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Recent advances in Rh(ı)-catalyzed enantioselective C-H functionalization

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Chiral carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds are pervasive and very essential in natural products, bioactive molecules, and functional materials, and their catalytic construction has emerged as one of the hottest research fields in synthetic organic chemistry. The last decade has witnessed vigorous progress in Rh(ı)-catalyzed asymmetric C-H functionalization as a complement to Rh(ıı) and Rh(III) catalysis. This review aims to provide the most comprehensive and up-to-date summary covering the recent advances in Rh(i)-catalyzed C-H activation for asymmetric functionalization. In addition to the development of diverse reactions, chiral ligand design and mechanistic investigation (innersphere mechanism, outer-sphere mechanism, and 1,4-Rh migration) will also be highlighted.

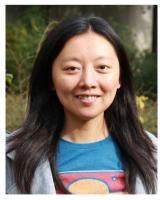
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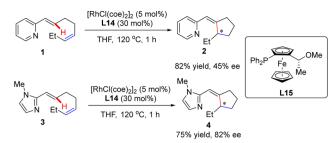
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1. Introduction

Review Article

Chiral carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds are pervasive and very essential in natural products, bioactive molecules, and functional materials, and their catalytic construction has emerged as one of the hottest research fields in synthetic organic chemistry. 1-3 Among various methodologies, direct asymmetric functionalization of C-H bonds, which are ubiquitous in organic molecules, via transition metal catalysis represents one of the most powerful approaches in this field benefiting from its atom- and step-economy. 4-8 Additionally, such an approach offers a new synthetic opportunity as well as an unconventional and complementary retro-synthetic disconnection compared with traditional methodologies requiring pre-activation or pre-functionalization of both reaction partners. Although C-H bonds are more difficult to be implemented than their pre-functionalized counterparts, they are, virtually, not completely inert, and could be cleaved by an appropriate catalyst to serve as latent surrogates of various functional groups.



Scheme 1 Rh(ı)-Catalyzed enantioselective intramolecular C(sp²)-H alkylation of alkenes

Actually, the past few decades have witnessed the successful implication of diverse transition metals in asymmetric C-H bond functionalization, including first, second, and third-row transition metals, as well as lanthanides. 9-31 Compared to other transition metals, one characteristic feature of rhodium catalysts resides in the availability of multifarious oxidation states (0, 1, 2, and 3), offering an opportunity to effect various catalytic reactions. In particular, rhodium catalysts have been extensively



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implementation in synthesis. A focus is placed on asymmetric C-H functionalizations enabled by novel ligand designs.



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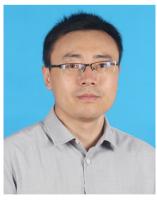
interest encompasses the discovery of new catalytic systems in organic chemistry and beyond to enable their implementation in the synthesis of biologically active molecules.

investigated in asymmetric C-H functionalization with diverse mechanisms.³²⁻⁴⁵ From the viewpoint of substrate activation modes, Rh-catalyzed C-H functionalization could be classified into two categories: inner-sphere mechanism and outer-sphere mechanism, which differ in the mechanism of the C-H activation step (Scheme 1). 46,47 Generally, Rh(III)-catalyzed asymmetric C-H functionalization adopts the inner-sphere mechanism by taking advantage of a chiral cyclopentadienyl (Cp) ligand, 35,38,39,48-51 whereas Rh(II) usually coordinates with a chiral carboxylic acid to achieve the effect of asymmetric C-H

functionalization via the outer-sphere mechanism, 14,52-54 both

Chem Soc Rev

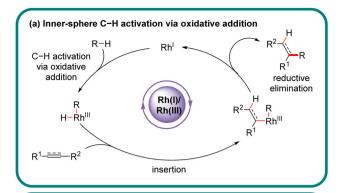
of which have been well reviewed elsewhere. Of note, the last decade has witnessed vigorous progress in Rh(1)-catalyzed asymmetric C-H functionalization as a complement to Rh(II) and Rh(III) catalysis. In the asymmetric Rh(I) catalysis, both inner-sphere and outer-sphere mechanisms could be involved, despite that the inner-sphere dominates (Fig. 1). Additionally, a special 1,4-Rh migration pathway may also be involved in the asymmetric Rh(1) catalysis. Notably, various types of chiral ligands could be implemented including phosphoramidite, phosphonate, carbodicarbene, bisoxazolinephosphane, BINAP, Segphos, Tangphos, Josiphos, diene, and so on (Fig. 2). As a consequence, a diversity of asymmetric C-H transformations, such as alkylation, alkenylation, allylation, arylation, and silvlation, have been developed. Despite these advances, a review comprehensively summarizing Rh(1)catalyzed asymmetric C-H functionalization is elusive. Herein, we aim to provide the most comprehensive and up-to-date summary covering the recent advances in Rh(1)-catalyzed asymmetric functionalization of both $C(sp^2)$ -H and $C(sp^3)$ -H bonds. Rh(1)-catalyzed hydroacylations and Friedel-Crafts reactions have been the subject of multiple reviews and are therefore not covered here. 55,56 We believe that this review will gain much attention from researchers with C-H functionalization and asymmetric transition metal catalysis backgrounds, stimulate

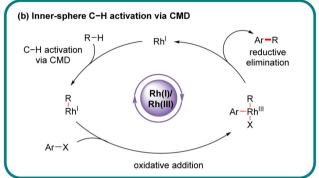


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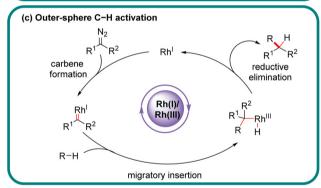


Fig. 1 Catalytic cvcles for Rh(ı)-catalyzed enantioselective C-H functionalization.

more future efforts in this area, and facilitate the synthetic application of these novel reactions. We have structured the literature according to substrate activation modes and reaction types.

Inner-sphere C-H functionalization

In the inner-sphere mechanism, the metal directly interacts with a specific C-H bond to effect its activation and cleavage, leading to a discrete organo-rhodium species to proceed with follow-up functionalization. For Rh(1)-catalyzed asymmetric C-H functionalization, the inner-sphere mechanism represents the most prevalent C-H activation pathway. Owing to the fundamental differences in substrate activation modes, the selectivity of multiple C-H bonds differs. Typically, the innersphere activation mode is highly sensitive to the steric factor surrounding C-H bonds.

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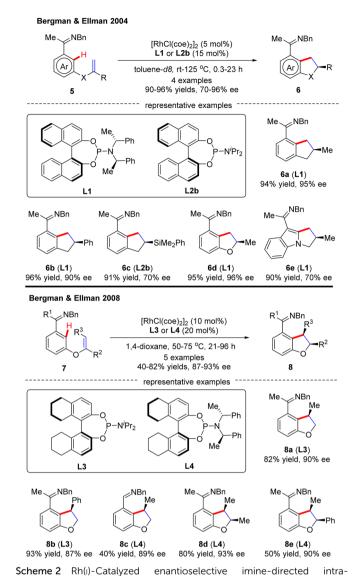
The generally used chiral ligands in Rh(ı)-catalyzed asymmetric C-H functionalization.

2.1 Functionalization of C(sp²)-H bonds

Compared with C(sp³)-H bonds, the sp²-hybridized counterparts are generally more sterically accessible and acidic, leading to more vigorous progress in C(sp²)-H functionalization. Additionally, rhodium usually possesses a good coordination affinity to unsaturated double and triple C-C bonds. Therefore, the use of alkenes, allenes, or alkynes as electrophiles can provide a good solution for the Rh(1)-catalyzed asymmetric functionalization of $C(sp^2)$ -H bonds.

2.1.1 Asymmetric addition of C(sp²)-H bonds to unsaturated bonds. In this part, Murai and co-workers pioneered a Rh(I)catalyzed asymmetric intramolecular alkene C(sp²)-H activation/ olefin coupling reaction of 1,5-dienes with a 2-pyridyl (1) or 2-imidazolyl (3) directing group in 1997 (Scheme 1).⁵⁷ By the use of monodentate planar chiral ferrocene phosphine ligand L15, the desired cyclopentane derivatives 2 and 4 were attained in 45% and

82% ee, respectively. Following this pioneering work, an elegant example was communicated at the beginning of this century, when Bergman and Ellman effected an imine-directed intramolecular addition of aromatic C-H bonds to 1,1-disubstituted alkenes (Scheme 2).⁵⁸ Using $[RhCl(coe)_2]_2$ as the catalyst and (S)binaphthol (BINOL)-derived monodentate phosphoramidite L1 or L2b as the chiral ligand, several five-membered carbo- and heterocycles 6 were accessed with impressive yields and enantioselectivities (up to 96% yield and 96% ee). Subsequently, the same group further expanded the substrate scope to 1,2disubstituted as well as 1,1,2-trisubstituted alkenes by taking advantage of (S)-octahydrobinaphthol-based phosphoramidite L3 as a chiral ligand, thus giving rise to 2,3-dihydrobenzofuran derivatives 8 in moderate to excellent yields (40-82%) and excellent enantioselectivities (87-93% ee).⁵⁹ For the cyclization of aldimine or 1,1,2-trisubstituted alkene substrates, ligand L4 provided better



enantiocontrol. Notably, only syn-selective products were achieved, owing to that the E-alkenes, which would lead to anti-selective products, were unreactive. More importantly, the application of this approach was validated by the total synthesis of a PKC inhibitor.⁶⁰

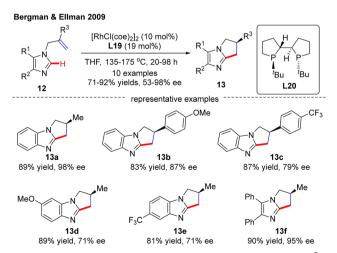
molecular C(sp²)-H alkylation.

Aside from several reports of imine-directed C(sp²)-H functionalization, carbonyl could also serve as an effective directing group to enable similar transformations. For example, in 2007, Shibata and co-workers described a carbonyl-directed cascade C(sp²)-H activation and cyclization with enynes via asymmetric Rh(I) catalysis. 61 With the chiral Rh-(S)-BINAP complex as a catalyst, both alkyl and aryl substituted N-tethered enynes readily reacted with the C(sp2)-H bond of benzophenone to furnish products 11a and 11b with 92% and 91% ee, respectively (Scheme 3). Apart from benzophenone, vinylic C-H functionalization of chalcone was also effected, thus affording the corresponding dienones 11c and 11d in excellent enantiocontrol. For the mechanism, the reaction was speculated to commence with carbonyl-directed C-H oxidative addition onto

Scheme 3 Rh(ı)-Catalyzed cyclization of enynes initiated by carbonyldirected activation of aromatic and vinylic C-H bonds.

Rh(I) to provide aryl- or alkenyl-rhodium complex Int-1. Hydrorhodation of Int-1 to the alkyne moiety of enyne 10 afforded intermediate Int-2, which then underwent intramolecular carbo-rhodation to the alkene moiety to afford metallacyclohexane Int-3. Finally, reductive elimination of Int-3 led to the release of the desired product 11.

In 2009, Bergman and Ellman documented a Rh(I)-catalyzed intramolecular asymmetric C(sp2)-H alkylation of imidazoles (Scheme 4). 62 While most bidentate ligands failed to deliver the desired product according to their previous work, 63 Tangphos (L20) represented an exception. At elevated temperatures (135-175 °C), the intramolecular cyclization of allyl-substituted imidazoles 12 readily proceeded to forge various dihydro-pyrroloimidazoles 13 in moderate to excellent yields (71-92%) and enantioselectivities (53-98% ee).



Scheme 4 Rh(i)-Catalyzed enantioselective intramolecular C(sp²)-H alkylation of imidazoles

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19e (ent-L11b) 19f (ent-L11b) 19g (ent-L11b) 59% vield, 88% ee 69% yield, 82% ee 61% vield, 92% ee Rh (i)-Catalyzed [3+2] annulations of aromatic ketimines with

19c (L11b)

74% yield, 80% ee

19b (L11b)

88% vield, 90% ee

O₂N

internal alkynes

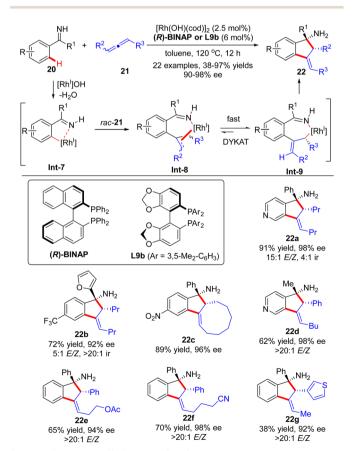
19d (L11b)

70% vield. 76% ee

>20:1 rr

In 2010, Zhao and co-workers reported a single example of a Rh(1)-catalyzed [3+2] annulation reaction of benzophenone imine 14 with diphenylacetylene 15.64 In this reaction, the imine group in benzophenone imine 14 not only served as a directing group to enable C(sp²)-H activation at the orthoposition, but also could be transformed into an amino group by an addition reaction across the C=N bond. To their disappointment, with bidentate phosphine (R,R)-DIOP L21 as the chiral ligand, only moderate enantioselectivity (51% ee) was achieved for the production of the tertiary 1H-inden-1-amine 16. Subsequently, the Cramer group disclosed an elegant approach for the [3+2] annulation reaction of aromatic ketimines 17 with internal dialkyl or arylalkyl alkynes 18 by taking advantage of the biphenyl diphosphine ligand DTBM-MeOBiphep (L11b) (Scheme 5).65 This approach allowed for the synthesis of a broad set of tertiary 1H-inden-1-amine derivatives 19 in 43-90% yields and good to excellent enantioselectivities (76-95% ee). The reaction was envisioned to be initiated by imine-directed ortho C(sp2)-H activation to form the cyclometalated rhodium complex Int-4. Notably, the C(sp²)-H activation step revealed a good positional preference for the more electron-poor aromatic substituent of the ketimine substrates. Subsequent removal of hydrogen from the metal center in Int-4 provided intermediate Int-5, which was essential to avoid undesirable hydroarylation reactivity. Migratory insertion of Int-5 into internal alkyne 18 then occurred to furnish an alkenyl-rhodium species Int-6, wherein the regioselectivity control could be achieved by using a potentially coordinating functional group in unsymmetrically substituted alkynes, such as ether (19a-c, 19g), ester (19e), phthalimide (19d), and sulfurcontaining group (15f). Finally, enantioselective addition of Int-6 across the ketimine group set the desired product 19.

Soon after, the Cramer group further devised a Rh(1)catalyzed dynamic kinetic asymmetric transformation (DYKAT) of racemic allenes 21 with ketimines 20 (Scheme 6).66,67 Similar to the above-described process with alkynes, this [3+2] annulation version of allenes with ketimines exhibited excellent regio-selectivity ranging from 4:1 (22a) to >20:1 (22b). The regio-selectivity resulted from the different positions of C-H activation of ketimines, which favored the electron-poor aryl and heteroaryl substituents. The coordination and migratory insertion of the initially generated cyclometalated species Int-7 into a racemic allene 21 gave rise to eight stereoisomers Int-8,



Scheme 6 Rhodium(i)-Catalyzed [3+2] annulations of aromatic ketimines

which rapidly equilibrated and isomerized to reach the appropriate (E)-allyl isomer Int-9 by either a β -H elimination/ re-addition sequence or a σ - π - σ mechanism.⁶⁸ Follow-up intramolecular 1,2-addition across the imine moiety in Int-9 prevailed to arrive at the desired indanylamine 22 with excellent diastereomeric (syn-diasteroselectivity) and enantiomeric control (90-98% ee). For unsymmetrically 1,3-disubstituted allenes, the selectivity in the equilibration process of Int-8 was intensively governed by electronic factors with a preference for the formation of a benzylic allyl rhodium intermediate over the alternative alkyl allyl intermediate. Notably, the ketimine part did not exert a significant effect on the enantioselectivity, and both aryl aryl and aryl alkyl ketimines were well suited for this reaction.

In 2015, Rovis and co-workers disclosed an asymmetric intermolecular C(sp²)-H alkylation of benzoxazole 23 with acrylates 24 via Rh(1)-catalysis (Scheme 7).69 Mechanistic studies indicated that this reaction was initiated by reversible C-H activation of benzoxazole 23 with the aid of the rhodium acetate catalyst, thus providing Rh-benzoxazole complex Int-10. Migratory insertion of Int-10 across acrylate 24 furnished Rh-enolate Int-11, which isomerized into heterobenzylic rhodium species Int-13 via a β -hydride elimination/hydrorhodation sequence. Protonation of Int-13 then occurred to set the alkylated benzoxazole 25, which was assumed to be the turnover limiting step. It

[RhOAc(cod)]₂ (5 mol%) L13 (10 mol%) w/ or w/o CsOAc (25 mol%) MeCN, 100 °C, 48 h 24 15 examples 31-98% yields, 68-96% ee steric repulsion Me) (RhLn Int-10 Int-14 EWĞ Int-11 Int-12 25a 25b $P(m-xy|y|)_2$ 88% vield, 94% ee 54% yield, 84% ee ÓΜε L13 25c 25d 65% yield, 93% ee 15% yield, <5% ee

Scheme 7 Rh(i)-Catalyzed asymmetric intermolecular C(sp²)-H alkylation of benzoxazoles with acrylates

25f

31% yield, 90% ee

was also demonstrated that 4-methylbenzoxazole, characteristic of a [1,3]-strain, disfavored strong coordination to rhodium in Int-14, thus exhibiting higher reactivity compared with its 6substituted or unsubstituted counterparts (25a vs. 25e vs. 25f). In this scenario, the authors took advantage of a bulky Segphos derivative CTH-(R)-Xylyl-P-Phos (L13) as chiral ligand to surmount the possible deleterious coordination of the heteroarene and harness the reactivity. As a consequence, a diversity of 2alkylated benzoxazoles 25 were attained in moderate to excellent yields (31-98%) and good to excellent enantioselectivities (68–96% ee). This reaction was tolerant of α-methyl substituted acrylate derivatives, whereas using β-substituted acrylate derivative crotonate as an alkylation reagent led to the racemic product 25c in extremely poor results (15% yield and <5% ee).

In addition to a number of reports on constructing central chirality, Rh(1)-catalyzed addition of C(sp²)-H to unsaturated bonds could also be applied in effecting axial chirality. In 2000, Murai and co-workers, for the first time, disclosed the construction of axially chiral biaryls 27 and 29 via Rh(1)-catalyzed C(sp²)-H alkylation of naphthylpyridine derivatives 26 & 28 with ethylene (Scheme 8).70 Unfortunately, only moderate yields and enantioselectivities could be achieved (up to 37% yield and 49% ee) with [RhCl(coe)₂]₂ as the catalyst and chiral ferrocenyl phosphine L15 as the ligand.

2.1.2 Asymmetric arylation of C(sp²)-H bonds. In 2019, You and co-workers reported a Rh(1)-catalyzed atroposelective C(sp²)-H arylation of heterobiaryls **30** with aryl and heteroaryl bromides (Scheme 9).71 By taking advantage of TADDOLderived monodentate phosphonite L10 as the chiral ligand and N-heterocycles as directing groups, a diverse set of axially chiral heterobiaryls 31 were released in moderate to excellent yields (58-99%) with high to excellent enantioselectivities (72-99% ee). Remarkably, this approach lays a foundation to synthesize various axially chiral heterobiaryl catalysts.

Recently, the implementation of planar chirality in Rh(I)catalyzed C(sp²)-H functionalization was also demonstrated by You and co-workers (Scheme 10A).72 With thioketone as the directing group and L5a as the chiral ligand, a range of aryl and

Scheme 8 Rh(i)-Catalyzed atroposelective C(sp²)-H alkylation of naphthylpyridine derivatives with ethylene

25g 56% yield, 77% ee

25e

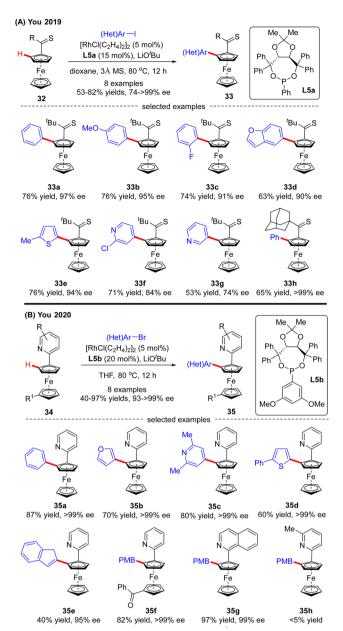
67% yield, 87% ee

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Scheme 9 Rh(ı)-Catalyzed atroposelective C(sp²)-H arylation of heterobiaryls with aryl and heteroaryl bromides.

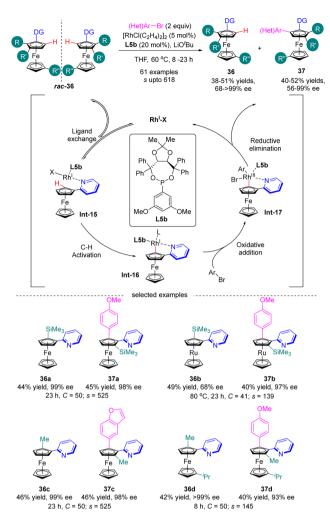
heteroaryl iodides were readily incorporated into thiocarbonylferrocene 32, thus providing direct access to various planar chiral ferrocenes 33 in moderate to good yields (53-82%) and excellent enantioselectivities (up to >99% ee). Subsequently, the same group further extended the ferrocene scope to pyridylferrocenes 34 by use of the Rh(1)/phosphonite catalytic system, wherein pyridine served as the directing group (Scheme 10B).73 As a consequence, a variety of (hetero)aryl bromides were readily coupled with pyridylferrocenes 34 to afford planar chiral ferrocene-based pyridine derivatives 35 in excellent yields (up to 97%) and enantioselectivities (93->99% ee). Additionally, aryl iodide and aryl chloride were competent coupling partners, leading to the formation of 35a in comparable results (95% and >99% ee, respectively). Notably, aside from (hetero)aryl halides, alkenyl bromide also proved compatible with this reaction, giving product 35e in 40% yield and 95% ee. Meanwhile, substitution on the pyridine ring or ferrocene part was also tolerated (35f, 35g). However, 5substituted pyridine was not a suitable substrate, which was probably attributed to its weak coordination with the rhodium catalyst (35h).

Most recently in 2023, You and co-workers further achieved the Rh($_1$)-catalyzed enantioselective C(sp 2)-H arylation of metallocenes for the synthesis of both planar chiral 1,2-disubstituted and 1,3-disubstituted metallocenes via kinetic resolution (Scheme 11). In the presence of Rh($_1$) catalyst and 3,5-(MeO) $_2$ -C₆H₃-substituted TADDOL-derived monodentate phosphonite



Scheme 10 Rh(i)-Catalyzed enantioselective $C(sp^2)$ -H functionalization of ferrocenes (PMB = p-methoxybenzyl).

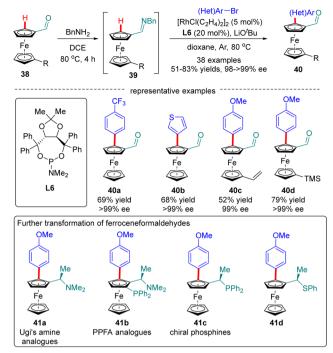
L5b as the chiral ligand, a broad range of aryl and heteroaryl bromides were readily incorporated into various directing group (*e.g.* 3- or 4-methyl, 4-phenyl and 4-methoxy pyridine) functionalized 1,2-disubstituted or 1,3-disubstituted ferrocenes and ferrocenes *rac-*36 containing diverse substituents, including alkyl groups, aryl groups, and even heteroatoms, thus giving rise to arylated products 37 with satisfactory selectivity factor values (s up to 618) and excellent enantiomeric control (up to 99% ee). For instance, ferrocene 36a and ruthenocene 36b with *ortho*-trimethylsilyl substituent acted as applicable substrates with outstanding selectivity (s = 525 for 37a and s = 139 for 37b). Additionally, the calculated conversion (C) matched well with the isolated yields. The underlying mechanism of this reaction has been studied using 2-pyridinylferrocenes and aryl bromides as



Scheme 11 Rh(i)-Catalyzed enantioselective C(sp²)-H arylation of metallocenes via kinetic resolution.

representative reagents by both experimental and computational studies (Scheme 11).75 The reaction was proposed to be initiated by the coordination of rhodium with 2-pyridinylferrocenes to afford intermediate Int-15. Subsequently, C-H activation of Int-15 occurred to generate intermediate Int-16, which then proceeded to oxidative addiction with aryl bromide to provide Int-17. Finally, reductive elimination of Int-17 readily proceeded to arrive at the expected product and release the rhodium catalyst.

Ferroceneformaldehydes constitute a vital type of platform molecules, which can be smoothly converted into diverse functionalities to provide facile access to chiral ligands and catalysts. However, it had been a long-standing challenge to synthesize enantiopure planar chiral ferroceneformaldehydes via a straightforward and highly efficient approach. To surmount this obstacle, You and co-workers recently disclosed a Rh(i)-catalyzed enantioselective $C(sp^2)$ -H arylation of ferroceneformaldehydes 38 with the assistance of a chiral phosphoramidite ligand L6 (Scheme 12).76 It was demonstrated that the formation of imine intermediates 39 was critical for the success of this transformation. A broad set of readily available aryl halides such as aryl iodides, aryl bromides, and even aryl



Scheme 12 Rh(ı)-Catalyzed enantioselective C(sp²)-H arylation of ferroceneformaldehydes.

chlorides are found to be competent substrates for this reaction, providing access to chiral ferroceneformaldehydes 40 in uniformly excellent enantioselectivity (98->99% ee). Among various functionalities derived from ferroceneformaldehydes by an elegant decoration of the aldehyde group, enantiopure Ugi's amine 41a and PPFA analogues 41b were particularly noteworthy, as the latter proved as a highly efficient ligand in Pd-catalyzed asymmetric allylic alkylation reactions.

2.1.3 Asymmetric silylation of C(sp²)-H bonds. In 2013, Takai and collaborators presented a Rh(1)-catalyzed dual dehydrogenative cyclization of bis(biphenyl)silanes 42 via C-H silylation (Scheme 13).77,78 By the use of [RhCl(cod)]₂ as a catalyst and (R)-BINAP as a ligand, several chiral spirosilabifluorenes 43 were constructed in favorable yields (73–85%) and enantiomeric control (70–81% ee). Subsequently, the same group found that the enantioselectivities of the products could be further enhanced to 72-95% ee without sacrificing the yields by lowering the temperature from 135 °C to 70 °C and extending the reaction time to 24 h.⁷⁹

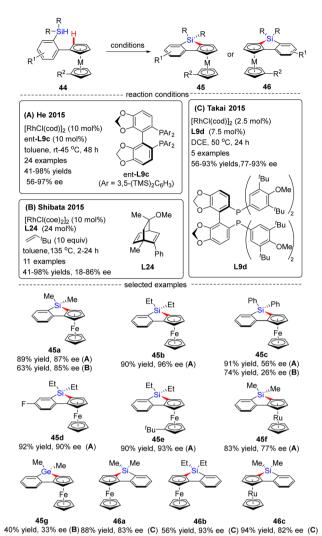
In 2015, He and co-workers opened the door to the untamed Rh(1)-catalyzed asymmetric C-H bond silylation under much milder reaction conditions (Scheme 14A).80 With the aid of chiral ligand (S)-TMS-Segphos (ent-L9c), a plethora of Fe and Ru metallocenes 44 proceeded intramolecular dehydrogenative cyclization at temperatures between room temperature and 45 °C, thus providing direct access to planar-chiral ferrocene and ruthenocene siloles 45 in good yields (up to 98%) with high to excellent enantioselectivities (up to 97% ee). In general, the enantioselectivity was largely independent of the substituents on the aryl or metallocene part. In contrast, the substituents on the silicon atom exerted a profound effect on the enantioselectivity,

bis(biphenyl)silanes.

Review Article Chem Soc Rev

and substrates with two ethyl or propyl groups on the silicon atom gave rise to better results (45b) compared with that with two methyl groups (45a). Besides, only moderate enantiocontrol (56% ee) was achieved for diphenyl silane 45c. Meanwhile, the Takai group realized the same transformation by using (R)-DTBM-Segphos L9d as a chiral ligand, which provided several planar-chiral ferrocene and ruthenocene siloles 46 in comparable enantioselectivities (77-93% ee) but with opposite absolute configuration (Scheme 14C).81,82 Remarkably, apart from Segphos-derived ligand, a chiral diene ligand L24 was also competent to effect this transformation, but with much lower yields (39-75%) and enantioselectivities (18-86% ee), as described by Shibata and co-workers (Scheme 14B).83 Additionally, this catalytic system was also applied for the intramolecular dehydrogenative coupling of the C(sp²)-H bond with the Ge-H bond in (dimethylhydrogermyl)phenylferrocene 45g. Unfortunately, the corresponding benzogermoloferrocene 45g was afforded with only 40% yield and 33% ee. It should be noted that an excess of 3,3-dimethylbut-1-ene as addictive was crucial for the maintenance of enantiocontrol.

In 2020, He and co-workers developed a Rh(1)-catalyzed cascade enantioselective C(sp2)-H silylation/alkene hydrosilylation of dihydrosilanes (Scheme 15).84 By the use of Josiphosderived chiral ligand L16, a diverse set of bi-(hetero)aryl dihydrosilanes 47 with different substituents at different positions were smoothly converted to silicon-stereogenic tetrasubstituted silanes 48 in 55-88% yields and good to excellent enantiocontrol (81-99% ee). For the scope of alkene partners, alkyl, aryl and heteroatom-substituted alkenes all proved as competent substrates. Alternatively, with (R)-Segphos as a chiral ligand, various ferrocene dihydrosilanes 49 were compatible with this transformation, which enabled streamlined construction of tetrasubstituted silicon-stereogenic and planar



Scheme 14 Rh(ı)-Catalyzed enantioselective intramolecular C-H silylation for the synthesis of planar-chiral metallocene siloles and germolane.

chiral benzosiloloferrocenes 50 as single diastereomers (dr > 20:1) with excellent enatioselectivities (90-99% ee). It is worth mentioning that several core scaffolds from pharmaceuticals, bioactive molecules, and materials, such as (-)-menthol, β-estradiol, p-ribofuranoside, and pitavastatin fragment, were well accommodated in this reaction to furnish the corresponding benzosiloloferrocenes 50a-d in 40-86% yields and 93-98% ee.

Most recently, He and co-workers described an elegant synthesis of chiral monohydrosilanes by Rh(1)-catalyzed intramolecular C-H silylation of dihydrosilanes (Scheme 16).85 Under mild conditions, a diverse set of chiral monohydrosilanes 52 were obtained in 55-83% yields with favorable enantioselectivities (up to >99% ee). Substrates with substituents on both aryl rings were also compatible with this transformation, resulting in decreased yields and enantioselectivities (52b). Furthermore, a wide array of silicon-stereogenic and planar chiral ferrocene monohydrosilanes were successfully accessed by this approach with consistently excellent enantioselectivities (93-99% ee, i.e. 52d). Unfortunately, only aryl alkyl

Scheme 15 Rh(i)-Catalyzed tandem enantioselective C-H silylation/ alkene hydrosilylation of dihydrosilanes.

dihydrosilanes proved as competent substrates, whereas the use of diaryl dihydrosilanes was not successful in delivering the corresponding products, due to their decomposition issue in the presence of highly reactive rhodium catalysts. It is noteworthy that the resulting chiral monohydrosilanes 52 served as critical building blocks to effect the facile synthesis of different stereogenic tetraorganosilanes 53. While alcoholysis with isopropanol and C-H functionalization with 2-methylthiophene furnished products 53a and 53b, respectively, hydrosilylation with π bond compounds such as alkenes, alkynes, and ketones, delivered chiral tetraorganosilanes 53c-e via the construction of Si-C(sp²), Si-C(sp³), and Si-O bonds. In all cases, high yields were achieved with intact enantiocontrol. Remarkably, tandem C(sp²)-H silylation/hydrosilylation of dihydrosilanes with alkenes and alkynes also proved

Scheme 16 Rh(I)-Catalyzed intramolecular C-H silvlation of arvl alkyl dihydrosilanes

successful, thus providing 53c and 53d in excellent yields and enantioselectivities.

Subsequently, He's group further expanded the substrate scope of the Rh(1)-catalyzed intramolecular C-H silylation reaction to diaryl dihydrosilanes (Scheme 17).86 The key to the success of this transformation relied on decreased rhodium catalyst loading (1 mol%) to address the decomposition issue of the monohydrosilane products. To the authors' delight, a variety of silicon-stereogenic and planar chiral trisubstituted 1H-benzosiloloferrocenes 55 were achieved as single diastereomers with excellent enantioselectivities (84-99% ee). Furthermore, a ruthenocene-containing substrate was also compatible with this transformation, thus affording 55d in 80% yield and 99% ee. Meanwhile, with this catalytic system, He and coworkers effected asymmetric intramolecular dehydrogenative C-H silylation of alkenyl dihydrosilanes (Scheme 17).⁸⁶ With 1 mol% of rhodium catalyst, various alkenyl dihydrosilanes containing a diverse set of substituents at different positions were readily transformed into trisubstituted silicon-stereogenic 1H-

Review Article Chem Soc Rev

Scheme 17 $\,$ Rh(ı)-catalyzed intramolecular C-H silylation of diaryl and alkenyl dihydrosilanes.

benzosiloles 57 in moderate to decent yields (41–72%) and good to excellent enantioselectivities (80–99% ee).

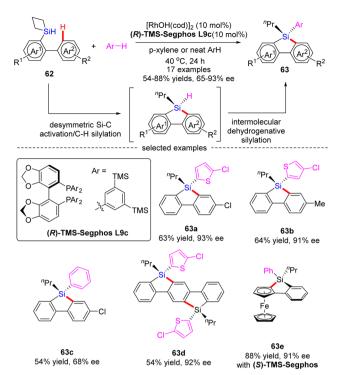
Aside from a number of reports on the Rh(1)-catalyzed enantioselective construction of five-membered siliconstereogenic silanes, most recently, He and co-workers disclosed a novel synthesis of six and seven-membered counterparts via asymmetric Rh(1) catalysis (Scheme 18).87 Under the catalysis of [RhCl(cod)]₂ and Josiphos ligand L16, various silicon-bridged biaryls 58 consisting of benzene and indole moieties smoothly underwent dehydrogenative C-H silvlation to provide a diverse set of six-membered silicon-stereogenic triorgano-substituted silanes 59 in 24-91% yields with excellent enantiocontrol (87-98% ee). It was found that high temperature was crucial to achieve high reactivity in this transformation. In addition to the indole scaffold, benzofurane, benzothiophene, and naphthalene counterparts were also well incorporated to afford silicon-stereogenic monohydrosilanes 59e-g in 94-99% ee. Furthermore, chiral silicon-bridged diphenylamine 59h could also be accessed by this approach, despite a much lower enantioselectivity (58% ee). It is noteworthy that several seven-membered carbazole-based silicon-stereogenic triorganosubstituted silanes 61 were readily obtained in moderate to good yields (40-80%) and decent enantioselectivities (85-91% ee) by simply replacing the chiral ligand L16 with L17.

Subsequently, He and co-workers disclosed a cascade desymmetric Si–C activation/C–H silylation and intermolecular dehydrogenative silylation reaction of silacyclobutanes (SCB) 62

Scheme 18 Rh(ı)-Catalyzed synthesis of six- and seven-membered silicon-stereogenic triorgano-substituted silanes.

with arenes *via* asymmetric Rh(i) catalysis (Scheme 19). ⁸⁸ As a result, a variety of quaternarily silicon-stereogenic dibenzosiloles **63** were attained in moderate to high yields (54–88%) and good enantioselectivities (65–93% ee). Aside from thiophene derivatives, benzene also proved as capable substrate to furnish the corresponding silole **63c** in comparable yield, but diminished enantiocontrol (68% ee). Notably, by taking advantage of this catalytic system, bis-silole **63d** and ferrocene silole **63e** were achieved in 92% ee and 91% ee, respectively.

Most recently, the Rh(I)-Catalyzed intermolecular asymmetric C-H silylation was independently successfully realized by W. He and C. He (Scheme 20). ⁸⁹ As described by W. He and co-workers, with biphenylphosphine **L11b** as a chiral ligand, various silacyclobutanes **64** were smoothly coupled with thiophene derivatives **65**, forging chiral acyclic monohydrosilanes **66** in moderate to excellent yields (50–82%) and stereo-control (54–96% ee). The reaction was proposed to commence with the generation of intermediate **Int-18** *via* thiophene coordination to the pre-formed [Rh]–H catalyst. Subsequent oxidative addition of silacyclobutane **64** onto Rh(I) in **Int-18** proceeded to afford a



Scheme 19 Rh(i)-Catalyzed asymmetric desymmetrization/C-H silylation/dehydrogenative silylation of silacyclobutanes.

five-membered rhodacycle Int-19. Reductive elimination of rhodacycle Int-19 occurred to form Int-20, which then underwent C-H activation to furnish oxidative addition intermediate Int-21. Finally, the desired acyclic stereogenic monohydrosilane 66 was obtained via a second reductive elimination of Int-21. Almost at the same time, C. He and co-workers also communicated a Rh(1)-catalyzed intermolecular asymmetric C-H silylation of heteroarenes via a direct dehydrogenative C-H/Si-H cross-coupling (Scheme 20).90 As a result, a diversity of acyclic heteroarylated silicon-stereogenic monohydrosilanes 69 including bis-Si-stereogenic silanes (69b, 69c) were generated in decent yields and enantioselectivities. Notably, apart from furan and thiophene derivatives, simple arenes were also compatible with this reaction, despite moderate stereo-control (69d). It was worth mentioning that the use of norbornene derivative NBE-OMe as a hydrogen acceptor was critical to maintaining the reactivity.

2.2 Functionalization of C(sp³)-H bonds

2.2.1 Functionalization of activated C(sp³)-H bonds. In 2012, Yu's group reported a Rh(1)-catalyzed asymmetric functionalization of activated allylic C(sp³)-H bonds for intramolecular addition to conjugated 1,3-dienes. 91 Various nitrotethered ene-2-dienes 70 containing either alkyl or aryl substituents were readily converted to pyrrolidine derivatives 71 in 45-91% yields with moderate to excellent enantioselectivities (63–94% ee), using [RhCl(coe)₂]₂ as a catalyst, AgOTf as a co-catalyst and (S)-binaphthol (BINOL)-derived monodentate phosphoramidite L2a as a chiral ligand. Moreover, carbonand oxygen-tethered ene-2-dienes were also suited to this

Scheme 20 Rh(i)-Catalyzed intermolecular asymmetric C-H silylation.

54% vield, 45% ee

transformation, providing cyclopentane and tetrahydrofuran derivatives 70d and 70e in 81% and 64% ee, respectively. Notably, two adjacent stereo-centers with one quaternary carbon center were constructed in excellent diastereoselectivities (dr > 19:1). The underlying mechanism was next thoroughly investigated based on the DFT (density functional theory) calculation (Scheme 21).92 As depicted in Scheme 21, the reaction was initiated by the coordination of the rhodium catalyst with the substrate, leading to the formation of Rh-complex Int-22. Follow-up allylic C-H activation provided rhodium-hydride species Int-23, which then underwent alkene insertion to furnish bis-allylic Rh-complex Int-24. Finally, di-π-allyl-assisted reductive elimination of Int-25 occurred to release the desired product.

In 2016, Glorius's group reported a Rh(1)-catalyzed asymmetric approach for the site- and enantio-selective intermolecular arylation of benzylic C(sp³)-H bonds (Scheme 22).⁹³ Diverse triarylmethanes 74 were achieved in 42-86% yields and with moderate to good enantioselectivities (62-80% ee) by reacting 8-benzyl quinolones 72 with aryl bromides 73 under the catalysis of RhCl(PPh₃)₂ and NHC (N-heterocyclic carbene)

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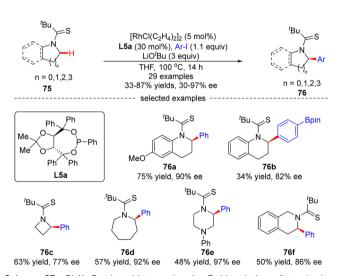
Scheme 21 Rh(i)-Catalyzed allylic C-H activation and addition to conjugated dienes.

pre-ligand L23. The underlying plausible reaction mechanism was proposed as depicted in Scheme 22. First, reactive intermediate Rh(I)-complex Int-26 was generated by the coordination of *in situ* generated free NHC to rhodium, followed by intramolecular activation of a benzylic C-H bond on the carbene ligand. Then, Rh(III) species Int-27 was formed by oxidative addition of aryl bromides into Int-26, with concomitant elimination of associated ligand PPh₃. Afterwards, Rhcomplex Int-28 was produced by a *trans*-metalation reaction of Int-27 with deprotonated substrate 72, which was generated by an excess amount of NaO^tBu. Finally, the desired product 74 was achieved *via* reductive elimination of Int-28.

Glorius's group later explored another Rh(1)-catalyzed approach for the enantioselective intermolecular C(sp3)-H arylation of tetrahydroquinolines and other saturated Nheterocycles with aryl iodides, without observation of the arylation of the adjacent C(sp2)-H bonds on tetrahydroquinolines (Scheme 23).94 In this reaction, the combination of [RhCl(C₂H₄)₂]₂ and chiral phosphonite ligand L5a acted as a powerful catalytic system producing a diversity of α-arylated Nheterocycles with high regio- and enantio-selectivity, while using tert-butyl thioamide as a directing group. Both electrondonating and electron-withdrawing substituents on the phenyl ring were well tolerated when the tetrahydroquinoline scope was concerned. Substituents such as cyano, thioanisoles, trifluoromethyl, and arylboronic pinacol esters were also compatible in the case of aryl iodides. Remarkably, the scope of saturated aza-heterocycles could be extended to piperidine, pyrrolidine, piperazine, azepane and azetidine, and the corresponding α-N-arylated products 76c-f were obtained in good regio- and enantio-selectivities (up to 97% ee).

2.2.2 Functionalization of unactivated C(sp³)–H bonds. In 2015, Takai's group shared their pioneering work on the enantioselective rhodium-catalyzed dehydrogenative silylation

Scheme 22 Rh(ı)-Catalyzed intermolecular C-H arylation of 8-benzyl quinolones and aryl bromides.



Scheme 23 Rh(i)-Catalyzed intermolecular C–H arylation of tetrahydro-quinolines and saturated aza-heterocycles.

of unactivated $C(sp^3)$ –H bonds (Scheme 24). ⁹⁵ In the presence of $[RhCl(cod)]_2$, C_2 -symmetric diphosphine ligand (R)-DTBM-Garphos L12 and hydrogen acceptor 3,3-dimethyl-1-butene, 2-isopropylphenylsilane 77 was converted to 2,3-dihydrobenzo[b]silole 78 in 83% yield without any formation of hydrosilylated product 79, in spite of the low enantiocontrol (37% ee) (Scheme 24). While ligand (R)-DTBM-Garphos was replaced

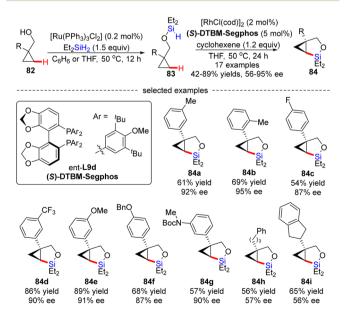
with (R)-H₈-BINAP L8, 1,1'-spirosilabiindane 81 with a new tetrasubstituted silicon-stereogenic center was achieved in comparable yield (75%) and enantioselectivity (40% ee) via dual asymmetric alkylation of dihydrosilane 80 at elevated temperature with increased catalyst and hydrogen acceptor loading. The mechanism of this unique reaction has also been proposed as given in Scheme 24. First, hydrosilane 77 was oxidatively added to the Rh(1)-Cl pre-catalyst, furnishing a Rh(I)-H species involving the reductive elimination of chlorosilane Int-29. The Rh(1)-H species was then added to the Si-H bond of 77, and the resulting intermediate Int-30 further reacted with 3,3-dimethyl-1-butene to produce intermediate Int-31. Instead of the hydrosilylated product 79, Rh-silyl species Int-32 was preferably formed by reductive elimination of H and 3,3-dimethylbutane groups on the rhodium center of Int-31, which might be attributed to the tendency of 3,3dimethylbutyl and sterically bulky silyl groups to keep distance from each other. The hydrosilylated product 79 might be generated by the reaction of Int-32 with 3,3dimethyl-1-butene via silylrhodation followed by the Sigmabond metathesis with 77. However, the electron-rich Rh center in Int-32 favored intramolecular oxidative addition over the silylrhodation to provide Int-33, which then underwent reductive elimination to generate the desired product 78.

[RhCl(cod)]₂ (1.5 mol%) (R)-DTBM-Garphos L12 (4.5 mol%) 3,3-dimethyl-1-butene (1 equiv) 1,4-dioxane, 50 °C, 24 h 83% vield, 37% ee reductive elimination IRh^II—H 77 Int-33 :[Rh^{III} Me₂ Int-30 ^tBu Int-32 Me₂ Int-31 Me₂ reductive elimination t_{Bu} [RhCl(cod)]₂ (3 mol%) -Me (R)-H₈-BINAP L8 (9 mol%) 3,3-dimethyl-1-butene (2 equiv) 1,4-dioxane, 100 °C, 24 h -Me 75% vield, 40% ee (R)-H₈-BINAP L8

Scheme 24 Rh(ı)-Catalyzed intramolecular C-H silylation of isopropylphenylsilane and dihydrosilane.

Soon after, Hartwig's group described an unprecedented enantioselective intramolecular silylation of cyclopropyl C-H bonds in the presence of a Rh catalyst.96 As displayed in Scheme 25, silyl ether 83 was in situ generated by Rucatalyzed dehydrogenative coupling of cyclopropylmethanols 82 with diethylsilane and was used in the follow-up reaction without further purification. In the presence of $[RhCl(cod)]_2/(S)$ -DTBM-Segphos and a hydrogen acceptor cyclohexene, the intramolecular silvlation of silvl ethers 83 readily occurred to generate various bicyclic silylcyclopropanes 84 in decent to high yields (42-89%) with moderate to good enantiomeric excesses (56-95% ee). Generally, aryl-substituted cyclopropylmethanols provided higher enantioselectivities compared with alkyl-substituted substrates (84a-g vs. 84h-i), which was contributed by an additional π - π interaction between the arvl moieties of the substrate and the Rh(I) catalyst. Mechanistic studies suggested that the C-H cleavage might be the turnoverlimiting step and determined the configuration of the product.

In 2020, He and co-workers developed a Rh(1)-catalyzed enantioselective silylation of unactivated C(sp³)-H bonds, thus providing an elegant access to silicon-stereogenic dihydrobenzosiloles (Scheme 26).97 This reaction comprises a two-step sequence, namely a highly asymmetric silylation of C(sp3)-H bonds in dihydrosilanes and a follow-up stereospecific alkene hydrosilylation. With (R,Sp)-Josiphos L16 as a chiral ligand, a diverse set of dihydrosilanes 85 and alkenes 86 were well compatible with this reaction to afford various siliconstereogenic tetrasubstituted silanes 87 in good to excellent yields (42-90%) and enantioselectivities (55-95% ee). Shortly after, He and co-workers further disclosed an elegant approach to axially chiral 6-member-bridged biaryl derived dihydrodibenzosilines with a silicon-stereogenic center via Rh(1)/L16 catalysis.⁹⁸ A diverse set of silicon-centrally and axially dihydrodibenzosilines 89 were conveniently generated in 35-78%



Scheme 25 Rh(i)-Catalyzed intramolecular C-H silylation of hydrosilyl

(R)-DTBM-Garphos L12

Review Article

He. 2020 [RhCl(cod)]₂ (2 mol%) L16 (4 mol%) DCE, 100 °C, Ar, 1 h 85 38 examples 42-90% yield, 55-95% ee selected examples 87h 87c 87a 87d 63% vield, 95% ee 70% yield, 80% ee 65% yield, 89% ee 73% vield, 93% ee 87f 65% vield, 93% de 82% vield, 91% ee from liquid crystal building block from D-ribofuranoside He, 2021 [RhCl(cod)]₂ (2 mol%) Ar

NBE-OMe (1.0 equiv) toluene, 60-100 °C, 1 h 27 examples

42% yield, 95% ee

Scheme 26 Rh(ı)-Catalyzed asymmetric silylation of unactivated $C(sp^3)$ -H bonds.

51% yield, 96% ee

yields and 83–96% ee. It was found that the presence of a hydrogen acceptor such as a norbornene derivative (NBE-OMe) was crucial to enhance the reactivity.

3. Outer-sphere C–H functionalization

The outer-sphere mechanism does not involve the direct interaction of the metal with the C–H bond, but instead commences with the formation of a rhodium-carbenoid, -nitrenoid, or -oxo species, followed by the reaction of this species with the C–H bond *via* either a direct insertion or a hydrogen atom transfer (HAT)/radical rebound pathway.

In 2020, Wang's group demonstrated an example of carbene *ortho*-selective $C(sp^2)$ -H insertion of phenols with diisopropyl diazomalonate *via* $Rh(\iota)$ /diene catalysis (Scheme 27). ⁹⁹ With a transient oxonium ylide as the directing group, the final triscarboxylate-substituted 2-benzofuranones **92** bearing a quaternary all-carbon center were produced in good yields (51–96%) and enantioselectivities (80–95% ee). The substrate scope investigation showed that various substituents at the *ortho*-,

meta- and para-position were all well tolerated, indicating the good functional-group tolerance of this reaction. The underlying mechanism was proposed as shown in Scheme 27. Generally, this reaction was initiated by Rh(I)-triggered N₂ extrusion from 91 to form a Rh-carbene intermediate, which then reacted with phenol to give an oxonium ylide Int-34. Int-34 promoted the extrusion of N₂ from a second 91, giving access to another Rh-carbene species Int-35. Subsequently, Int-35 underwent ortho-C(sp²)-H oxidative addition/migratory insertion sequence to produce Int-36 or Int-37, which then experienced a reductive elimination to provide Int-38. Afterwards, Int-40 was formed by dissociation of the oxonium ylide Int-38 and follow-up cyclization of Int-39. Finally, Int-40 proceeded with electrophilic addition to another Rh-carbene, followed by proton transfer to release the desired product 92.

In 2021, Xu and co-workers developed an elegant Rh(i)/ diene-catalyzed regiospecific and enantioselective arylvinylcarbene insertion of the $C(sp^2)$ -H bond of aniline derivatives (Scheme 28). The reaction was characterized by multiple merits, such as unusual regio-selectivity at the vinyl terminus site, excellent *E*-selectivity and enantioselectivities (82–95% ee), simple and mild conditions, and broad functional group

Scheme 27 Rh($_1$)-Catalyzed enantioselective C(sp 2)-H functionalization of phenols with diisopropyl diazomalonate.

tolerance, offering access to a diversity of chiral γ, γ -gemdiarylsubstituted α,β-unsaturated esters 95. Synthesis applications of this protocol were featured by several versatile product transformations. Apart from arylvinyldiazoacetates, a more challenging arylvinyldiazoketone substrate was also found to be compatible with this transformation, giving rise to the expected C-H functionalization product 95e in moderate yield (40%) and good enantioselectivity (84% ee). Combined experimental and computational studies were carried out to elucidate the reaction mechanism. Initially, arylvinyldiazoacetate reacted with the active monorhodium catalyst Rh-Cl to afford the Rh(1)arylvinylcarbenoid intermediate Int-41. The ensuring addition of the electron-rich phenyl ring of aniline onto Int-41 siteselectively occurred at the vinyl terminus site to furnish zwitterionic species Int-42, which then proceeded a 1,5-proton transfer event to provide Rh(III) species Int-44. Finally, reductive elimination of Int-44 happened, leading to the desired product 95 and the regeneration of the monorhodium catalyst. Of note, an inverse deuterium kinetic isotope effect was observed in this reaction, supporting the C-C bond-formation step as a ratedetermining step. Encouraged by this elegant work, Xu and coworkers further realized a one-pot rhodium-catalyzed C-H functionalization/organocatalyzed oxa-Michael addition cascade reaction

Scheme 28 Rh(ı)-Catalyzed enantioselective arylvinylcarbene insertion of the C-H Bond of aniline derivatives.

40% yield, 90% ee

Scheme 29 Rh(ı)-Catalyzed enantioselective C-H functionalization/oxa-Michael addition cascade.

of 3-hydroxylaniline derivatives 96 with arylvinyldiazoacetate 93 (Scheme 29).101 Under mild conditions, a diverse set of 2,3disubstituted dihydrobenzofurans 97 were attained in good yields (up to 99%) and excellent stereoselectivity (92–98% de, uniformly 99% ee). It was noteworthy that the two contiguous stereogenic centers of product 97 were independently controlled by two chiral catalysts via a one-pot two-step operation. As a consequence, the full complement of stereoisomers could be accessed at will by appropriate permutations of the two chiral catalysts.

In 2021, Xu's group developed an asymmetric Rh(1)/dienecatalyzed C(sp³)-H functionalization of 1,4-cyclohexadiene 99 with α-aryl-diazoacetate 98, which provided a direct access to various chiral 2-arylacetates 100 in good yields (up to 90%) and enantiomeric excess (up to 99%) (Scheme 30).102 The application of this reaction was further highlighted by the follow-up oxidation of the products with DDQ with the generation of diverse enantioenriched α,α -diarylacetates 101. Notably, the steric factor had a great impact on the reactivity of different $C(sp^2)$ -H bonds, and only the less sterically hindered $C(sp^2)$ -H bonds were functionalized.

In 2022, Xu and co-workers communicated an elegant Rh(I)diene catalyzed highly enantioselective C(sp²)-H allylation of simple unprotected indoles, pyrroles, and their common analogues such as furans, thiophenes, and benzofurans with arylvinyldiazoesters, offering a facile and reliable access to a diversity of diarylmethane-containing α,β-unsaturated esters 104 & 106 in favorable yields (73-99%), and excellent enantioselectivities (70-97% ee) (Scheme 31).103 For unprotected indole substrates 103 without a substituent at the C3 position, the carbene insertion site selectively occurred at the C3 position of indoles. In contrast, when unprotected pyrroles were used or the C3 position of indoles, furans, thiophenes and benzofurans (105) were occupied by a protected amino group, only C2 carbene insertion proceeded. Notably, the bulky 2,4,6-

40% yield, 84% ee

82% yield, 91% ee

Review Article Chem Soc Rev

Scheme 30 Rh(ı)-Catalyzed enantioselective C(sp³)-H functionalization of 1,4-cyclohexadiene with α -aryl-diazoacetates

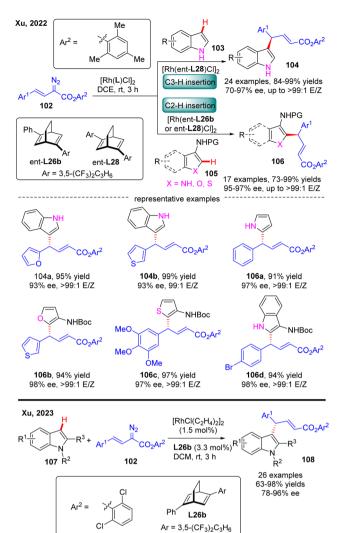
trimethylphenyl substituent on arylvinyldiazoesters was found to be critical to guarantee the excellent enantioselectivity of this reaction and this reaction was also characterized by an uncommon site-selectivity at the vinyl terminus of arylvinylcarbene. Mechanistic experiments and DFT calculations indicated that the C-C addition barrier was lowered by the more electron-rich indole substrate, thus changing the rate-determining step to the reductive elimination step. Soon after, Xu and co-workers further extended the substrate scope of Rh(1)-diene catalysed arylvinylcarbene insertion process to N-protected indoles 107, giving rise to an interesting class of chiral indole scaffolds 108 containing a gem-diaryl carbon stereocenter in good yields (up to 99%) and excellent enantioselectivities (up to 96% ee). 104

4. C-H functionalization via 1,4-Rh migration

Aside from the above-described Rh(1)-catalyzed direct C-H activation via either an inner- or outer-sphere mechanism, 1,4-Rh migration represents an alternative approach to promote C-H activation to form unique carbon-Rh bonds, which could be further transformed into a diversity of valuable scaffolds. More importantly, 1,4-Rh migration could facilely introduce a rhodium moiety into a specific position of an organic molecular skeleton, which would be otherwise difficult to be obtained via classic approaches. Currently, the most prevalent 1,4-Rh migration for asymmetric C-H functionalization is from alkenyl to aryl, despite that several other modes such as alkylto-aryl, aryl-to-alkenyl, allyl-to-allyl, and alkenyl-to-allyl 1,4-Rh migration may also exist.

4.1. $C(sp^2)$ -H functionalization via 1,4-Rh migration

4.1.1 $C(sp^2)$ -H functionalization *via* alkenyl-to-aryl 1,4-Rh migration. In 2006, Hayashi's research group developed an



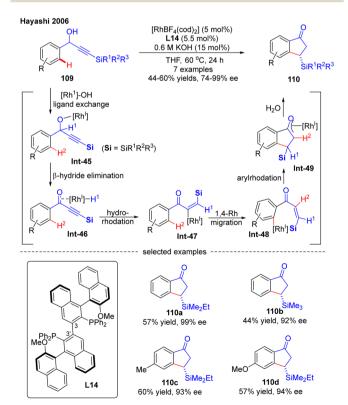
Scheme 31 Rh(ı)-Catalyzed enantioselective C(sp²)-H functionalization of simple unprotected indoles, pyrroles and heteroanalogues and protected indoles.

effective Rh(1)-catalyzed asymmetric synthesis of 3-substituted 1-indanones via an alkenyl-to-aryl 1,4-Rh migration (Scheme 32). 105 By employing a newly designed axially chiral bisphosphine ligand L14, wherein the absolute configuration of the 3-3' axis was fixed to (R) after complexation to transition metal rhodium, they successfully prepared several indanones 110 in 44-60% yields with 92-99% ee via an asymmetric isomerization of racemic α -arylpropargyl alcohols 109. The underlying mechanism was studied, suggesting that this reaction was initiated by the ligand exchange of 109 by Rh(I) catalyst to generate alkoxylrhodium Int-45. Subsequent β-H elimination of Int-45 followed by conjugate hydrorhodation resulted in alkenylrhodium species Int-47, which further underwent 1,4rhodium migration to provide Int-48. Afterwards, Int-49 with a new emerging stereocenter was produced by intramolecular 1,4-addition of Int-48. The Rh/(R,R)-L13 complex played an important role in this step, as it could recognize the enantiotopic face of the C-C double bond in Int-48 to create a new

stereocenter with high enantioselectivity. The desired product 110 was finally obtained by the hydrolysis of Int-49.

In 2007, Hayashi and co-workers further reported a $[RhOH(cod)]_2/(R)$ -Segphos catalytic system for high enantioselective addition of boronates 112 to aryl silylethynyl ketones 111 (Scheme 33). With this system, a variety of 3,3disubstituted 1-indanones 113 were obtained in impressive vields (51-91%) and excellent enantiomeric excess (87-99%). Aside from the silyl substituents on the ethynyl ketones, a germyl substituted substrate was also compatible with this reaction to give the corresponding product 113e in 88% yield and 97% ee. The underlying mechanism of the reaction was also proposed (Scheme 33). First, insertion of the alkyne group in 111 into the [Rh]-carbon bond generated the alkenyl rhodium species Int-50, which underwent a 1,4-Rh migration process to produce the aryl rhodium intermediate Int-51. Subsequent 1,4-intramolecular addition in Int-51 occurred to deliver the oxa- π -allyl rhodium species Int-52, wherein the stereochemistry was determined. Follow-up transmetalation of Int-52 with boronates 112 released the boron enolate Int-53 along with the [Rh]-R³ species for the next cycle. Finally, the desired product 113 was achieved by hydrolysis of Int-53.

The asymmetric synthesis of enantiopure spirocabocycles, a class of prevalent scaffolds in natural products, biologically active molecules and chiral ligands, has gained great attention in organic chemistry. In 2010, Hayashi's group communicated a facile access to chiral spirocarbocycles via a Rh(1)/diene catalyzed enantioselective addition of sodium tetraarylborates



Scheme 32 Rh(i)-Catalyzed enantioselective isomerization of racemic α arylpropargyl alcohols.

Scheme 33 Rh(i)-Catalyzed enantioselective addition of aryl boronates to aryl alkynyl ketones.

83% vield, 98% ee

115 to alkyne-tethered 2-cycloalken-1-ones 114 (Scheme 34). 107 With sodium tetraarylborates 115 as surrogates of 1,2dimetalloarenes and the chiral diene L28 as a ligand, a variety of spirocycles 116 bearing a quaternary carbon stereocenter were prepared in good yields (55-76%) and a decent enantiomeric excess (91-97%). This reaction was proposed to be initiated by the generation of an aryl-Rh species Int-54 via the transmetalation of 115 with [Rh]-Cl. Int-54 underwent insertion of the alkyne group in 114 to generate alkenyl-Rh intermediate Int-55, which was then converted to aryl-Rh species Int-56 via a 1,4-Rh migration process. Successive intramolecular 1,4-addition onto the tethered enone moiety in Int-56 resulted in oxa-π-allyl-Rh intermediate Int-57. The final hydrolysis of Int-57 released the desired product 116 along with concurrent regeneration of the Rh(1) catalyst.

Afterwards, Matsuda and co-workers reported the asymmetric synthesis of indanes 119 possessing a quaternary all-carbon center from 1,4-enynes 117 with arylboronic acids 118 via a Rh(I)-catalyzed arylation/annulation process (Scheme 35). 108 The desired indanes 119 were readily obtained with yields of 61-75% and enantiomeric excess of 84-92% by taking advantage of the [Rh(cod)OH]₂/(R)-MeO-BIPHEP catalytic system. As far as this reaction mechanism was concerned, four key steps including intermolecular alkyne insertion, 1,4-Rh migration, intramolecular addition onto the tethered alkene moiety, and protonolysis were proposed to be involved.

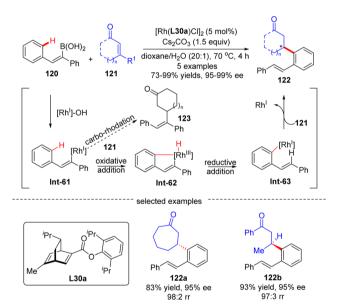
Review Article Chem Soc Rev

Scheme 34 Rh(i)-Catalyzed enantioselective addition of sodium tetraarylborates to alkyne-tethered 2-cycloalken-1-ones.

In 2012, Hayashi's group reported a tandem 1,4-Rh migration/1,4-addition process of 2-arylethenylboronic acid 120 to enones 121 by use of chiral ligand L30a, a new chiral diene derivative from (R)-phellandrene (Scheme 36). 109 With regard to the variability of the substrates, both cyclic and acyclic enones 121 were tolerated to produce the rearranged products 122 with high yields and excellent regio- and enantio-selectivities. The catalytic cycle of this reaction involved a transmetalation to form the 2-phenylethenyl-Rh(1) intermediate Int-61, 1,4-Rh migration to give Int-63, and enantioselective 1,4-addition onto enones 121 to arrive at the desired products 122. Density functional theory (DFT) studies indicated that the 1,4-Rh migration proceeded via an oxidative addition onto the aryl C-H bond in Int-61, leading to a distorted square-pyramidal Rh(III)-H species Int-62, and followed by reductive elimination of Int-62 to afford Int-63.

In 2019, by using the chiral diene derivative L31 with an anthracen-9-yl substituent as a ligand, Darses' group successfully developed an asymmetric arylative cyclization of propargylic malonates 124 with arylboronic acids 125, giving access to chiral 1tetralones 126 with a quaternary carbon stereocenter via the desymmetrization of the malonate moiety (Scheme 37). 110 This reaction involved a regioselective alkyne insertion, an alkenyl-toaryl 1,4-Rh migration and an acylation process. The 2,4bis(trifluoromethyl)phenyl substituent on propargyl malonates 124 played an important role in controlling the regioselectivity of alkyne insertion (>99:1). Alkyl-, alkoxyl, and aminosubstituted alkynylmalonates were all competent substrates to generate the desired 1-tetralones 126 in favorable yields (up to 96%) and enantioselectivities (up to 96% ee). Of note, one enantioselective variant of 1-tetralone was also prepared from bis(2,2,2-trifluorethyl)-malonate by Lam's group under the catalysis of $[RhCl(C_2H_4)_2]_2$ and (R)-MeO-BIHEP. 111

Scheme 35 Rh(ı)-Catalyzed asymmetric indane synthesis from 1,4envnes and arylboronic acids



Scheme 36 Rh(ı)-Catalyzed 1,4-migration/1,4-addition of 2-arylethenylboronic acid to enones

In 2020, Lam's group developed a Rh(1)-catalyzed asymmetric arylation/annulation reaction of 2-propargyl-1,3diketones 127 with arylboronic acids 128 involving an alkenylto-aryl 1,4-Rh migration as the key step, thus giving access to densely functionalized polycarbocycles 129 containing two contiguous quaternary stereogenic centers (Scheme 38). 112 By the use of the $[RhCl(C_2H_4)_2]_2$ catalyst combined with (S)-DTBM-Segphos ligand ent-L9d, the desired products 129 were achieved in excellent enantioselectivities (up to 99% ee) and diastereoselectivities (in most cases dr > 19:1). A broad range of functional groups on both reaction partners were well tolerated

Scheme 37 Rh(i)-Catalyzed arylative cyclization of propargylic malonates with arylboronic acids

89% ee

regardless of the electronic effect, whereas the steric factor played a critical role in the reactivity as reflected by the failure of 2-methylphenylboronic acid as a substrate (129b). It was also found that 3-substituted arylboronic acids favored affording the less sterically hindered products (129c). When cyclic 1,3-diketones were used as a substrate, favorable results were also achieved to give 129d-f in 60-74% yields and 97-99% ee. It was hypothesized that this reaction might experience a transmetalation/migratory insertion/1,4-Rh migration/1,2-addition sequence. The similar transformation between 1,3-diketones and aryl boronic acids was also realized by Darses and co-workers by use of chiral diene L32 as a ligand, providing straightforward access to 1-tetralols 132 containing two contiguous quaternary stereogenic centers in good enantioselectivities (81-92% ee) and diastereoselectivities (>99% de) (Scheme 38). 113 Diverse 2-propargyl-1,3-diketones including cyclic and acyclic substrates with various functional groups were all well tolerated in this reaction. It is worth mentioning that the 2trifluoromethyl-phenyl substituent (Ar') on the alkyne moiety of 130 was essential to achieve high regioselectivity for alkyne insertion.

Darses's research group also investigated the cascade reactions of eneyne derivatives with arylboronic acids by taking advantage of asymmetric catalysis with Rh(1)/chiral diene complexes. In 2017, they disclosed the preparation of various 7membered chiral azepane 135 in moderate to high yields (36-93%) and good enantiomeric excess (86–97%) by using the Ntethered alkyne enoates 133 and aryl boronic acids 134 as substrates and chiral diene L32 or L33 as a ligand (Scheme 39). 114 This reaction displayed good functional group tolerance. Shortly after, Darses and co-workers further developed an efficient access to chiral tetrahydrofurans 138 and tetrahydrobenzo[d]oxepines 139 in decent stereo-control from

99% vield, 85% ee Scheme 38 Rh(ı)-Catalyzed arylative cyclization of 2-propargyl-1,3diketones with arylboronic acids

132h

132a

yield, 85% ee

simple O-tethered alkyne enoates 136.115 When the R1 substituent in 136 was methyl, the chiral 5-membered tetrahydrofurans 138 were obtained, whereas the enantioenriched 7membered tetrahydrobenzo[d]oxepines 139 was produced when the R¹ substituent was aryl. The differed product structures were ascribed to a switch of the regioselectivity of alkyne insertion by the alkyne substituent, suggesting that the regioselectivity of the alkyne insertion may be impacted by the steric and electronic properties of R1 substituents.116

4.1.2 $C(sp^2)$ -H functionalization via alkyl-to-aryl 1,4-Rh migration. In 2007, Murakami's group developed a Rh(I)catalyzed cascade reaction of 3-(2-hydroxyphenyl)-cyclobutanones 140 with electron-deficient alkenes 141 via an alkyl-to-aryl 1,4-Rh

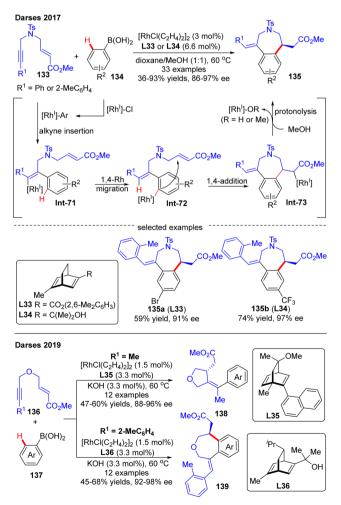
1326

80% vield, 83% ee

Review Article Chem Soc Rev

migration (Scheme 40).117 Using [RhOH(cod)]₂ as a catalyst and (R)-Tol-BINAP L7a as a chiral ligand, several 4,4-disubstituted 3,4dihydrocoumarins 142 were obtained in high yields (65-93%) and enantioselectivities (91-97% ee). It was proposed that this cascade reaction might involve a carbonyl addition, a ring opening via β-C elimination, a 1,4-Rh migration, and an intermolecular 1,4addition. Specifically, rhodium aryloxide Int-74 was first generated from 140 with [RhOH(cod)]₂. Intramolecular addition onto the carbonyl group in Int-74 happened to produce the rhodium cyclobutanolate Int-75, which readily proceeded β-C elimination, forging ring-opening alkyl rhodium species Int-76. This step was believed as the stereochemistry-determining step of this reaction. Afterwards, the arylrhodium species Int-77 was then generated from Int-76 via a 1,4-rhodium migration process. A final intermolecular 1,4-addition of Int-77 onto electron-deficient alkenes 141 arrived at the enantioenriched 3,4-dihydrocoumarins 142.

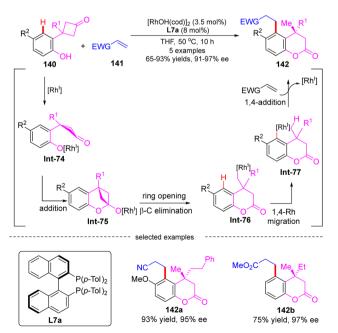
In 2009, Cramer and co-workers successfully prepared enantioenriched 1-indanols **144** from cyclobutanols **143** under the catalysis of [RhOH(cod)]₂ (Scheme 41).¹¹⁸ When 3-aryl-3'-methyl-cyclobutanols were used as substrates, Josiphos-type ligand **L19** with an electron-withdrawing trifluoromethyl group



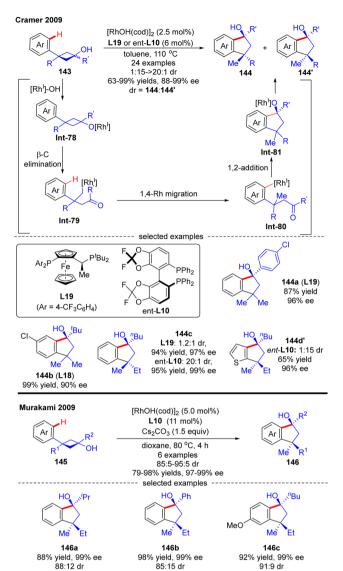
Scheme 39 Rh(I)-Catalyzed arylative cyclization of N- or O-tethered alkyne enoates with arylboronic acids.

demonstrated as the optimal, providing products 144a and 144b as a single stereoisomer with decent yields and stereocontrol. Interestingly, when the 3'-position of cyclobutanols was not methyl, diastereo-isomers existed and the chiral ligand had a great influence on the diastereomeric ratios, as reflected by the increased diastereoselectivity by taking advantage of the difluorophos ligand ent-L10 (144c, 20:1 vs. 1.2:1 with L19 and ent-L10, respectively). As illustrated in Scheme 41, the reaction was proposed to be initiated by the formation of the rhodium cyclobutanolate Int-78 via deprotonation of 143. Fragmentation of the cyclobutane ring in Int-78 occurred to form the alkyl rhodium species Int-79 via β-C elimination. Following a 1,4-Rh migration process of Int-79, the aryl rhodium species Int-80 bearing one quaternary carbon was produced, which was further turned into Int-81 containing two quaternary carbons through intramolecular 1,2-addition. The desired product 1indanols 144 was finally released by protonation of Int-81. A similar approach to stereoselective restructuring of 3arylcyclobutanols 145 into 1-indanols 146 was also reported by Murakami's group, 119 and the underlying mechanism was systematically studied by Dang's group with DFT calculations in 2014. 120 The results showed that the stereoselectivity of this reaction was contributed by three main factors including the relative stability of β-C elimination product, the kinetic feasibilities of 1,4-Rh migration, and the relative free energies of C=O insertion step.

As an extension of the above-described transformation, in 2010, Cramer's group further achieved the asymmetric synthesis of indanones **148** bearing a quaternary stereogenic center from 1-arylcyclobutanols **147** (Scheme 42). Similar to the previous transformations, rhodium alkoxide **Int-85** was also generated in this reaction through a four-step sequence



Scheme 40 Rh(i)-Catalyzed cascade reaction of 3-(2-hydroxyphenyl)cyclobutanones with electron-deficient alkenes.



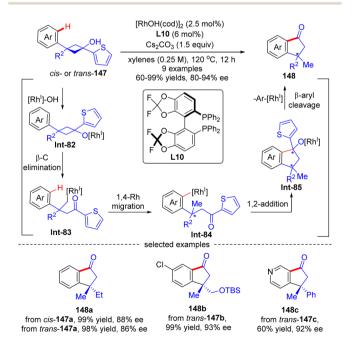
Scheme 41 Rh(i)-Catalyzed asymmetric synthesis of 1-indanols from 3arylcyclobutanols

comprising Rh-catalyzed deprotonation of 1-arylcyclobutanols 147, cyclobutane fragmentation via β-C elimination, alkyl-toaryl 1,4-Rh migration, and intramolecular 1,2-addition. Next, by contrast to the direct protonolysis in previous transformations, herein Int-85 underwent a further β-aryl cleavage, leading to indanones 148 with a quaternary carbon center. The aryl substituent on prototype cyclobutanols 147 had a great impact on the reaction pathway of Int-85, and the 2-thienyl substituent performed the best to selectively furnish indanones 148 via βaryl cleavage instead of indanols via direct protonation. This reaction tolerated a broad range of functional groups, giving the corresponding indanones 148 in 60-99% yields and 80-94% ee. Notably, the geometry of substrates 147 revealed minimal effect on the stereo-control of the desired products (148a).

In 2016, Hayashi's group further disclosed a sequential 1,4-Rh migration/arylation reaction of enones 150 with potassium

aryloxymethyltrifluoroborates 149 to yield β-(2-methoxylaryl)substituted ketones 151 in high yields (67-97%) and excellent enantioselectivities (88-99% ee) via asymmetric Rh(1)/diene catalysis (Scheme 43).122 Both cyclic and linear enones displayed good compatibility. The mechanistic investigation suggested that this reaction involved an alkyl-to-aryl 1,4-Rh migration of aryloxymethyl-Rh intermediate Int-86, which forged 2-methoxyaryl-Rh species Int-87. This 1.4-Rh migration between C(sp³)-H and C(sp²)-H was reversible as revealed by the deuterium-labeling studies, and C-H bond cleavage was not the turnover-limiting step. Notably, the regioselectivity for 1,4-Rh migration was impacted by the steric factor, as the less hindered isomer (151d) was preferably formed.

4.1.3 $C(sp^2)$ -H functionalization *via* aryl-to-alkenyl 1,4-Rh migration. Aside from the intensively studied alkenyl-to-aryl and alkyl-to-aryl 1,4-Rh migration process, a novel aryl-toalkenyl 1,4-Rh migration process was also developed by Lin and co-workers to effect enantioselective $C(sp^2)$ -H functionalization. In 2019, they reported a Rh(1)/BINAP-catalyzed asymmetric alkenylation of enones 153 with 2-ethenyl-arylboronic acids 152, providing facile access to a wide range of βalkenylated ketones 154 in high yields (65-99%) and excellent enantiomeric excess (70-99% ee) (Scheme 44).123 In addition to enones, cyclic aldimines 156 were also compatible with this strategy to prepare a set of chiral allylic sulfonamides 157 by employing (S)-difluorphos L10 as a chiral ligand. The key to the success of this reaction relied on a highly efficient aryl-toalkenyl 1,4-Rh migration, which offered a new mode to prepare stereodefined alkenyl-rhodium species Int-90. DFT calculations revealed that the aryl-to-alkenyl 1,4-Rh migration was a kinetically favored process, comprising a C-H oxidative addition to form distorted Rh-H species Int-89 and follow-up reductive



Scheme 42 Rh(i)-Catalyzed asymmetric synthesis of indanones from 1-(2-thienyl)cyclobutanols

Review Article Chem Soc Rev

Scheme 43 Rh(ı)-Catalyzed conjugate arylation of enones with potassium aryloxymethyltrifluoroborates

elimination to generate a stereodefined (E)-alkenylrhodium intermediate Int-90.

4.2 C(sp³)-H functionalization via 1,4-Rh migration

In 2014, Lam's group described a facile synthesis of chiral homoallylic sulfonamide 160 from 5-membered cyclic imine 158 and potassium prenyltrifluoroborate 159 via a Rh(1)/diene asymmetric catalysis (Scheme 45). 124 Allyl-Rh species Int-91 was first generated through transmetalation of potassium prenyltrifluoroborate 159 with [Rh]-Cl. With the less reactive saccharinderived imine 158, it is disfavored to forge the reverse prenylation product 160' with sterical congestion via direct addition of Int-91 to the imine substrate as per the previous report. 125 Instead, an allyl-to-allyl 1,4-Rh migration occurred, furnishing another alkyl-Rh species Int-92. Finally, nucleophilic addition of Int-92 onto cyclic imine 158 proceeded to arrive at the desired homoallylic sulfonamide 160 as the major isomer in decent yield and excellent *enantio*-control. Notwithstanding, the minor isomer 160' was also observed via the direct addition of Int-91 onto cyclic imine 158. It is worth mentioning that the 1,4-Rh migration was a reversible process and the steric hindrance of allyltrifluoroborates may promote the following isomerization of allyl-Rh species Int-94 to afford Int-95. Indeed, with the more sterically hindered allyltrifluoroborates 162 and chiral ligand ent-L26a, homoallylic sulfonamide 163 was produced as a single isomer via nucleophilic addition of Int-93 onto more reactive aldimine 161.

In 2017, Lam's group further reported an enantioselective Rh(1)-catalyzed three-component coupling of 1,3-enynes 164, arylboronic acids 165 and cyclic aldimines 166 (Scheme 46). 126 The

Scheme 44 Rh(ı)-Catalyzed alkenylation of enones and cyclic imines with 2-ethenyl-arylboronic acids

efficient catalytic system of [RhCl(C2H4)2]2/chiral tetrafluorobenzobarrelene L37 enabled a straightforward access to a diverse of branched homoallylic sulfamates 167 bearing tertiary or quaternary carbon stereogenic centers in decent yields (33-77%), high enantioselectivities (up to 99% ee) and excellent diastereoselectivities (in most cases >19:1). The underlying mechanism was proposed as exhibited in Scheme 46. First, transmetalation of arylboronic acid 165 with in situ generated [Rh]-Cl produced the arylrhodium species Int-96. Then, the migratory insertion of Int-96 across 1,3-enynes 164 occurred, furnishing alkenylrhodium species Int-97. Afterwards, Int-97 underwent a reverse alkenyl-toallyl 1,4-Rh migration to produce Int-98, which was considered as the key step of this reaction. Subsequent intermolecular nucleophilic addition of Int-98 to cyclic imine 166 proceeded to form Int-99. The final protonolysis of Int-99 released the homoallylated product 167 with the regeneration of the rhodium complex.

Conclusion and outlook

Among the various rhodium complexes, Rh(1) has mainly been utilized for the direct functionalization of C-H bonds via

Scheme 45 Rh(i)-Catalyzed allylation of cyclic imines with potassium prenyltrifluoroborates

oxidation addition in both directed and undirected patterns. Although some related reactions could also be effected by other transition metals, Rh(1) catalysis provides the advantage of finetuning due to the commercial availability of a diversity of chiral ligands. As illustrated in this review, organic chemists have successfully used Rh(I) catalysis to enable a plethora of asymmetric C-H functionalization reactions including arylation, alkylation, and silvlation, which serve as a versatile and efficient synthetic complement to Rh(II) and Rh(III) catalysis. Despite these impressive progresses, several major limitations still remain in the realm of Rh(1)-catalyzed C-H activation for asymmetric functionalization, such as the requisite of directing group for C-H functionalization, the confine of unactivated C(sp³)-H functionalization into an intramolecular fashion, the lack of applications in forging carbon-heteroatom bonds (e.g., C-O, C-N, C-S, C-X, and C-P) aside from C-Si bonds (partially owing to the competing coordination of heteroatoms with the chiral ligands), and the elusive 1,4-Rh migration to general C(sp³)-H bonds. Therefore, it is still of immense demand to devote more efforts to developing transient directing group strategy or non-directed Rh(1)-catalyzed asymmetric C-H functionalization, uncovering intermolecular asymmetric silylation and unactivated C(sp3)-H functionalization reactions, and designing novel chiral ligands to circumvent the catalyst poison issue by heteroatoms. More importantly, a deeper understanding of the mechanism in Rh(1)-catalyzed asymmetric C-H

Scheme 46 Rh(i)-Catalyzed three-component allylation of cyclic imines with arvlboronic acids and 1.3-envnes.

functionalization reactions is highly desirable to facilitate the rational design of new asymmetric reactions. Additionally, the synthetic implementation in the late-stage functionalization of natural products or other complex molecules also needs to be validated. As such, one can forecast that more novel Rh(I)catalyzed asymmetric C-H functionalization reactions will be well-designed and applicable in the near future.

Conflicts of interest

There are no conflicts to declare.

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