CHEMICAL REVIEWS

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Rhodium-Catalyzed Asymmetric C−H Functionalization Reactions

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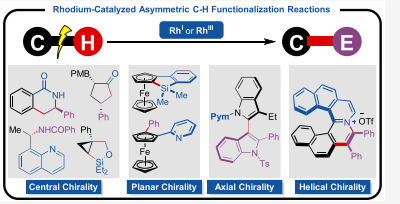
ABSTRACT: This review summarizes the advancements in rhodium-catalyzed asymmetric C−H functionalization reactions during the last two decades. Parallel to the rapidly developed palladium catalysis, rhodium catalysis has attracted extensive attention because of its unique reactivity and selectivity in asymmetric C−H functionalization reactions. In recent years, Rh-catalyzed asymmetric C−H functionalization reactions have been significantly developed in many respects, including catalyst design, reaction development, mechanistic investigation, and application in the synthesis of complex functional molecules. This review presents an explicit outline of catalysts and ligands, mechanism, the scope of coupling reagents, and applications.



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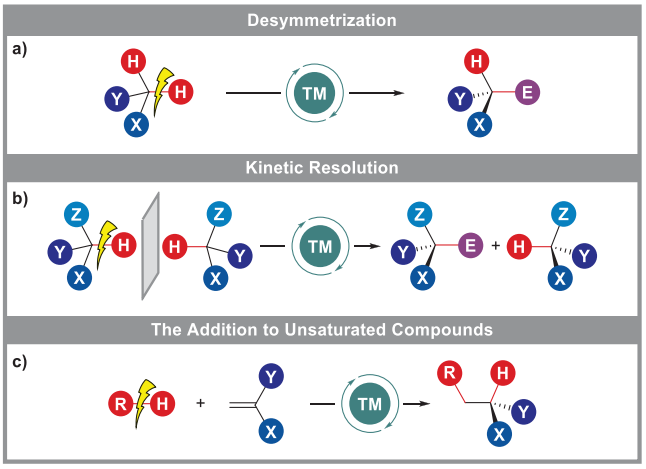
1. INTRODUCTION

Transition-metal-catalyzed coupling reactions offer unparalleled advantages for constructing carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds. Among these, transition-metal-catalyzed asymmetric C−H functionalization reactions have provided powerful access to the synthesis of diverse enantioenriched compounds in a highly enantioselective manner.[1−8] Generally speaking, there are three different pathways for achieving asymmetric C−H functionalization reactions, desymmetrization, kinetic resolution, and the addition to unsaturated compounds (Scheme 1). Asymmetric C−H functionalization reactions can be catalyzed by various transition-metal complexes including palladium (Pd),[9−19] rhodium (Rh),[20−26] iridium (Ir),[27−30] ruthenium (Ru),[31−34] and other 3d transition metals.[35−38] Among these, Pd and Rh catalysts have received the most attention due to their applications in diverse enantioselective reactions with broad substrate scope. In this regard, Pd-catalyzed asymmetric C−H functionalization reactions have been extensively investigated and well-reviewed. Rhodium catalysis has also attracted close attention due to its unique reactivity and selectivity in asymmetric C−H functionalization reactions. In the past decade, significant advances in Rh-catalyzed asymmetric C−H functionalization reactions have been achieved in many respects, including novel chiral catalysts and ligands, unusual C−C and C−X bond disconnections, and the facile synthesis of structurally diverse molecules.

Despite the emergence of Rh-catalyzed asymmetric C−H functionalization reactions, a review covering ligand/catalyst and reaction development, mechanistic investigation, and synthetic application, especially the latest works reported in the past five years, is elusive. Meanwhile, under Rh-catalysis, structurally diverse chiral molecules bearing central chirality, planar chirality, axial chirality and helical chirality can be efficiently synthesized. Therefore, this review aims at providing a summary of this topic. However, the Rh(II)-catalyzed C−H insertion, which has been extensively discussed elsewhere,[39−46] will not be discussed here. This review is organized primarily by the type of catalytic systems, including Rh(I) and Rh(III)-catalysis.

Scheme 1. Transition-Metal (TM)-Catalyzed Asymmetric C−H Functionalization Reactions



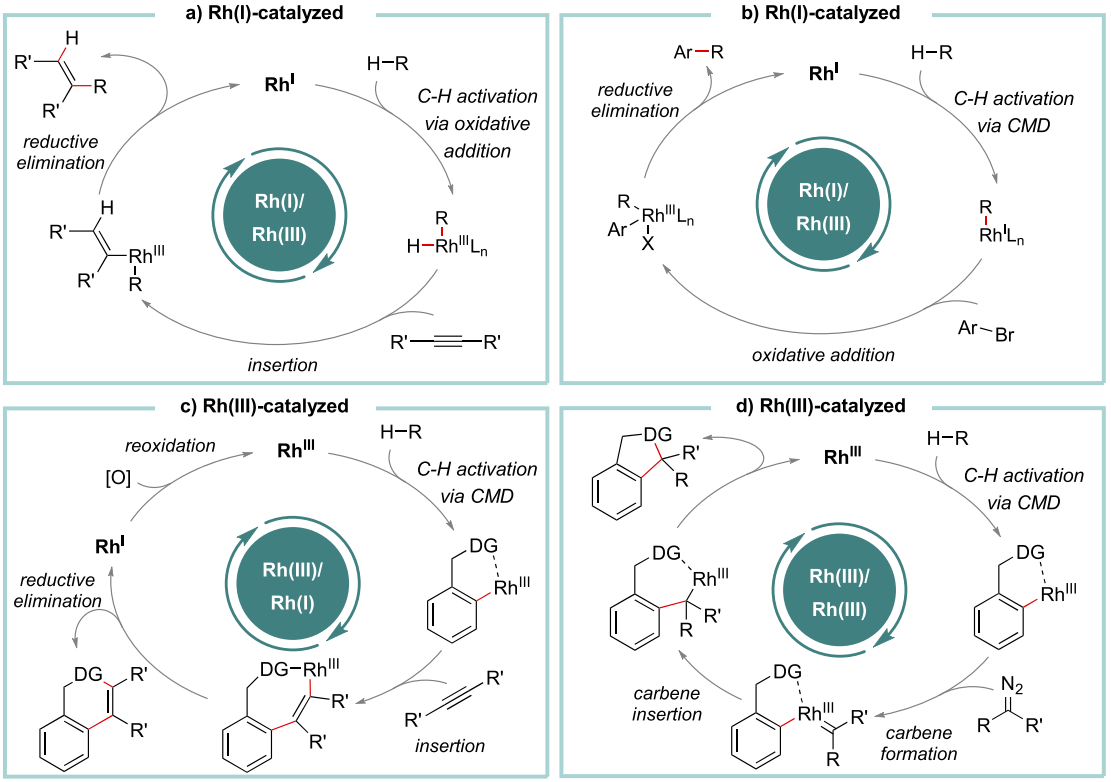


Figure 1. Catalytic Cycles for Rh-Catalyzed Asymmetric C−H Functionalization Reactions

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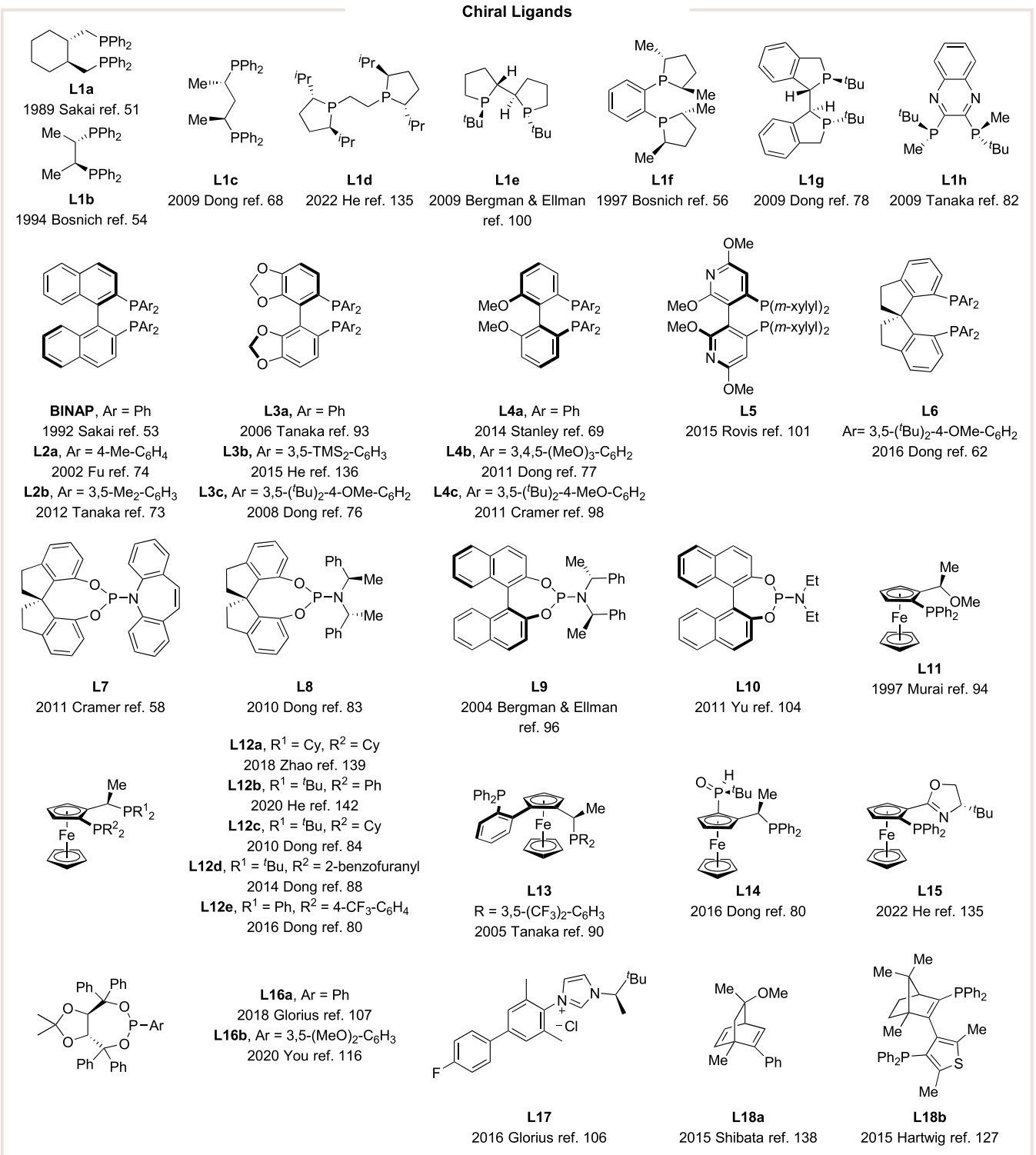

Figure 2. Chiral Ligands Used in Rh(I)-Catalyzed Asymmetric C−H Functionalization Reactions.

2. CATALYTIC CYCLES FOR RH-CATALYZED ASYMMETRIC C−H FUNCTIONALIZATION REACTIONS

To the best of our knowledge, Rh-catalyzed asymmetric C−H functionalization reactions often operate via four catalytic cycles: (a) Rh(I)/Rh(III) catalytic cycle (C−H activation via oxidative addition), (b) Rh(I)/Rh(III) catalytic cycle (C−H activation via concerted-metalation-deprotonation), (c) Rh(III)/Rh(I) catalytic cycle, and (d) Rh(III)/Rh(III) catalytic cycle. Rh(I)/Rh(III) catalytic cycle often initiates via the oxidative addition of a Rh(I) species into the C−H bond, giving the Rh−H complex (Figure 1a). Subsequent migratory insertion into the alkene, followed by reductive elimination, provides the product and regenerates the active Rh(I) catalyst. Alternatively, Rh(I)-catalyzed C−H arylation reaction initiates via concerted-metalation-deprotonation (CMD), resulting in the Rh−R complex (Figure 1b).[47] Subsequent oxidative addition of aryl

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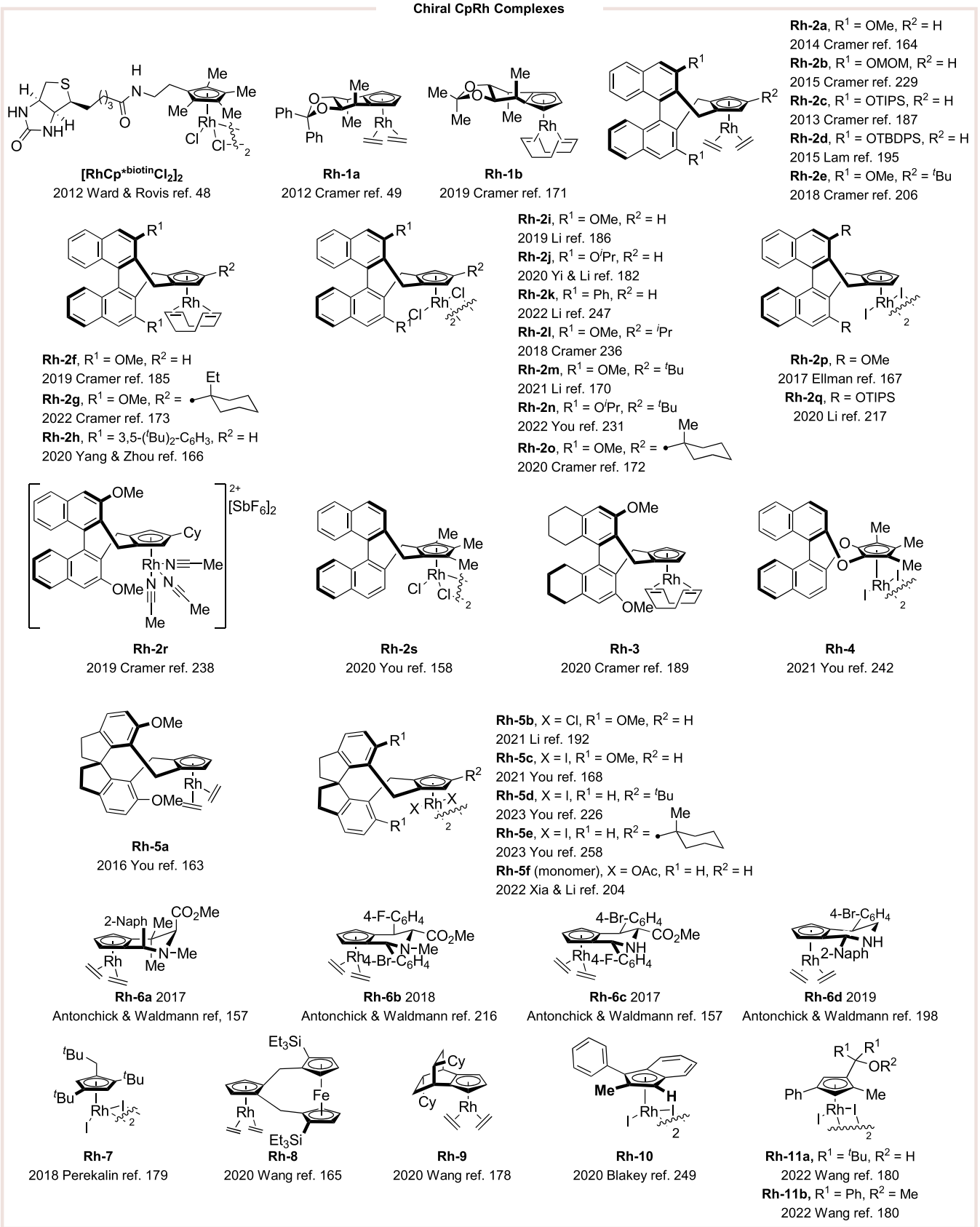

Figure 3. Chiral Cyclopentadiene-Rh Catalysts Used in Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions.

halide, followed by reductive elimination, generates the arylation product and regenerates the active Rh(I) catalyst. For Rh(III)/Rh(I) catalytic cycle (Figure 1c), the C−H bond activation step with the aid of the directing group occurs via concerted-

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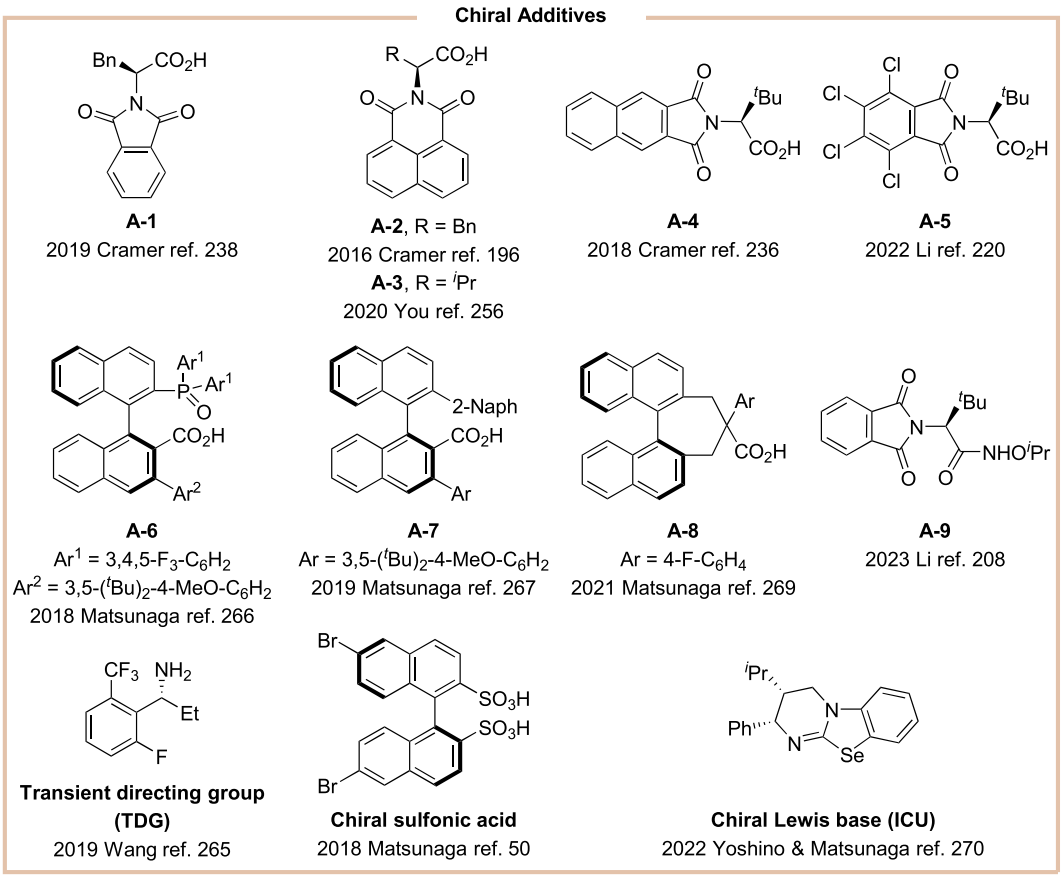
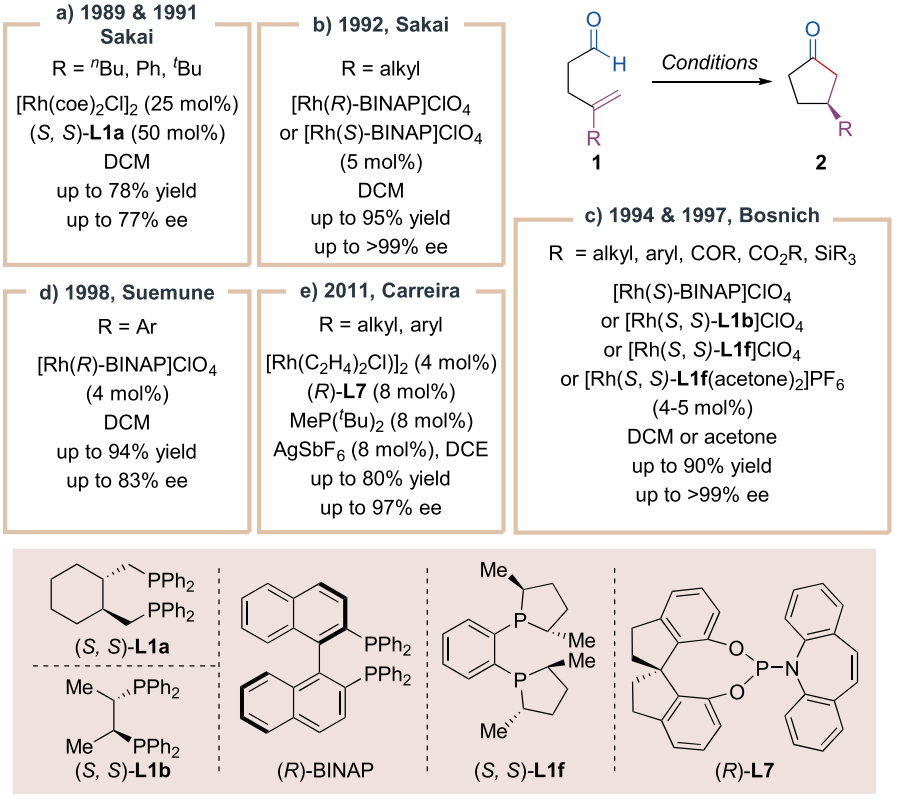


Figure 4. Chiral Additives Used in Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions.

Scheme 2. Enantioselective Synthesis of 3-Substituted Cyclopentanones



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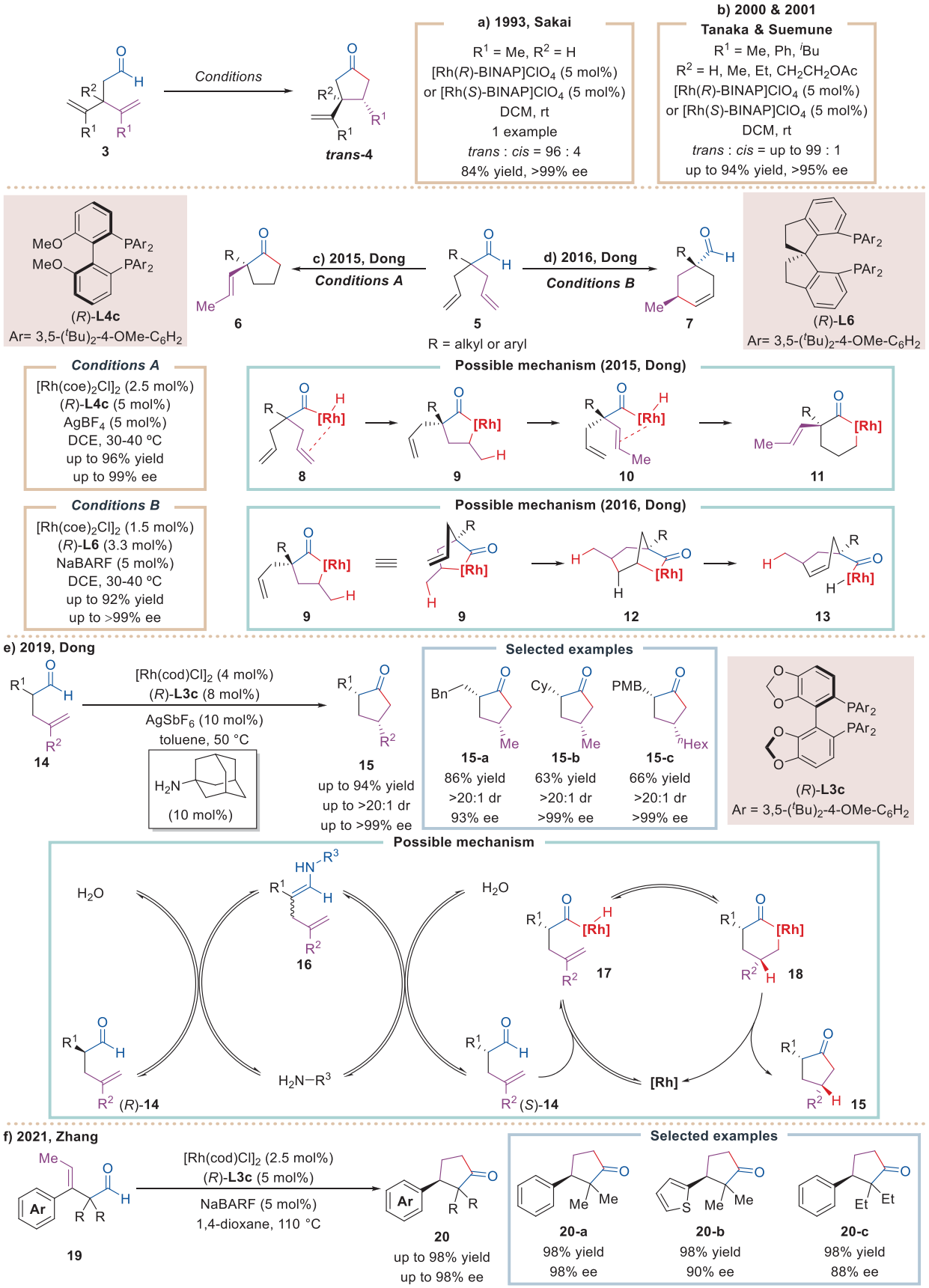
Scheme 3. Enantioselective Intramolecular Hydroacylation Reaction via Desymmetrizations



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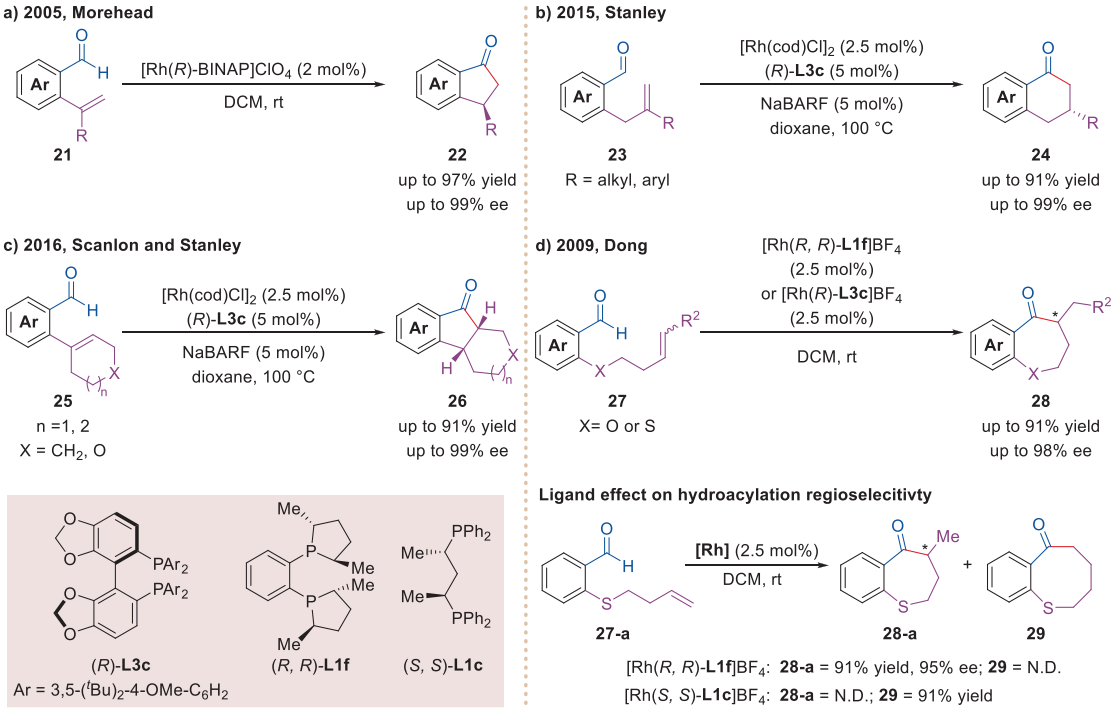
Scheme 4. Enantioselective Synthesis of Chiral Benzo-fused Ketones via Intramolecular Hydroacylation Reaction



metalation-deprotonation (CMD), giving aryl−Rh(III) intermediate. The latter inserts unsaturated compounds such as alkene, alkyne, allene, or aldehyde compounds to form a rhodacycle intermediate. Then reductive elimination gives the desired product and a Rh(I) species which undergoes oxidation to afford the active Rh(III) species. For Rh(III)/Rh(III) catalytic cycle (Figure 1d), it is similar to Rh(III)/Rh(I) catalytic cycle as exemplified for a reaction with diazo compounds. The aryl−Rh(III) intermediate is generated via CMD mechanism and inserts diazo compounds to form a rhodacycle intermediate. Then, the rhodacycle intermediate is followed by carbene insertion and protonation to afford the desired product and regenerate the active Rh(III) species.

3. LIGANDS AND CATALYSTS FOR RH-CATALYZED ASYMMETRIC C−H FUNCTIONALIZATION REACTIONS

Various chiral catalysts and ligands have been applied in Rh-catalyzed asymmetric C−H functionalization reactions. Among these, chiral phosphine ligands are undoubtedly the most used ones. Various privileged chiral backbones such as BINOL, SPINOL, TADDOL, ferrocene, etc., based ligands show good results in selectivity and activity. At the same time, other chiral ligands, such as *N*-heterocyclic carbenes and diene ligands, are also suitable for use. Some representative ligands are summarized in Figure 2.

While chiral phosphine ligands are often used in Rh(I)-catalyzed asymmetric C−H functionalization reactions, for Rh(III) catalysis, chiral cyclopentadiene (Cp) ligands are applied most frequently. The chiral Cp^{x}Rh complexes were first utilized in asymmetric C−H activation/[4 + 2] cyclization reactions by the Ward and Rovis groups,[48] and the Cramer group simultaneously.[49] Various chiral Cp^{x}Rh complexes are summarized in Figure 3. Furthermore, combining chiral additives, such as chiral acid, chiral Lewis base (isochalcogenureas, ICU), and chiral transient directing group with achiral Cp^{x}Rh complexes, first reported by the Matsunaga group,[50] also achieves good enantioselective control. Various chiral additives are summarized in Figure 4.

4. RH(I)-CATALYZED ASYMMETRIC C−H FUNCTIONALIZATION REACTIONS

4.1. Rh(I)-Catalyzed Asymmetric Hydroacylation

The asymmetric hydroacylation reaction is one of the early developed enantioselective C−H functionalization processes.[22] Remarkably, the entire process is completely atom economical and thus offers a particularly attractive route to chiral ketones and esters. Various coupling partners such as alkene, allene, alkyne, and ketone compounds have been utilized in enantioselective both intra- and intermolecular manner. Meanwhile, combining cationic rhodium complexes with a chiral bisphosphine ligand is the most widely employed catalytic system.

4.1.1. Rh(I)-Catalyzed Asymmetric Intramolecular Hydroacylation. Alkene is one of the most frequently employed coupling partners for asymmetric intramolecular hydroacylation. The first example of enantioselective intramolecular hydroacylation for the synthesis of 3-substituted cyclopentanones was reported by Sakai et al. in 1989 (Scheme 2a).[51,52] Using [Rh(coe)$_2$Cl]$_2$ and chiral bisphosphine ligand (*S*,*S*)-**L1a**, an intramolecular cyclization reaction was achieved to give cyclopentanones **2** in up to 78% yield and 77% ee. Later, this intramolecular asymmetric hydroacylation reaction of **1** was also achieved by Sakai[53] (Scheme 2b), Bosnich[54−56] (Scheme 2c) and Suemune[57] (Scheme 2d) groups by using various chiral bisphosphine ligands. In 2011, Carreira and co-workers introduced a chiral ligand, now known as the Carreira ligand, incorporating a potentially coordinating alkene moiety. Among them, SPINOL-derived **L7** was shown to provide high enantioselectivity. Interestingly, adding an achiral phosphine such as MeP(^{t}Bu)$_2$ could facilitate the reaction (Scheme 2e).[58]

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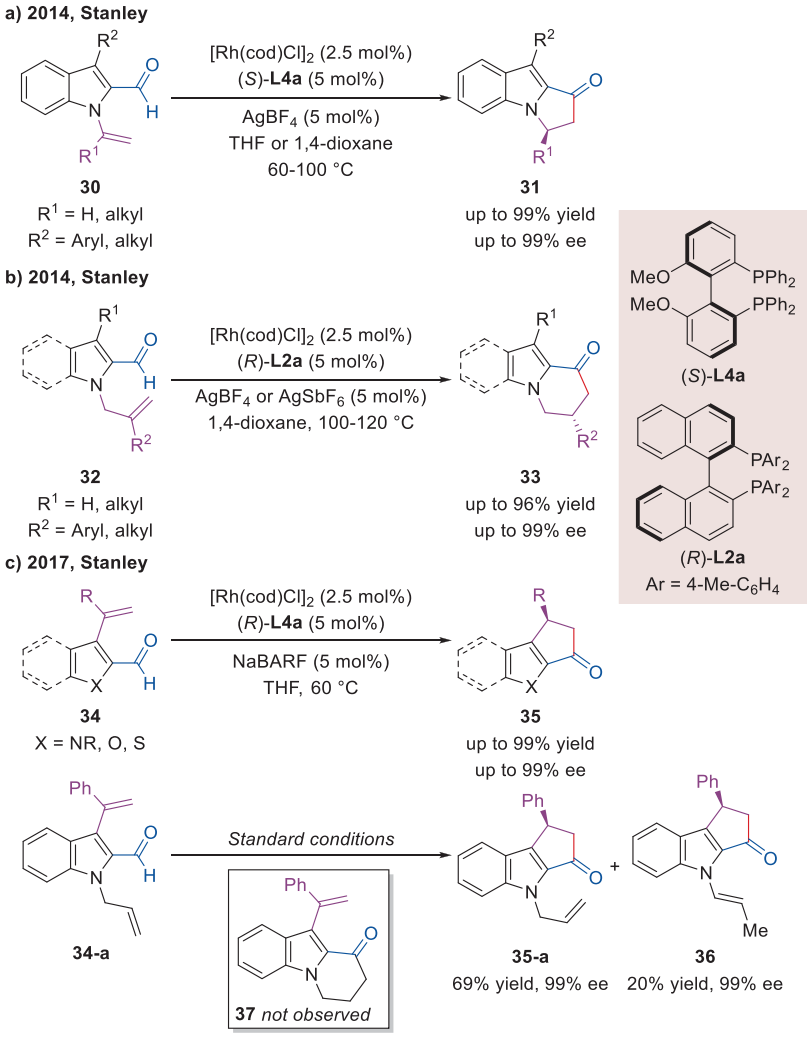
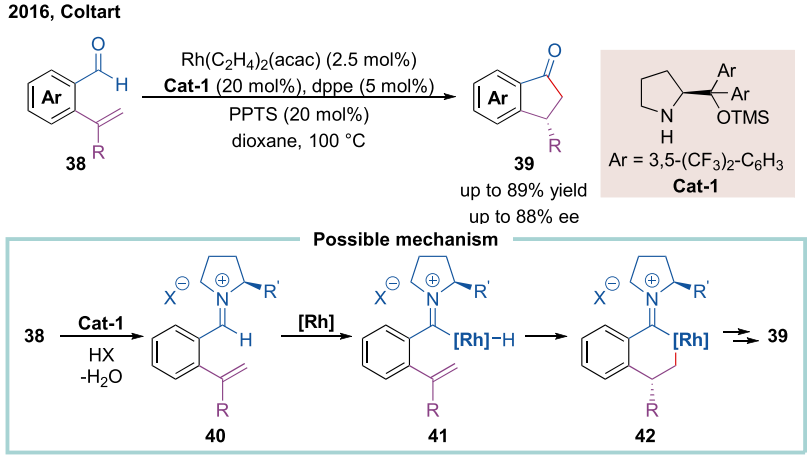
Scheme 5. Enantioselective Synthesis of Indoles and Pyrroles Derivatives via Intramolecular Hydroacylation Reaction



Scheme 6. Enantioselective Synthesis of Chiral Indanones by Cooperative Transition-Metal and Organo-Catalysis



The desymmetrization of prochiral dienes has been achieved by Rh(I)-catalyzed enantioselective hydroacylation. In 1993, Sakai and co-workers accomplished a highly diastereo- and enantioselective hydroacylation of 3,4-disusbtituted 4-pentenals **3** by Rh(I)/BINAP complex, generating the diastereoisomer *trans*-**4** with >99% ee (Scheme 3a).[59] Later, Tanaka, Suemune group broadened the substrate scope using the same conditions (Scheme 3b).[60] Next, Dong and co-workers accomplished Rh(I)-catalyzed intramolecular desymmetrization reactions of prochiral α,α-bisallylaldehydes **5** (Scheme 3c).[61] Divergent cyclization pathways were operated depending on different chiral phosphine ligands. When the reaction was carried out with a cationic Rh(I)/(*R*)-**L4c** complex, exclusive formation of cyclopentanones **6** containing α-quaternary stereocenters was

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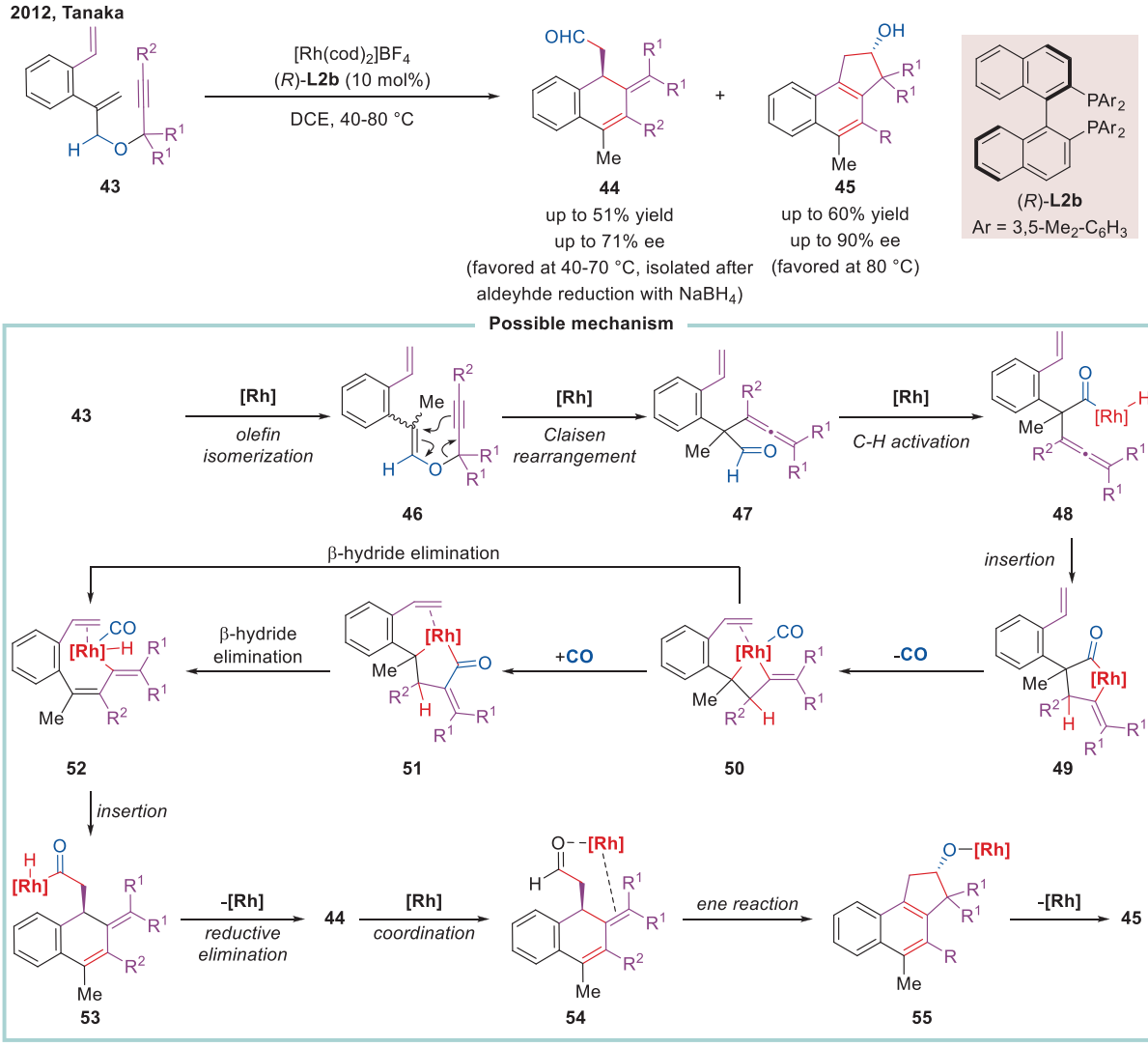
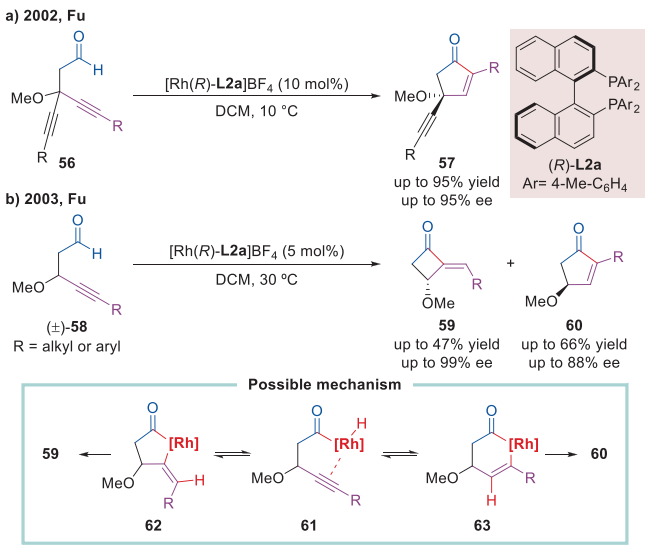
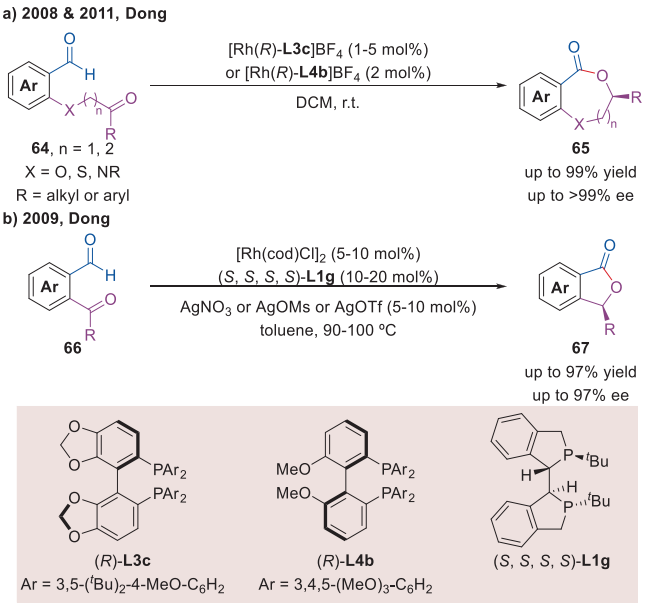
Scheme 7. Enantioselective Cascade Reactions of Dienynes via Intramolecular Hydroacylation Reaction



Scheme 8. Enantioselective Intramolecular Hydroacylation Reaction of Alkynes



Scheme 9. Enantioselective Intramolecular Hydroacylation Reaction of Ketones



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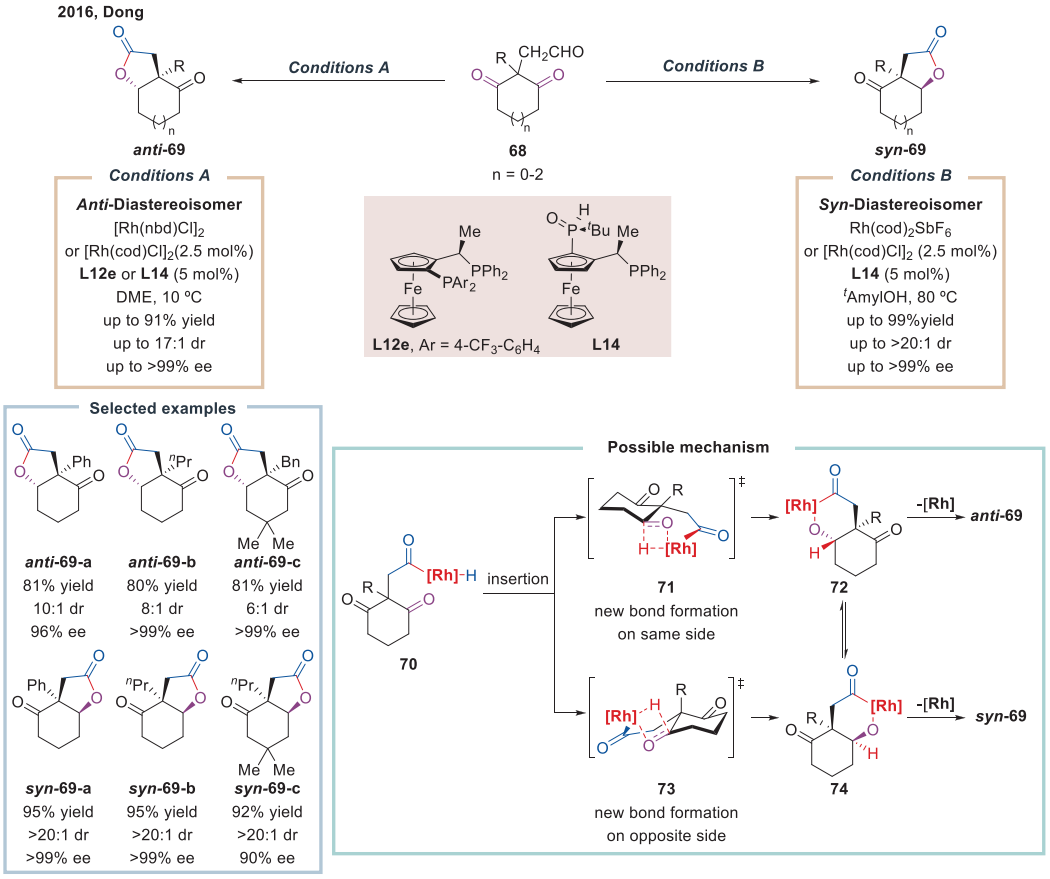
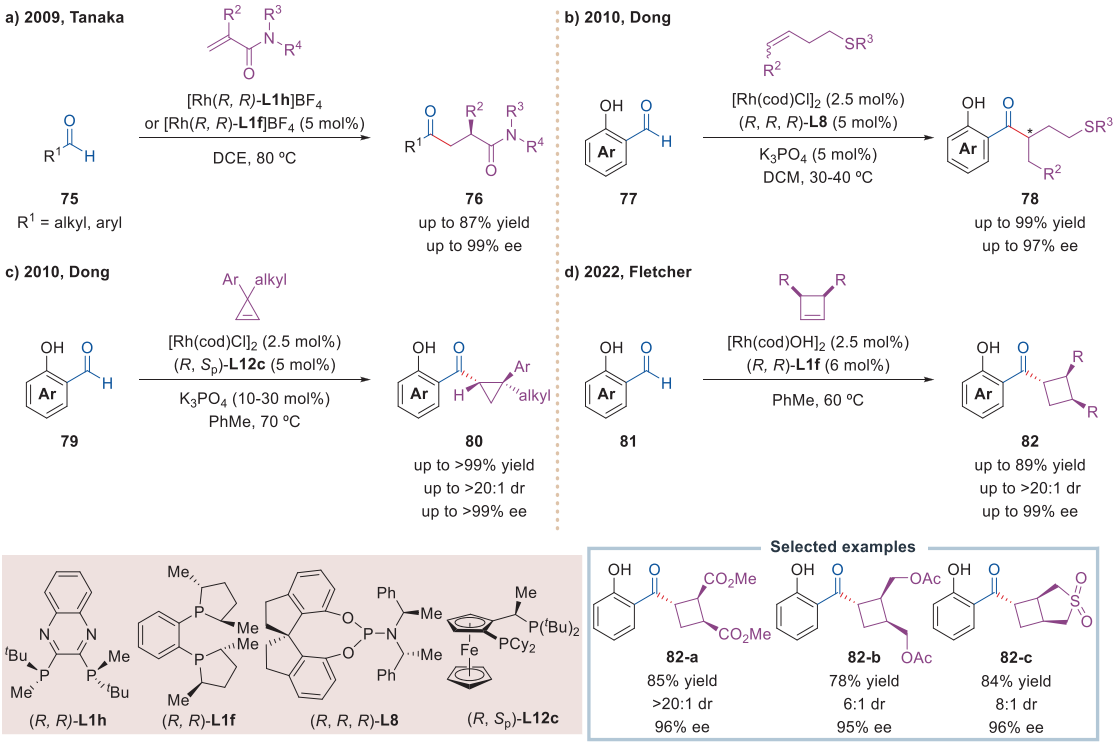
Scheme 10. Diastereodivergent Intramolecular Hydroacylation of Ketones



Scheme 11. Enantioselective Intermolecular Hydroacylation Reaction of Alkenes



observed in up to 96% yield and 99% ee. The authors proposed the reaction mechanism, which proceeds via an isomerization/ hydroacylation sequence. The intermediate **8** undergoes an intramolecular migratory insertion of an alkene into the Rh−H

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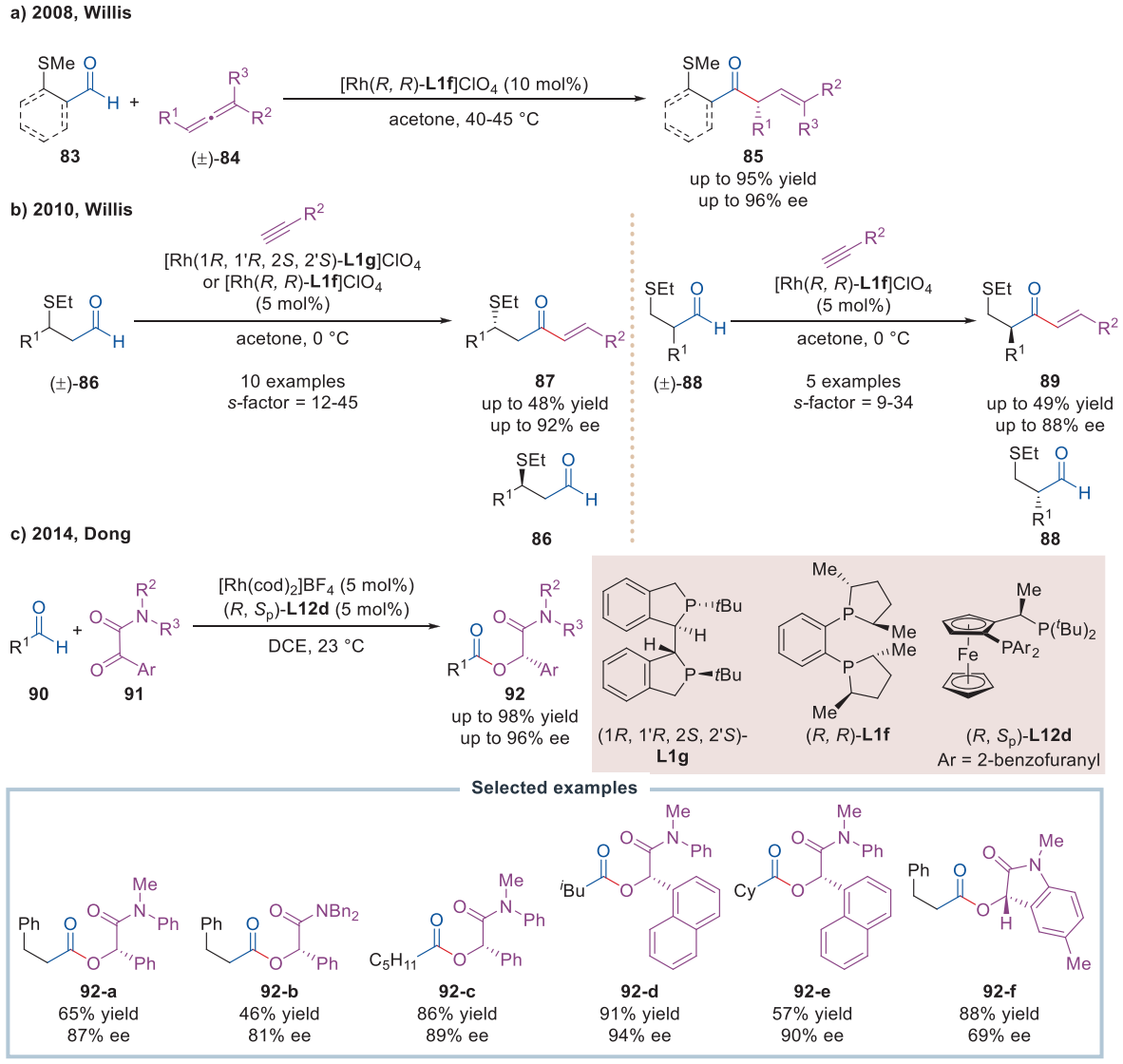
Scheme 12. Enantioselective Intermolecular Hydroacylation Reaction of Allenes, Alkynes, and Ketones



bond, affording the five-membered rhodacycle **9**. The β-hydride elimination produces the isomerized Rh-acyl intermediate **10**, which subsequently undergoes an olefin-directed hydrometalation to yield the intermediate **11**. Finally, reductive elimination yields the cyclopentanone products **6** and regenerates the active rhodium catalyst. However, changing chiral ligand (*R*)-**L4c** to SPINOL-derived bisphosphine (*R*)-**L6**, chiral cyclohexenes **7** were isolated in good results (up to 92% yield, >99% ee) under similar conditions (Scheme 3d).[62] The reaction mechanism is believed to occur through the same five-membered rhodacycle **9**. However, carboacylation of the pendant olefin predominately occurred, leading to intermediate **12**. The bite angle of the ligand is essential for promoting carboacylation rather than isomerization/hydroacylation. Then, β-hydride elimination proceeded to generate acyl−Rh(III)−H intermediate **13**, which underwent reductive elimination to afford the chiral cyclohexenes **7**. In 2019, Dong and co-workers reported a dynamic kinetic resolution (DKR) of chiral 4-pentenals **14** by asymmetric hydroacylation (Scheme 3e).[63] The presence of 1-adamantylamine could racemize the aldehyde **14** via enamine formation and hydrolysis. Combining with cationic rhodium catalyst, α,γ-disubstituted cyclopentanones **15** with high diastereo- and enantioselectivity were generated. The authors proposed a mechanism involving two catalytic cycles. The primary amine catalyst reversibly condenses with aldehyde **14** to form an achiral enamine **16**, which then undergoes hydrolysis to racemize the aldehyde **14**. The enantiomer (*R*)-**14** undergoes oxidative addition with the rhodium catalyst to deliver the rhodium acyl hydride **17**. Then, migratory insertion occurs to generate intermediate **18**, which undergoes reductive elimination to yield cyclopentanone **15**. Zhang and co-workers recently came up with an asymmetric intramolecular hydroacylation via a five-membered rhodacycle intermediate (Scheme 3f).[64] 3-Enals **19** were smoothly converted to cyclopentanones **20** in satisfactory yields, diastereo- and enantioselectivities.

The asymmetric intramolecular hydroacylation of *ortho*-vinyl- and *ortho*-allylbenzaldehydes derivatives enables efficient access to various benzo-fused cyclic ketones. In 2005, Morehead and co-workers achieved that [Rh(*R*)-BINAP]ClO_4 catalyzed asymmetric intramolecular hydroacylation reaction of substituted styrenes **21** to generate chiral indanones **22** in high yields and excellent levels of enantiocontrol (up to 97% yield, 99% ee, Scheme 4a).[65] In 2015, Stanley and co-workers reported that Rh(I)-catalyzed hydroacylation of *ortho*-allylbenzaldehydes **23**

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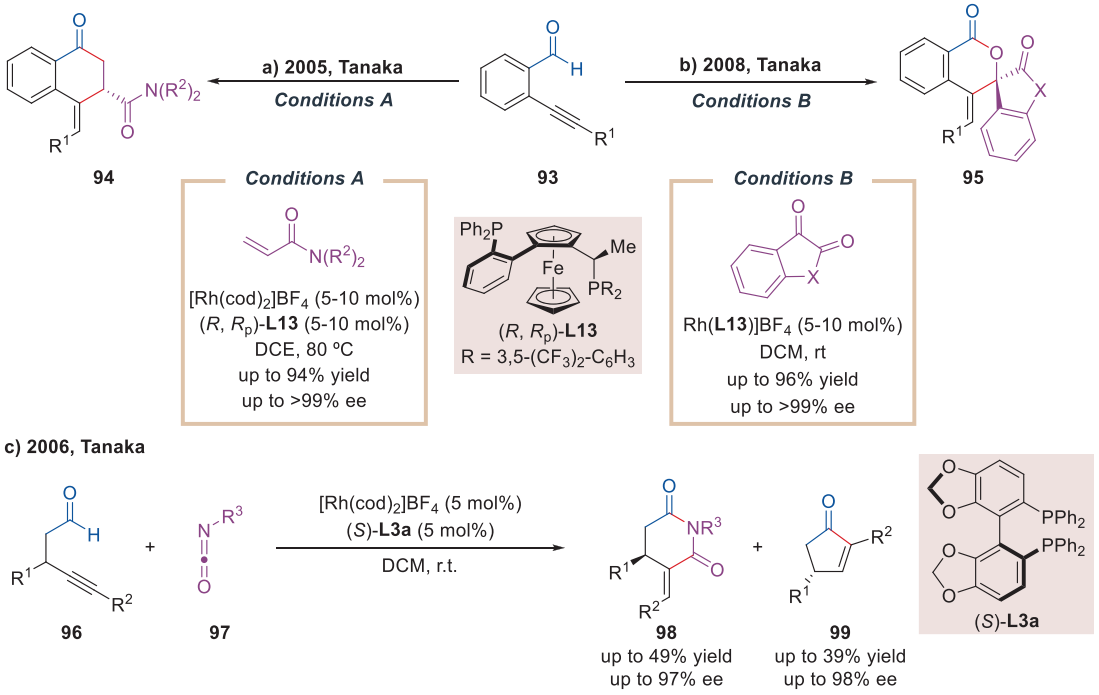
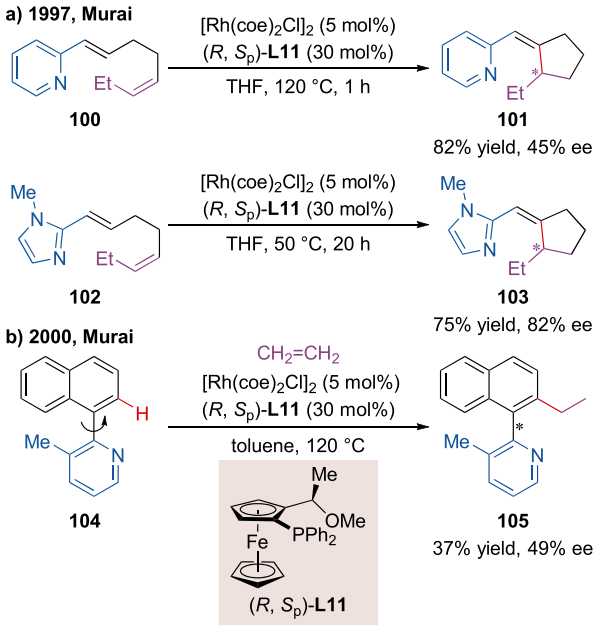
Scheme 13. Rh(I)-Catalyzed Enantioselective Intermolecular Annulation of Aldehydes



Scheme 14. Rh(I)-Catalyzed Asymmetric C−H Alkylation Using 2-Pyridyl or 2-Imidazoyl as the Directing Group



with chiral ligand (*R*)-**L3c** (Scheme 4b).[66] Only a six-membered cyclic product was observed in this reaction, affording 3,4-dihydronaphthalen-1(2*H*)-ones **24** in excellent enantioselectivity (up to 91% yield, 99% ee). Due to steric hindrance, trisubstituted olefins in Rh(I)-catalyzed asymmetric hydroacylation are often challenging. Scanlon, Stanley and co-workers achieved Rh(I)-catalyzed hydroacylation of trisubstituted cycloalkenes **25** to synthesize various tetracyclic hexahydro-9*H*-fluoren-9-ones **26** in 2016 (Scheme 4c).[67] In 2009, Dong and co-workers applied an intramolecular hydroacylation to obtain seven or eight-membered cyclic ketones (Scheme 4d).[68] It should be noted that the regioselectivity was partly dependent on the chiral ligand. For example, with (*R*,*R*)-**L1f**, branched cycloheptenone **28-a** was obtained in 91% yield and 95% ee. On the contrary, when (*S*,*S*)-**L1c** was used, the formation of achiral cyclooctanone **29** was observed.

Apart from benzaldehydes, aromatic heterocyclic formaldehyde derivatives could also be used in asymmetric hydroacylation reactions. Stanley and co-workers disclosed in 2014 that Rh(I)-catalyzed asymmetric intramolecular hydroacylation of **30** afforded the cyclic product **31** in good yields and enantioselectivity (up to 99% yield, 99% ee, Scheme 5a).[69] The authors found that the level of enantioselectivity could be maintained with only 0.2 mol % catalyst. Meanwhile, the same group achieved the enantioselective synthesis of six-membered rings via a similar asymmetric hydroacylation reaction (Scheme 5b).[70] Olefin fragments can be attached to the N atom of indole and the 3-position. In 2017, the Stanley group reported Rh(I)-catalyzed intramolecular alkene hydroacylation to achieve the enantioselective synthesis of polycyclic nitrogen, oxygen, and sulfur containing heterocycles (Scheme 5c).[71] It is worth noting that hydroacylation of *N*-allyl substituted **34-a** was overwhelmingly selective for the vinyl alkene to generate a five-membered cyclic product **35-a** over the allyl alkene, which would generate a six-membered cyclic product **37**.

Combining organo-catalysis with transition-metal catalysis, Coltart and co-workers achieved enantioselective aldiminium C(sp^2)−H bond functionalization in up to 89% yield and 88% ee in 2016, allowing a one-pot conversion of benzaldehydes **38** to indanones **39** (Scheme 6).[72] The pyrrolidine derivative **Cat-1** first condenses with the aldehyde substrates **38** to generate aldiminium species **40**. Then, oxidative insertion of an achiral Rh species into the aldiminium C−H bond occurs to deliver the metal-complex **41**. Next, migratory insertion of the alkene moiety into the Rh−H bond generates a six-membered cyclorhodium intermediate **42**, and final reductive elimination and hydrolysis provide the chiral indanones **39** and regenerate the catalyst.

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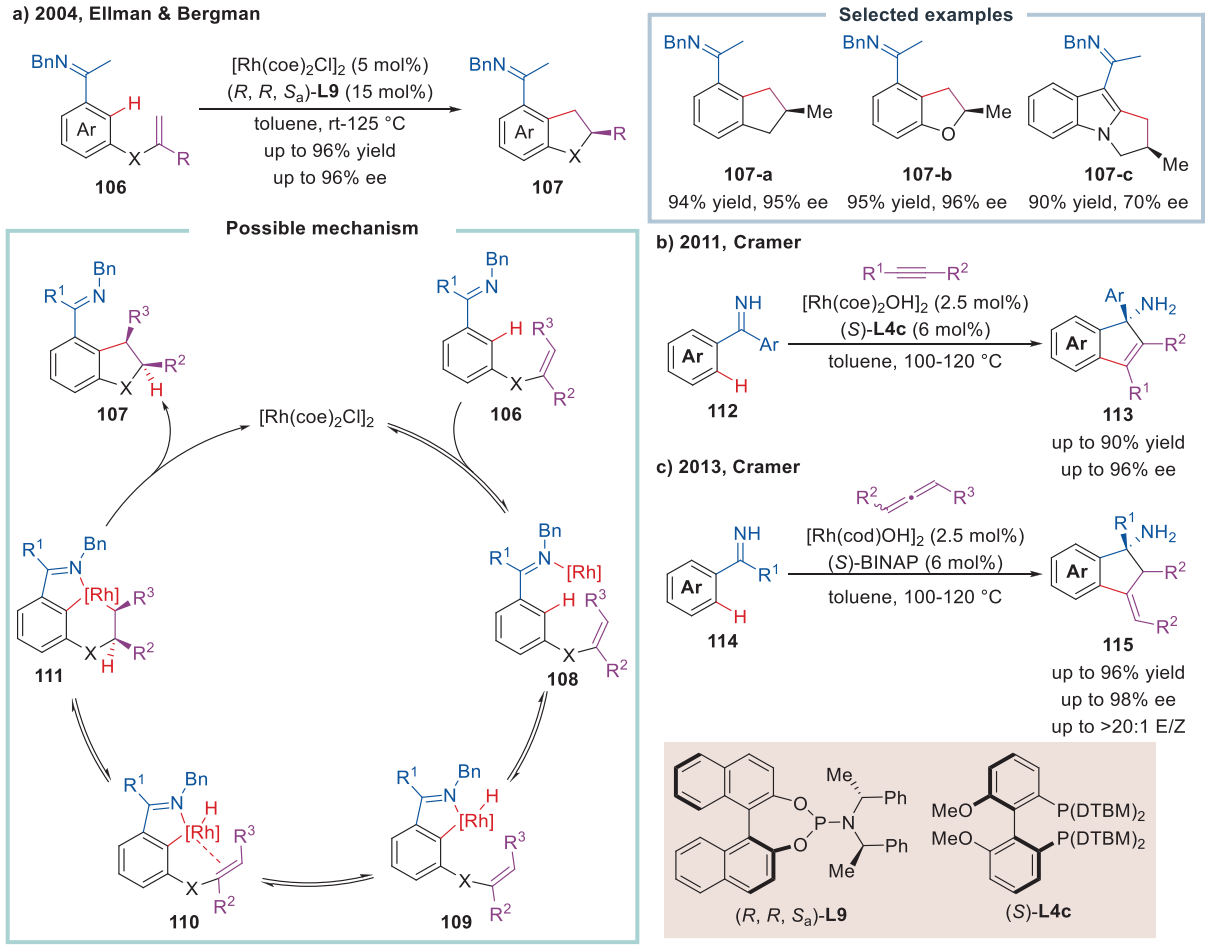
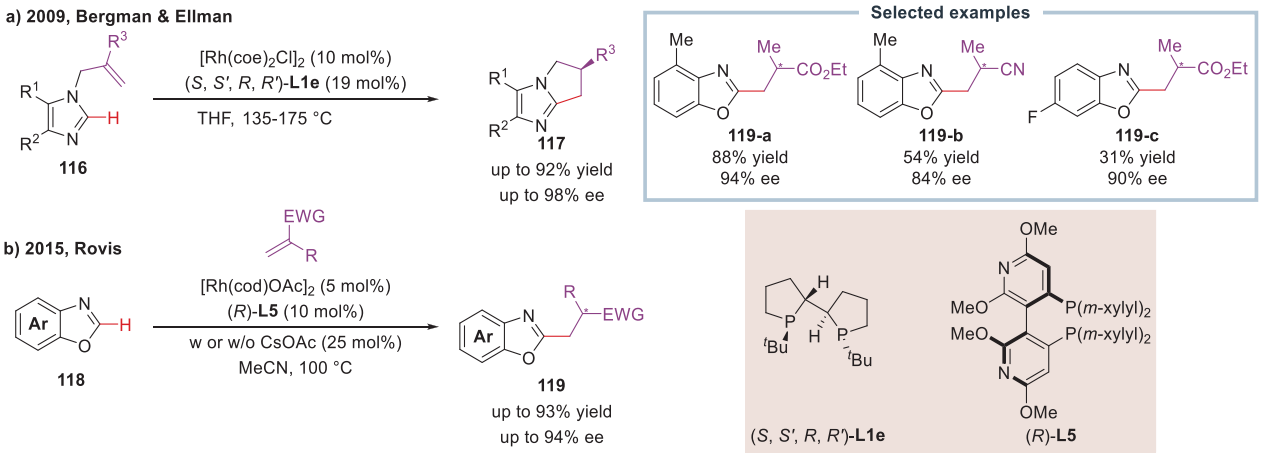
Scheme 15. Rh(I)-Catalyzed Asymmetric Cyclization Using Imine as the Directing Group



Scheme 16. Rh(I)-Catalyzed Asymmetric C−H Alkylation of Imidazoles and Benzoxazoles



In 2012, Tanaka and co-workers achieved Rh(I)-catalyzed asymmetric cascade reaction of dienynes **43**, favoring the selective formation of bicyclic aldehydes **44** or tricyclic alcohols **45** depending on the temperature of the reaction (Scheme 7).[73] The transformation was conducted using a cationic rhodium (*R*)-**L2b** complex, tolerating alkyl and aryl-substituted alkynes. A possible mechanism was also proposed. The reaction begins with olefin isomerization to afford enol ether **46**, which consequently undergoes the Claisen rearrangement to afford allenic aldehyde **47**. Then, oxidative addition of the aldehyde C(sp^2)−H bond, followed by the intramolecular migratory insertion to form rhodacycle **49**. Next, migratory extrusion of CO to intermediate **50** is followed by CO migratory insertion to generate **51**. Then **51** undergoes *β*-hydride elimination to generate intermediate **52**. Alternatively, the same intermediate **52** can be delivered by a direct *β*-hydride elimination from **50**. Subsequently, intermediate **52** undergoes an asymmetric carboformylation process, generating acyl-rhodium complex

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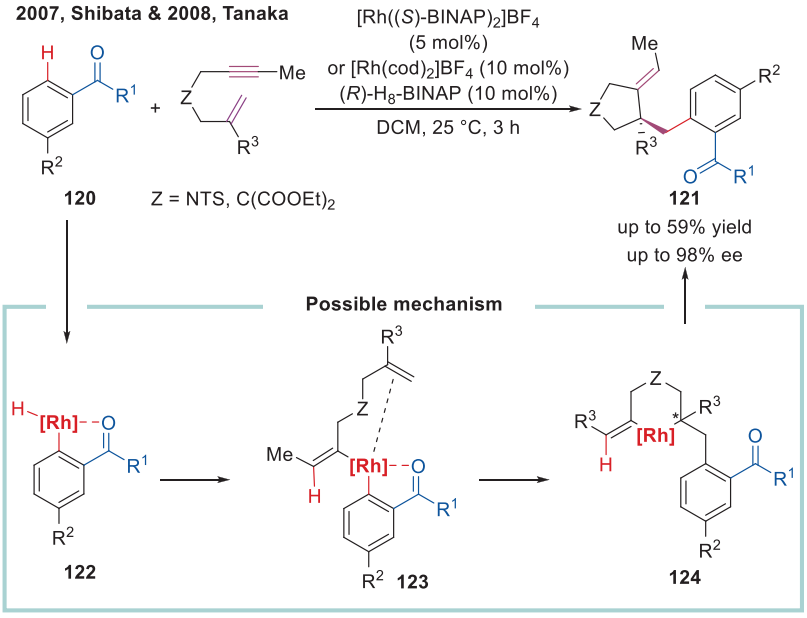
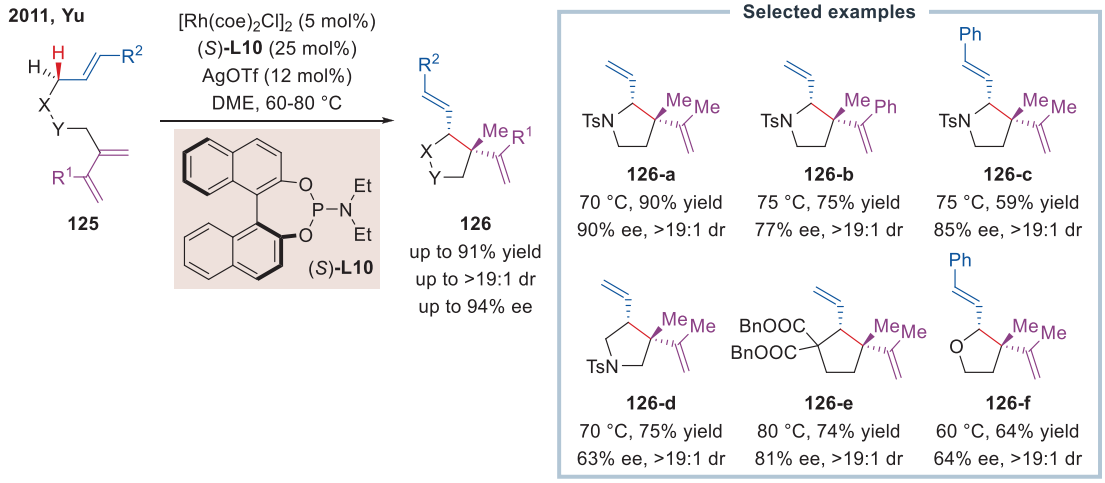
Scheme 17. Rh(I)-Catalyzed Asymmetric Cyclization Using Ketones as the Directing Group



Scheme 18. Rh(I)-Catalyzed Asymmetric Allylic C−H Functionalization



53, which proceeds a reductive elimination to provide aldehyde **44**. Finally, the subsequent stereoselective carbonyl ene reaction occurs to afford alcohol **45** at a higher temperature.

The enantioselective hydroacylation of alkynes has also been realized. In 2002, Fu and co-workers proved that prochiral diynes **56** could be effectively desymmetrized in the presence of 10 mol % [Rh(*R*)-**L2a**]BF_4, enabling access to chiral cyclopentenones **57** in good results (up to 95% yield, 95% ee, Scheme 8a).[74] In 2003, the same group also achieved a kinetic resolution of several related racemic alkynals (±)-**58** (Scheme 8b).[75] The regiodivergent parallel kinetic resolution occurred, delivering cyclobutanones **59** in up to 47% yield and 99% ee, as well as cyclopentenones **60** in up to 66% yield and 88% ee. The Rh−H species **61**, generated by oxidative addition of (±)-**58**, could undergo the migratory insertion to form the five-membered rhodacycle **62**, leading to cyclobutane **59**. Alternatively, if the migratory insertion proceeds to the six-membered rhodacycle **63**, reductive elimination provides cyclopentenone **60**.

Ketone could also participate in asymmetric intramolecular hydroacylation as the coupling partner. In 2008, Dong and co-workers reported a Rh(I)-catalyzed asymmetric hydroacylation of ketones (Scheme 9a).[76] Various ketones **64** could be hydroacylated in an intramolecular manner with [Rh(*R*)-**L4b**]BF_4, forming seven-membered cyclic products **65** in good enantioselectivity. Dong's group further demonstrated that nitrogen is also a competent linkage by using chiral bisphosphine ligand (*R*)-**L4b** (Scheme 9a).[77] In 2009, the Dong group achieved the cyclization of 2-ketobenzaldehydes **66** with (*S*,*S*,*S*,*S*)-**L1g**, affording the phthalide motif **67** in good results (up to 97% yield, 97% ee, Scheme 9b).[78,79]

In 2016, Dong and co-workers achieved a diastereodivergent desymmetrization of 4,4′-diketo aldehydes **68** (Scheme 10).[80] By adjusting the reaction conditions, either *anti*- or *syn*-bicyclic γ-lactones **69** could be synthesized efficiently. A possible mechanism was proposed based on the computational and experimental studies and the literature precedent. First, oxidative addition of the rhodium catalyst into the aldehyde C(sp^2)−H bond generates intermediates **70**, and then migratory insertion in diastereodivergent manner can occur. The C−C bond is formed on the same or opposite side of the carbocycle

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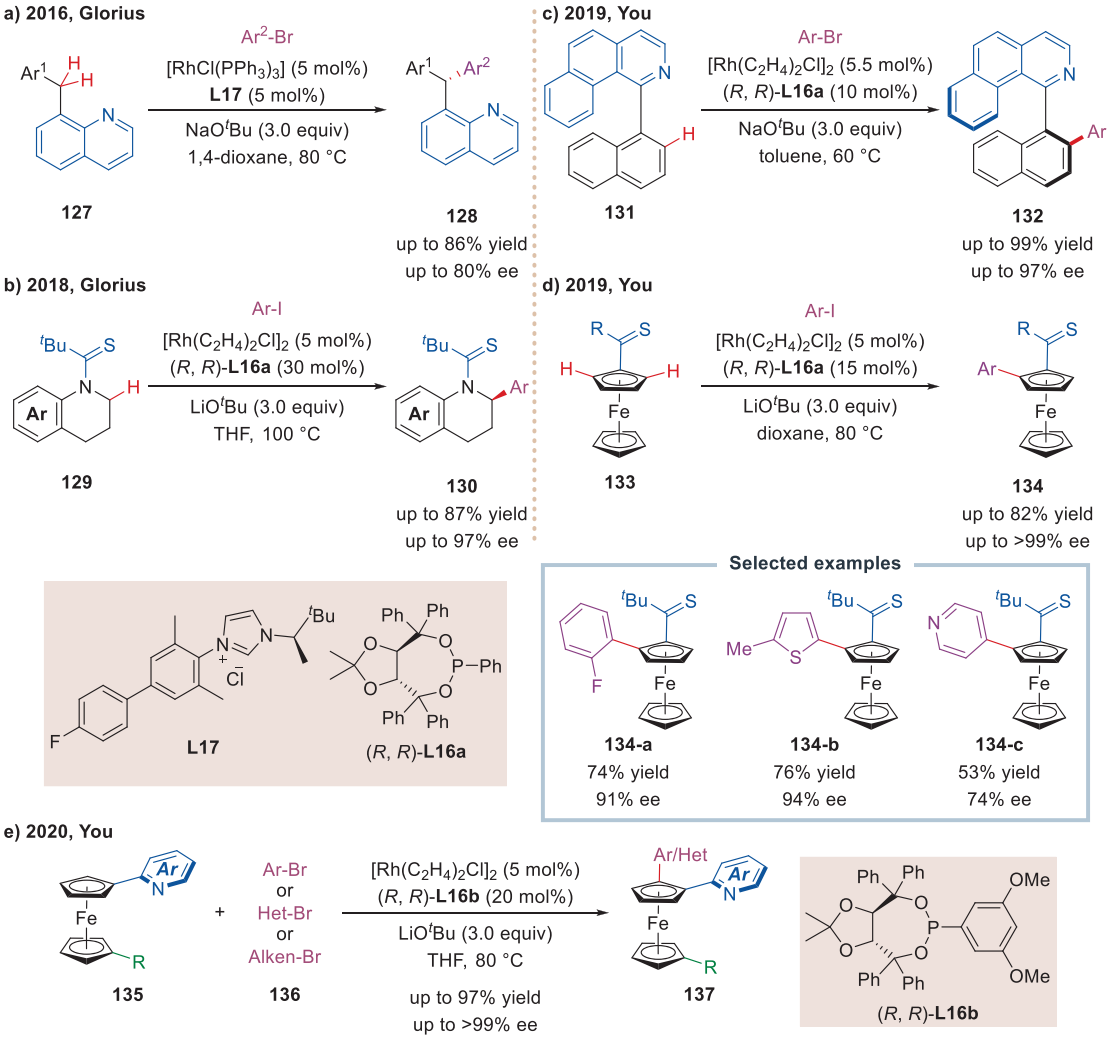
Scheme 19. Rh(I)-Catalyzed Asymmetric C−H Arylation with Aryl Halides



(via **71** or **73**). The solvent and counterion coordination capabilities affect the relative transition state energies and geometries. Since the process is reversible, the resulting rhodacycles **72** and **74** are in equilibrium, and the irreversible reductive elimination produces the corresponding products *anti*-**69** and *syn*-**69**.

4.1.2. Rh(I)-Catalyzed Asymmetric Intermolecular Hydroacylations. In 2007, Bolm and co-workers described strain-driven asymmetric intermolecular hydroacylation reactions of norbornene or norbornadiene.[81] Coordinating with phenolic oxygen on the aryl aldehyde group was demonstrated to play a key role in suppressing decarbonylation reaction. Although only modest enantioselectivity was accessed, the reactions could occur in good yields and diastereoselectivity. In 2009, Tanaka and co-workers reported an intermolecular hydroacylation reaction with nonchelating aldehydes **75** (Scheme 11a).[82] In this case, aryl and alkyl substituted aldehydes **75** underwent the intermolecular hydroacylation reaction with acrylamides by using a cationic Rh(I) complex derived from chiral bisphosphine ligand (*R*,*R*)-**L1h** or (*R*,*R*)-**L1f**. In 2010, Dong and co-workers employed the chiral monodentate phosphoramidite (*R*,*R*,*R*)-**L8** as the ligand to achieve the regio- and enantioselective intermolecular hydroacylation of salicylaldehyde derivatives **77** with homoallylic sulfides, affording structurally diverse α-substituted ketones **78** in good yields and enantioselectivity (up to 99% yield, 97% ee, Scheme 11b).[83] The same group also reported an asymmetric intermolecular hydroacylation of strained cyclic alkenes. Using Josiphos-type ligand (R,S_p)-**L12c**, a strain-releasing hydroacylation reaction with achiral cyclopropenes was carried out to generate *trans*-cyclopropylketones **80** bearing a quaternary stereocenter (Scheme 11c).[84] Recently, Fletcher and co-workers reported a Rh(I)-catalyzed asymmetric intermolecular hydroacylation of various *meso*-cyclobutenes with salicylaldehydes. A range of cyclobutenes was used to provide the target products in up to 89% yield, >20:1 dr and 99% ee (Scheme 11d).[85]

In 2008, enantioselective intermolecular hydroacylation of aryl and alkyl β-*S*-aldehydes **83** with racemic allenes (±)-**84** was described by the Willis group (Scheme 12a).[86] Detailed mechanistic studies suggested that the isomerization of allenes occurred under the reaction conditions, showing a dynamic kinetic asymmetric transformation. Later, the same group achieved an asymmetric intermolecular alkyne hydroacylation of racemic β-ethylthio substituted aldehydes (±)-**86** with terminal alkynes, generating the corresponding chiral α,β-unsaturated ketones **87** in up to 48% yield and 92% ee and recovering the optically pure β-ethylthio substituted aldehydes **86**, racemic α-substituted aldehydes (±)-**88** was also suitable for the kinetic resolution in moderate *s* factor (Scheme 12b).[87] In 2014, Dong and co-workers accomplished an enantioselective

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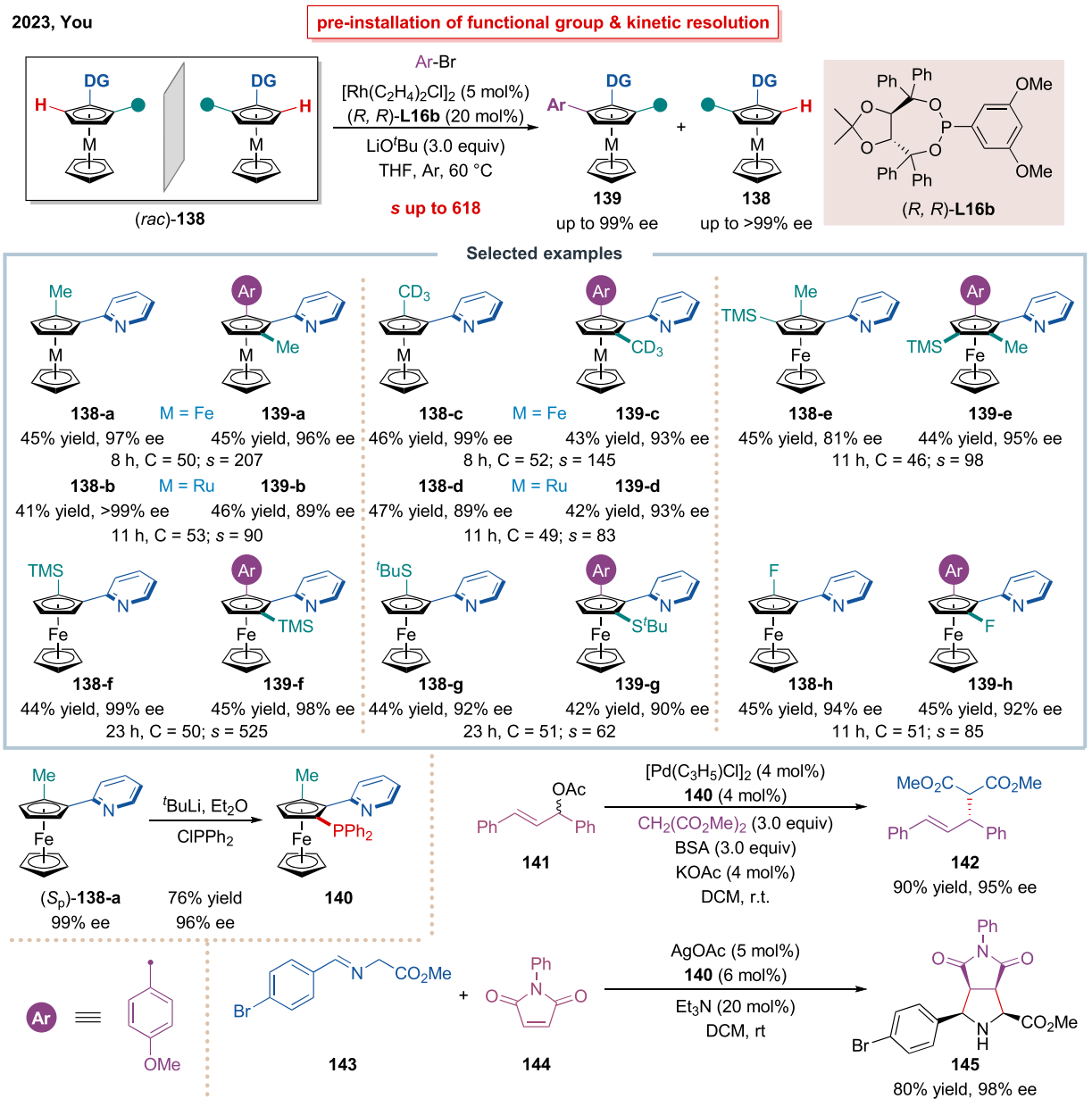
Scheme 20. Kinetic Resolution of 1,2-Disubstituted Metallocenes Using Rh-Catalyzed Asymmetric C−H Arylation



intermolecular hydroacylation by using Josiphos-type ligand (R,S_p)-**L12d**, involving the cross-coupling of simple aldehydes **90** with α-ketoamides **91**, enabling the diverse synthesis of various functionalized esters **92** in up to 98% yield and 96% ee (Scheme 12c).[88,89]

Meanwhile, a series of enantioselective Rh(I)-catalyzed [4 + 2] annulation via intermolecular hydroacylation was developed by Tanaka and co-workers. In 2005, the Tanaka group achieved coupling of **93** with *N*,*N*-dialkylacrylamides to afford chiral cyclohexanones **94** (Scheme 13a).[90] Combining a cationic Rh(I) complex with Walphos (R,R_p)-**L13** could generate good yields and high levels of enantioinduction. Then, the same group changed the coupling partners to cyclic 1,2-diketones, enabling the synthesis of spirocyclic benzopyranones **95** in good yields and enantioselectivity by using the same ligand (R,R_p)-**L13** (Scheme 13b).[91,92] In 2006, the Tanaka group reported a Rh(I)-catalyzed parallel kinetic resolution of racemic 3-substituted 4-alkynals **96** with isocyanates **97** in an [4 + 2] annulation process, providing chiral glutarimides **98** and cyclopentenones **99** (Scheme 13c).[93] The utilization of the cationic [Rh(cod)$_2$]-BF$_4$/(*S*)-**L3a** catalytic system provided the best combination of yield and enantioselectivity, enabling a small library of aryl, alkyl, and alkenyl substituted products.

4.2. Rh(I)-Catalyzed Asymmetric C−H Functionalization Reactions with Alkenes and Alkynes

In 1997, the seminal Rh(I)-catalyzed asymmetric C−H activation with alkenes was reported by Murai and co-workers. The catalyst derived from [Rh(coe)$_2$Cl]$_2$/(*R*,*S*)-**L11** afforded cyclopentanes **101** in 82% yield and 45% ee and **103** in 75% yield and 82% ee, respectively (Scheme 14a).[94] Meanwhile, in 2000, Murai and co-workers disclosed a Rh(I)-catalyzed atropoenantioselective alkylation of naphthalene **104**, generating the axially chiral product **105** in 37% yield and 49% ee (Scheme 14b).[95] This reaction proceeds via oxidative addition to yield a Rh−H intermediate, followed by a migratory insertion and reductive elimination to provide **105**.

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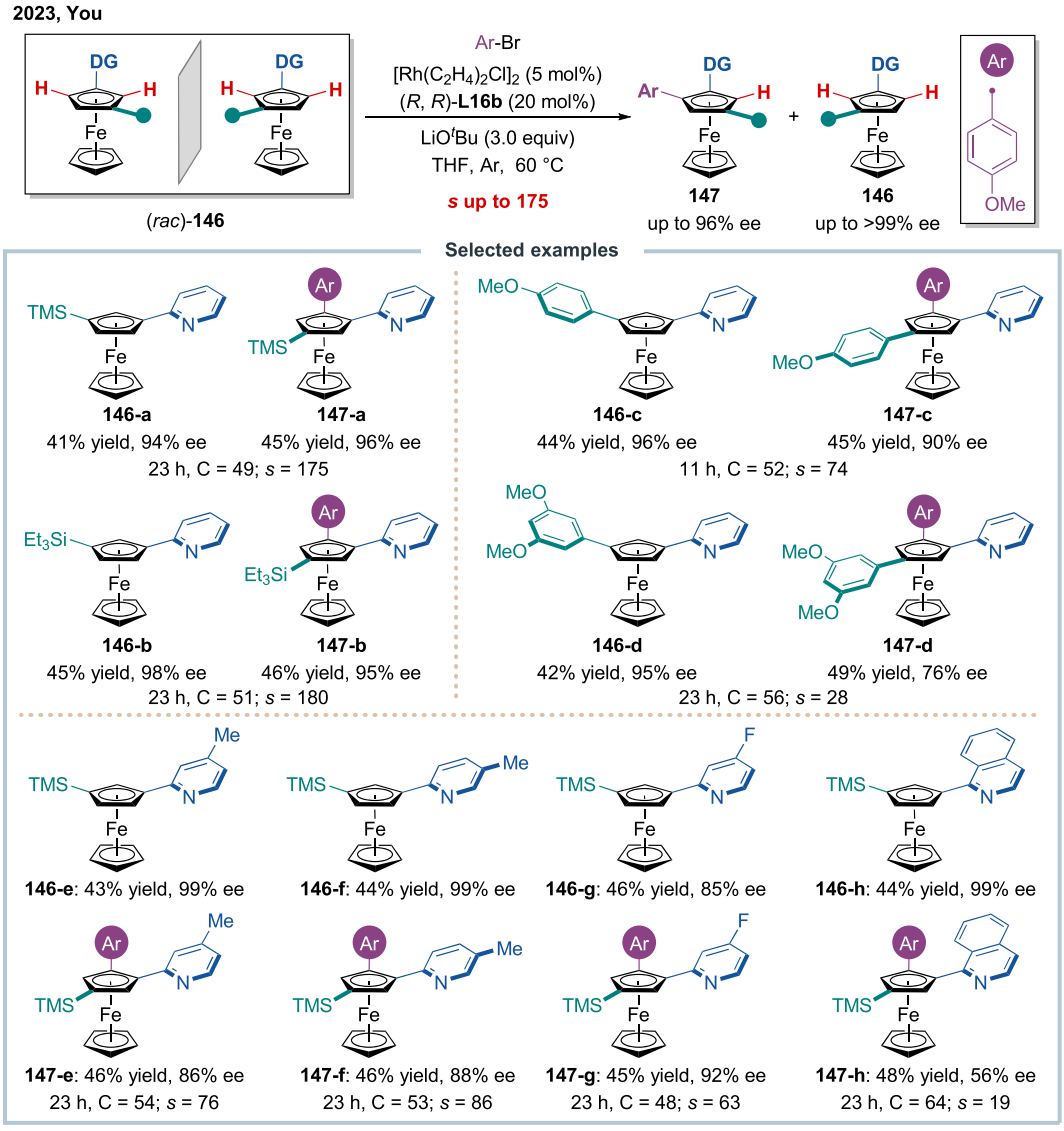
Scheme 21. Kinetic Resolution of 1,3-Disubstituted Ferrocenes Using Rh-Catalyzed Asymmetric C−H Arylation



In 2004, Ellman, Bergman, and co-workers accomplished a highly enantioselective catalytic reaction involving aromatic C−H activation using imines as the directing group (Scheme 15a).[96,97] Hydroarylation of ketimines **106** provided **107** in up to 96% yield and 96% ee via Rh(I)/Rh(III) catalytic cycle. A possible mechanism was proposed. The rhodium catalyst coordinates with imine, and oxidative addition of the C−H bond delivers a Rh−H intermediate **109**. Subsequently, the metal center coordinates with the alkenyl group. Then migratory insertion of the alkenyl group into the Rh−H bond provides intermediate **111**, which undergoes reductive elimination to generate products **107**. In 2011, the Cramer group employed the imine directing group in asymmetric intermolecular reactions (Scheme 15b).[98] An asymmetric synthesis of indenamines **113** in high enantioselectivity, incorporating both symmetrical and unsymmetrical internal alkynes, was disclosed. Later, they extended the Rh(I)-catalyzed asymmetric [3 + 2] annulation of imines with achiral allenes (Scheme 15c).[99] In this reaction, aryl ketimines **114** were coupled with racemic allenes via C−H activation and [3 + 2] annulation process. Highly functionalized indenylamines **115** were generated in up to 96% yield and 98% ee in the presence of $[Rh(cod)(OH)]_2$/(*R*)-BINAP.

In 2009, Bergman, Ellman and co-workers accomplished an intramolecular C−H alkylation of imidazole substrates **116** by using chiral bisphosphine (*S*,*S*′,*R*,*R*′)-**L1e**, affording the corresponding 5,5-fused ring products **117** in up to 92% yield and 98% ee (Scheme 16a).[100] In 2015, Rovis and co-workers reported an asymmetric hydroheteroarylation reaction of benzoxazoles **118** with α-substituted methacrylates. This reaction delivered various elaborated benzoxazole products **119** in good yields and enantioselectivity (up to 93% yield, 94% ee, Scheme 16b).[101]

Simultaneously, the Shibata group[102] and the Tanaka group[103] independently achieved a carbonyl-directed asymmetric C(sp^2)−H functionalization of ketones **120** with enynes (Scheme 17). Shibata and co-workers used [Rh((*S*)-BINAP)$_2$]-BF_4 complex to provide the coupled products **121** in up to 98% ee, involving the functionalization of aryl C−H bonds. Under similar conditions, Tanaka and co-workers described three examples of aromatic ketone functionalization with high levels of enantiocontrol (up to 98% ee). The Shibata group first proposed that the rhodium catalyst occurs through directed oxidative addition of proximate C(sp^2)−H bond to afford the intermediate **122**. Then, followed by an intermolecular

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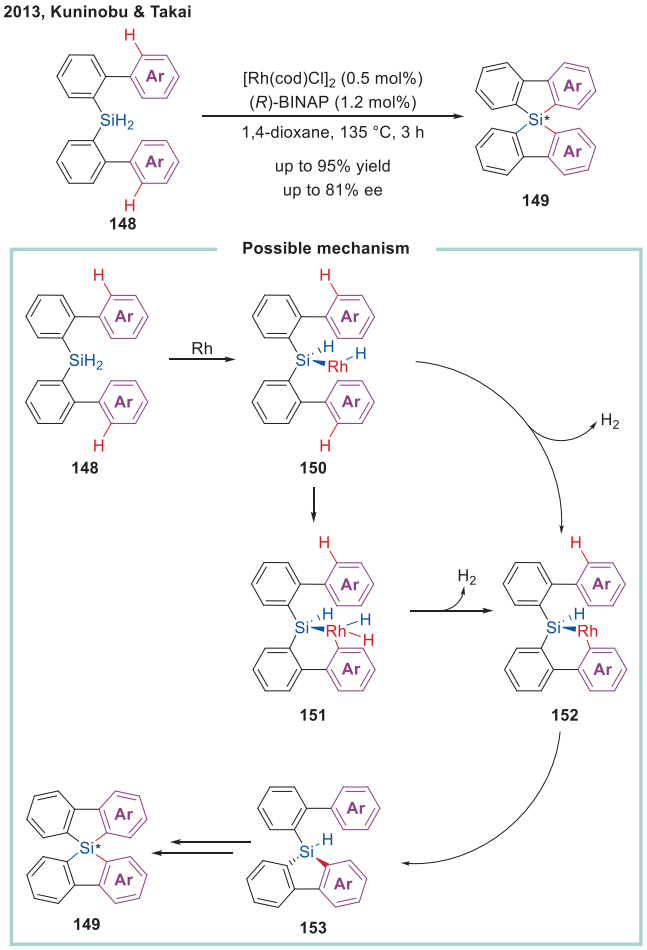
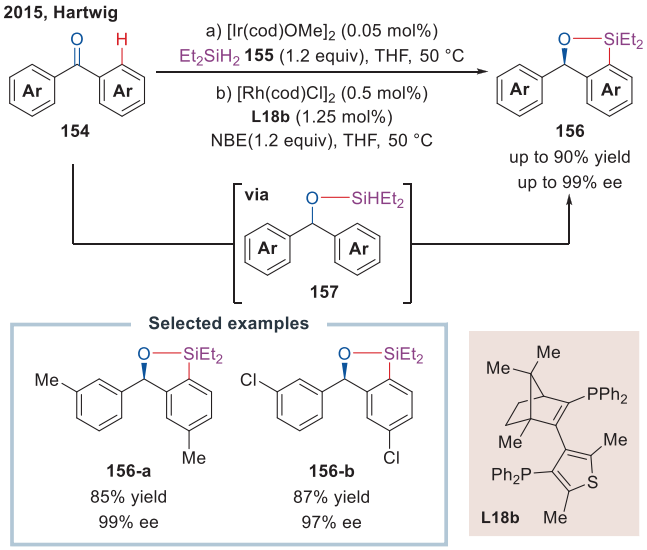
Scheme 22. Enantioselective Synthesis of Spirosilabifluorene Derivatives via Rh(I)-Catalyzed C(sp^2)−H Silylation



Scheme 23. Rh(I)-Catalyzed Asymmetric C(sp^2)−H Silylation of Diarylmethanols via Desymmetrization



hydrorhodation of the alkyne moiety, the intermediate **123** is generated. Subsequently, an intramolecular carborhodation process delivers the intermediate **124**, which gives the desired products **121** after reductive elimination.

In 2011, the Yu group developed a Rh(I)-catalyzed asymmetric allylic C(sp^3)−H activation and intramolecular cyclization of trienes **125** (Scheme 18).[104,105] Screening various chiral ligands found that the diphosphine ligands inhibited the reaction, and promising yields and selectivities were obtained by changing to monodentate phosphoramidites. Chiral phosphoramidite ligand (*S*)-**L10** provided the best enantiocontrol, affording the cyclized products **126** bearing a quaternary all-carbon stereocenter up to 91% yield, >19:1 dr, and 94% ee.

4.3. Rh(I)-Catalyzed Asymmetric C−H Functionalization Reactions with Aryl Halides

In 2016, Glorius and co-workers disclosed the asymmetric intermolecular C(sp^3)−H arylation of 8-benzyl quinolines **127** with aryl bromides using a Rh(I)/NHC catalytic system (Scheme 19a).[106] Screening ligands found that the newly designed unsymmetrical NHC **L17** gave the best results, providing moderate levels of enantiocontrol and good site selectivity. The triarylmethanes **128** were obtained in up to 86% yield and 80% ee. Subsequently, the same group reported an enantioselective arylation of various heterocycles **129** such as tetrahydroquinolines, pyrrolidines, piperidines, piperazines, azepanes and azetidines with aryl iodides (Scheme 19b).[107] The employment of $[Rh(C_2H_4)_2Cl]_2$/(*R*,*R*)-**L16a** showed an efficient approach to yield various enantioenriched arylative heterocycles **130**. This redox-neutral method provided a new platform for synthesizing *α*-*N*-arylated heterocycles **130** with high chemo- and enantioselectivity (up to 97% ee). Notably, You and co-workers accomplished an atroposelective Rh(I)-catalyzed C−H arylation of heterobiaryls **131** under similar conditions. The axially chiral products **132** were obtained in up to 99% yield and 97% ee (Scheme 19c).[108] Metallocenes with planar chirality have proven to be privileged catalysts or ligands for asymmetric catalysis.[109−114] Later, they reported enantioselective Rh(I)-catalyzed thioketone-directed C−H arylation of ferrocenes **133** (Scheme 19d).[115] Planar chiral ferrocenes could be obtained in good yields and excellent enantioselectivity (up to 82% yield, >99% ee) using aryl iodides as the coupling partners. More recently, they developed Rh(I)-catalyzed pyridine directed asymmetric C−H arylation of ferrocenes with various aryl halides including chlorides, bromides, and iodides (Scheme 19e).[116] This method features high catalytic efficiency and excellent levels of mono/diselectivity, enantioselectivity (up to 97% yield, >99% ee).

The You group recently developed a strategy for the kinetic resolution of diverse planar chiral *multi*-substituted metallocenes through enantioselective Rh(I)-catalyzed C−H arylation of *pre*-functionalized metallocenes (Scheme 20).[117−119] This method provides an approach to introduce planar chirality with high catalytic efficiency, regioselectivity and *s*-value. The combination of $[Rh(C_2H_4)_2Cl]_2$ and (*R*,*R*)-**L16b** was the best choice as the catalyst. The chiral metallocene product **138-a** has been applied to synthesize *P*,*N*-chiral ligand **140**, which was highly efficient in both Pd-catalyzed asymmetric allylic substitution reaction and Ag-catalyzed asymmetric [3 + 2]-cycloaddition reaction.

Notably, the catalytic system was suitable for 1,3-disubstituted ferrocenes, which were difficult to be synthesized in the past. To our delight, racemic 1,3-disubstituted ferrocenes containing trimethylsilyl **146-a**, triethylsilyl **146-b**, 4-methoxyphenyl **146-c**, and 3,5-dimethoxy phenyl **146-d** underwent the arylation reaction in a kinetic resolution manner with good regioselectivity and enantioselectivity (Scheme 21).[118] The modification

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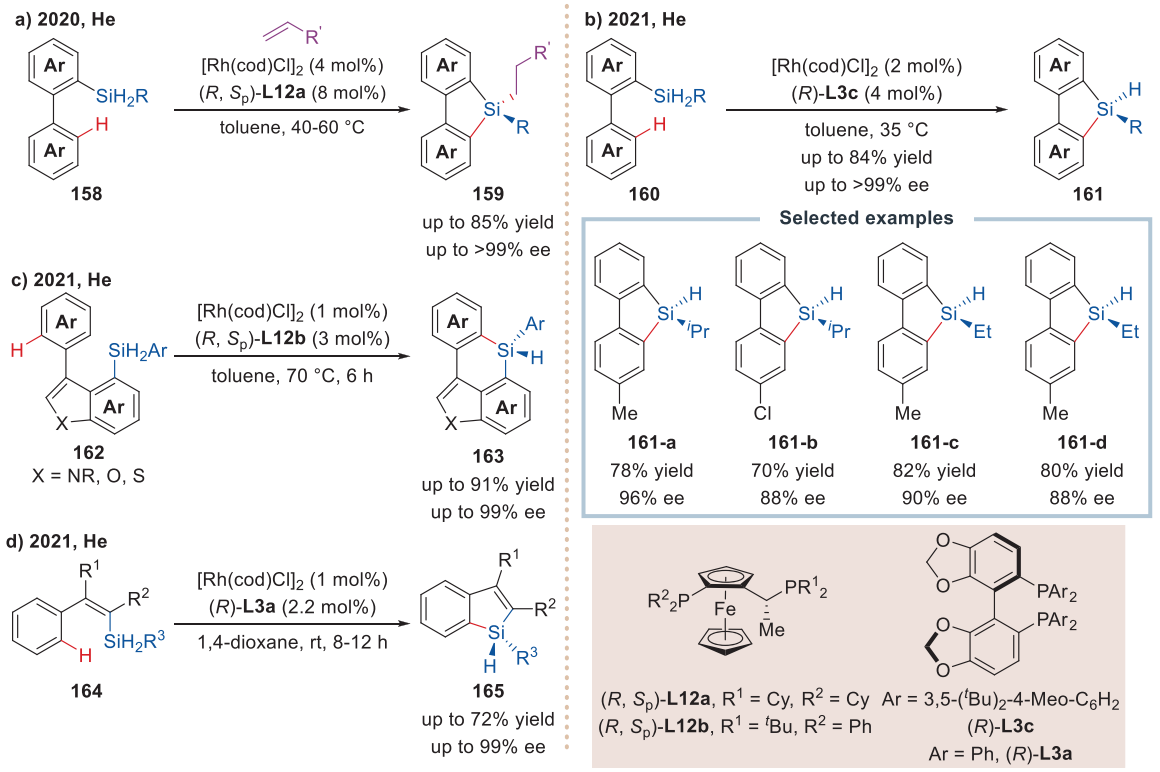
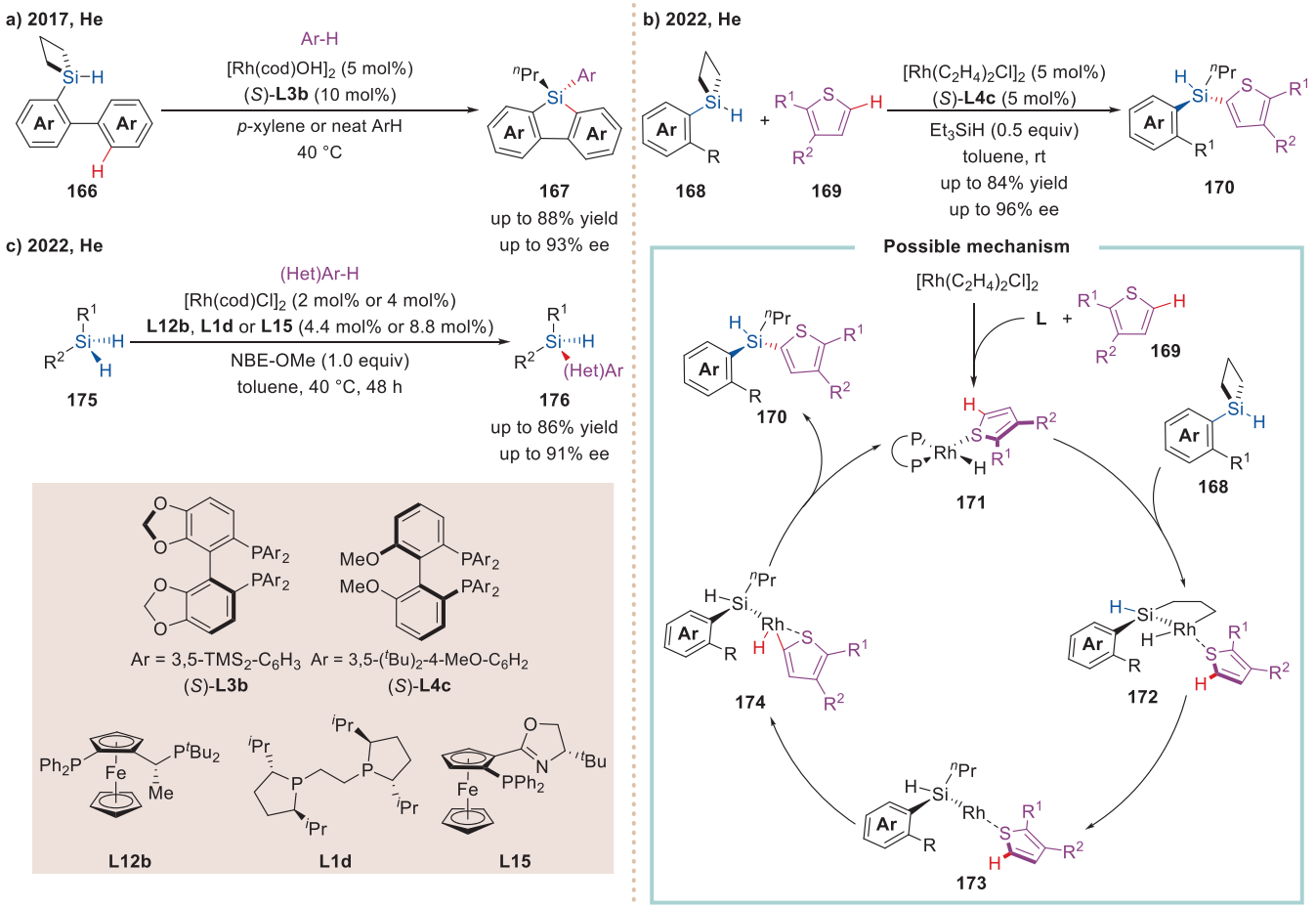
Scheme 24. Rh(I)-Catalyzed Asymmetric C(sp^2)–H Silylation for the Synthesis of Hydrosilanes



Scheme 25. Rh(I)-Catalyzed Asymmetric C(sp^2)–H Silylation with Simple Arenes



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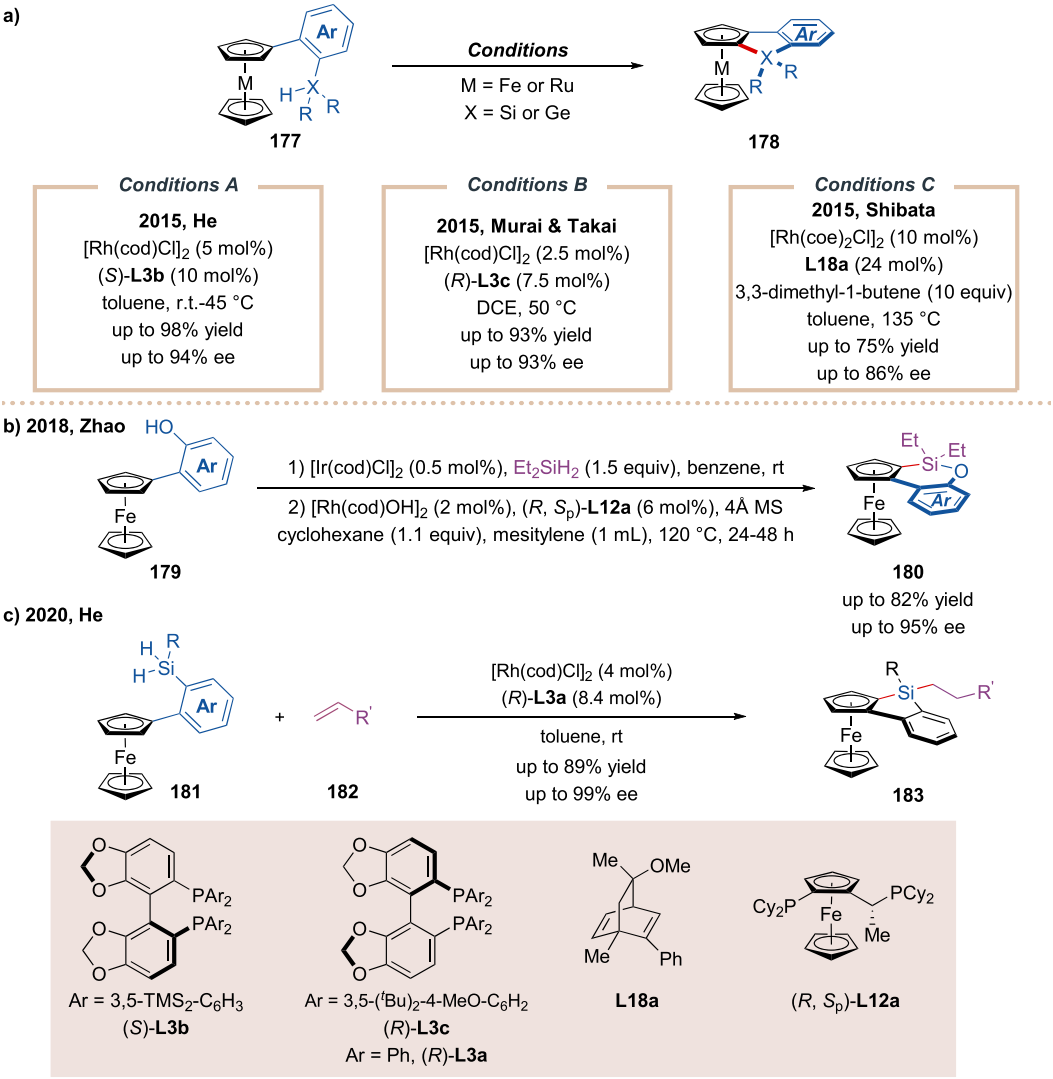
Scheme 26. Rh(I)-Catalyzed Asymmetric C(sp^2)−H Silylation of Metallocenes



of the directing group, such as 4-methyl **146-e**, 5-methyl **146-f**, 4-fluoro **146-g**, and 2-isoquinolinyl **146-h** did not affect the yield and selectivity of the reaction. The general synthesis of planar chiral metallocenes will likely benefit the further development of chiral ligands, catalysts and materials based on metallocene scaffolds.

4.4. Rh(I)-Catalyzed Asymmetric C−H Silylation

Apart from constructing C−C bonds, the formation of C−X bonds, especially C−Si bonds by Rh-catalyzed asymmetric C−H silylation reactions, has also been rapidly developed.[120−124]

4.4.1. Rh(I)-Catalyzed Asymmetric C(sp^2)−H Silylation. In 2013, Kuninobu, Takai and co-workers accomplished an asymmetric synthesis of chiral spirosilabifluorene derivatives **149** in up to 95% yield and 81% ee, with $[Rh(cod)Cl]_2$/(*R*)-BINAP as the catalytic system (Scheme 22).[125,126] A possible mechanism for the asymmetric C−H silylation reaction toward chiral spirosilabifluorenes was proposed. First, the Rh−H intermediate **150** is formed from $[Rh(cod)Cl]_2$ in the presence of **148**, sequentially oxidative addition of the aromatic C−H bond generates the intermediate **151**. Reductive elimination of **151** releases H_2 to afford Rh−Si intermediate **152**. Another possible pathway for forming the intermediate **152** may be through the σ-complex-assisted metathesis process. Finally, reductive elimination of intermediate **152** delivers chiral monohydrosilane **153**, which conducts the second C−H silylation to yield spirosilabifluorene **149**.

In 2015, the Hartwig group reported an asymmetric C−H silylation of simple arenes, generating the chiral benzoaxasiloles **156** via Ir-catalyzed hydrosilylation of diaryl ketones **154** with diethylsilane **155**, followed by Rh(I)-catalyzed directed asymmetric C−H silylation (Scheme 23).[127] This approach was also suitable for the parallel kinetic resolution of chiral diarylmethanols via site-selective asymmetric C−H silylation.

In 2020, the He group achieved a Rh(I)−catalyzed tandem asymmetric intramolecular C−H silylation of arenes and intermolecular alkene hydrosilylation with the aid of Josiphos (R,S_p)-**L12a** (Scheme 24a).[128] A series of tetrasubstituted Si-stereogenic silanes **159** bearing various substituents was synthesized smoothly in good yields and excellent enantioselectivities with broad functional-group tolerance (up to 85% yield, >99% ee). Later, various chiral 1*H*-dibenzosiloles **161** were accessed employing $[Rh(cod)Cl]_2$/(*R*)-**L3c** by the He group in up to 84% yield and >99% ee (Scheme 24b).[129] Diverse stereospecific transformations of monohydrosilanes **161** via alcoholysis, hydrosilylation, nucleophilic substitution, and cross-coupling with aryl C−H bonds were carried out smoothly. Then,

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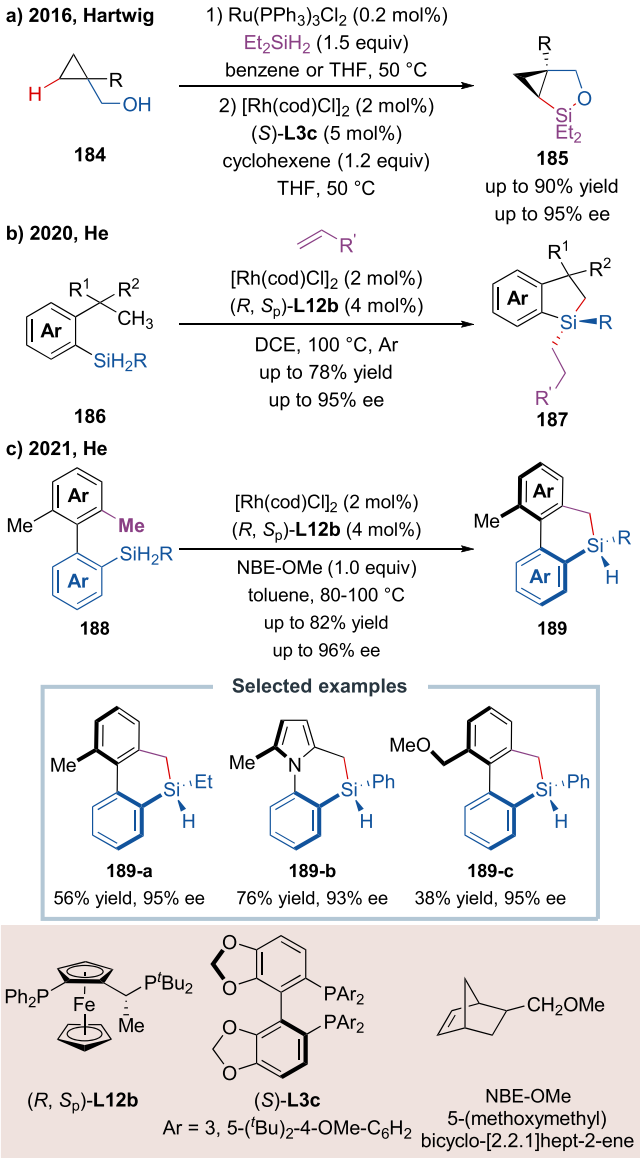
Scheme 27. Rh(I)-Catalyzed Asymmetric C(sp^3)−H Silylation



the He group reported Rh/Josiphos-catalyzed desymmetrization of **162**, accessing chiral monohydrosilanes in six- and seven-membered heterocycles **163** in up to 91% yield and 99% ee (Scheme 24c).[130] A wide range of functionalized heterocycles, such as indole, benzofuran, benzothiophene, and carbazole functional groups, bearing silicon stereocenters were efficiently constructed. The same group recently accomplished the synthesis of various chiral 1*H*-benzosiloles **165** in good yields and excellent enantiopurity (Scheme 24d).[131]

In 2017, the He group disclosed a Rh(I)-catalyzed asymmetric C−H silylation of arenes, constructing the Si-stereogenic center by desymmetrizing silacyclobutanes via a tandem ring-opening/intramolecular asymmetric C−H silylation and intermolecular dehydrogenative silylation of simple arenes (Scheme 25a).[132] Various dibenzosiloles and bis-siloles containing Si-stereogenic centers were accessed in good yields and excellent enantioselectivity (up to 88% yield and 93% ee). Later, He, Yu, Zhang, and co-workers described a detailed mechanistic study about the Rh(I)-catalyzed asymmetric C−H silylation through desymmetrization of silacyclobutanes via combined experimental and computational studies.[133] The Rh−H species were found to be the active catalytic species rather than the previously proposed Rh−Cl species. Undoubtedly, enantioselective intermolecular C−H silylation for constructing acyclic Si-stereogenic chirality is more attractive and challenging. Based on their previous studies, in 2022, the He group published a Rh(I)-catalyzed intermolecular asymmetric C−H silylation of silacyclobutanes with heteroarenes using MeO-Biphep (*S*)-**L4c** as the optimal chiral ligand, yielding various chiral acyclic monohydrosilanes **170** in good results (up to 84% yield and 96% ee, Scheme 25b).[134] Then, a possible mechanism was proposed. The reaction proceeds with the coordination of thiophene to the Rh−H catalyst (**171**), followed by the oxidative addition of silacyclobutanes to afford the intermediate **172**. Reductive elimination of **172** occurs to generate the intermediate **173**, and subsequent C−H activation and reductive elimination produces the desired acyclic chiral monohydrosilane **170** and regenerates the Rh−H catalyst. Recently, the He group also accomplished an intermolecular asymmetric C−H silylation of heteroarenes, delivering various acyclic silicon-stereogenic heteroaryl monohydrosilanes **176** from simple dihydrosilanes **175** (Scheme 25c).[135] The presence of NBE-OMe (5-(methoxymethyl)bicyclo-[2.2.1]hept-2-ene), as a bulky hydrogen acceptor, could accelerate the dehydrogenative C−H silylation process.

In 2005, several research groups independently achieved Rh(I)-catalyzed enantioselective intramolecular C−H silylation of metallocenes **177**, affording a series of planar chiral scaffolds **178** (Scheme 26a). The He group[136] and the Murai, Takai group[137] independently demonstrated that the SEGPHOS analogues (*S*)-**L3b** and (*S*)-**L3c** could be utilized in asymmetric dehydrogenative silylation reactions. At the same time, the Shibata group[138] employed chiral diene **L18a** in a dehydrogenative coupling reaction, forming silylation products in up to 75% yield and 86% ee. In 2018, Zhao and co-workers accomplished an enantioselective dehydrogenative C−H silylation of 2-ferrocenyl-substituted phenolic silyl ethers, synthesizing various planar chiral ferrocenes bearing a six-membered silacycle in up to 82% yield and 95% ee (Scheme 26b).[139] Recently, the He group achieved a Rh(I)−catalyzed tandem asymmetric intramolecular C−H silylation of arenes and intermolecular alkene hydrosilylation (Scheme 24a). They found that metallocenes were compatible with this catalytic system. Benzosilolometallocene products were easily accessed with silicon central and planar chirality by altering the chiral ligand (Scheme 26c).[128]

4.4.2. Rh(I)-Catalyzed Asymmetric C(sp^3)-H Silylation. Compared with C(sp^2)−H silylation reaction, C(sp^3)−H silylation is more challenging due to the stronger bond energy of C(sp^3)−H. In 2015, Takai, Murai and co-workers achieved a challenging intramolecular asymmetric C(sp^3)−H silylation reaction.[140] Under similar conditions to the former asymmetric C(sp^2)−H silylation reported by the same group (Scheme 22), the combination of $[Rh(cod)Cl]_2$ and (*R*)-H_8−BINAP as the catalytic system could generate the best results (75% yield, 40% ee). Notably, the utilization of 3,3-dimethyl-1-butene as the hydrogen acceptor could remarkably accelerate the reaction rate and allow the reaction to occur at a lower temperature. In 2016, Hartwig and co-workers accomplished the catalytic enantioselective C(sp^3)−H silylation of methylene (Scheme 27a).[141] Using $[Rh(cod)Cl]_2$ and the bulky (*S*)-DTBM-SEGPHOS ligand (*S*)-**L3c**, this reaction could provide the silylated products **185** in excellent results. The presence of cyclohexene as the hydrogen acceptor plays a crucial role in achieving good yields

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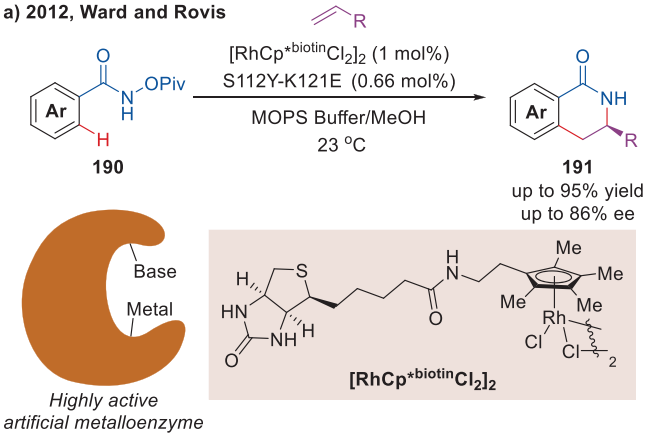
and enantioselectivity (up to 90% yield and 95% ee). Kinetic isotope effect experiments suggested that C−H bond cleavage may be the rate-limiting step, and the C−H activation is the enantio-determining step. In 2020, the He group realized an asymmetric intramolecular C(sp^3)−H silylation by Rh/Josiphos, obtaining a series of functionalized silicon-stereogenic dihydrobenzosiloles **187** in good results (up to 78% yield and 95% ee, Scheme 27b).[142] Several structurally complex molecules, such as *β*-estradiol, D-ribofuranoside, (−)-menthol, dehydrocholesterol, pitavastatin fragment, and diacetonefructose were successfully installed into the chiral dihydrobenzosiloles **187** in good yields and excellent stereoselectivity.

Meanwhile, axially chiral compounds have been recognized as fundamental structural units with multiple applications. Hence, various methods have been developed for their synthesis.[143−146] Recently, He and co-workers developed an elegant enantioselective synthesis of silicon-stereogenic dihydrodibenzosilines **189** containing axially chiral six-member bridged biaryls (Scheme 27c).[147] A range of dihydrodibenzosiline analogues **189** with axial and silicon-central chiralities were smoothly constructed in up to 82% yield and 96% ee via a dehydrogenative asymmetric C(sp^3)−H silylation.

5. RH(III)-CATALYZED ASYMMETRIC C−H FUNCTIONALIZATION REACTIONS

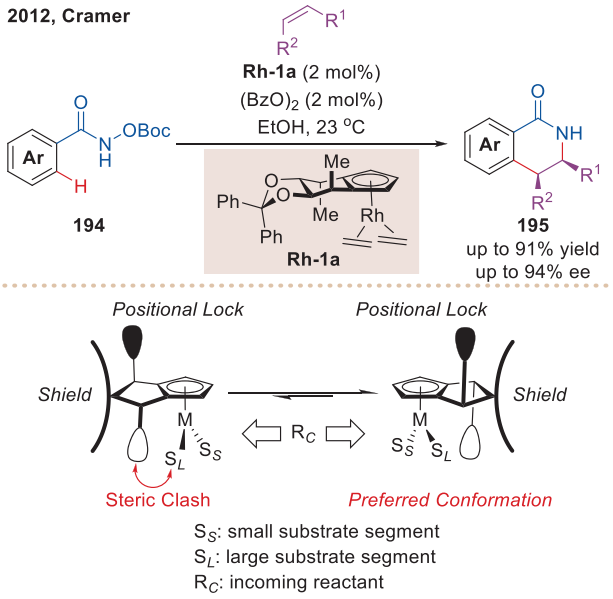
Compared with Rh(I)-catalyzed asymmetric C−H functionalization reactions, Rh(III)-catalytic system appeared late.

Scheme 28. Biotinylated Rh(III)-Catalyzed Asymmetric C−H Functionalization with Alkenes

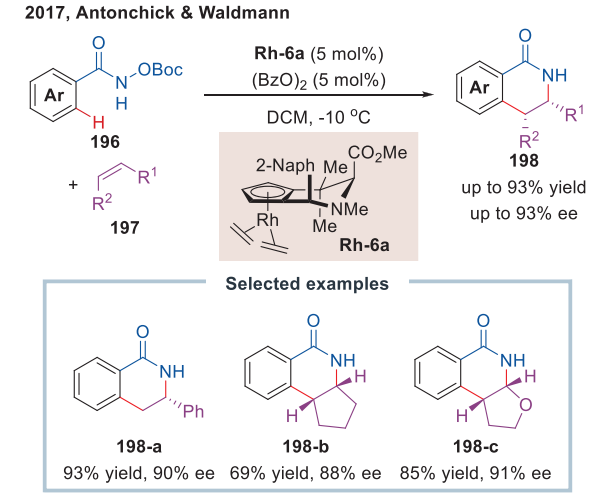


However, thanks to the pioneering works by Rovis, Ward, and Cramer in 2012, this domain has become one of the most active topics in the field of asymmetric C−H functionalization.[148−154] Various molecules bearing central, planar, axial, and helical chirality were enantioselectively synthesized via this approach.

Scheme 29. Rh(III)-Catalyzed Asymmetric C−H Functionalization of Benzamides



Scheme 30. Rh(III)-Catalyzed Asymmetric C−H Functionalization of Benzamides with Alkenes



5.1. Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions using Chiral Cp^xRh Complexes

In contrast to the applicability of chiral phosphine ligands for Rh(I)-catalyzed asymmetric C−H functionalization reactions, the Rh(III)-catalytic system suffered from the lack of proper chiral ligands. To date, chiral cyclopentadienes remain the most promising ligands. Thus, the development of this area heavily depended on the invention of chiral CpRh complexes.

5.1.1. Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions with Alkenes. The seminal works in Rh(III)-catalyzed asymmetric C−H functionalization reactions were reported by Ward, Rovis, and co-workers in 2012 (Scheme 28a).[48] A docked biotinylated Rh(III) complex was developed to achieve asymmetric C−H activation of *N*-OPiv benzamides **190** with acrylates, using $[RhCp^{*biotin}Cl_2]_2$ as the catalyst precursor and S112Y−K121E as the optimal enzyme, which gave isoquinolones **191** in up to 95% yield and 86% ee. In 2019, the wt-mSav:$RhCp^{*biotin}X_2$ developed by the same group was

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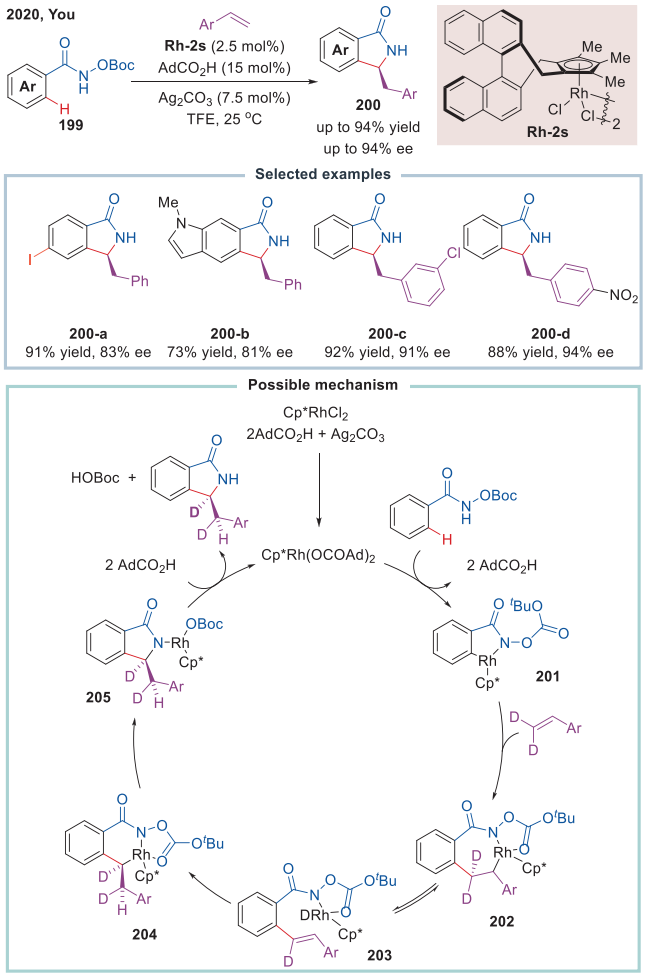
Scheme 31. Enantioselective Synthesis of Isoindolinone via Rh(III)-Catalyzed C−H Functionalization



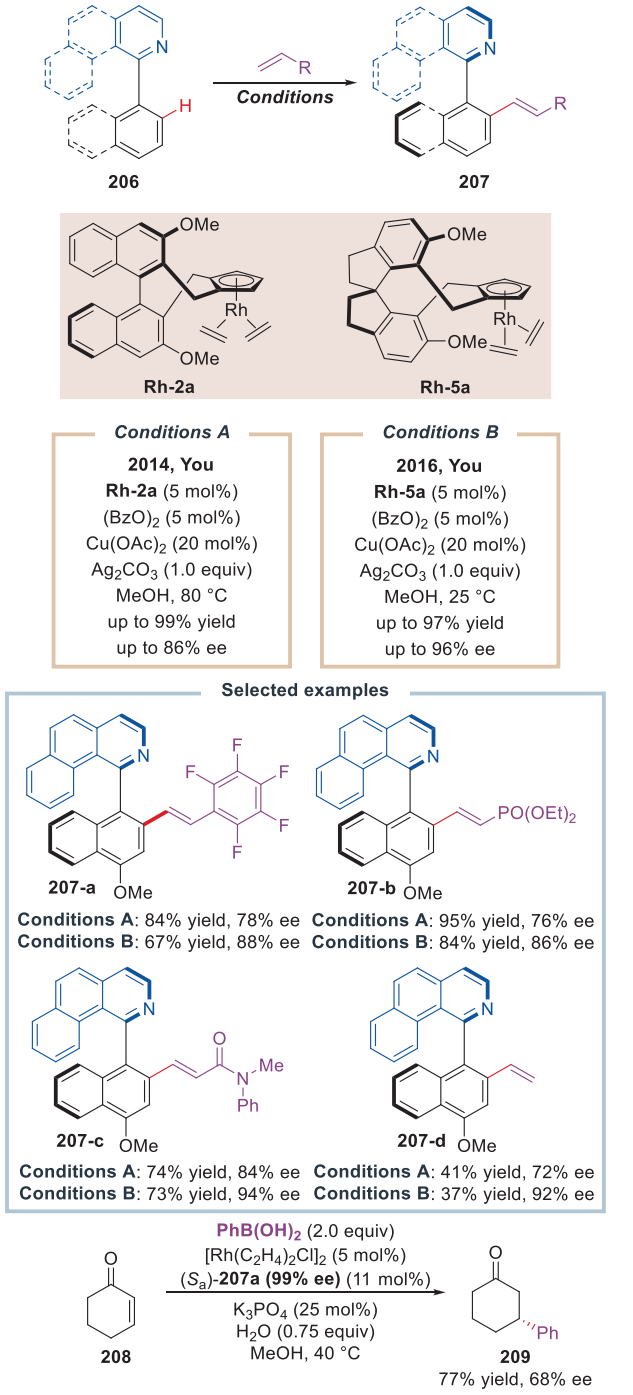
able to catalyze the asymmetric C−H activation/[4 + 2] cyclization of *N*-OPiv acrylamides **192**, affording the corresponding pyridones **193** in good yields and enantioselectivity (up to 99% yield, 97% ee, Scheme 28b).[155,156]

At the same time, Cramer and co-workers developed a chemosynthetic Cp^{x}Rh complex **Rh-1a** (Scheme 29).[49] Utilization of this complex in enantioselective C−H activation was elegantly demonstrated by the synthesis of isoquinolones **195** via C−H activation of *N*-OBoc benzamides **194** with multiple alkenes under mild conditions in up to 91% yield and 94% ee. These authors proposed a model for the stereochemical preference, which explained the origin of enantioselective control. These pioneering works resulted in an upsurge in Rh(III)-catalyzed asymmetric C−H functionalization.

A class of piperidine-fused Cp^{x}Rh complexes with easily accessible and efficiently tunable characteristics was reported in 2017 by Antonchick, Waldmann, and co-workers. The Cp^{x}Rh complex **Rh-6a** bearing an ester group on the piperidine ring could promote asymmetric C−H activation/[4 + 2] cyclization with *O*-Boc benzamide **196** in good yields and enantioselectivity (Scheme 30).[157] Various mono- or disubstituted alkenes were compatible, generating isoquinolones **198** in up to 93% yield and 93% ee.

You and co-workers applied [2 + 2 + 1] Pauson-Khand reaction as a key step to access a class of Cp^{x}Rh complexes derived from penta-substituted cyclopentadiene (Scheme

Scheme 32. Rh(III)-Catalyzed Asymmetric Oxidative Coupling of Biaryl Compounds with Alkenes



31).[158] With complex **Rh-2s**, an unexpected [4 + 1] cyclization took place, affording isoindolinones **200** rather than isoquinolones in good yields and excellent enantioselectivity (up to 94% yield and 94% ee). The following mechanism was proposed. The reaction occurs via initial C−H activation to form intermediate **201**, which undergoes migratory insertion of olefin substrates to afford intermediate **202**. It is followed by a *β*-hydrogen elimination/migratory insertion to generate the intermediate **204**. Subsequent reductive elimination/oxidative addition of **204** affords the intermediate **205**, which finally undergoes protonation to release the isoindolinone **200** and regenerate the catalyst.

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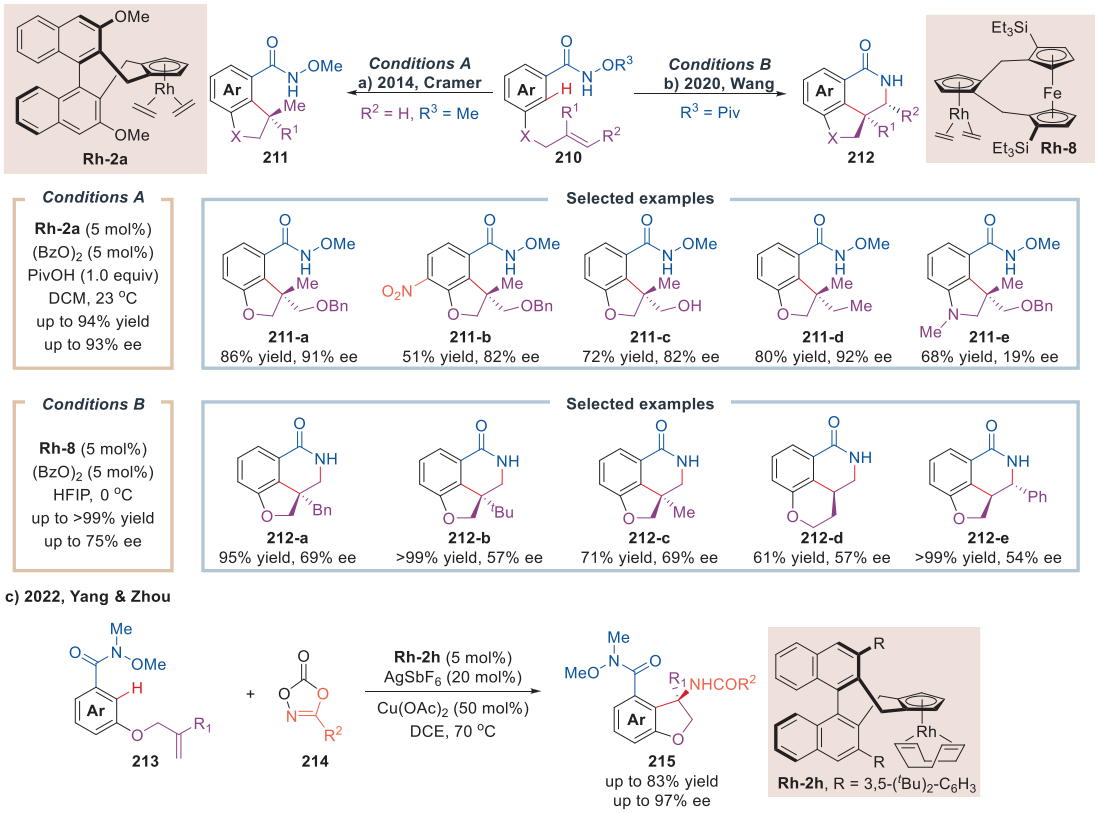
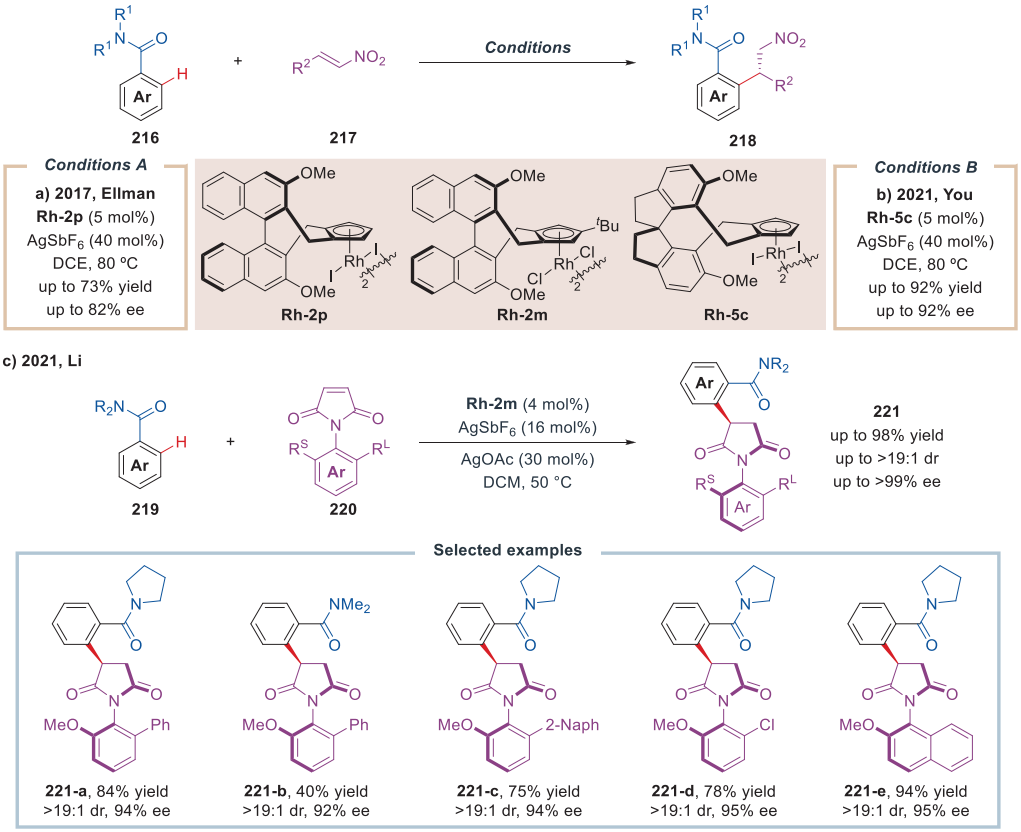
Scheme 33. Rh(III)-Catalyzed Asymmetric Hydroarylation with Alkenes



Scheme 34. Rh(III)-Catalyzed Enantioselective Aryl C−H Addition to α,β-Unsaturated Alkenes



In 2014, You and co-workers realized a Cp^{x}Rh catalyzed atroposelective oxidative Heck reaction of isoquinoline derivatives with alkenes (Scheme 32).[159] With the aid of complex **Rh-2a**, various isoquinoline-fused biaryls **207** were

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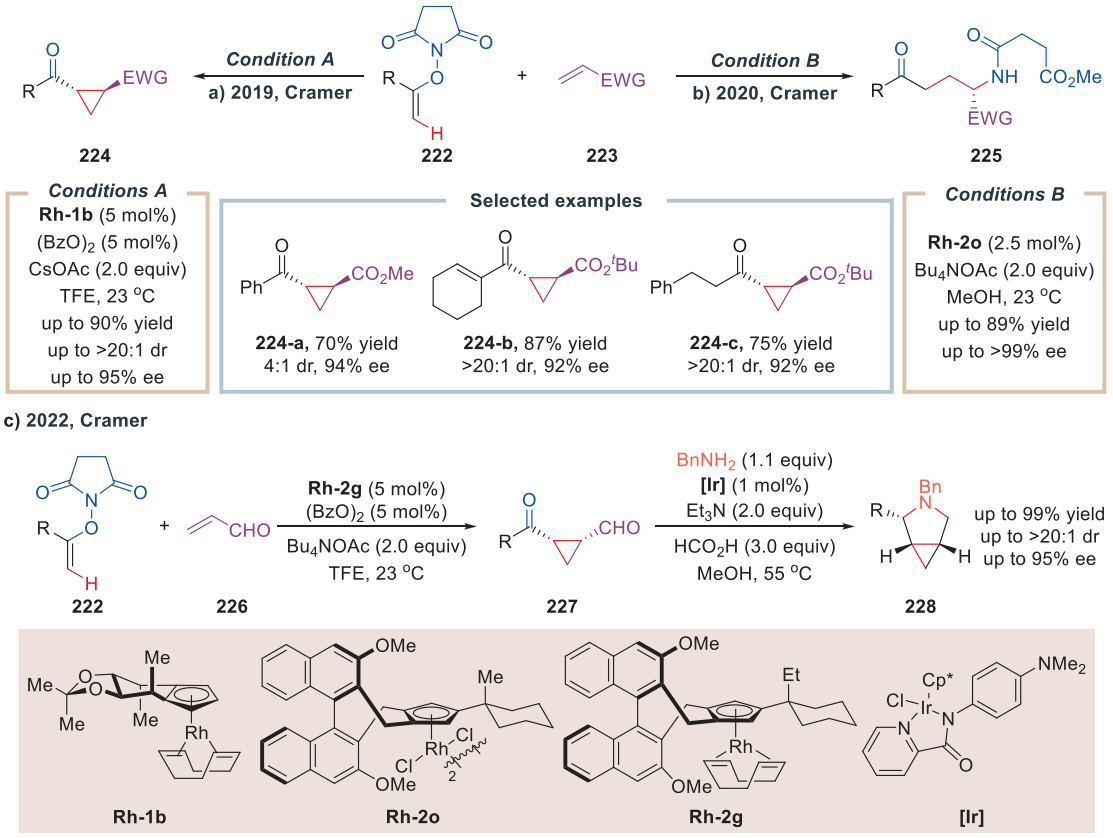
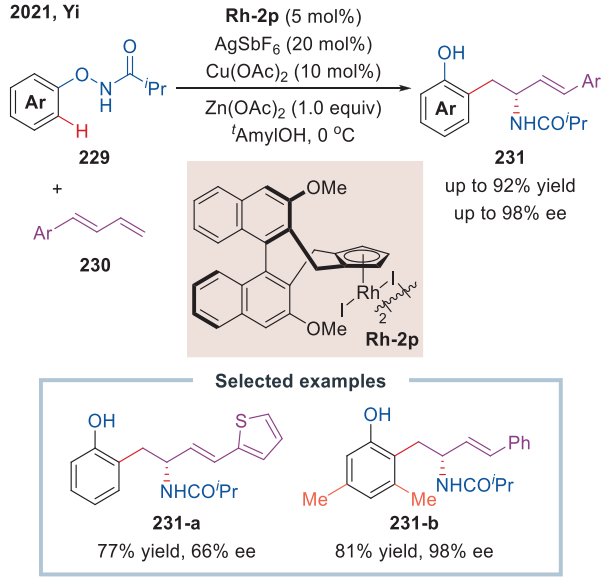
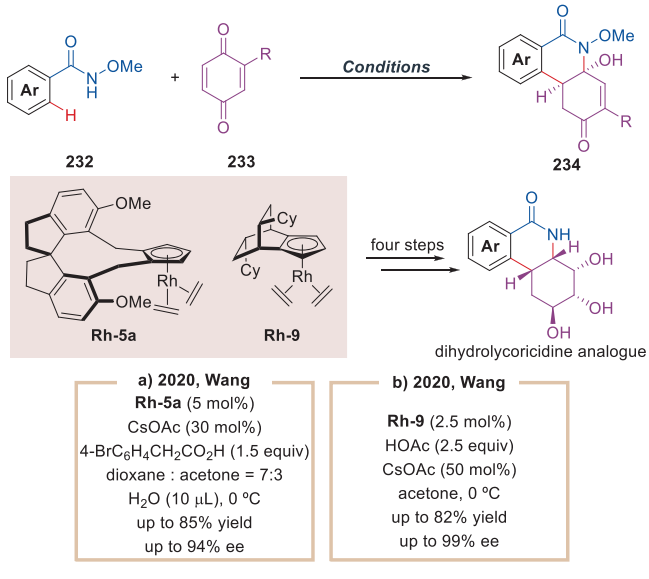
Scheme 35. Rh(III)-Catalyzed Asymmetric C−H Functionalization of Enol



Scheme 36. Rh(III)-Catalyzed Asymmetric Carboaminations of 1,3-Dienes



Scheme 37. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization of *N*-Methoxybenzamide with Quinone



constructed in up to 99% yield and 86% ee with a wide range of electron-deficient olefins including acrylate, acrylamide, pentafluorostyrene, and vinyl phosphate. Notably, ethylene could also be involved in the reaction, affording the corresponding product **207-d** in 41% yield and 72% ee. In 2016, the same group utilized a newly designed catalyst [SCpRh] **Rh-5a** based on 1,1′-spirobiindane[160−162] to enhance enantioselective induction (up to 96% ee) compared with **Rh-2a**.[163] Notably, with enantiomerically pure **207-a** as a ligand, Rh(I)-catalyzed asymmetric conjugate addition of phenylboronic acid **208** to cyclohexanone was realized in 77% yield and 68% ee, which demonstrated the potential application of this method.

In 2014, Cramer and co-workers realized an intramolecular C−H alkylation with BINOL-derived Cp*Rh complex **Rh-2a**, providing various enantioenriched dihydro-benzofurans **211** in good yields and excellent enantioselectivity (up to 94% yield, 93% ee, Scheme 33a).[164] In 2020, a Cp*Rh complex **Rh-8** with

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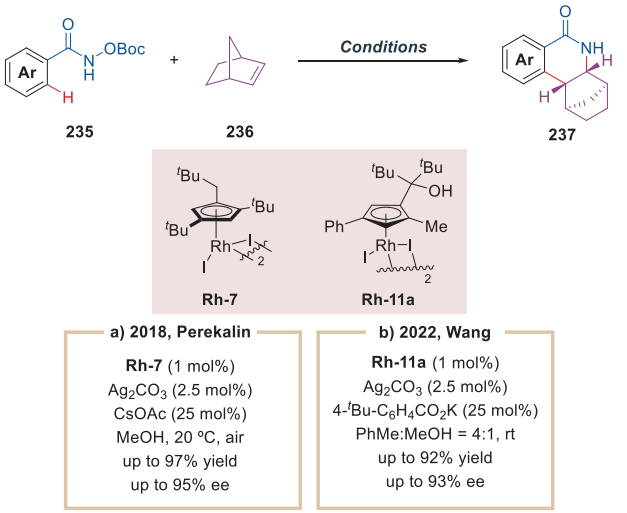
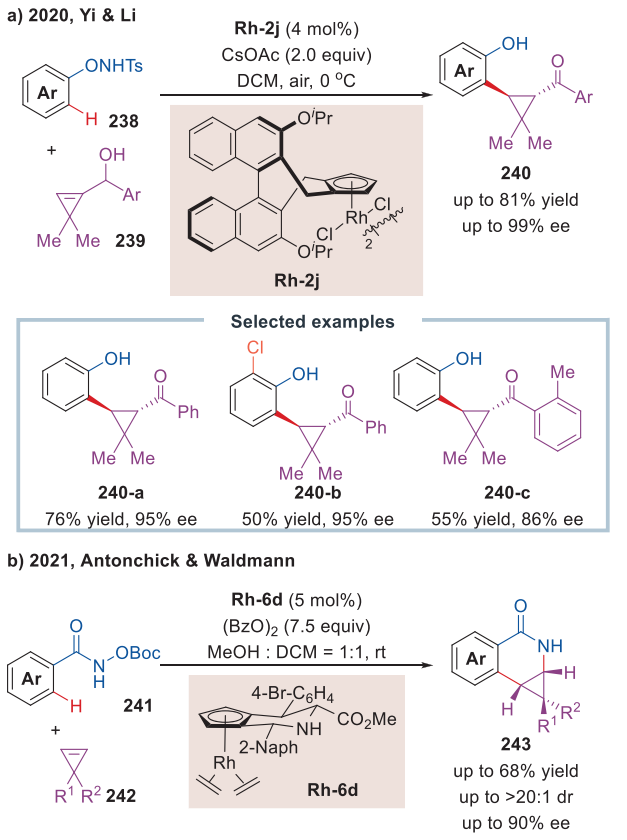
Scheme 38. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization of *N*-Methoxybenzamide with Norbornene

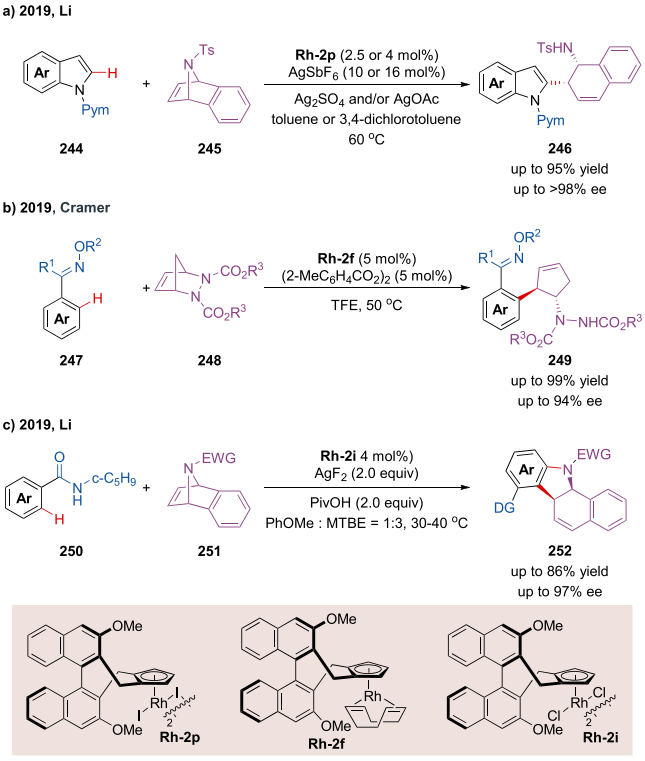


Scheme 39. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization with Cyclopropene Derivatives

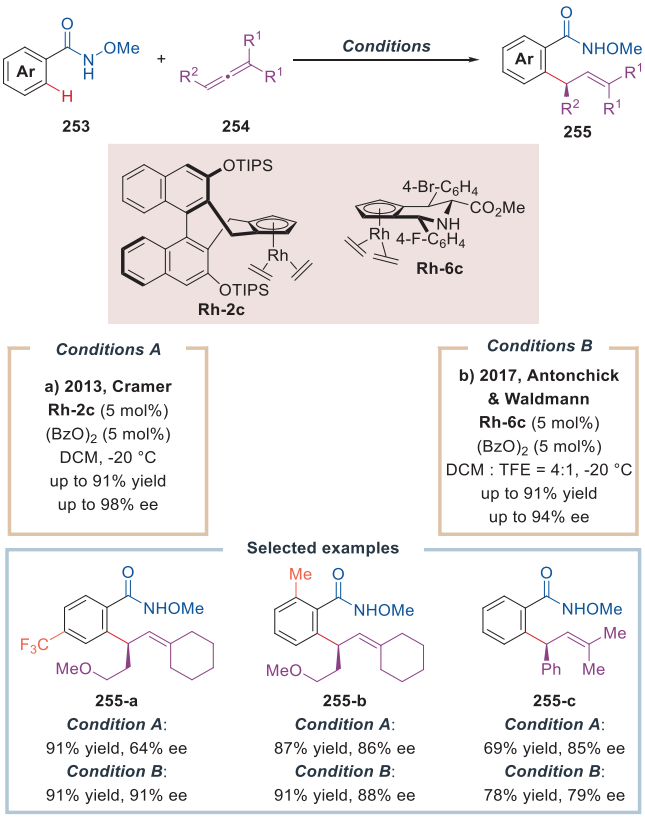


planar chiral ferrocene-fused cyclopentadiene ligand was synthesized by Wang and co-workers, which enabled the formation of chiral isoquinolones **212** in good yields, albeit with moderate enantiomeric excesses (up to >99% yield, 75% ee, Scheme 33b).[165] Recently, Yang, Zhou, and co-workers reported a tandem intramolecular C−H alkylation/intermolecular amidation with Cp^{x}Rh complex **Rh-2h** bearing bulky substituents at 3,3′-position, affording the chiral dihydrobenzofurans **215** in up to 83% yield and 97% ee with Weinreb amide as the directing group (Scheme 33c).[166]

Scheme 40. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization with Azabicyclic Alkenes



Scheme 41. Rhodium(III)-Catalyzed Asymmetric C−H Allylation of Benzamides



In 2017, Ellman and co-workers described a Cp^{x}Rh complex **Rh-2p** catalyzed asymmetric hydroarylation of nitroalkenes **217**

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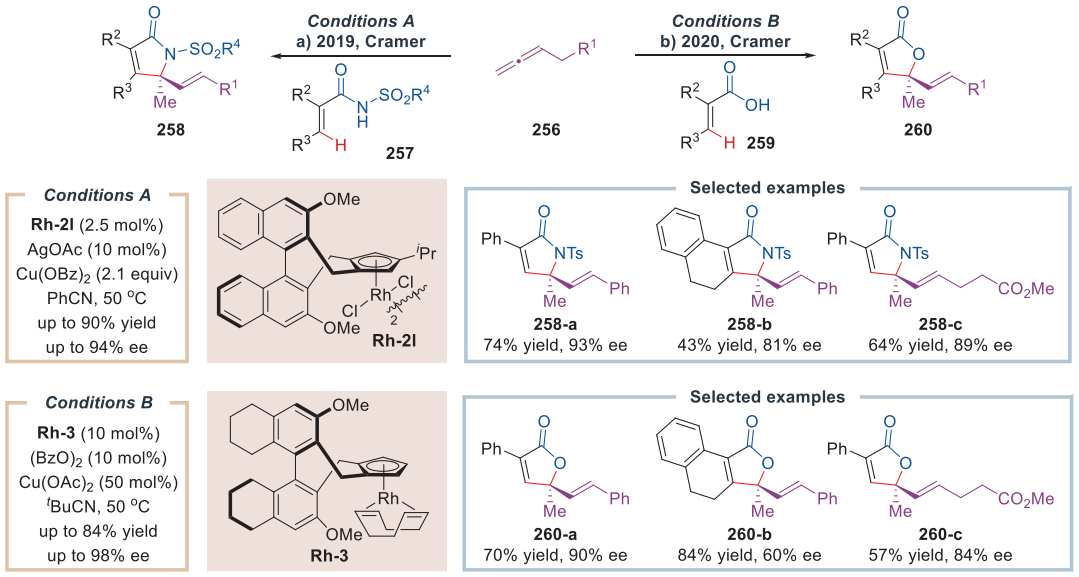
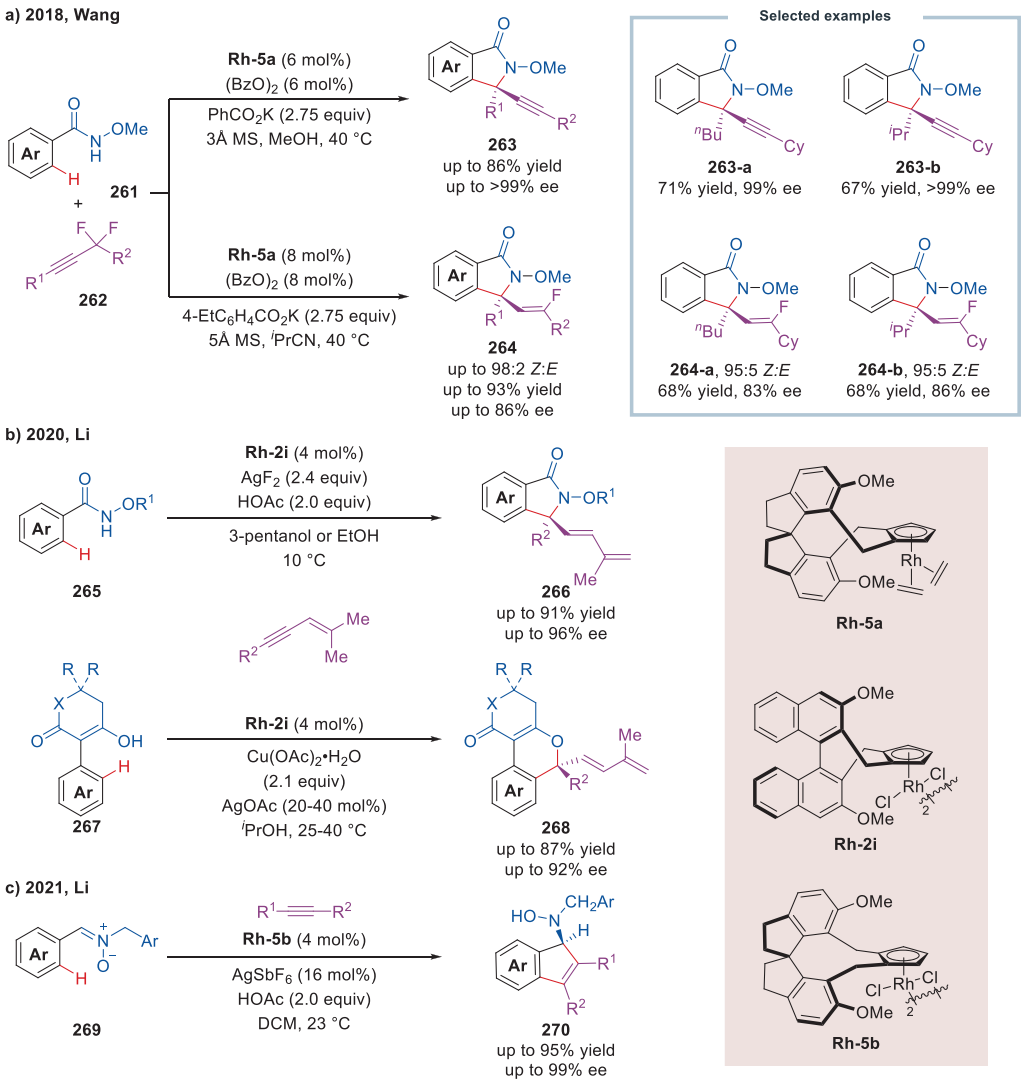
Scheme 42. Rhodium(III)-Catalyzed Asymmetric C−H Annulation with Allenes



Scheme 43. Rh(III)-Catalyzed Asymmetric Annulation with Alkynes



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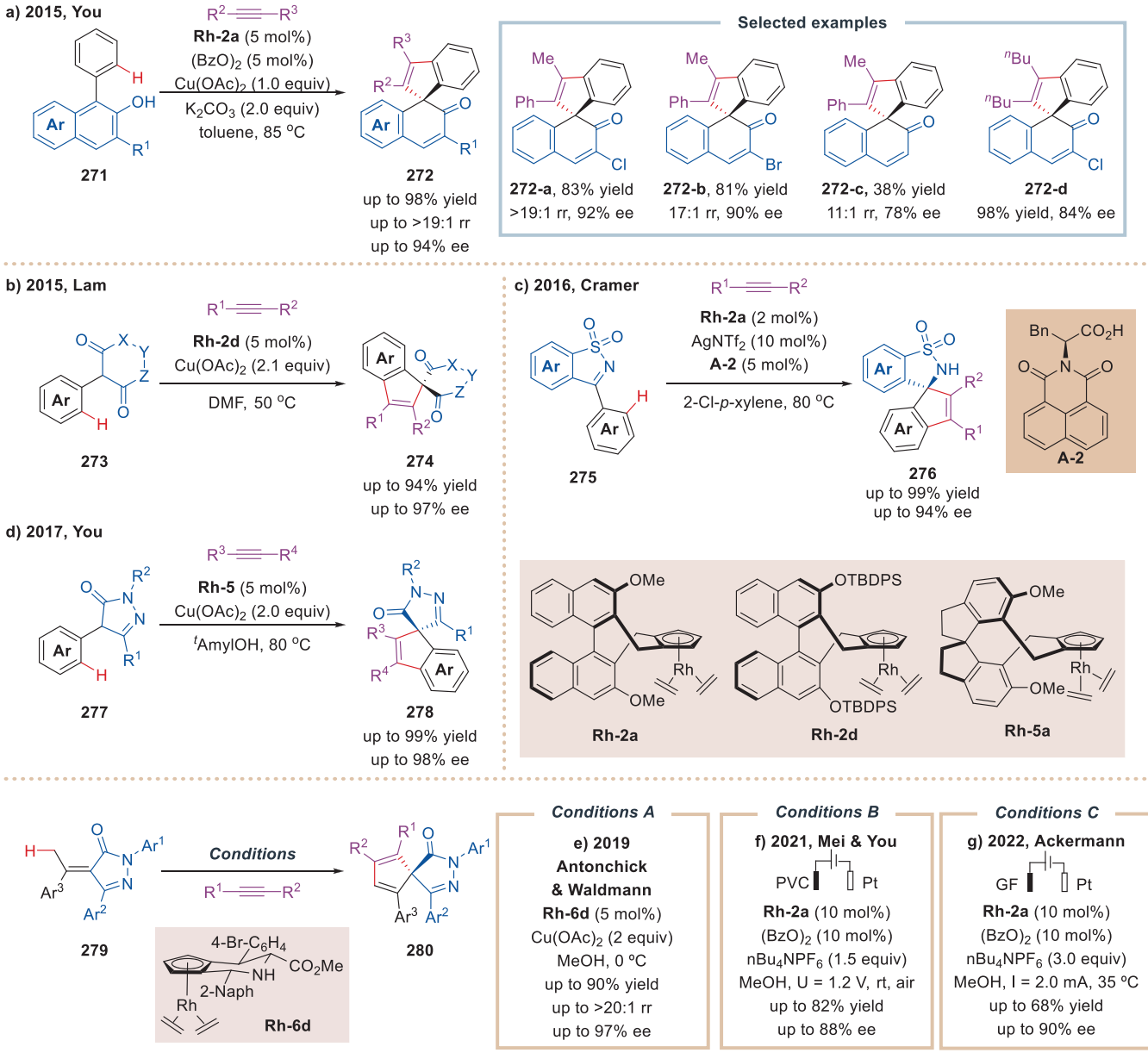
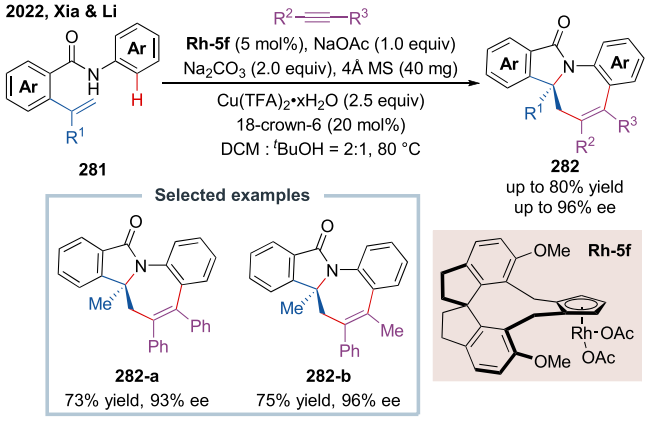
Scheme 44. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization and Spiroannulation



Scheme 45. Rhodium(III)-Catalyzed Asymmetric [3 + 2 + 2] Annulation with Alkynes



(up to 73% yield, 82% ee, Scheme 34a).[167] Later in 2021, a new catalytic system involving [SCpRh] **Rh-5c** was reported by You and co-workers, which could enhance both yield and enantioselectivity of the reaction (up to 92% yield, 92% ee, Scheme 34b).[168] Very recently, a class of BCSCpRh-complexes were designed by You and co-workers, which led to comparable results in the asymmetric synthesis of **218** (up to 88% yield, 98% ee).[169] In 2021, Li and co-workers used *N*-aryl maleimide **220** as the electrophile, and diverse amides **221** bearing both C−N axial and central chirality were synthesized in good yields, diastereo- and enantioselectivities (up to 98% yield, >19:1 dr and >99% ee, Scheme 34c).[170]

Meanwhile, Cramer and co-workers applied succinimide as a directing group in Rh(III)-catalyzed asymmetric C−H functionalization of enol derivatives **222** with acrylate **223** (Scheme 35a). With Cp^{x}Rh complex **Rh-1b** as the optimal catalyst and CsOAc as the base, 1,2-disubstituted cyclopropanes **224** could be generated in up to 90% yield, >20:1 dr and 95% ee.[171] In 2020, the same group found that amidation products

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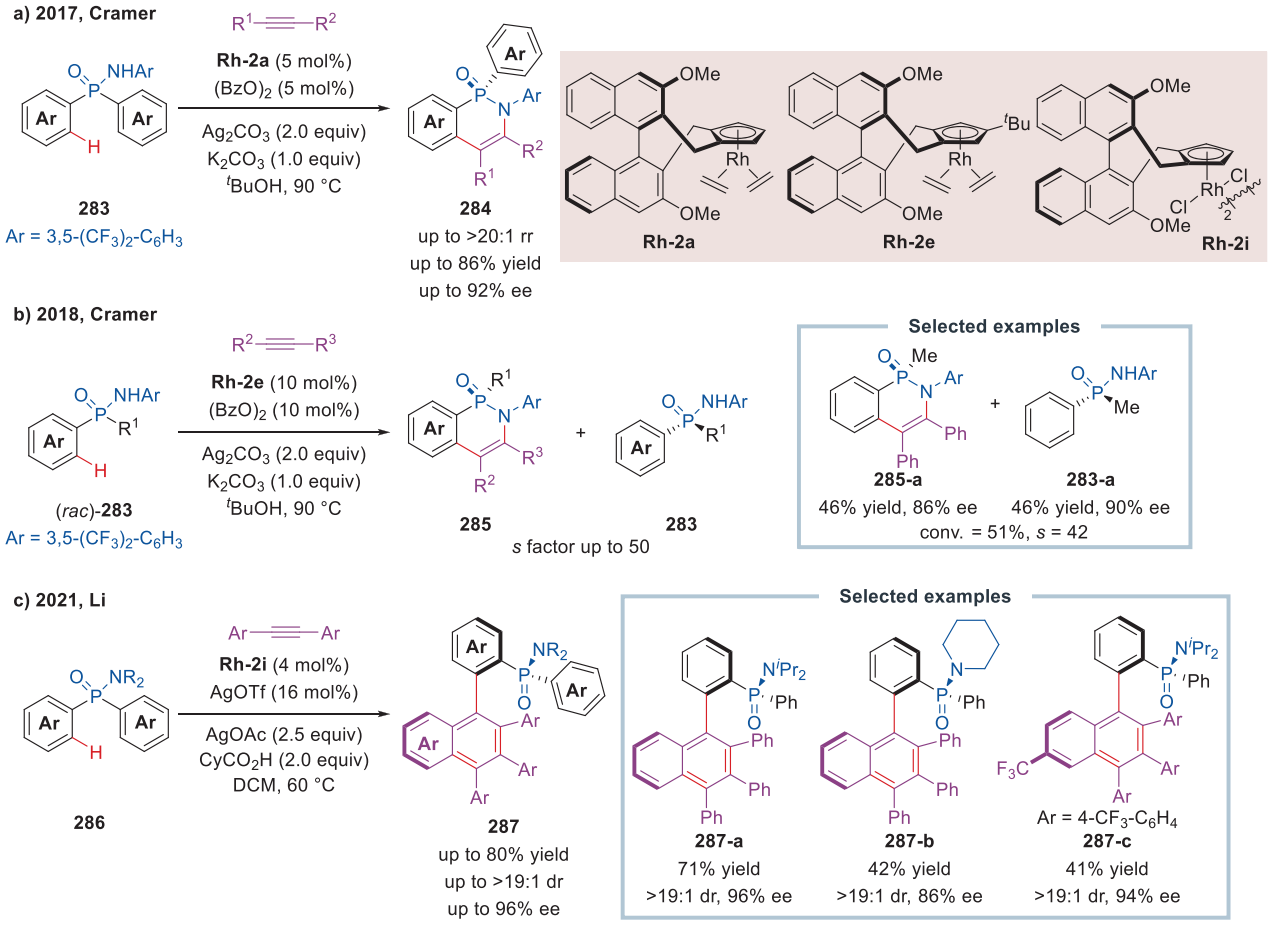
Scheme 46. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization Enables Access to *P*-Chiral Center



225 were formed when Bu_4NOAc was added instead of CsOAc. In the presence of Cp*Rh complex **Rh-2o**, enantioenriched **225** were given in up to 89% yield and >99% ee (Scheme 35b).[172] Recently, Cramer and co-workers expanded the method of enantioselective synthesis of cyclopropane, using acrylaldehyde as the substrate to afford various formylcyclopropane derivatives **227**, which could further undergo Ir-catalyzed condensation with benzylamine (Scheme 35c).[173] As a result, a class of 3-azabicyclo[3.1.0]hexanes **228** were generated in excellent yields, diastereo- and enantioselectivities (up to 99% yield, >20:1 dr and 95% ee).

Various enantioenriched allylic amides **231** were synthesized through **Rh-2p**-catalyzed C−H functionalization with 1-aryl dienes **230**, reported by Yi and co-workers (Scheme 36). This method allowed for the carboamination of a wide array of dienes in high yields and enantioselectivity (up to 92% yield and 98% ee).[174] Very recently, a variety of dihydrobenzofurans was synthesized through enantioselective annulation of *N*-phenoxyacetamides **229** with 1,3-dienes **230** by You and co-workers. Impressively, the annulation products could be formed instead of allylic amides by simply changing the Cp*Rh catalysts.[175] In 2023, an elegant C−H activation/amide migration reaction was reported by Li and co-workers. With Cp*Rh complex **Rh-5b** as optimal catalyst, a series of enantioenriched amino alcohols could be synthesized in up to 99% ee.[176]

The Cp*Rh-catalyzed enantioselective C−H alkylations of benzamide derivatives have been further studied with a variety of alkene coupling partners beyond simple monosubstituted alkenes. Wang and co-workers reported an asymmetric addition of *N*-methoxy benzamides **233** to quinones **234** with [SCpRh] **Rh-5a** as the optimal catalyst, affording various chiral tricyclic hydrophenanthridinones **234** in up to 85% yield and 94% ee (Scheme 37a).[177] Notably, **234** could undergo further four-step transformation to give a dihydrolycoricidine analogue. Later, the same group developed chiral bicyclo[2.2.2]octane-fused Cp*Rh complex to promote this reaction, generating **234** in better enantiomeric excess values (up to 82% yield, 99% ee, Scheme 37b).[178]

As a highly reactive substrate, norbornene was employed in the asymmetric C−H alkylations of *N*-OBoc benzamide **235**. In 2018, Perekalin and co-workers developed a planar chiral Cp*Rh complex **Rh-7** through the resolution of its racemate with (*S*)-proline (Scheme 38a).[179] With this unique catalyst, chiral tetracyclic compounds **237** could be forged in up to 97% yield and 95% ee. In 2022, Wang and co-workers reported another class of planar chiral complex **Rh-11a** via resolution of racemic Cp*Rh complex by HPLC, which could be utilized as the catalyst in the same reaction, giving enantioenriched **237** in satisfactory results (up to 92% yield, 93% ee, Scheme 38b).[180] Recently, a new type of chiral CpRh catalyst bearing a chiral 3,3,3′,3′-tetramethyl-1,1′-spirobiindanyl backbone was also developed to realize the enantioselective synthesis of **237**.[181]

In 2020, Yi, Li, and co-workers utilized cyclopropene derivatives **239** as the coupling partner, −ONHTs as the directing group, and a series of 1,2-disubstituted cyclopropanes **240** was afforded in up to 81% yield and 99% ee (Scheme 39a).[182] Further mechanistic studies suggested that the O−N bond cleavage may occur via the formation of a Rh(V) nitrenoid

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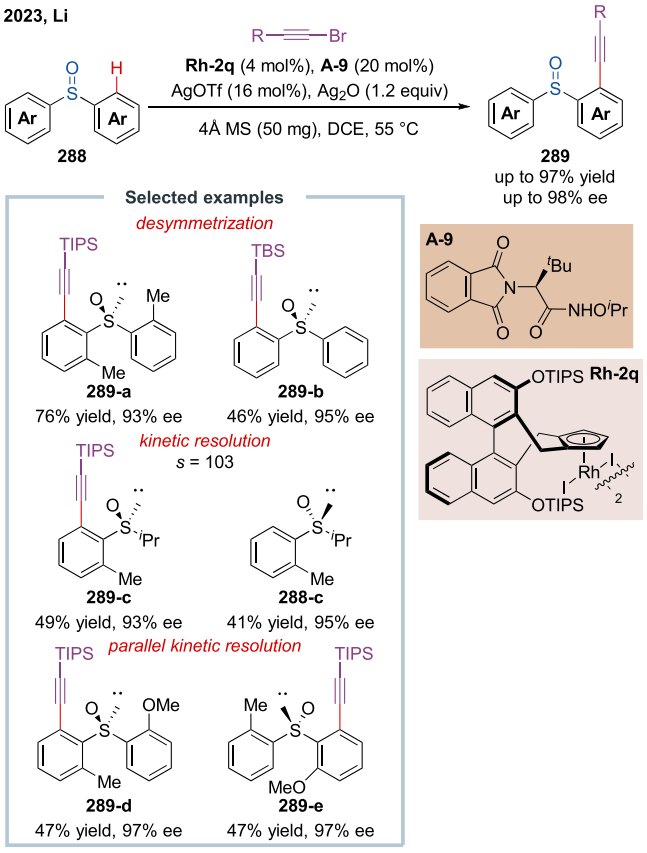
Scheme 47. Sulfoxide-Directed Rh(III)-Catalyzed Asymmetric C−H Alkynylation



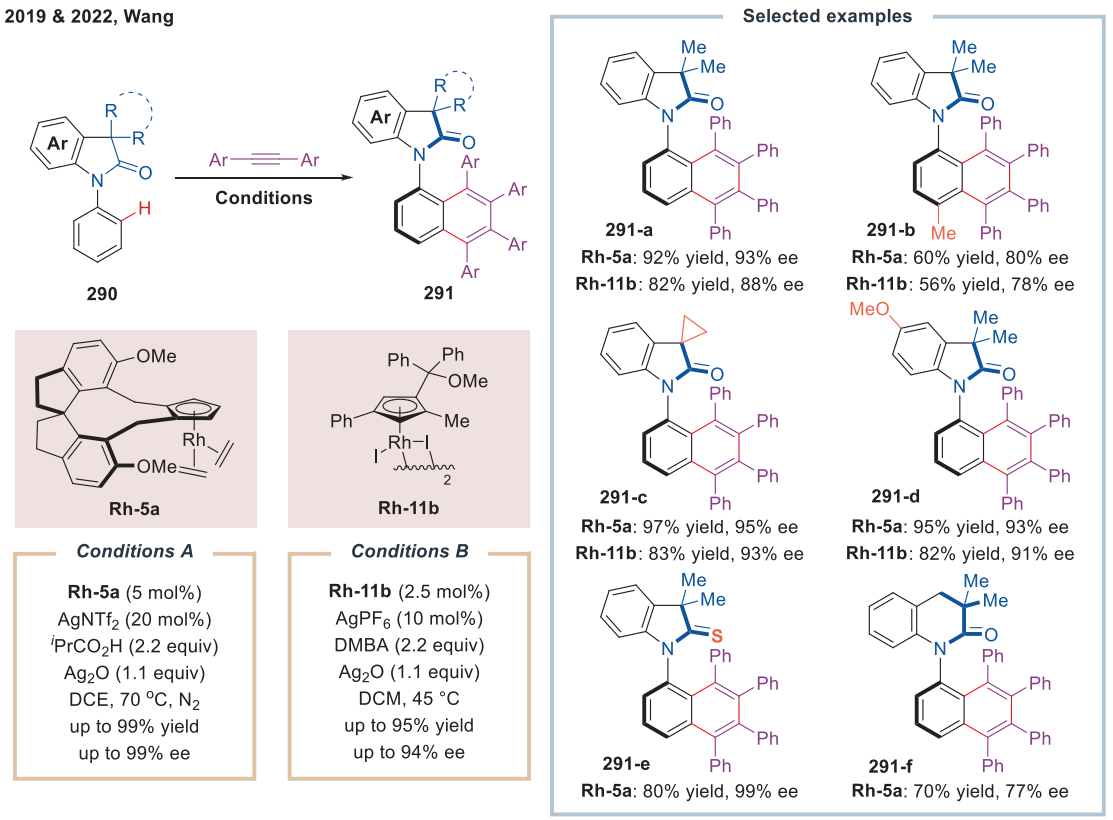
species. Then, Antonchick, Waldmann, and co-workers disclosed a [*Jas*CpRh^{III}] **Rh-6d** catalyzed C−H alkylation of *N*-OBoc benzamides with cyclopropene derivatives **242**, generating enantioenriched tricyclic isoquinolones **243** in up to 68% yield and 90% ee (Scheme 39b).[183]

In 2019, Li and co-workers developed an asymmetric ring opening (ARO) reaction of 7-azabenzonorbornadienes **245** with *N*-pyrimidine indoles **244** as coupling partners, yielding a series of *cis*-**246** (up to 95% yield, >98% ee, Scheme 40a).[184] Meanwhile, Cp*Rh complex **Rh-2f** catalyzed ARO reaction of 2,3-diazabicyclo[2.2.1]hept-5-enes **248** was achieved by Cramer and co-workers, generating chiral cyclopentenylamines *anti*-**249** in up to 99% yield and 94% ee (Scheme 40b).[185] Later, Li and co-workers expanded the substrate scope of ARO reaction to 7-azabenzonorbornadienes **251**, using *N*-alkyl indoles **250** as the coupling partners. As a result, such 2-fold C−H activation led to the formation of [3 + 2] annulation products **252** in up to 86% yield and 97% ee (Scheme 40c).[186]

Cramer and co-workers disclosed an asymmetric addition to allenes through **Rh-2c** catalyzed C−H allylation of *N*-methoxy benzamides **253** (Scheme 41a).[187] Under the mild conditions, chiral alkenes **255** could be afforded in up to 91% yield and 98% ee, with various substituents at different positions of benzamides. In 2017, [*Jas*CpRh^{III}] **Rh-6c** developed by Antonchick, Waldmann, and co-workers was employed in the reaction, enabling the asymmetric synthesis of chiral alkenes **255** in good to excellent yields and enantioselectivity (up to 91% yield and 94% ee, Scheme 41b).[157]

Cramer and co-workers further expanded the asymmetric addition of allenes to Cp*Rh catalyzed C−H functionalization of olefins (Scheme 42a).[188] When acrylamides **257** were

Scheme 48. Rhodium(III)-Catalyzed Asymmetric Dual C−H Activation for the Construction of C−N Axis



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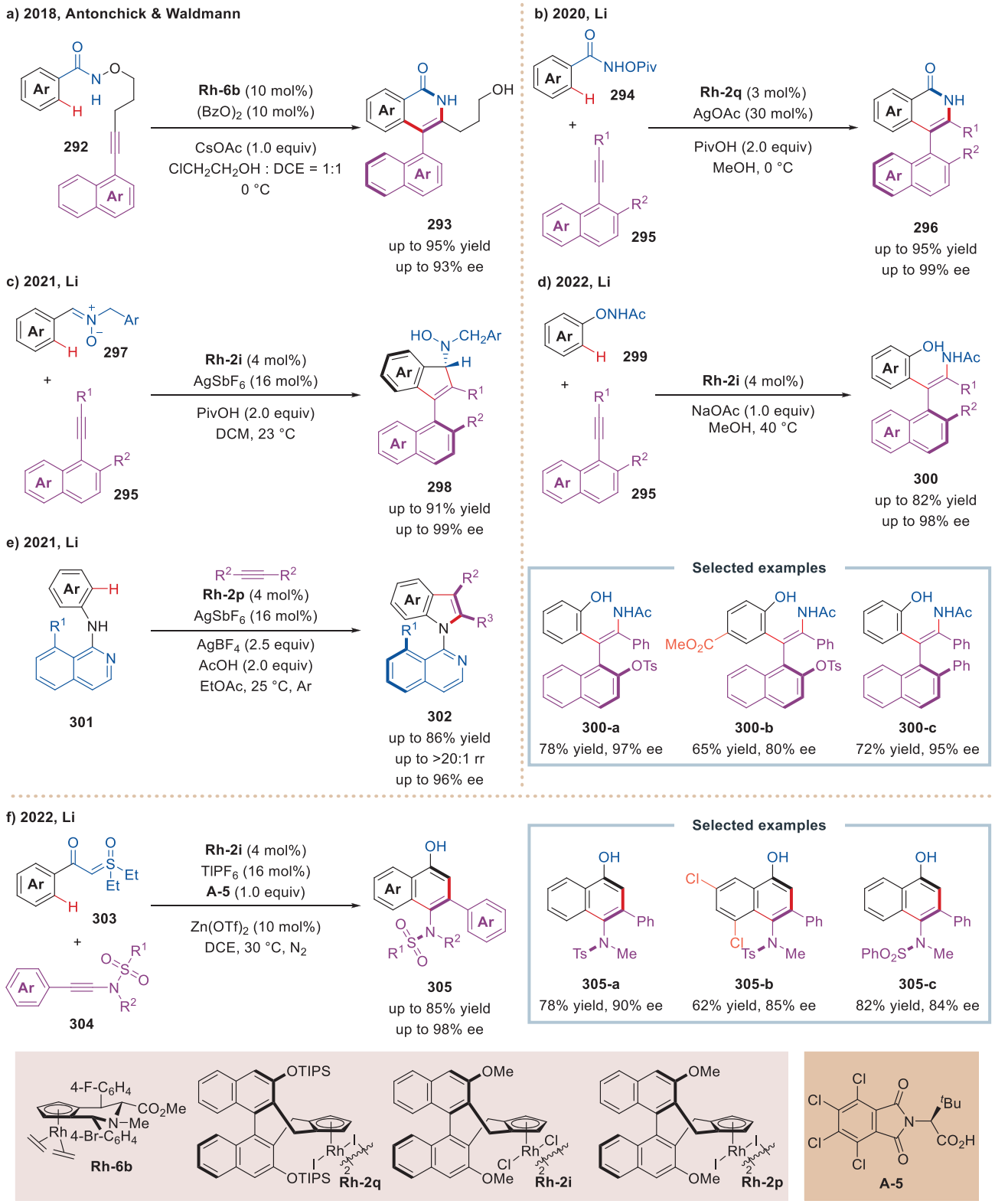
Scheme 49. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization of Alkynes for the Synthesis of Atropisomers



employed, [4 + 1] cyclization products **258** were formed rather than allylation products in previous work. **Rh-2l** bearing an ^{i}Pr group on the Cp ring was demonstrated to be the optimal catalyst, affording lactams **258** in up to 90% yield and 94% ee. In 2020, they expanded the substrate scope to acrylic acid **259**, with the aid of H_8−BINOL-derived complex **Rh-3**, achieving the asymmetric synthesis of γ-lactones **260** in good yields and enantioselectivity (up to 84% yield, 98% ee, Scheme 42b).[189]

5.1.2. Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions with Alkynes. In 2018, Wang and co-workers realized enantioselective [SCpRh] **Rh-5a** catalyzed C−H alkenylation of *N*-methoxy amide **261** using α,α-difluoromethylene alkynes **262** as the coupling partners, leading

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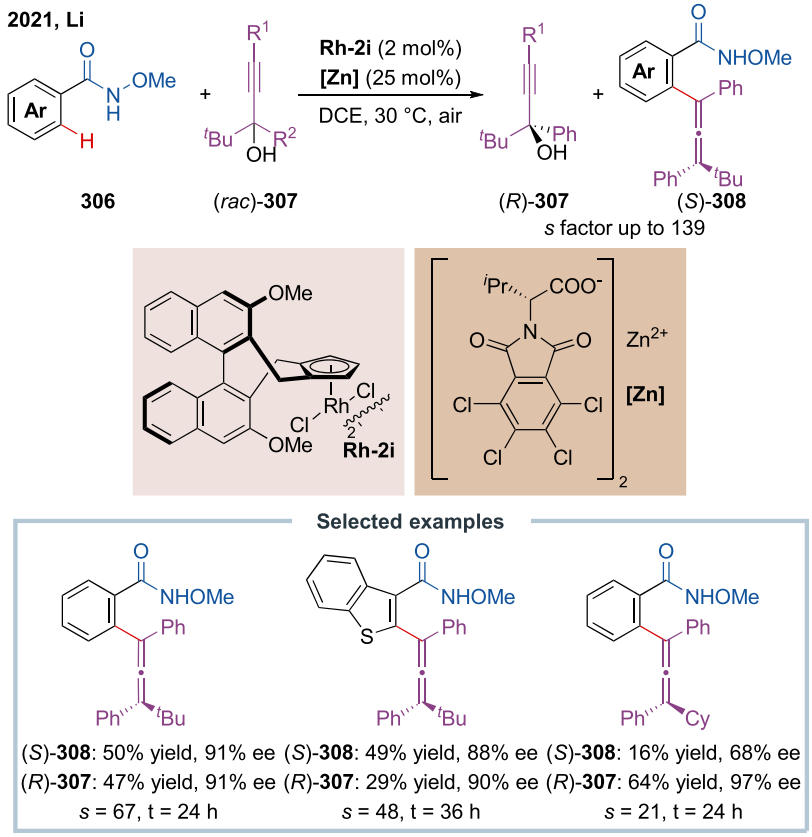
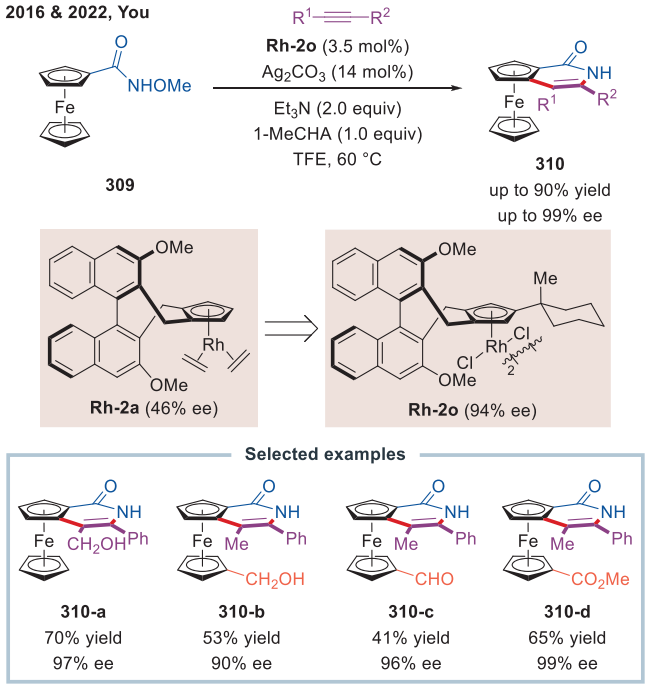
Scheme 50. Rh(III)-Catalyzed Carboxylate-Assisted Asymmetric Allenylation



Scheme 51. Rh(III)-Catalyzed Asymmetric C−H Annulation of Ferrocenes with Alkynes



to the formation of alkynyl isoindolinones **263** in good yields and excellent enantioselectivity (up to 86% yield, >99% ee, Scheme 43a).[190] Interestingly, when ^{i}PrCN was used as the solvent instead of methanol, monofluoroalkenyl isoindolinones **264** were generated in up to 93% yield, 98:2 *Z*:*E*, and 86% ee.

Another example utilizing 1,3-enynes in Rh(III)-catalyzed C−H activation was revealed by Li and co-workers in 2020 (Scheme 43b).[191] Both benzamides **265** and 2-aryl-3-hydroxy-2-cyclohexenones **267** were able to react, affording the corresponding [4 + 1] and [5 + 1] products in good yields and enantioselectivity (up to 91% yield and 96% ee, up to 87% yield and 92% ee, respectively). In 2021, they further studied [SCpRh] **Rh-5b** catalyzed cyclization of nitrones **269** with alkynes, affording enantioenriched indenes **270** in up to 95% yield and 99% ee (Scheme 43c).[192]

In 2015, You and co-workers developed **Rh-2a**-catalyzed enantioselective C−H spiroannulation reaction of naphthols **271** with alkynes, affording spirocyclic dearomatization products **272** in up to 98% yield, >19:1 rr, and 94% ee (Scheme 44a).[193] The origins of regio- and enantioselectivity were further clarified by the DFT calculation study.[194] After this pioneering work, the Lam group (Scheme 44b),[195] the Cramer group (Scheme 44c),[196] the You group (Scheme 44d),[197] and the Antonchick, Waldmann group (Scheme 44e)[198] realized the asymmetric synthesis of various spirocyclic compounds **274**, **276**, **278**, and **280** from well-designed substrates, respectively. Recently, exciting modifications were carried out by the You, Mei group (Scheme 44f)[199] and the Ackermann group (Scheme 44g)[200] respectively. The utilization of electrochemistry methods in the absence of the stoichiometric amount of chemical oxidants could give the products with comparable enantioselectivity.[201−203]

In 2022, Xia, Li, and co-workers realized [SCpRh] **Rh-5f** catalyzed [3 + 2 + 2] annulation with alkynes, constructing two rings to afford chiral *N*-fused 5/7 bicycles **282** in up to 80% yield and 96% ee (Scheme 45).[204]

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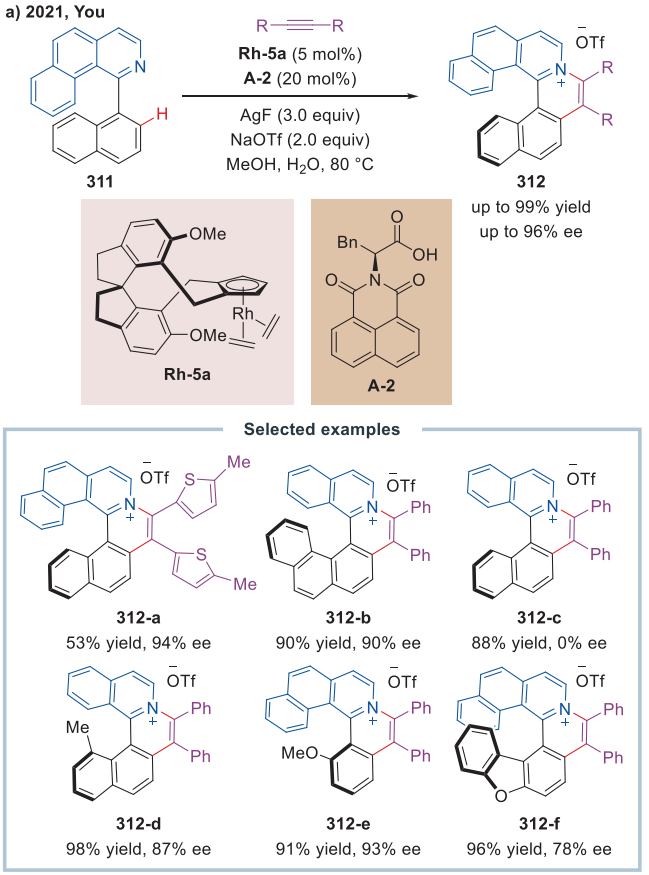
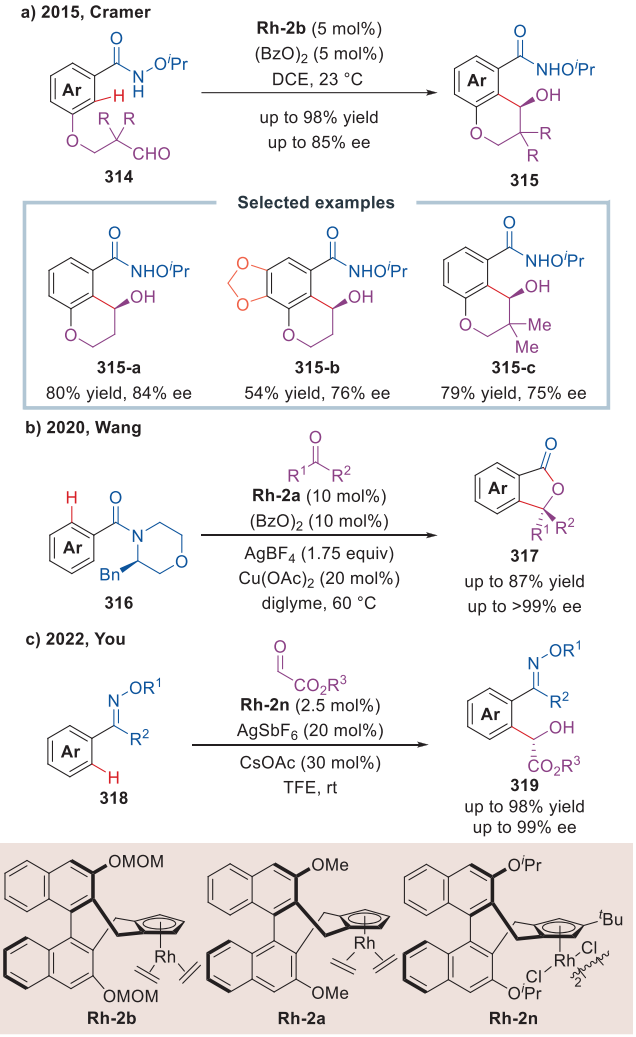
Scheme 52. Rh(III)-Catalyzed Asymmetric C−H Functionalization for the Synthesis of Azoniahelicenes



Scheme 53. Rh(III)-Catalyzed Asymmetric C−H Addition to Aldehydes



The method of accessing enantioenriched *P*-chiral cyclic phosphinamides **284** via desymmetrization of biaryl phosphoramides **283** via C−H annulation was developed by Cramer and co-workers in 2017 (Scheme 46a).[205] The optimal *N*-3,5-trifluoromethyl aryl directing group was critical for the highly enantioselective formation of **284** (up to 86% yield, 92% ee). Later, the kinetic resolution of racemic phosphoramides **283** bearing either an aryl group or an alkyl group was achieved by utilizing Cp*Rh complex **Rh-2e**, affording chiral phosphoramides **285** with *s* factor up to 50 (Scheme 46b).[206] In 2021, Li and co-workers employed the secondary amine-derived phosphinamides **286**, which occurred 2-fold C−H activation and simultaneously constructed both *P*-central and axial chirality in up to 80% yield, > 19:1 dr, and 96% ee. (Scheme 46c).[207]

Li and co-workers recently revealed a sulfoxide-directed, Rh(III)-catalyzed asymmetric C−H alkynylation.[208] Utilizing the combination of **Rh-2q** and **A-9** as cocatalyst, the enantioselective synthesis of various *S*-chiral sulfoxides **289** was achieved in good yields and enantioselectivity (up to 97% yield and 98% ee, Scheme 47). Impressively, under the same conditions, both kinetic and parallel kinetic resolution could be realized in good results.

Compared with well-studied six-membered ring axially chiral biaryls, asymmetric synthesis of five-membered-ring axially chiral compounds is more challenging mainly due to their relatively low rotation barriers.[209−214] In 2019, Wang and co-workers described an amide-directed, [SCpRh] **Rh-5a**-catalyzed asymmetric Satoh-Miura reaction, generating a class of *N*-aryl oxindole derivatives **291** bearing C−N chiral axis in good yields and excellent enantioselectivity (up to 99% yield, 99% ee, Scheme 48).[215] Impressively, thioamide and quinolinone derived products **291-e** and **291-f** could be afforded with comparable results. Later in 2022, the Wang group carried out the same reaction with the aid of planar chiral complex **Rh-11b**, with excellent results (up to 95% yield, 94% ee).[180]

The de novo construction of a ring is a reliable strategy in the enantioselective construction of atropisomers. Among them, alkyne was commonly applied as a C2 motif due to its accessibility and high reactivity. In 2018, Antonchick, Waldmann, and co-workers developed an intramolecular annulation to synthesize axially chiral 4-arylisoquinolones **293** in up to 93% ee, with the aid of Cp*Rh complex **Rh-6b** (Scheme

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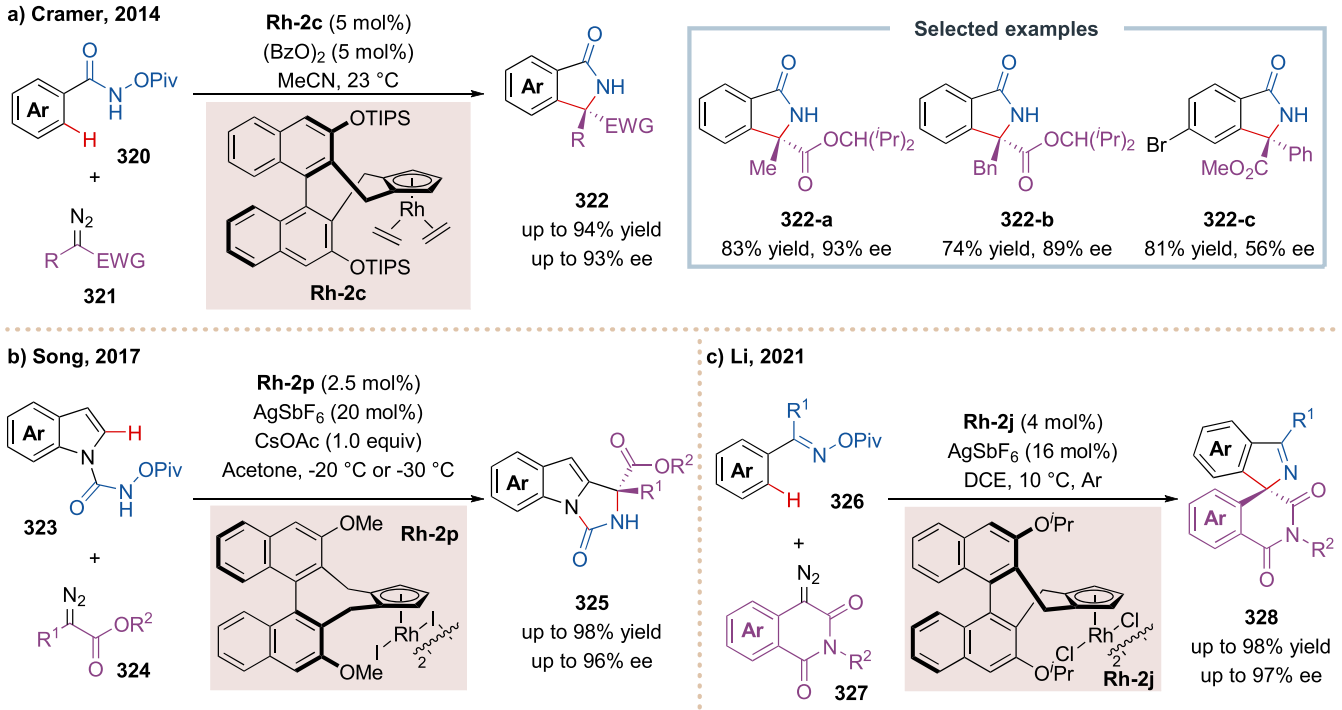
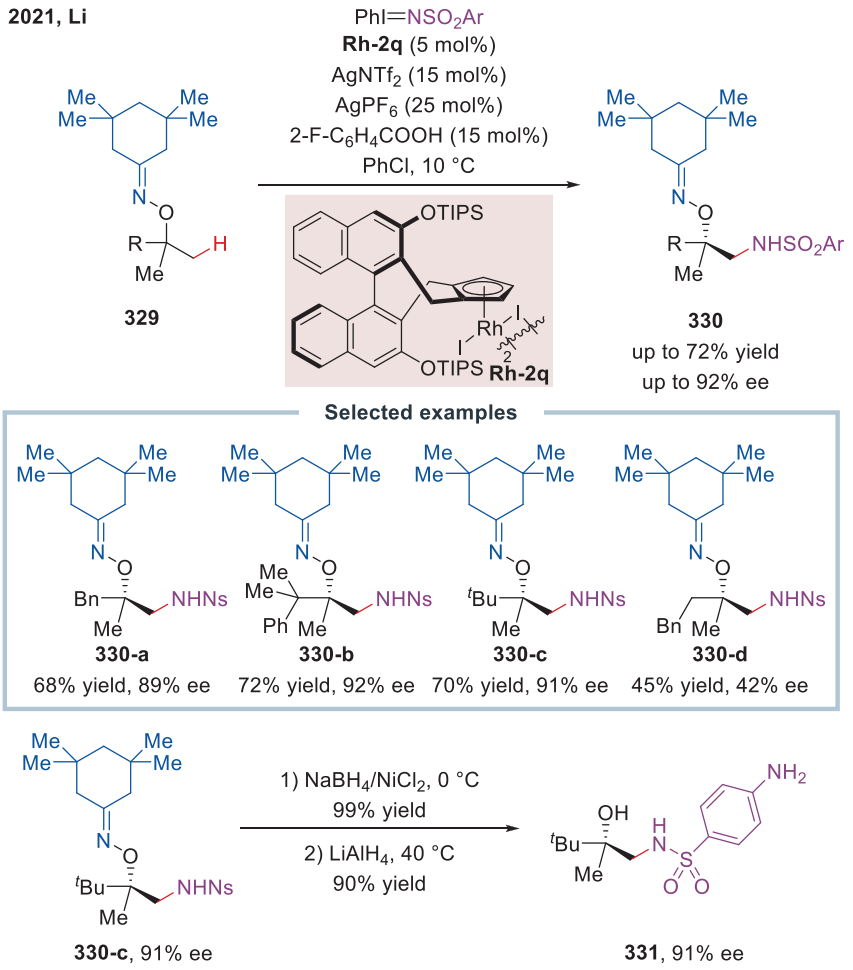
Scheme 54. Rh(III)-Catalyzed Asymmetric C−H Annulation with Diazo Compounds



Scheme 55. Enantioselective Synthesis of β-Amino Alcohols via Rh(III)-Catalyzed C−H Functionalization



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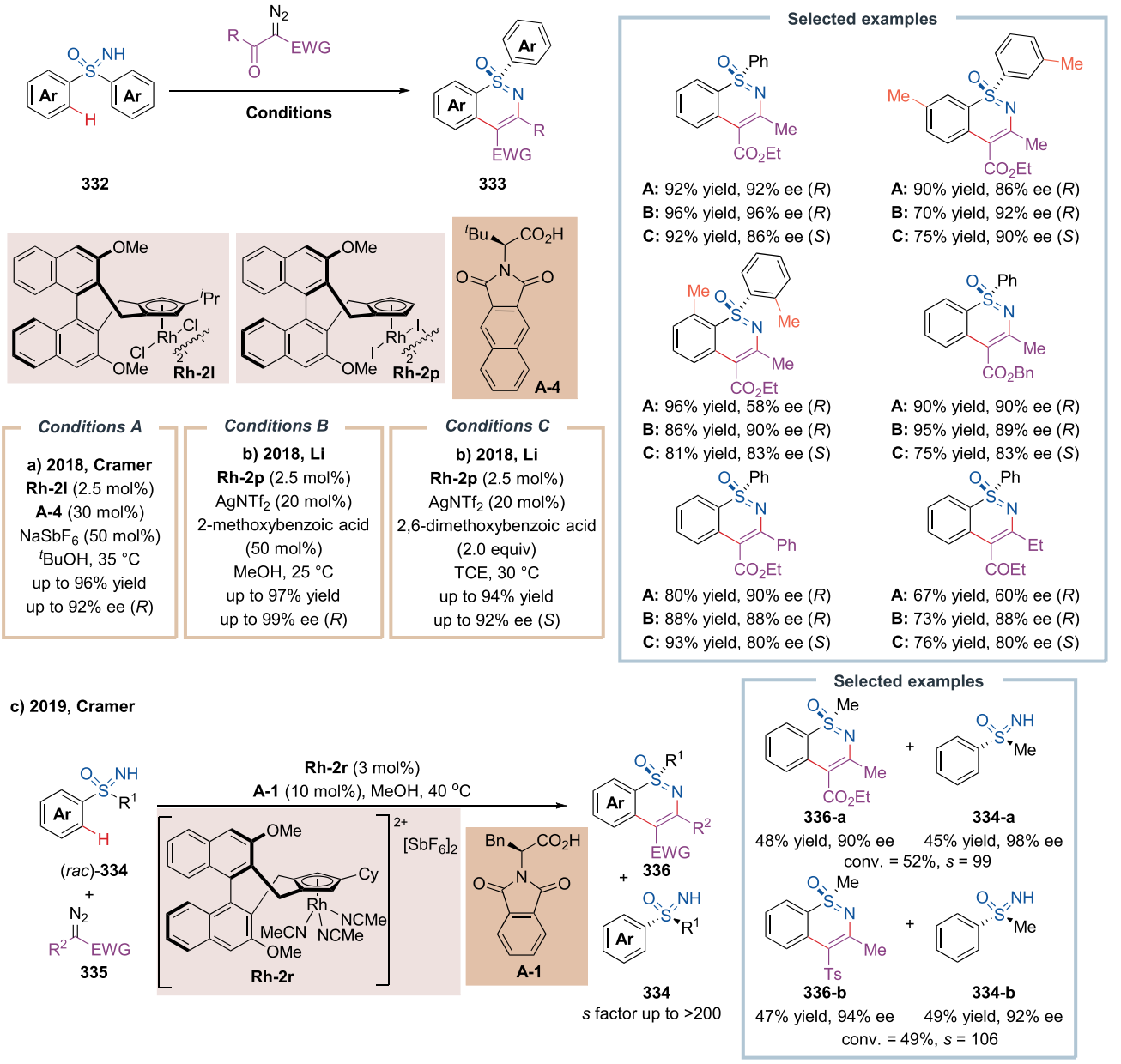
Scheme 56. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization Enables Access to S-Chiral Center



49a).[216] Later in 2020, Li and co-workers further studied the asymmetric construction of chiral 4-arylisoquinolones **296** from sterically hindered alkynes **295**. With the optimal catalyst **Rh-2q**, various benzamide derivatives could undergo this reaction smoothly, giving the corresponding products **296** in excellent yields and enantioselectivity (up to 95% yield, 99% ee, Scheme 49b).[217] Meanwhile, Li and co-workers disclosed a protocol allowing for the enantioselective synthesis of chiral indene derivatives **298** bearing axial and central chiralities in up to 91% yield and 99% ee (Scheme 49c).[192] In addition, when −ONHAc was applied as a directing group, styrenes **300** were formed rather than cyclization products, mainly due to the migration of directing group. Axially chiral olefins **300** with relatively lower rotational barriers were also given in up to 82% yield and 98% ee, showcasing the practicability of this method (Scheme 49d).[218] In 2021, Li and co-workers designed the *N*-isoquinoline anilines **301**, which could undergo atroposelective C−N reductive elimination with an alkyne. With Cp^{x}Rh complex **Rh-2p** as the catalyst and $AgBF_4$ as oxidant, axially chiral indoles **302** were afforded in good yields and enantioselectivity (up to 86% yield, 96% ee, Scheme 49e).[219] Sulfoxonium ylide **303** was utilized as both C−H coupling partner and carbene precursor in Rh(III)-catalyzed asymmetric C−H functionalization (Scheme 49f).[220] With the combination of complex **Rh-2i** and chiral acid **A-5**, the cyclization between **303** and alkynyl amides **304** afforded axially chiral naphthylamines **305** in up to 85% yield and 98% ee.

An amide-directed enantioselective C−H allenylation with racemic propargyl alcohol derivatives **307** was developed in 2018 by Li and co-workers (Scheme 50).[221] Using Cp^{x}Rh complex **Rh-2i** as the catalyst together with chiral zinc carboxylate as the additive, the corresponding aryl allenes **308** were afforded with good enantiomeric excess values. Under mild conditions, the kinetic resolution of racemic propargyl alcohols was realized with an *s* factor up to 139.

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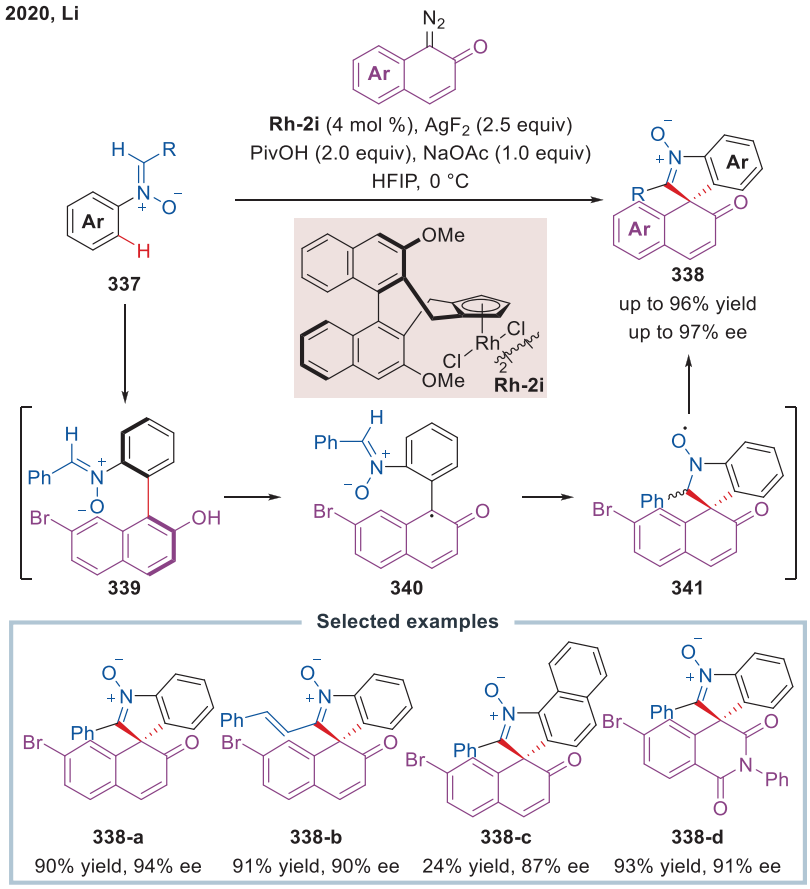
Scheme 57. Rhodium(III)-Catalyzed Asymmetric C−H Functionalization Enables Access to Spirocycles



The well-studied Rh(III)-catalyzed [4 + 2] cyclization between *N*-methoxy benzamides and alkynes was utilized in the enantioselective formation of planar chiral ferrocenes by You and co-workers (Scheme 51). In 2016, ferrocene-based pyridinones **310** were formed in moderate ee value (46%) using **Rh-2a** as the catalyst.[222] After further studies, they found that **Rh-2o** bearing a bulky substituent on the Cp ring proved more effective, affording **310** in up to 90% yield and 99% ee.[223] Notably, various functionalities on ferrocene **309**, such as unprotected hydroxy group, aldehyde and ester, were well tolerated under mild conditions.

Catalytic enantioselective synthesis of chiral helicenes has become an emerging research area due to their numerous applications in materials science and asymmetric catalysis.[224] The enantioselective synthesis of chiral helicenes via C−H functionalization was reported by You and co-workers in 2021 (Scheme 52a).[225] Using [SCpRh^{III}] **Rh-5a** and chiral acid **A-2** as the cocatalyst, AgF as the oxidant and NaOTf as the additive, chiral helicenes **312** could be given in up to nearly quantitative yield and excellent enantioselectivity (up to 99% yield, 96% ee). Further experiments demonstrated the chiral stability of these ionic helicenes. Later in 2022, further studies carried out by the You group showed that the shift of oxidant to $Cu(OAc)_2$ would lead to the formation of Satoh-Miura-type products **313** instead of helicenes (Scheme 52b).[226] With [SCpRh^{III}] **Rh-5d** as the optimal catalyst, the dual C−H activation could undergo in good yields and enantioselectivity (up to 85% yield, 96% ee). Both experimental and computational studies revealed that the difference of counteranions plays a crucial role in switching reaction pathways.

5.1.3. Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions with Aldehydes. Besides the processes involving the insertion of key Rh(III)-C species to C═C bonds, aldehydes could also participate in the enantioselective insertion of Rh(III)−C species.[227,228] In 2015, an intramolecular asymmetric addition of the arene C−H bond to aldehyde was reported by Cramer and co-workers (Scheme 53a).[229] With **Rh-2b** as the catalyst, hydroxychromane derivatives **315** were formed in up to 98% yield and 85% ee. Later, an amide-directed intermolecular addition of C−H bond to aldehydes was disclosed by Wang and co-workers in 2020, leading to a class of chiral phthalides **317** in good yields and excellent enantioselectivity (up to 87% yield, >99% ee, Scheme 53b).[230] It should be noted that the absence of the benzyl group would cause a significant decrease in enantiomeric excess, indicating the essential chirality of the morpholine amide group. In addition, the chiral morpholine auxiliary could be directly recovered during the reaction, enhancing the synthetic utility of this method. Recently, You and co-workers realized oxime ether-directed C−H addition to glyoxylate ester, giving enantioenriched benzyl alcohol derivatives in up to 98% yield and 99% ee (Scheme 53c).[231]

5.1.4. Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions with Diazo Compounds. A concise synthesis of chiral isoindolinones was realized by Cramer and co-workers via Rh(III)-catalyzed C−H activation/[4 + 1] cyclization of benzamides with diazo compounds (Scheme 54a).[232] With **Rh-2c** complex bearing bulky -OTIPS substituents at the 3,3′-position of BINOL scaffold, diverse isoindolinones **322** with the quaternary chiral stereogenic

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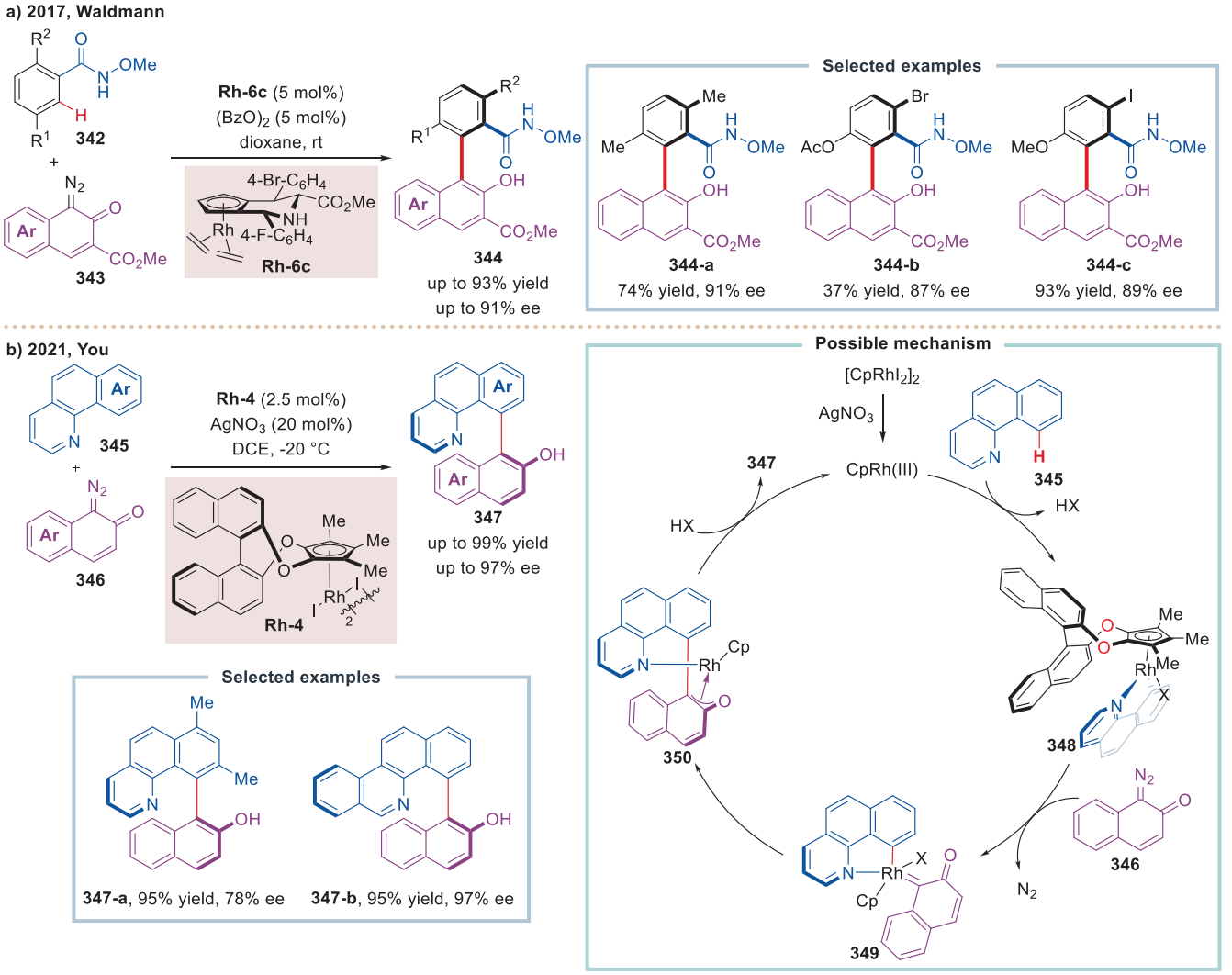
Scheme 58. Enantioselective Synthesis of Atropisomers via Rh(III)-Catalyzed C−H Functionalization with 1-Diazonaphthoquinones



center were afforded in up to 94% yield and 93% ee. Later in 2017, Song and co-workers expanded the enantioselective [4 + 1] annulation employing indole derivatives **324** as C−H substrate partners, giving indole-fused lactams **325** in good yields and enantioselectivity (up to 98% yield, 96% ee, Scheme 54b).[233] In 2021, *O*-pivaloyl oxime was applied as a directing group in Rh(III)-catalyzed asymmetric [4 + 1] annulation with diazo compounds **327**, allowing for the generation of various chiral five-membered aza-rings **328** in up to 98% yield and 97% ee (Scheme 54c).[234]

In sharp contrast to the well-developed Rh(III)-catalyzed C(sp^2)−H functionalization, C(sp^3)-H functionalization is a more challenging task, mainly due to the low reactivity of the C(sp^3)−H bond. Nevertheless, Li and co-workers achieved an elegant enantioselective Rh(III)-catalyzed C(sp^3)−H amination, forming various β-amino alcohols **330** (Scheme 55).[235] A bulky oxime directing group proved efficient in this desymmetrization of *gem*-dimethyl groups, delivering the corresponding products in up to 72% yield and 92% ee. Further studies showed that the steric hindrance of the substituent adjacent to the *gem*-dimethyl group greatly impacted the enantioselective induction, as the less bulky group led to lower enantiometric excess values (**330-d**). Removal of the oxime directing group proceeded successfully in good yield, without losing the enantiopurity.

Cramer and co-workers applied a combination of rhodium complex **Rh-2l** and chiral acid **A-4** for accessing enantioenriched 1,2-benzothiazines **333** bearing a sulfur-central chirality (Scheme 56a).[236] Desymmetrization of diaryl sulfoximines **332**, bearing substituents at the ortho-, meta-, or para-position could all deliver cyclization products in good yields and enantioselectivity (up to 96% yield, 92% ee). Meanwhile, Li and co-workers realized the same reaction in the presence of catalyst **Rh-2p**, affording **333** in satisfactory results (up to 97% yield, 99% ee, Scheme 56b).[237] Interestingly, trichloroethanol (TCE) instead of methanol as the solvent led to the product with the opposite absolute configuration. With the same catalyst **Rh-2p**, (*S*)-**333** could be formed in up to 94% yield and 92% ee. Later, kinetic resolution of racemic sulfoximines **329** featuring an aryl group and an alkyl group was realized by Cramer and co-workers by employing complex **Rh-2r** and chiral acid **A-1** (Scheme 56c).[238] High resolution efficiency (*s* factor up to >200) was obtained to yield highly enantioenriched **336**.

An elegant synthesis of spirocycles **338** was disclosed by Li and co-workers in 2020 via nitrone-directed Rh(III)-catalyzed C−H functionalization with 1-diazonaphthoquinones (Scheme

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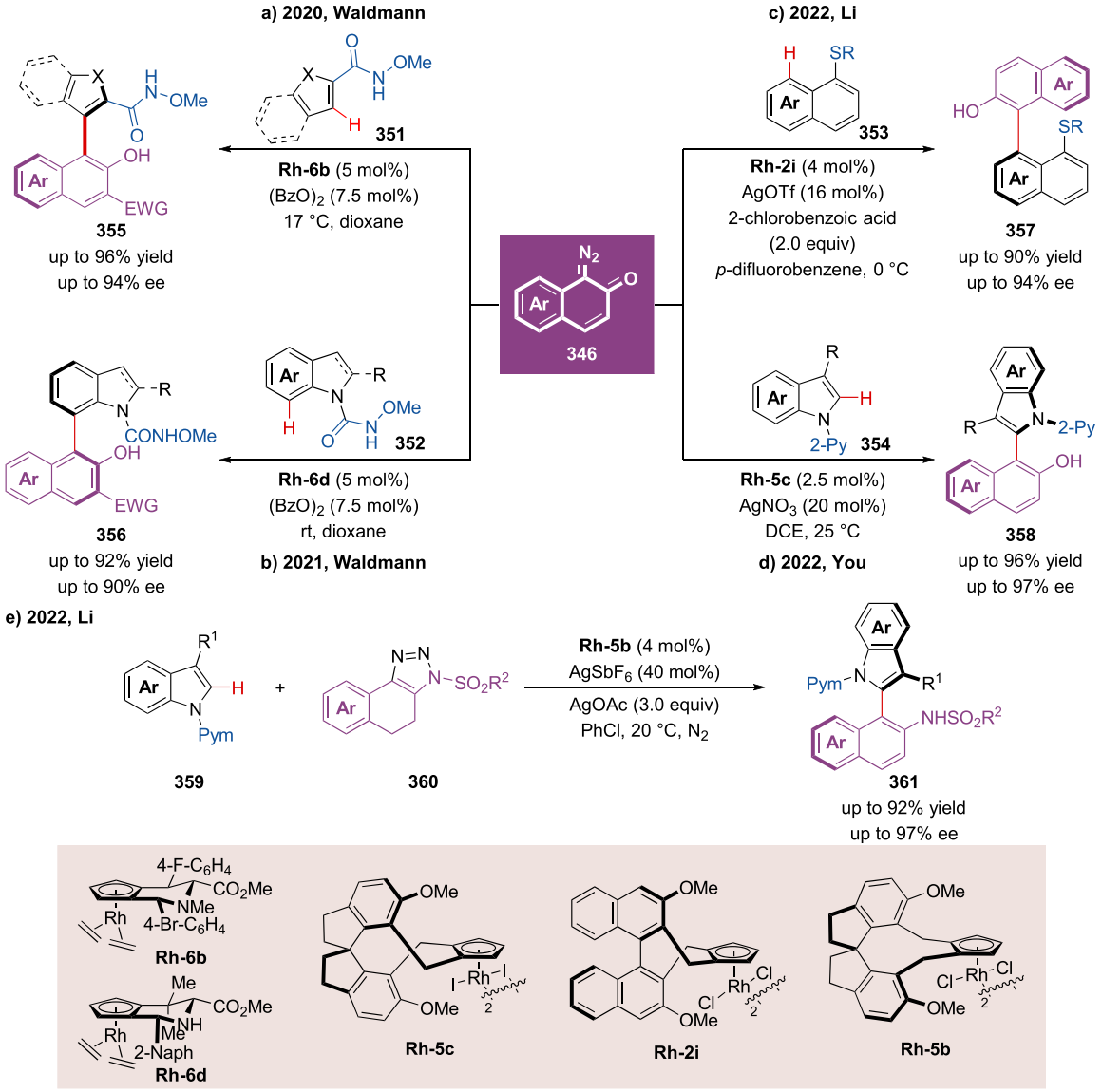
Scheme 59. Rh(III)-Catalyzed Asymmetric C−H Functionalization with 1-Diazonaphthoquinones



57).[239] The reaction first proceeds by C−H activation of **337**, forming biaryl intermediate **339** with less stable axial chirality. This intermediate then undergoes a SET process with the aid of AgF_2, generating radical intermediate **340**. Further cyclization of **340** forms oxygen radical **341**, which might undergo additional oxidation to give product **338**. Such an axial-to-central chirality transfer strategy could afford **338** in 96% yield and 97% ee.

Due to the high reactivity and steric hindrance, 1-diazonaphthoquinone is a promising platform for constructing axially chiral biaryls via Rh(III)-catalyzed C−H activation.[240,241] In 2017, Waldmann and co-workers reported an asymmetric aryl−aryl cross-coupling between benzamides **342** and diazonaphthoquinones **343** (Scheme 58a).[157] [*Jas*CpRh^{III}] **Rh-6c** was employed to build up a series of biphenyl atropisomers **344** in up to 93% yield and 91% ee. In 2021, You and co-workers realized asymmetric arylation of benzo[*h*]quinolines **345** with diazonaphthoquinones **346** in excellent yields and enantioselectivity (up to 99% yield and 97% ee, Scheme 58b).[242] The utilization of a newly designed BOCp ligand proved essential to the excellent enantioselective control. A further mechanistic study showed that the reaction initializes from the C−H bond activation of benzo[*h*]quinolines **345**, followed by the formation of Rh carbene **349**. Then the intermediate **350** is formed by the migratory insertion of carbene into the Rh−C bond. The final protonation of **350** releases product **347** and regenerates the catalyst.

In 2020, Waldmann and co-workers expanded this strategy to the asymmetric construction of five-membered ring-based atropisomers (Scheme 59a).[243] The utilization of [*Jas*CpRh^{III}] **Rh-6b** delivered a series of axially chiral (benzo)furan, (benzo)thiophene, and indole derivatives in up to 96% yield and 94% ee. Subsequently, the asymmetric C−H arylation at the 7-position of 2-substituted indoles and indolines **352** was realized using **Rh-6d** (up to 92% yield, 90% ee, Scheme 59b).[244] In 2022, Li and co-workers reported thioether-directed asymmetric C−H arylation with diazonaphthoquinones **346**. Atropisomeric 1,1′-binaphthyl derivatives **357** were obtained in good yields and enantioselectivity (up to 90% yield, 94% ee, Scheme 59c).[245] Recently, asymmetric synthesis of axially chiral C2-arylated indoles **358** was reported by You and co-workers (Scheme 59d).[246] Excellent yields and enantioselectivity (up to 96% yield, 97% ee) could be achieved with the aid of [SCpRh^{III}] **Rh-5c**.

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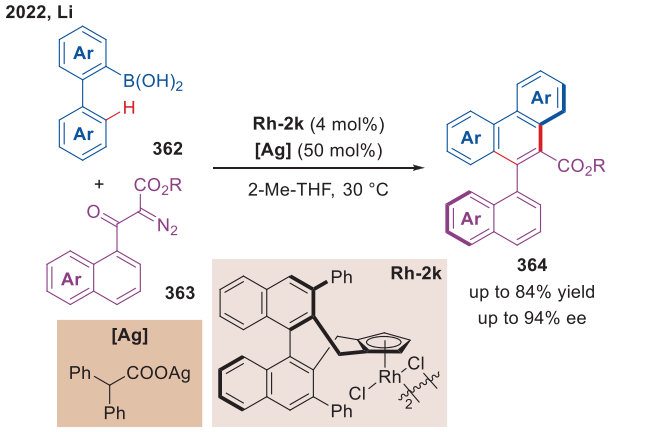
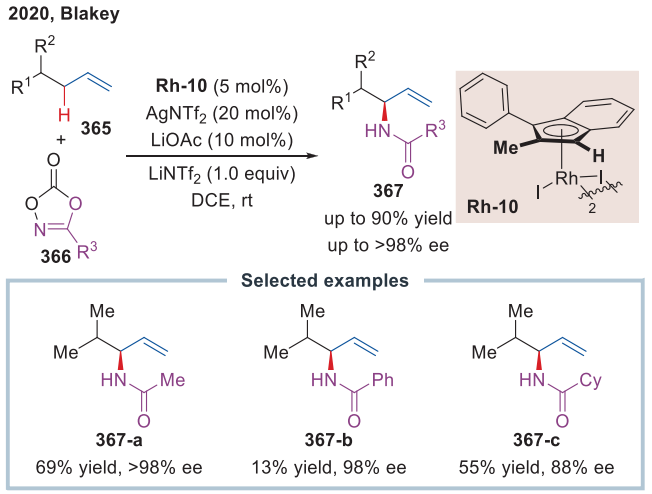
Scheme 60. Rh(III)-Catalyzed Atroposelective C−H Activation with Biphenyl-2-boronic Acid



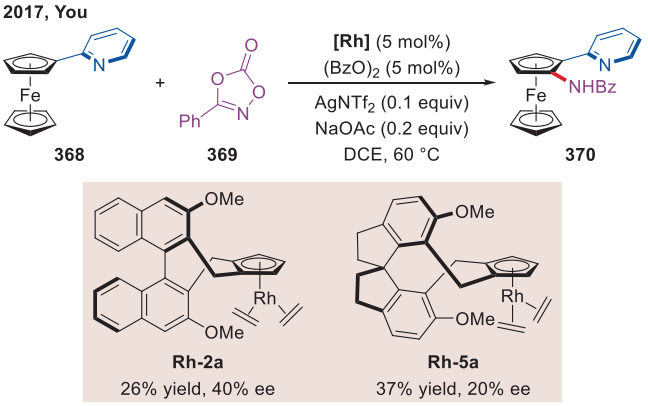
Scheme 61. Rh(III)-Catalyzed Asymmetric Allylic C−H Amidation



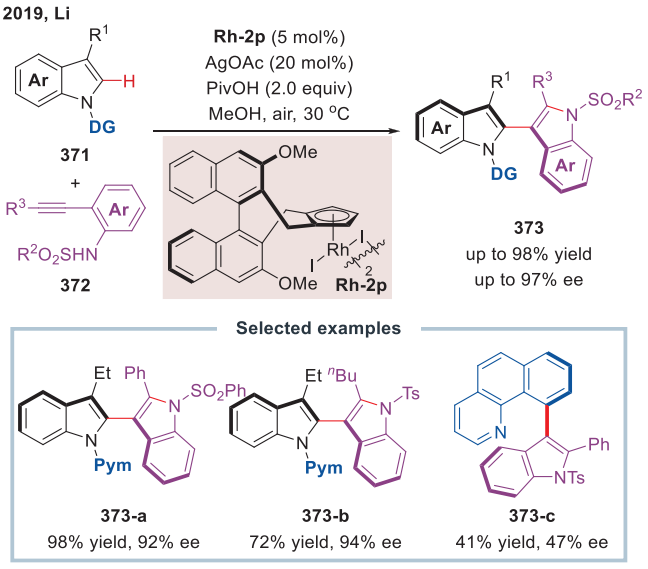
Besides the widely used diazonaphthoquinones, Li and co-workers utilized triazoles **360** as the carbene precursors in Rh(III)-catalyzed asymmetric C2−H activation of indoles, affording atropisomeric β-naphthylamine derivatives in up to 92% yield and 97% ee (Scheme 59e).[245]

Besides the widely used 1-diazonaphthoquinone derivatives, acceptor-acceptor diazo compounds **363** were employed in Rh(III)-catalyzed atroposelective C−H activation with biphenyl-2-boronic acid **362** by Li and co-workers.[247] With **Rh-2k** as the optimal catalyst, a wide array of axially chiral biphenyl compounds **364** could be afforded in up to 84% yield and 94% ee (Scheme 60). Further mechanistic study showed that forming an intermediate bearing a C(sp^2)−C(sp^3) chiral axis is vital for enantioselective control. In 2023, a **Rh-5b**-catalyzed atroposelective annulation was realized by Huang, Crabtree, and Li and co-workers. Utilizing imidoyl sulfoxonium ylides as carbene precursor, various atropisomers bearing C−N axis were afforded in good yields and enantioselectivity (up to 85% yield and 99% ee).[248]

Scheme 62. Rh(III)-Catalyzed Asymmetric C−H Amidation of Ferrocenes



Scheme 63. Enantioselective Synthesis of Axially Chiral Biindolyls via Rh(III)-Catalyzed C−H Functionalization



In sharp contrast to well-studied palladium-catalyzed asymmetric allylic C−H functionalization, the reaction catalyzed by Cp^{x}Rh(III) was rarely reported. In 2020, Blakey and co-workers developed a class of planar chiral Cp^{x}Rh(III) complexes **Rh-10**, which could promote enantioselective allylic C−H bond amidation of terminal alkenes **365** (Scheme 61).[249] With dioxazolone **366** as a nitrene precursor, allylic amides **367** could be afforded in good yields and enantioselectivity (up to 90% yield, > 98% ee). Notably, chiral Cp^{x}Rh complex **Rh-10** was easily accessible through the resolution of racemic complex by HPLC.

Cp^{x}Rh(III) catalyzed enantioselective C−H amidation was also applied in the synthesis of planar chiral ferrocenes. In 2017, You and co-workers investigated the performance of Cp^{x}Rh complexes **Rh-2a** and **Rh-5a** in asymmetric C−H amidation of pyridylferrocenes **368** (Scheme 62).[250] However, both catalysts afforded the amidation product **370** in relatively low yields and enantioselectivity (26% yield and 40% ee, 37% yield and 20% ee,

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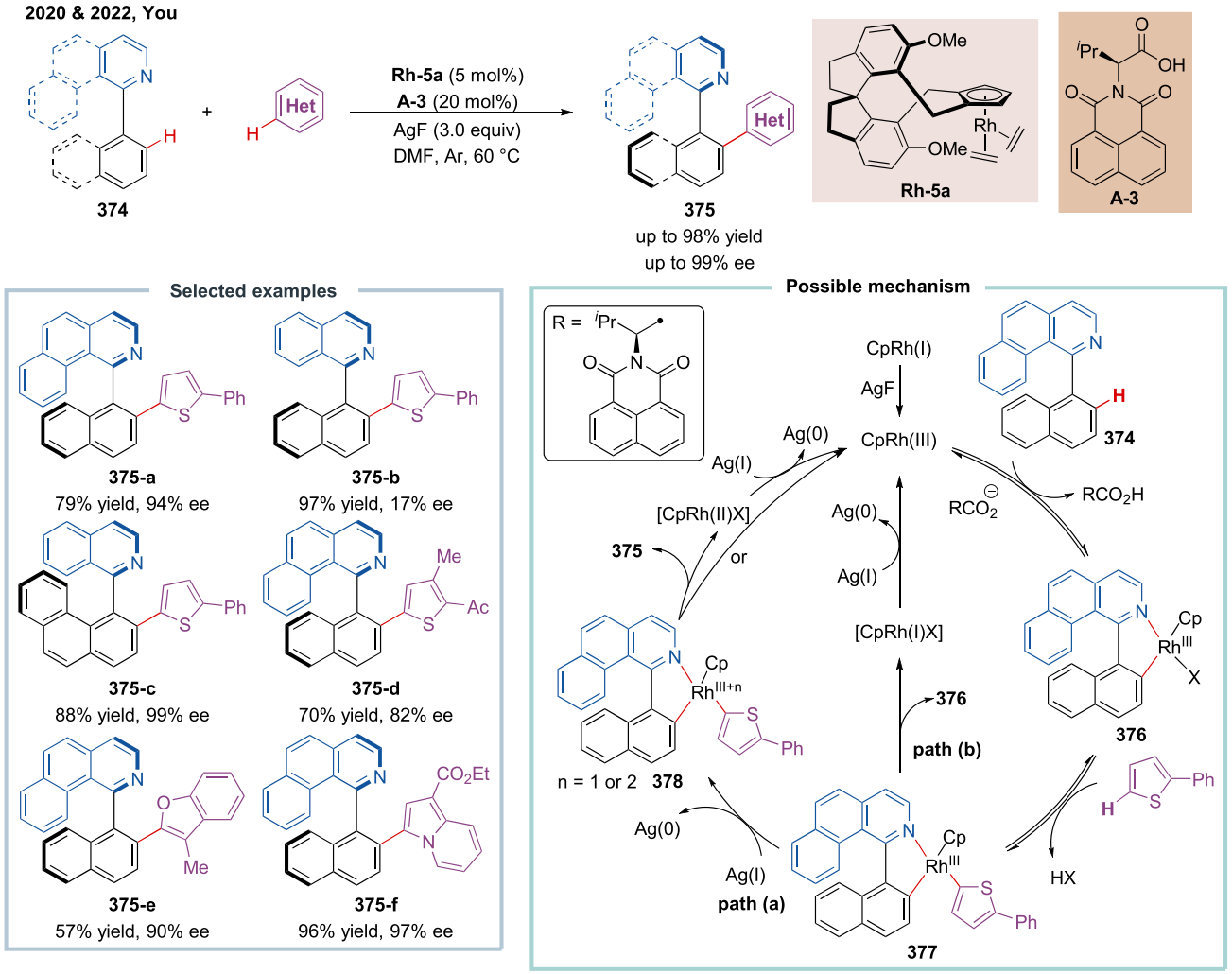
Scheme 64. Rh(III)-Catalyzed Asymmetric C−H Functionalization with Electron-Rich Heteroarenes



respectively), which provided the proof-of-concept for further studies.

5.1.5. Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions with Aromatic Compounds. The synthesis of axially chiral 2,3′-biindolyls **373** featuring a low rotation barrier was challenging. Li and co-workers recently documented an elegant method using complex **Rh-2p** to merge C−H activation and nucleophilic cyclization (up to 98% yield, 97% ee, Scheme 63).[251] Notably, benzo[h]quinolone, rather than *N*-pyrimidine indole, could also be used as C−H functionalization substrate partner, albeit with moderate conversion and enantioselectivity (**373-c**, 41% yield, 47% ee).

Oxidative C−H/C−H cross-coupling could directly form a C−C bond, avoiding the prefunctionalization of either substrate. However, it is a particularly challenging task mainly due to the low reactivity of C−H bonds and the formation of homocoupling products. In 2020, the You group achieved Pd(II)-catalyzed C−H/C−H cross-coupling of ferrocenes with various electron-rich arenes.[252−255] Then, asymmetric synthesis of a class of isoquinoline-based biaryl atropisomers **375** was achieved through Rh(III)-catalyzed C−H/C−H cross-coupling by You and co-workers (Scheme 64).[256] Using [SCpRh^{III}] **Rh-5a** and chiral acid **A-3** as cocatalyst, products **375** could be afforded in good to excellent yields and atropo-enantioselectivity (up to 98% yield and 99% ee). The proposed reaction mechanism commences with the C−H activation of isoquinoline derivatives **374**, likely through a CMD process. A secondary C−H activation occurs between rhodacycle complex **376** and 2-phenylthiophene to afford intermediate **377**, which may undergo oxidation-induced reductive elimination with the Ag(I) oxidant, affording product **375**. The KIE experiment showed that neither of the two C−H activation processes is included in the rate-determining step. Therefore, reductive elimination was suggested as the turnover-limiting step. In 2021, they further expanded the substrate scope to indolizines, affording the corresponding product **375-f** in excellent yield and enantioselectivity (96% yield and 97% ee).[257]

5.1.6. Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions with Iodination Compounds. Although great progresses have been achieved in rhodium-catalyzed enantioselective C−C bond and C−N bond formation, asymmetric construction of carbon−halogen bond remains an elusive area. Very recently, You and co-workers realized [SCpRh]-catalyzed atroposelective C−H iodination of 1-aryl isoquinolines **374** with NIS, affording **379** in up to 99% yield and 97% ee. Remarkably, the corresponding iodinated products **379-a** could be easily transformed to the QUINAP-type ligand in 77% yield without the loss of enantiopurity (Scheme 65).[258]

5.1.7. Rh(III)-Catalyzed Asymmetric (Carbo)Amidation Reactions. In 2019, Ellman and co-workers described a three-

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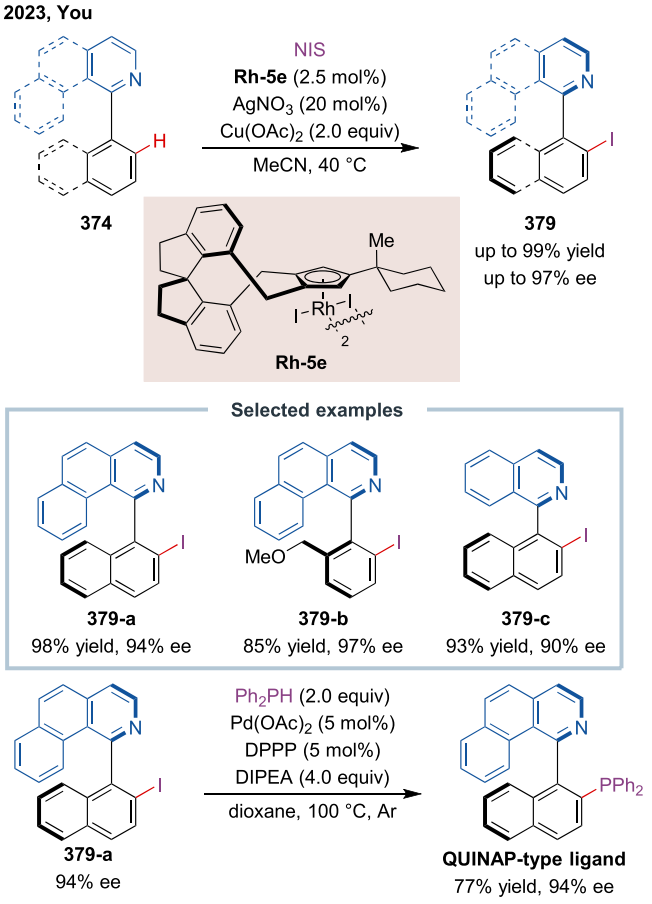
Scheme 65. Rh(III)-Catalyzed Atroposelective C−H Iodination with NIS



component 1,1-addition carboamidation of ethylene via **Rh-2p**-catalyzed asymmetric C−H functionalization directed by oxime ether or pyrazole (Scheme 66a).[259] With dioxazolone **382** as nitrene precursor, amides **383** could be afforded in up to 71% yield and 84% ee. Then asymmetric 1,2-carboamidation with norbornene derivatives **384** as coupling partners was realized in 2021, affording amides **385** in up to 59% yield and 84% ee (Scheme 66b).[260] In addition, asymmetric 1,2-carboamidation was revealed by Li and co-workers, with 1-aryl dienes **387** as C2-component and **Rh-2m** as the catalyst, accessing enantioenriched allylic amines **388** in good yields and enantioselectivity (94% yield and 99% ee, Scheme 66c).[261]

5.2. Rh(III)-Catalyzed Asymmetric C−H Functionalization Reactions using Chiral Additives

Although significant progresses in asymmetric C−H activation have been achieved by utilizing chiral Cp*Rh(III) complexes in the past decade, the tedious synthetic route of most chiral Cp ligands greatly restricted the practicality of these methods. Thus, the combination of achiral CpRh(III) complex and chiral additive, including chiral transient directing group, chiral Brønsted acid, and chiral Lewis base, has received more attention due to their ready availability, which provided alternative strategies for Rh(III)-catalyzed asymmetric C−H functionalization.

Despite the outstanding achievements in Pd(II)-catalyzed asymmetric C−H functionalization reaction by utilizing chiral transient directing strategy,[262−264] analogous works were less applied in Rh(III)-catalyzed asymmetric C−H functionalization reactions, mainly due to the lack of proper transient directing group. In 2019, Wang and co-workers elegantly applied this strategy to realize Rh(III)-catalyzed asymmetric C−H activation/[3 + 2] cycloaddition with aldehydes (Scheme 67).[265] Chiral benzylamine (*R*)-**TDG** was chosen as the optimal chiral transient directing group, affording a class of chiral phthalide derivatives. It is worth mentioning that both homo- and cross-coupling products **390** could be afforded with excellent enantioselectivity (up to >99% ee), albeit in relatively low yields. Besides this, no other example was reported, which made this area yet to be developed.

In 2018, Matsunaga and co-workers reported a CpRh(III) complex with [6,6′-Br_2-(*S*)-BINSate] as an additive, which enabled asymmetric conjugate addition to *α,β*-unsaturated ketones with 2-phenylpyridine in up to 95% yield and 90% ee (Scheme 68a).[50] The authors suggested that enantioselective protonation might be the enantioselectivity-determining step rather than the counterion-pairing mechanism, mainly due to the weak solvent effect observed in this reaction. Mechanism details remained unclear and were expected to be revealed in future studies. Subsequently, the same group revealed a $[Cp^*RhCl_2]_2$/chiral carboxylic acid **A-6** cooperative catalyst, enabling desymmetrization of diarylmethanamines **394** with diazo compounds **395**, forming lactams **396** in up to 87% yield and 97% ee (Scheme 68b).[266] A selective C−H bond cleavage via a CMD process was suggested to be essential to enantioselective control. Utilizing this strategy, Matsunaga and co-workers further realized asymmetric amidation (Scheme 68c)[267] and alkylation (Scheme 68d)[268] of 8-ethyl quinoline with corresponding electrophiles, both achieving good yields and enantioselectivity (up to 99% yield and 88% ee, up to 93% yield and 84% ee, respectively). In a further development, a pyridine directed-desymmetrization of *gem*-dimethyl groups/intermolecular amidation was disclosed with $[Cp^{*tBu}RhCl_2]_2$/chiral carboxylic acid **A-8**, affording the corresponding amides **403** in up to 98% yield and 92% ee (Scheme 68e).[269]

Taking advantage of the combination of achiral CpRh(III) complex and chiral acid, Matsunaga and co-workers have made impressive contributions in Rh(III)-catalyzed asymmetric C−H functionalization. However, this strategy still suffers from the weak interaction between the chiral catalyst and reactant, leading to poor enantioselective control in some cases. However, isochalcogenureas (ICU) as a common Lewis base catalyst was widely used in the enantioselective conjugate addition of *α,β*-unsaturated carbonyl compounds. Interestingly, a combination of achiral CpRh(III) complex and chiral ICU catalyst was developed by Matsunaga and co-workers in 2022, realizing the enantioselective [4 + 3] cyclization in up to 91% yield and 98% ee (Scheme 69).[270] Remarkably, the slow addition of acyl fluoride **405** led to significant enantioselectivity promotion, which might inhibit the racemic background reaction. To provide more insights into the mechanism, both (*E*)- and (*Z*)-**405a** were tested under the standard reaction conditions, affording product **406** with nearly identical results (83% yield and 92% ee, 85% yield and 96% ee, respectively), which indicated that the migratory insertion step is reversible. Thus, the authors proposed that the enantioselectivity might be determined by an irreversible intramolecular cyclization of **411**, further supported by DFT calculations.

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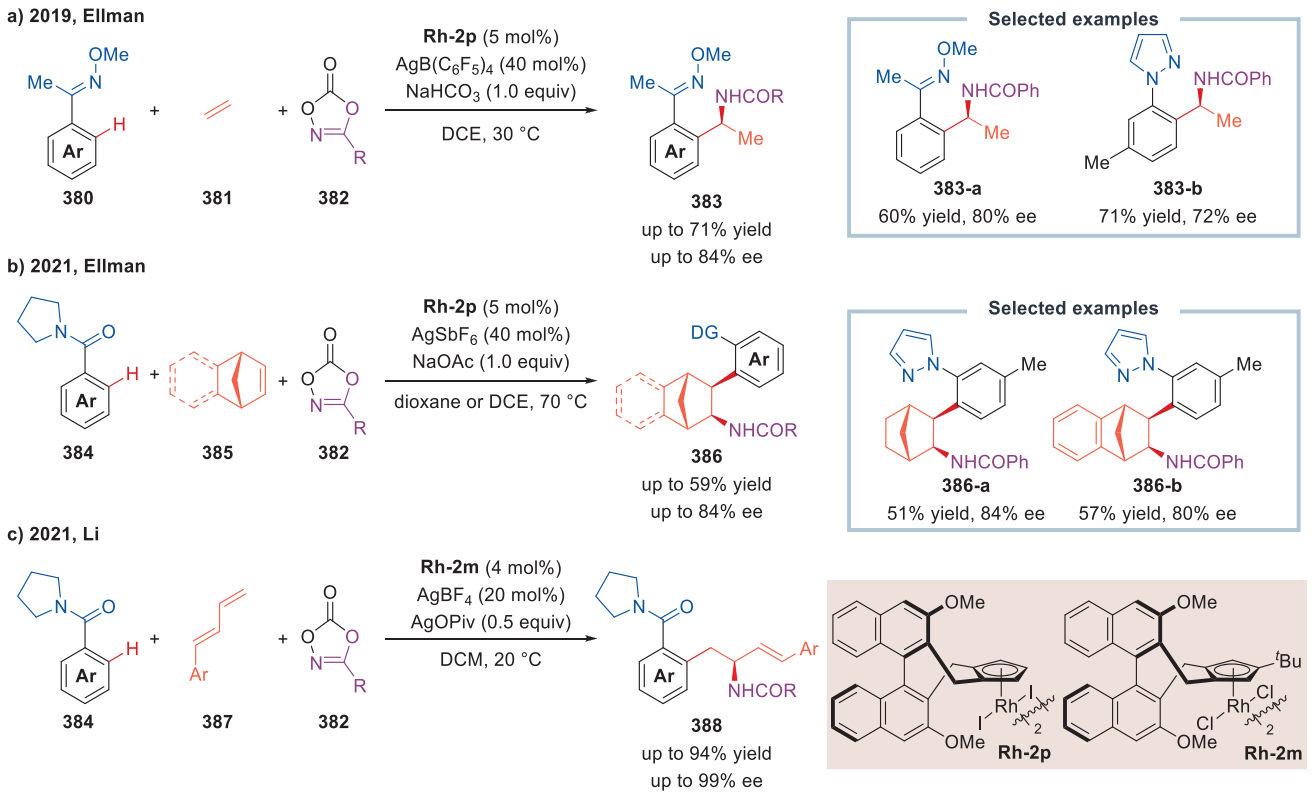
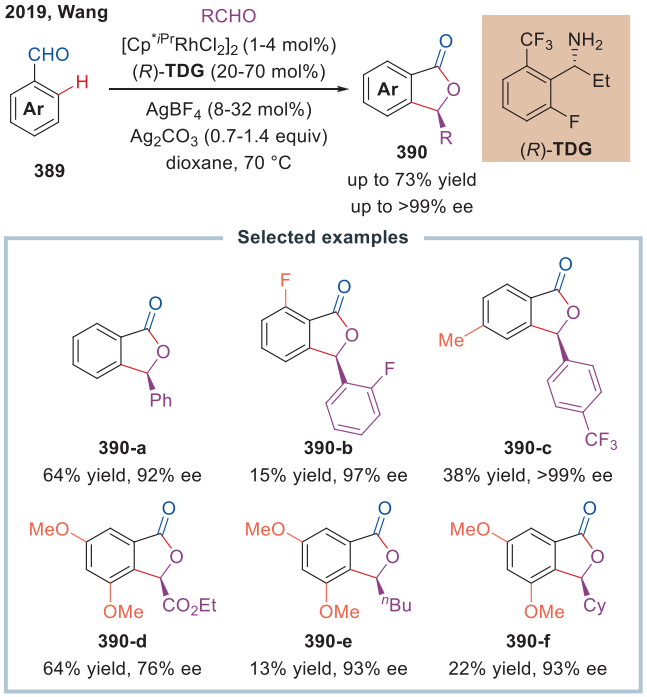
Scheme 66. Rh(III)-Catalyzed Asymmetric (Carbo)Amidation Reactions



Scheme 67. Rh(III)-Catalyzed Asymmetric C−H Functionalization using the Chiral Transient Directing Group



6. APPLICATIONS OF RH-CATALYZED ASYMMETRIC C−H FUNCTIONALIZATION REACTIONS

Enantioselective C−H functionalization was widely used to synthesize natural products and bioactive molecules.[271] Several examples utilizing Rh-catalyzed asymmetric C−H activation as key steps were reported in the past two decades. In 1999, Rousseau, Mioskowski, and co-workers carried out a [Rh(*S*)-BINAP]BF_4-catalyzed intramolecular hydroacylation reaction of racemic aldehyde **412**, generating *cis*- and *trans*-**413** in 90% yield with 96% ee, which underwent subsequent transformations to afford **419** (Scheme 70).[272] Thus, the formal synthesis of brefeldin A was realized through Rh-catalyzed enantioselective hydroacylation as the key step.

In 2006, Bergman, Ellman, and co-workers accomplished the asymmetric synthesis of PKC inhibitor featuring dihydropyrroloindole structure with Rh(I)-catalyzed, imine-directed enantioselective indole C2−H alkylation as the key step. In the presence of 10 mol % $[Rh(coe)_2Cl]_2$ and 20 mol % (*R*,*R*,S_a)-**L9**, the cyclization of **422** occurred in 61% yield and 90% ee (Scheme 71).[273] The subsequent four-step transformations afforded the PKC inhibitor.

In 2008, the Castillón group reported a new procedure to build carbocyclic nucleosides. It was worth noting that this procedure involved an enantioselective Rh/Duphos-catalyzed hydroacylation reaction as the key step, which gave good yield and enantioselectivity (85% yield, >95% ee), greatly improving atom-economy and selectivity of the entire route (Scheme 72).[274]

In 2014, Stanley and co-workers developed an effective route to enantioselectively synthesize aromatase inhibitor MR 20492, the key transformation of which was an intramolecular alkylation through Rh-catalyzed asymmetric C−H functionalization of aldehyde (Scheme 73).[70] The subsequent aldol-condensation efficiently afforded the final product.

In 2016, Stanley and co-workers further utilized the Rh-catalyzed enantioselective C−H functionalization of aldehyde to synthesize yuremamine (Scheme 74).[275] Ultimately, the

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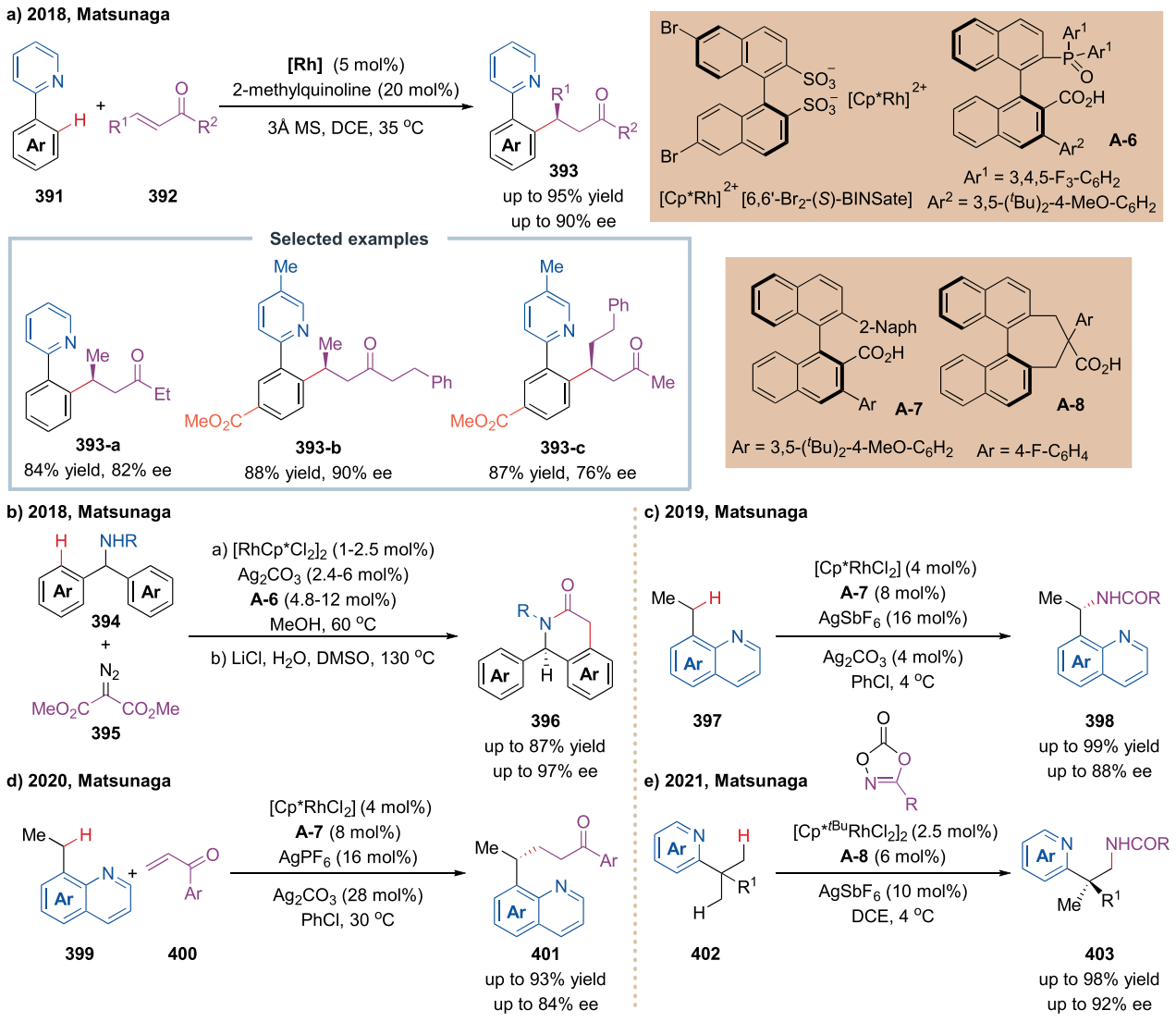
Scheme 68. Rh(III)-Catalyzed Asymmetric C−H Functionalization with Chiral Acid



cyclization of **440** proceeded in 90% yield and 97% ee in the presence of 2.5 mol % $[Rh(cod)Cl]_2$, 5 mol % (*R*)-MeO-BINAP, and 5 mol % $AgBF_4$ as an additive at 60 °C. The subsequent three-step transformation efficiently afforded the final product.

In 2016, Dong and co-workers reported an in situ-formed $[Rh^I/L14]$ complex as the catalyst for the asymmetric annulation of **441** via desymmetrization approach, affording lactone **442** in 92% yield with >20:1 dr and 97% ee (Scheme 75).[80] Further transformations of the key intermediate **445** led to the generation of **446**, a known intermediate for the total synthesis of (−)-mesembrine.

Compared with Rh(I) catalytic system, synthetic applications of Rh(III)-catalyzed asymmetric C−H functionalization were less reported. Nevertheless, remarkable works were reported by Cramer and co-workers (Scheme 76).[171] Intermediate **448**, which could be easily accessed through Au(I)-catalyzed addition of *N*-hydroxysuccinimide to alkyne **447**, underwent Rh(III)-catalyzed asymmetric cyclopropanation with acrylamide, affording Weinreb amide **449** in 89% yield with 20:1 dr and 94% ee. The subsequent reduction and esterification of **449** would form lactone **451**, a key intermediate in synthesizing both *ent*-eicosanoid and constanolacton A and B. Besides, a potent inhibitor UPF 648 could be enantioselectively synthesized by utilizing Rh-catalyzed asymmetric C−H activation/cyclopropanation of **453** as the key step (Scheme 77).[171]

Chiral sulfoximines **457** and **460** were the key precursors of *ent*-PYK2 inhibitor and roniciclib, respectively. In 2019, Cramer and co-workers carried out a kinetic resolution of corresponding sulfoximines with complex **Rh-2p** and chiral acid **A-1** as cocatalysts. Enantioenriched **455** and **458** (96% ee) were afforded and both of which would undergo two-step reactions to generate **457** and **460**, respectively (Scheme 78).[238]

7. CONCLUSIONS AND PERSPECTIVES

Rapid progress in Rh-catalyzed asymmetric C−H functionalization reactions has been witnessed over the past decade. Many chiral ligands and catalysts have been synthesized and successfully applied in Rh-catalyzed asymmetric C−H functionalization reactions. For Rh(I)-catalyzed asymmetric C−H functionalization reactions, diverse chiral phosphine ligands based on privileged backbones, including BINOL, SPINOL, TADDOL, ferrocene, etc., afforded excellent results in terms of both reaction efficiency and stereoselective control. For Rh(III)-catalyzed asymmetric C−H functionalization reactions, various chiral cyclopentadienes (Cp) have been designed and found to

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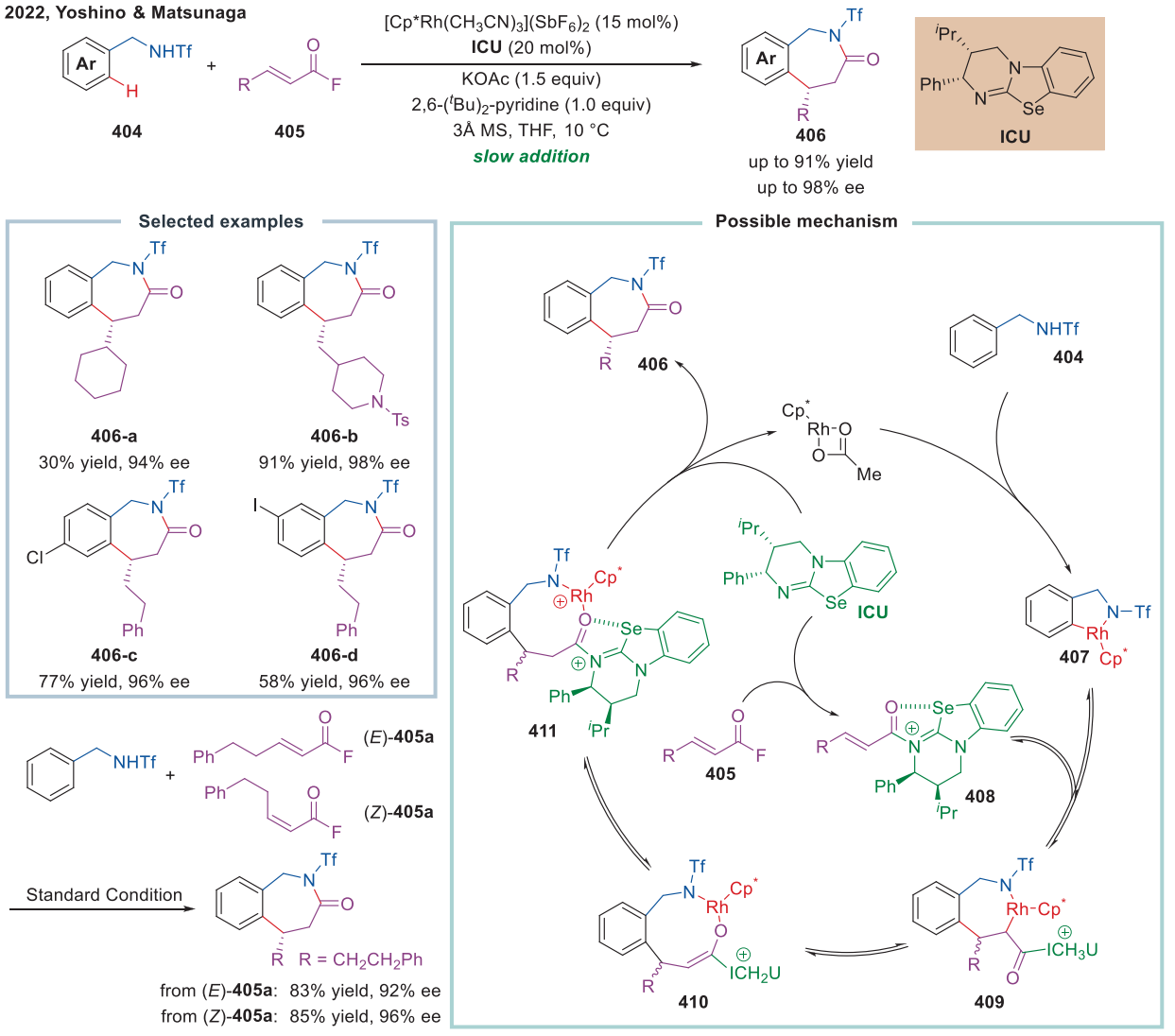
Scheme 69. Rh(III)-Catalyzed Asymmetric C−H Functionalization with Chiral Lewis Base



be the most promising ligands. In addition, the combination of achiral CpRh(III) complex and chiral additives avoids the tedious synthetic route of most chiral Cp ligands and provides a promising alternative strategy.

Despite the rapid progresses, many unsolved problems remain in the field of Rh-catalyzed asymmetric C−H functionalization reactions:

(1) Currently, Rh-catalyzed asymmetric C−H functionalization reactions always require the aid of a directing group, which is usually not part of the target molecule and must be installed before and removed after C−H functionalization reactions. In this regard, the transient directing group strategy provides a new opportunity. Moreover, the development of nondirected Rh-catalyzed asymmetric C−H functionalization reactions may further enhance the practicality.

(2) The highly enantioselective Rh-catalyzed C−H functionalization forming carbon−heteroatom bonds (e.g., C−P, C−N, and C−S) has been rarely reported, mainly due to the strong coordination of heteroatoms. The design of novel chiral catalysts or ligands may be an effective way to avoid catalyst poisoned by heteroatom.

(3) The catalyst loading in Rh-catalyzed asymmetric C−H functionalization reactions is often high (usually around 5 mol %), limiting the practical application of this reaction. A deeper understanding of the mechanism and the development of efficient catalysts may provide a solution to this problem.

(4) The tedious synthetic procedures of chiral cyclopentadienyl (Cp) ligands and their metal complexes limited the development of this field. The search for convenient method for synthesizing of chiral Cp will greatly facilitate the development of this reaction.

(5) The understanding of the reaction mechanism still needs to be improved, and the lack of mechanistic information significantly limited the power to design C−H functionalization reactions rationally. Moreover, a deeper understanding of the reactivity differences between rhodium and other metals would have great opportunities to design new enantioselective reactions.

(6) The synthetic applications are limited due to the narrow substrate scope and the practicality also needs improvement given the fact that expensive chiral catalysts and chiral ligands have been used so far.

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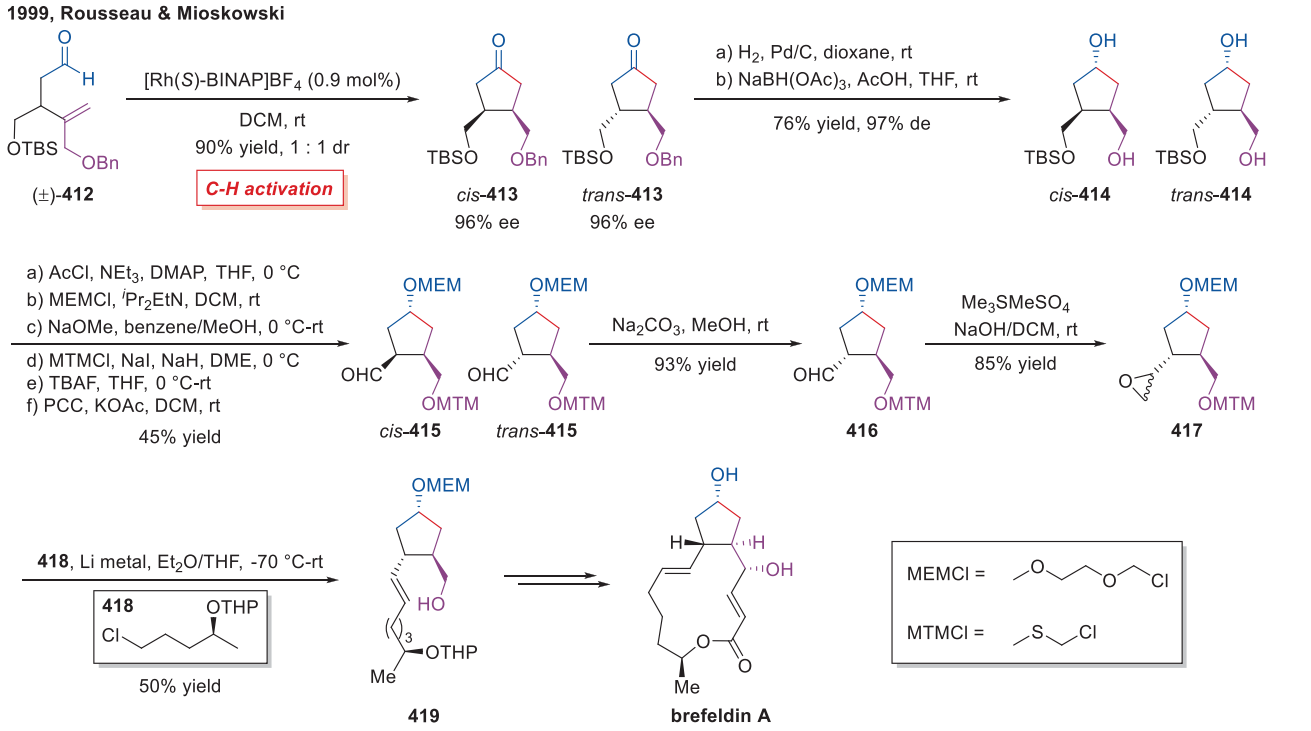
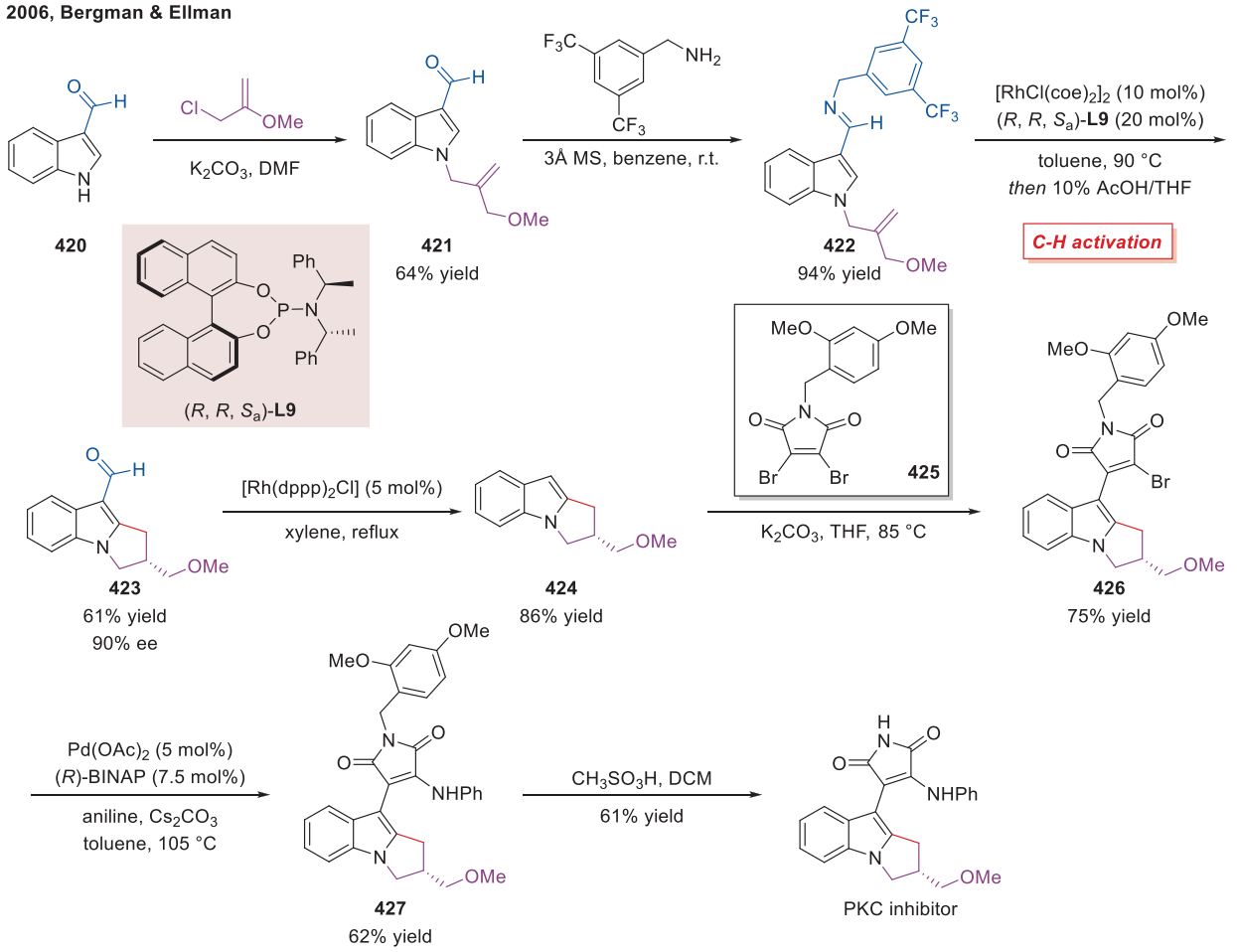
Scheme 70. Enantioselective Synthesis of Brefeldin A



Scheme 71. Enantioselective Synthesis of PKC Inhibitor



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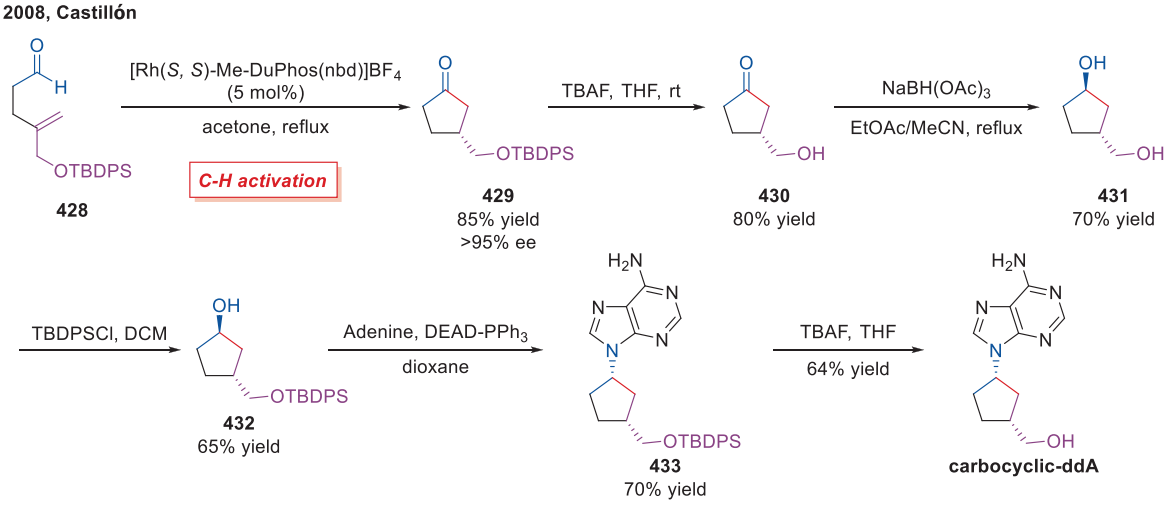
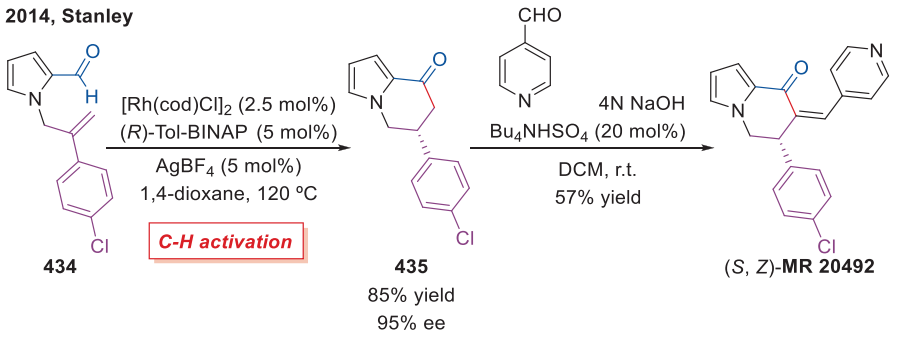
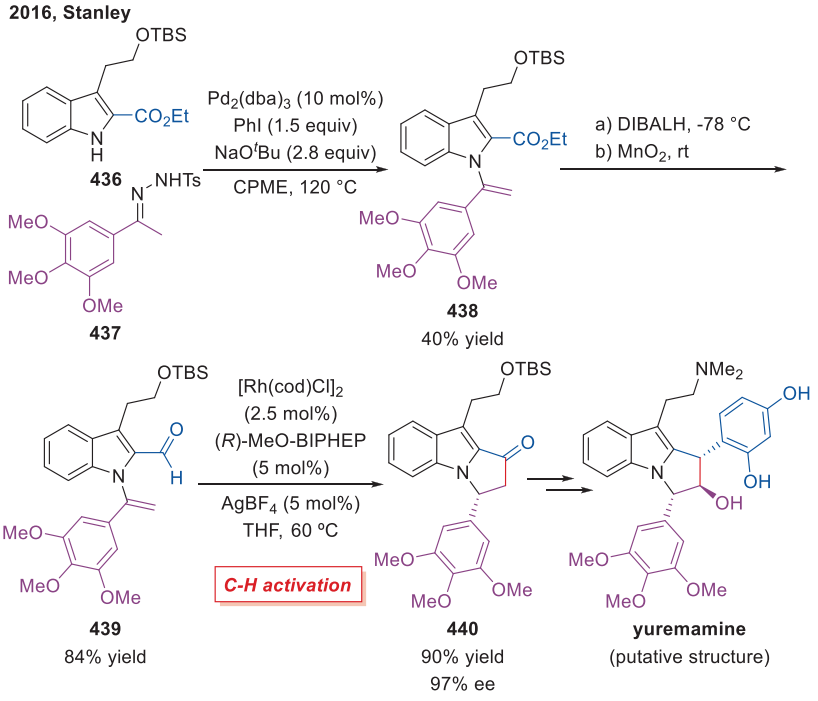
Scheme 72. Enantioselective Synthesis of Carbocyclic-ddA



Scheme 73. Enantioselective Synthesis of MR 20492



Scheme 74. Enantioselective Synthesis of Yuremamine



Thus, more efforts are required to overcome these challenges in this research area. We believe that further development in this field will solve the above-mentioned problems and bring more opportunities to Rh-catalyzed asymmetric C−H functionalization reactions.

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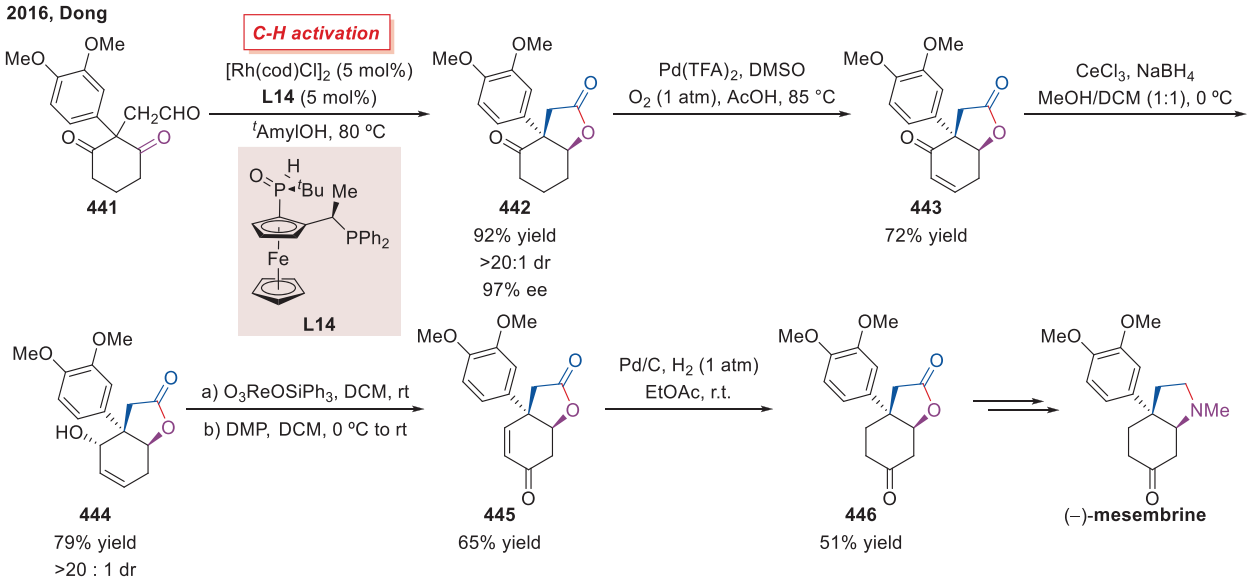
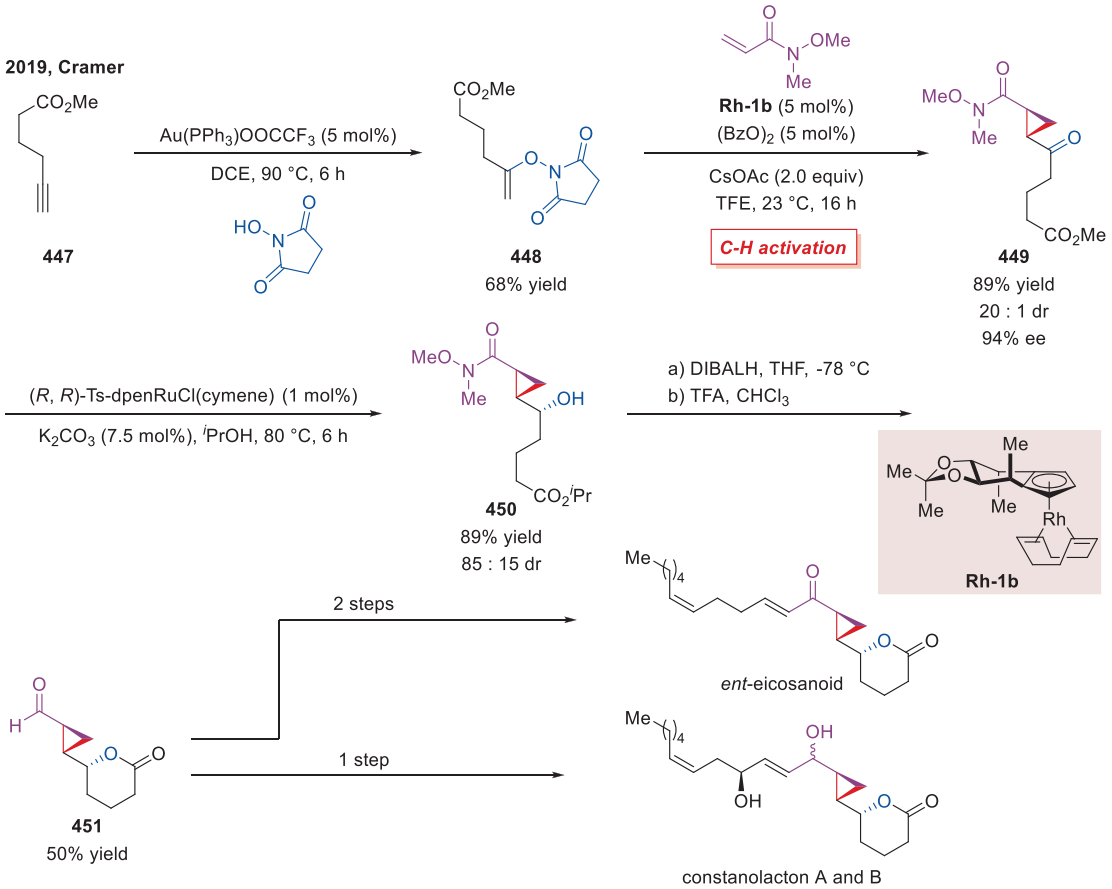
Scheme 75. Enantioselective Synthesis of (−)-Mesembrine



Scheme 76. Enantioselective Synthesis of *ent*-Eicosanoid and Constanolacton A and B



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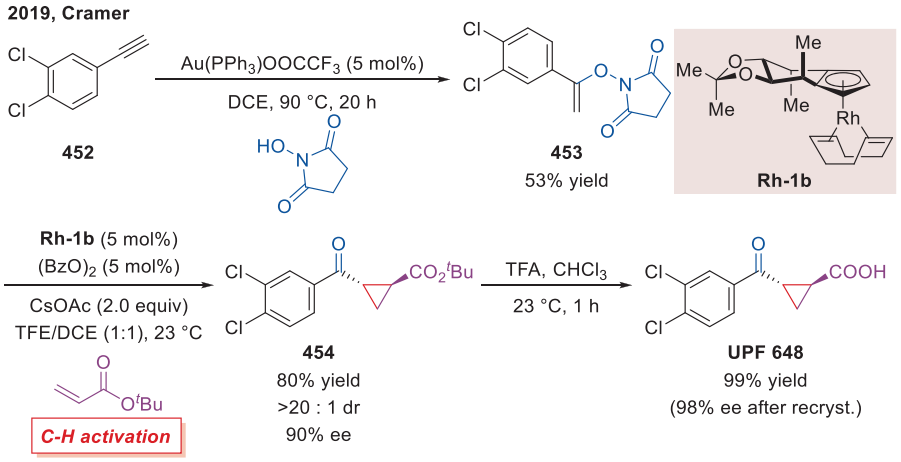
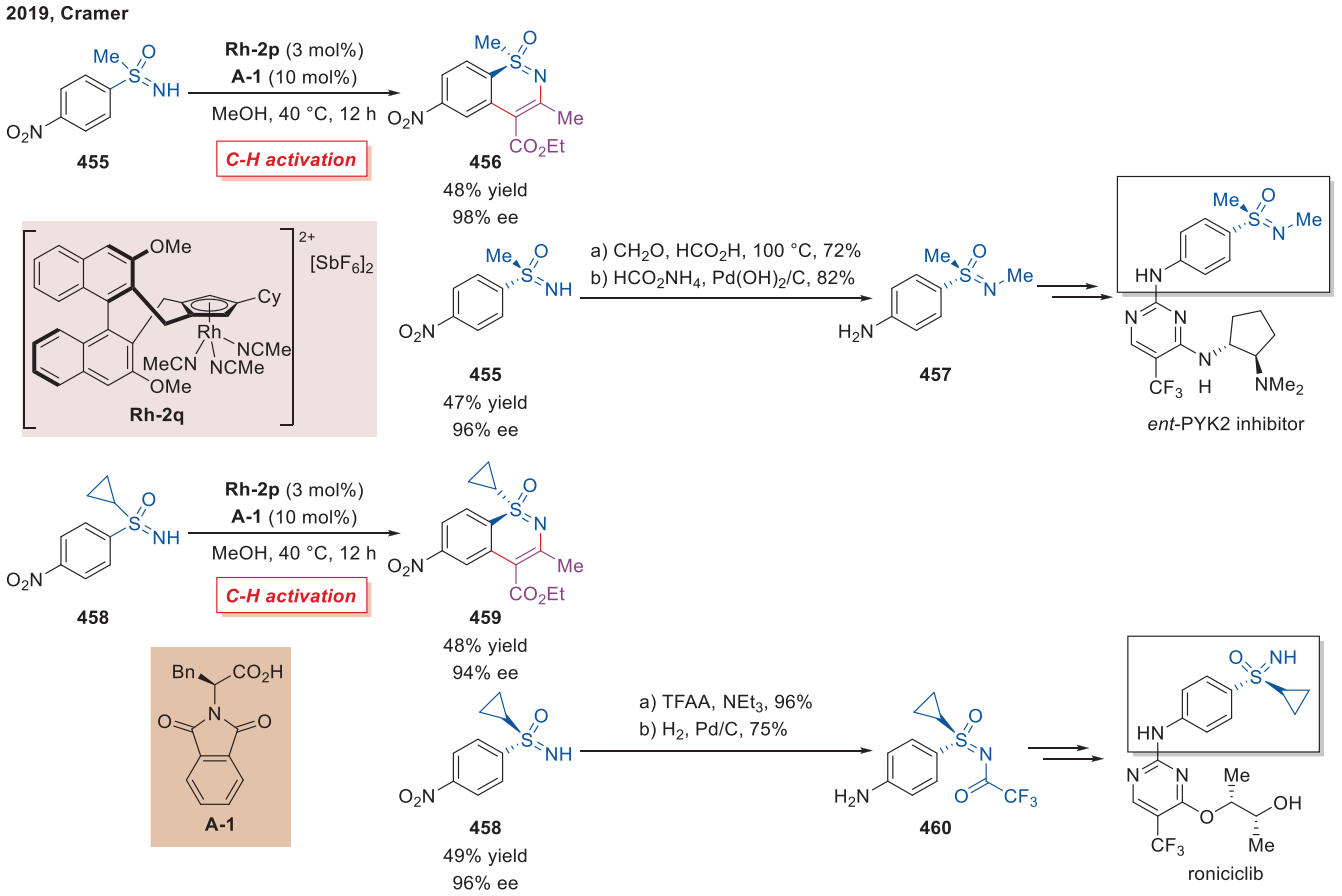
Scheme 77. Enantioselective Synthesis of UPF 648



Scheme 78. Enantioselective Synthesis of *ent*-PYK2 Inhibitor and Roniciclib



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The authors declare no competing financial interest.

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NOTE ADDED IN PROOF

After the acceptance of this manuscript, a series of new papers on Rh-catalyzed asymmetric C−H functionalization reactions appeared (refs 276−279).

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