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Review

Enantioselective annulation reactions through C(sp^2)–H activation with chiral Cp^xM^{III} catalysts

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SUMMARY

Chiral poly(hetero)cyclic compounds are extensively found in numerous bioactive molecules, natural products, and even functional materials. Synthesis of this class of molecules follows tedious classical synthetic procedures in general. Recent advancement of the transition-metal-catalyzed directed C–H bond activation followed by an intra-/intermolecular cyclization reaction provides an upfront approach to the construction of numerous poly(hetero)cyclic compounds. However, synthesis of chiral annulated products remains challenging. In general, chiral annulated products are synthesized by a conventional organocatalytic pathway employing suitable chiral ligand systems. Lack of suitable chiral ligands and difficulties in the design and synthesis of appropriate ligands constrain the exploration of the chemistry. Remarkably, recent advances on chiral transition-metal catalysis and chiral ligand-controlled asymmetric C(sp^2)–H bond functionalization chemistry demonstrate a way forward to access chiral annulated products. This review provides an overview of recent advancements in chiral Cp^xM(III)-catalyzed asymmetric annulation reactions, emphasizing the mechanistic understanding of the developed protocols.

INTRODUCTION

Several bioactive molecules, natural products, and functional materials contain different chiral poly(hetero)cyclic cores.[1–5] Representative examples of potent and biologically active poly(hetero)cyclic compounds are shown in Figure 1. Widespread pertinence of polycyclic compounds impelled the synthetic community to invest much effort in synthesizing polycyclic compounds. The journey started by following the classical organic synthetic pathway.[6] However, tedious synthetic procedures, mainly multistep synthesis, followed by laborious purification procedures limited the efficacy of the protocols and thus gradually constrained the exploration of the chemistry. Since the pioneering report of Murai's group in 1993,[7] transition-metal-catalyzed directed C–H bond functionalization chemistry has experienced a stupendous growth, emerging as an effective alternative in numerous organic transformations owing to its intrinsic step-economic and environmentally benign nature. Moreover, this approach provides a straightforward protocol as an alternative to the classical multistep synthetic procedures (see Scheme 14). In particular, direct C–H bond functionalization chemistry introduces a new direction in drug design and drug discovery engaging single-step C–H bond functionalization with varied functionalities at previously inaccessible carbon centers.[8–13] Several natural products, pharmaceutically relevant molecules, agrochemicals, and several complex molecules have been synthesized by elegantly employing this concept.[8,13–15] The success

THE BIGGER PICTURE

Synthesis of chiral poly(hetero)cyclic compounds was first achieved by following tedious classical synthetic routes, mainly multistep synthesis, and also needs suitable chiral ligand systems. Exploration of this strategy has been restricted by the lack of suitable chiral ligands and apparent difficulties in design and synthesis of appropriate ligand systems. Arguably, a transition-metal-catalyzed C–H functionalization strategy provides a forthright protocol as an alternative to classical multistep synthetic procedures and offers a candid approach to construction of numerous poly(hetero)cyclic compounds by regioselective C–H bond activation followed by an intra-/intermolecular cyclization reaction. Importantly, recent developments in chiral transition-metal catalysis and chiral ligand-controlled methods provide a way forward to access enantioenriched poly(hetero)cyclic compounds by selectively controlling the stereochemical environments during the annulation process.

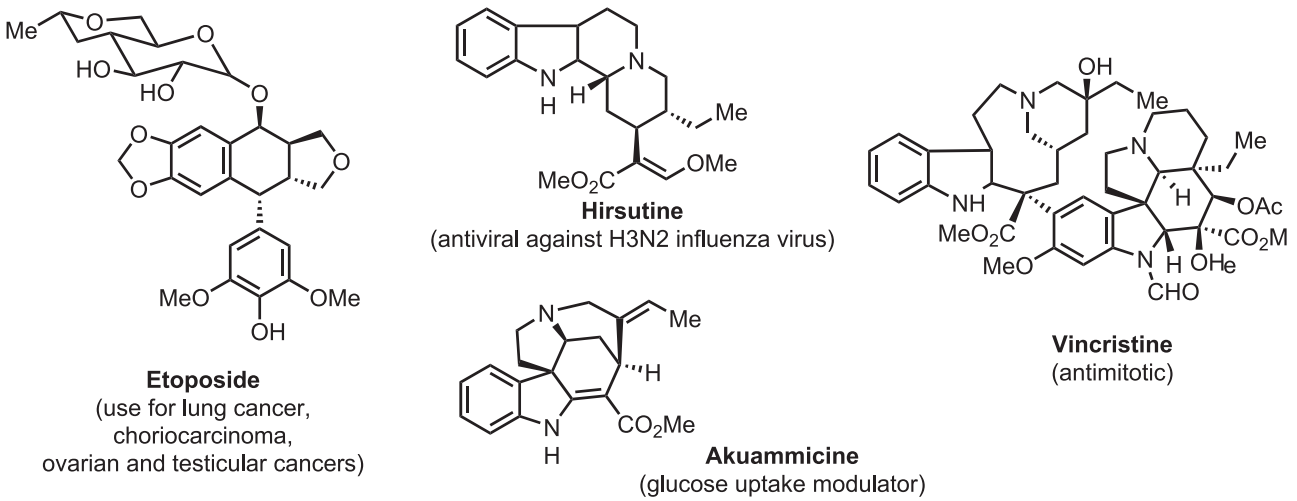

Figure 1. Biologically active poly(hetero)cyclic compounds

of this strategy invigorated the synthetic community to explore the possibility of synthesis of poly(hetero)cyclic compounds. Transition-metal-catalyzed regioselective C–H bond activation followed by intra-/intermolecular annulation reaction provides an upfront approach to construction of numerous poly(hetero)cyclic compounds.

The practicality of C–H bond functionalization strategies has been realized upon successful introduction of chirality in skilful manner to an organic molecule by precise synthetic manipulation of a C–H bond in a stereo-controlled approach. However, certain challenges of direct C–H activation should not be neglected. Achieving regioselective C–H functionalization of aromatic or aliphatic compounds bearing similar electronic and steric properties of C–H bonds is an ultimate challenge. Besides this, a suitable ligand system is highly desirable for a successful C–H activation reaction. In general, C–H functionalization chemistry requires a high-temperature protocol, in contrast to the strategy for asymmetric synthesis. Conformational rigidity of the catalyst system or transition state is necessary to afford excellent stereoselectivity, and this is possible generally at very low temperature. Nonetheless, generous efforts of the synthetic community have helped to develop potential techniques, e.g., chiral transition-metal catalysis, chiral ligands controlled methods, and enzymatic protocols, for enantioselective C–H bond functionalization.[16] Despite the immense progress of the annulation reaction, synthesis of chiral annulated products remains challenging.[3,5] In general, chiral annulated products are synthesized by a conventional organocatalytic pathway or by employing a metal catalyst with the assistance of chiral ligand.[5,17] However, recent developments of asymmetric C–H bond functionalization strategies illustrate a way forward to afford chiral annulated products. Suitable chiral ligands have been utilized mostly in the synthesis of chiral annulated products with the assistance of transition-metal catalysts.[18–23] However, the major challenges lie in the design and synthesis of various suitable chiral ligand systems. The lack of suitable chiral ligands eventually hinders the development of efficient protocols. Besides, chiral metal catalysts have been found to be an efficient system for controlling the stereochemical environments selectively during the annulation process, leading to the achievement of excellent enantioselectivity. Of several developed ligand systems, cyclopentadienyl (Cp) anion was found to be an appropriate ligand system for the synthesis of chiral metal catalysts owing to its high stability in wide temperature ranges and ease of electronic modulation by substituting the Cp ring (vide infra). The chemistry of chiral metal catalysts in the synthesis of

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chiral annulated products has been reviewed intermittently with regard to asymmetric C–H bond functionalization chemistry.[16,17,24,25] Considering the importance of the chemistry, we intended to highlight the notable advances of the chiral $Cp^xM(III)$ catalysts in asymmetric annulation reactions developed thus far since 2012. In this review, we focus on providing a detailed overview of the chemistry with emphasis on mechanistic considerations.

DESIGNING PRINCIPLE OF CHIRAL CP LIGANDS

A ligand enables activation of inert C–H bonds with the assistance of transition-metal catalysts.[26,27] A suitable ligand helps to reduce the activation barrier of an inert C–H bond by lowering the transition-state energy.[28–30] A chiral metal catalyst, a blend of suitable metal and chiral ligands, can activate the inert C–H bond in a stereo-controlled manner, leading to asymmetrically functionalized products. Representative valuable ligand scaffolds that enable a wide variety of enantioselective transformations include BINOL,[31] BINAP,[32] tartaric acid-derived TADDOLs,[33] and chiral SALEN derivatives.[34] Since the discovery of ferrocene,[35] Cp has been widely used as an ancillary ligand for a range of metals. Cp, bearing 6π electrons, is a very good σ- and π-donor and in general binds to the metal in η5 mode, thus providing remarkable stability of the metal complexes (CpM). This feature helps to sustain the metal complexes in a chemical transformation while the reaction occurs at the metal center without affecting the ligand moiety, unlike other ligands (e.g., indenyls) where η3 coordinations are more favored.[36] Considering the application in catalysis, stereoelectronic properties of the metal center could be modulated by varying the substitution on the Cp moiety whenever required. Moreover, suitable substitution on the Cp ring could restrict facile rotation around the Cp-metal axis, providing conformational rigidity to the metal complex and thus making it appropriate for asymmetric catalysis. The Cp ligand and pentamethyl substituted derivative (Cp*) have fascinated the synthetic community through utilization of their metal complex in various catalytic transformations.

Despite noteworthy efficacy of Cp-based metal complexes as catalyst in numerous organic transformations,[37–40] their utilization in asymmetric synthesis has been mostly avoided, seemingly due to the intrinsic difficulties in the design and synthesis of appropriate chiral Cp ligand systems.[41] In principle, Cp complexes could be utilized in enantioselective transformations in three different ways (Figure 2A): (1) coordination of external chiral ligand to the achiral CpM complex (**A**); (2) tethering an additional ligand side to the Cp ring (**B**); and (3) employing a chiral Cp ligand (**C**). Each of these furnishes different and complementary reaction classes owing to the different number of free coordination sites on the metal center. Many complexes of type A and type B have been successfully implemented in various catalytic asymmetric transformations.[42–45] However, there are various catalytic transformations that require more coordination sites on the metal center, which are fulfilled by type C. Because of somewhat limited applicability of type A and type B complexes, the synthetic community has paid limited attention to their further development. In 1990, Erker and van der Zeijden first reported the type C complex, (+)-camphor derived $ZrCp^x$-complex (**D**), and its application.[46] Similarly, in 2004, Heller's group demonstrated (−)-menthol-derived $CoCp^x$ complex (**E**).[47] Despite facile synthesis of these two complexes, their application was impeded because of the severely restricted alteration of ligand backbone by the chiral pool approach, thus hindering optimization of the catalyst structure.

In 2012, Ye and Cramer[48] introduced the Cp^x ligand system for the asymmetric C–H bond functionalization reaction (Figure 2B). They strategically developed the

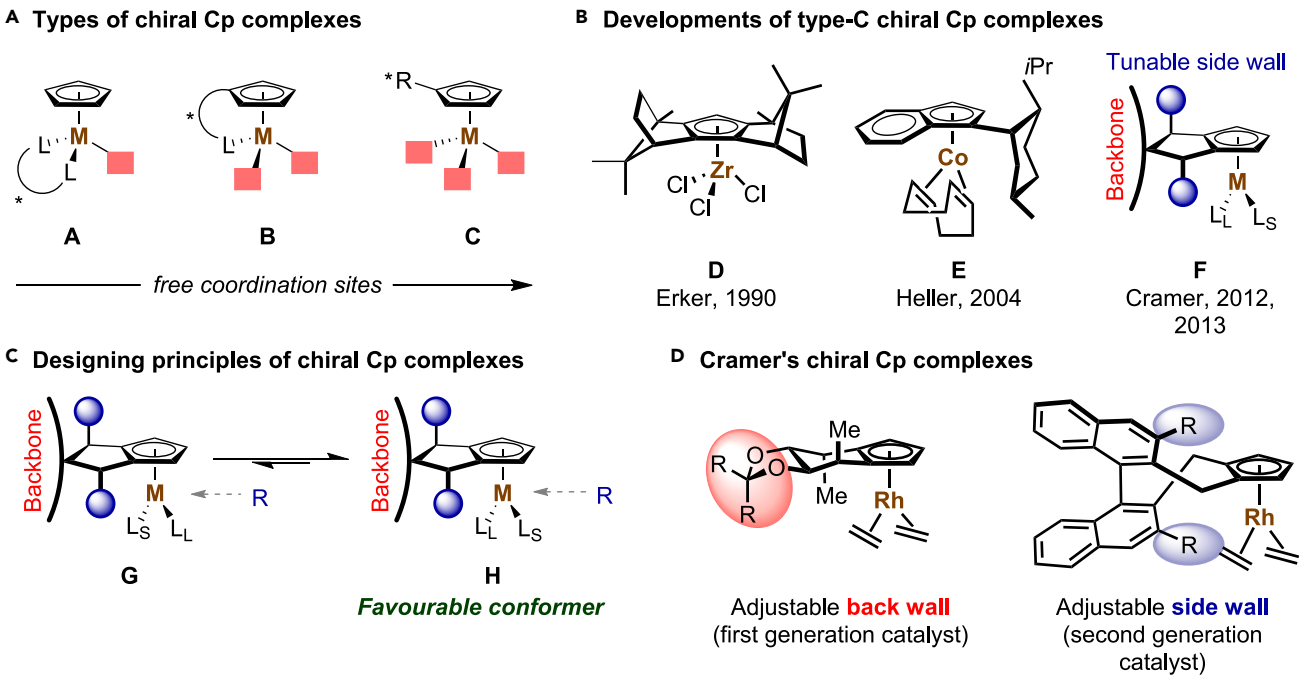


Figure 2. Chiral Cp ligands

(A) Types of chiral complexes.

(B) Developments of type C chiral complexes.

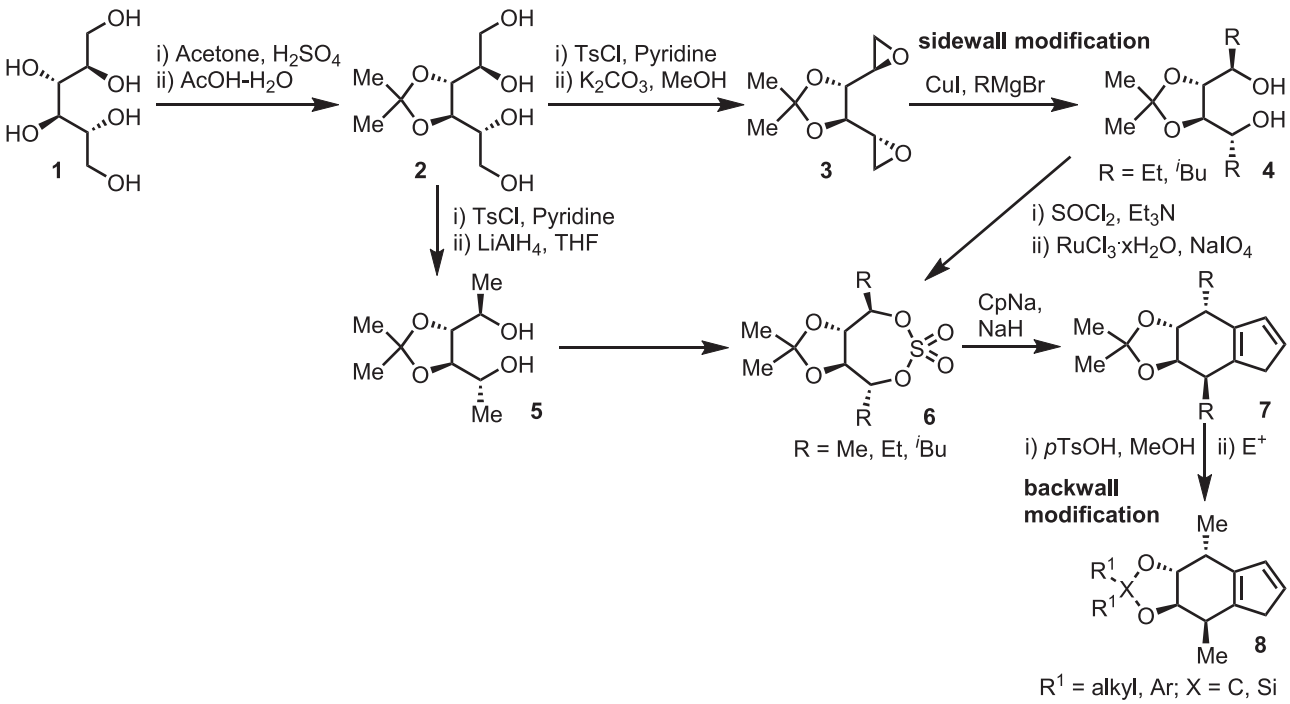
(C) Design principles of chiral Cp complex.

(D) Cramer's first- and second-generation catalyst.

Cp^x ligand system in such a way that the facial selectivity of the ligand imposed by the chiral space originated in the enantiopure Cp congener, which could be utilized as a key parameter in determining the stereoselectivity. They came up with the idea of synthesis of 1,2-disubstituted Cp ligand, which indulges two possible orientations of the small and large substrates parallel to the positional locks while the bulky backbone dictates the pathway of the incoming reactant R from the unsubstituted side of Cp congener (structures **G** and **H**, Figure 2C). The preferential approach of the incoming reactant from the less sterically crowded side, dictated by C2-symmetric chiral space, leads to a single diastereomer. The first-generation catalyst (Figure 2D) transferred ligand chirality to chirality at the metal center utilizing the combined effect of the adjusted back wall and defined side wall. The low selectivity of the first-generation catalyst in the C–H allylation reaction[48] encouraged them to develop additional ligand systems. In 2013, they designed and synthesized tunable chiral Cp ligands with C2-symmetric axial-chiral biaryl moiety (second-generation catalyst, Figure 2D). The lower naphthyl portion turns as back wall and dictates the incoming reactant's approach from the unsubstituted face, and the substituents at *ortho* position strongly influence the selectivity by inflecting the chiral pocket. Importantly, the second-generation catalysts bear an axially chiral binaphthyl backbone synthesized from BINOL and thus provide an ample opportunity for the generation of a series of catalyst backbones by substituting at different positions. In the following sections, we discuss several chiral catalysts (Cp^xM catalysts) and their employment in various asymmetric annulation reactions via selective C(sp^2)–H bond activation.

SYNTHESIS OF Cp^xH LIGAND SYSTEMS

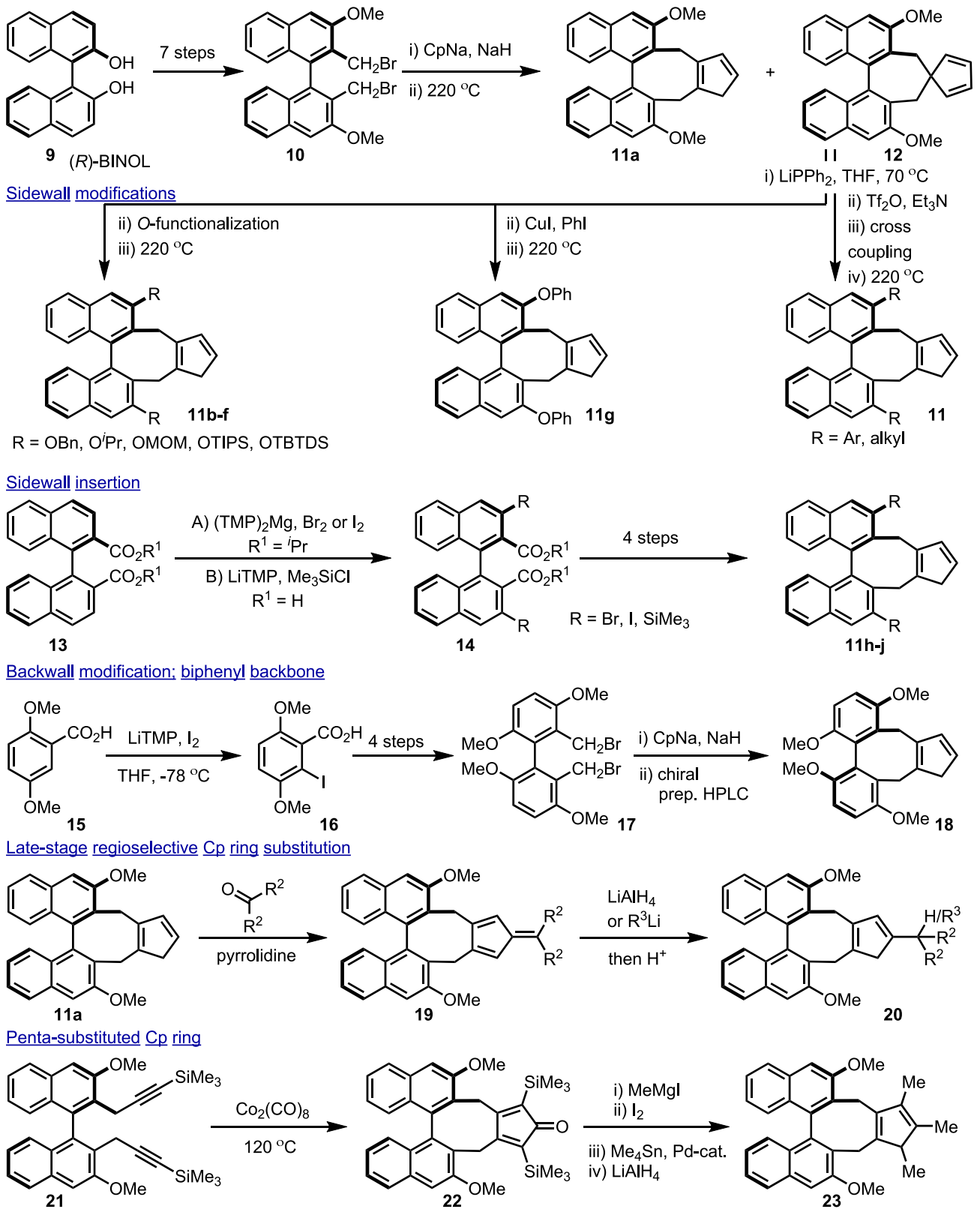
Over the last decade, several different classes of chiral Cp ligand systems have been developed.[49] Here we discuss synthetic procedures based on their structural



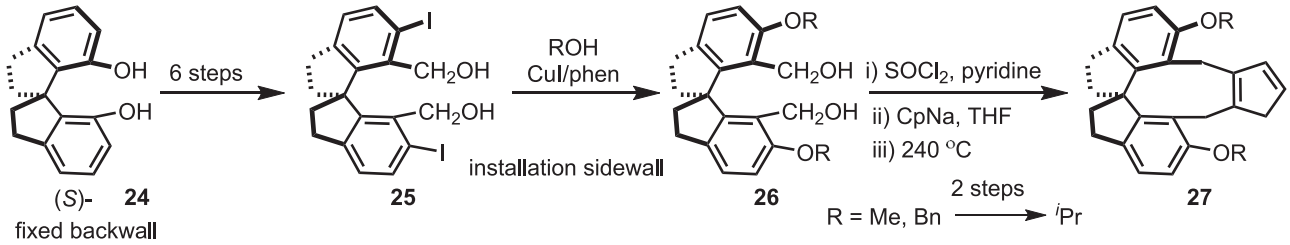
Scheme 1. Cramer's first-generation Cp^{x}H ligand systems: D-mannitol-derived cyclopentadiene synthesis

footprint. Cramer's first-generation ligand system was developed on the basis of D-mannitol (Scheme 1).[50,51] Synthesis of the ligands start from the natural D-mannitol and involve eight to nine steps to afford the desired ligand systems. The common intermediate cyclic sulfate **6** can be accessed by following two different alternative routes, one of which offers diverse alkyl substituted (R, side wall) derivatives, which basically provides the scope for a library of ligand systems. Treatment of the common intermediate **6** with sodium cyclopentadienide afforded **7** bearing an acetonide-derived back wall. Furthermore, sterically different ketals and silylethers as ligand back wall were synthesized in a two-step sequence from acetonide back-wall moiety to first ketal cleavage and then diol functionalization.

Cramer's second-generation ligand **Rh7** (vide infra) is arguably the most employed member from the BINOL-Cp family. Synthesis of this class of ligands starts from the easily accessible *R*- or *S*-enantiomeric form of 1,1′-bis(2-naphthol) **BINOL** (Scheme 2). Dibromide derivative **10** bearing *ortho*-methoxy substituents was synthesized from BINOL by a seven-step linear synthetic protocol.[52] Dialkylation of **10** with sodium cyclopentadiene afforded 1,2 disubstituted cyclopentadiene **11a** and spirocyclic diene **12** in 2:1 mixture.[48] This mixture could easily be separated by trituration in ethylacetate. **12** could be subjected to side-wall modification in a three-step sequence of demethylation and *O*-functionalization followed by thermal rearrangement to afford **11b–11f**. The phenyl ether derivative **11g** was synthesized by copper-catalyzed Ullmann coupling with iodobenzene and subsequent thermal rearrangement of spirocyclic diene. On the other hand, *ortho*-ether linkage was switched to C–C bond through cross-coupling reactions of the bis(triflate) derivative in four steps overall.[53] Additionally, the halide or silyl group substituted cyclopentadienes **11h–11j** were synthesized recently via *ortho*-metalation/electrophilic quenching of diester **13**.[54] Overall, a library of cyclopentadiene ligands is achievable with stereoelectronic modulations at the side wall. The authors disclosed the



Scheme 2. Cramer's second-generation atrop-chiral biaryl Cp*H ligand synthesis



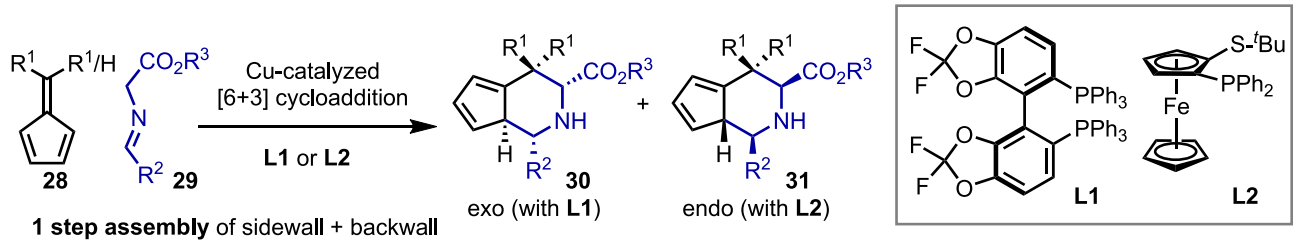
Scheme 3. Synthesis of You's SPINOL-derived chiral SCpH ligand systems

naphthyl back-wall modification by a simple atropochiral biphenyl backbone. A mixture of *R*- and *S*-enantiomers of cyclopentadiene **18** was synthesized from achiral carboxylic acid **15** in six steps. Finally, both of the isomers were separated by preparative chiral high-performance liquid chromatography (HPLC). Furthermore, bulkier Cp ligands were prepared by substituting the Cp ring. Condensation of **11a** with ketone led to formation of fulvenes **19**, after which subsequent hydride or organolithium addition to the double bond led to the formation of trisubstituted Cp analogs.[55] Recently, You and co-workers demonstrated the synthesis of penta-substituted Cp analogs.[56] Cobalt-promoted carbonylative cyclization of dialkynes, followed by multistep alteration of resulting dienone intermediates **22**, led to the formation of penta-substituted Cp analogs.

In 2016, You and co-workers reported a different class of chiral Cp ligands, synthesized from a fixed 1,1-spirobiindane skeleton in ten steps (Scheme 3).[57] Synthesis of this class of ligands is strategically similar to Cramer's second-generation ligands from BINOL. Chirally pure SPINOL **24** was converted into the diaryl iodide in six linear steps. The Ullmann coupling step, the key step for this synthetic sequence, aids the insertion of sterically different alkoxy substituents at the *ortho* position of the ligand side wall. The remaining synthetic steps are similar to previous ones: dehalogenation, dialkylation with sodium cyclopentadiene, and thermal rearrangement of spirocyclic diene.

The ligands discussed above were synthesized on the basis of a chiral pool strategy, starting from an optically pure molecule and then being subjected to series of functional group alterations. Synthesis of these ligand systems follows quite complex procedures, which are time consuming and sometimes require expensive chiral starting materials. In this regard, conceptual advances of various chiral catalysts are arguably high primacies to broaden the scope of this chemistry. Synthesis of chiral ligands by asymmetric catalysis from achiral simple building blocks is one an attractive approach. In 2017, Waldmann and co-workers demonstrated a forthright method to access a library of novel class of rhodium complexes with chiral Cp ligands fused with a nitrogen-containing six-membered ring (Scheme 4).[58] Cu-catalyzed enantioselective [6 + 3] cycloadditions of imino esters with fulvenes lead to the formation of chiral ligands (**30** and **31**). This is a key step in constructing chiral ligands and also provides plenty of scope to vary and tune the core structure. Varying the chiral phosphine ligands (**L1** or **L2**) exo- and endo-products, respectively was achieved with excellent diastereoselectivity. Even synthesis of racemate analogs followed by chiral preparative HPLC might be more convenient for synthesis of a library of ligands. The authors also demonstrated in the same way their synthesis of the most employed catalyst system of this class.

In 2018, Cramer and co-workers developed a two-step synthetic protocol for the synthesis of cyclopentane-fused diaryl ligands starting from achiral



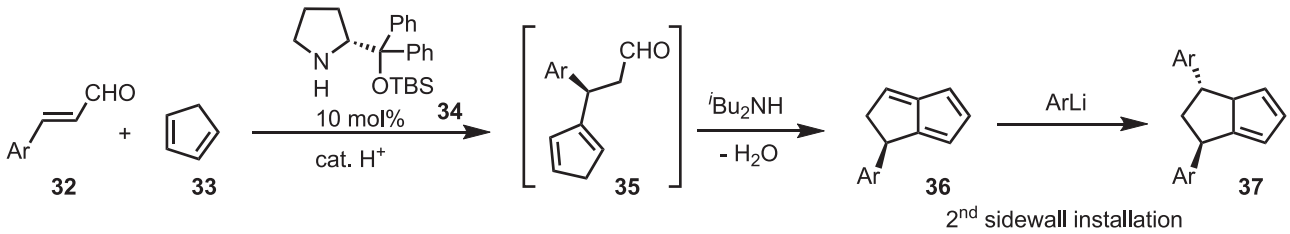
Scheme 4. Synthesis of Waldmann's JasCpH ligand systems

cinnamaldehydes and CpH (Scheme 5).[59] In the first step, enantioselective tandem organocatalyzed ene-type reaction and subsequent intramolecular condensation of transient intermediate **35** led to the formation of chiral cyclopentane-fused fulvenes **36**. Addition of aryl lithium to the fulvenes then afforded C2-symmetric cyclopentadiene ligands **37** as single diastereoisomers with enantio purity. Without any further optical purification, these ligands can be used in catalysis.

In 2020, Wang and co-workers developed a new class of C_2-symmetric chiral Cp ligands based on a chiral ferrocene backbone (Scheme 6).[60] The chiral ligands were synthesized using simple ferrocene as a starting building block in six to eight steps. Chiral ferrocenyl diamine **39** was synthesized in two-step dilithiation-formylation and subsequent reductive amination with (*S*)-2-(methoxymethyl)pyrrolidine **A**. Highly diastereoselective difunctionalized products **40** were yielded upon lithiation with S-BuLi and subsequent quenching with electrophiles. This particular step provides an opportunity to synthesize a library of ligand systems. Ferrocenyl moieties with ethereal substituents were synthesized from a corresponding iodo derivative by Cu-mediated hydroxylation followed by *O*-functionalization **41**. Planar chiral 1,1′,2,2′-tetrasubstituted ferrocenes **40** and **41** were then attached to cyclopentyl moiety by following the regular procedures. Finally, thermal rearrangement of spirocyclic moieties afforded the desired planar chiral Cp ligands **44**. Advantageously, this protocol provides pure single diastereomers and can be used as such in catalysis.

Soon after, the same group reported the use of another class of C2-symmetric chiral bridge-ring-fused CpH ligands in asymmetric catalysis (Scheme 7).[61] These ligands were primarily reported by Halterman and Vollhardt in 1988.[50,51] 1,4-Dialkyl benzene derivatives were used to synthesize this class of ligands. Birch reduction and subsequent asymmetric hydroboration-oxidation reaction with chiral reducing agent, monoisopinocampheylborane ($IpcBH_2$), afforded C_2-symmetric chiral *cis*-cyclohexane-1,4-diols **47**. Annulated cyclopentadienes **48a** and **48b** were obtained upon mesylation of **47**, and subsequent reaction with CpNa in the presence of sodium hydride. A limitation of this protocol is the lack of opportunity for late-stage modification of the side wall.

Besides the development of ligand families, suitable complexation methods are required to obtain the pre-catalyst, given the tolerability and stability of different functionalities present in the ligand systems. In general, two different methods are widely employed for metalation: (1) ligand transmetalation and (2) direct metalation.[48,62,63] The first method relies on the deprotonation of Cp^xH by organolithium or thallium salt and subsequent metal substitution with an appropriate halogenated/olefin complex. A complex of base metals was naturally achieved by LiCpx or direct reaction with Cp^xH followed by oxidation.

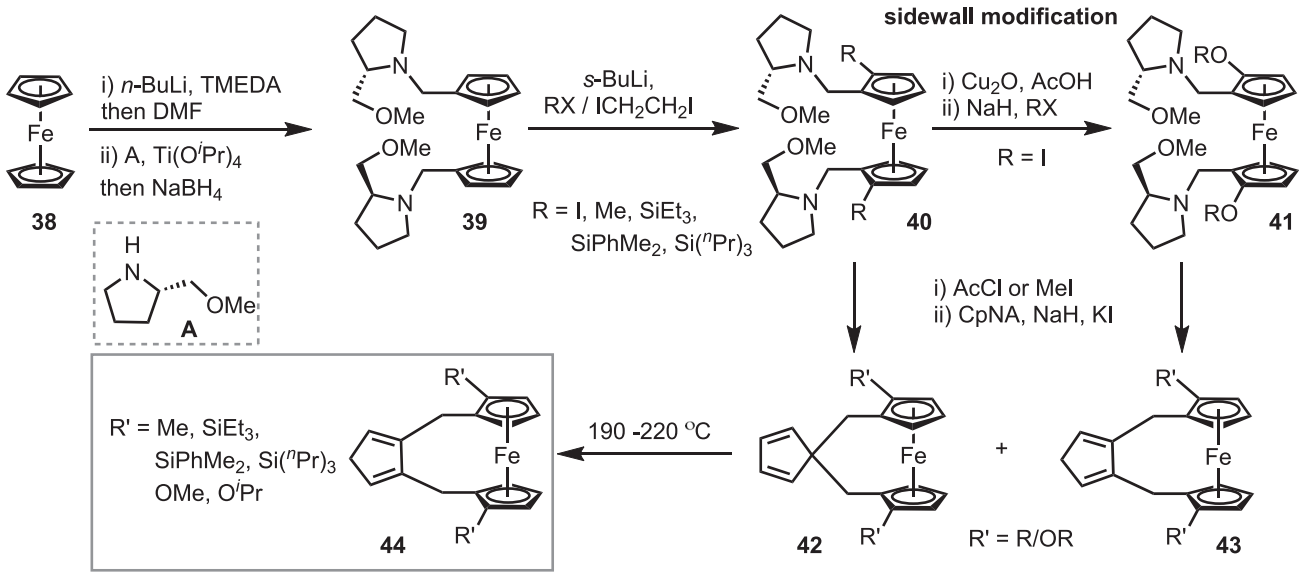


Scheme 5. Synthesis of Cramer's cyclopentane-fused chiral dienes

APPLICATIONS IN ASYMMETRIC ANNULATION REACTIONS

Chiral transition-metal-catalyzed inter-/intramolecular annulation

In 2012, Cramer's group synthesized a series of diversely substituted Cp^{x}Rh(I) complexes[62] and utilized them to check the viability of the hypothesis in the well-developed annulation reactions of hydroxamic acid derivatives with olefins through C–H activation (Scheme 8A).[64,65] It was found that the steric factors near the Cp ring and at the pseudo-axial position, which basically provides the steric bulk near the metal center, plays a crucial role in achieving very good enantioselectivity. Catalyst **Rh2** bearing steric bulk near the Cp ring delivered the annulated product with modest selectivity (27:73 enantiomeric ratio [er]). Catalyst **Rh1** bearing benzophenone acetal moiety turned out to be optimal, delivering the annulated products in excellent yields and selectivities (up to 91%, 97:3 er). **Rh3**, bearing relatively less steric bulk (i.e., Me group) at benzophenone acetal moiety, could not provide sufficient steric bulk to the metal center by pushing the moiety into the pseudo-axial position and failed to be the best catalyst system (92:8 er). Besides the conformational effect, the bulky acetal group of **Rh1** helped to hinder the backside approach of the olefin. Various olefins were found to be competent reaction partners with aryl hydroxamates. Different steric and electronic disparities of coupling partners were having very little impact on yield and selectivity. A plausible mechanistic pathway of the reaction is shown in Scheme 8A. Coordination of the Cp^{x}Rh catalyst leads to the formation of intermediate **53**, which then follows the carboxylate-assisted concerted metalation-deprotonation (CMD) pathway, leading to the formation of C–H activated rhodacycle **54**. The steric environment of the catalyst helps to provide the preferred conformation of the intermediate **54**, which then dictates the olefin coordination diastereoselectively. Enantiodetermining the migratory insertion of olefins to the stereogenic metal center (complex **55**) then yields rhodacycle **56**, which subsequently undergoes reductive elimination and delivers dihydroisoquinolones **52**. Steric bulk of the catalyst and *N*-substitutions of hydroxamates control the regioselective insertion of olefins. At the same time, Rovis's group independently reported a [4 + 2] annulation reaction of hydroxamic acid derivatives with acrylates utilizing SavCp metalloenzyme **Rh4** as catalyst (Scheme 8B).[66] These two reports highlight the importance of Cp-based chiral ligands in asymmetric C–H functionalization chemistry. Inspired by these works, Waldmann and co-workers reported a straightforward method to access a library of a new class of rhodium complexes with chiral fused Cp ligands, JasCp.[58] To explore the potential of the catalyst, they tested the catalyst's performance in the well-established annulation reaction with hydroxamates and olefins (Scheme 8C). The immensely functionalized ligand **Rh5** provided the desired annulated products in good to excellent yields and enantioselectivities. Importantly, cyclic internal olefins were also found to be competent coupling partners under catalysis conditions. The bulkiness of the substituents on the ligand helps to develop a chiral pocket around the Rh center, which accommodates the hydroxamates in a sterically feasible fashion by positioning the Boc on

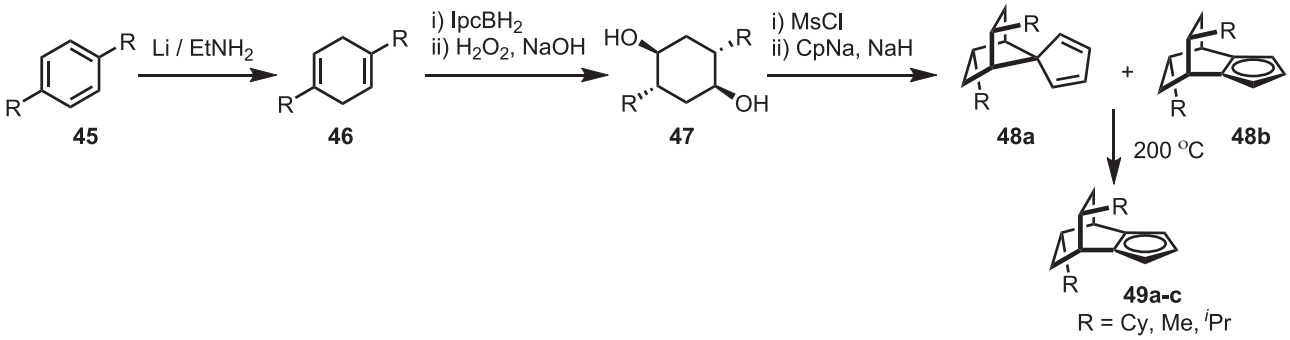


Scheme 6. Synthesis of Wang's ferrocene-based chiral cyclopentadienyl ligands

the less hindered side. Incoming olefins coordinate with the rhodacycle intermediate from the open face of the ligand to avoid unfavorable steric interactions.

In 2018, Perekalin's group developed planar chiral rhodium catalyst $[(C_5H_2{}^tBu_2CH_2{}^tBu)RhI_2]_2$ (**Rh6**) in a very affordable synthetic pathway from commercially available $[(cod)RhCl]_2$ and *tert*-butylacetylene in two steps. They screened their catalyst system in the enantioselective annulation reaction for the synthesis of dihydroisoquinolones from aryl hydroxamic acids and olefins (Scheme 8D).[67] A varied range of dihydroisoquinolones was synthesized using cyclic olefins with moderate to very good yields and enantioselectivities. Likewise, the origin of enantioselectivity could be comprehended by the less hindered approach of the alkene to the open face of the proposed intermediate metallacycle (**57**) as shown in Scheme 8D.

In a subsequent study, Cramer's group demonstrated the synthesis of dihydrobenzofurans comprising methyl-substituted quaternary stereocenters by intramolecular annulation of hydroxamates affixed with 1,1-disubstituted olefins at *meta* positions with the assistance of the second-generation catalyst **Rh7** (Scheme 9A).[68] Mechanistic understanding of this catalysis could be apprehended by Rh-catalyzed directed *ortho*-C–H bond activation followed by enantioselectivity determining 5-*exo*-trig cyclization, with appended olefin resulting in the annulated product. Presumably the presence of an adjacent coupling partner, appended 1,1-disubstituted olefins, helps to drive the equilibrium of the carboxylate-assisted reversible CMD pathway for the activation of sterically encumbered *ortho*-C–H bond (**60**) over the non-hindered *ortho* position (**61**). In a similar approach, in 2015 the same group extended the scope of alternative π-bond coupling partners, reporting aldehydes attached to the carboxamate moiety through phenolic oxygen instead of 1,1-disubstituted olefins (Scheme 9B).[53] OMOM substituted second-generation catalyst **Rh8** was found to be more suitable for this transformation than OMe substituted catalyst **Rh7**. In 2020, Wang and co-workers reported a novel class of C_2-symmetric Cp^xRh-complex (**Rh9**) centered on planar chiral ferrocene scaffolds.[60] They demonstrated the application of this new class of **Rh9** complexes in Rh(III)-catalyzed intramolecular [4 + 2] annulation of olefin tethered



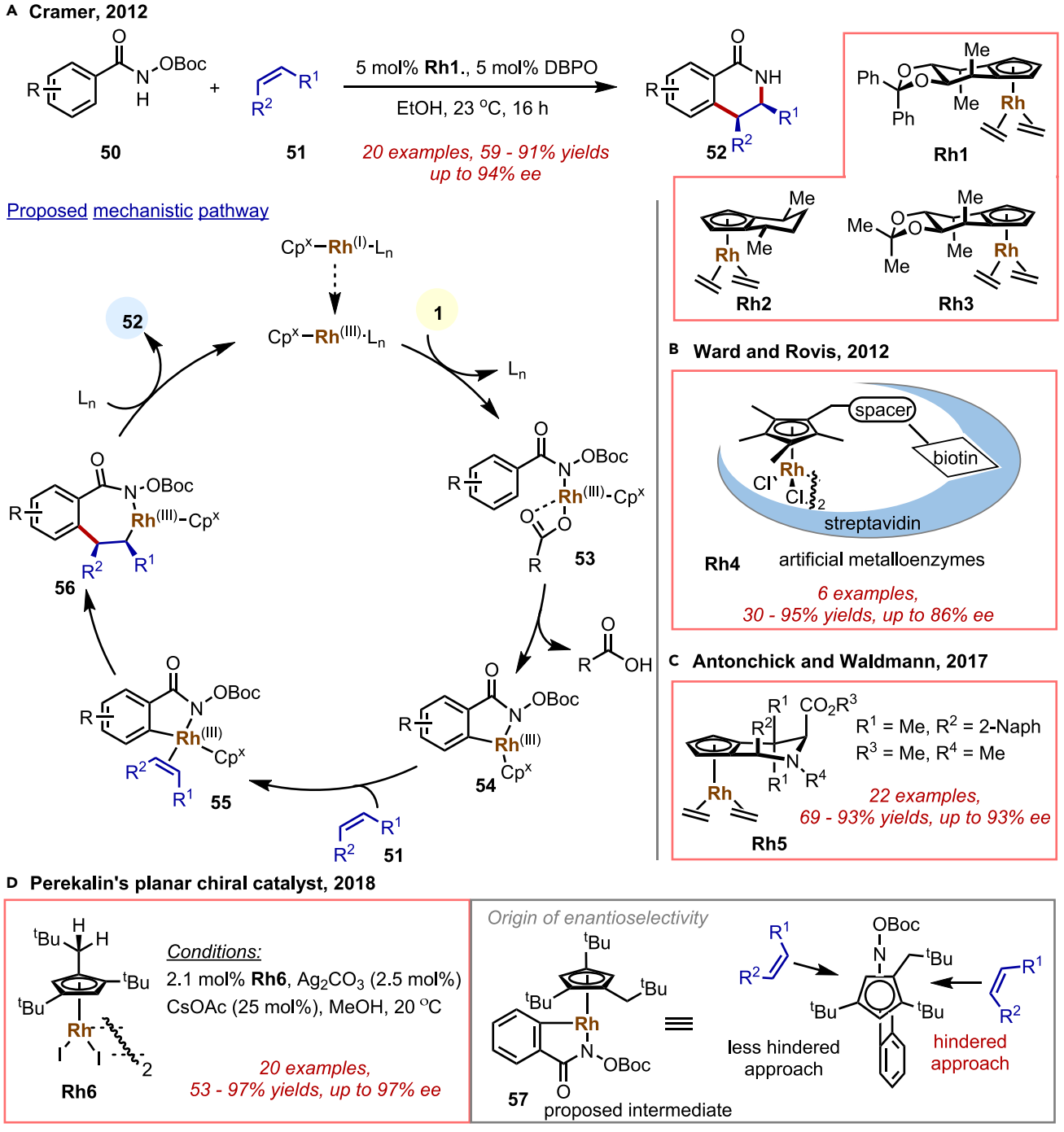
Scheme 7. Synthesis of Wang's chiral bridge-ring-fused CpH ligands

benzamide **65** to dihydroxybenzofurans, with moderate to good enantioselectivity (Scheme 9C).

In 2014, Cramer and co-workers demonstrated a straightforward way to access enantiomerically enrich isoindolones from hydroxamates and diazo derivatives as one-carbon components utilizing geometric and conformational constraints of the catalyst and substrates (Scheme 10A, top).[69] In this particular reaction, suitable substitution at diazo components is highly desirable for the formation of a sterically favorable tetrahedral chiral-at-metal intermediate, which eventually would afford excellent enantiopure isoindolones. A diverse range of isoindolones **70** was synthesized with very good to excellent enantioselectivity using various hydroxamates and diazo esters. Stereochemical models for the isoindolone formation helped to rationalize the origin of enantioselectivity. A large unfavorable steric interaction between hydroxamate and a large ester substituent of diazo ester in the stereochemical model **72** leads to a minor isomer. By contrast, absence of such interaction in the stereochemical model **71** helps to achieve major isomers with excellent enantioselectivity. Later, Song and co-workers extended the scope of this work to indolyl hydroxamates **73** utilizing Cramer's second-generation catalyst **Rh11** (Scheme 10A, bottom).[70]

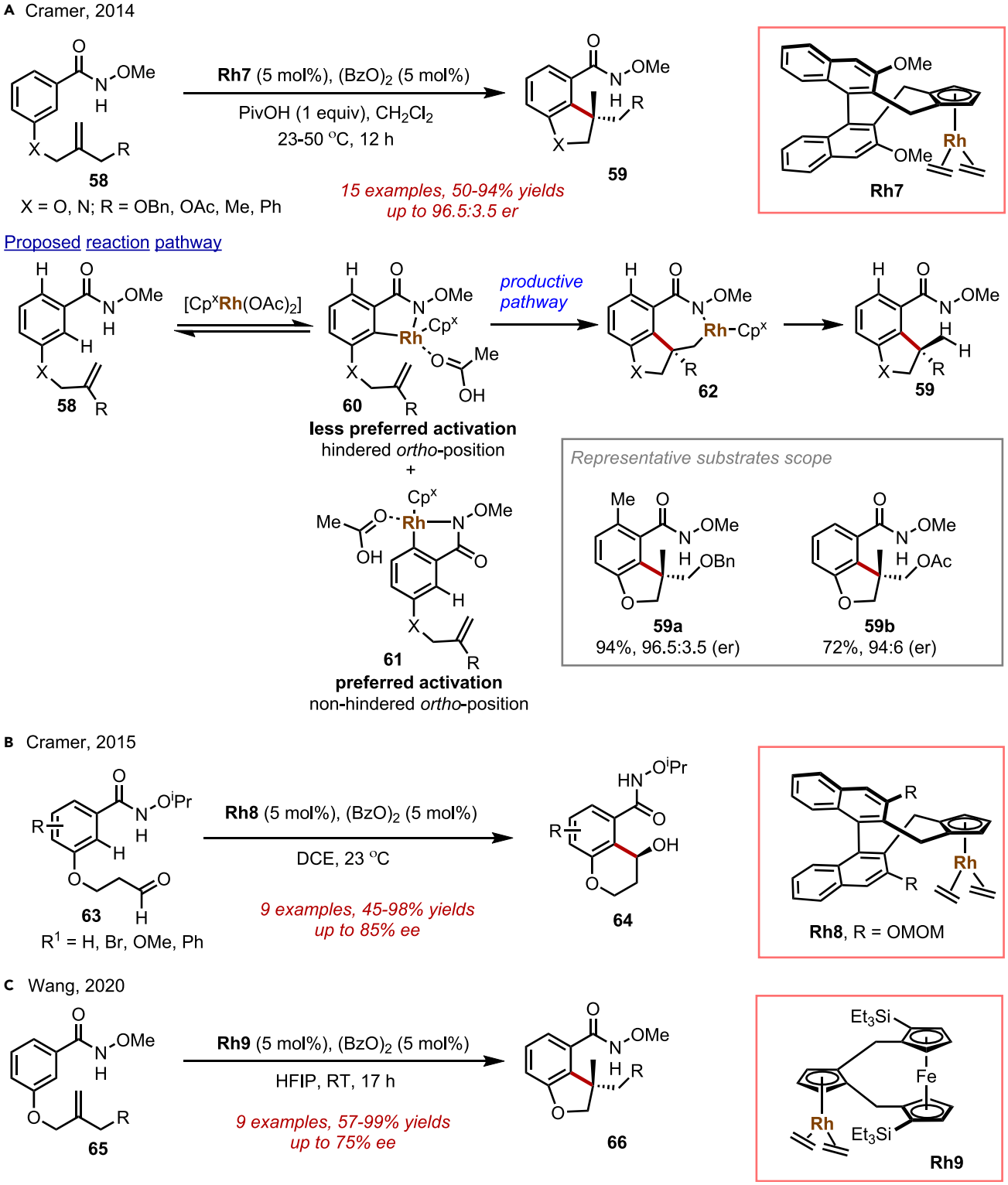
In 2019, Li's group reported Cp^{x}Rh(III)-catalyzed enantioselective oxidative [3 + 2] transannulation of arenes with 7-azabenzonorbornadienes through 2-fold C–H activation (Scheme 10B).[71] The flexible directing group, amides, enables the first C–H activation at the *ortho* position while accommodating the second C–H activation at the *meta* position of arenes with the help of azabenzonorbornadienes, providing enantioenriched [3 + 2] annulated products **77**.

In 2019, Cramer's group demonstrated enantioselective C–H functionalization of acryl amides using their well-established pre-catalyst Cp^{x}Rh(I) complex (Scheme 11A).[72] In general, asymmetric functionalization of alkenyl C–H bonds is relatively not feasible, presumably because of intrinsic reactivity and selectivity issues. However, Cramer and co-workers devised a forthright way to access enantioenriched 2H-pyrrole-2-one derivatives from acryl amides and allenes through C–H bond activation utilizing the Cp^{x}Rh(I) catalyst system. Notably, allene participates as a one-carbon unit in the [4 + 1] annulation reactions, resulting in five-membered heterocycles. Trisubstituted Cp^{x}Rh(III) complex **Rh12** bearing a third substitution at the Cp ring was found to be an effective catalyst for this transformation. Bulkiness and position of the third substituents (^{i}Pr group) on the Cp ring play a crucial role in both catalysis and selectivity. Numerous acryl amides and allenes were assessed to check the viability of the methodology for the synthesis of α,β-unsaturated γ-lactams

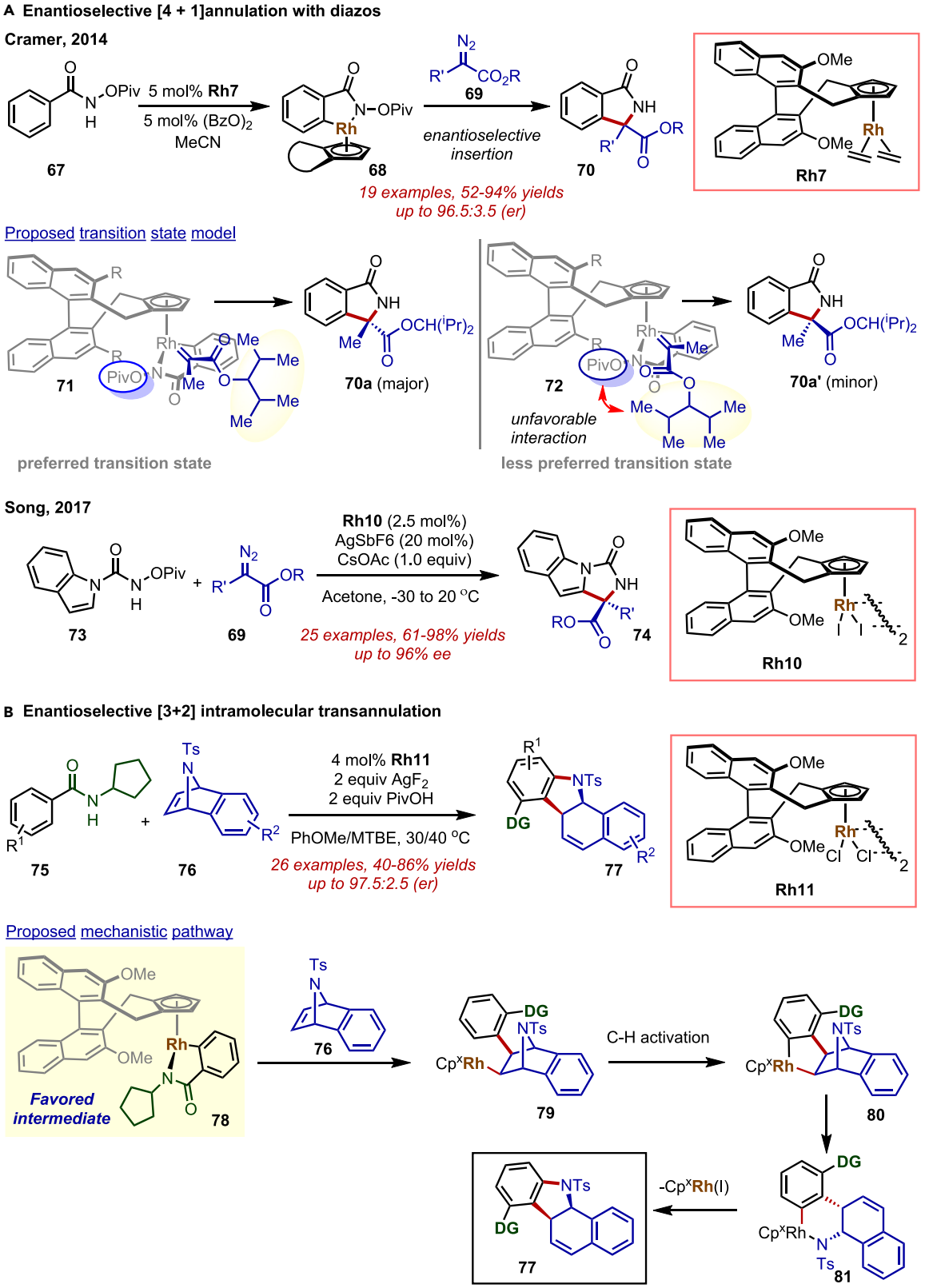


Scheme 8. Chiral Cp^{x}Rh(III)-catalyzed enantioselective annulation of hydroxamic acid derivatives with olefins

bearing a quaternary stereocenter. The reaction was presumed to follow amide-directed C–H bond activation via the carboxylate-assisted CMD pathway, leading to the intermediate rhodacycle **85**. Subsequent coordination and migratory insertion of allene delivers three different interconvertible allyl-rhodium species, which undergo β-H elimination to produce diene **88**. Enantioselective hydride transfer from rhodium to the double bond led to rhodacycle **89**, which subsequently undergoes reductive elimination, affording the lactum **84** and pre-catalyst Cp^{x}Rh(I) species. In



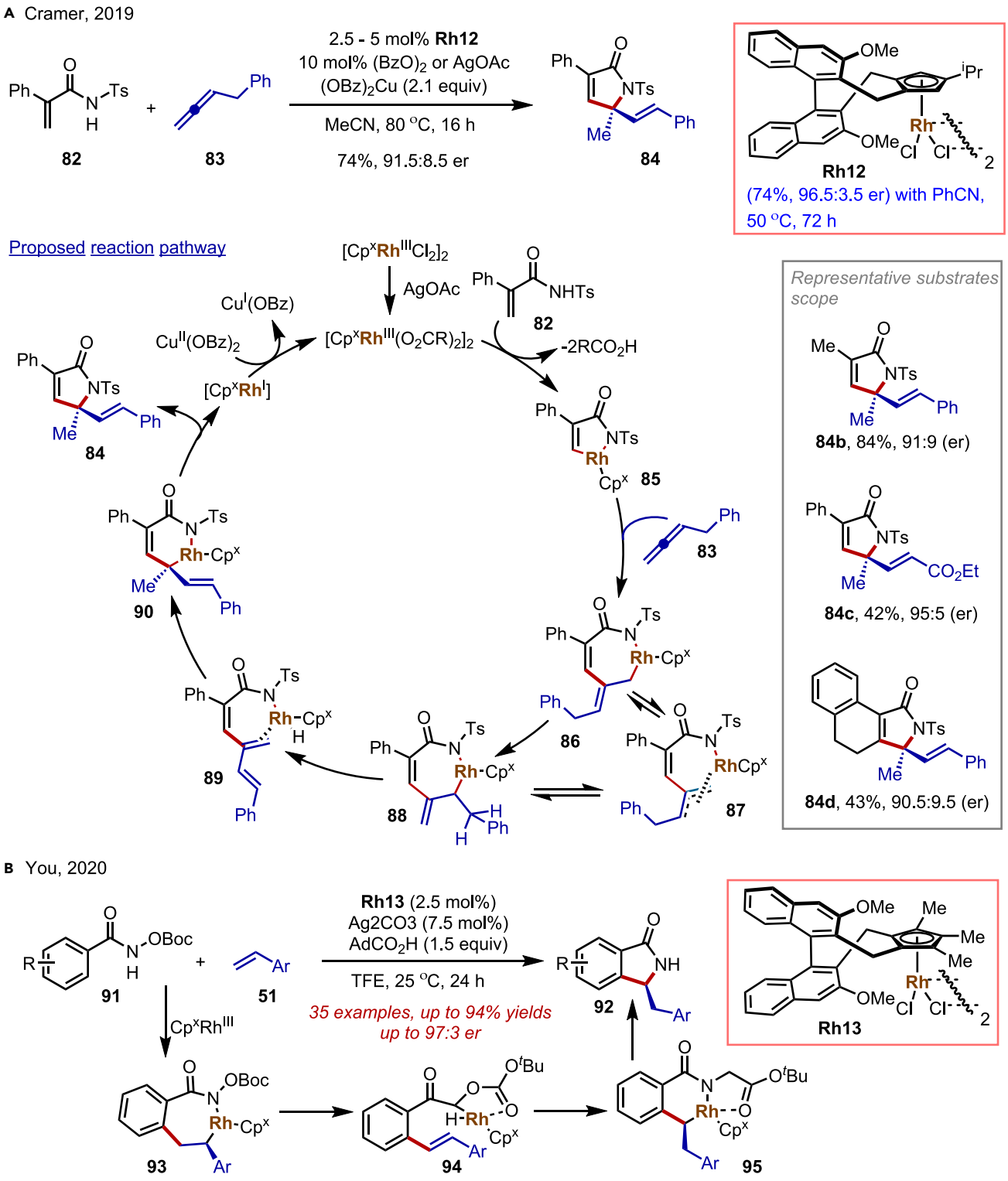
Scheme 9. Chiral Cp^{x}Rh(III)-catalyzed intramolecular hydroarylative enantioselective annulation reactions through C–H activation



Scheme 10. Chiral Cp^{x}Rh(III)-catalyzed annulation reactions

(A) Intermolecular enantioselective synthesis of isoindolone derivatives.

(B) Enantioselective [3 + 2] intramolecular transannulation of arenes with 7-azabenzonorboranadienes.



Scheme 11. Chiral Cp^{x}Rh(III)-catalyzed [4 + 1] annulation

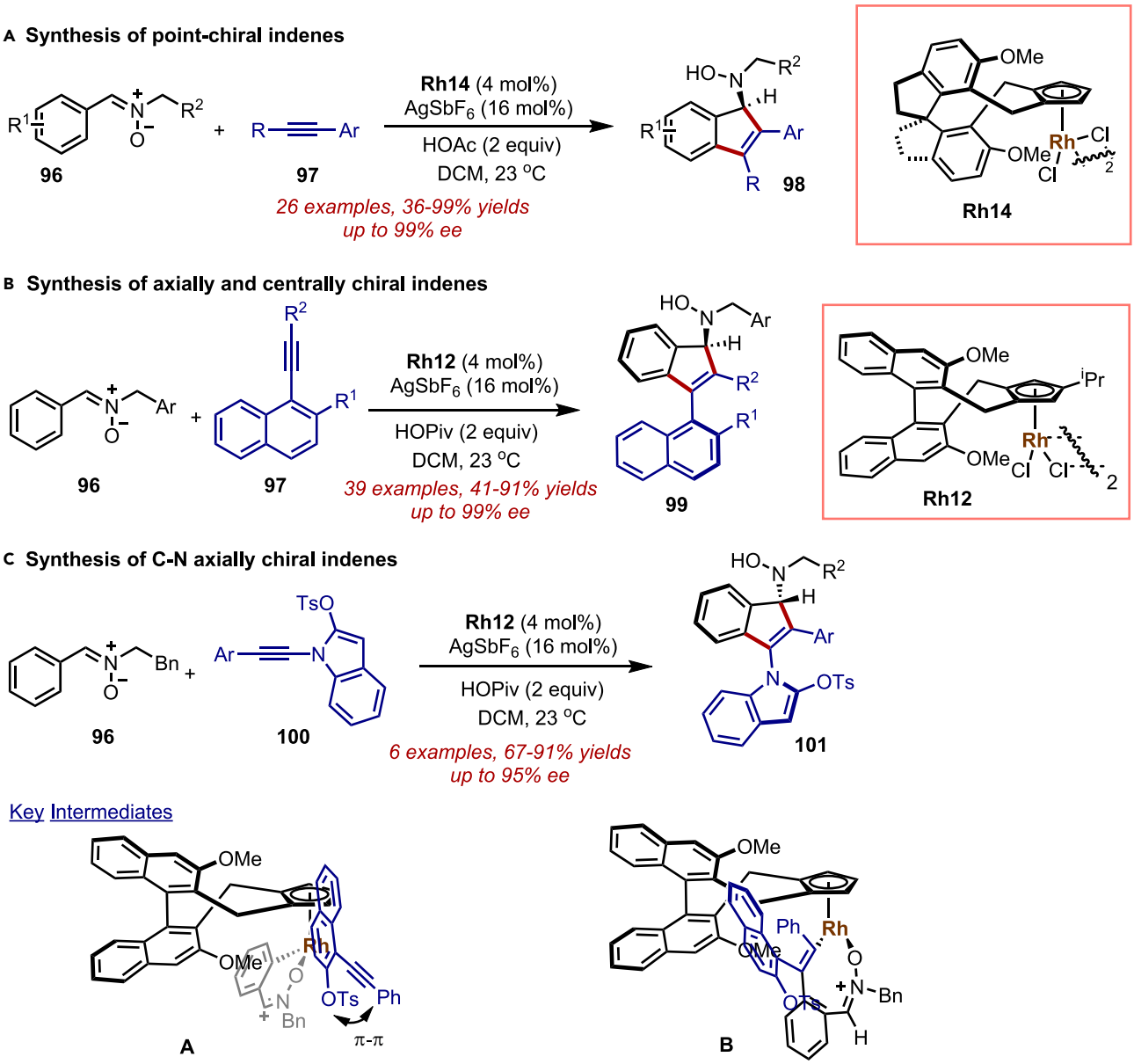
(A) Synthesis of enantioenriched 2H-pyrrole-2-one derivatives via intermolecular [4 + 1] annulation reaction.

(B) Synthesis of enantioenriched isoindolinones.

2020, You and co-workers demonstrated the utilization of olefins as one-carbon coupling partners in an asymmetric [4 + 1] annulation reaction with benzamides **91** (Scheme 11B).[56] Enantioenriched isoindolinones **92** were synthesized with excellent regio- and enantioselectivity using penta-substituted **Rh13** catalyst. Mechanistic understanding of the reaction was realized by D-isotope labeling experiments. C–H activation of benzamide **91** followed by migratory insertion of olefin **51** afforded rhodacycle **93**. Sterically hindered **Rh13** complex helps the formation of Heck-type intermediate **94** by favoring β-H elimination. Intermediate **94** then undergoes enantiodetermining migratory insertion leading to the formation of **95**, which subsequently undergoes N–O oxidative addition followed by C–N reductive elimination to afford the desired annulated product.

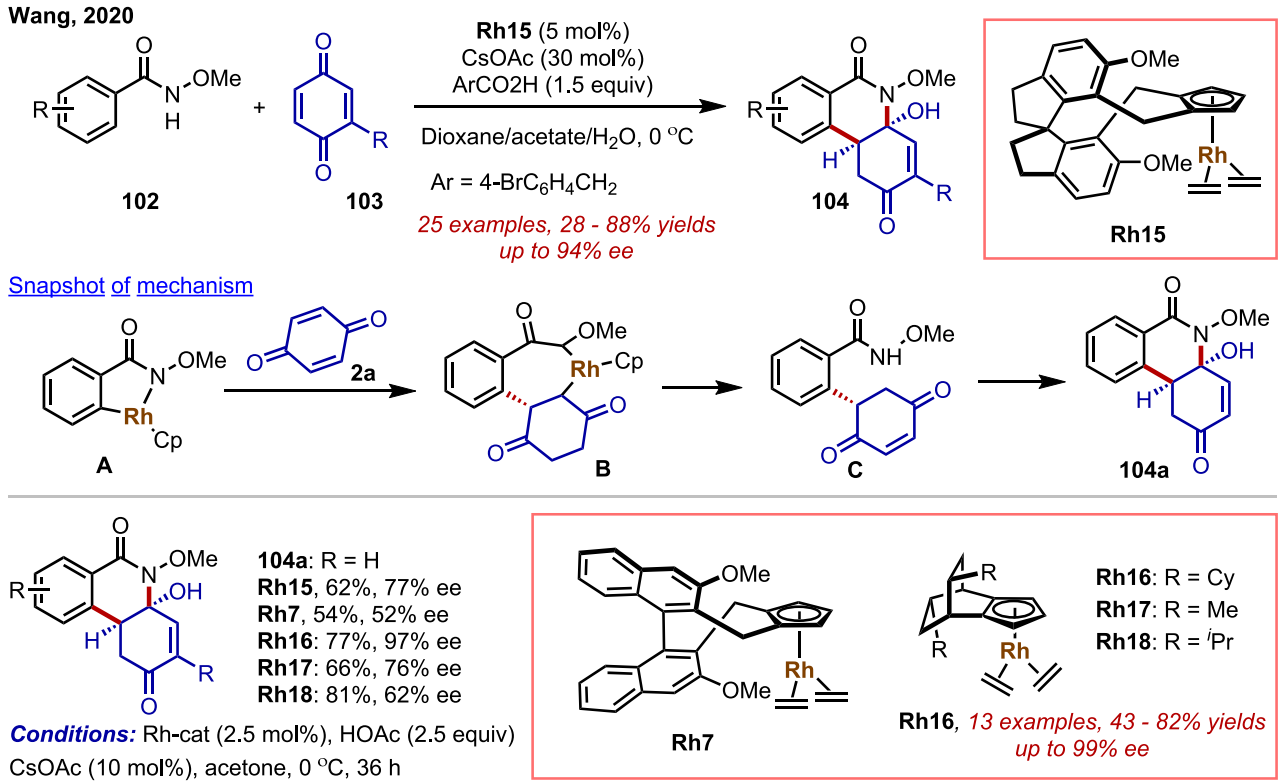
In 2016, You and co-workers reported a different class of chiral Cp ligands and their Rh complexes, synthesized from spirocyclic dicarboxylic acid (vide supra),[57] which they designated SCp ligands. The ligand-designing principle is similar to that of Cramer's ligand system, whereby the spirocyclic unit acts as a back wall whereas substitutions at the spirocyclic unit act as a side wall. The authors utilized this catalyst system in the oxidative alkenylation of hetero biaryl moieties using alkenes to afford the axially chiral products. This catalyst system turned out to be superior to Cramer's second-generation catalyst for this particular transformation.[73,74] Recently, Li and co-workers utilized this catalyst system (SCp^xM) for the synthesis of enantioselective indenes via asymmetric [3 + 2] annulation of arylnitrones with different classes of alkynes (Scheme 12).[75] Based on the different types of alkyne systems, centrally chiral, C–C, and C–N atropochiral pentatomic biaryls were afforded with C-centered point chirality, delivering excellent enantioselectivity and diastereoselectivity. Although You's catalyst **Rh14** appears to be optimal for the synthesis of centrally chiral indenes (Scheme 12A), for the synthesis of others two kinds of indene derivatives of Cramer's second-generation catalyst system **Rh12** turned out to be superior (Schemes 12B and 12C). Electrophilic nitrones act as a directing group and promoted the Rh-catalyzed *ortho*-C–H bond activation and subsequent alkyne insertion, followed by nitrone insertion leading to the formation of chiral indenes. Utilization of sterically hindered alkyne led to the construction of atropochiral pentatomic biaryls with C-centered point chirality (**99** and **101**). The enantioselective control of the axial and central chirality could be rationalized from the key intermediates depicted in the down side of Scheme 5. Density functional theory calculation suggested that intermediate **A** is more energetically favorable, minimizing all short of steric interactions between the catalyst backbone and the coupling partners. Thus, migratory insertion of the alkyne is likely to be more kinetically favored, resulting in the anticipated [S] axial chirality in the alkenyl intermediate **B**, which subsequently undergoes another migratory insertion between the Rh-alkenyl bond and nitrone from (*Re*) face, furnishing the C-centered central chirality to the annulated products.

In 2020, Wang and co-workers extended the hydroarylation of benzamide to intermolecular Michael acceptors as coupling partners (Scheme 13).[76] Enantioenriched tricyclic hydrophenanthridinone scaffolds **104** were obtained with moderate to very good yields and enantioselectivity while *N*-methoxybenzamides **102** were treated with quinones **103**. You's SCp-based Rh complex (**Rh15**) was found to be suitable for this transformation. The proposed mechanism suggests that the reaction proceeded as the usual Rh-catalyzed directed C–H activation, followed by enantioselective conjugate addition leading to the formation of **C**, which subsequently underwent intramolecular nucleophilic cyclization to the adjacent carbonyl group, affording the desired annulated tricyclic products. The authors further demonstrated the synthesis of enantioenriched dihydrolycoricidine, a potent and bioactive



Scheme 12. Chiral Cp^{x}Rh(III)-catalyzed axially and centrally chiral indene synthesis through C–H activation

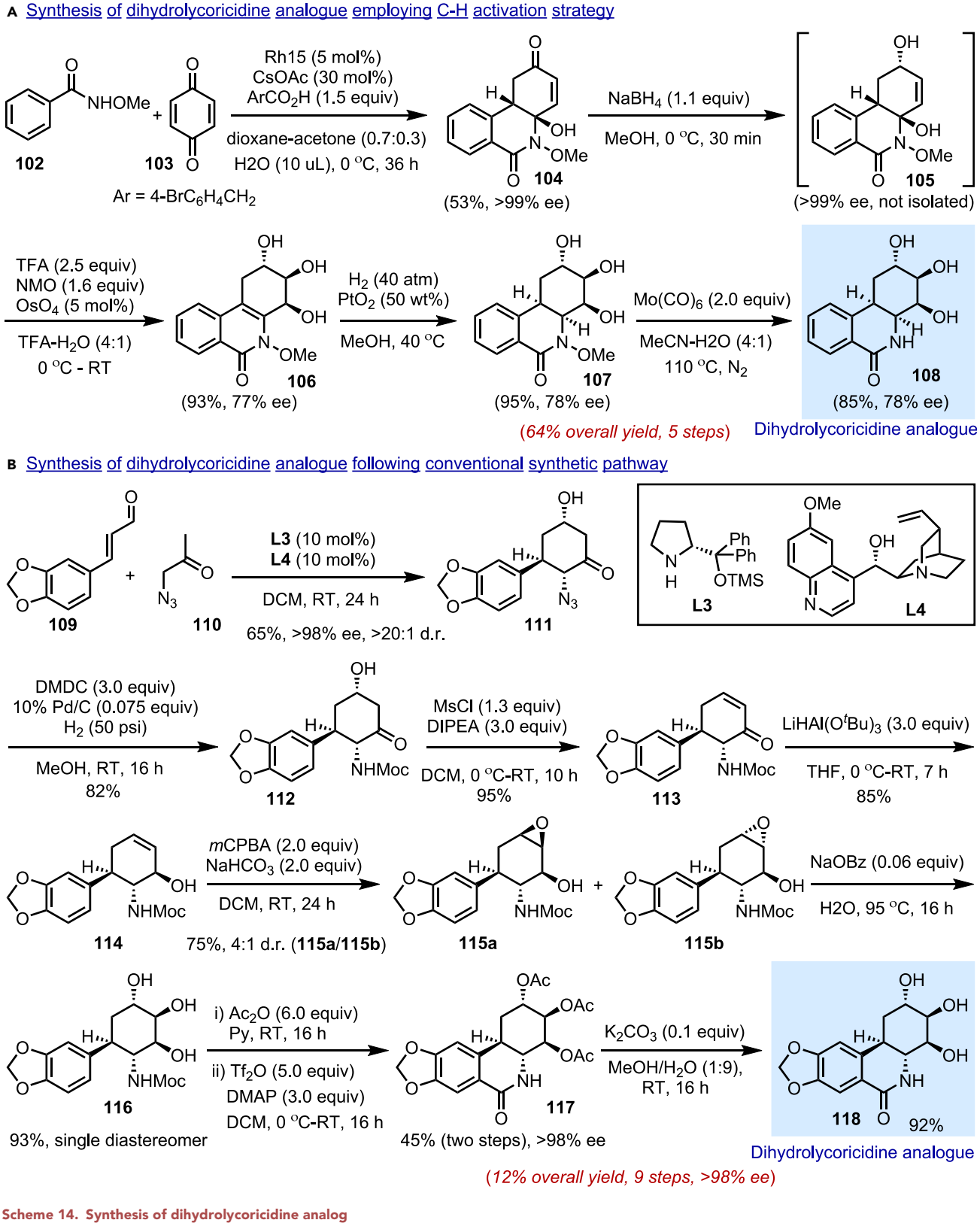
compound, utilizing this developed protocol as a key step (Scheme 14A). Enantioenriched dihydrolycoricidine **108** was synthesized in five steps starting from *N*-methoxybenzamides **102** and quinones **103**, with overall yield of 64%. In 2014, McNulty's group reported a conventional synthetic protocol for the synthesis of (+)-*trans*-dihydrolycoricidine **118** (Scheme 14B).[77] This anticancer natural product was obtained from cinnamaldehyde **109** and α-azidoacetone **110** precursors in nine synthetic steps with 12% overall yield and >98% enantiomeric excess. This particular example clearly demonstrates the advantages of enantioselective C–H activation strategy for the synthesis of chiral annulated products over the classical synthetic procedures. Later, the same authors reported the improved enantioselectivity of this [4 + 2] annulation protocol by employing a new class of C2-symmetric chiral bridged-ring-fused CpRh complex.[61] The novel CpRh complexes (**Rh16–Rh18**) turned out to be superior



Scheme 13. Synthesis of enantioenriched tricyclic hydrophenanthridinone via [4 + 2] annulation

in terms of yield and selectivity than Cramer's second-generation catalyst (**Rh7**) and You's SCpRh catalyst (**Rh15**). Obtained lower yields with **Rh7** and **Rh15** could be explained by realizing greater accessibility of the metal center by the reactants in horizontally less extended **Rh16–Rh18** complexes. Moderately hindered **Rh16** was found to be a better catalyst than less hindered or bulky catalyst systems.

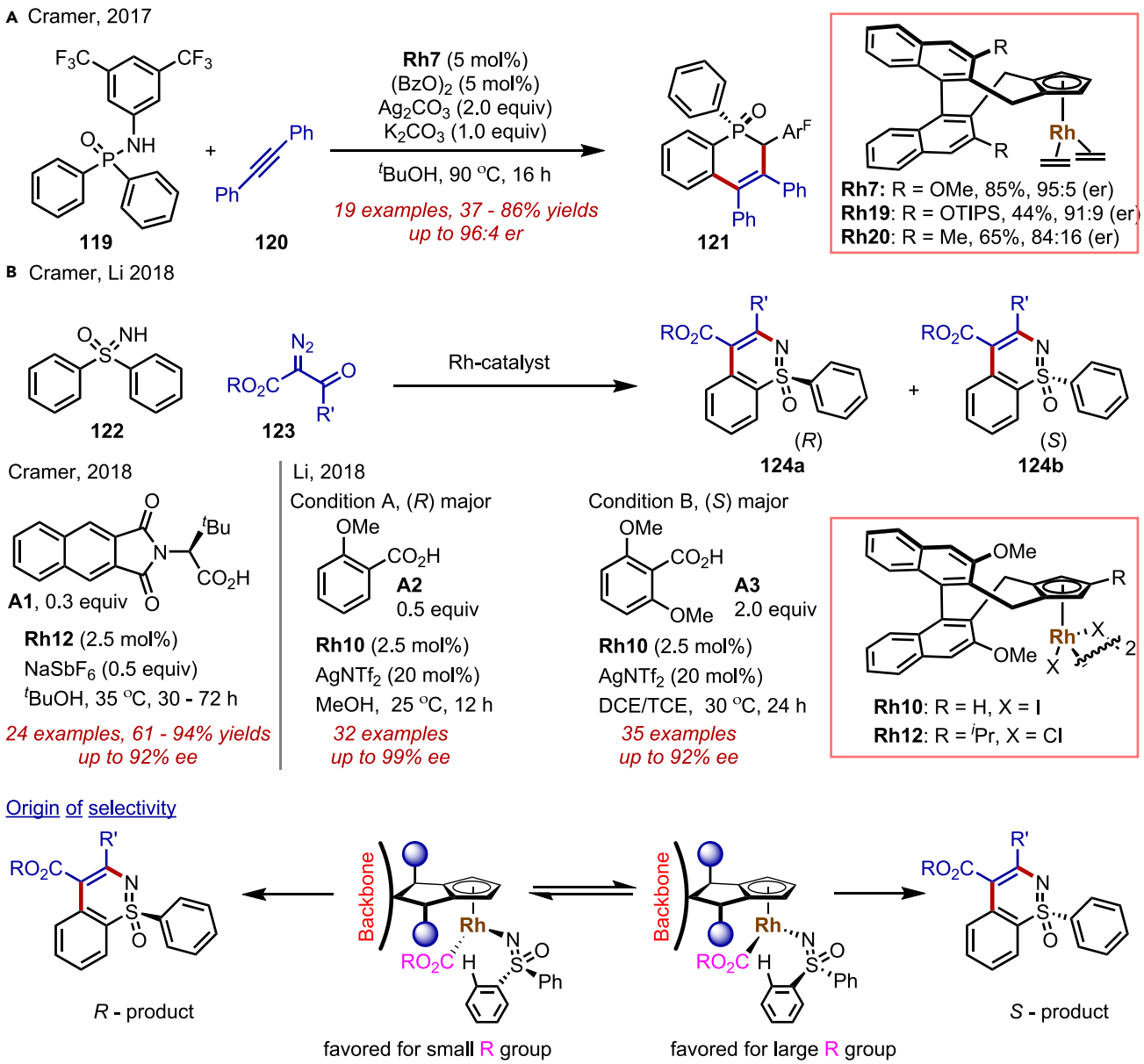
In recent times, an entantioselective C–H bond functionalization strategy has been successfully applied to generate a noncarbon stereogenic center.[78] In most cases the Cp^xM catalyzed asymmetric C–H activation strategy has been found to be a powerful protocol for synthesis of chiral-at-heteroatom molecules. In 2017, Cramer's group demonstrated the synthesis of enantioenriched P-chiral cyclic phosphinamides **121** (Scheme 15A).[79] **Rh12**-catalyzed enantiotopic C–H activation and subsequent intermolecular oxidative [4 + 2] annulation of phosphinamides **119** with alkyne **120** led to the formation of P-chiral phosphinamides **121**. The parent ligand **Rh7** turned out to be best for this transformation. Other chiral Cp ligands bearing larger (**Rh19**) or much smaller (**Rh20**) substituents at the naphthyl backbone were revealed to have reduced reactivity and selectivity. Following this work, Cramer's and Li's groups independently demonstrated the synthesis of S-chiral 1,2-benzothiazines via chiral Rh(III)-catalyzed desymmetrizative C–H activation of symmetric diaryl sulfoximines **122** and subsequent [4 + 2] annulation with diazo compounds **123** (Scheme 15B).[80,81] Cramer's group employed trisubstituted **Rh12** along with chiral carboxylic acid **A1** and afforded the S-chiral 1,2-benzothiazines with very good yield and enantioselectivity (Scheme 15B, left).[80] Li's group showcased the switching of enantio divergence by employing **Rh10** with different achiral carboxylic acids (Scheme 15B, right).[81] The authors recognized that steric bulk of carboxylic acid



Scheme 14. Synthesis of dihydrolycoricidine analog

(A) Via C–H activation chemistry.

(B) Via conventional route.

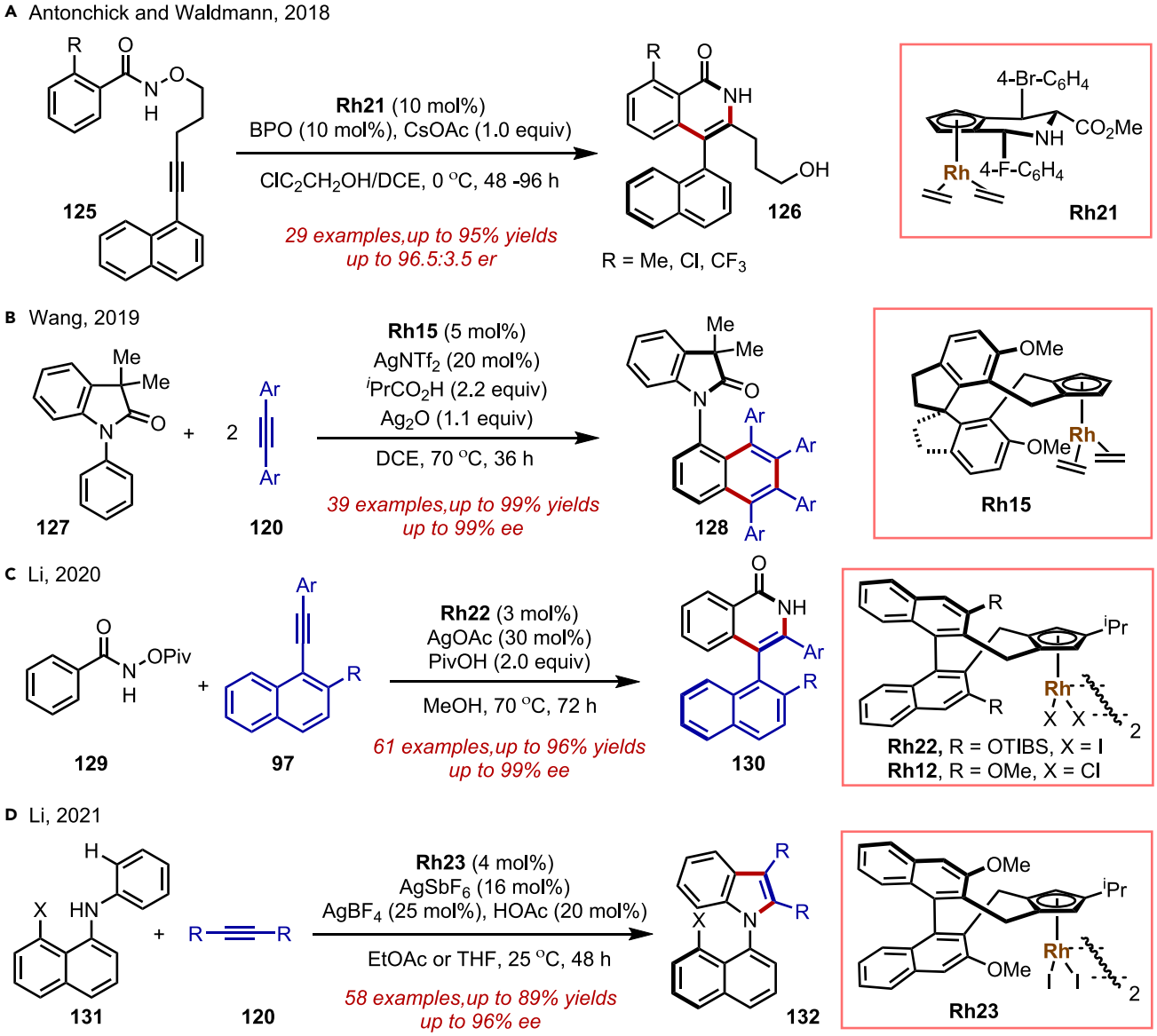


Scheme 15. Cp^{x}Rh(III)-catalyzed generation of heteroatom chiral stereocenters by desymmetrization via [4 + 2] annulation

impacted the stereochemical outcome in desymmetrizing C–H activation. Sterically hindered carboxylic acid favored the formation of *S* isomer by switching from the S_L to the S_S side (vide supra, Figure 1C), which eventually inverts the enantioselectivity in the stereochemistry-determining C–H activation step. Similarly, less hindered carboxylic acid favored the formation of *R* isomers.

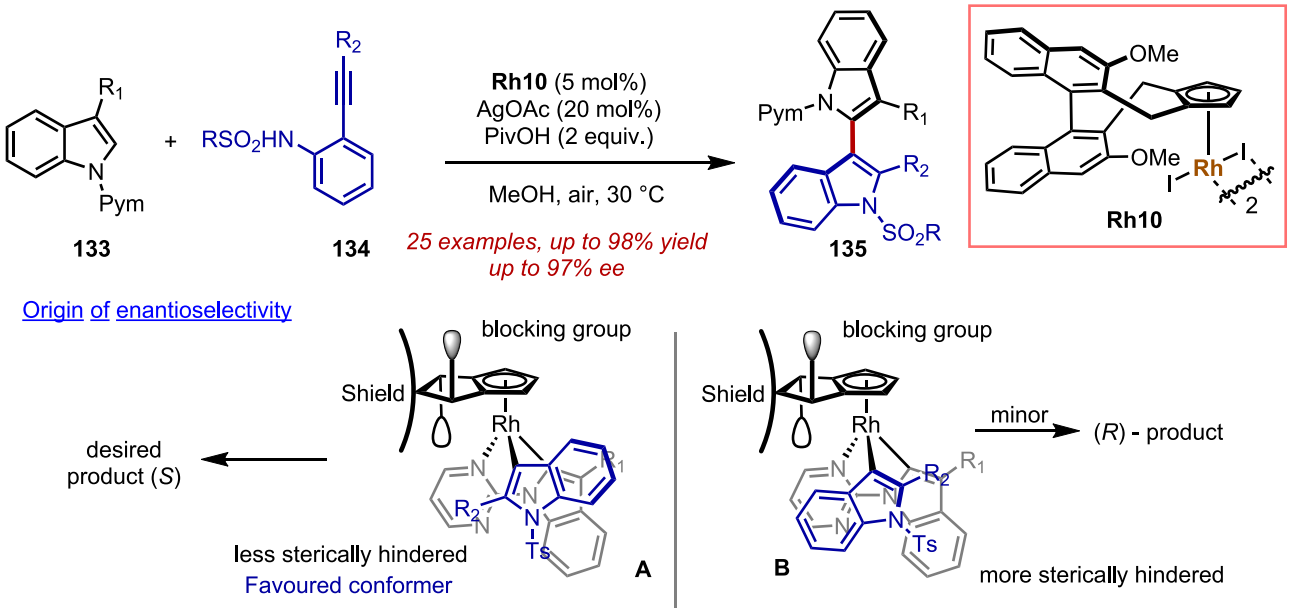
Chiral Cp^{x}Rh(III)-catalyzed enantioselective C–H activation for axial chirality

Axially chiral biaryl scaffolds have extensive application in asymmetric catalysis and are also gaining increasing importance in the natural products and pharmaceutical industries. In recent times, the most attractive strategy for the synthesis of chiral biaryls is atroposelective C–H functionalization.[82] Creation of a biaryl axis is one attractive strategy in this regard.



Scheme 16. Cp^{x}Rh(III)-catalyzed oxidative [4 + 2] and [3 + 2] annulation for atroposelective synthesis of biaryls

In 2018, Waldmann and co-workers demonstrated the enantioselective synthesis of 4-arylisoquinolones **126** via Rh(III)-catalyzed intramolecular [4 + 2] annulation of alkyne-tethered *N*-alkoxybenzamides **125** utilizing their developed **JasCp-RhX** catalyst system (Scheme 16A).[83] Importantly, the *ortho* substituent of benzamide is necessary in order to gain high enantioselectivity. In 2019, Wang and co-workers developed an enantioselective Satoh-Miura-type reaction for the construction of C–N axial chirality (Scheme 16B).[74] A wide range of C–N axially chiral *N*-aryloxindoles **128** was afforded with high yields and enantioselectivities by employing **Rh15**. As expected, bulkier alkynes favored better enantioselectivity. In 2020, Li's group developed an intermolecular form of [4 + 2] annulation between benzamides **129** and hindered alkynes **97** (Scheme 16C).[84] Axially chiral biaryl N–H isoquinolones **116** were afforded in excellent yields and selectivities by employing **Rh22** containing bulky substituent (OTIBS). The origin of enantioselectivity could be rationalized by the enantiodetermining migratory insertion of alkyne to introduce axial chirality,



Scheme 17. Cp^{x}Rh(III)-catalyzed C–H activation for atroposelective synthesis of axially chiral 2,3′-biindolyls

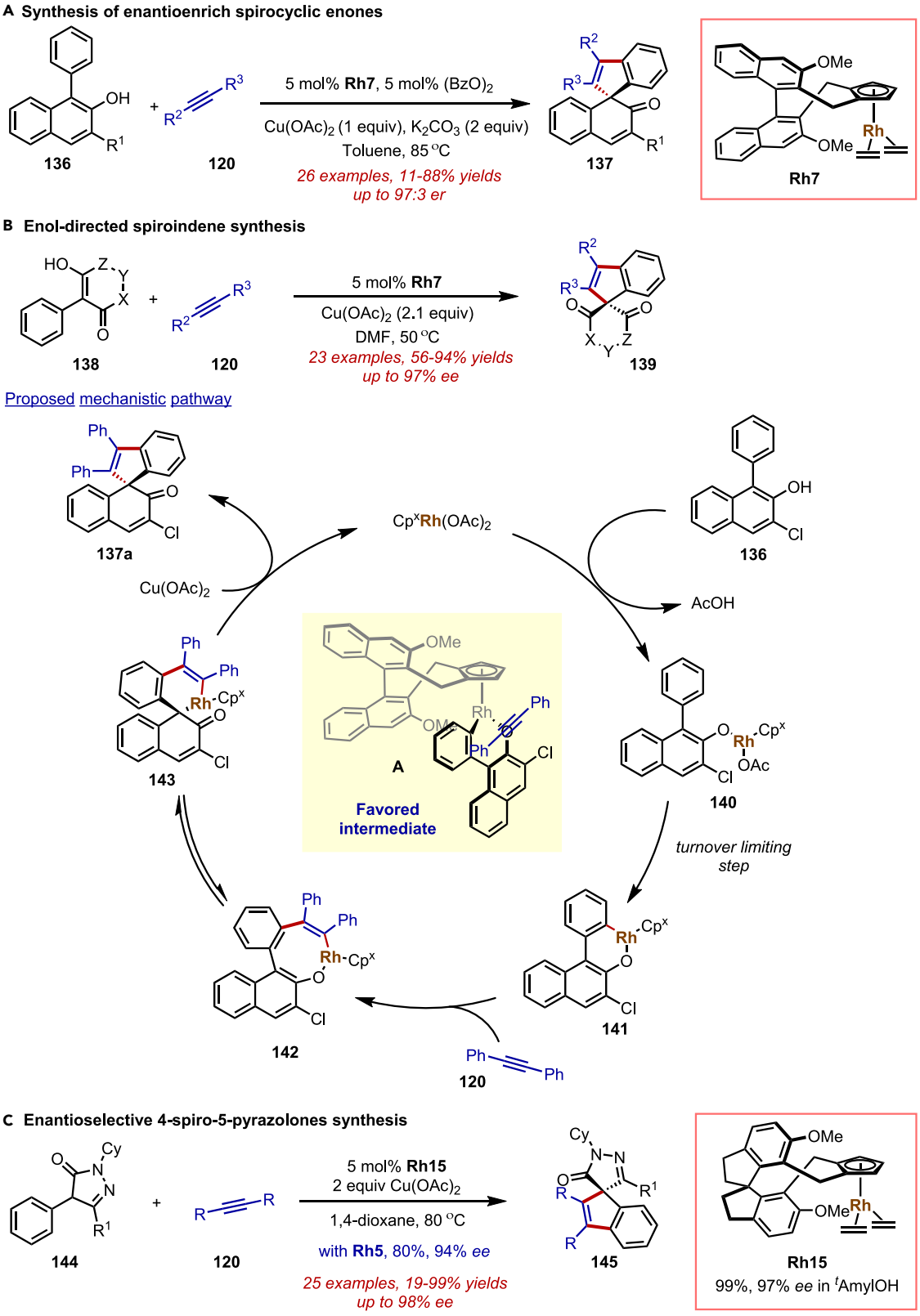
followed by axial-to-axial chirality transfer leading to the formation of **130**. In 2021, the same group extended this system to the synthesis of C–N axially chiral *N*-arylindoles **132**. A wide range of axially chiral *N*-arylindoles was synthesized by C–H activation followed by [3 + 2] annulation of aniline derivatives **131** with alkyne **120** (Scheme 16D).[85]

In 2019, Li and co-workers demonstrated the synthesis of penta-atomic biaryls (Scheme 17).[86] In general, construction of atropoisomeric penta-atomic biaryls is quite challenging because of conformational instability. However, the chiral Rh(III)-catalyzed strategy delivered a broad range of atroposelective biaryls **135** with very good to excellent yields and enantioselectivities. Mechanistically, this reaction proceeded via directed C–H activation of indole derivatives **133**, providing rodacycles. On the other hand, cyclometalation of alkynes **134** at the same metal center led to the formation of plausible intermediates **A** and **B**. Sterically favored intermediate **A** undergoes reductive elimination, leading to the desired (*S*)-2,3′-biindolyls.

Chiral transition-metal-catalyzed spirocycle synthesis

Chiral spirocyclic scaffolds constitute the prevalent structural core of numerous complex natural and pharmaceutical products.[87–90] Widespread biological activities of spirocyclic scaffolds have stimulated the synthetic community to design and synthesize new catalysts and develop new protocols for the synthesis of novel spirocyclic structures.[91–94] Significant efforts have been made to access the various spirocyclic skeletons over the past decade.[95–100] Here, we highlight the employment of chiral Cp^{x}M catalysts in enantioselective synthesis of spirocyclic skeletons.

In 2015, You's group reported an intermolecular enantioselective [3 + 2] spiroannulation reaction. All-carbon quaternary stereogenic centers containing spirocyclic enones **137** were synthesized from 1-aryl-2-naphthols **136** and internal alkynes **120** utilizing Cramer's second-generation catalyst (Scheme 18A).[101] Numerous enantioenriched spirocyclic enones were synthesized with the catalyst **Rh7** with $Cu(OAc)_2$ and air (oxygen) as oxidants. The hydroxyl group of naphthol acts as a



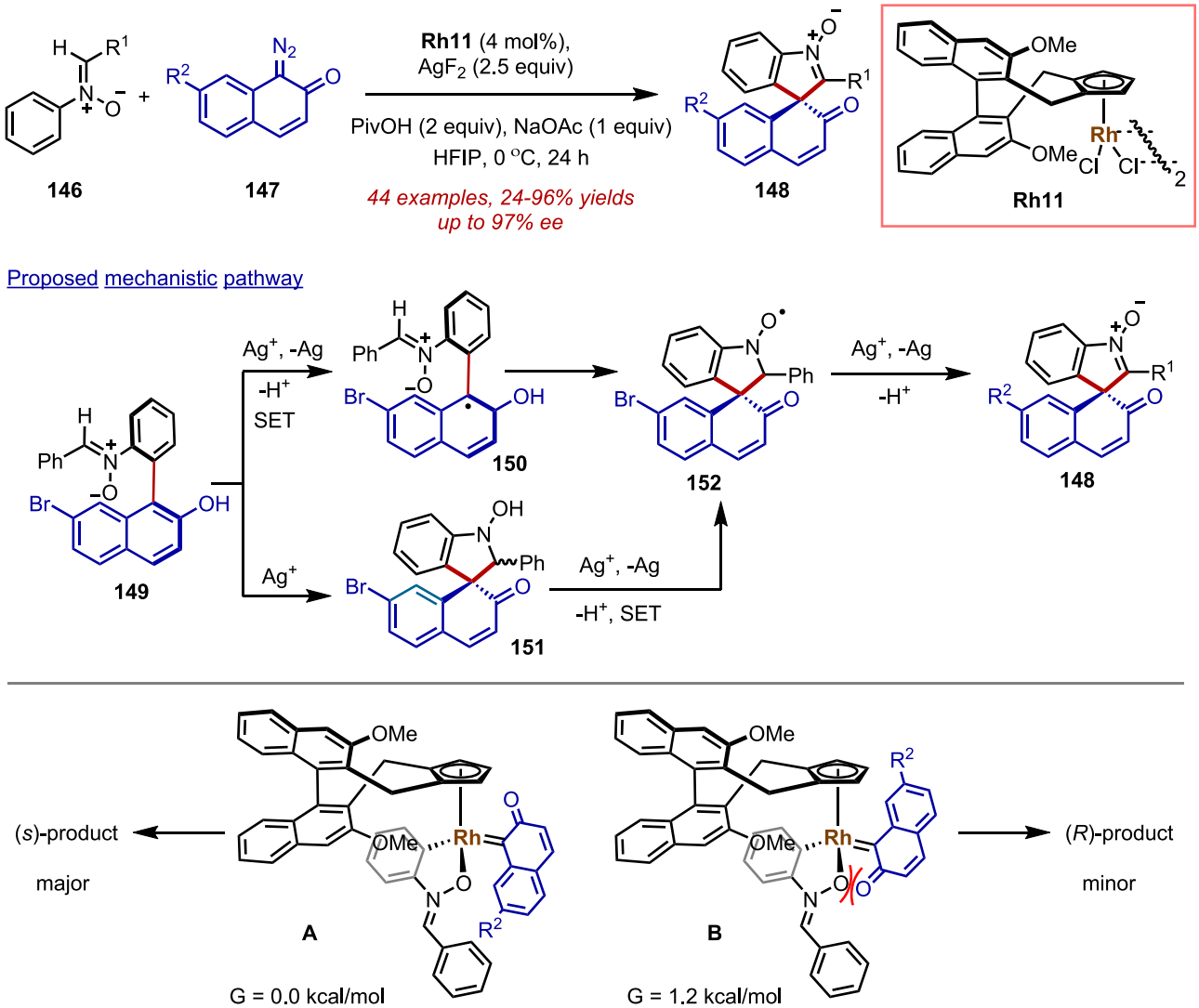
Scheme 18. Chiral Cp^{x}Rh(III)-catalyzed intermolecular enantioselective [3 + 2] spiroannulation reactions through C–H activation

directing group upon deprotonation by the Rh catalyst, leading to the formation of intermediate **140**, which subsequently activates the *ortho*-C–H bond and provides rhodacycle **141**. The combined effect of back and side wall of the biaryl complex influences the formation of an energetically favorable tetrahedral complex with the 1-aryl-2-naphthols minimizing the steric interaction (Scheme 18, **A**). This is followed by coordination of alkyne to the Rh, and subsequent migratory insertion delivers a stressed eight-membered rhodacycle **142**, which is likely to be in equilibrium with six-membered isomers **143**. The intrinsic steric nature of the catalyst dictates the rotation of rhodacycle **143** in adaptation toward reductive elimination to afford the desired product **137a**. The activated Rh(III) catalyst is engendered by concomitant oxidation of Rh(I) species, released upon reductive elimination by $Cu(OAc)_2$ and oxygen.

At the same time, Lam and co-workers described a candid strategy for enantioselective spiroindene synthesis from aryl cyclic 1,3-dicarbonyl compounds **138** and internal alkyne **120** via oxidative annulation reaction utilizing the same chiral Cp rhodium complex, **Rh7** (Scheme 18B).[102] Enol-directed enantioselective C(sp^2)–H activation and subsequent annulation with alkyne were recognized to afford spiroindenes **139** containing all-carbon quaternary stereocenters.

Soon after their first report on the spiroannulation reaction, You's group reported the synthesis of enantioenriched five-membered-ring 4-spiro-5-pyrazolones, an imperative pharmaceutically relevant scaffold (Scheme 18C).[100] Chiral SCpRh(III)-catalyzed C–H activation of 4-aryl-5-pyrazolones and subsequent [3 + 2] annulation reaction with alkynes afforded 4-spiro-5-pyrazolone with good yields and excellent enantioselectivities. Cramer's catalyst **Rh7** was found to be an effective catalyst system in this transformation. However, the authors' own catalyst system, chiral SCpRh catalyst (**Rh15**), was recognized as superior in terms of both yields and selectivities, providing the desired products in quantitative yields with excellent enantioselectivities.

In 2020, Li and co-workers demonstrated an axial-to-central chirality transfer strategy for the synthesis of enantioenriched spirocycles using chiral $Cp^xRh(III)$ catalyst (Scheme 19).[103] The origin of enantioselectivity could be realized by the steric factor of diazo molecule and C=O group of nitrone in transition state of rhodacycle. In the rhodacycle intermediate, the less hindered *N*-arene ring is directed to backward in order to minimize the steric interactions. The plausible orientation of the diazo reagent approaching the Rh center dictates the formation of the enantiomer. In transition state **B**, strong steric repulsion of C=O counterpart of diazo with nitrone functionality leads to the minor isomer, whereas in transition state **A** there is no such interaction, leading to the formation of major (*S*) isomers. First, directed enantioselective C–H arylation of *N*-aryl nitrone with *ortho*-quinone diazide led to formation of atropomerically metastable biaryl **149**, which subsequently underwent intramolecular dearomative trapping under oxidative conditions resulting in enantioenriched spirocycles. Judicious choice of the nitrone-directing group plays a crucial role in chirality transfer, which first provides enantioselective biaryl **149** without racemization as well as not hindering chirality transfer. Additionally, C-7 substitution of quinone diazides plays a pivotal role in affording highly enantioselective products by indulging steric impact on enantioselectivity. Transformation of metastable biaryls to spirocycles could be explained by AgF_2-promoted electrochemical oxidation. Intermediate **149** either might undergo AgF_2-promoted SET oxidation followed by radical cyclization with nitrone to provide a stable nitroxide radical **152** or firstly

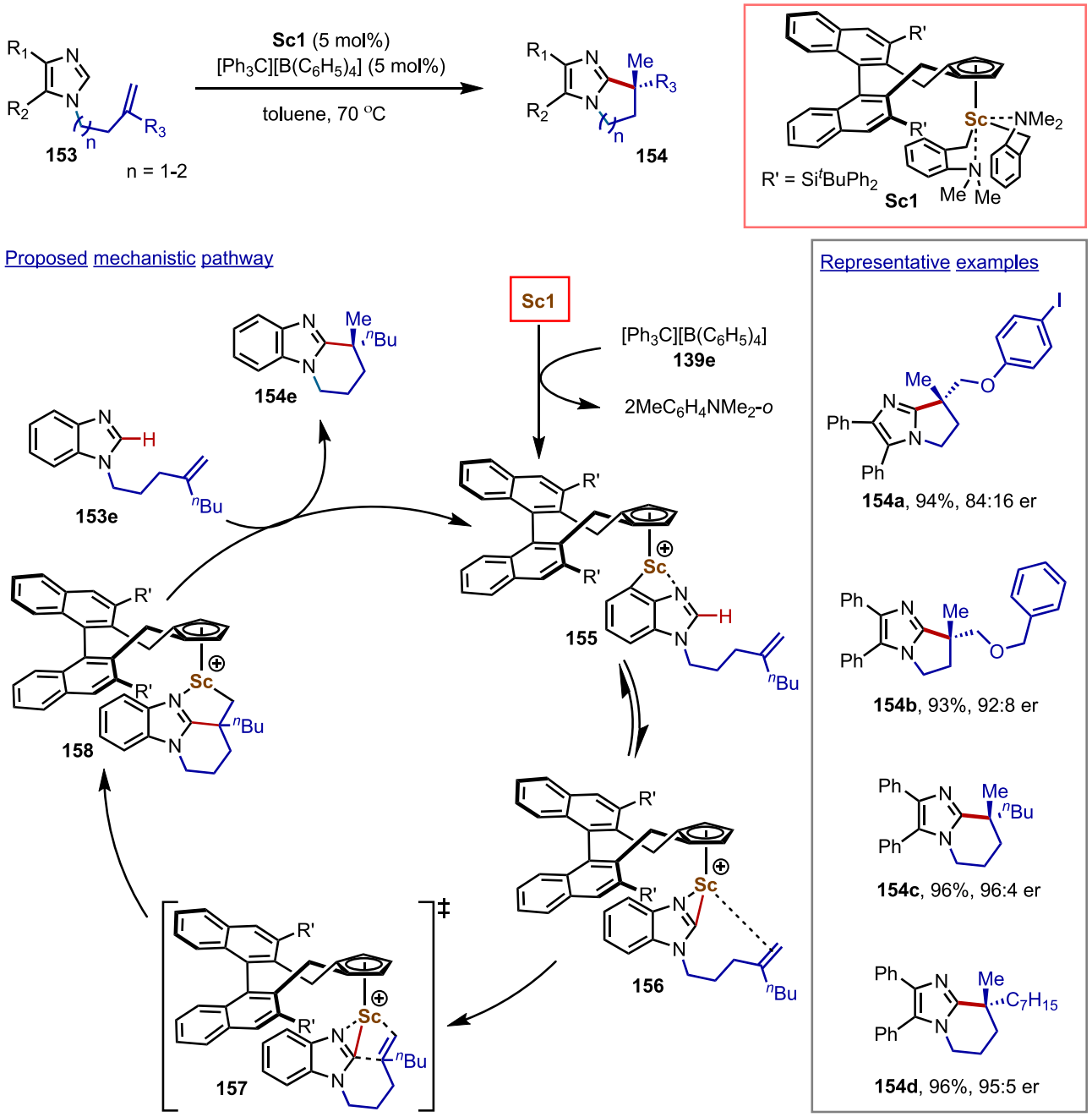


Scheme 19. Chiral Cp^{x}Rh(III)-catalyzed enantioselective spirocycle synthesis utilizing axial-to-central chirality transfer strategy

cyclization with the nitrone (**151**) and subsequent SET oxidation to radical **152**, which further undergoes SET oxidation to deliver spirocycles **148**.

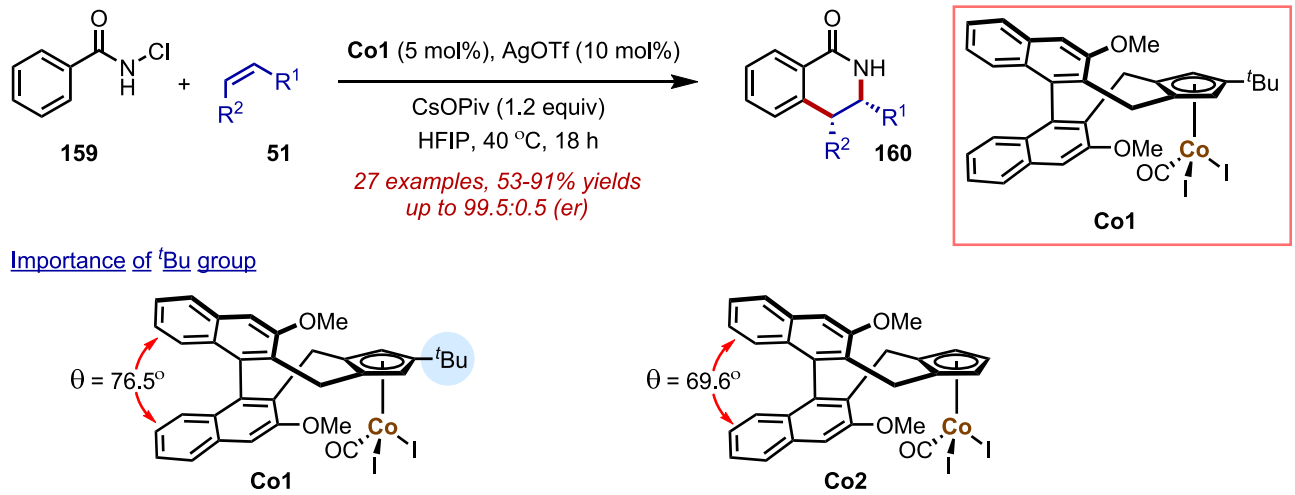
3d transition-metal catalysis

Enantioselective annulation methodologies typically have been advanced based on 5d transition-metal catalysts, in particular rhodium.[17,104–107] Despite successful application of 3d transition-metal catalysts in enantioselective synthesis, the chemistry remains underdeveloped presumably due to the lack of appropriate ligand systems. However, recent development of various chiral ligand systems prompted the community to reinvestigate the 3d transition metals in enantioselective catalysis. In 2014, Hou and co-workers reported a chiral scandium complex equipped with Cramer's chiral Cp ligand and utilized it in an enantioselective version of their previously developed method,[108,109] enantioselective addition of pyridine C–H bond to various 1-alkenes.[63] In 2020, they reported an intramolecular asymmetric C–H annulation of imidazoles containing 1,1-disubstituted alkene **153** by using chiral scandium catalyst **Sc1** (Scheme 20).[110] The exo-selective asymmetric annulation



Scheme 20. Chiral Cp^{x}Sc-catalyzed intramolecular enantioselective annulation reactions

reaction delivered numerous bicyclic imidazole derivatives having β-all-carbon-substituted quaternary stereocenters (e.g., **154a–154e**) with excellent enantioselectivities. First, deprotonative C–H activation at either C2 or C3 position by the Sc catalyst could lead to the formation of intermediates **155** and **156**. The population of interconvertible intermediates **155** and **156** might be influenced by anchored olefinic moiety, leading to the dominance of intermediate **156**, which then underwent intramolecular insertion of the olefinic part into the Sc-imidazolyl bond and provided the intermediate **157**. Subsequently, hydrogen abstraction of **153e** by the Sc–C σ-bond in **158** led to release of the annulated product (**154e**).



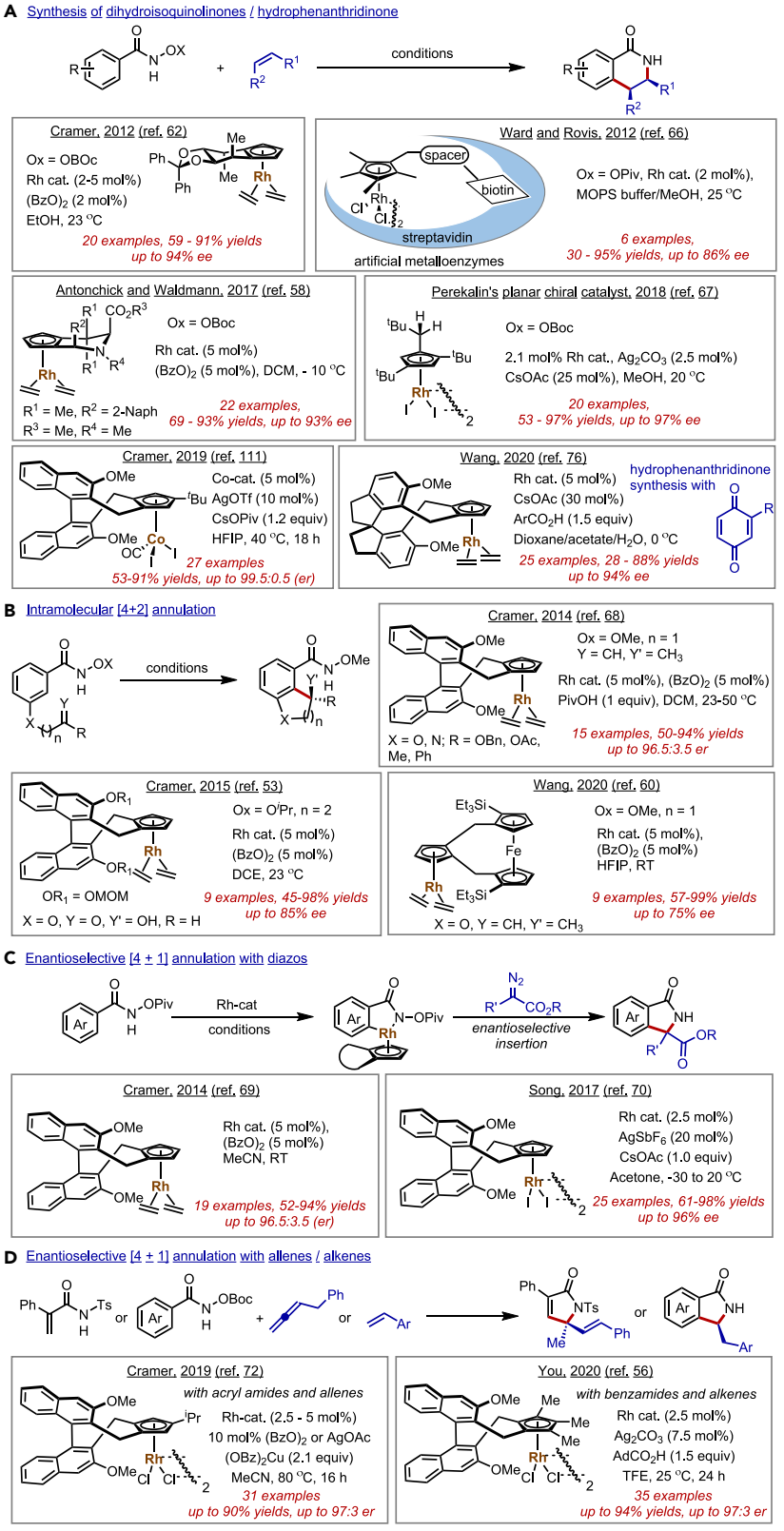
Scheme 21. Chiral Cp^{x}Co(III)-catalyzed enantioselective dihydroisoquinolones synthesis

The exo-selectivity of this transformation could be realized by the steric and electronic effects of the ligand.

In 2019, Cramer's group devised a Co(III)-catalyst system using a trisubstituted chiral Cp ligand. They utilized this chiral Co catalyst in the annulation reaction toward synthesis of dihydroisoquinolones from *N*-chlorobenzamides and numerous alkenes (Scheme 21).[111] Notably, this catalyst turned out to be superior to the Rh(I)-based catalysts for this particular class of reaction. The larger dihedral angle of **Co1**, developed with the help of *tert*-butyl substitution on Cp^x ligand, accomplishes gain of a specific orientation of the incoming alkenes, diminishing the steric repulsion and hence affording an excellent enantioselectivity of up to 99.5:0.5 (er). The *tert*-butyl group on the Cp^x ligand (**Co1**) remotely affected the dihedral angle θ of the binaphthyl backbone and helped to open up the pocket somewhat more compared with the unsubstituted **Co2** catalyst. Finally, the back wall of the chiral catalyst dictated the orientation and alignment of the metallocycle with incoming alkenes.

CONCLUSIONS AND OUTLOOK

In this review we have discussed the recent developments of chiral metal catalyzed asymmetric annulation reactions, emphasizing the mechanistic understanding. Enantiocontrolled C(sp^2)–H bond functionalization followed by intra-/inter molecular cyclization led to the achievement of chiral annulated products with the assistance of the cooperative effect of suitable metals and chiral ligand systems. In Figure 3, we summarize the extensively explored strategies for the synthesis of enantioenriched annulated compounds. Since the first independent reports by Cramer's and Rovis's groups on asymmetric annulation reactions, several elegant enantioselective annulation approaches have been demonstrated. However, progress of this chemistry is not up to the level expected by now, which might be due to the existence of several formidable challenges. The chemistry mostly relies on the Cp ligand systems. Synthesis of Cp ligand is quite complicated, follows tedious and linear multistep protocols, and requires expensive chiral starting material. Designing simple yet effective chiral ligand systems which could activate different kinds of C–H bonding with the assistance of metal catalysts should be the prime interest of the synthetic community. Special attention needs to be paid to straightforward ligand synthesis protocols and late-stage modification of the ligand core for the preparation of ligand libraries. Further attention also needs to be paid to


A Synthesis of dihydroisoquinolinones / hydrophenanthridinone
conditions
Cramer, 2012 (ref. 62)
Ox = OBOc
Rh cat. (2-5 mol%)
(BzO)2 (2 mol%)
EtOH, 23 °C
20 examples, 59 - 91% yields
up to 94% ee
Ward and Rovis, 2012 (ref. 66)
spacer
biotin
streptavidin
artificial metalloenzymes
Ox = OPiv, Rh cat. (2 mol%),
MOPS buffer/MeOH, 25 °C
6 examples,
30 - 95% yields, up to 86% ee
Antonchick and Waldmann, 2017 (ref. 58)
Ox = OBoc
Rh cat. (5 mol%)
(BzO)2 (5 mol%), DCM, - 10 °C
R1 = Me, R2 = 2-Naph
R3 = Me, R4 = Me
22 examples,
69 - 93% yields, up to 93% ee
Perekalin's planar chiral catalyst, 2018 (ref. 67)
Ox = OBoc
2.1 mol% Rh cat., Ag2CO3 (2.5 mol%)
CsOAc (25 mol%), MeOH, 20 °C
20 examples,
53 - 97% yields, up to 97% ee
Cramer, 2019 (ref. 111)
Co-cat. (5 mol%)
AgOTf (10 mol%)
CsOPiv (1.2 equiv)
HFIP, 40 °C, 18 h
27 examples
53-91% yields, up to 99.5:0.5 (er)
Wang, 2020 (ref. 76)
Rh cat. (5 mol%)
CsOAc (30 mol%)
ArCO2H (1.5 equiv)
Dioxane/acetate/H2O, 0 °C
25 examples, 28 - 88% yields
up to 94% ee
hydrophenanthridinone
synthesis with
B Intramolecular [4+2] annulation
conditions
Cramer, 2014 (ref. 68)
Ox = OMe, n = 1
Y = CH, Y' = CH3
Rh cat. (5 mol%), (BzO)2 (5 mol%)
PivOH (1 equiv), DCM, 23-50 °C
X = O, N; R = OBn, OAc,
Me, Ph
15 examples, 50-94% yields
up to 96.5:3.5 er
Cramer, 2015 (ref. 53)
Ox = OiPr, n = 2
Rh cat. (5 mol%)
(BzO)2 (5 mol%)
DCE, 23 °C
OR1 = OMOM
X = O, Y = O, Y' = OH, R = H
9 examples, 45-98% yields
up to 85% ee
Wang, 2020 (ref. 60)
Ox = OMe, n = 1
Rh cat. (5 mol%),
(BzO)2 (5 mol%)
HFIP, RT
X = O, Y = CH, Y' = CH3
9 examples, 57-99% yields
up to 75% ee
C Enantioselective [4 + 1] annulation with diazos
Rh-cat
conditions
enantioselective
insertion
Cramer, 2014 (ref. 69)
Rh cat. (5 mol%),
(BzO)2 (5 mol%)
MeCN, RT
19 examples, 52-94% yields
up to 96.5:3.5 (er)
Song, 2017 (ref. 70)
Rh cat. (2.5 mol%)
AgSbF6 (20 mol%)
CsOAc (1.0 equiv)
Acetone, -30 to 20 °C
25 examples, 61-98% yields
up to 96% ee
D Enantioselective [4 + 1] annulation with allenes / alkenes
or
Cramer, 2019 (ref. 72)
with acryl amides and allenes
Rh-cat. (2.5 - 5 mol%)
10 mol% (BzO)2 or AgOAc
(OBz)2Cu (2.1 equiv)
MeCN, 80 °C, 16 h
31 examples
up to 90% yields, up to 97:3 er
You, 2020 (ref. 56)
with benzamides and alkenes
Rh cat. (2.5 mol%)
Ag2CO3 (7.5 mol%)
AdCO2H (1.5 equiv)
TFE, 25 °C, 24 h
35 examples
up to 94% yields, up to 97:3 er

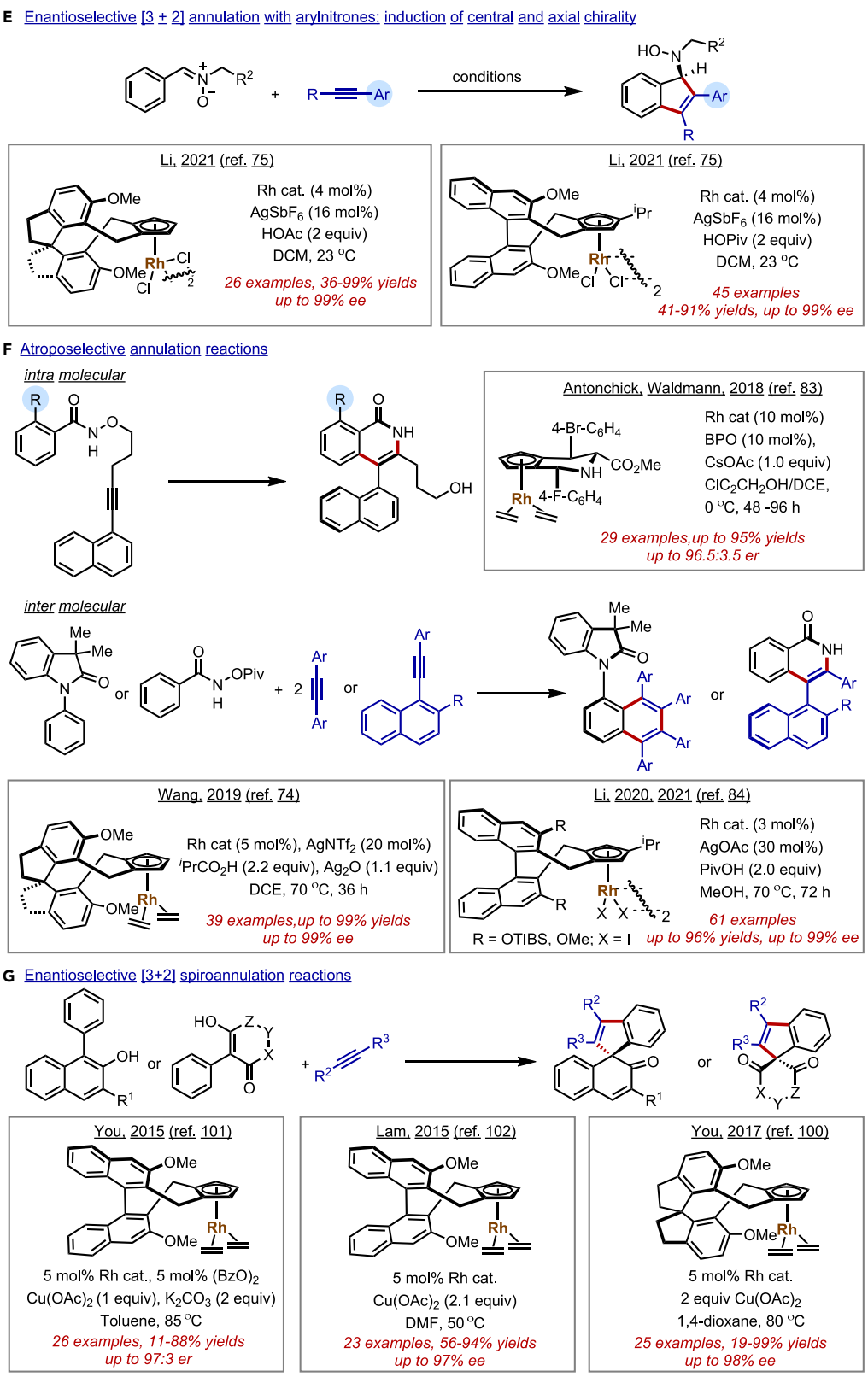


Figure 3. Summary of much explored general strategies for the synthesis of enantioenriched annulated compounds

developing simplified metal-ligand complexation protocols, e.g., *in situ* formation of active catalyst systems, which eventually will provide a rapid catalyst screening setup. Besides this, the development of operational simplicity of the catalysis should be another aspect that demands attention. Enhanced operational simplicity of catalysis could attract the attention of industrial chemists to apply the developed enantioselective annulation protocols from a wider perspective. In line with the recent trends on sustainable chemistry developments, exploration of Cp complexes of first-row transition metals in catalysis should be a priority in order to avoid the use of expensive metals. Use of alternative energy sources such as electric or photochemical irradiation might be advantageous for activation of catalyst systems so that stoichiometric metal or chemical oxidants could be avoided. Here, we have tried to highlight the importance, growth, and limitations of this promising domain in a methodical manner to expedite the chemist's attention toward the synthesis of chiral annulated molecules from simple chemical feedstock. We assume that this short review will provide readers with an inclusive understanding of this developing area of asymmetric annulation protocols and encourage them to develop further state-of-the-art strategies.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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