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Mini-review

Chiral metal complexes: Design strategies for precision in asymmetric C–H activation

Devesh Chandra [a], Tammana Sharma [a], Sarthi [a], Sachin [a,b], Upendra Sharma [a,b,*]

[a] C-H Activation & Phytochemistry Lab, Chemical Technology Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur 176061, HP, India
[b] Academy of Scientific & Innovative Research (AcSIR), Ghaziabad 201002, India

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ABSTRACT

Due to their unique design, *chiral metal* complexes play an important role in asymmetric synthesis. In this review, we have focused on the design strategy and its applications in asymmetric C–H functionalization. This review provides a comprehensive overview of chronological development and the future perspective of *chiral metal* complexes. A brief discussion on the relation between the molecular design of transition metal complex and stereo differentiation in products leading to enantiomeric induction is also included.

1. Introduction

Chirality is the fundamental property of nature and is found essential for living organisms. All important molecules for the living organism, i.e., sugars, nucleic acid, DNA, enzymes, etc., are chiral. The synthesis of chiral molecules is one of the most intense research areas of modern organic chemistry due to the potential application of chiral species in medicinal, material, and analytical fields. Synthesis of a chiral molecule requires either a chiral auxiliary or a chiral catalyst. Thus, the design and synthesis of chiral metal complexes are closely related to this study area. There are several examples in nature where chiral metal complexes (from enzymes) trigger the organic transformations in a stereospecific pattern. Cytochrome P-450 is a group of enzymes with a heme group (iron porphyrin complex) in their structure, capable of converting alkane into alcohol stereo specifically. Inspired from such enzymatic reactions, several metal complexes have been synthesized, which can provide a synthetic route for the biased formation of molecules of interest. Thus, the investigation of chiral metal complexes as catalysts is continuously increases in asymmetric synthesis. Indeed, various industrial processes currently utilize chiral metal complexes in their production [1]. Chiral metal complexes are employed to achieve asymmetric C–H activation, emphasizing the significance of chiral metal complexes in imparting chirality to the reaction products.

Chirality on the metal complexes can be induced in two ways: *ligand* induced chirality and *metal* induced chirality (Fig. 1). In the former case, chiral ligands are solely responsible for chirality in metal complexes since the chiral information is conveyed by the coordination sphere in the complexes. The ligands dictate the substrate's entry at the metal center in a stereoselective way for subsequent chemical transformations and transfer the chirality to the final product. Indeed, this is the mainstream of the field. At the end of the 19th century, Werner witnessed another possibility where ligands associated with the metal do not have any inherent chiral information. However, their arrangement around the metal can form enantiomeric complexes [2]. These types of complexes are also known as *chiral-at-metal* complexes, as metal is the source of chirality. For a basic understanding of the *chiral-at-metal* complex, Bauer *et al.* have complied excellent review and is not the focus of current review [3]. Since 1960s, the chiral metal complex has been systematically investigated in organic synthesis and they have found wide applications in asymmetric C–H functionalization.

In this review, we have reviewed the progress made in the design strategy of chiral metal complexes and their applications in asymmetric C–H functionalization.

2. Design strategy of various chiral metal complexes employed in C–H functionalization

Various metal complexes have been synthesized for subsequent applications in asymmetric C–H functionalization. To achieve high enantiomeric excess, the design strategy of the metal complexes plays an important role. This section discusses the basic design strategies of several chiral metal complexes with their stereo induction properties.

* Corresponding author.
E-mail address: upendra@ihbt.res.in (U. Sharma).

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2.1. Chiral paddle wheel catalyst

Chiral paddle wheel complexes are exceptionally excellent catalysts used for enantioselective C–H functionalization. This type of complexes have a larger design spectrum. For instance, considering the dirhodium paddle wheel complex, $Rh_2(OAc)_4$ is the precursor of the complexes, and the final complex consists of dirhodium core surrounded by four ligands. The symmetry of the ligand is the crucial feature in the design of dirhodium paddle wheel complexes, higher the symmetry of the ligand, better the prediction of stereo model in the transition state. Mainly, C1 symmetrical ligands (prolinates, mono-protected amino acids, and carboxamidates) and C2 symmetrical ligands (binaphthylphosphonates or bridged prolinates) are compatible with dirhodium paddle wheel complexes. C1-symmetric ligands leads to complexes with C2– or D2-symmetric conformations, however, C2-symmetric ligands form complexes of D2-symmetry.

To understand the influence of the ligand in the space around the axial active sites of the chiral wheel paddle complexes, a generalized model [4] is illustrated in Fig. 2. Such a complex can be represented by a wheel having a plane (O-M−O) with metal in the center. To achieve high enantioselectivity, the complex geometry must feature such a pattern which can favour only one enantiotopic substrate trajectory [5]. This implies the sterically blocking groups from the equatorial ligands must point toward the plane. With these models, one can consider the symmetries inherent in such systems [6]. Different transition metal centres are expected to result in varied reactivity and selectivity in catalytic transformations. Therefore, the design of new chiral paddle wheel complexes has been explored, incorporating various metal centres i.e., Rh, Ru, Co, Bi, etc [7,8].

2.2. Metal complexes with porphyrin ring as ligands

Porphyrin is an important class of molecules not only as the catalyst but also highly important for life. Menghini demonstrated the presence of iron in the blood, and Hoppe and Seyler in 1871 isolated porphyrins from blood as iron porphyrin complex i.e. Heme. Heme is responsible for cellular respiration and several other metal porphyrin complexes also play key roles in biological processes. Metalloporphyrins have been widely investigated as biomimetic analogues of cytochrome P-450 (hemoproteins), which can demonstrate selective catalytic mono oxygenation reactions *via* the generation of high valent metal–oxygen complex intermediate (See Fig. 3).

For C–H functionalization, carbene and nitrenes are most often used substrate which metalloporphyrins can catalytically decompose, apparently forming metal carbenes/ nitrenes surrounded by chiral porphyrin as the key intermediates. The chiral ligand environment and metal coordination modes serve the chirality during the synthetic transformation of the reactant into the product.

2.3. Metal complexes with chiral cyclopentadienyl as ligands

Transition metal complexes of cyclopentadiene possess a special place in organometallic chemistry. Owing to the importance of cyclopentadiene metal complexes in organic synthesis, the idea of synthesizing chiral counterpart of cyclopentadiene ligands was triggered in date back to 1978. Several chiral cyclopentadiene ligands based on the chiral natural products i.e., (−)-menthol, (+)-tartaric acid, and (+)-camphor were synthesized. A brief chronological development in the design of chiral cyclopentadienyl is depicted in Fig. 4 [9].

In 2012, Cramer group designed a new chiral C2 symmetrical Cp ligand complex with two equal substituents on the sidewall and a bulkier substituent at the back wall of the ligand for asymmetric C–H activation. This kind of design modification is crucial to achieve high enantiocontrol governed by stereo-electronic repulsion in transition state. The C2 symmetry of the chiral Cp was also found critical, as both faces of the ligand became equally accessible after metalation, avoiding the formation of diastereomer of metal–ligand complex. The bulkier substituent at the back wall controls the entry of incoming ligand from one end only

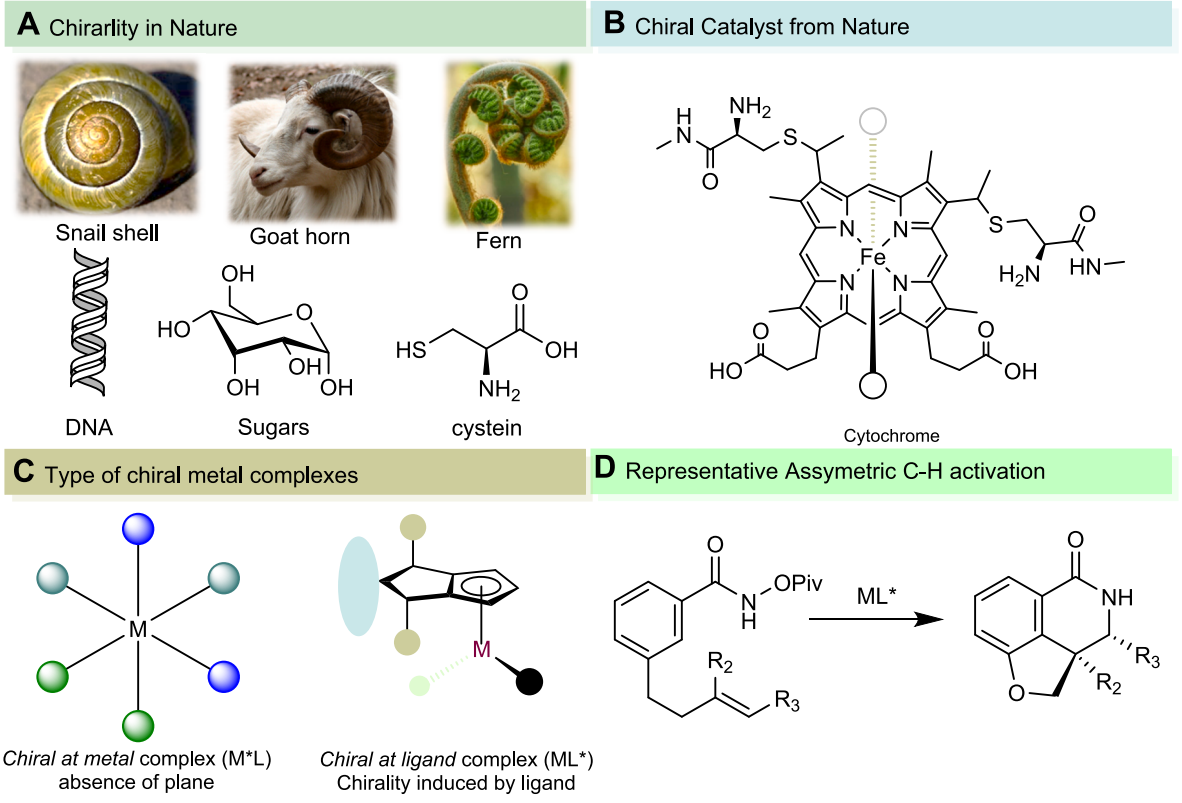


Fig. 1. Chirality from nature to laboratory.

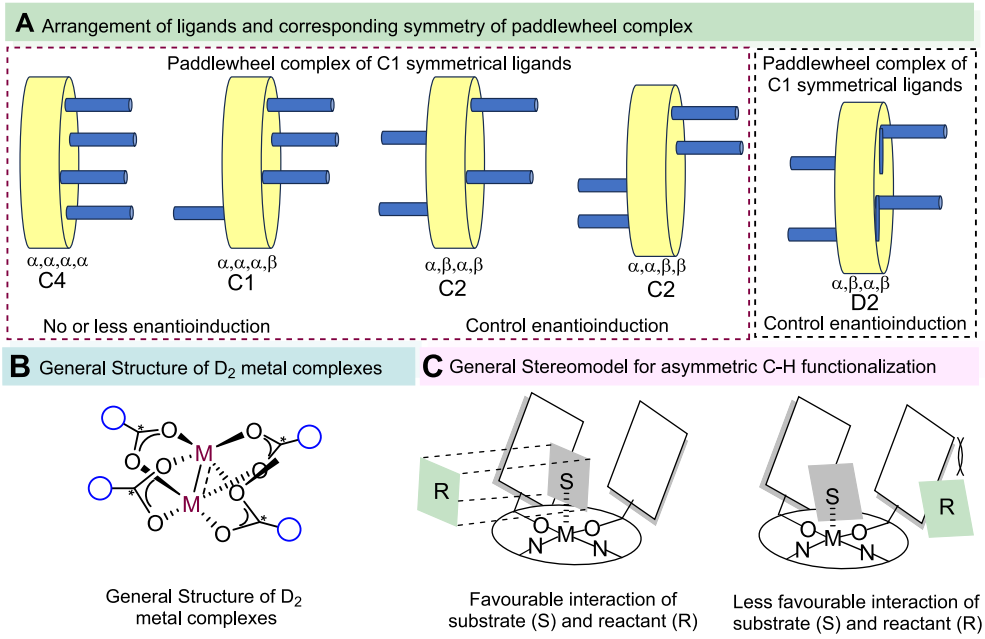


Fig. 2. Chiral paddle wheel complexes.

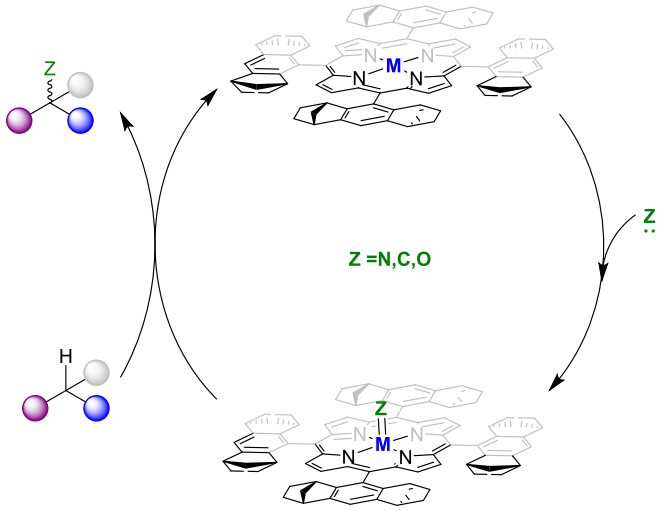


Fig. 3. Metal porphyrin complexes in asymmetric C–H functionalization.

and the substituent at the sidewall generates the stereo repulsion, governing the orientation of the ligands present in metal complex.

2.4. Metal complexes with planar chiral ligands

Planar chirality is another important class of chirality. Several cyclopentadienyls based planar complexes were also synthesized by Cramer, Waldmen and You group to control the enantioselectivity in C–H functionalization event [10].

In 2022, Wang group designed a protocol for the construction of chiral pseudo *ortho*-disubstituted [2.2]paracyclophanes with C2 symmetry and chiral skeletons composed of benzene rings were explored for their potential use as η^6-coordinating groups. The ligand incorporates two benzene rings, providing four benzene faces. To establish an effective chiral environment in the surroundings of the metal [M] center, it was hypothesized that alkyl groups would serve as suitable substituents on [2.2]paracyclophane. This configuration offers the flexibility to adapt the chiral environment around the metal by varying the substituent. Furthermore, it was anticipated that the stability of the arene metal complexes would be enhanced. Additionally, the unique *trans*-annular electronic interactions among the benzene rings in the paracyclophane structures contribute to the improved stability of these complexes.

2.5. Miscellaneous

Other than the above-mentioned chiral complexes, various other complexes i.e. Pincer complexes [11], Salox complexes [12–14] and *Chiral at metal* complexes [15] also impart important role in enantioselective C–H functionalization.

3. Applications of chiral metal complexes in asymmetric C–H functionalization

3.1. Chiral paddle wheel catalyst in asymmetric C–H functionalization

Inspired by C–H insertion of metal-carboxylate catalyst, a series of chiral paddle wheel rhodium complex for enantioselective C–H activation have been designed (Fig. 5) [16–18]. In 1986, Cotton and coworker disclosed the synthesis of chiral dirhodiumtetracarboxylato complexes [19] Later, in 1990, *N*-sulphonated L-proline were used as ligand by McKervey for the synthesis of chiral Rh paddle wheel complexes.

These complexes were further utilized for the asymmetric intramolecular C–H insertion of diazo compounds. However only moderate enantioselectivity were observed [16] In 1993, Hashimoto and Ikegami modify the complexes and utilized *N*-phthaloyl-(*S*)-phenylalanine as ligand to increase the efficiency of **Rh-1** complexes for enantioselective C–H insertion. **Rh-1b** was found to be suitable complex for enantioselective C–H insertion with 80 % ee (Scheme 1**a**) [20] Hashimoto developed a protocol for the intermolecular 1,3-dipolar cycloaddition of α-diazo ketones with internal alkynes using newly designed **Rh-1d,** where thalamido ring was designed with one extra benzene ring. This reaction proceeded with moderate to high enantiomeric excess in cycloaddition reaction [21] In 2001, Hoshimato group used **Rh-1a** for the formation of benzofuran-3-ones bearing anallenic group with up to 79 % ee [22].

In 2002, Hoshimato used the analogy between carbene and nitrene and applied chiral paddle wheel complex for enantioselective

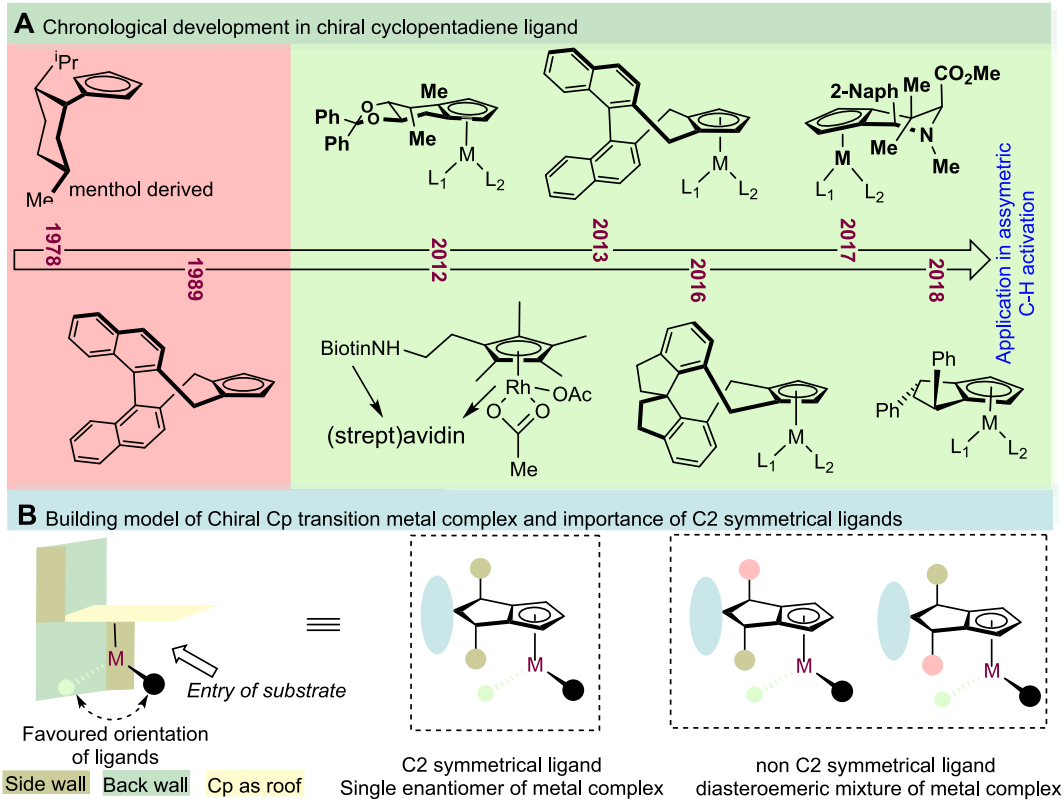


Fig. 4. Chiral cyclopentadiene in asymmetric synthesis.

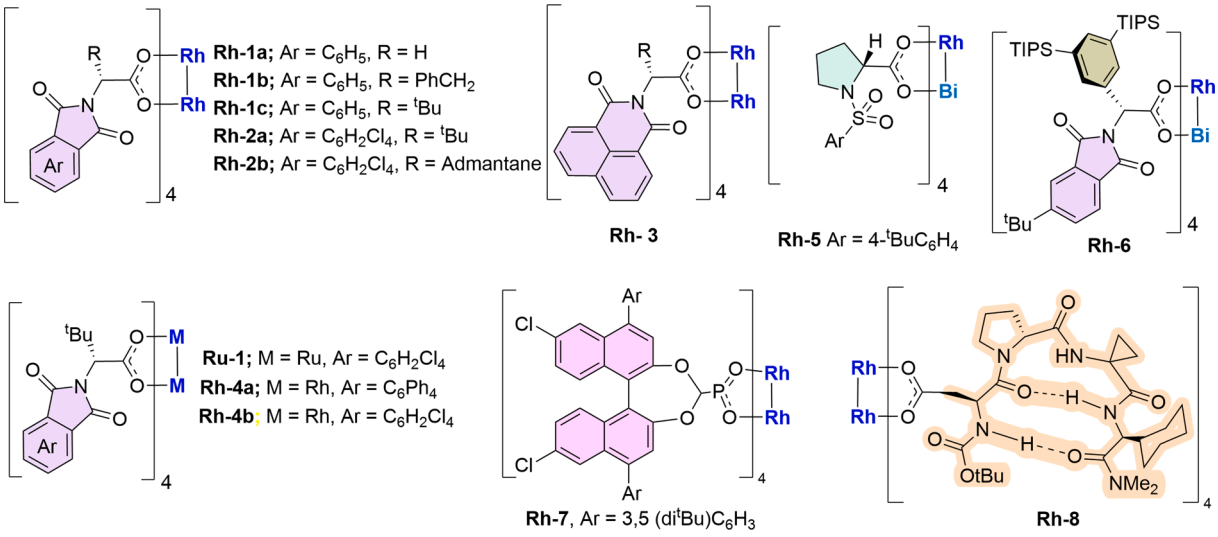


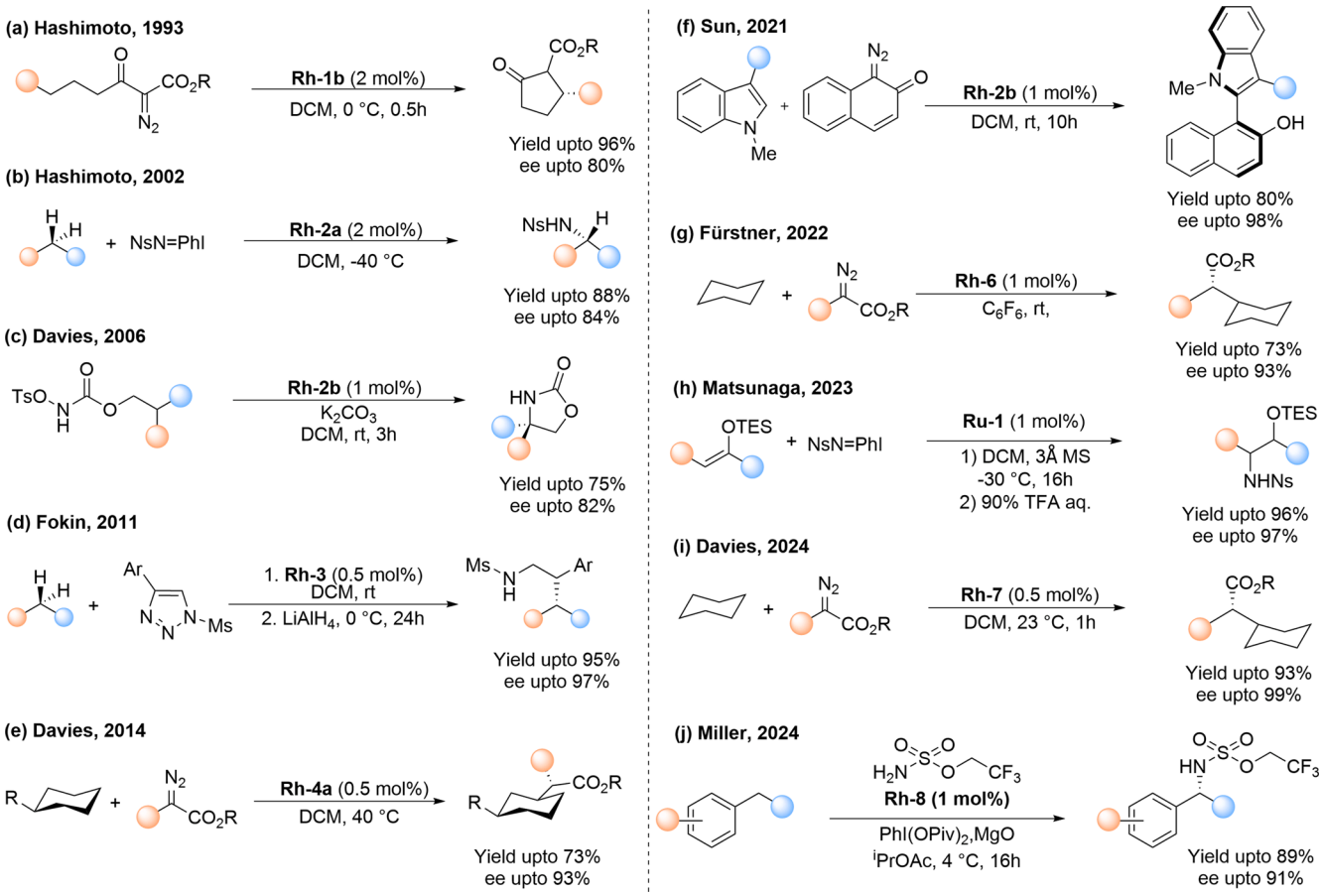
Fig. 5. Chiral paddle-wheel complexes.

amidation. A new complex **Rh-2a** was synthesized through the electronic tuning. **Rh-2a** demonstrated asymmetric induction in the reaction of [(4-nitrophenyl)sulfonylimino]phenyliodinane and indan (Scheme 1**b**) [23].

Later, Reddy and Davies modified the complex and replaced *tert*-butyl group of ligand to form a new complex **Rh-2b** with adamantane. **Rh-2b** was found to be effective catalyst for intramolecular enantioselective C–H amination of *N*-tosyloxycarbamate. (Scheme 1**c**) [24].

Fokin and coworkers in 2011, used the **Rh-3** for C–H amination of the unsaturated C–H bond by 1-sulfonyl-1,2,3-triazoles for the synthesis of chiral amine derivatives (Scheme 1**d**). 1-sulfonyl-1,2,3-triazoles served as precursor for the Rh-nitrene intermediate [25].

In 2014, Davies group efficiently developed a methodology for the C–H alkylation of primary C–H bonds using **Rh-4a**. The developed protocol was efficiently applied to functionalized complex scaffolds such as (−)- α-cederene and steroids (Scheme 1**e**) [26]. Later, the same group observed the chemo-selective C − H functionalization of substituted cyclohexane with high enantioselectivity using chiral paddle wheel complex **Rh-4b** *via* desymmetrization [27]. In 2018, heterobimetallic chiral paddle wheel complex **Rh-5** of bismuth and rhodium was developed by Davies group [28] for enantioselective C–H insertion. Sun group in 2022 developed a novel protocol for a highly efficient atroposelective



Scheme 1. Chiral paddlewheel complexes in asymmetric C–H functionalization.

construction of axially chiral arylindoles catalyzed by rhodium metal catalyst **Rh-2**. Various chiral C2-arylindoles were isolated in moderate to good yields with excellent enantioselectivity in the presence of chiral rhodium catalyst **Rh-2** under mild reaction conditions (Scheme 1**f**) [29]. Further, Furstner in 2022 designed heterobimetallic complex **Rh-6**, which provides C–H alkylation of unsubstituted cyclohexane, cyclic hydrocarbons alkene, and alkynes (Scheme 1**g**) [30]. In 2023, Matsunaga group reported enantioselective amination of enol silyl ethers using the diruthenium **Ru-1** complex. The reaction involves nitrene transfer with silyl ethers (Scheme 1**h**) [31]. Recently Davies group designed a D4 symmetrical chiral paddle wheel complex **Rh-8** for asymmetric functionalization of unactivated C–H bonds [32] C2 symmetrical ligand binaphthylphosphate was utilized for the synthesis of D4 symmetrical **Rh-7** complex. The conformational mobility of the **Rh-7** was found exceptional for C–H functionalization of cyclohexane providing functionalized cyclohexane in 99 % ee **(**Scheme 1**i)**.

A series of new class of peptide based dirhodium(II) complexes were described by Miller group in 2024. Aspartic acid-containing *β*-turn-forming tetramers were used as ligands in these chiral paddle wheel complexes. The utility of these catalyst were illustrated by the enantioselective benzylic C(sp^3)–H bond amination with excellent enantioselectivity, even for substrates that present challenges with previously reported catalyst systems **(**Scheme 1**j)** [33].

3.2. Porphyrin-metal complexes as catalysts in asymmetric C–H functionalization

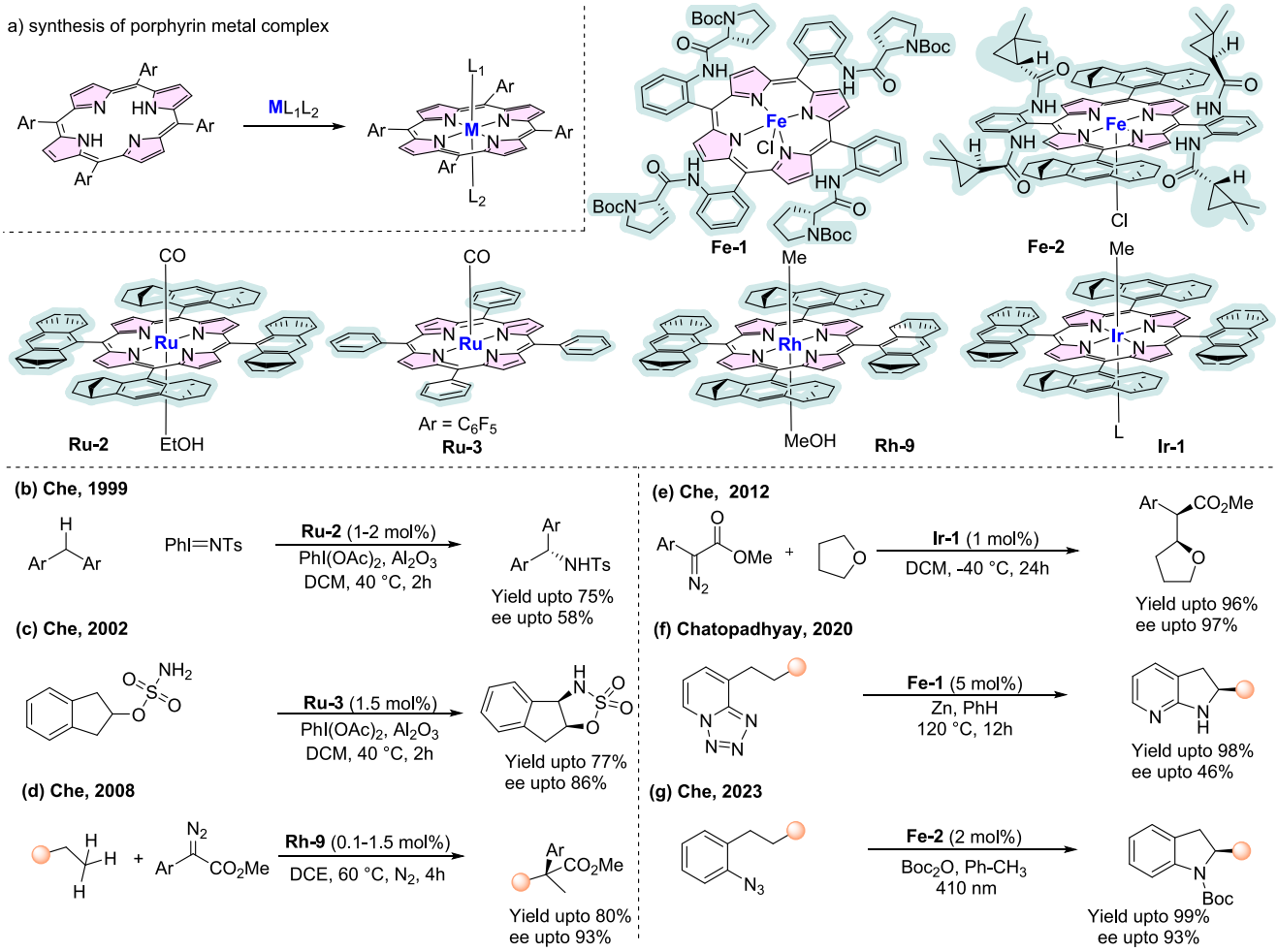
Che group in 1999 introduced a new decorum for asymmetric saturated C–H bond amidation *via* a ruthenium porphyrin catalyst **Ru-2** where the Halterman's method was used for the synthesis of chiral porphyrin ring (Scheme 2**a**). The **Ru-2** catalyst complex was very effective for C–H amination of ethylarene using *N*-tosyliminobenzyliodinane (Scheme 2**b**). Intermediate of the reaction was isolated and characterized, which lead to an enantioselective C–H insertion of the NTs group [34].

In 2002, **Ru-2** porphyrin complex was further applied for intramolecular amidation of sulfamate esters. Interestingly, the reaction proceeds with the formation of cis product only with high enantiomeric excess. (Scheme 2**c**) [35].

Inspired by seminal work of Callot and Sulick group on carbenoid insertions, Che and coworkers developed a protocol for the enantioselective C–H carbene insertion using **Rh-9** as catalyst. **Rh-9** provides the metal carbene complex with diazo compound, which upon C–H insertion with alkanes gives corresponding alkylated products (Scheme 2**d**). Porphyrin ligands impose a significantly larger steric hindrance for secondary C–H bonds than for primary C–H bonds thus provides higher selectivity towards primary C–H alkylation [36].

In 2012, Che group designed a chiral **Ir-1** porphyrin complex for C–H carbene insertion. The complex was synthesized from $Ir(COD)Cl_2$ on treatment with D4-symmetric Halterman porphyrin ligand followed by $NaBH_4$ and MeI. C–H alkylation of tetrahydrofuran with methyl phenyldiazoacetate proceeded anti alkylated tetrahydrofuran as major product with high enantiomeric excess and excellent yield at low temperature (Scheme 2**e**) [37].

In 2020, Chatopadhyay group disclosed the utilization of a chiral iron porphyrin complex, **Fe-1**, as a catalyst for the intramolecular C–H amination of 1,2,3,4-tetrazoles. This approach led to the formation of azaindolines. Despite the promising results, the enantiomeric excess achieved was only moderate, reaching up to 46 %. (Scheme 2f) [38]. Che and coworkers modified porphyrin ring and synthesized the iron porphyrin complex **Fe-2** with highly earth-abundant iron metal and applied it to catalytic C–H amination of C(sp^3)-H bond in intermolecular



Scheme 2. Porphyrin metal complexes in asymmetric C–H functionalization.

fashion for the synthesis of protected indoline derivatives (Scheme 2g). DFT calculations revealed that the reaction proceeds by a stepwise HAT/rebound mechanism. The larger steric repulsion in transition state were explained by the larger distortion of the substituents on the porphyrin ligand, which determined the enantioselectivity of product [39].

Cobalt complexes with chiral porphyrin ligands, as stable 15e$^-$ metalloradicals can work as efficient catalysts for asymmetric synthesis involving radical pathways [40]. In this respect, Zhang and coworkers designed a series of chiral cobalt complexes, which was coordinated by D2-symmetric chiral amidoporphyrin. (Scheme 3). These metal-stabilized organic radicals which can serve as key intermediates to undergo subsequent radical reactions, such as radical addition to C=C bonds and hydrogen-atom abstraction of C–H bonds, as well as radical substitution for C–C/C–N bond formation, leading to the development of new catalytic radical processes.

Further **Co-1** was demonstrated as effective metalloradical catalyst (MRC) for asymmetric 1,5-C–H intramolecular alkylation leading to the synthesis of 5-membered sulfolane derivatives with high stereoselectivities (Scheme 4**a**) [41].

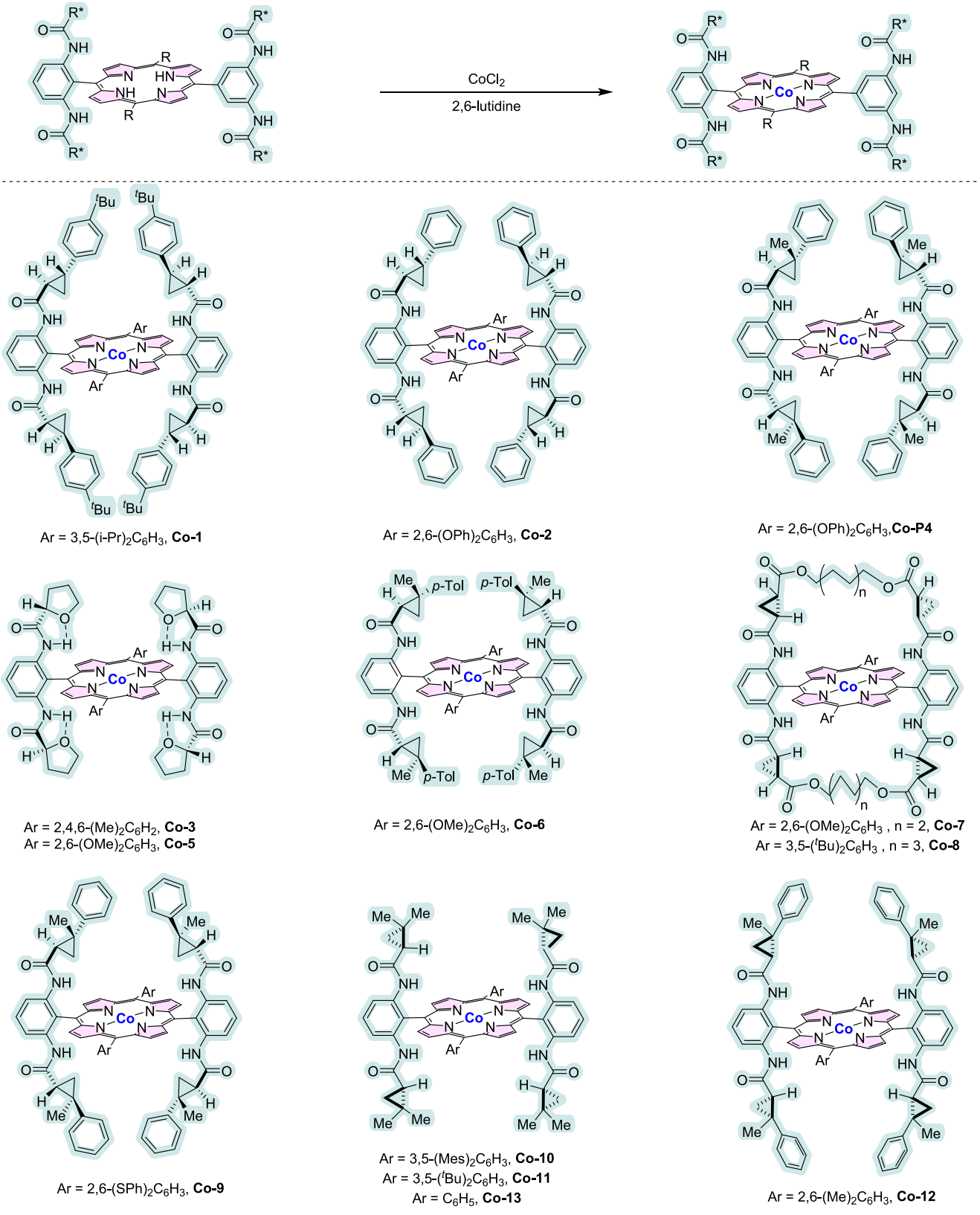
Next same group examined the o-aminobenzaldehyde-derived hydrazone under metalloradical catalysis **Co-2** to deliver the stereoselective synthesis of 2-arylindoline *via* intermolecular radical C(sp^3)-H alkylation (Scheme 4**b**). This protocol offers a range of substituted 2-arylindoline with high yield and enantioselectivity. Bis-TEMPO capped intermediate were also isolated and characterized by XRD during mechanistic studies, which suggest the reaction proceeded *via* MRC pathway [42,43].

Harnessing the concept of MRC, radical cyclization of sp^3 C–H bonds were demonstrated by Zhang group for the stereoselective synthesis of different unsaturated five membered heterocycles. Aldehyde derived tosylhydrazone were subjected under Co-3 to provide a range of pyrrole, furans and thiophene in stereoselective manner via H-atom abstraction and radical substitution (HAA-RS) (Scheme 4**c**). Steric environment of the ligand pocket in cobalt-porphyrin complex majorly effect the enantioslectivity of the product [28].

In 2019, Zhang group report the first enantioselective amination by cobalt porphyrin complex. **Co-4** was found to be suitable catalyst for the enantioselective intramolecular 1,6-C(sp^3)-H radical amination of diverse sulfamoyl azides to get six-membered chiral heterocyclic sulfamides with a high functional group tolerance [44] (Scheme 4**d**). The enantioselectivity of the product was accomplished by careful identification of a bulkier porphyrin ligand with a proper chiral environment which differentiate the two prochiral faces of the Co-alkyl radical for C–N bond formation.

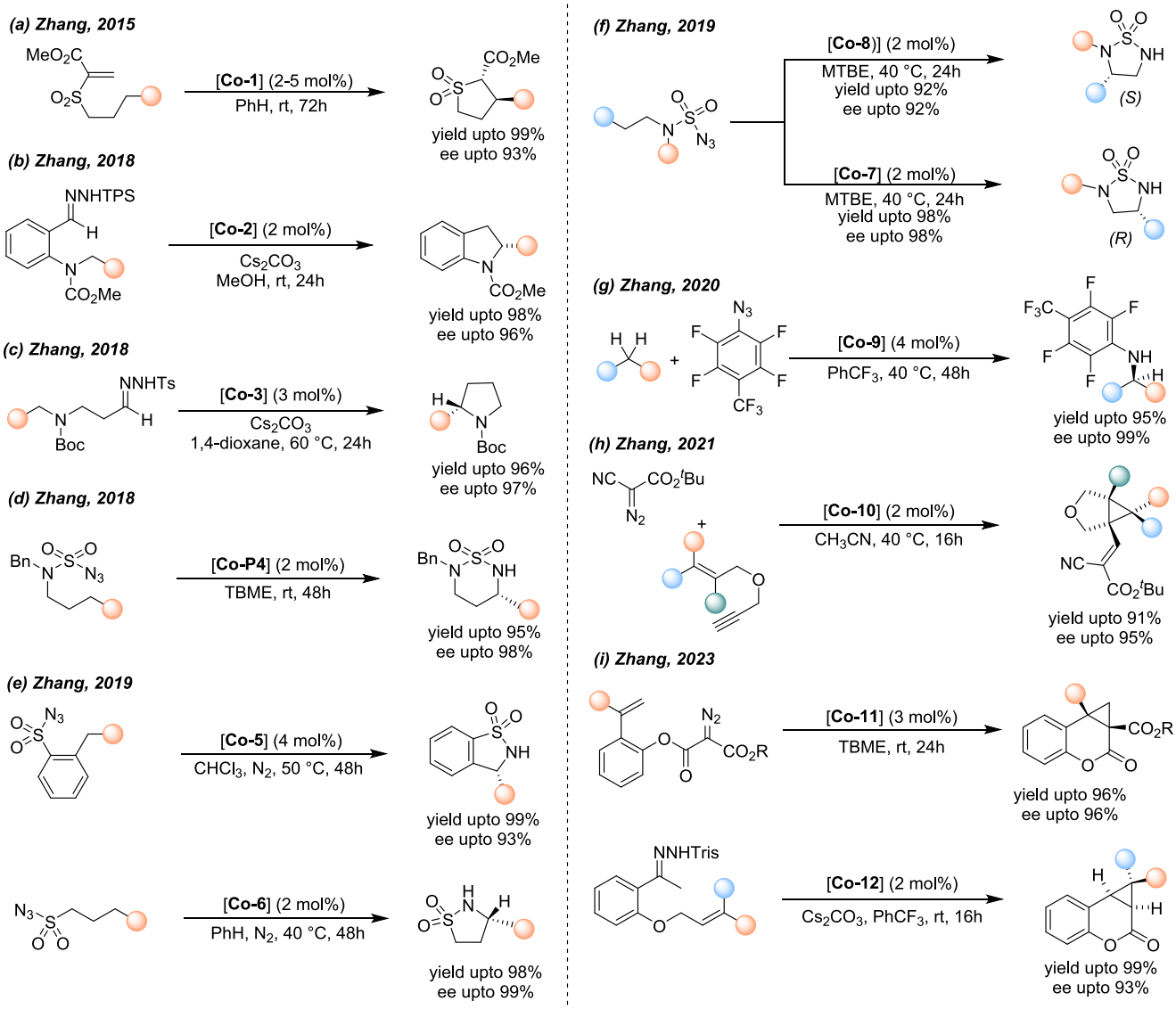
In 2019, Zhang group reported another intramolecular 1,5- C–H amination of aryl and alkyl sulfonyl azides with **Co-5** and **Co-6** respectively. These sulfonyl azides bearing different groups with different electronic properties afforded excellent enantioselectivities and high yield (Scheme 4**e**) [45]. *In-situ* generated Co(III)-aminyl radical undergo stereoselective 1,5-H abstraction to give chiral five membered heterocyclic sulfonamide.

Zhang's group extended their work on the porphyrin-based cobalt metal complexes and reported new D2-symmetric chiral porphyrins ligands for metalloradical catalysis. These new ligands have two chiral amide units on each side of the porphyrin plane connected with alkyl bridges (called "*HuPhyrin*"). *HuPhyrin*-based Co(II) complexes presented



Scheme 3. Synthesis of cobalt porphyrin complexes.

as a new generation metalloradical catalysts, where the metal-centered *d*-radical is present within a cavity with much more rigid chiral system and good hydrogen-bonding formation capability [46]. In 2019, Zhang and coworkers came up with enantiodivergent cyclization with two different Co(II) complexes of HuPhyrin ligands (**Co-7** and **Co-8**) having the same chiral amidoporphyrin backbone with different alkyl bridge. The key feature of this work was enantiodivergent intramolecular amination with sulfamoyl azide leading to strained cyclic sulfamides with



Scheme 4. Cobalt porphyrin complexes in asymmetric C–H functionalization.

both enantiomers in high stereoselectivities (Scheme 4**f**) [47].

In 2020, Zhang group extend the strategy of asymmetric metalloradical C–H functionalization to intermolecular radical amination. **Co-9** was found to be a suitable HuPhyrin-Co complex for amidation of carboxylic acid esters using fluoroaryl azides to yield chiral amino acid derivatives (Scheme 4**g**) [48].

In 2021, Zhang group also reported asymmetric bicyclization of 1,6-enynes with diazo compounds involving stepwise radical pathway mechanism by using **Co-10** complex. The main feature of this reaction was control of enantioselectivity and diastereoselectivities under milder condition with high yield (Scheme 4**h**) [49].

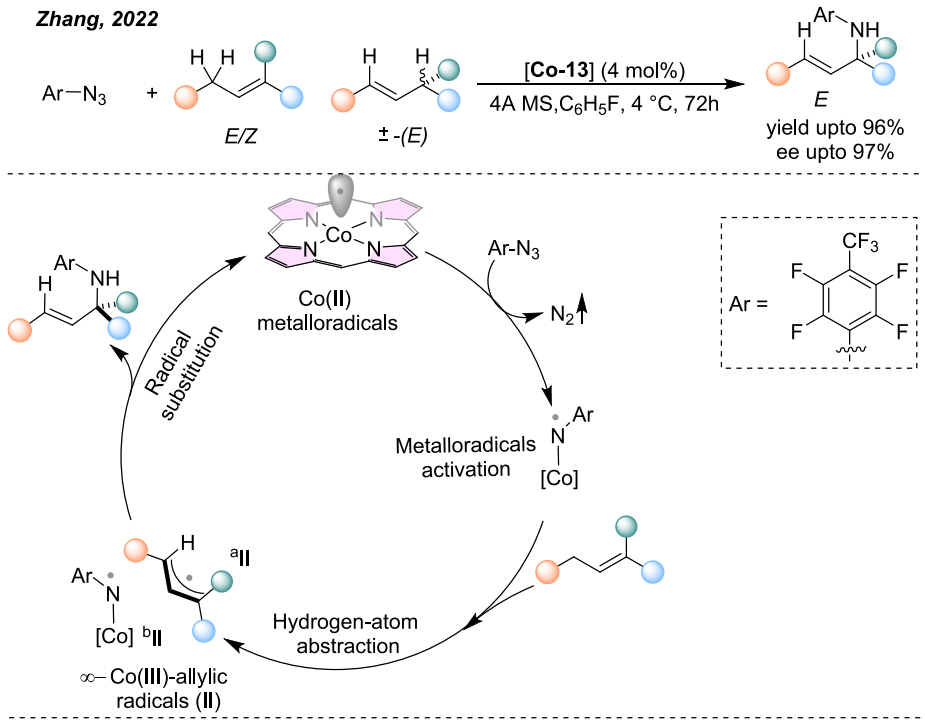
In 2023, Zhang group achieved stereoselective bicyclization of 2-vinylaryl diazomalonates leading to the formation of cyclopropane fused chromanones and chromanes. This asymmetric radical bicyclization *via* Co(II)-metalloradical system involved the two different porphyrin ligands, applicable for both diazomalonates and α-aryldiazomethanes derivatives. The key feature of the report was control on the stereoselective product by two new radical paths, which was modulated by two different cobalt complexes **Co-11** and **Co-12** of D2-symmetric chiral amidoporphyrin to form a suitable rigid environment that enhanced the mutual noncovalent attractive interactions (Scheme 4**i**) [50].

Recently, Zhang group developed a protocol for the intermolecular amination of allylic C–H bond with aryl azides. Despite possibilities of multiple pathways being radical reaction, the authors successfully got the desired product with high stereoselectivity. In proposed mechanism the first step involve metalloradical activation of azide by a Co(II) complex (**Co-13**) tuned with porphyrin ligand by forming a pocket-like environment. In next step α-Co(III)-aminyl radical cause *in situ* hydrogen atom abstraction (HAA) from allylic C–H bond of alkene followed by amino radical substitution with allyl radical. The key feature of this report was highly chemoselective and regioselective synthesis of important α-tertiary amino acid derivatives with high yields (Scheme 5) [51].

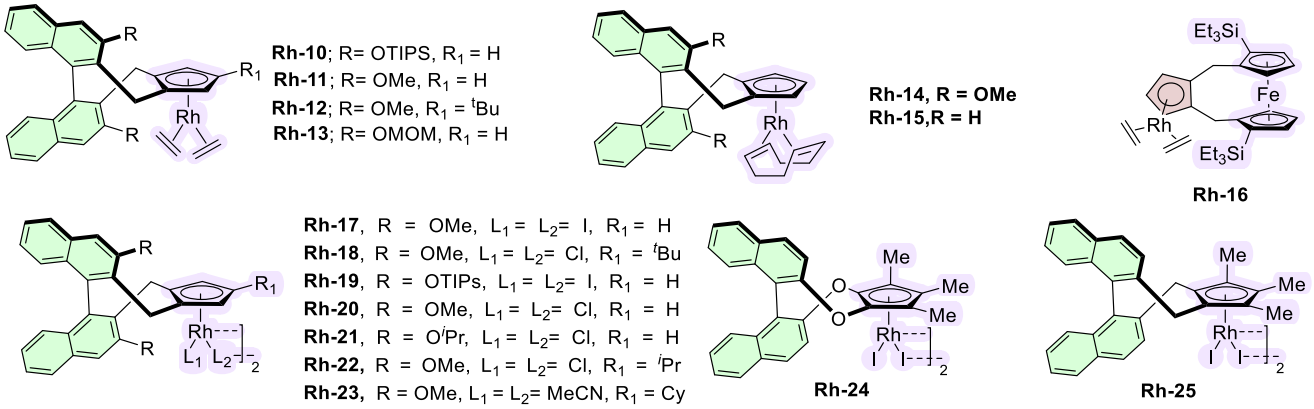
3.3. Chiral cyclopentadiene metal complexes as catalyst in asymmetric C–H functionalization

Cramer group introduced a class of chiral cyclopentadienyl metal complexes with adjustable chiral pockets (Scheme 6).

The authors reported the **Rh-10** catalyzed enantioselective allylation of benzamides using allenes at low temperature. Oxidation of the Rh(I) complexes **Rh-10** with dibenzoyl peroxide provides active Rh(III) carboxylate species. The chiral backbone of the ligand, bulkier



Scheme 5. Cobalt porphyrin complexes catalyzed asymmetric C–H amidation.



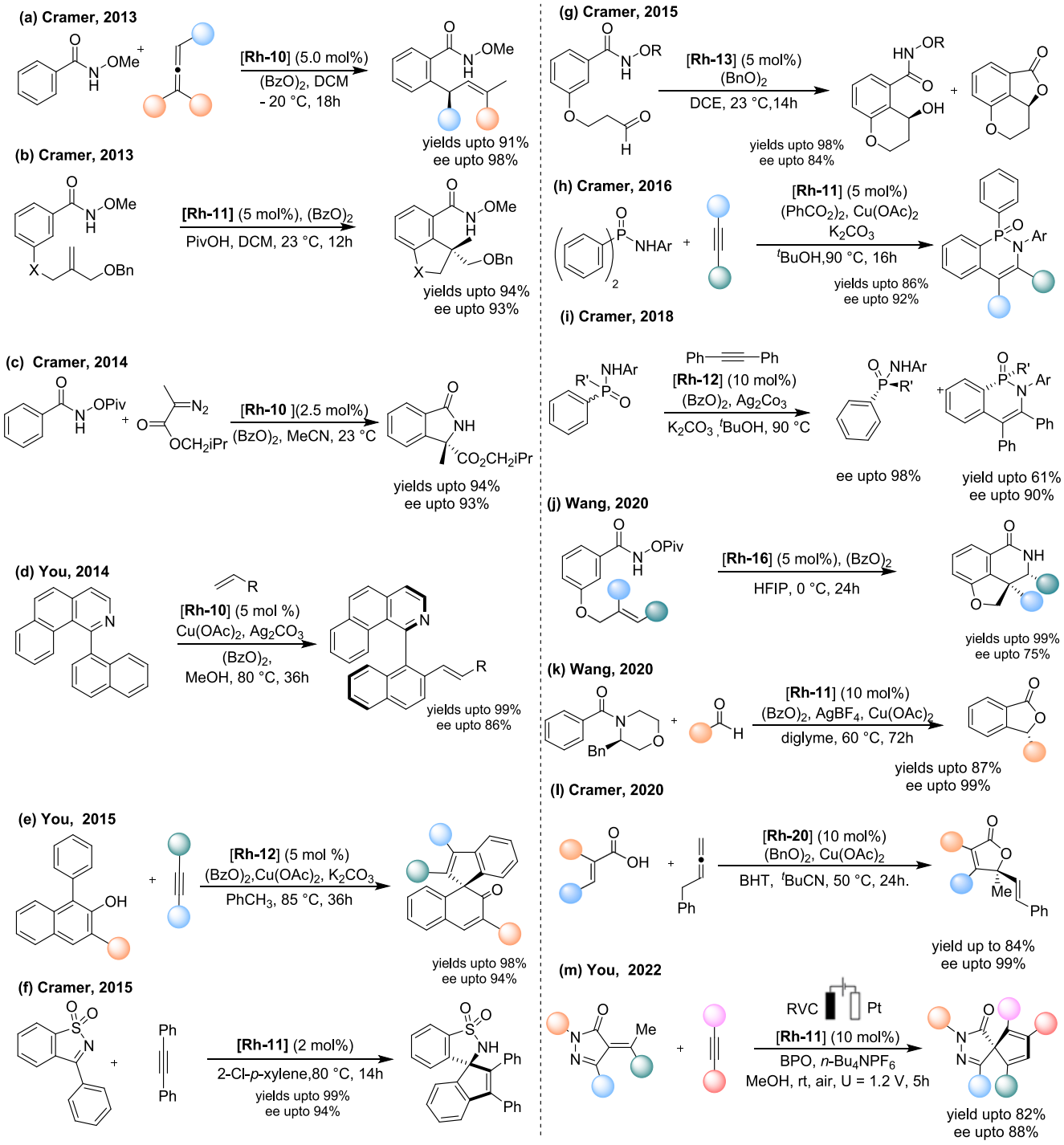
Scheme 6. Rh chiral cyclopentadienyl complexes used in C–H activation.

substituent at 3,3′ position of biaryl and temperature all affect the selectivity of product. The developed protocol showed excellent selectivity with high yields (Scheme 7**a**) [52]. Cramer group further extended the scope of the developed chiral **Rh-11** catalyst for enantioselective hydroarylation of alkenes. The developed method furnished functionalized dihydrobenzofurans with moderate to high yields. A wide range of alkenes reacted efficiently under the developed methodology. Methoxy substituent at ortho position of biaryl backbone of the **Rh-11** enhanced the selectivity of the reaction (Scheme 7**b**) [53].

In 2014 a mild asymmetric synthesis of isoindolones were carried out using a rhodium complex (**Rh-10**) *via* C–H annulation of arylhydroxamates and diazo compounds. Diazo components were found to serve as one carbon component[54]. The origin of enantioselectivity was rationalized by the stereochemical model as depicted in Fig. 6 hydroxamate group favored orientation away from the bulky *ortho*-OTIPS, and carbene unit follow the favoured stereochemical model A to give the major product (Scheme 7**c**).

Zheng and You constructed axially chiral biaryls by direct olefination of various substituted biaryl scaffolds. The axially chiral biaryl moieties were synthesized in high yields with good enantioselectivity using a chiral **Rh-10** catalyst. Further the synthesized products have been demonstrated to be appropriate ligands in rhodium catalyzed conjugate addition reaction of phenyl boronic acid to cyclohexanone (Scheme 7**d**) [55]. In 2015, You group disclosed enantioselective annulative dearomatization of naphthols with internal alkynes *via* chiral rhodium catalyst **Rh-12**. The reaction unveils the conversion of simple naphthol derivatives into chiral spirocyclic *β*-naphthalenones (Scheme 7**e**). Various substituted naphthols and alkynes furnished the product smoothly. Further dueteration experiments were also carried to get the insight of the mechanism [56]. Cramer group uncovered a chiral rhodium(III)-catalyzed formation of spirocyclic indenyl sultams. The reaction occurs *via* enantioselective [3 + 2] annulation of ketimines and alkynes. The product was obtained in high yield and e.r (Scheme 7**f**) [57].

Cramer group has extended the library of chiral cyclopentadienyl ligands and their rhodium complexes. Moreover, the potential of these chiral catalyst (**Rh-13**) was explored by carrying out the reaction of aryl hydroxamate to synthesize biologically significant hydroxychromane



Scheme 7. Chiral cyclopentadienyl Rh(I) complexes used in C–H functionalization.

and phthalide structures. The furnished products were isolated in high yield and enantioselectivity (Scheme 7**g**) [58]. Cramer group in 2016, reported chiral **Rh-11** catalyzed enantioselective formation of cyclic phosphinamides containing a phosphorus central chirality. The authors observed that the use of base enhanced the e.r. by reducing the reversibility of the *cyclo*-metalation step. Further, the synthesized product was converted to P(III)-chiral compounds (Scheme 7**h**) [59].

Cramer group further developed a new trisubstituted Cp ligand based on axially chiral Cp ligands. The selectivity of **Rh-12** is amplified *via* introduction of a bulky group as a third substituent at the central position of the Cp ring. The reaction proceeds *via* kinetic resolutions pathway. The advantages of these trisubstituted ligands are showcased by C–H activation of amides furnishing compounds with stereogenic phosphorus(V) atoms (Scheme 7**i**) [60].

In 2020, Wang group constructed a new class of C2-symmetric, planar chiral Cp ligands based ferrocene scaffolds. The catalytic efficiency of these chiral ferrocenyl-Cp metal complexes has been demonstrated by **Rh-16** catalyzed enantioselective intramolecular amidoarylation of olefin-connected benzamides *via* C–H activation. Various substituted benzamides delivered the product in good yields with high enantiomeric excess (Scheme 7**j**) [61].

Later Wang group, uncovered chiral **Rh-11** catalyzed Grignard type addition for the synthesis of chiral 3-substituted phthalides. Mechanistically, the reaction initiated by activation of C(sp^2)–H bond of

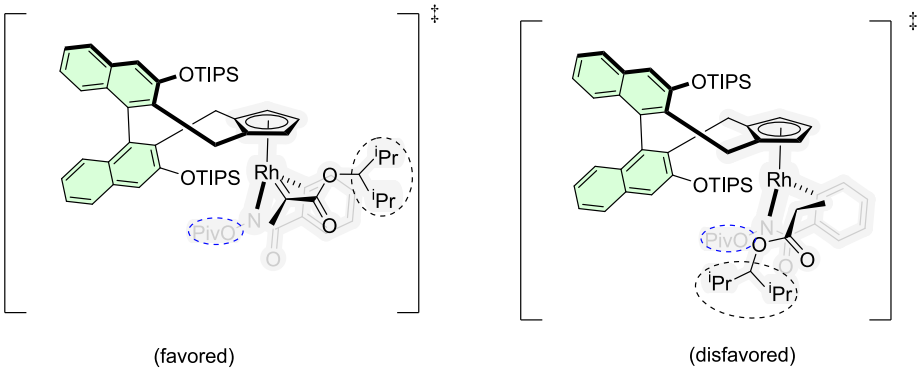


Fig. 6. Stereochemical modal for the scheme 7c

benzamide, followed by the addition of aldehyde, than finally lactonization (Scheme 7**k**) [62]. Further continued, Wang group synthesized a new class of chiral ligands with C2-symmetric chiral bridged-ring-fused Cp and their corresponding rhodium catalyst. The synthesized chiral catalyst was effectively applied to the enantioselective C–H functionalization of *N*-methoxybenzamides and quinones. The reaction furnished a sequence of chiral hydrophenanthridinones products [63].

Cramer group in 2020, reported a chiral Cp ligand having a semi-saturated H8-binaphthyl backbone. The potential of the developed catalyst was demonstrated by carrying out the reaction of acrylic acids with allenes. Chiral **Rh-14** was used as catalyst for this [4 + 1]-enantioselective annulation. (Scheme 7**l**) [64].

In 2022, You and Mei proposed the first illustration of the electrochemical construction of spiropyrazolones by chiral **Rh-11** catalyzed enantioselective C–H annulation with internal alkynes in an undivided cell. The method smoothly proceeds with several chiral spiropyrazolones in high yields and enantioselectivities. Preliminary mechanistic experiments revealed the oxidation-induced reductive elimination is vital for spiroannulation (Scheme 7**m**) [65].

Song group in 2017, design chiral Rh(III) complex i.e. **Rh-17** and further synthesized the many enantioenriched moieties with a tetra-substituted chiral center *via* **Rh-17** catalyzed enantioselective C − H annulation of indolehydroxamic acid and diazo ester (Scheme 8**a**) [66]. In 2018, Cramer and Li group independently reported **Rh-17** catalyzed enantioselective C–H functionalization of sulfoximine yielding a central chirality at sulfur atom. Mechanistically, it was found out that chiral carboxylic acid and **Rh-17** synergistically induce the enantioselectivity in developed protocol (Scheme 8**b**) [67–68]. Li group in 2019 reported **Rh-20** catalyzed asymmetric [3 + 2] *trans*-annulation of amides with azabicyclic olefins for the construction of *cis*-fused dihydrocarbazoles *via* C–H activation. Herein two diverse classes of arenes were utilized as valuable substrates (Scheme 8**c**). The authors were able to isolated chiral rhodium intermediate, confirming its role in inducing chirality [69].

Chiral **Rh-22** complex was utilized for asymmetric olefinic C–H functionalization of acrylamides with allenes to get α,β-unsaturated γ-lactams with a quaternary chiral center with high enantioselectivities under milder condition. Allene act as a one-carbon unit in [4 + 1]-annulation and various functional groups were well tolerated under the devloped condition (Scheme 8**d**). [70].

A synthetic route for the construction of acyclic enantio-enriched aryl/alkyl sulfoximinesc and cyclic benzothiazines *via* an efficient KR-based C–H functionalization with **Rh-23** was developed by Cramer. Various functional group were well tolerated on both the coupling partners and the product and the remaining substrate were obtained in high yields and enantioselectivity (Scheme 8**e**). Post-transformation of the products was also carried out to synthesize, key intermediates of two pharmacologically significant kinase inhibitors [71]. Li group in 2019 reported the construction of 2,3′-biindolyls *via* integration of C–H activation and nucleophilic alkyne cyclization using **Rh-17**. The reaction proceeded *via* oxidative coupling of indoles and *ortho*-alkynylanilines followed by alkyne cyclization (Scheme 8**f**). A highly enantioenriched rhodacyclic intermediate was isolated as a single isomer from a stoichiometric reaction of a 2-methylindole and (R)-**Rh-17**. In crysal structure of intermediate**,** bulky iodide group is disposed distal to the steric shielding group of the Cp^E ligand. The orientation of ligands around the Rh(III) center provides direct support to the model proposed in Fig. 4b [72].

Later, Li and coworkers disclose the concept of integrating C–H activation and chirality transfer and developed **Rh-20** catalyzed spiroannulation between nitrones and quinone diazides under milder reaction condition. The study suggest that an atropomerically metastable biaryl intermediate undergoes axial to central chirality transfer in this protocol to provide chiral spirocycles [73].

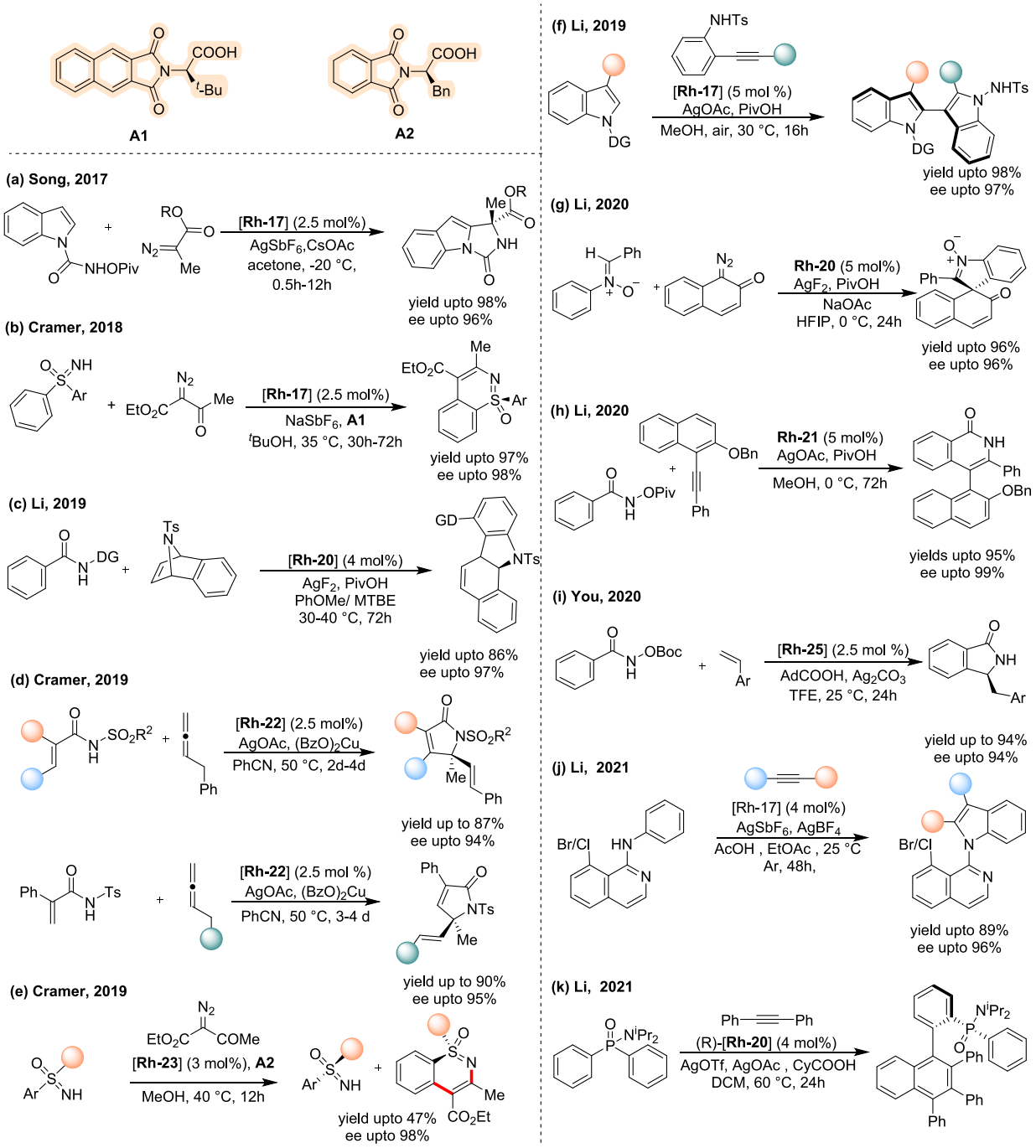
Li group further reported, [4 + 2] annulation of benzamides and sterically hindered alkynes using chiral **Rh-21**. The methodology proceeds effortlessly with a broad substrate scope of alkynes and carboxamides (Scheme 8**h**). The regio- and enantioselectivity of the reaction is dictated by the steric interaction between the two coupling partners. In the crystal structure of the intermediate, the benzamide's less hindered benzene ring is oriented towards the chiral ligand to minimize steric hindrance interactions. This establishes a chiral environment for the incoming alkyne [74].

Usually [4 + 2] annulation reactions takes place between benzamides and alkenes in the presence of Rh/Cp complexes. You group disclosed first [4 + 1] annulation reaction of benzamides and alkenes for the synthesis of isoindolines using **Rh-25** as catalyst (Scheme 8**i**). The reaction proceeded under milder reaction condition to furnish the product with high regio- and enantioselectivity. Mechanistic studies indicate the occurrence of an oxidative Heck-type coupling initially, followed by syn β-H elimination and subsequent migratory insertion. The enantioselectivity in the product is attributed to the chiral nature of the Cp ligand [75].

Further, Li group reported **Rh-17** catalyzed atroposelective [3 + 2] annulation of *N*-isoquinolylaniline with different internal alkynes affording indoles *via* dynamic kinetic resolution pathway (Scheme 8**j**). A DFT study suggests that steric repulsion between the methoxy group in **Rh-17** and the phenyl group of the styrene skeleton favors the selective formation of one enantiomer of the product over the other [76].

In 2021, Li group unveiled the **Rh-20** catalyzed desymmetrized coupling of phosphinamides with diarylacetylenes for the formation of axially chiral biaryls with P stereogenic center. The reaction involved dual C–H activation and furnished the product with high enantioselectivity and excellent diastereoselectivity (Scheme 8**k**) [77].

In addition to the annulation protocol, the asymmetric C–H activation protocol is also applicable for the C–H functionalization of organic species. Li group in 2019, reported **Rh-17**/$AgSbF_6$ catalyzed atroposelective desymmetrizative C–H functionalization of *N*-pyrimidylindoles with 7-azabenzonorbornadienes (Scheme 9**a**). The author revealed that

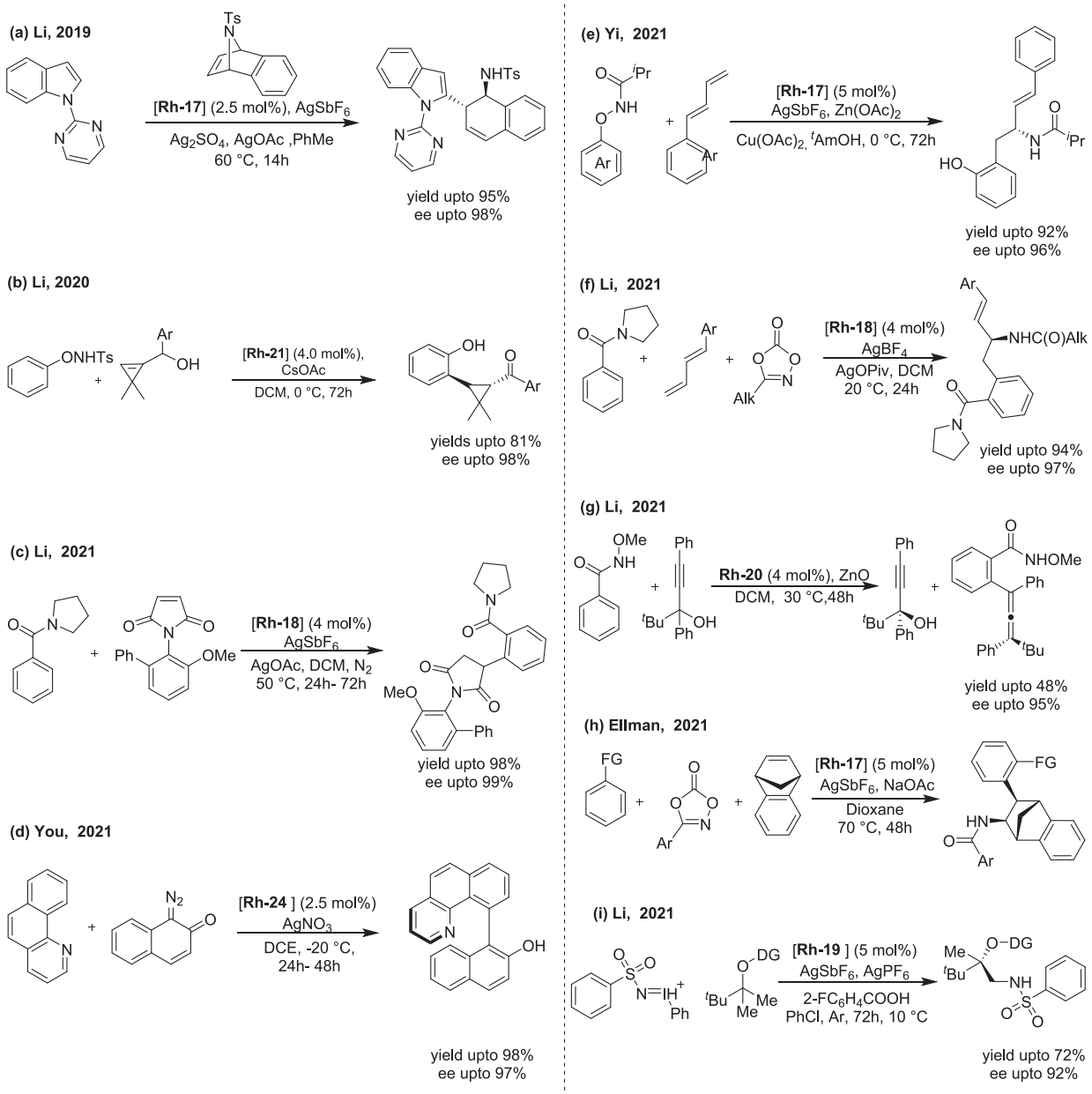


Scheme 8. Chiral cyclopentadienyl Rh(III) complexes used in C–H annulation.

$AgSbF_6$ significantly enhances the catalytic activity of the Rh complex in this protocol, facilitating the C2-H activation of the indole in competition with C2 and C3 of the indole. The enantioselectivity of the reaction can be defined using cramers model (Fig. 4a) [78].

Later Li group, in 2020, reported **Rh-21** catalyzed enantioselective and diastereoselective formation of cyclopropanes *via* coupling of arenes and cyclopropenes under mild and redox neutral reaction conditions (Scheme 9**b**). Trans selectivity in the product were confirmed by the X-ray analysis of the product. Mechanistic studies showed that the reaction occurs *via* a Rh(V) nitrenoid intermediate, and Noyori-type proton hydride transfer. Experimental mechanistic studies and DFT calculations, suggest involment of tandem C–H activation, alkyne migratory insertion, oxidative addition, outer-sphere concerted protonhydride transfer, reductive elimination, and protonolysis provide the desired product. Enantioselectivity were secured by the chiral Cp ligand coordinated in the **Rh-21** [79]. Li group further disclosed the alkylation of benzamides with *N*-arylmaleimide where a synergistic axial and central chirality has been installed *via* **Rh-18** catalyzed C–H activation. In the developed protocol, the migratory insertion step is the stereodeterming step that establishes both axial and central chirality in a single step. (Scheme 9**c**) [80].

You group in 2021, designed a novel class of chiral cyclopentadienyl ligands known as BoCps where oxygen atom served as linkers. The **Rh-24** served as potent catalyst in asymmertric C–H arylation of benzo-[h] quinolines in high yields and enantioselectivity (Scheme 9**d**). In the in-situ NMR monitoring of the reaction, benzo-[h]quinolines-Rh complex were observed within 15 min of the reaction, which were further characterized by XRD analysis. In the crystal structure of intermediate the



Scheme 9. Chiral cyclopentadienyl Rh(III) complexes used in C–H functionalization.

bulky chlorine were found to be oriented far away to the steric shielding group and pyridine ring of the benzo-[h]quinolines parallel to the steric shielding group. Thus indicating the C–H activation of the benzo-[h] quinolines prior to the Rh-carbene formation [81].

Later Yi group, reported enantioselective carboamination of 1,3-dienes with *N*-phenoxy amides *via* **Rh-17** catalyzed C–H activation. The intermolecular reaction allows the direct synthesis of various chiral allylic amines under mild conditions in good yield and enantioselectivity (Scheme 9**e**). Experimental and computational studies revealed an unusual Rh(III) – Rh(I) – Rh(III) catalytic pathway. The amide transfer step was found to be the stereodetermining step in this protocol [82].

Li group further reported enantioselective three-component coupling of arene, diene, and dioxazolone *via* **Rh-18** catalyzed C–H activation. This carboamination reaction proceeds *via* formation of π-ally intermediates. The key feature of the reaction is that the reaction works excellently under mild conditions with high 1,2-regio- and enantioselectivities (Scheme 9**f**). According to the stereomodel, the sterically bulky amide directing group is oriented to the front in the C–N reductive elimination process, which leaves the allyl group to the back affording the (*S*)-enantiomer as major product [83].

Li group, in 2021 successfully achieved kinetic resolution of propargyl alcohols through **Rh-20** catalyzed asymmetric C–H allenylation of benzamides. This accomplishment was facilitated by the strategic incorporation of a chiral zinc carboxylate additive. The reaction exhibited broad substrate compatibility, yielding coupled products and recovered propargyl alcohols with high s-factor of up to 139. The observed high enantioselectivity can be attributed to the steric bias inherent in the two propargylic groups, further enhanced by the chiral zinc additive (Scheme 9**g**) [84].

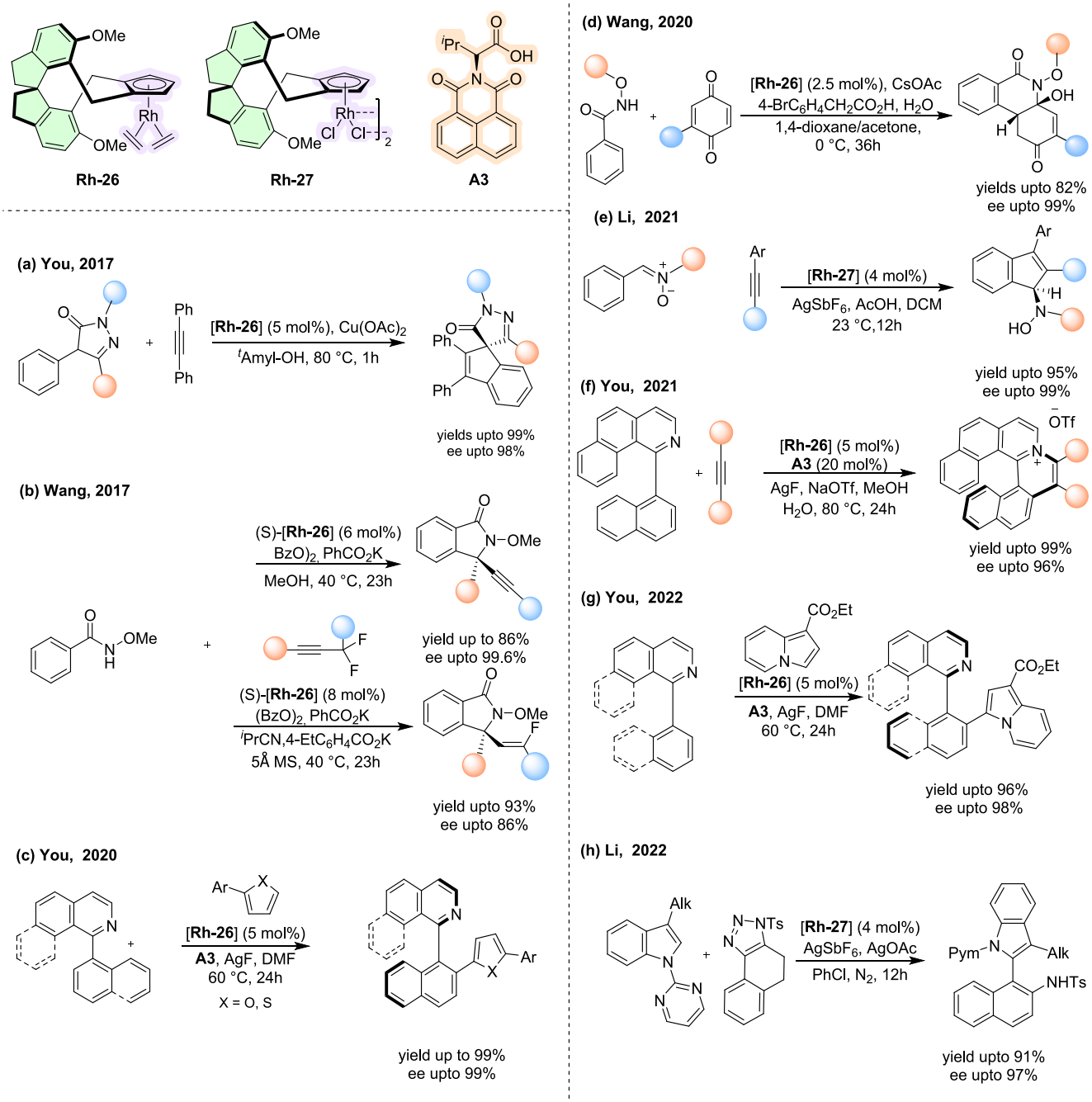
Ellman and coworkers developed a three component enantioselective 1,2-carboamidation of bridged bicyclic alkenes using **Rh-17** (Scheme 9**h**).The reaction goes well with norbornene and benzonorbornadiene. However, it encountered challenges with oxygen and nitrogen bridged bicyclic alkenes due to the elimination of the heteroatomic bridge and non-productive anionic coordination to the metal center [85].

Li group reported, chiral **Rh-20** catalyzed C–H amidation of gem dimethyl scaffolds leading to the formation of *β*-amino alcohol moieties; which also serve as important chiral auxiliaries. The methodology proceeds efficiently with different substrates, furnishing the product in moderate to good yield with high enantioselectivity (Scheme 9**i**) [86].

In 2017, You group reported the first enantioselective synthesis of spiropyrazolones by [3 + 2] annulation of pyrazolones with alkynes in the presence of a chiral **Rh-26** catalyst. The method facilitated the formation of a wide range of spiropyrazolones having quaternary carbons as stereogenic centers. The resulted product was furnished up to 99 % yield and 98 % ee (Scheme 10**a**). The migratory insertion step in the catalytical cycle, might be the enantio-determining step in the synthesis of spiropyrazolones [87].

Continuing the work, Wang group in the same year, reported chiral **Rh-26** catalyzed solvent reliant asymmetric construction of isoindolinones by reacting *N*-methoxy benzamides with *α*,*α*-difluoromethylene alkynes. In methanol, alkynyl isoindolinones were formed whereas, monofluoroalkenyl isoindolinones were produced in isobutyronitrile. Mechanistic studies confirmed that the reaction proceeds by the formation of *E*-alkenyl rhodium intermediate, giving the *Z*-monofluoroalkene on protonation in the isobutyronitrile system, whereas the formation of the alkyne product by anti *β*-F elimination was observed in the methanol system. (Scheme 10**b**) [88].

You group, in 2020, reported the **Rh-26** catalyzed enantioslective oxidative dual C–H/C–H cross-coupling of 1-aryl isoquinolines with heteroarenes. Mechanistic studies showed that both C–H bond breaking may not be the rate-determining step. A number of axially chiral compounds were obtained in excellent yields and enantioselectivities (Scheme 10**c**) [89]. Further, a method for the formation of axially chiral biaryl systems using **Rh-26** catalyst and chiral carboxylic acid as ligands



Scheme 10. Rh chiral cyclopentadienyl complexes with spirobackbone used in C–H functionalization.

was developed by You and coworkers. This catalytic method involves the reaction of 1-aryl isoquinolines and indolizines *via* asymmetric oxidative C–H activation (Scheme 10**d**) [90].

Li group, in 2021, reported chiral **Rh-27** catalyzed asymmetric synthesis of chiral indenes/indenones *via* [3 + 2] annulation. The method involves the reaction of arylnitrones with various internal alkynes under moderate conditions (Scheme 10**e**).[91] Later, You group, reported chiral **Rh-26** and a chiral acid-catalyzed C–H annulation of 1-aryl isoquinoline derivatives with alkynes. Chiral azoniahelicenes were obtained in yields up to 99 % and enantioselectivity up to 96 %. (Scheme 10**f**) [92].

In 2022, Li group reported **Rh-27** catalyzed atroposelective arylation of hindered (hetero)arenes using diazo scaffolds and triazoles as arylating source under milder reaction condition. *N*-sulfonyltriazoles and indoles with C3 substitution furnished the product with C(2) chiral axis, while chiral binaphthyls was formed on arylation of 1-naphthyl thioether (Scheme 10**g**) [93]. In the same year, Li group also reported enantioselective synthesis of two classes of tetra-substituted olefins using different arenes with sterically hindered alkynes in the presence of chiral rhodium catalyst **Rh-27** (Scheme 10**h**). The DFT studies showed that the reaction involves migration of the directing group *via* β-nitrogen elimination pathway that resulted in the generation of an isocyanate intermediate. Post-transformations revealed that the product can be used as a promising chiral additive in asymmetric C–H activation [94].

In 2017 Cramer group reported chiral cyclopentadienyl (Cp^x) ligand bearing **Ir-2** catalyst asymmetric C–H amidation of phosphine oxide with tosyl azide. This efficient transformation occurred because of the strong obliging effect among chiral Cp^x ligand and a catalyst (Scheme 11**a**) [95]. In 2018 same group reported enantioselective C–H arylation of phosphine oxide with o-quinone diazides. In this report the former chiral **Ir-2** catalyst bearing an axially chiral cyclopentadienyl ligand and phthaloyl amino acid behave a co-catalyst. Enantioselective phosphorous chiral center of phosphorus oxide as well atropo-enantioselective construction of biaryls of phosphorus oxide were constructed simultaneously with excellent selectivity of diastereomers (>20/1) and enantiomers (99 %) (Scheme 11**b**) [96].

Later same group in 2021 group reported asymmetric C–H arylation of tetralone with aryl boronic acids under milder conditions with **Ir-3** which act as a nucleophilic component. They also explored atropochiral oxime-derived derivative like chromanone and flavone products as well (Scheme 11**c**) [97].

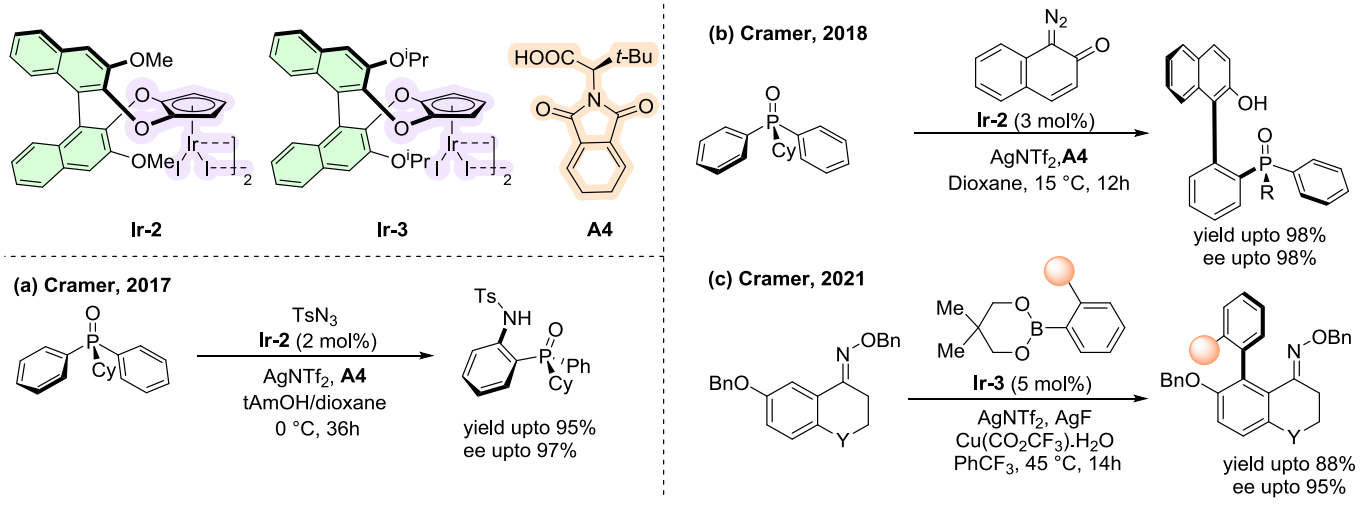
In 2019, the Cramer group reported a new family of catalysts containing cyclopentadienyl as a chiral backbone for asymmetric synthesis with cobalt(III) metal complexes.[98] These synthesized Co(III) complexes were well exploited as catalysts for enantioselective applications. First Cramer group reported annulation of *N*-chlorobenzamides with olefins by taking application of **Co-14** led to high yields and excellent enantioselectivity by using trisubstituted chiral Cp* ligands. Main reason behind the success was presence of a bulky *tert*-butyl group on the chiral Cp ligand, which directly affected the dihedral angle of the binaphthyl backbone (Scheme 12**a**) [99].

Next year, Cramer and coworkers achieved enantioselective intermolecular carboaminations of alkenes. This High-valent **Co-15** catalyzed approach was applicable to acrylates as well as bicyclic olefins. Important feature of the work is that the regioselectivity is opposite to the Rh(III)-catalyzed approach (Scheme 12**b**).[100] In 2021, Cramer and coworkers have further established that earth-abundant cobalt based Co(III) complexes **Co-16** loaded with a 1-methyl cyclohexyl substituted chiral cyclopentadienyl ligand (Cp*). **Co-16** were also applicable for multi-component functionaliztions. This new protocol provides direct access to substituted β-hydroxyketones with yields up to 77 % and excellent enantiomeric excess involving chiral cyclopentadienyl ligand complex **Co-16** as catalyst and three-component cascade system (pyrazol-1-yl) arenes with alkenes and aldehydes (Scheme 12**c**) [101].

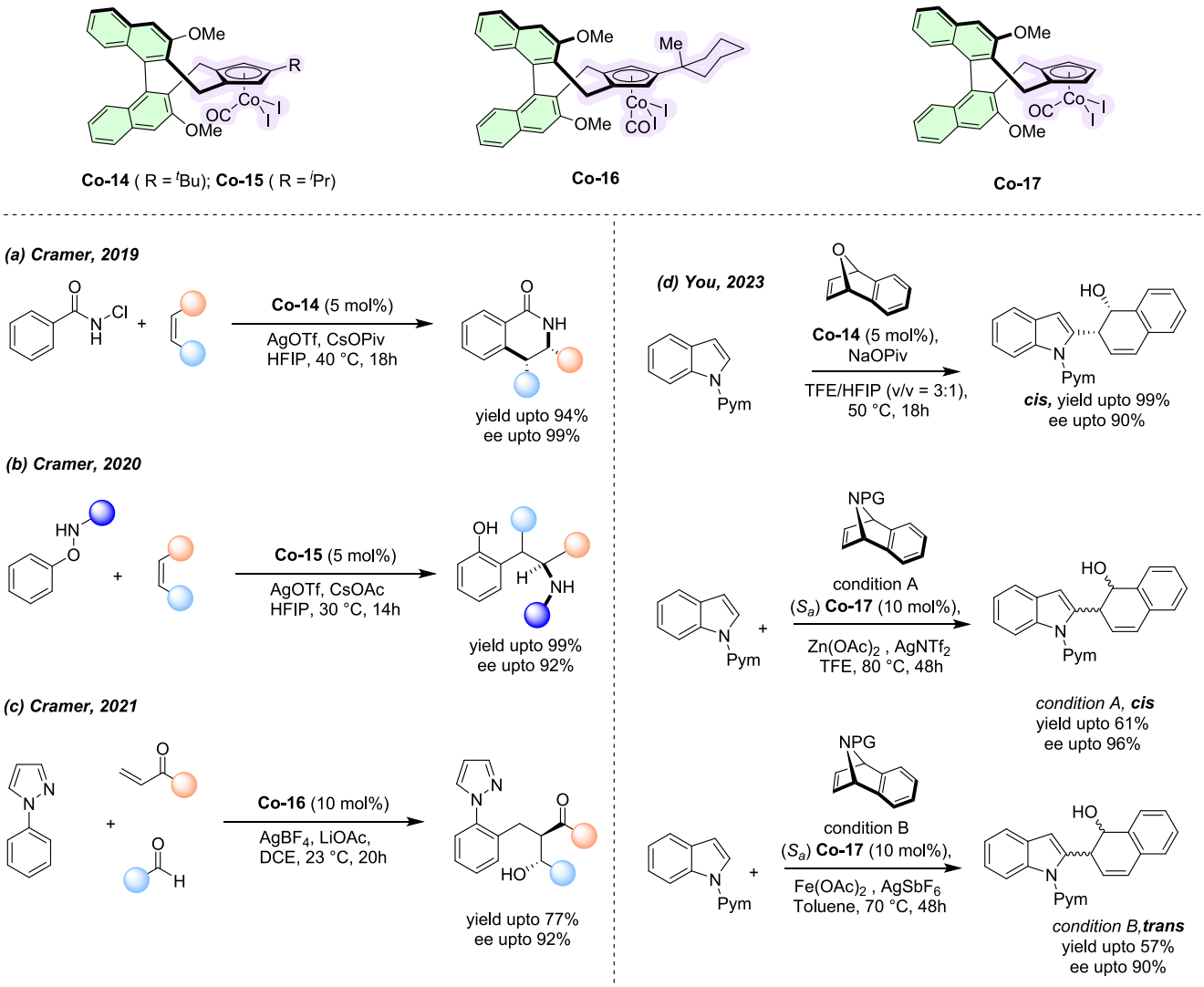
Recently, You group demonstrated asymmetric functionalization of 7-oxabenzonorbornadienes with ring opening at indole. Interestingly the use of chiral **Co-14** and **Co-17** with binaphthyl-derived trisubstituted cyclopentadienyl ligand provides high yield and excellent stereoselectivity. Mechanistic studies revealed the reason for opposite diastereoselectivities with chiral Co-catalyst and key step of the reaction involves β-oxygen elimination, which determines the diastereoselectivities (Scheme 12**d**) [102].

Scandium, the first transition metal with a high abundance in nature, shows three oxidation states +3, +2, +1, from which +3 is most dominant to form a complex. Knowing the application of scandium salt as lewis acid and in organic synthesis, many research groups have explored scandium catalysis in asymmetric synthesis.[103] In 2014, Hou group reported a number of chiral half-sandwich dialkylated metal complexes and examined the scandium catalyzed enantioselective C–H bond addition of pyridines to unactivated olefins. Scandium complex **Sc-2** charged with mono cyclopentadienyl ligand having chiral binaphthyl backbones catalyzed tthe formation of a wide range of alkylated pyridine product with high yields and enantioselectivitives(Scheme 13**a**) [104].

In 2018, Hou group reported chiral half-sandwich scandium complex **Sc-3** catalyzed first intermolecular hydrosilylation of alkenes with dihydrosilanes. This hydrosilation leads to the formation wide range of silicon based stereogenic silanes with remarkable yield. The high sterioselectivity resulted from sigma-bond metathesis across Si–H bond in a



Scheme 11. Ir chiral cyclopentadienyl complexes used in C–H functionalization.



Scheme 12. Co chiral cyclopentadienyl complexes used in C–H functionalization.

prochiral dihydrosilane and a Sc–alkyl bond, which differs from mechanisms involvedin late transition metal catalysis (Scheme 13**b**) [105].

In 2020, Hou and coworkers established a new protocol for synthesizing intramolecular symmetric and asymmetric C–H alkylation of imidazoles with disubstituted olefins. After establishing achiral reaction condition, they screened scandium complexes for asymmetric cyclization of imidazoles with disubstituted olefins *via* C–H bond alkylation. Catalyst **Sc-2**, with bulky silyl ether substituents in the ligand backbone, exhibited excellent levels of enantioselectivity with different fused derivatives of imidazole, leading to the formation of enantioenriched product in high yield and enantioselectivity (Scheme 13**c**) [106].

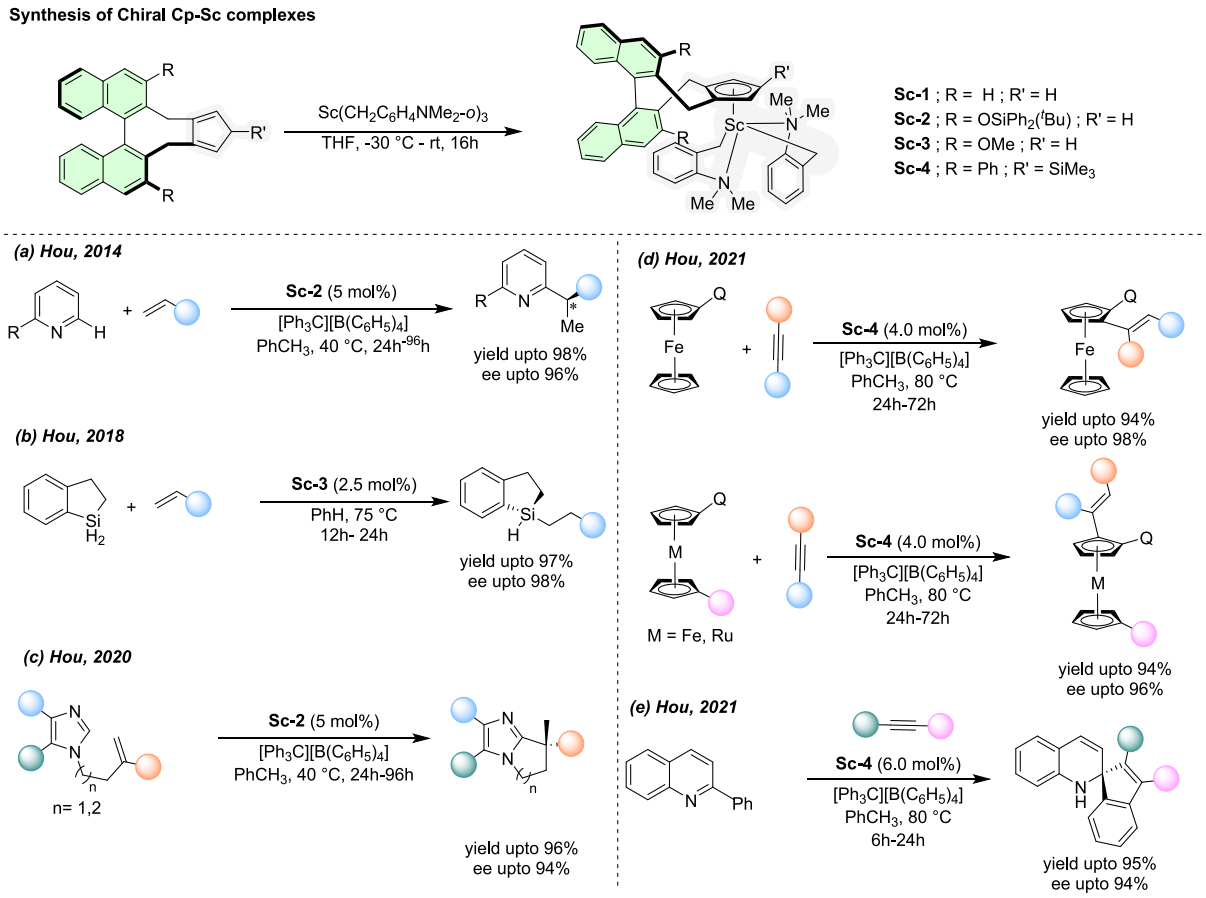
Hou and coworkers also demonstrated asymmetric C–H alkenylation of ferrocenes with alkynes. They screened number of half sandwich scandium complexes loaded with different substituents at the 3,3′-positions of the binaphthyl backbone. Out of this, **Sc-4** functionalized with bulky $SiMe_3$ substituent to the Cp ring of the catalyst was able to provide an alkenylated product with high enantioselectivity and yields. Further same group also reported **Sc-5** catalyzed synthesis of a new family of heterocyclic rings containing alkene functionalized planar-chiral ferrocenes and demonstrated the application of these ferrocene product's as a chiral ligand for asymmetric synthesis. (Scheme 13**d**) [107].

Later, Hou group reported asymmetric annulation of quinoline with alkyne, leading to spiro-dihydroquinolines with dearomatization of quinolines. In this report, they have screened various half sandwich scandium based achiral and chiral catalysts. After the establishment of a protocol for achiral dearomative spiro-annulation, they developed assymetric-version of the reaction with **Sc-4** having binaphthyl backbone with substituted trimethylsilyl at the cyclopentadienyl ring. This approach has 100 % atom efficiency, wide substrate scope and high yields with excellent enantioselectivity (Scheme 13**e**) [108].

3.4. Planar chiral ligand coordinated metal complexes in C–H functionalization

In 2012, Cramer group developed a varied range of Rhodium(I) complexes coordinated with different shielding groups from the corresponding C2-symmetric cyclopentadiene (Cp). The efficiency and practicality of the developed complexes was established by **Rh-28** catalyzed enantioselective C–H annulation of hydroxamic acid under mild reaction conditions, in high yields and enantiomeric excess (Scheme 14**a**). In the enantio determining step, coordination of the olefin with rhodacycle in a highly diastereoselective manner leads to 18-electron *chiral-at-metal* intermediate, which upon migration and reductive elimination gives the annulated product in stereoselective manner [109].

Waldmann group in 2017, constructed tuneable and easily accessible chiral Cp ligands and corresponding Rh(I) complexes *via* enantioselective [6 + 3] cycloadditions of azomethine ylides and fulvenes. The structures and configurations of the ligands can be easily adjusted with



Scheme 13. Sc chiral cyclopentadienyl complexes used in C–H functionalization.

rhodium metal to form active catalyst **Rh-29.** JasCp coordinated **Rh-29** resulted in enantiocontrol in the C–H annulation of *N*-Boc hydroxamic acid and styrene. Free-energy profiles suggested that the stereochemical model aligned with the previously proposed Cramer model [110]. Allylation of methyl benzohydroxamate was also effective in generating ortho functionalized benzohydroxamate in good yield and enantioselectivity using **Rh-30** (Scheme 14**b**). Biaryl atropisomers were also achieved by reacting diazonaphthoquinones and *N*-methoxybenzamide in presence of **Rh-30.**

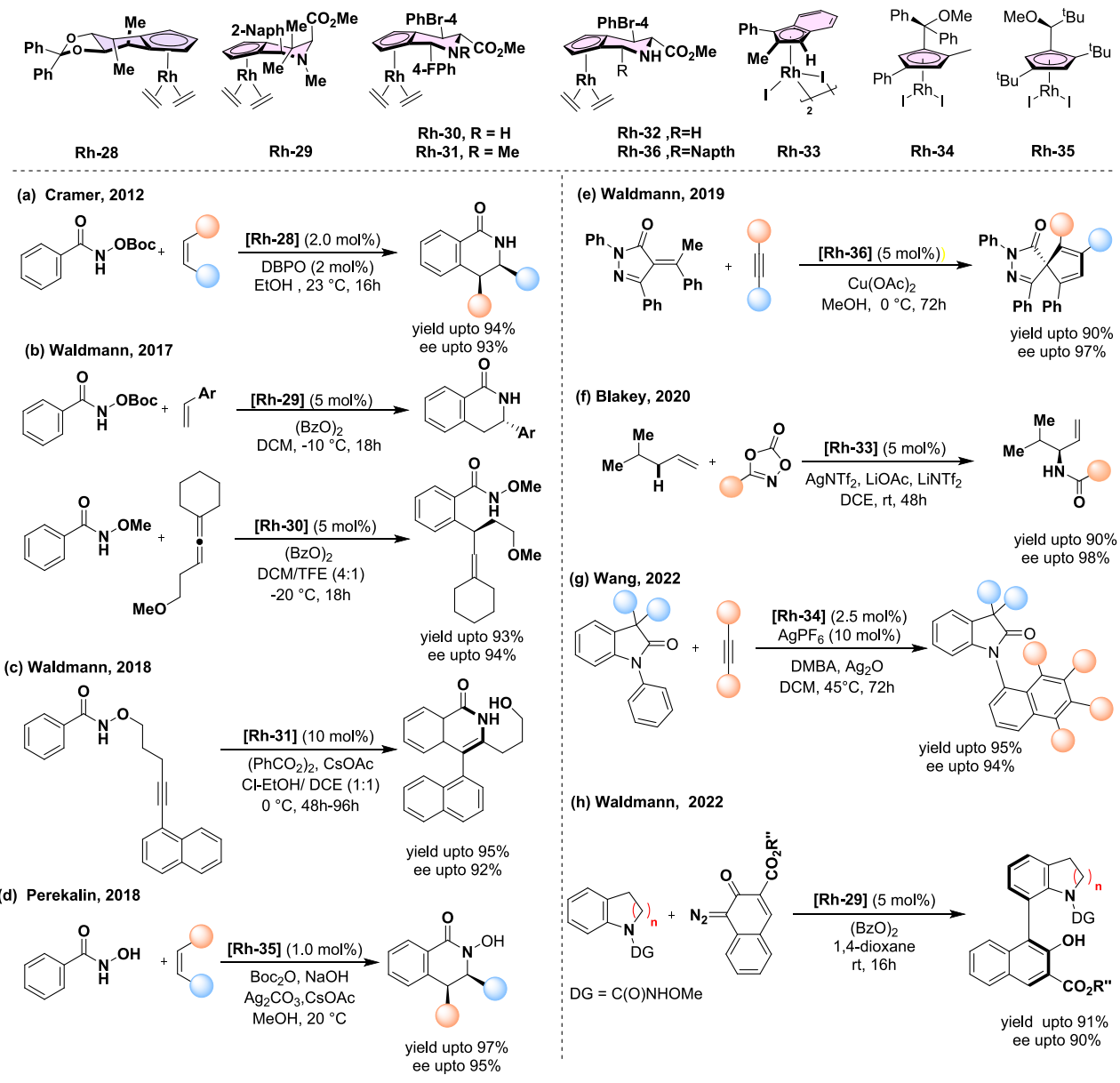
In 2018, Perekalin group react $[Rh(COD)Cl]_2$ and ^{t}butylacetylene in presence of $AgPF_6$ followed by nucleophilic addition of hydride from $NaBH_3CN$ to get planar-chiral rhodium complex. Further oxidation using iodine provide the activated complex **Rh-35** (Fig. 7). The robustness of the newly designed planar complex **Rh-35** was tested in an enantioselective C–H activation reaction of hydroxamic acids with cyclic alkenes, which provide the annulated products in good yield and enantioselectivity (Scheme 14**d**). The selectivity of the product was explained on the basis alkene approach from the the less hindered sides of the proposed intermediate metallacycle [111].

Later Waldmann *et al.*, unveiled the first **Rh-31** catalyzed asymmetric construction of axially chiral 4-arylisoquinolones by intramolecular annulation. The biaryl product was isolated in high yields and enantioselectivity (Scheme 14**c**) [112]. Waldmann in 2019, reported **Rh-36** catalyzed the first asymmetric annulation of α-arylidene pyrazolones *via* C(sp^3)–H bond activation under moderate conditions with a broad substrate scope, excellent yields and enantioselectivities (Scheme 14**e**). Further late-stage functionalization was also carried out to demonstrate the synthetic utility of this methodology. Preliminary biological investigations also revealed that spiropyrazolones are a unique class of Hedgehog pathway inhibitors [113].

In 2020, Blakey group synthesized a novel chiral **Rh-33** catalyst *via* complexation of $[Rh(COD)Cl]_2$ and 2-methyl-3-phenylindene followed by the separation using chiral HPLC. Both enantiomer of the Rh(I) complexes were further oxidized to Rh(III) complexes using iodine. **Rh-33** were applied for the enantioselective allylic C–H amidation. The developed protocol exhibits a broad substrate scope and furnishes enantioenriched products (Scheme 14**f**) [114].

Wang and coworkers evaluated **Rh-34** in enantioselective C–H annulation of 2-indolinones with diarylacetylenes to form axially chiral *N*-aryloxindoles with good yield and excellent enantioselectivity. However, absolute stereochemistry of product were not defined (Scheme 14**g**). Later, the Waldmann group reported **Rh-29** catalyzed enantioselective C–H functionalization method to get axially chiral C7-indolines under mild conditions. Different 2-substituted indoles were well tolerant and yielded the desired axially chiral product in good yields and enantiomeric excess (Scheme 14**h**) [115].

In 2022 Wang group introduced [2.2] paracyclophane-derived chiral arene ligands with C2-symmetrical ligand. This ligand derived **Ru-4a** complex has been successfully utilized in the enantioselective C- H functionalization with effective axially chiral molecules (up to 99 % yield and 96 % ee). With η^6-arene ligand this is the first report for stereocontrol and enantioselective C–H functionalization (Scheme 15**b**). The complex were synthesized by reaction of chiral pseudo-*ortho*-disubstituted[2.2]paracyclophanes and $[Ru(p\text{-cymene})Cl_2]_2$ in stoichiometric amount of $AgBF_4$ followed by treatment of Red-Al and HCl (Scheme 15**a**). The proposed stereochemical models provide insight into the chiral induction mechanisms governing the observed absolute configuration of the product. For instance, the steric hindrance posed by the isopropyl group positioned lower in the [2.2]paracyclophane ligand and two $–CH_2CH_2$- bridges within the ligand contribute significantly. Additionally, the orientation of the methoxy group of the amide is directed away from the isopropyl group, while the alkyne moiety favors



Scheme 14. Planar chiral metal complexes used in C–H functionalization.

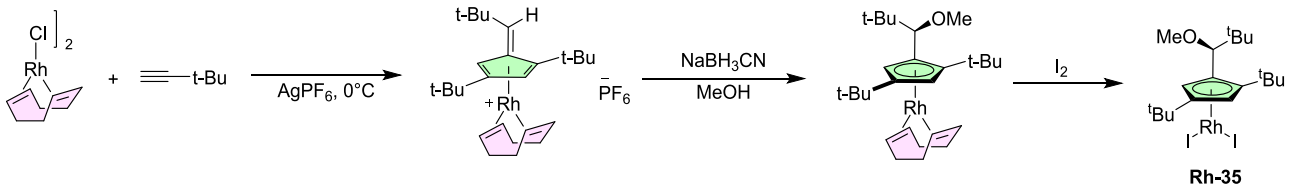
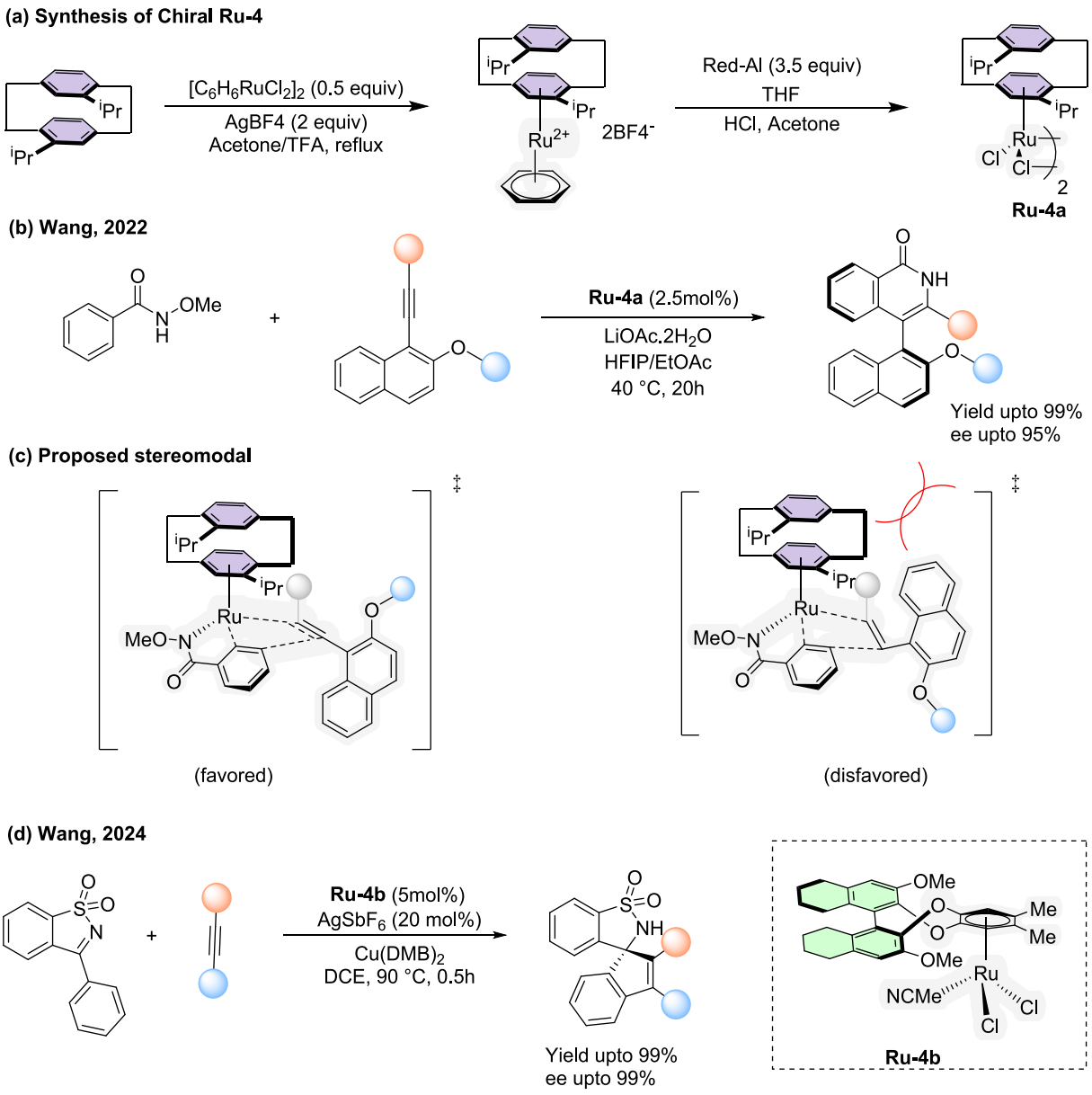


Fig. 7. Synthesis of complex **Rh-35** from $[Rh(COD)Cl]_2$.

approaching the ruthenium catalyst from the least congested side, specifically the unsubstituted region of the [2.2]paracyclophane ligand. Furthermore, the PMB substituent is oriented towards the [2.2]paracyclophane ligand to minimize steric repulsions effectively. These structural arrangements collectively orchestrate the observed stereochemical outcome with the desired absolute configuration of the product. (Scheme 15**c**). [116] Later in 2024, Wang and coworkers designed a (*S*)-H8-BINOL-derived chiral η^6-benzene ligands which were further subjected to complex formation with Ru to form **Ru-4b.** This newly designed complex **Ru-4b** provides chiral spirocyclic sultams in excellent yields with up to >99 % ee *via* asymmetric C − H annulation of *N*-sulfonyl ketimines with alkynes [117].

3.5. *Miscellaneous*

Various chiral complexes have been harnessed in C–H activation reactions, showcasing their versatility and efficacy in controlling stereochemistry. These complexes span different metal catalysts and ligand



Scheme 15. Planar chiral Ru complexes used in C–H functionalization.

architectures, contributing to a rich understanding of asymmetric transformations. In addition to the previously discussed chiral complexes, a diverse array of miscellaneous metal complexes has been instrumental in advancing C–H activation chemistry. Examples include iridium complexes bearing bulky ligands, cobalt catalysts featuring tailored chiral ligands, and ruthenium complexes with unique electronic properties (Fig. 8). These complexes offer distinct reactivity profiles and selectivities, enriching the toolbox of synthetic chemists for complex molecule synthesis.

Katsuki group in 2009 introduced **Ir-4** salen chiral complex for C–H carbene insertion at α-position of THF and the methylene position of 1,4-cyclohexadiene with high enantioselectivity and diastereoselective (Scheme 16**a**) [118]. In 2011, the Katsuki group extend the potential of Ir-salen complexes and disclosed the C–H amination of benzenesulfonyl azide to form a five-membered sultams with high enantioselectivity and good yield using **Ir-5** salen complex (Scheme 16**b**) [119]. However, the exact mode of the enantiocontrol were not discussed in these studies.

Later in 2013, Blakey group designed and synthesized **Ir-6** pincer complex. C–H alkylation of 1,4-cyclohexadiene with diazo compounds were carried out using the low loading of catalyst **Ir-6** (Scheme 16**c**). Predictive model explains that in the most stable axial metallocarbene the benzyl group of the oxazoline ligand of complex **Ir-6** blocks the Si-face of the metallocarbene, and Re-face exposed to 1,4-cyclohexadiene forming the (R)-enantiomer with high selectivity[120]. Same group in 2016 reported asymmetric C–H alkylation of phthalan and dihydrofuran with the precursor of diverse diazoacetate using iridium complex **Ir-7** (Scheme 16**d**) [121]. Park and Chang reported asymmetric synthesis of γ-lactams *via* **Ir 8** catalyzed C–H amidation (Scheme 16**e**). Stereochemical origin of the selectivity were also studied by DFT studies [122].

Later 2019 Chen group synthesized a chiral **Ir-9** catalyst with alpha-amino acid and applied it for the catalytic synthesis of optically enriched gamma-lactams *via* a C–H amidation of dioxazolones. The Cp*, AQ, and Phth groups introduced in the chiral ligand form a chiral pocket around the Ir centre which helped in achieving an excellent yield with outstanding enantiomeric excess under very mild condition for both activated and unactivated C(sp^3)-H (Scheme 16**f**).[123] Continue with chiral iridium catalyst in 2021 Chang group reported chiral spiro-lactam molecules *via* the nitrenoid transfer to aromatic *ipso* carbon. This is first

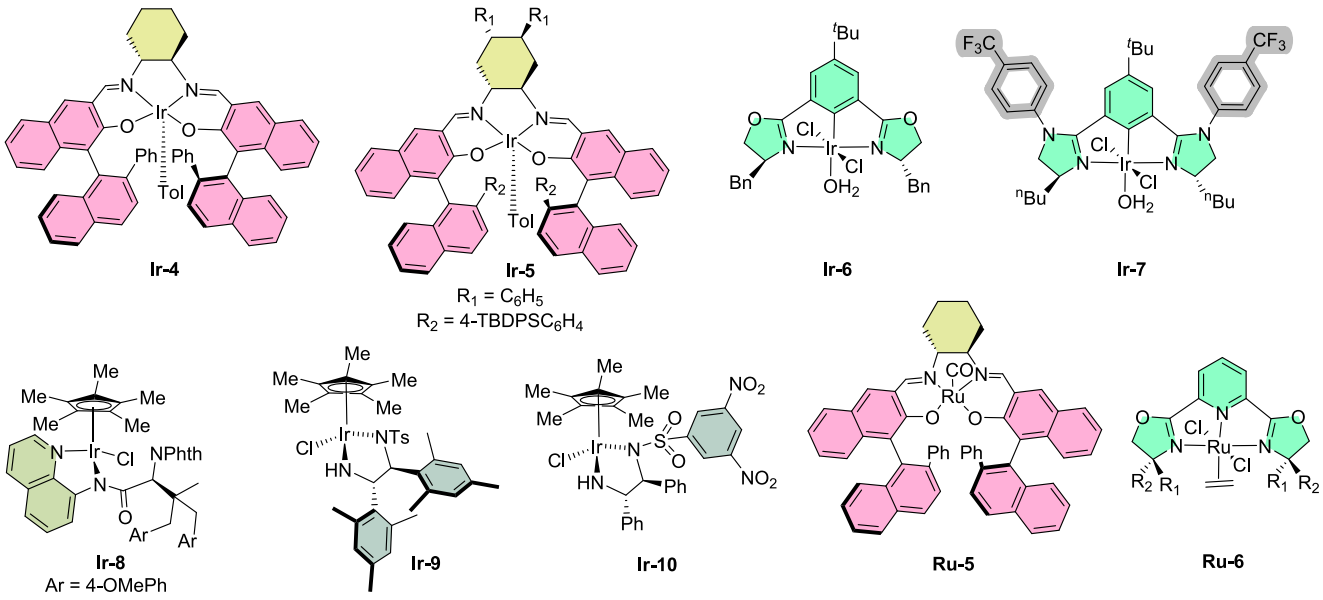
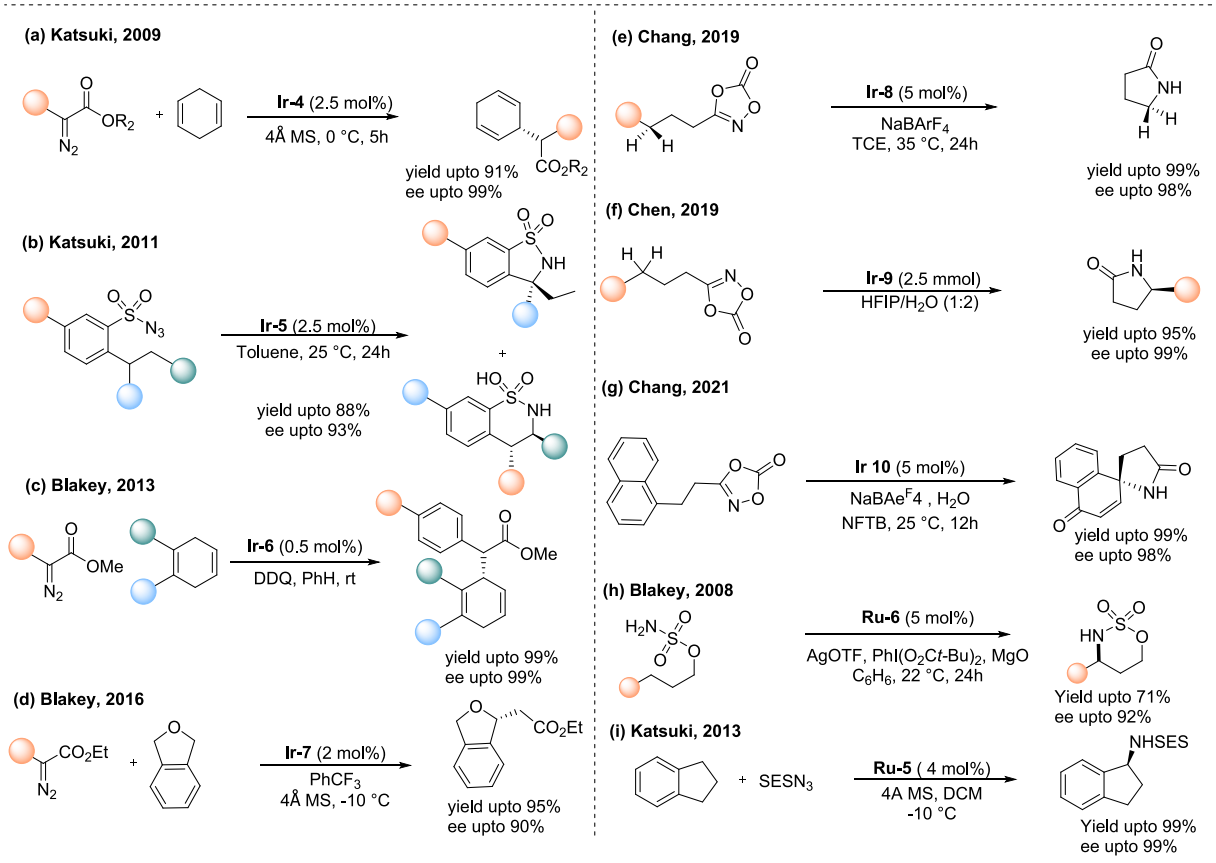


Fig. 8. Miscellaneous chiral metal complexes.



Scheme 16. Miscellaneous Ir complexes used in C–H functionalization.

example of spiro-lactams synthesise with **Ir-10** (Scheme 16**g**).[124].

In 2008, the Blakey group reported intramolecular benzylic and allylic C–H amination using the **Ru-6** pincer complex to synthesize chiral sulfolactums (Scheme 16**h**). Stereomodel suggests that the C_2 symmetric cationic bisimido-ruthenium(VI) complex was an active intermediate, and the steric clash between phenyl ring of the substrate and the ligand of the **Ru-6** induced the enantioselectivity. [125] In 2013, Katsuki group reported enantioselective intramolecular benzylic and allylic C–H bond amidation, and **Ru-5** is an effective catalyst with 2-(trimethylsilyl)ethanesulfonyl azide as a nitrene source. The developed protocol proceeds with high yield and excellent ee upto 99 % (Scheme 16**i**). [126].

Meggers group synthesized a series of *chiral at metal* complex **Ru-7** to **Ru-11** for enantioselective C–H functionalization. In 2018, Meggers and

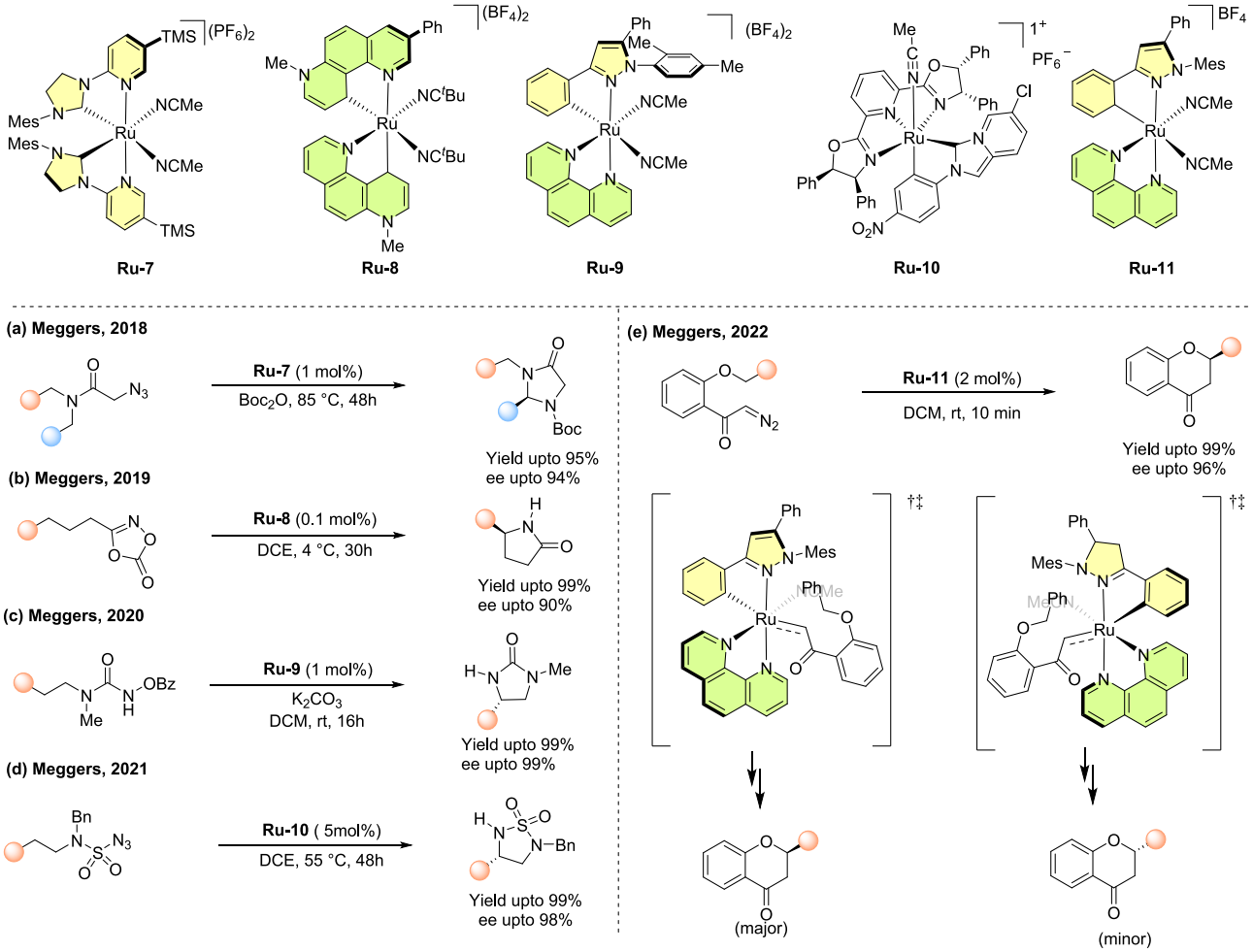
coworkers disclosed Ru-7 catalyzed enantioselective C(sp^3)-H amination of 2-Azidoacetamides *via* an intramolecular ring-closing (Scheme 17**a**). Flexibility of *chiral at metal bis*(pyridyl-NHC) ruthenium complex **Ru-7** were demonstrated as asymmetric catalysis [127]. In 2019, they introduced non C2 symmetrical *chiral at metal* catalyst **Ru-8**, and explained the metal-centered configuration and electronic characteristics of the coordinated NHC ligands for better catalytic activity. **Ru-8** was found to display excellent catalytic activity for the intramolecular C − H amidation of 1,4,2-dioxazol-5-ones (Scheme 17**b**). [128] Thereafter in 2020, **Ru-9** catalyzed enantioselective ring-closing C–H amination of urea derivatives to synthesize imidazolidinone were disclosed with good yield and high enantioselectivity (Scheme 17**c**). This was the first report on the enantioselective ring closing C–H amination for constructing cyclic urea. The synthetic application of the chiral imidazolidinone were demonstrated by the synthesis of drug molecules i.e. levamisole, dexamisole etc. [129] In 2021, Meggers *et al.*, reported enantioselective intramolecular C–H amination of sulfamoyl azides using **Ru-10**, allowing efficient access to cyclic sulfanimides. The reaction typically proceeds with high yields and high enantioselectivities at C(sp^3)–H bond is in a benzylic position (Scheme 17**d**) [130]. Recently, enantioselective ring-closing C(sp^3)–H carbene insertion *via* a cyclometalated *chiral-at-ruthenium* catalyst **Ru-11** were reported by Meggers group for the synthesis of flavones derivatives. Transition states governing the formation of major and minor enantiomers of flavanone products indicate a preference for the coordination site trans to the Ru–C bond for the carbene moiety in the transition state leading to the major flavanone enantiomer, which were further supported by DFT studies (Scheme 17**e**) [131].

Meggers group designed the chiral at osmium **Os-1** metal complex. The non-C2-symmetric chiral-at-osmium complex contains two cyclometalated remote *N*-heterocyclic carbene (rNHC) ligands. The octahedral coordination sphere contains one CO and one acetonitrile ligand. Enantiomerically pure *chiral-at-osmium* complexes were obtained by resolution with chiral oxazoline ligand as a chiral auxiliary (Scheme 18**a**). The synthetic utility of the newly designed **Os-1** were screened for intramolecular sp^3 C–H amination of sulfonyl azide and azidoformate, which provides the corresponding products in good to excellent ee. (Scheme 18**b**) [132].

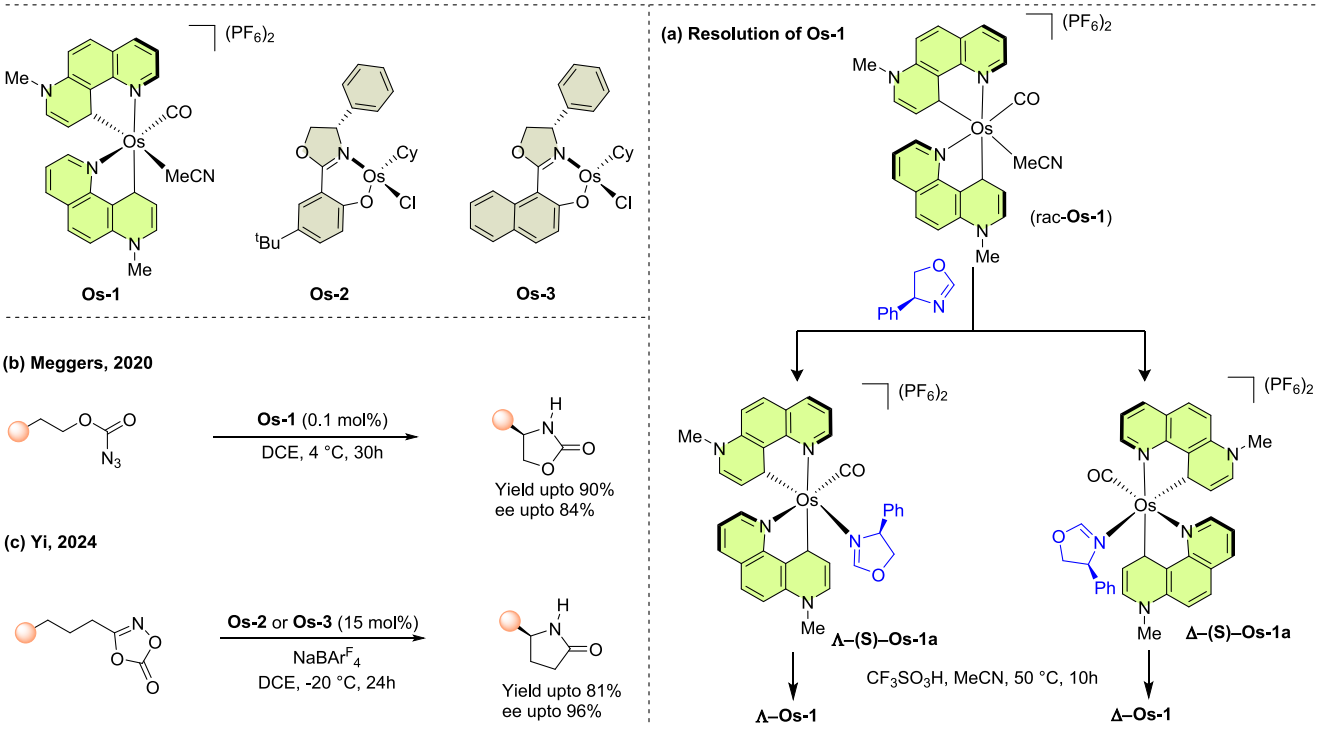
Yi group in 2024, developed an osmium/salox based chiral metal complex **Os-2** and **Os-3** for enantioselective γ-sp^3 intramolecular C–H amidation (Scheme 18**c**). These *chiral at osmium* complexes were found to be superior than their Ru(II)-counter species for chiral induction. The DFT studies suggested that the less flexible nature of transition states involing Os complex than Ru complex favour the chiral induction *via chiral at osmium* complex.[133].

4. Conclusion and future perspective

Chiral transition metal complexes play a pivotal role in asymmetric C–H functionalization, eliminating the need for external chiral ligands during synthetic transformations. In contrast, using external chiral ligands can sometimes be challenging as the reaction medium may not facilitate the formation of an ideal chiral environment, leading to undesired enantioselectivity in synthetic transformations. To overcome such limitations, the utilization of chiral transition metal complexes emerges as a promising protocol for asymmetric organic synthesis, particularly in C–H activation.



Scheme 17. Chiral at Ru complexes used in C–H functionalization.



Scheme 18. Chiral at Osmium complexes used in C–H functionalization.

Numerous metal complexes have been designed and synthesized for application in asymmetric C–H functionalization. This review compiles recent literature on transition metal complex catalyzed asymmetric C–H functionalization, focusing on chiral paddle wheel complexes predominantly associated with rhodium and ruthenium metals. Exploring complexes with other metals promises to offer new insights into the chemistry of chiral paddle wheel complexes as catalysts. Porphyrin metal complexes can also be extended beyond nitrene and carbene insertion reactions.

Significant advancements have been made in synthesizing chiral cyclopentadiene and planar complexes in recent decades. However, synthesizing these complexes remains challenging. Developing a generalized and cost-effective method for their synthesis would undoubtedly enhance the application of these metal complexes beyond academic research and facilitate their adoption in industrial settings.

Although predominantly utilized chiral complexes fall under type 1, where chirality is controlled by the coordination sphere, type 2 complexes, which are chiral at the metal, are rarely employed as catalysts in asymmetric C–H functionalization. Utilizing chiral at metal complexes as catalysts can bring about substantial changes in asymmetric C–H functionalization, owing to their intriguing structure and geometry.

This review serves as a comprehensive guide for researchers engaged in asymmetric C–H functionalization by employing chiral metal complexes both in application and design strategy.

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CRediT authorship contribution statement

Devesh Chandra: Writing – original draft, Methodology, Formal analysis, Data curation. **Tammana Sharma:** Writing – review & editing, Methodology, Data curation. **Sarthi:** Writing – original draft, Methodology, Data curation. **Sachin:** Writing – original draft, Methodology, Data curation. **Upendra Sharma:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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