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Trends in Chemistry

Review

Synthesis of atropisomers via transition-metal-catalyzed enantioselective carbene transformations

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Atropisomerism is a prominent stereochemical behavior arising from the restricted rotation around a σ bond, which has been recognized as a unique skeleton in bioactive natural products, privileged ligands and catalysts, and materials science. In the past decade, the synthesis of atropisomers has witnessed a booming development. In this regard, catalytic enantioselective carbene transformation reactions provide an effective strategy to realize the extraordinary stereocontrol of axial chirality due to the versatility and high reactivity of metal carbenes. This review highlights advances in transition-metal-catalyzed asymmetric carbene transformation reactions towards atropisomers, focusing on the mechanistic classes of axial chirality generation.

Introduction to atropisomers

A unique manifestation of molecular chirality, atropisomerism is the consequence of hindered rotation around a σ bond, which was first correctly recognized by Christie and Kenner in 1922. Atropisomers, especially axially chiral biaryls, exist widely in natural products and bioactive molecules. For instance, (–)-steganacin bearing an (*M*)-configuration at the biaryl axis exhibits significant cytotoxicity, a marked inhibitory effect on tubulin assembly, and *in vivo* antitumor activity (Figure 1A, Key figure) [1–5]. Atropisomers are also the core skeletons of numerous privileged ligands and catalysts known as BINOL (1,1′-binaphthyl-2,2′-diol), BINAP [2,2′-bis (diphenylphosphino)-1,1′- binaphthyl], chiral phosphoric acids (CPAs), etc. [6–8]. In addition, they have been applied to material science, such as in host–guest chemistry and as fluorescent sensors [9–12]. In the past few decades, especially the past decade, remarkable progress has been made in the catalytic asymmetric synthesis of atropisomerically chiral compounds, and a variety of elegant strategies, including oxidative coupling and cross-coupling, *de novo* (hetero)arene synthesis, **desymmetrization** (see Glossary), and **(dynamic) kinetic resolution**, have been developed (Figure 1B) [13–26]. The means to realize these strategies include transition-metal catalysis and organocatalysis.

Transition-metal-catalyzed carbene transformation reactions have been well established in modern organic synthesis due to the versatility and high reactivity of metal carbenes [27–32]. In the past decades, catalytic asymmetric carbene transformations to generate central chirality have progressed remarkably [33–35]. By sharp contrast, significant advances in the synthesis of axially chiral atropisomers by enantioselective carbene transformations have been made only more recently, largely due to the inherent steric hindrance that needs to be overcome to construct the stable axis, resulting in deterioration of the metal-carbene intermediate. Nevertheless, these encounters have been addressed, benefiting from the outstanding protocols, which in turn has attracted increasing attention to these carbene strategies. According to the reported examples, two classes of chiral induction can be summarized to realize axial chirality

Highlights

Atropisomerism has been recognized as a unique skeleton in bioactive natural products, privileged ligands and catalysts, and material science.

Due to the high reactivity and versatility of metal carbenes, transition-metal-catalyzed enantioselective carbene transformations provide a highly effective strategy to realize the extraordinary stereocontrol of axial chirality under relatively mild conditions.

The diverse atropisomeric products obtained from enantioselective carbene transformation provide a convenient platform to afford effective ligands and catalysts in asymmetric catalysis and are used as a key step for quick synthesis of the atropisomeric natural product (–)-isoplagiochin D.

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Key figure

Introduction to atropisomers

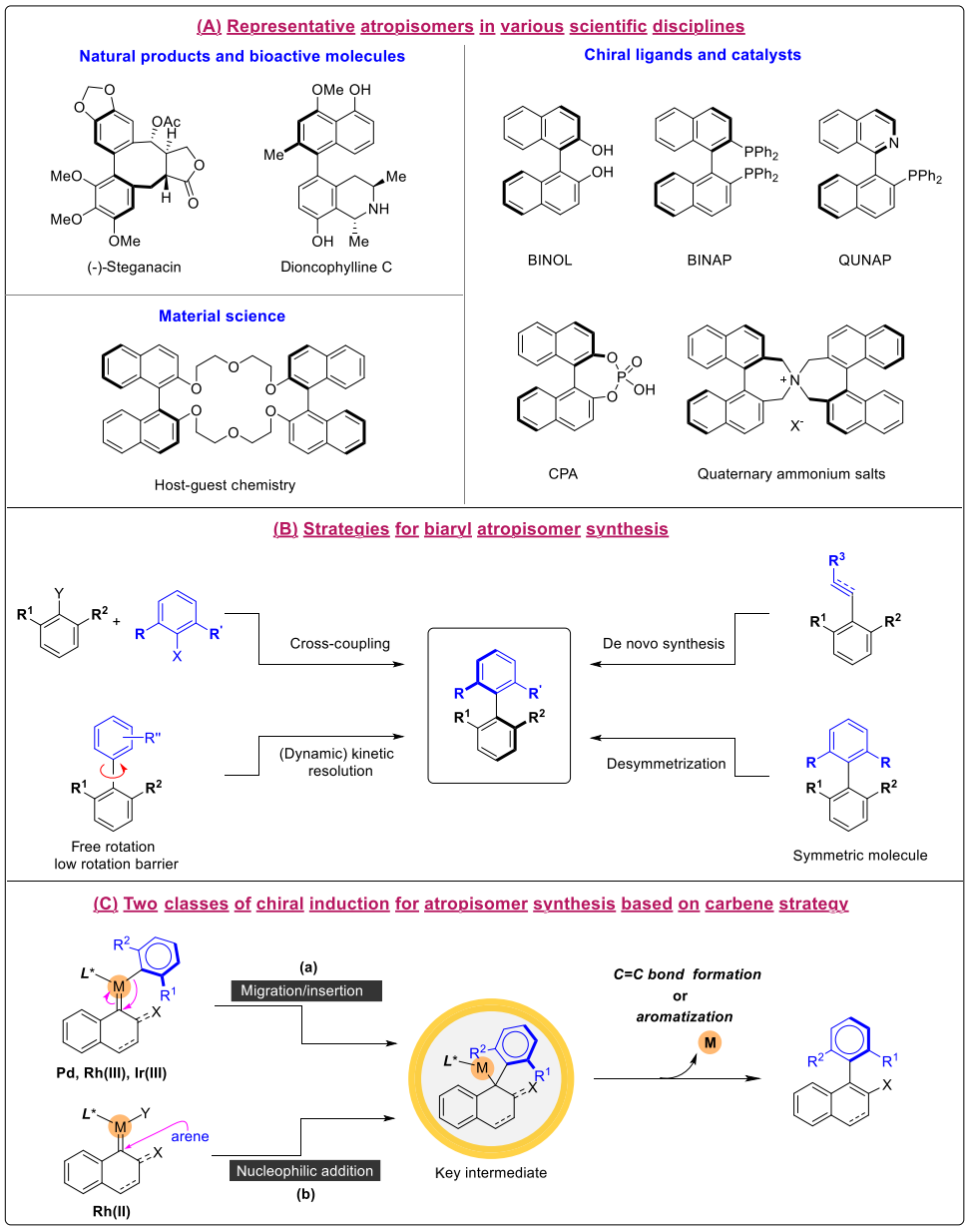


Figure 1. (A) Representative atropisomers in various scientific disciplines. (B) Elegant strategies to construct axial chirality. (C) Classes of chiral induction for the synthesis of atropisomers via transition-metal-catalyzed asymmetric carbene transformations. Abbreviations: BINAP, [2,2′-bis(diphenylphosphino)-1,1′- binaphthyl]; BINOL, (1,1′-binaphthyl-2,2′-diol); CPA, chiral phosphoric acid; QUNAP, [1-(2-(diphenylphosphaneyl)naphthalen-1-yl)isoquinoline].

transformation reactions provide an effective strategy to realize the extraordinary stereocontrol of axial chirality due to the versatility and high reactivity of metal carbenes. This review highlights advances in transition-metal-catalyzed asymmetric carbene transformation reactions towards atropisomers, focusing on the mechanistic classes of axial chirality generation.

construction (Figure 1C). In general, a transient quaternary carbon center intermediate bearing a C–metal bond is firstly generated via intramolecular **migratory insertion** of metal carbene into σ bonds (class a) or by intermolecular nucleophilic addition of electron-rich (hetero)arenes towards the metal-carbene pathway (class b). Then, the configurationally stable axis is fixed via central-to-axial **chirality transfer** accompanied by C=C bond formation or an aromatization process [36–39]. This review is classified into three parts depending on the mechanisms of axial chirality generation.

Intramolecular metal-carbene migratory insertion pathway (class a)

The intramolecular migratory insertion mechanism for metal carbene to access atropisomers is achieved by palladium (Pd)(0), rhodium (Rh)(III), and iridium (Ir)(III) catalysis. Commonly, all of these reactions proceed through: (i) the formation of an aryl metal species (oxidative addition for Pd, C–H activation for Rh and Ir); (ii) reaction of the aryl metal with a diazo compound (generated from *N*-tosylhydrazones for Pd, 1-diazonaphthoquinones for Rh and Ir) to form an aryl metal carbene; (iii) intramolecular migration insertion; and (iv) atropisomeric axis-forming demetallation (***β*-hydride elimination** for Pd, proton-transfer-mediated aromatization for Rh and Ir).

Pd/carbene involving migratory insertion and β-hydride elimination reactions

Pd-catalyzed carbene transformation reactions involving migratory insertion and *β*-hydride elimination have been widely studied since Van Vranken's seminal work in 2001 [40]. However, studies on the asymmetric catalysis in such types of reaction have received less attention because a new chiral center cannot be generated in the process [41].

Gu and Feng anticipated that atropisomeric styrene skeletons can be generated when C=C bonds are formed under certain circumstances. However, compared with axially chiral biaryls, this styrene atropisomerism exhibited lower stability due to the less rigid skeletons, which rendered effective stereocontrol more challenging [42]. A Pd-catalyzed **atropo-enantioselective** carbene migratory insertion reaction was first achieved in 2016 (Figure 2A) [43]. Axially chiral vinyl arenes **3** were obtained from aryl bromides **1** with *N*-tosylhydrazones **2** by employing TADDOL-derived phosphoramidite **L1**. A proposed catalytic cycle is shown in Figure 2A. Arylpalladium specie **A** was generated from the oxidative addition reaction of Pd(0) with aryl bromide **1a**, which then reacted with the diazo compound **B** (generated *in situ* from hydrazone **2a** in the presence of *t*BuOLi) to form the Pd carbene intermediate **C** with the release of N_2. Migration/insertion of **C** afforded **D** with a quaternary carbon center, and then *β*-hydride elimination occurred to access the desired vinylarene atropisomer **3a**. However, a low level of asymmetric induction was observed when a substrate with diethyl phosphonate was used, suggestive of the existence of a π–π interaction between the phenyl ring of the phosphine oxide and the tetrahydronaphthalene moiety in either intermediate **C** or **D**. In Wu's further related studies, substrates were further extended to alkoxyl-substituted phosphine oxides and *N*-tosylhydrazones with five- or six-membered rings by utilizing *P*-stereogenic chiral phosphine BI-BOP ligand **L2**, in 2017 (Figure 2B) [44]. However, asymmetric induction of a seven-membered ring *N*-tosylhydrazone remained challenging, albeit the target product was obtained in good yield.

Rh(III) or Ir(III)/carbene involving migratory insertion and aromatization reactions

Relying on significant breakthroughs in the synthesis of novel chiral cyclopentadienyl (Cp) ligands [45–56], $Cp^xM(III)$-catalyzed enantioselective C–H arylation through migratory insertion reactions of metal carbenes provide a straightforward approach for the synthesis of axially chiral (hetero)biaryls. In such types of reactions, metal carbene is generated from the directed C–H activation and sequential denitrogenation of 1-diazonaphthoquinones by the $Cp^xM(III)$ complex. After migratory insertion with the initial formation of central chirality, the protonation for

Glossary

***β*-Hydride elimination:** the process by which an alkyl group bonded to a metal center and with a hydrogen atom in the metal center can be converted to an alkene and a metal hydride.
Atropo-enantioselective: an enantioselective reaction with the formation of a configurationally stable chiral axis.
Chirality transfer: the process of transferring one form of chirality (e.g., central chirality, planar chirality, axial chirality, helical chirality) to another form.
Desymmetrization: an enantioselective reaction accessing enantiomerically enriched molecules from prochiral or mesocompounds.
Dynamic kinetic resolution: the process of transforming only one configuration of racemic substrates into only one configuration of enantiomerically enriched products.
Kinetic resolution: the process of transforming one configuration of racemic substrates into corresponding enantiomers.
Migratory insertion: the process of inserting one ligand of a metal center into another metal–ligand bond.

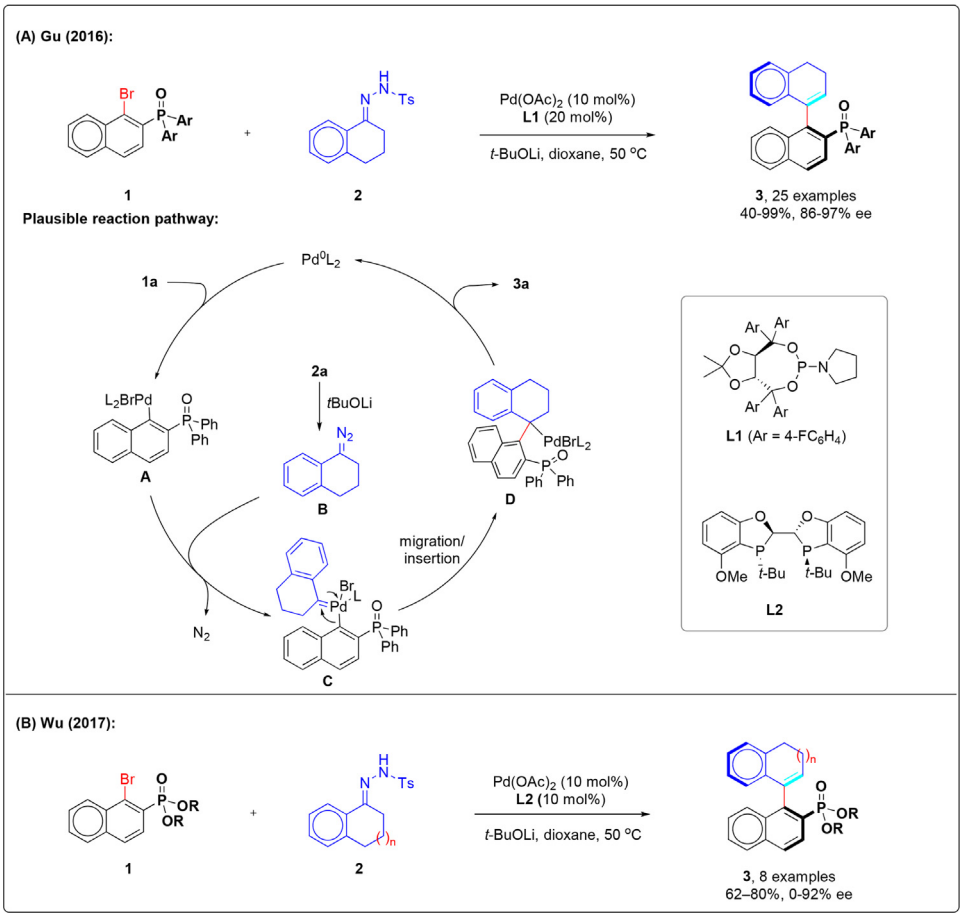
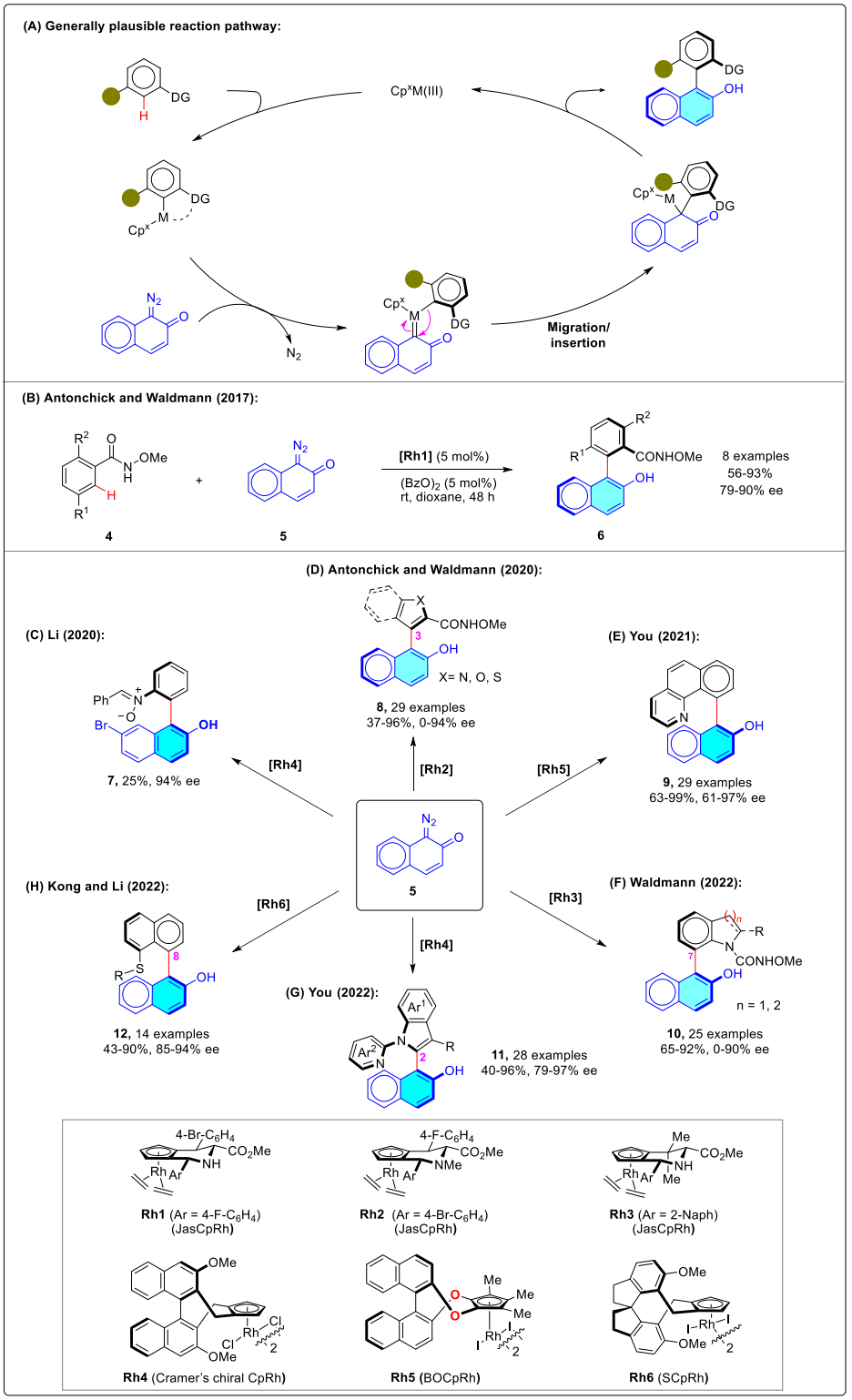


Figure 2. Pd-catalyzed atropo-enantioselective carbene transformations for the synthesis of vinylarene atropisomers (A,B). See [43,44]. Abbreviations: ee, enantiomeric excess; Ts, 4-toluenesulfonyl.

aromatization process occurs with the accomplishment of a locked chiral axis formation. This strategy strongly relies on the utilization of sterically hindered diazo reagents (Figure 3A).

An unprecedented example of a CpRh(III)-catalyzed atroposelective carbene migratory insertion reaction was achieved by the group of Waldmann and Antonchick in 2017, by an amide-directed C–H arylation of benzamides **4** with 1-diazonaphthoquinones **5** (Figure 3B) [57]. With a newly developed piperidine-fused cyclopentadienyl rhodium complex JasCpRh (**Rh1**), a variety of axially chiral biaryls **6** could be obtained with excellent enantioselectivity [up to 91% enantiomeric excess (ee)]. Benzamides bearing various electron-rich substituents in the meta position and various substituents at the 3-position of 1-diazonaphthoquinones were compatible in this reaction. In 2020, Li and coworkers disclosed the synthesis of conformationally metastable biaryl intermediate **7** from the reaction of monosubstituted arene substrate (nitrone) with 1-diazonaphthoquinone compound **5** enabled by Cramer's chiral CpRh(III) catalysts **Rh4** (Figure 3C) [58]. Subsequently, the group of Waldmann and Antonchick realized the synthesis of the five-membered-ring axially (benzo)furano, axially (benzo)thiopheno, and indolo atropisomer **8** with a C(3)–C chiral axis, in up to 96% yield and 94% ee (Figure 3D) [59]. Furthermore, in view of the significant effect on the reactivity and selectivity of the substituents on the Cp ring, the You group developed a new class of



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binaphthyl 'O'-linked chiral cyclopentadienyl ligands (BOCp) in 2021 (Figure 3E) [60]. In an enantioselective migratory insertion process for benzo[*h*]quinolines with 1-diazonaphthoquinones **5**, BOCp displayed much greater catalytic efficiency than the well-studied 'C'-linked chiral Cp [61], affording atropisomeric heterobiaryls **9** in up to 99% yield and 97% ee. The reaction was compatible with substituted 1-diazonaphthoquinones at the 3-, 6-, or 7-position, regardless of the steric or electronic properties. In 2022, catalytic atroposelective C7 arylation of indolines and indoles with 1-diazonaphthoquinones **5** was achieved by using **Rh3**, reported by the group of Waldmann under mild conditions (Figure 3F) [62]. Afterwards, the You group accomplished catalytic atroposelective C2 arylation of indoles with 1-diazonaphthoquinones **5** by employing SCpRh (**Rh4**), affording axially chiral indole-based frameworks **11** in good yields with excellent enantioselectivity (Figure 3G) [63]. At the same time, Li and coworkers explored the reaction of thioether-directed atroposelective C8-arylation of 1-naphthyl thioether with 1-diazonaphthoquinones **5** (Figure 3H) [64].

In addition to 1-diazonaphthoquinone compounds, other sterically hindered carbene precursors were explored for the synthesis of atropisomers in such a carbene strategy. For example, in 2022, *N*-sulfonyltriazoles **14** were first employed as arylating reagents for the construction of atropisomeric 2-naphthylamine derivatives **15**, reported by the groups of Kong and Li (Figure 4) [64].

Compared with the achievements attained via CpRh(III)-catalyzed atroposelective carbene transformations, studies on Ir-catalyzed systems have received less attention. An impressive example in Ir-catalyzed enantioselective synthesis of atropisomers through a carbene migratory insertion reaction was reported by the Cramer group in 2018 (Figure 5) [65]. Axially chiral biaryl phosphine oxides **17** with point chirality at phosphorus were obtained by an Ir(III) complex (**Ir1**) bearing an atropochiral cyclopentadienyl ligand in cooperation with chiral amino acid **CCA1** in up to 96% yield, 98% ee, and >20:1 diastereomeric ratio (dr). Control experiments confirmed that the carboxylic acid additive was crucial in achieving the higher reactivity and enantioselectivity.

As shown above, Cp^{x}M(III)-catalyzed asymmetric carbene transformation reactions have made outstanding progress for the synthesis of atropisomers. Nevertheless, tedious synthetic procedures for chiral Cp might impede their practical applications. Future studies should be encouraged to design and synthesize more synthetically available chiral cyclopentadienyl ligands and their complexes.

Intermolecular nucleophilic addition of electron-rich (hetero)arenes towards metal-carbene pathway (class b)

In the past decades, chiral dirhodium tetracarboxylates stood out as privileged catalysts in asymmetric reactions [66,67]. Rh(II)-catalyzed asymmetric N–H or C–H of electron-rich arene insertion reactions provide another successful approach for the synthesis of atropoisomers. Different from carbene transformation pathways for migratory insertion, intermolecular nucleophilic addition to metal carbene is exhibited in such types of reactions (Figure 6A).

Inspired by the work on catalytic asymmetric carbene insertions into N–H bonds [68,69], the Wang group reported a Rh(II)-catalyzed atroposelective N–H insertion (NHI) reaction of indolocarbazoles **18** with 1-diazonaphthoquinones **5** in 2021 (Figure 6B) [70]. Phthalimido-derived dirhodium catalyst Rh_2(*S*-PTAD)$_2$ proved crucial to achieve high enantioselectivity, and

Figure 3. CpRh-catalyzed atropo-enantioselective carbene transformations of 1-diazonaphthoquinones (A) with benzamides (B), a nitrone compound (C), (benzo)furans, (benzo)thiophenes, and indoles to construct a C(3)–C chiral axis (D), benzo[*h*]quinolones (E), indolines and indoles to construct a C(7)–C chiral axis (F), indoles to construct a C(2)–C chiral axis (G), and 1-naphthylthioethers (H). See [57–60,62–64]. Abbreviation: ee, enantiomeric excess.

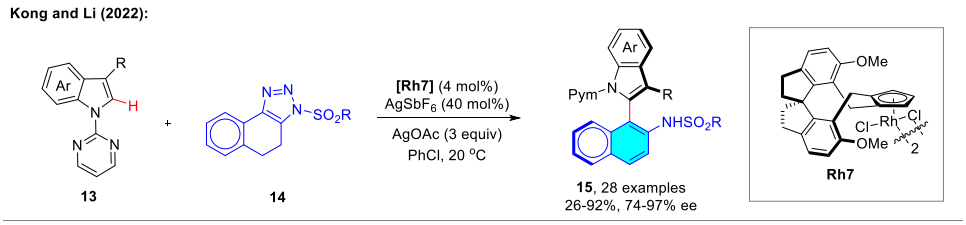


Figure 4. CpRh-catalyzed atropo-enantioselective carbene transformations with *N*-sulfonyltriazoles as arylation reagents. See [64]. Abbreviation: ee, enantiomeric excess.

various axially chiral *N*-arylindolocarbazoles **19** were obtained in up to 75% yield and 99% ee. It is worth mentioning that this work provides an alternative strategy to construct axially chiral heterobiaryls bearing an C–N axis by the direct formation of a new C–N bond. Afterwards, the groups of Yu and Sun successfully prepared *N*-arylindoles and *N*-arylcarbazoles **20** with excellent ee values (up to 98% ee) by this rhodium-catalyzed NHI reaction likely to be via a concerted process (Figure 6C) [71]. In 2021, the groups of Zhang and Sun realized a Rh(II)-catalyzed asymmetric C–H bond insertion reaction for electron-rich arenes for the synthesis of biaryl atropisomers **21** enabled by the 1,8-naphthalimido-derived dirhodium catalyst Rh_2(*S*-NTTL)$_4$ (Figure 6D) [72]. Subsequently, the Sun group successfully applied this method to the catalytic atroposelective C2 arylation of indoles with 1-diazonaphthoquinones **5**, affording axially chiral indole-based frameworks **22** in up to 80% yield and 98% ee (Figure 6E) [73].

Other classes of chiral induction for the synthesis of atropisomers via metal-carbene transformations

In addition to the two classes of asymmetric induction mentioned earlier, there are several other classes for the synthesis of atropisomers via metal-carbene transformations. Although these reactions undergo intramolecular metal-carbene migratory insertion or an intermolecular nucleophilic addition mechanism, metal-carbene transformation steps are not involved in the construction of the atropisomeric C–C bond. For example, in 2020 Gu and Xi locked a flexible C–C atropisomeric axis of the substrate **23** to access the strained macrocyclic olefin **24** by utilizing the ligand WingPhos **L3**, which could be a key step to furnish the synthesis of the atropisomeric natural product (–)-isoplagiochin D (**25**) (Figure 7A) [74]. Later, the construction of atropisomeric heterobiaryl styrenes **28** was achieved by a Pd-catalyzed dynamic kinetic

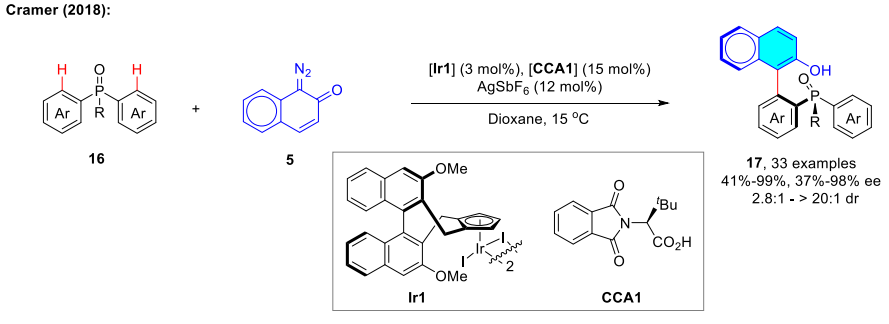


Figure 5. Cramer's CpIr/CCA-catalyzed atropo-enantioselective C–H arylation of phosphine oxides with 1-diazonaphthoquinones. See [65]. Abbreviation: ee, enantiomeric excess.

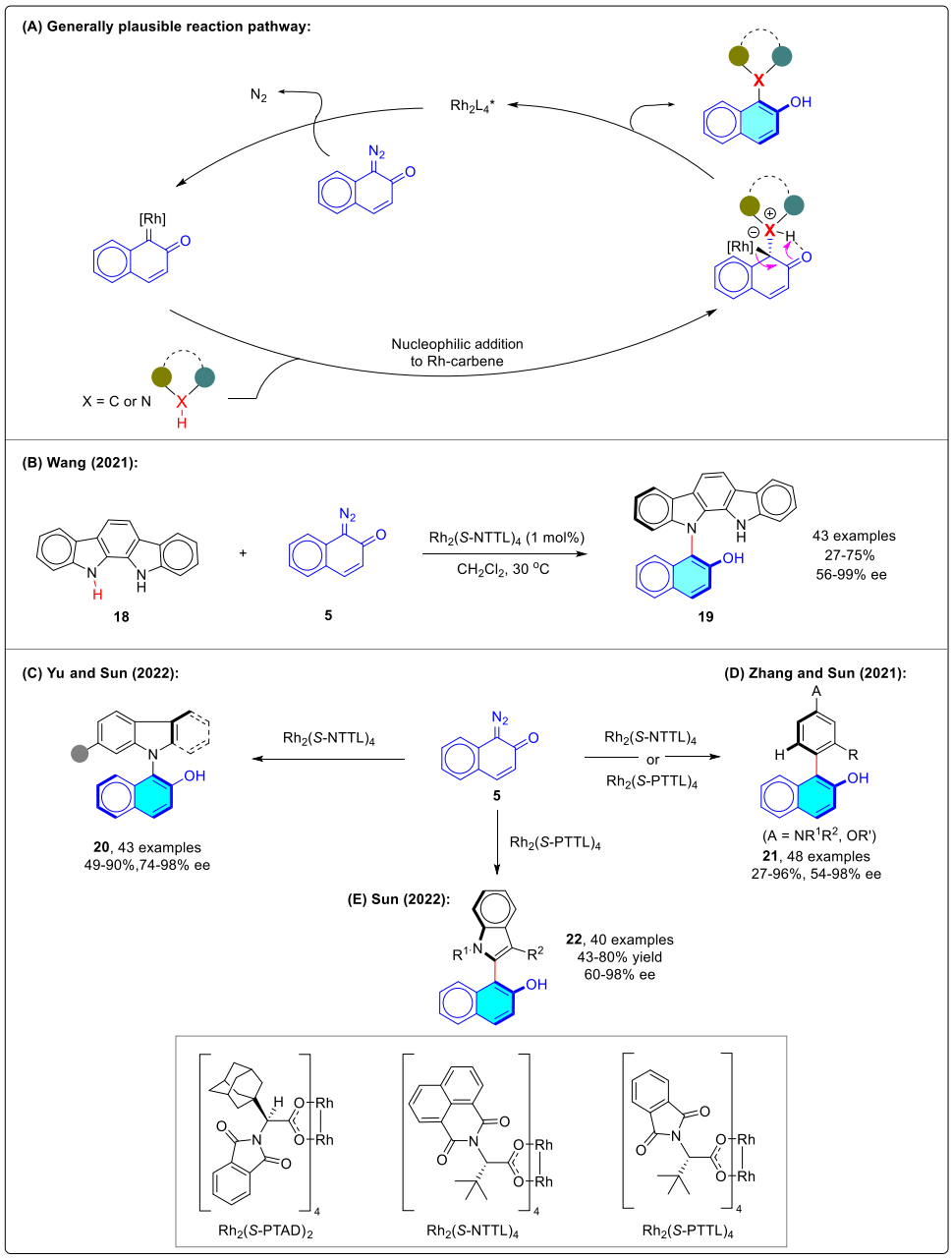


Figure 6. Rh(II)/carbene-involved nucleophilic addition and aromatization reactions. (A) Generally plausible reaction pathway. (B,C) Rh(II)-catalyzed N–H insertion reaction of 1-diazonaphthoquinones with indolocarbazoles, or *N*-arylindoles and *N*-arylcarbazoles. (D,E) Rh(II)-catalyzed formal C–H insertion of electron-rich arenes, or indole. See [70–73]. Abbreviation: ee, enantiomeric excess.

asymmetric coupling (DYKAT) reaction by means of racemic heterobiaryl bromides **26** with carbene precursors **27** via a five-membered labile carbenoid intermediate, reported by the group of Fernández and Lassaletta (Figure 7B) [75]. In 2022, the Li groups have extended the range of diazo reagents to *α*-diazo *β*-ketoester compounds **30** bearing a flexible C–C axis, to

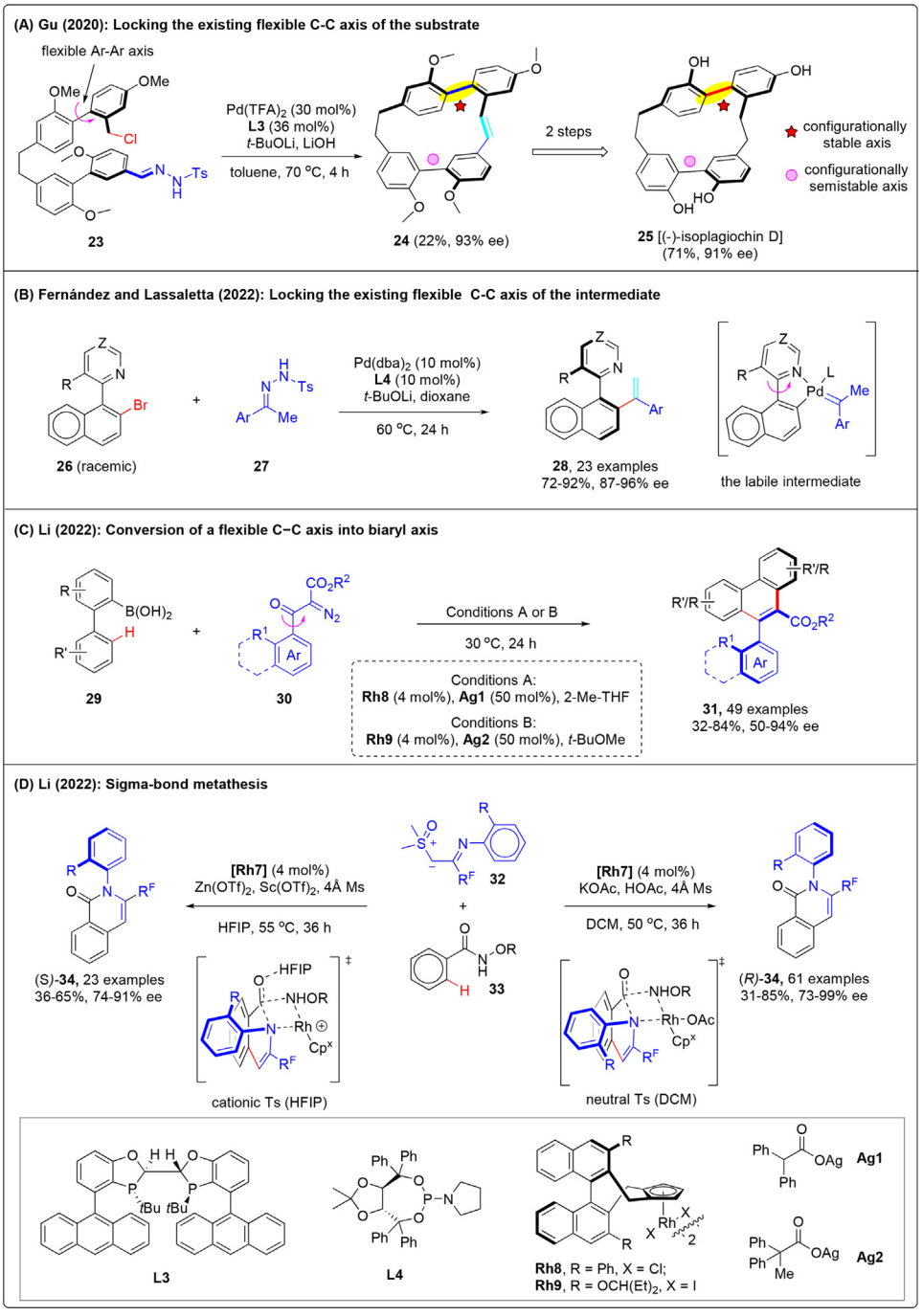
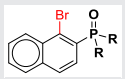
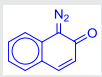
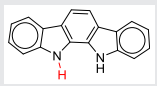
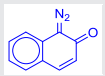
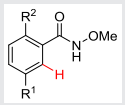
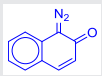
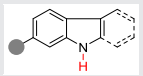
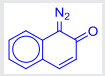
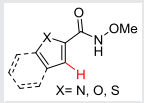
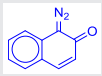
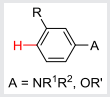
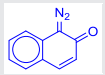
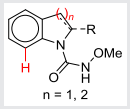
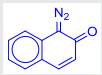
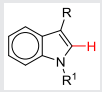
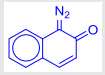
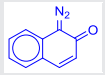
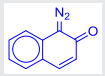
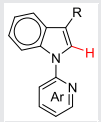
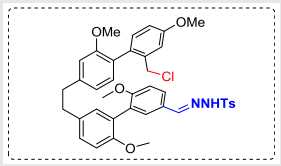
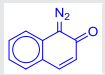
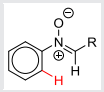
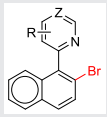
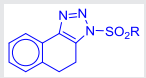
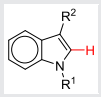
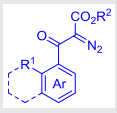
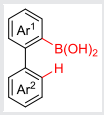
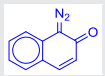
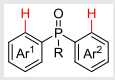
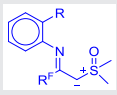
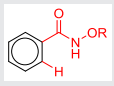


Figure 7. Other classes of chiral induction for the synthesis of atropisomers via metal-carbene transformations. (A) Locking the existing flexible atropisomeric C–C axis of substrates. (B) Locking the existing flexible atropisomeric C–C axis of intermediates. (C) Conversion of a flexible C–C axis in α-diazo β-ketoesters into a biaryl axis. (D) Sigma-bond metathesis. See [74–77]. Abbreviations: ee, enantiomeric excess; Ts, 4-toluenesulfonyl.

Table 1. Summary of transition-metal-catalyzed atropo-enantioselective carbene transformations

Intramolecular metal-carbene migratory insertion pathway				Intermolecular nucleophilic addition to metal-carbene pathway			
Carbene precursor	Substrate	Transition metal	Refs	Carbene precursor	Substrate	Transition metal	Refs
		Pd	[43] [44]			Rh_2(*S*-PTAD)$_4$	[70]
		JasCpRh	[57]			Rh_2(*S*-NTTL)$_4$ or Rh_2(*S*-PTTL)$_4$	[71]
		JasCpRh	[59]			Rh_2(*S*-NTTL)$_4$	[72]
		JasCpRh	[62]			Rh_2(*S*-PTTL)$_4$	[73]
		BOCpRh	[60]	Other classes of chiral induction			
		Cramer's CpRh	[64]	Carbene precursor	Substrate	Transition metal	Refs
		SCpRh	[63]			Pd	[74]
		Cramer's CpRh	[58]			Pd	[75]
		SCpRh	[64]			Cramer's CpRh	[76]
		Cramer's CpIr	[65]			SCpRh	[77]

obtain atropisomeric phenanthrenes **31** (Figure 7C) [76]. In this reaction, the C–C bond present in the α-diazo β-ketoesters converted into the configurationally stable biaryl axis. Recently, the groups of Huang, Crabtree, and Li reported a solvent-dependent enantiodivergent reaction with imidoyl sulfoxonium ylides **32** as effective partners for the synthesis of C–N axially chiral isoquinolones **34** (Figure 7D) [77]. Experimental and computational studies revealed sigma-bond metathesis as an enantiodetermining step, where the Rh carbene is not involved in the construction of the atropisomeric axis or in the asymmetric induction step.

Concluding remarks and future perspectives

Transition-metal-catalyzed atropo-enantioselective carbene transformation reactions have progressed rapidly due to the increasing attention on atropisomers and the fast development of chiral ligands and catalysts. Hence, we summarize the advances in transition-metal-catalyzed atropo-enantioselective carbene transformations focusing on mechanistic classes of axial chirality generation (Table 1). Compared with traditional synthetic approaches, relatively mild conditions are commonly employed in the asymmetric carbene transformation strategy, resulting in extraordinary stereocontrol of axial chirality. In this context, axially chiral vinyl arenes, (hetero)biaryls, ring-strained macrocyclic biaryls, *N*-arylindoles, and *N*-arylindolocarbazoles are obtained.

Despite the significant achievements so far, catalytic atropo-enantioselective carbene transformations remain in their infancy (see Outstanding questions). For example, 1-diazonaphthoquinone compounds as sterically hindered arylation reagents are strongly required in the current research, so structurally diverse carbene precursors remain to be explored based on the mechanistic understanding of asymmetric induction. Second, much attention is currently concentrated on the construction of atropisomers bearing C–C bonds, so the design and synthesis of atropisomers beyond C–C axial chirality, such as C–O, C–S, or C–B bonds, is in great demand. Third, instead of the noble metals Pd, Rh, and Ir, Earth-abundant and cost-friendly first-row transition metals such as Fe, Ni, and Cu may be highly worth trying in catalytic atroposelective carbene transformations. Fourth, desymmetrization has been proven a reliable strategy in asymmetric catalysis [78–81]. How to apply desymmetrization strategies to transition-metal-catalyzed atropo-enantioselective carbene transformations will be an attractive topic. In addition, catalytic enantioselective carbene transformations towards atropisomers is not yet a common strategy for the synthesis of chiral ligands and catalysts. How to design more effective axially chiral ligands and catalysts, especially those that are currently difficult to obtain, based on these new methods will be another important direction of development in this field. Encouraged by the pioneering work on Pd-catalyzed asymmetric macrocyclization reactions as a key step towards atropisomeric (–)-isoplagiochin D, the development of more effective catalytic systems to construct atropisomeric natural products and medicinal molecules especially in chembiology are highly expected, starting from suitable substrates and carbene precursors. It is our hope that this review will encourage future studies to address the outstanding synthesis challenges and that the development of more efficient synthesis of atropisomers taking advantage of catalytic atropo-enantioselective carbene transformations will continue to grow.

Outstanding questions

How can we design structurally diverse carbene precursors for diverse atropisomeric products?

Is it possible to synthesize atropisomers beyond C–C axial chirality (e.g., C–O, C–S, or C–B bond) by the carbene strategy?

Is it possible to realize catalytic enantioselective carbene transformations towards atropisomers by utilizing abundant and cheaper first-row transition metals (e.g., Fe, Ni, Cu)?

Can a desymmetrization strategy be applied for transition-metal-catalyzed asymmetric carbene transformation reactions to access atropisomers?

Will catalytic atropo-enantioselective carbene transformations become a commonly convenient strategy to obtain effective chiral ligands and catalysts that are currently difficult to obtain?

How can catalytic atropo-enantioselective carbene transformations be widely used as effective strategies in the synthesis of atropisomeric natural products and drug molecules in chembiology?

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Declaration of interests

The authors declare no interests.

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