobaltaelectrocatalyzed enantioselective C−H activation reactions,[3,27] where electrolysis facilitates the oxidation of the cobalt catalyst via a single electron transfer (SET) process, we proposed that merging photochemistry with cobalt/Salox catalysis could be a viable strategy.

Recently, we introduced cobaltaphotoredox-catalyzed enantioselective C−H functionalization utilizing (*S*)-**Salox-9**. This novel strategy enabled catalytic asymmetric dearomatization of indoles, providing chiral indolines with excellent enantioselectivities (up to >99% ee) (Scheme 20).[36] Electron paramagnetic resonance (EPR) studies confirmed the formation of superoxide radical, and the radical anion 4CzIPN$^{\bullet-}$ could be reoxidized to ground-state 4CzIPN by molecular oxygen. The Sundararaju group independently reported a similar study,[76] and subsequent work along these lines was also published by Ackermann and co-workers.[77]

3.4. Summary of Ligand Structure−Enantioselectivity Relationships

Based on our mechanistic studies and reaction developments, we have elucidated the ligand structure−enantioselectivity relationships (Scheme 21). For substrates derived from amides and amines, several critical factors have emerged: (1) the presence of a phenyl group at R_1 is essential to facilitate $\pi-\pi$ interactions with the quinoline moiety of the directing group (DG), which promote precise self-assembly coordination around the Co(III) catalyst; (2) the $\pi-\pi$ interaction between the phenolic moiety and one of the phenyl groups is instrumental in enabling either desymmetrization or (D)KR; (3) the introduction of a bulky substituent (R_2) at the *ortho* position of the phenolic ring effectively guides the orientation of olefin insertion; and (4) substituents on the phenolic ring (R) serve to modulate the reactivity. In the case of hydrazones, the incorporation of a bulky substituent adjacent to the nitrogen atom of the oxazoline (R_1) is a prerequisite for directing the orientation of olefin insertion. These insights contribute to a

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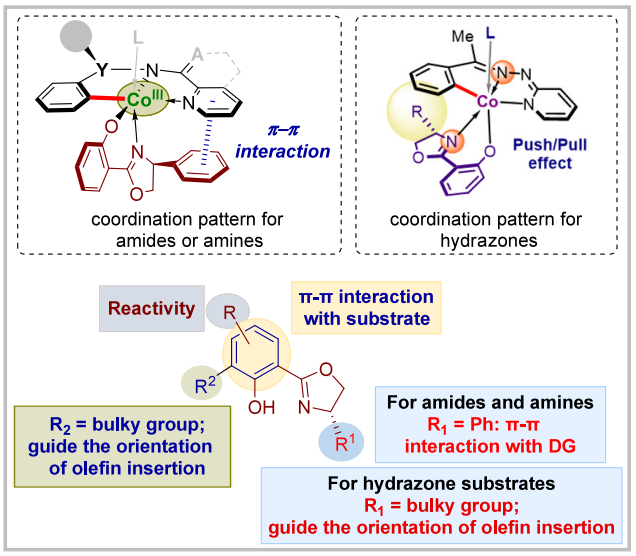
Scheme 21. Ligand Structure–Enantioselectivity Relationships



more comprehensive understanding of the factors influencing enantioselectivity in cobalt/Salox catalysis and will inform future developments.

4. COBALT/CPA SEQUENTIAL CATALYSIS

Encouraged by recent advances in metal–organic cooperative catalysis,[78,79] we conceptualized a strategy for enantioselective sequential catalysis in which a CPA-catalyzed asymmetric process utilizes an intermediate generated *in situ* through C–H functionalization (Scheme 1D, ***Catalysis III***). This design focuses on programming synergistic processes rather than solely on the development of chiral ligands for cobalt catalysts, which distinguishes it from the strategies discussed above (***Catalysis I and II***).

In 2021, we reported the synthesis of chiral spiro-γ-lactams catalyzed by cobalt/CPA sequential catalysis. In this process, cobalt(III) served as catalyst for C–H olefination, while sterically bulky (*S*)-**STRIP** acted as chiral organocatalyst for the subsequent asymmetric spirocyclization (Scheme 22).[4] We proposed that this transformation occurs in two cascade steps: (1) *in situ*-generated cobalt(III)-catalyzed C–H olefination to form intermediate **INT-O** and (2) subsequent CPA-catalyzed asymmetric [4 + 1] spirocyclization, which operates synergistically with the cobalt(III) catalyst. In 2023, Ackermann and co-workers expanded this reaction to an electrochemical version.[71]

5. CONCLUSION AND OUTLOOK

In summary, our laboratory has made significant strides in developing a range of cobalt(III)-catalyzed enantioselective C–H functionalization reactions. This includes the exploration of achiral Cp*Co(III)/CCA catalysis, cobalt/Salox catalysis, and cobalt/CPA sequential catalysis. We further investigated the potential of integrating electrochemistry and photoredox catalysis, providing a more sustainable alternative to traditional chemical oxidants. These advancements have expanded the landscape of earth-abundant 3d transition-metal-catalyzed asymmetric C–H activation. However, several limitations still exist: (1) enantioselective C(sp^3)–H activation remains underdeveloped, and (2) for octahedral cobalt(III)-catalyzed enantioselective C–H activation reactions, the preinstallation of bidentate DGs on substrates is still necessary. We anticipate that ongoing innovations will address these limitations, further expanding the applicability of cobalt(III)-catalyzed enantioselective C–H functionalization reactions and opening new avenues for the synthesis of valuable chiral frameworks.

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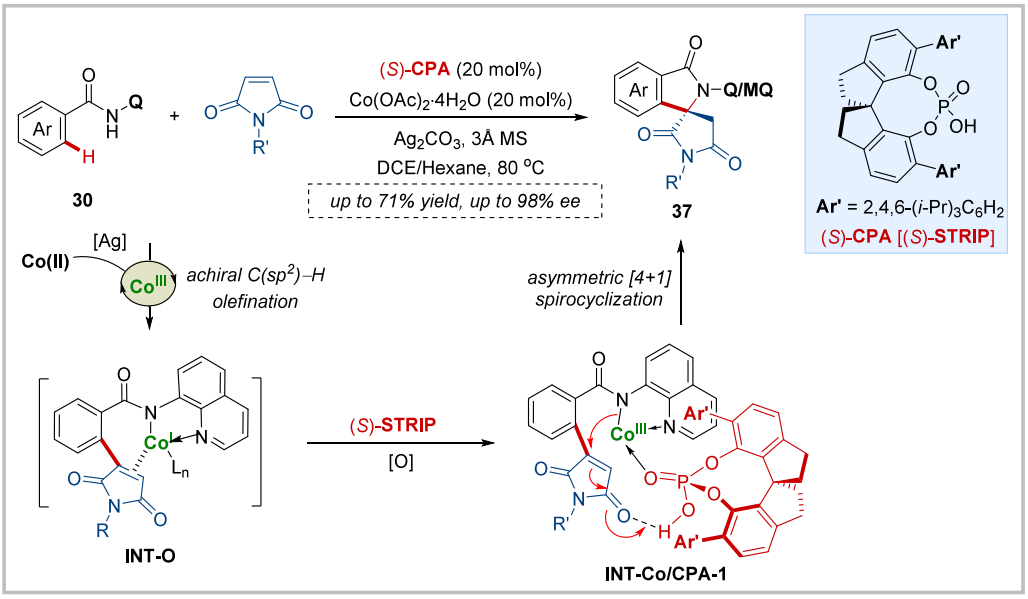
Scheme 22. Cobalt/CPA-Catalyzed Sequential C–H Olefination/Asymmetric [4 + 1] Spirocyclization



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Notes

The authors declare no competing financial interest.

Biographies

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Bing-Feng Shi received his B.Sc. from Nankai University and his Ph.D. from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, with Professor Biao Yu in 2006. Following a postdoctoral fellowship at the University of California, San Diego (2006−2007), he moved to The Scripps Research Institute, working with Professor Jin-Quan Yu as a research associate. In 2010 he joined the Department of Chemistry at Zhejiang University as a professor. His research is focused on asymmetric C−H functionalization.

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■ REFERENCES

(1) Liu, Y.-H.; Li, P.-X.; Yao, Q.-J.; Zhang, Z.-Z.; Huang, D.-Y.; Le, M. D.; Song, H.; Liu, L.; Shi, B.-F. Cp*Co(III)/MPAA-Catalyzed Enantioselective Amidation of Ferrocenes Directed by Thioamides under Mild Conditions. *Org. Lett.* **2019**, *21*, 1895−1899.

(2) Yao, Q.-J.; Chen, J.-H.; Song, H.; Huang, F.-R.; Shi, B.-F. Cobalt/Salox-Catalyzed Enantioselective C−H Functionalization of Arylphosphinamides. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202202892.

(3) Yao, Q.-J.; Huang, F.-R.; Chen, J.-H.; Zhong, M.-Y.; Shi, B.-F. Enantio- and Regioselective Electrooxidative Cobalt-Catalyzed C−H/N−H Annulation with Alkenes. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202218533.

(4) Yuan, W.-K.; Shi, B.-F. Synthesis of Chiral Spirolactams via Sequential C−H Olefination/Asymmetric [4 + 1] Spirocyclization under a Simple Co^{II}/Chiral Spiro Phosphoric Acid Binary System. *Angew. Chem., Int. Ed.* **2021**, *60*, 23187−23192.

(5) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C−H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908−8976.

(6) Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. From $Pd(OAc)_2$ to Chiral Catalysts: The Discovery and Development of Bifunctional Mono-*N*-Protected Amino Acid Ligands for Diverse C−H Functionalization Reactions. *Acc. Chem. Res.* **2020**, *53*, 833−851.

(7) Zhan, B.-B.; Jin, L.; Shi, B.-F. Palladium-Catalyzed Enantioselective C-H Functionalization via C-H Palladation. *Trends Chem.* **2022**, *4*, 220−235.

(8) Liu, C.-X.; Yin, S.-Y.; Zhao, F.; Yang, H.; Feng, Z.; Gu, Q.; You, S.-L. Rhodium-Catalyzed Asymmetric C−H Functionalization Reactions. *Chem. Rev.* **2023**, *123*, 10079−10134.

(9) Yoshino, T.; Satake, S.; Matsunaga, S. Diverse approaches for Enantioselective C−H Functionalization Reactions using Group 9 Cp^xM^{III} Catalysts. *Chem.—Eur. J.* **2020**, *26*, 7346−7357.

(10) Woźniak, Ł.; Cramer, N. Enantioselective C-H Bond Functionalizations by 3d Transition-Metal Catalysts. *Trends Chem.* **2019**, *1*, 471−484.

(11) *CRC Handbook of Chemistry and Physics*, 97th ed.; Haynes, W. M., Ed.; CRC Press, 2016.

(12) Hapke, M.; Hilt, G. *Introduction to Cobalt Chemistry and Catalysis*; Wiley-VCH, 2020.

(13) Gao, K.; Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C−H Functionalization. *Acc. Chem. Res.* **2014**, *47*, 1208−1219.

(14) Zheng, Y.; Zheng, C.; Gu, Q.; You, S.-L. Enantioselective C−H functionalization reactions enabled by cobalt catalysis. *Chem. Catal* **2022**, *2*, 2965−2985.

(15) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. Cobalt-Catalyzed Hydroarylation of Alkynes through Chelation-Assisted C−H Bond Activation. *J. Am. Chem. Soc.* **2010**, *132*, 12249−12251.

(16) Yang, J.; Yoshikai, N. Cobalt-catalyzed enantioselective intramolecular hydroacylation of ketones and olefins. *J. Am. Chem. Soc.* **2014**, *136*, 16748−16751.

(17) Kim, D. K.; Riedel, J.; Kim, R. S.; Dong, V. M. Cobalt catalysis for enantioselective cyclobutanone construction. *J. Am. Chem. Soc.* **2017**, *139*, 10208−10211.

(18) Zhang, H.; Huang, J.; Meng, F. Cobalt-catalyzed diastereo- and enantioselective allyl addition to aldehydes and a-ketoesters through allylic C−H functionalization. *Cell Rep. Phys. Sci.* **2021**, *2*, 100406.

(19) Whyte, A.; Torelli, A.; Mirabi, B.; Prieto, L.; Rodriguez, J. F.; Lautens, M. Cobalt-catalyzed enantioselective hydroarylation of 1,6-enynes. *J. Am. Chem. Soc.* **2020**, *142*, 9510−9517.

(20) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. A Cationic High-Valent Cp^*Co^{III} Complex for the Catalytic Generation of Nucleophilic Organometallic Species: Directed C−H Bond Activation. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207−2211.

(21) Yoshino, T.; Matsunaga, S. (Pentamethylcyclopentadienyl)-cobalt(III)-Catalyzed C−H Bond Functionalization: From Discovery to Unique Reactivity and Selectivity. *Adv. Synth. Catal.* **2017**, *359*, 1245−1262.

(22) Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed, Aminoquinoline-Directed $C(sp^2)$−H Bond Alkenylation by Alkynes. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209−10212.

(23) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon−Hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053−1064.

(24) Zhou, Y.-B.; Zhou, T.; Qian, P.-F.; Li, J.-Y.; Shi, B.-F. Synthesis of Sulfur-Stereogenic Sulfoximines via Co(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective C−H Amidation. *ACS Catal.* **2022**, *12*, 9806−9811.

(25) Liu, Y.-H.; Xie, P.-P.; Liu, L.; Fan, J.; Zhang, Z.-Z.; Hong, X.; Shi, B.-F. Cp*Co(III)-Catalyzed Enantioselective Hydroarylation of Unactivated Terminal Alkenes via C-H Activation. *J. Am. Chem. Soc.* **2021**, *143*, 19112−19120.

(26) Chen, J.-H.; Teng, M.-Y.; Huang, F.-R.; Song, H.; Wang, Z.-K.; Zhuang, H.-L.; Wu, Y.-J.; Wu, X.; Yao, Q.-J.; Shi, B.-F. Cobalt/Salox-Catalyzed Enantioselective Dehydrogenative C−H Alkoxylation and Amination. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202210106.

(27) Zhou, G.; Chen, J.-H.; Yao, Q.-J.; Huang, F.-R.; Wang, Z.-K.; Shi, B.-F. Base-Promoted Electrochemical Co(II)-Catalyzed Enantioselective C−H Oxygenation. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202302964.

(28) Wang, Z.-K.; Wu, Y.-J.; Yao, Q.-J.; Shi, B.-F. Synthesis of Chiral Diarylmethylamines by Cobalt-Catalyzed Enantioselective C-H Alkoxylation. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202304706.

(29) Teng, M.-Y.; Wu, Y.-J.; Chen, J.-H.; Huang, F.-R.; Liu, D.-Y.; Yao, Q.-J.; Shi, B.-F. Cobalt-Catalyzed Enantioselective C−H Carbonylation

towards Chiral Isoindolinones. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202318803.
(30) Wu, Y.-J.; Chen, J.-H.; Teng, M.-Y.; Li, X.; Jiang, T.-Y.; Huang, F.-R.; Yao, Q.-J.; Shi, B.-F. Cobalt-Catalyzed Enantioselective C−H Annulation of Benzylamines with Alkynes: Application to the Modular and Asymmetric Syntheses of Bioactive Molecules. *J. Am. Chem. Soc.* **2023**, *145*, 24499−24505.
(31) Wu, Y.-J.; Wang, Z.-K.; Jia, Z.-S.; Chen, J.-H.; Huang, F.-R.; Zhan, B.-B.; Yao, Q.-J.; Shi, B.-F. Synthesis of Axially Chiral Biaryls through Cobalt(II)-Catalyzed Atroposelective C−H Arylation. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202310004.
(32) Huang, F.-R.; Zhang, P.; Yao, Q.-J.; Shi, B.-F. Construction of Planar Chiral Ferrocenes by Cobalt-Catalyzed Enantioselective C−H Acyloxylation Enabled by Dual Ligand. *CCS Chem.* **2024**, *6*, 2783−2793.
(33) Qian, P.-F.; Zhou, G.; Hu, J.-H.; Wang, B.-J.; Jiang, A.-L.; Zhou, T.; Yuan, W.-K.; Yao, Q.-J.; Chen, J.-H.; Kong, K.-X.; Shi, B.-F. Asymmetric Synthesis of Chiral Calix[4]arenes with Both Inherent and Axial Chirality via Cobalt-Catalyzed Enantioselective Intermolecular C−H Annulation. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202412459.
(34) Wang, B.-J.; Xu, G.-X.; Huang, Z.-W.; Wu, X.; Hong, X.; Yao, Q.-J.; Shi, B.-F. Single-Step Synthesis of Atropisomers with Vicinal C−C and C−N Diaxes by Cobalt-Catalyzed Atroposelective C−H Annulation. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202208912.
(35) Huang, F.-R.; Yao, Q.-J.; Zhang, P.; Teng, M.-Y.; Chen, J.-H.; Jiang, L.-C.; Shi, B.-F. Cobalt-Catalyzed Domino Transformations via Enantioselective C−H Activation/Nucleophilic [3 + 2] Annulation Towards Chiral Bridged Bicycles. *J. Am. Chem. Soc.* **2024**, *146*, 15576−15586.
(36) Teng, M.-Y.; Liu, D.-Y.; Mao, S.-Y.; Wu, X.; Chen, J.-H.; Zhong, M.-Y.; Huang, F.-R.; Yao, Q.-J.; Shi, B.-F. Asymmetric Dearomatization of Indoles through Cobalt-Catalyzed Enantioselective C−H Functionalization Enabled by Photocatalysis. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202407640.
(37) Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem.—Eur. J.* **2010**, *16*, 11212−11222.
(38) Song, G.; Wang, F.; Li, X. C−C. C−O and C−N bond formation via rhodium(iii)-catalyzed oxidative C−H activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678.
(39) Ye, B.; Cramer, N. Chiral Cyclopentadienyls: Enabling Ligands for Asymmetric Rh(III)-Catalyzed C−H Functionalizations. *Acc. Chem. Res.* **2015**, *48*, 1308−1318.
(40) Wang, Q.; Liu, C.-X.; Gu, Q.; You, S.-L. Chiral Cp^{x}Rh complexes for C−H functionalization reactions. *Sci. Bull.* **2021**, *66*, 210−213.
(41) Ozols, K.; Jang, Y.-S.; Cramer, N. Chiral Cyclopentadienyl Cobalt(III) Complexes Enable Highly Enantioselective 3d-Metal-Catalyzed C−H Functionalizations. *J. Am. Chem. Soc.* **2019**, *141*, 5675−5680.
(42) Ozols, K.; Onodera, S.; Woźniak, Łu.; Cramer, N. Cobalt(III)-Catalyzed Enantioselective Intermolecular Carboamination by C−H Functionalization. *Angew. Chem., Int. Ed.* **2021**, *60*, 655−659.
(43) Zheng, Y.; Zhang, W.-Y.; Gu, Q.; Zheng, C.; You, S.-L. Cobalt(III)-catalyzed asymmetric ring-opening of 7-oxabenzonorbornadienes via indole C−H functionalization. *Nat. Commun.* **2023**, *14*, 1094.
(44) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective Activation of C(sp^2)−H and C(sp^3)−H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882−4886.
(45) Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. From Pd(OAc)$_2$ to Chiral Catalysts: The Discovery and Development of Bifunctional Mono-*N*-Protected Amino Acid Ligands for Diverse C−H Functionalization Reactions. *Acc. Chem. Res.* **2020**, *53*, 833−851.
(46) Lin, L.; Fukagawa, S.; Sekine, D.; Tomita, E.; Yoshino, T.; Matsunaga, S. Chiral Carboxylic Acid Enabled Achiral Rhodium(III)-Catalyzed Enantioselective C−H Functionalization. *Angew. Chem., Int. Ed.* **2018**, *57*, 12048−12052.
(47) Yoshino, T.; Matsunaga, S. Chiral Carboxylic Acid Assisted Enantioselective C−H Activation with Achiral Cp^x M^{III} (M = Co, Rh, Ir) Catalysts. *ACS Catal.* **2021**, *11*, 6455−6466.
(48) Fukagawa, S.; Kato, Y.; Tanaka, R.; Kojima, M.; Yoshino, T.; Matsunaga, S. Enantioselective C(sp^3)−H Amidation of Thioamides Catalyzed by a Cobalt^{III}/Chiral Carboxylic Acid Hybrid System. *Angew. Chem., Int. Ed.* **2019**, *58*, 1153−1157.
(49) Knowles, R. R.; Jacobsen, E. N. Attractive Noncovalent Interactions in Asymmetric Catalysis: Links between Enzymes and Small Molecule Catalysts. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20678−20685.
(50) Fanourakis, A.; Docherty, P. J.; Chuentragool, P.; Phipps, R. J. Recent Developments in Enantioselective Transition Metal Catalysis Featuring Attractive Noncovalent Interactions between Ligand and Substrate. *ACS Catal.* **2020**, *10*, 10672−10714.
(51) Trouvé, J.; Gramage-Doria, R. Beyond hydrogen bonding: recent trends of outer sphere interactions in transition metal catalysis. *Chem. Soc. Rev.* **2021**, *50*, 3565−3584.
(52) Zhou, T.; Qian, P.-F.; Li, J.-Y.; Zhou, Y.-B.; Li, H.-C.; Chen, H.-Y.; Shi, B.-F. Efficient Synthesis of Sulfur-Stereogenic Sulfoximines via Ru(II)-Catalyzed Enantioselective C−H Functionalization Enabled by Chiral Carboxylic Acid. *J. Am. Chem. Soc.* **2021**, *143*, 6810−6816.
(53) Li, J.-Y.; Xie, P.-P.; Zhou, T.; Qian, P.-F.; Zhou, Y.-B.; Li, H.-C.; Hong, X.; Shi, B.-F. Ir(III)-Catalyzed Asymmetric C−H Activation/Annulation of Sulfoximines Assisted by Hydrogen Bonding Interaction. *ACS Catal.* **2022**, *12*, 9083−9091.
(54) Hirata, Y.; Sekine, D.; Kato, Y.; Lin, L.; Kojima, M.; Yoshino, T.; Matsunaga, S. Cobalt(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective Synthesis of Benzothiadiazine-1-oxides via C-H Activation. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202205341.
(55) Liu, L.; Liu, Y.-H.; Shi, B.-F. Synthesis of Amino Acids and Peptides with Bulky Side Chains via Ligand-Enabled Carboxylate-Directed γ-C(sp^3)−H Arylation. *Chem. Sci.* **2020**, *11*, 290−294.
(56) Satake, S.; Kurihara, T.; Nishikawa, K.; Mochizuki, T.; Hatano, M.; Ishihara, K.; Yoshino, T.; Matsunaga, S. Pentamethylcyclopentadienyl rhodium(III)-chiral disulfonate hybrid catalysis for enantioselective C-H bond functionalization. *Nat. Catal.* **2018**, *1*, 585−591.
(57) Pesciaioli, F.; Dhawa, U.; Oliveira, J. C. A.; Yin, R.; John, M.; Ackermann, L. Enantioselective Cobalt(III)-Catalyzed C-H Activation Enabled by Chiral Carboxylic Acid Cooperation. *Angew. Chem., Int. Ed.* **2018**, *57*, 15425−15429.
(58) Kurihara, T.; Kojima, M.; Yoshino, T.; Matsunaga, S. Cp*Co^{III}/Chiral Carboxylic Acid-Catalyzed Enantioselective 1,4-Addition Reactions of Indoles to Maleimides. *Asian J. Org. Chem.* **2020**, *9*, 368−371.
(59) Maity, S.; Kancherla, R.; Dhawa, U.; Hoque, E.; Pimparkar, S.; Maiti, D. Switch to Allylic Selectivity in Cobalt-Catalyzed Dehydrogenative Heck Reactions with Unbiased Aliphatic Olefins. *ACS Catal.* **2016**, *6*, 5493−5499.
(60) Lukasevics, L.; Cizikovs, A.; Grigorjeva, L. C−H Bond Functionalization by High-Valent Cobalt Catalysis: Current Progress, Challenges and Future Perspectives. *Chem. Commun.* **2021**, *57*, 10827−10841.
(61) Bauer, E. B. Chiral-at-metal complexes and their catalytic applications in organic synthesis. *Chem. Soc. Rev.* **2012**, *41*, 3153−3167.
(62) Steinlandt, P. S.; Zhang, L.; Meggers, E. Metal Stereogenicity in Asymmetric Transition Metal Catalysis. *Chem. Rev.* **2023**, *123*, 4764−4794.
(63) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. Synthesis of Optically Active Bis(2-Oxazolines): Crystal Structure of a 1,2-Bis(2-Oxazolinyl) Benzene $ZnCl_2$ Complex. *Chem. Ber.* **1991**, *124*, 1173−1180.
(64) Das, A.; Mandal, R.; Ravi Sankar, H. S.; Kumaran, S.; Premkumar, J. R.; Borah, D.; Sundararaju, B. Reversal of Regioselectivity in Asymmetric C−H Bond Annulation with Bromoalkynes under Cobalt Catalysis. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202315005.
(65) Li, T.; Zhang, Y.; Du, C.; Yang, D.; Song, M.-P.; Niu, J.-L. Simultaneous construction of inherent and axial chirality by cobalt-

https://doi.org/10.1021/acs.accounts.5c00013
Acc. Chem. Res. 2025, 58, 971−990

catalyzed enantioselective C-H activation of calix[4]arenes. *Nat. Commun.* **2024**, *15*, 7673.
(66) Si, X.-J.; Yang, D.-D.; Sun, M.-C.; Wei, D.; Song, M.-P.; Niu, J.-L. Atroposelective isoquinolinone synthesis through cobalt-catalysed C−H activation and annulation. *Nat. Synth.* **2022**, *1*, 709−718.
(67) Si, X.-J.; Zhao, X.; Wang, J.; Wang, X.; Zhang, Y.; Yang, D.; Song, M.-P.; Niu, J.-L. Cobalt-catalyzed enantioselective C−H/N−H annulation of aryl sulfonamides with allenes or alkynes: facile access to C−N axially chiral sultams. *Chem. Sci.* **2023**, *14*, 7291−7303.
(68) Zhang, Y.; Liu, S.-L.; Li, T.; Xu, M.; Wang, Q.; Yang, D.; Song, M.-P.; Niu, J.-L. N. O-Auxiliary Enabled Cobaltaelectro-Catalyzed Atroposelective C−H Annulation. *ACS Catal.* **2024**, *14*, 1−9.
(69) Li, T.; Shi, L.; Wang, X.; Yang, C.; Yang, D.; Song, M.-P.; Niu, J.-L. Cobalt-catalyzed atroposelective C−H activation/annulation to access N−N axially chiral frameworks. *Nat. Commun.* **2023**, *14*, 5271.
(70) Sun, Y.; Yang, T.; Wang, Q.; Shi, L.; Song, M.-P.; Niu, J.-L. Atroposelective N−N Axes Synthesis via Electrochemical Cobalt Catalysis. *Org. Lett.* **2024**, *26*, 5063−5068.
(71) von Münchow, T.; Dana, S.; Xu, Y.; Yuan, B.; Ackermann, L. Enantioselective electrochemical cobalt-catalyzed aryl C−H activation reactions. *Science* **2023**, *379*, 1036−1042.
(72) Liu, T.; Zhang, W.; Xu, C.; Xu, Z.; Song, D.; Qian, W.; Lu, G.; Zhang, C.-J.; Zhong, W.; Ling, F. Synthesis of P-stereogenic cyclicphosphinic amide via electrochemical enabled cobalt-catalyzed enantioselective C−H annulation. *Green. Chem.* **2023**, *25*, 3606−3614.
(73) Xia, X.; Zheng, C.; Hang, Y.; Guo, J.; Liu, T.; Song, D.; Chen, Z.; Zhong, W.; Ling, F. Electrochemically enabled cobalt catalyzed enantioselective C−H acyloxylation of aryl phosphamide with carboxylic acid. *Green Chem.* **2024**, *26*, 8323−8329.
(74) Lin, Y.; von Münchow, T.; Ackermann, L. Cobaltaelectro-Catalyzed C−H Annulation with Allenes for Atropochiral and P-Stereogenic Compounds: Late-Stage Diversification and Continuous Flow Scale-Up. *ACS Catal.* **2023**, *13*, 9713−9723.
(75) Cai, J.; Li, L.; Wang, C.; Qin, S.; Li, Y.; Liao, S.-Y.; Wang, S.; Gao, H.; Zhou, Z.; Huang, Y.; Yi, W.; Zeng, Z. N−N atropisomer synthesis via electrolyte- and base-free electrochemical cobalt-catalysed C−H annulation. *Green Chem.* **2024**, *26*, 11524−11530.
(76) Das, A.; Kumaran, S.; Ravi Sankar, H. S.; Premkumar, J. R.; Sundararaju, B. A Dual Cobalt-Photoredox Catalytic Approach for Asymmetric Dearomatization of Indoles with Aryl Amides via C−H Activation. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202406195.
(77) Xu, Y.; Lin, Y.; Homölle, S. L.; Oliveira, J. C. A.; Ackermann, L. Enantioselective Cobaltaphotoredox-Catalyzed C−H Activation. *J. Am. Chem. Soc.* **2024**, *146*, 24105−24113.
(78) Chen, D.-F.; Gong, L.-Z. Organo/Transition-Metal Combined Catalysis Rejuvenates Both in Asymmetric Synthesis. *J. Am. Chem. Soc.* **2022**, *144*, 2415−2437.
(79) Tran, V. T.; Nimmagadda, S. K.; Liu, M.; Engle, K. M. Recent applications of chiral phosphoric acids in palladium catalysis. *Org. Biomol. Chem.* **2020**, *18*, 618−637.

https://doi.org/10.1021/acs.accounts.5c00013
Acc. Chem. Res. 2025, 58, 971−990