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Review

Recent advances in asymmetric synthesis of 2-substituted indoline derivatives

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ABSTRACT

Enantiomerically pure 2-substituted indolines are an important class of nitrogen heterocycles that occur frequently in many alkaloid natural products and biologically active compounds. Consequently, the synthesis of such skeletons is of great significance. The past years have witnessed a number of remarkable advances in the development of efficient strategies to construct this class of chiral compounds. This review summarizes the recent advances in asymmetric synthesis of 2-substituted indoline derivatives. Due to the limitation of the length, this review only summarizes those works published from January of 2012 to January of 2019. Meanwhile, methods towards synthesis of fused and spirocyclic indolines will not be discussed in this review.

1. Introduction

Chiral indolines are an important class of nitrogen heterocycles because of their prevalence in many alkaloid natural products, pharmaceuticals, and biologically active compounds [1]. Of them, enantiomerically pure 2-substituted indolines have been utilized as chiral auxiliaries in asymmetric synthesis [2], therapeutic reagents [3] as well as a common motif of biologically significant compounds such as oleraceins A–D [4a], neuronal cell-protecting substances benzastatins E–G [4b], the antihypertensive drug Pentopril [4c], anticancer agent [4d], the antitumor agent [4e], and an oral antihypertensive/diuretic Indapamide [4f] (Fig. 1).

Given their extensive applications, chiral 2-substituted indolines have drawn the increasing interest of synthetic chemists [5]. Not surprisingly, in recent years, a number of efficient methods have been developed for the synthesis of these chiral compounds, including kinetic resolution, indole functionalization, asymmetric synthesis from chiral reagents, and asymmetric catalysis. This review concentrates on the typical strategies developed since 2012.

2. Kinetic resolution

Kinetic resolution of racemates is an effective method for the preparation of enantiomerically pure compounds, which is most widely used in the industrial sector [6]. In this regard, many enzymatic and non-enzymatic protocols have been well developed for the enantioselective synthesis of 2-substituted indolines. Thus, in this section, some representative achievements in this context will be discussed.

2.1. Enzymatic kinetic resolution

Strategies employing enzymes as catalysts for kinetic resolution of enantiomers have been proved to be one of the most elegant and sustainable protocols in synthetic organic chemistry [7]. Gotor-Fernández *et al.* developed an efficient chemoenzymatic process to afford 2,3-disubstituted indoline diastereoisomers [8]. The combination of *Candida antarctica* lipase type A (CAL-A) and allyl-3-methoxyphenyl carbonate **2** in TBME (*tert*-butyl methyl ether) as a solvent at 30 °C and 250 rpm for the necessary time allowed the isolation of the carbamate **3** and indoline (2*S*,3*S*)-**1** with excellent enantioselectivity (Scheme 1).

2.2. Non-enzymatic kinetic resolution

In addition to the kinetic resolutions based on the use of enzymes, transition-metal and organocatalyzed kinetic

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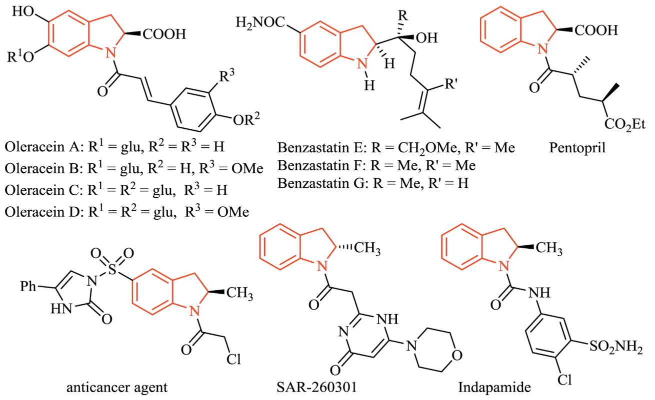
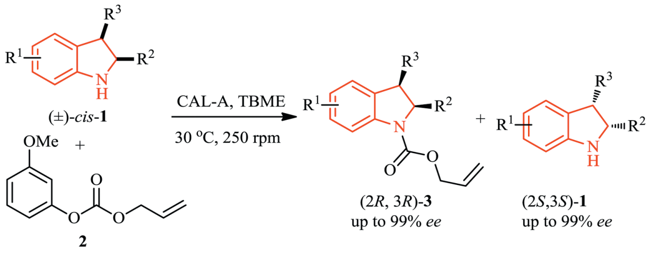


Fig. 1. Representative examples of biologically active 2-substituted indoline derivatives.



Scheme 1. Enzymatic kinetic resolution of (±)-*cis*-**1** with CAL-A and carbonate **2**.

resolutions also gain popularity recently due to the progress made in the discovery of novel chiral catalysts. So far, many approaches based on the catalytic non-enzymatic kinetic resolution have been developed with high enantioselectivity [9].

In 2013, Akiyama's group disclosed an oxidative kinetic resolution of 2-substituted indoline derivatives **1** [10a]. This transformation was achieved by asymmetric transfer hydrogenation to aromatic imines **4** by means of chiral phosphoric acid **5a**. A series of alkyl- or aryl-substituted indolines (2*S*,3*S*)-**1** were obtained in good yield with excellent enantioselectivity (Scheme 2a).

Subsequently, the same group reported another oxidative kinetic resolution of 2-substituted indoline derivatives **8** based on a self-redox reaction with a chiral phosphoric acid catalyst **5b**. This method featured an asymmetric intermolecular hydride transfer from indoline (*S*)-**8** to iminium intermediate **10** generated from the condensation reaction of indoline (*S*)-**8** with salicylaldehyde **9**. The oxidative kinetic resolution afforded another enantiomers (*R*)-**8** in high yield and excellent enantioselectivity (Scheme 2b) [10b].

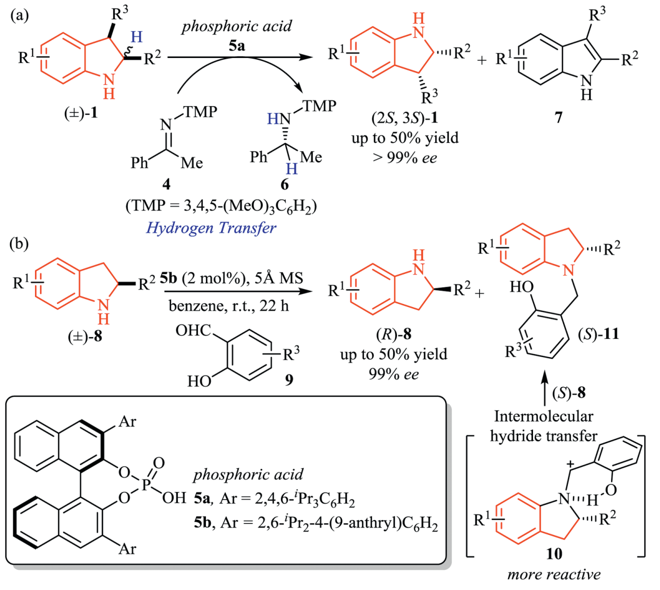
Moreover, Zhao *et al.* developed a protocol for obtaining the *N*-benzyl indolines (*S*)-**14** *via* oxidative kinetic resolution of *in situ* formed aldiminium intermediate in good yield with moderate to excellent enantioselectivity [11]. Different parameters such as hydride donor, catalyst, molecular sieves, and temperature were screened in order to establish the optimal reaction conditions (Scheme 3).

In 2017, Spivey and co-workers described a catalytic kinetic resolution of 2-substituted indoline derivatives by *N*-sulfonylation using an atropisomeric 2-aryl-4-DMAP-*N*-oxide catalyst **(-)-16**, affording the optically active 2-substituted indolines (*S*)-**17** [12]. The use of catalyst **16** in combination with 2-isopropyl-4-nitrophenylsulfonyl chloride **15** was crucial to achieve high enantioselectivity and facile deprotection of the sulfonamide products (*S*)-**17** could be easily realized with thioglycolic acid. A qualitative model **18** was established to rationalize the substrate scope for the stereodiscrimination (Scheme 4). The kinetic resolution of racemic indolines was extensively explored, mainly through acylation on the nitrogen atom [6].

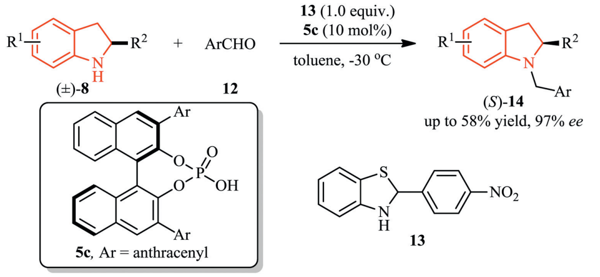
There are also some other impressive works in the field of kinetic resolution for the synthesis of chiral indolines. For instance, in 2013, Cai and co-workers found that the kinetic resolution of racemic 2-amino-3-(2-iodoaryl)propanoates **19** could be successfully achieved *via* Cu(I)/BINOL system-catalyzed intramolecular *N*-arylation [13] (Scheme 5). The reaction afforded chiral indolines (*S*)-**21** bearing chiral carbon centers at C2 position, and the starting materials (*R*)-**19** could be recovered with excellent enantioselectivity.

In 2016, the Fan group found that a kinetic resolution of 3*H*-indoles **22a**, **22b** bearing different substituents at C3 position could be realized by asymmetric hydrogenation [14]. Under the optimized reaction conditions, two hydrogenated products (2*R*, 3*R*)-**24a** (83% *ee*), (2*R*,3*R*)-**24b** (64% *ee*) as well as two recovered chiral substrates (*S*)-**22a** and (*S*)-**22b** were obtained with excellent enantioselectivity (97% *ee* and 93% *ee*) (Scheme 6).

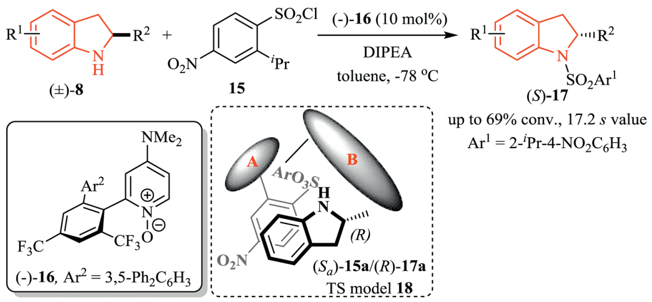
Zhang, Wang, and co-workers disclosed a Ru(II)-catalyzed dynamic kinetic resolution-asymmetric transfer hydrogenation of racemic 2-substituted-*N*-acetyl-3-oxoindolines **25** to *cis*-2-substituted-*N*-acetyl-3-hydroxyindolines **26** (Scheme 7) [15]. This method provided 2-substituted *N*-acetyl-3-hydroxyindoline derivatives **26** as only *cis* diastereomers in high yield (up to 98% yield)



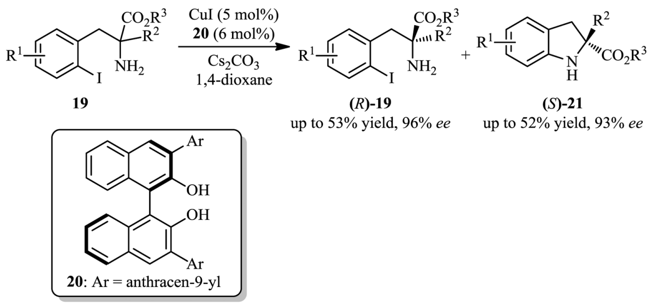
Scheme 2. Oxidative kinetic resolutions catalyzed by chiral phosphoric acid for the synthesis of optically active indolines.



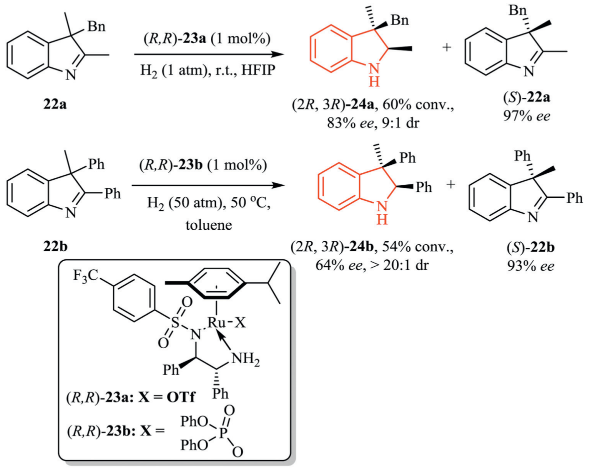
Scheme 3. Kinetic resolutions of indolines through reductive amination of aldehyde by indolines by chiral phosphoric acid.



Scheme 4. *N*-Sulfonylative kinetic resolutions of indolines using an atropisomeric 4-DMAP-*N*-oxide organocatalyst. DIPEA: *N*,*N*-diisopropylethylamine.



Scheme 5. Kinetic resolution of racemic 2-amino-3-(2-iodoaryl)propanoates by intramolecular *N*-arylation *via* Cu(I)/BINOL system.



Scheme 6. Kinetic resolution of racemic 3,3-disubstituted 3*H*-indoles by asymmetric hydrogenation. HFIP: hexafluoroisopropanol.

with excellent diastereoselectivity (>99:1 dr) and enantioselectivity (up to >99% *ee*). This result might arise from the proposed transition state **27**, wherein the orientation of the Ru-H catalyst **23c** and the phenyl group of the substrate played an important role.

3. Indole functionalization

3.1. Asymmetric hydrogenation of indoles

Chiral palladium complex have been extensively applied in asymmetric hydrogenation of a large number of substrates, including heteroaromatics [16]. In 2012, Zhou and co-workers accomplished an efficient asymmetric hydrogenation reaction of 2-substituted 3-(toluenesulfonamidoalkyl)indoles **28** using a chiral Pd catalyst in the presence of a Brønsted acid TsOH (Scheme 8a) [17]. In this reaction, the key vinylogous iminium intermediate **31** was initially generated from indole substrate **28** in the presence of Brønsted acid, which then underwent an asymmetric hydrogenation reaction to afford the chiral 2,3-disubstituted indolines **30** with up to 97% *ee*. Moreover, the one-pot tandem reaction (Friedel-Crafts/asymmetric hydrogenation) of 2-substituted indoles **32** also proceeded smoothly without erosion of the enantioselectivity (up to 95% *ee*) (Scheme 8b).

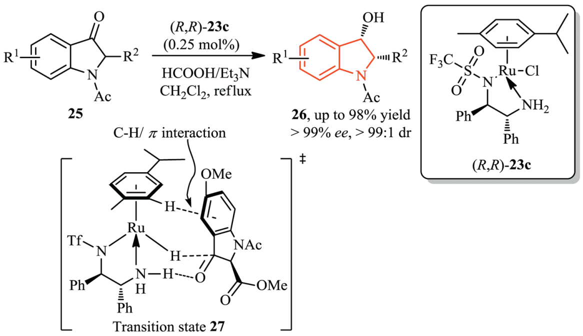
Taking advantage of this substrate activation strategy, Fan and Zhou *et al.* subsequently developed an efficient Pd-catalyzed asymmetric hydrogenation of an array of diversely substituted indoles **32** and **7** including 2-substituted and 2,3-disubstituted indoles (Schemes 9a and b) [18]. This methodology was also applied in the synthesis of biologically active indoline skeleton, a neuroleptic agent **34**. The mechanism of this process was extensively investigated by the control experiments and DFT (density functional theory) calculations. The isotope-labeling experiments and ESI-HRMS suggested that the involvement of the iminium intermediate should be formed *in situ via* the protonation of the C2 = C3 bond of simple unprotected indoles with Brønsted acid; this step was crucial for full conversion and high enantioselectivity in this reaction. This key intermediate was then hydrogenated by the chiral Pd catalyst through an outer-sphere mechanism involving stepwise proton and hydride transfers from active Pd-H species. The reaction took place well in highly polar solvents such as TFE (trifluoroethanol) due to its ability to stabilize the ionic intermediate **35** (Scheme 9c). The authors reported an asymmetric hydrogenation of unprotected indoles **7** by the same strategy with ligand **36** and $EtSO_3H$ as a Brønsted acid activator, although the results obtained, in terms of enantioselectivity, were not as good (up to 87% *ee*; Scheme 9d) as that with *p*-TsOH (up to 98% *ee*; Scheme 9b) [19].

Shortly thereafter, Liu, Zhang and co-workers also reported the Pd-catalyzed enantioselective hydrogenation of differently substituted indoles **7** using an axially chiral diphosphine (S)-C10-BridgePhos ligand **37** with a large bite angle. With D-CSA (D-camphorsulfonic acid) as activator, chiral indoline products (2*S*, 3*S*)-**1** were obtained in quantitative conversion and excellent enantioselectivity (up to 98% *ee*, Scheme 9e). The authors proposed that the substituent at 2-position played an important role in the hydrogenation process [20].

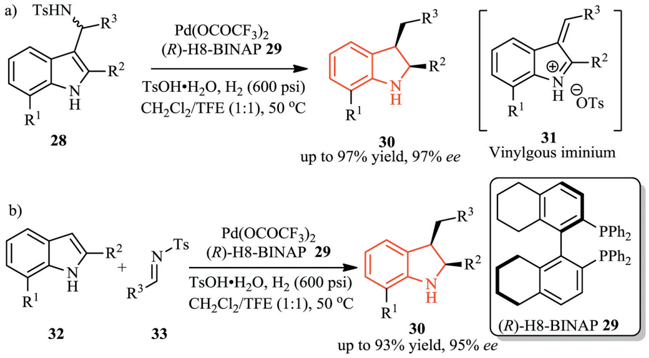
In 2018, Zhou's group accomplished a more concise and enantioselective route for the chiral indoline synthesis through a one-pot procedure, which involved a sequential intramolecular condensation, deprotection and palladium-catalyzed asymmetric hydrogenation [21]. Again, it was found that the Brønsted acid played a significant role in this process (Scheme 10). Notably, this methodology could be scaled up without obvious loss of reactivity and enantioselectivity.

In 2018, Chung, Zhang and co-workers reported a Brønsted acid-promoted Rh-catalyzed asymmetric hydrogenation of *N*-unprotected indoles **7** (Scheme 11). Fluorinated alcohol was avoided in this reaction, which made this methodology more economic to chiral indolines with high enantioselectivity (up to 99% *ee*, up to 400 TON). Mechanistically, the reaction proceeded via the substrate activation with Brønsted acid, thiourea anion binding, and rhodium/ZhaoPhos complex. In addition, DFT calculations revealed an outer-sphere mechanism in this transformation [22].

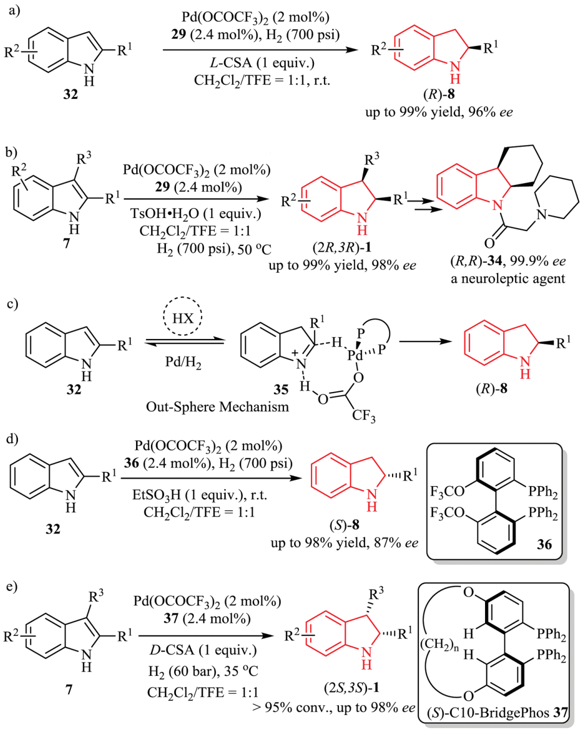
Despite the above-mentioned powerful methods, several challenges still remained: the use of stoichiometric amounts of Brønsted acid as the activator and the relatively high catalyst loading. In order to tackle these challenges, Vidal-Ferran and co-workers employed enantiomerically pure iridium complexes



Scheme 7. Ru(II)-catalyzed dynamic kinetic resolution-asymmetric transfer hydrogenation of racemic 2-substituted-N-acetyl- 3-oxoindolines.



Scheme 8. Pd-catalyzed asymmetric hydrogenation of 3-(toluenesulfonamidoalkyl)indoles and its tandem process.



Scheme 9. Pd-catalyzed asymmetric hydrogenation of indoles.

derived from their P-OP ligand **42** (relatively low loading: 1 mol%) and (easily recyclable and reusable) Brønsted acids for the efficient asymmetric hydrogenation of unprotected indoles, which allowed the formation of optically pure indolines with up to 78% yield and 91% *ee* (Scheme 12) [23]. Remarkably, the DOWEX^{TM} 50WX8 resin could be recovered, recycled, and reused for twice, showing comparable catalytic activity.

The above results showed that easily accessible phosphite and phosphoramidite ligands could compete with chiral phosphine ligands in asymmetric hydrogenation of unsaturated substrates. Lyubimov *et al.* further performed a Ir-catalyzed asymmetric hydrogenation of 2-methylindole **32a** using phosphoramidite **43** or **44** as ligand and I_2 as additive, delivering the product (*R*)-**8a** in quantitative conversion with good enantioselectivity (Scheme 13) [24].

Cationic Ru/chiral diamine complexes are very efficient catalysts for the asymmetric hydrogenation of several *N*-heteroaromatic compounds and ketimines with excellent enantioselectivity [25]. The superiority of these catalysts were demonstrated by Fan and co-workers, who established a highly enantioselective synthesis of indolines by asymmetric hydrogenation of unprotected 1*H*-indoles **7** (Scheme 14a) [14]. This protocol featured broad substrate scope, excellent enantioselectivity and diastereoselectivity, mild reaction conditions (ambient temperature and pressure), and no use of additives. Further mechanism study revealed that the indole substrate was activated by the *in situ* generated TfOH from dihydrogen and the cationic ruthenium complex, and a Ru-H species was also formed to reduce the activated substrate **45** *via* a hydride transfer process.

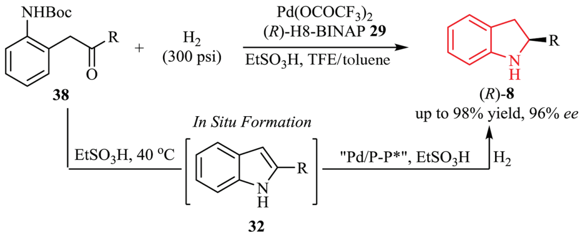
They further expanded this catalytic system to 3*H*-indoles **46**, leading to the synthesis of 2,3,3-trisubstituted indolines (*R*)-**47** (Scheme 14b) [14]. It is worthy to mention that 3*H*-indoles are much more difficult substrates for hydrogenation, and transition-metal-catalyzed asymmetric hydrogenation of this class of substrates has not been reported yet [26]. Shortly after, Rueping *et al.* also reported an asymmetric iridium-catalyzed hydrogenation protocol of 3*H*-indoles **46** with (*R*)-DM-Seg-Phos ligand **48** (Scheme 14c) [27].

Almost at the same time, Touge and Arai discovered that various unprotected indole compounds **7** could be efficiently hydrogenated by diamine-Ru(II)-BF_4 catalysts **23** with weakly acidic HFIP as the solvent (Scheme 15) [28]. Moreover, the solvent could be easily recovered quantitatively by simple distillation and reused in the next hydrogenation without loss of yield or enantioselectivity. The isotopic labeling experimental results proved that unprotected indole compounds were activated in the acidic HFIP solvent to form an iminium intermediate, which was then hydrogenated efficiently by the diamine-Ru(II)-BF_4 complexes **23** through cooperation interaction between ruthenium-hydride, amine-NH and iminium intermediate, enabling asymmetric indoline synthesis. CH/π interaction between a hydrogen atom on the η^6-arene and the aromatic ring of a substrate was also proposed in the transition state **49**.

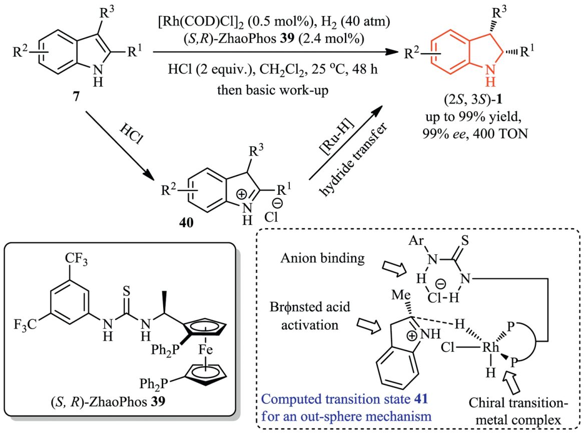
3.2. Asymmetric hydrosilylation of indoles

Catalytic hydrosilylation has been established as a powerful strategy for the reduction of unsaturated compounds, such as carbonyl, enamino and heteroaromatic compounds [29]. For example, works from the Sun group demonstrated that employment of the organic Lewis base catalyst **50**/$HSiCl_3$ (trichlorosilane) system allowed for the easy preparation of chiral 2,3-disubstituted indolines **30** (Scheme 16) [30]. Starting from the simple 2-substituted indoles **32** and aldehydes **12**, a tandem reaction occurred, giving the corresponding products with high yield and enantioselectivity.

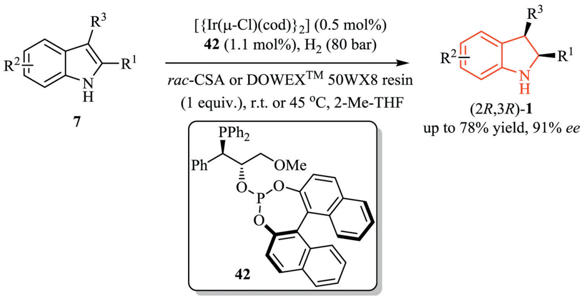
A possible reaction mechanism was also proposed. The 3-(α-hydroxyalkyl)indoles **51** could be easily formed through the Friedel-Crafts reaction of the activated indole substrate **32** with



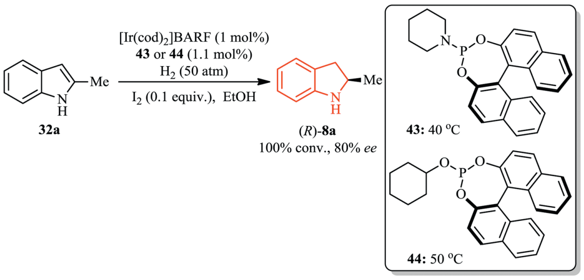
Scheme 10. Asymmetric hydrogenation of *in situ* generated indoles.



Scheme 11. Asymmetric hydrogenation of indoles with simple Brønsted acid: a cocatalysis of transition metal and anion binding.



Scheme 12. Ir-catalyzed asymmetric hydrogenation of indoles with reusable Brønsted acid. THF: tetrahydrofuran.



Scheme 13. Ir-catalyzed asymmetric hydrogenation of 2-methylindole using phosphoramidite ligand and I_2 additive.

aldehyde **12**, which subsequently underwent dehydration to give vinylogous iminium intermediate **52** in the presence of Brønsted acid. Then, reduction of **52** with trichlorosilane led to **53**. Notably, the water formed as by-product in the dehydration step could be easily consumed by trichlorosilane, which not only facilitates water elimination, but also releases hydrochloride as Brønsted acid activator for the indole intermediate in the hydrosilylation. As a result, no external Brønsted acid was needed.

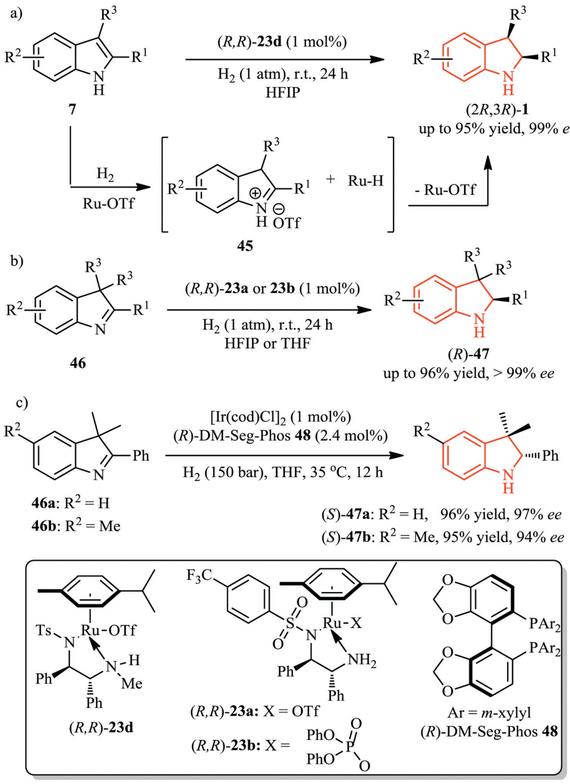
3.3. Reactions of indoles at C2 or C3 position

Enantioselective dearomatization reactions of indoles are a powerful class of transformations in the field of indole functionalization [31]. In 2015, Ito *et al.* realized an asymmetric borylative dearomatization of indole-2-carboxylates **54** using a chiral bisphosphine-Cu(I) catalyst and a diboron reagent **55** (Scheme 17) [32]. The experimental results and DFT calculation showed that the electron-withdrawing substituent at the 2-position in the indole substrates facilitated the addition of an active borylcopper(I) species to the indoles. Then, diastereoselective protonation of the resulting copper(I) enolate **57** by alcohol additives gave the corresponding chiral indoline derivatives **58** with excellent diastereo- and enantioselectivity.

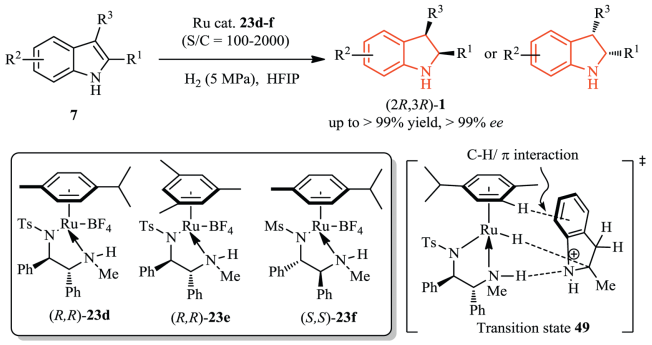
In addition to 2-substituted indoles, Xu and co-workers developed an asymmetric copper(I)-catalyzed dearomative borylation of 3-substituted indoles **59**, affording highly functionalized 2,3,3-trisubstituted chiral indolines **61** with generally excellent yield, diastereo- and enantioselectivity (Scheme 18a) [33]. Subsequently, they extended this strategy to an asymmetric dearomative silylation of 3-substituted indoles **62** (Scheme 18b) [34]. In this transformation, chiral NHC (*N*-heterocyclic carbene)-copper(I) complex was chosen as the catalyst instead of using phosphine ligand, which was probably due to the competitive decomposition of the silylation reagent $PhMe_2Si$-Bpin. Mechanistic studies suggested that facile epimerization of the 3-acyl group at C3-position was responsible for the observed high diastereoselectivity.

In 2017, the Ready group reported an enantioselective three-component coupling of indoles **66**, boronic esters **67** and allylic acetate **68** to provide chiral indolines **72** with high diastereoselectivity and enantioselectivity (Scheme 19a) [35]. The reaction involved the formation of boronate intermediates **70** from boronic esters and 2-lithiated indoles, outer sphere addition of this intermediate to a Pd(II) (π-allyl) complex, and protodeborylation. In an extension of this concept, they further found that unsubstituted allyl acetate was also applicable for the synthesis of indoline boronic esters **77** using phosphoramidite **76** in asymmetric Pd-catalyzed reaction for the first time [36]. Several boronic esters were well incorporated, and selected ones were treated for the prodeborylation. Enantioselectivity was maintained at high level, while the diastereoselectivity was somewhat decreased in certain cases.

3*H*-Indoles have also been used in several transformations, such as hydrogenation mentioned above, nucleophilic additions, Diels-Alder (DA) reactions, which provide a direct and efficient access to chiral 2-substituted indolines [14]. In 2012, Tian *et al.* described a qunidine-based thiourea **80-**catalyzed enantioselective Strecker reaction of 3*H*-indoles **79** with ethyl cyanoformate **81** as a CN source, giving 2-cyanoindoline **82** with excellent yield and enantioselectivity (Scheme 20a) [37]. Both two enantiomers of the products could be obtained by using catalyst **80** and its pseudoenantiomer **80'**, respectively. In this process, HCN was formed as the actual cyanating agent. The high enantioselectivity might be attributed to the simultaneous activation of both indole substrate and the cyanide anion by the qunidine-based thiourea catalyst. The same group further expanded this organocatalytic strategy to the Mannich reaction of 3*H*-indoles **84** with ketone **86**. Through this transformation, a range of optically active 2-acylmethylindolines **87** were prepared in good yield with excellent *ee* value. However, the scope of the ketone substrates was limited.



Scheme 14. Asymmetric hydrogenation of unprotected 1*H*- and 3*H*-indoles.



Scheme 15. Asymmetric hydrogenation of unprotected 1*H*-indoles catalyzed by Ru/chiral diamine complexes.

Less active ketones such as acetophenone and cyclohexanone were not suitable for this reaction. A possible chair-like transition state model **88** was proposed, in which hydrogen-bond interaction between enamine and 3*H*-indole could rationalize the asymmetric induction (Scheme 20b) [38].

4. *De novo* construction of chiral 2-substituted indolines

In addition to indole functionalization, the *de novo* construction is an alternative efficient method to access enantioenriched 2- or 2,3-disubstituted indolines from versatile starting materials. Most of the methods are based on the construction of pyrrolidine ring, which avoid the use of preformed indole substrates. In this section, chiral synthons strategy, organocatalysis and metal catalysis are briefly discussed.

4.1. Chiral synthons strategy

In 2013, Xiao and co-workers reported an interesting [4 + 1] annulation of chiral sulfur ylides **89** derived from (*R*)-BINOL and *N*-(*ortho*-chloromethyl)aryl amides **90** to access chiral 2-substituted indolines in moderate to high yield and enantioselectivity (up to 93% yield, 91% *ee*) (Scheme 21) [39]. Significantly, after the completion of the reaction, chiral sulfide **92** could be recovered in 95% yield, and reused in the preparation of chiral sulfur ylide.

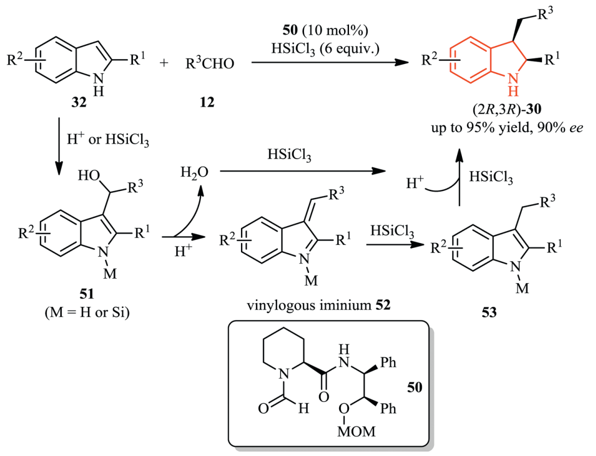
Besides [4 + 1] annulation strategy [40], [3 + 2] cycloaddition is also an effective protocol for the construction of the pyrrole ring in the indoline unit. In 2017, Sudalai *et al.* demonstrated a one-step formal [3 + 2] cycloaddition of *in situ*-generated arynes as two-atom component and γ-amino-α,β-unsaturated esters that were easily accessible from α-amino acids (Scheme 22a) [41]. This methodology featured readily accessible starting materials, mild reaction conditions, good yield and excellent level of regio- and diastereoselectivity, leading to the synthesis of 2,3-disubstituted indolines with good yield and diastereoselectivity. The Ikawa group also reported a similar work almost at the same time. Notably, substrates with electron-withdrawing cyano group could lead to retention of the optical integrity of the arynophile, thus allowing its diverse further transformations into other functional groups (Scheme 22b) [42].

In 2018, Chang and co-workers described an intramolecular Buchwald-Hartwig cross coupling of methyl (*R*)-2-amino-3-(2-bromoaryl)propanoates **99**, prepared from Williams intermediate **98**, for the synthesis of enantiopure 2-substituted indolines **100** in excellent yield (Scheme 23) [43]

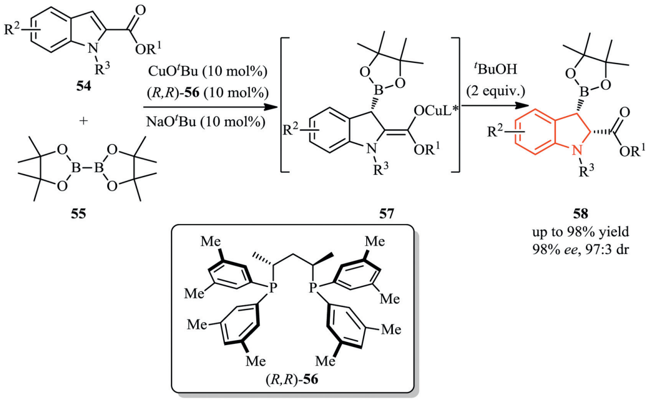
4.2. Organocatalysis strategy

Asymmetric organocatalysis has witnessed a significantly explosive growth over the past decades [44]. The development of new and efficient processes to synthesize chiral indolines *via* asymmetric organocatalysis has also become and will continue to be an intriguing research topic in recent years. In 2013, Asano and Matsubara demonstrated a novel method for the asymmetric synthesis of a variety of 2-substituted indolines **103** *via* intramolecular *aza*-Michael addition approach using a bifunctional aminothiourea catalyst **102**. The reaction was applicable to a wide range of different substrates mediated by activation *via* hydrogen bonding (Scheme 24a) [45]. In 2017, Kim *et al.* also developed an organocatalytic intramolecular Michael addition reaction of (*E*)-3-(2-(2-oxopropylamino)aryl)-1-arylprop-2-en-1-ones **104a**, employing a primary amine catalyst **105** derived from cinchona alkaloid (Scheme 24b) [46]. The corresponding *cis*-2,3-disubstituted indoline derivatives **107a** were obtained in high yield with excellent enantioselectivity and moderate diastereoselectivity. Moreover, the organocatalytic reaction of (*E*)-3-(2-(2-oxopropylamino)aryl)-1-alkylprop-2-en-1-ones **104b** also worked quite well, delivering *trans*-2,3-disubstituted indoline derivatives **107b** with excellent results. As illustrated in transition state **108**, the *Si*-face of the enamine genertated from the substrate and catalyst approached the *Re*-face of *tert*-butyl α,β-unsaturated ketone moiety, forming the final *S,S*-configured *trans*-indoline **107b**.

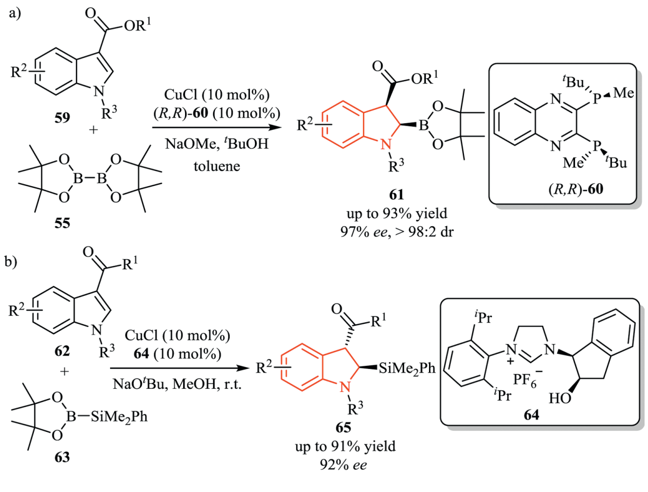
Enantioselective halogenations of alkenes have recently received much attention from the synthetic community [47]. In 2014, the Wirth group reported an organocatalytic stereoselective iodoamination reaction of alkenes **109** with NIS (*N*-iodosuccinimide) **111** as the electrophilic iodine source using a chiral thiohydantoin catalyst **110**. The reaction proceeded through halogen bonding interaction between the Lewis-basic sulfur center and the electrophilic iodine atom (Scheme 25a). On the



Scheme 16. Asymmetric organocatalytic tandem hydrosilylation of 2,3-disubstituted indoles. MOM: methoxymethyl.



Scheme 17. Enantioselective borylative dearomatization of 2-substituted indoles by Cu(I) catalysis.



Scheme 18. Enantioselective borylative and silylative dearomatization of 3-substituted indoles through Cu(I) catalysis.

basis of the experimental results and NMR studies, it was suggested that the additives and the electronic properties of the aromatic ring in the substrate could influence the regioselectivity of the cyclization step [48].

In 2017, Deng and co-workers achieved an enantioselective bromoamination of allyl anilines **114** with NBS (*N*-bromosuccinimide) **116** with BINOL-derived monosulfide **115** as catalyst. This protocol provided a series of chiral 2-bromomethyl indolines **117** in good to excellent yield with high enantioselectivity (Scheme 25b). Importantly, the products could be easily transformed into other useful building blocks [49].

4.3. Metal catalysis

4.3.1. Cu(II)-catalyzed enantioselective alkene amination reactions

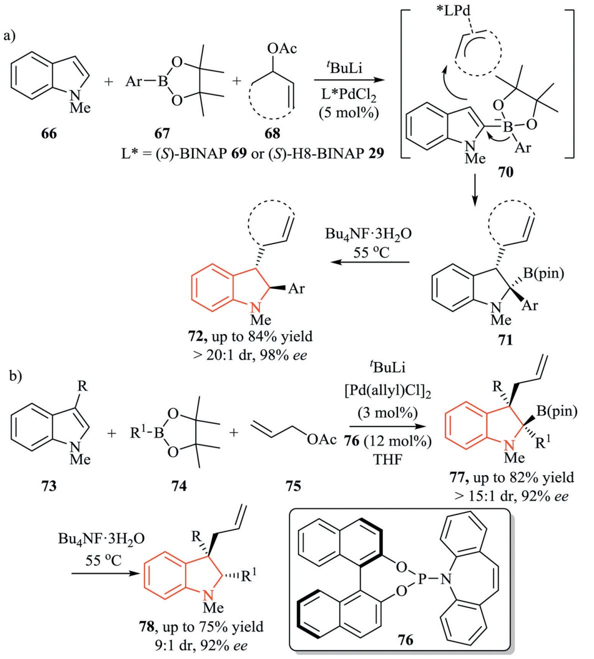
The Chemler group developed a series of Cu(II)-catalyzed enantioselective alkene amination reactions toward C-N bond formation. They firstly reported an enantioselective intramolecular alkene aminooxygenation of γ-aminoalkenes **118** using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO) **120** as the oxygen source for the synthesis of chiral indoline derivatives **121** [50a]. The N-O bond of the products could be reduced to the corresponding alcohols without loss of enantiopurity. The reaction could also be performed on a multigram scale [50b]. In addition, mechanistic analysis supported that the reaction occurred through an enantioselective *cis* aminocupration of the γ-aminoalkene **118a** followed by C-Cu(II) homolysis, thereby generating a chiral β-aminoalkyl radical **124a**, which was trapped with TEMPO to afford the aminooxygenation product **121a** (Scheme 26a).

The generated radical **124a** could also be intercepted by other radical acceptors, affording the corresponding difunctionalized products. In 2012, they described an enantioselective intramolecular alkene amination/intermolecular Heck-type coupling cascade process. The addition of the generated chiral carbon radical **124** to another vinyl arene **125** and subsequent oxidation provided the functionalized chiral indolines **127** (Scheme 26b) [50c]. They further developed an enantioselective alkene aminohalogenation/cyclization based on atom transfer of the generated chiral carbon radical **124** to give a wide range of chiral 2-halomethyl indolines **129** with good to excellent yield and enantioselectivity (Scheme 26c) [50d]. Based on this previous work, they reasoned that a hydroamination product could be obtained by atom transfer *via* hydrogen abstraction from a hydrogen donor, and thus developed a successful implementation of this strategy using 1,4-cyclohexadiene **130** as a hydrogen source (Scheme 26d) [50e]. In 2014, they also expanded the scope of copper-catalyzed inter/intramolecular alkene diamination protocol for the synthesis of 2-aminomethyl indolines **133** (Scheme 26e) [50f].

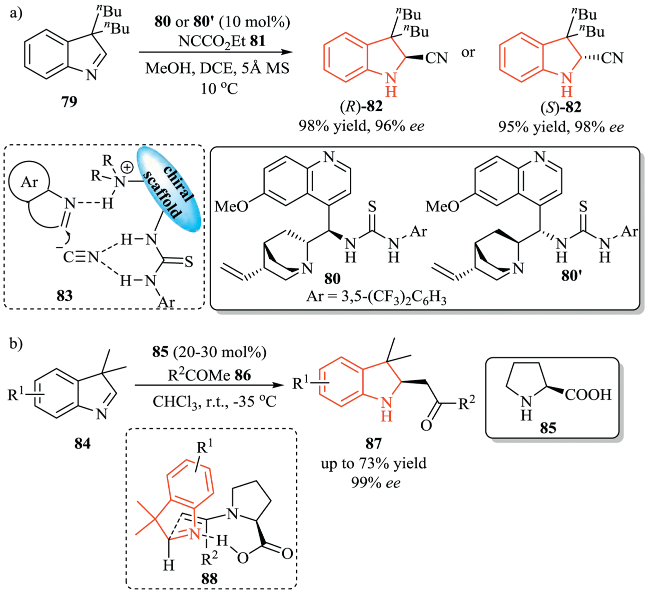
4.3.2. Pd-catalyzed C(sp^3)-H bond activation/cyclization

Pd-catalyzed C(sp^3)-H bond activation/cyclization has been established as one of the most efficient methods in the field of heterocycle synthesis [51]. In 2012, Cramer and co-workers disclosed a Pd-catalyzed C(sp^3)-H bond activation/cyclization of aryl triflates **134** to form indolines **137** in a highly enantioselective fashion using modular monodentate phosphine ligands **135** (Scheme 27). It was found that the ligand and carboxylic acid **136** were necessary for the metalation and played an important synergistic role in the reaction [52].

In the same year, the Kündig group reported a Pd-catalyzed C(sp^3)-H/C(Ar) coupling of racemic carbamates **138** with chiral NHC ligands **139**. 2-Methylindolines **141** were obtained with high enantioselectivity using $PCy_3 \cdot HBF_4$, IPr·HCl and (*R*,*R*)-Me-DUPHOS as the chiral ligand. However, when (*S*,*S*)-**139a**, (*S*,*S*)-**139b** were used, regiodivergent reactions of racemic mixtures occurred to yield enantioenriched 2-substituted and 2,3-disubstituted indolines *via* asymmetric methyl C-H activation or methylene C-H activation (Scheme 28) [53]. The combined theoretical and experimental studies showed that the Pd-NHC catalyzed C(sp^3)-H arylation proceeds *via* a concerted metalation-deprotonation



Scheme 19. Pd-catalyzed asymmetric three-component coupling of boronic esters, indoles and allylic acetates.



Scheme 20. Organocatalytic transformations of 3*H*-indoles. DCE: 1,2- dichloroethane.

(CMD) pathway. The stereoselectivity was determined by this CMD step [54]. In 2014, they continued to probe the scope and limitations of this transformation, and found that single regioisomeric, enantiopure products rather than mixtures were produced with enantiopure starting materials. Based on the DFT study, the reactivity of methyl *versus* methylene groups was analyzed for the rationalization of the selectivity observed in regiodivergent reaction of a racemic mixture [55].

In 2016, Duan *et al.* reported Pd-catalyzed asymmetric C(sp^3)-H activation of *N*-aryl carbamate **142** with chiral phosphoric acid **5d**. After condition optimizations, 2-methylindolines **143** were obtained with moderate yield and enantioselectivity (Scheme 29) [56].

Meanwhile, the Baudoin group developed a Pd-catalyzed enantioselective C(sp^3)–H activation/cyclization reaction of **144** using a BINOL-derived phosphoric acid **5a** and an achiral phosphine ligand (Scheme 30). High levels of enantioselectivity for a variety of indoline products **145** were achieved by fine tuning phosphoric acid pre-catalyst, and other reaction parameters (solvents, additives *etc.*) [57].

4.3.3. Decarboxylation/cycloaddition sequence

1,4-Dipoles, generated by transition-metal catalysis from readily available substrates, were found to be versatile intermediate in the field of cycloaddition reactions [58]. In 2014, the group of Lu and Xiao developed a Pd-catalyzed asymmetric decarboxylation/cycloaddition sequence of vinyl benzoxazinanones **146** as 1,4-dipole precursors and sulfur ylides **147** (Scheme 31) [59]. A wide range of *trans* 2-acyl-3-vinyl indolines **149** were synthesized in high yield with excellent diastereo- and enantioselectivity by using the chiral phosphoramidite ligand **148**. Notably, the Pd-stabilized zwitterionic intermediates **150** were firstly trapped with nucleophilic dipolarophiles (sulfur ylides) and found to be crucial for controlling the branched selectivity.

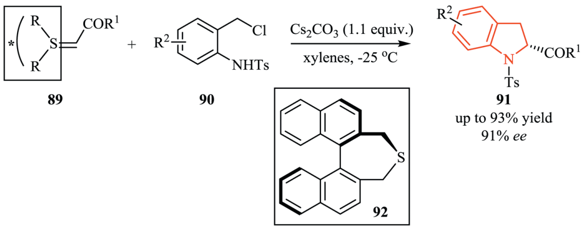
In 2016, they further expanded the application of vinyl benzoxazinanone **146a** to the synthesis of chiral indolines **154** *via* the combination of two Pd-catalyzed sequential reactions (decarboxylative amination and haloamination) in one pot with good synthetic efficiency and excellent enantiocontrol (Scheme 32) [60].

Soon after, they designed and synthesized ethynyl benzoxazinones **155**, which showed similar reactivity as compared to vinyl benzoxazinanones **146**. They found that the Cu-catalyzed decarboxylative asymmetric [4 + 1] cycloaddition reactions of ethynyl benzoxazinones **155** with sulfur ylides **156** also proceeded smoothly using PyBOX ligand **157** (Scheme 33) [61]. The reaction produced 3-ethynyl-substituted indolines **158** in high yield with excellent asymmetric induction. Remarkably, based on the experimental results of non-linear effects, they suggested that a cooperative bi-Cu complex **160** participated in the enantiodetermining step of the reaction. As depicted in the proposed model **161**, the orientation of sulfur ylides was governed by one copper. Thus the sulfur ylide approached the *Re*-face of the Cu-allenylidene intermediate **159'**, which was formed from the ethynyl benzoxazinon **155** and another copper in the decarboxylation step, acting as the reactive 1,4-dipole. Notably, the use of *in situ*-generated sulfur ylides by deprotonation of the corresponding sulfonium salt with an excess of ^{i}Pr$_2$NEt dramatically improved the selectivity.

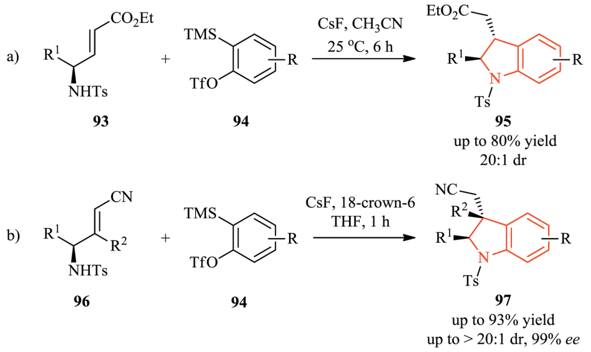
4.3.4. Intramolecular capture of organocuprate intermediates with imines as electrophiles

In 2015, the Buchwald group reported a Cu-catalyzed intramolecular cyclization of various vinyl arenes **162** with an imine moiety at the *ortho*-position (Scheme 34a) [62]. This protocol allowed for the synthesis of 2,3-disubstituted indolines **164** with high diastereo- and enantioselectivity, featuring mild reaction conditions and high functional group tolerance. It was postulated that the reaction proceeded *via* a CuH-catalyzed Markovnikov addition of styrenes, thus forming organocuprate intermediate **165** and subsequent intramolecular trapping with tethered imine electrophiles. The active L*CuH species could be formed by reacting Cu(OAc)$_2$ with a chiral ligand **163** and a stoichiometric amount of the hydrosilane DEMS (diethoxymethylsilane).

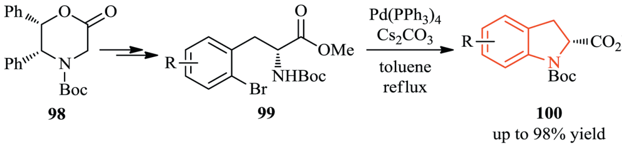
In 2018, the Yun group [63] and Xiong group [64] independently developed a Cu-catalyzed enantioselective intramolecular borylative cyclization of the same starting material with B$_2$(Pin)$_2$ **55** at the same time. In this process, the *in situ* generated L*Cu-BPin catalyst played the same role as L*CuH species mentioned above. As a result, a wide range of enantioenriched 2,3-disubstituted indolines bearing the versatile BPin functional group **167** were



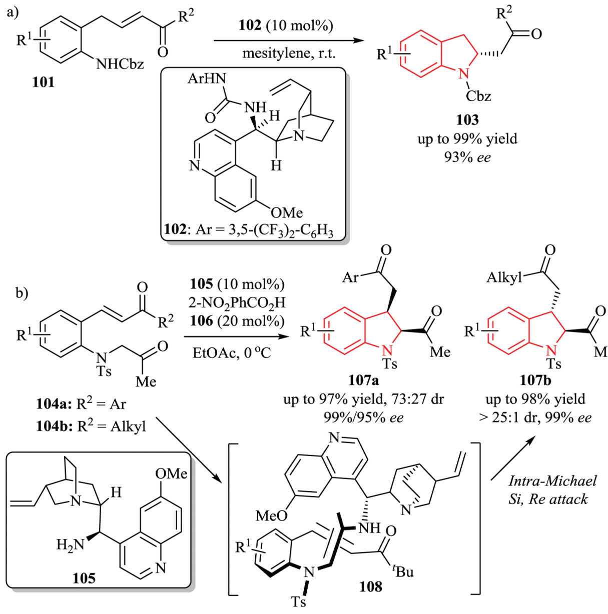
Scheme 21. Formal [4 + 1] annulation of chiral sulfur ylides and *N*-(*ortho*-chloromethyl)aryl amides.



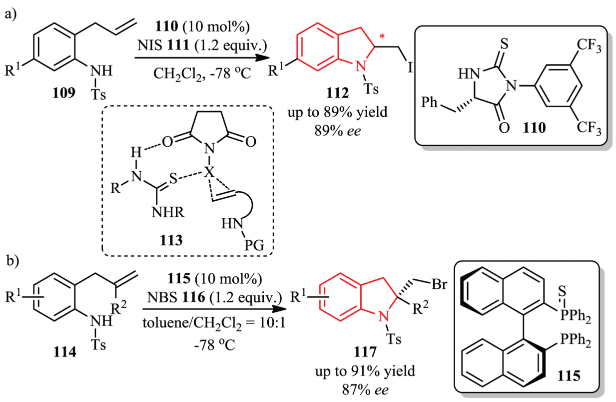
Scheme 22. Formal [3 + 2] annulation of γ-amino-α,β-unsaturated alkenes and arynes.



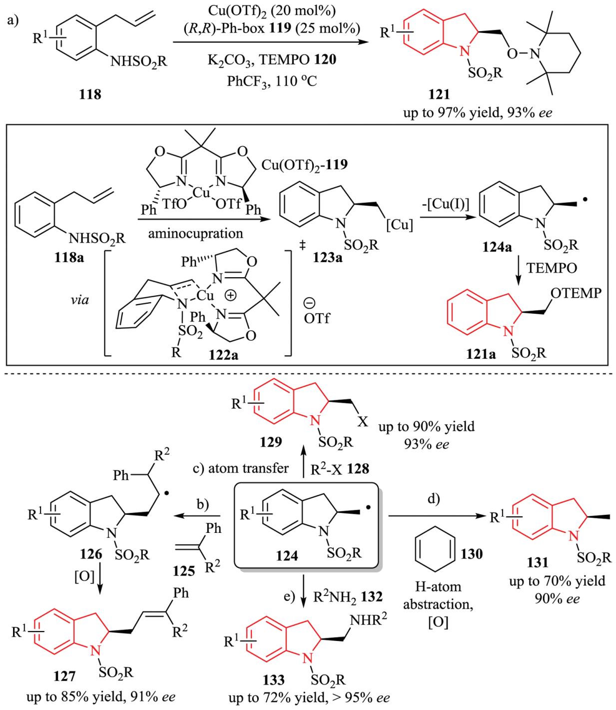
Scheme 23. Synthesis of enantiopure 2-substituted indolines through Buchwald-Hartwig cross-coupling.



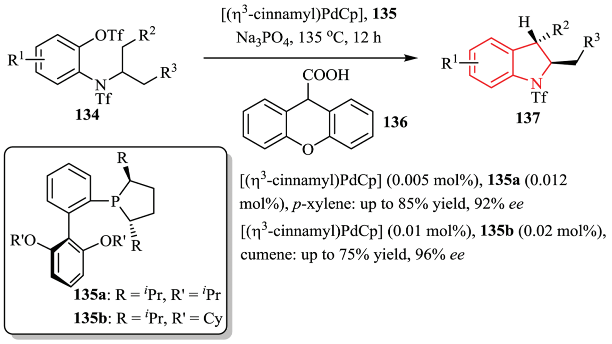
Scheme 24. Organocatalytic intramolecular Michael addition reaction for synthesis of chiral indolines.



Scheme 25. Organocatalytic stereoselective haloaminocyclization for synthesis of chiral indolines.



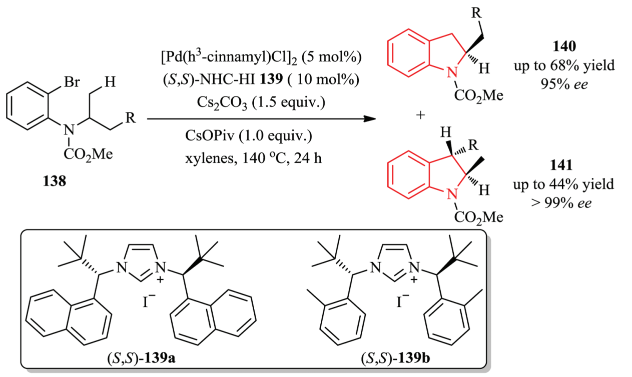
Scheme 26. Cu(II)-catalyzed enantioselective alkene amination reactions for synthesis of chiral indoline derivatives.



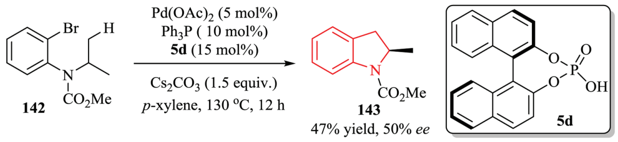
[(η^3-cinnamyl)PdCp] (0.005 mol%), **135a** (0.012 mol%), *p*-xylene: up to 85% yield, 92% *ee*

[(η^3-cinnamyl)PdCp] (0.01 mol%), **135b** (0.02 mol%), cumene: up to 75% yield, 96% *ee*

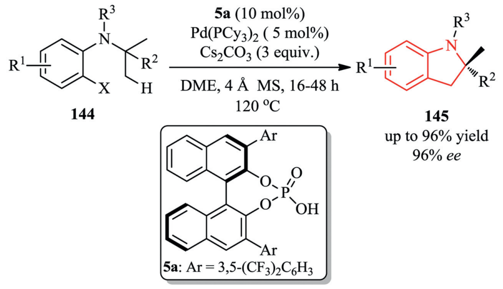
Scheme 27. Pd-catalyzed C(sp^3)-H bond activation toward synthesis of chiral indoline derivatives.



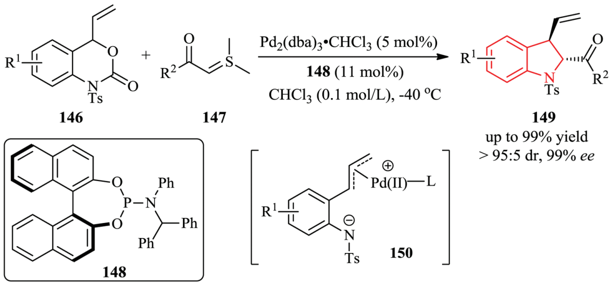
Scheme 28. Pd-catalyzed C(sp^3)-H/C(Ar) coupling of racemic carbamates with chiral NHC ligands.



Scheme 29. Pd-catalyzed C(sp^3)-H activation reaction of *N*-aryl carbamates with chiral phosphoric acid.



Scheme 30. Pd-catalyzed C(sp^3)-H activation/cyclization reaction of carbamates in the presence of chiral phosphoric acid. DME: 1,2-dimethoxyethane.

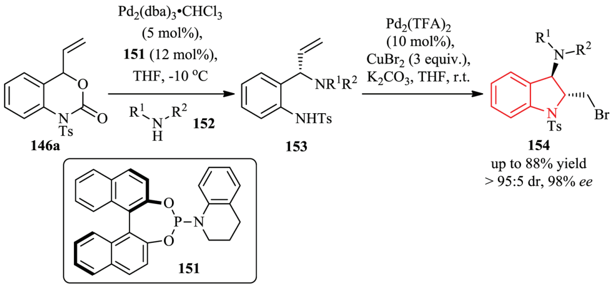


Scheme 31. Pd-catalyzed asymmetric [4 + 1] cycloaddition reactions of vinyl benzoxazinones with sulfur ylides.

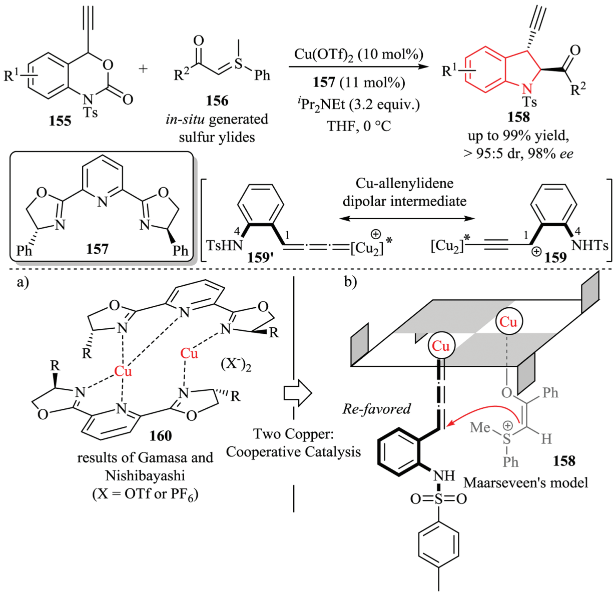
obtained in a highly regio-, diastereo-, and enantioselective manner by single operation (Scheme 34b).

4.3.5. Metal carbenes

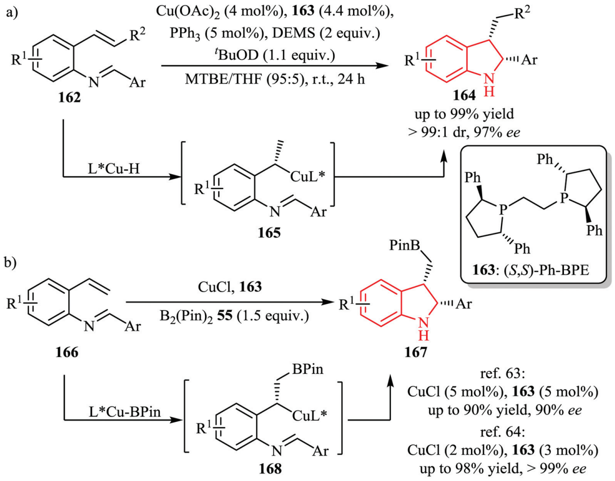
Carbenes have also been well established as versatile intermediates in organic synthesis, and aroused much research interest. Thus, the versatile reactivity modes of carbenes, especially the



Scheme 32. Pd-catalyzed asymmetric allylic amination reaction and subsequent one-pot cyclization.

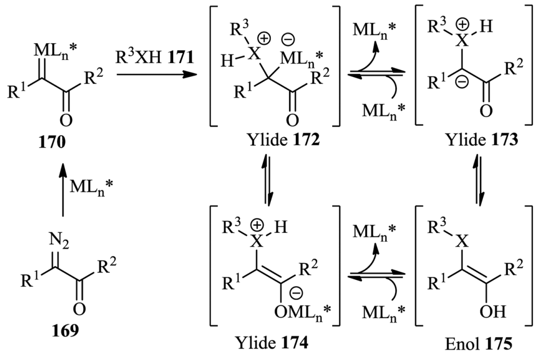


Scheme 33. Cu-catalyzed decarboxylative asymmetric [4 + 1] cycloaddition reactions of ethynyl benzoxazinones with sulfur ylides using PyBOX ligand.

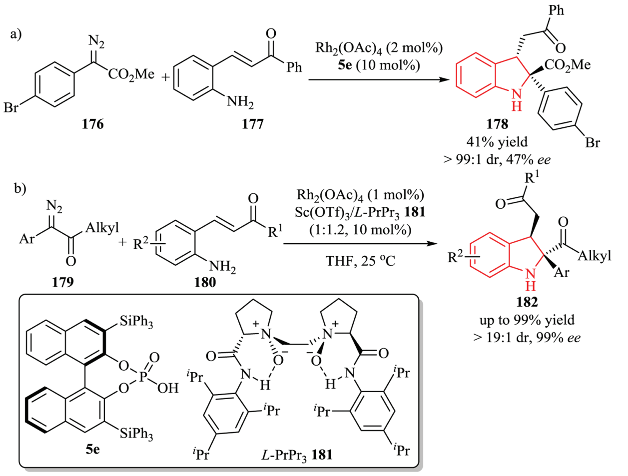


Scheme 34. Cu-catalyzed strategy of various vinyl arenes with an imine moiety at the *ortho*-position for the synthesis of 2,3-disubstituted indolines. MTBE: methyl *tert*-butyl ether.

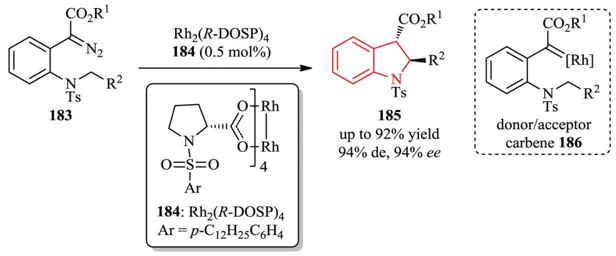
metal carbenes, rendered them to be one of the most significant and useful intermediates in the past decades [65]. Diazo compounds are commonly used as carbene precursors [66]. Asymmetric catalytic cascade reactions involving trapping of the



Scheme 35. Formation of the active ylides from the reaction of diazo compounds with a nucleophile.



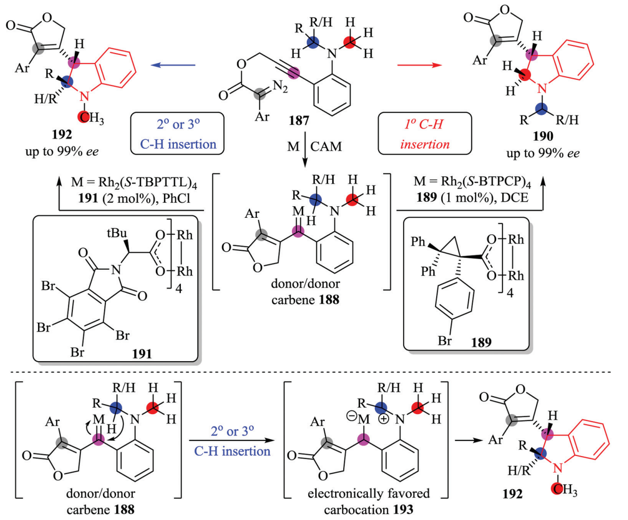
Scheme 36. Intramolecular trapping of ammonium ylides with enones for synthesis of chiral 2,2,3-trisubstituted indolines by cooperative catalytic systems.



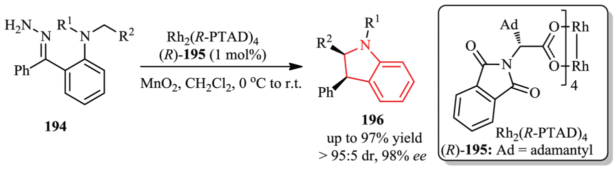
Scheme 37. Chiral dirhodium-catalyzed C-H insertion of α-diazocarbonyl compounds.

active ylides **172**, generated from the reaction of diazo compounds **169** with a nucleophile **171**, could enable rapid and efficient assembly of complex molecules (Scheme 35) [67].

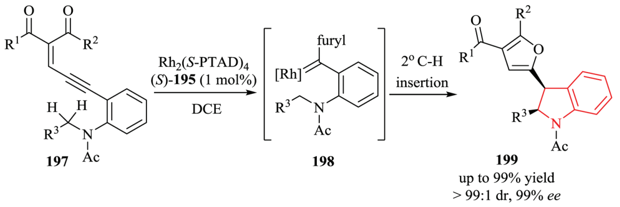
For example, Hu *et al.* disclosed a highly diastereoselective intramolecular trapping of ammonium ylides with enones **177** through a Rh(II)/Brønsted acid cooperative catalytic system. Chiral BINOL-derived phosphoric acid **5e** was used for the asymmetric synthesis of 2,2,3-trisubstituted indoline **178** with 47% *ee* (Scheme 36a) [68]. In 2018, Liu, Feng and co-workers reported a Rh(II)/chiral *N.N'*-dioxide-Sc(III) complex bimetallic relay catalytic system for the reaction of α-diazoketones **179** with enones **180**. The use of α-diazoketones improved the reactivity and enantioselectivity with respect to α-diazoesters. A series of chiral 2,2,3-trisubstituted indolines **182** were constructed with high yield (up to 99% yield), high enantioselectivity (up to 99% *ee*), and excellent diastereoselectivity (up to > 19:1 dr) (Scheme 36b) [69].



Scheme 38. Chiral dirhodium-catalyzed asymmetric cascade CAM reaction /intramolecular C(sp^3)-H bond insertion.



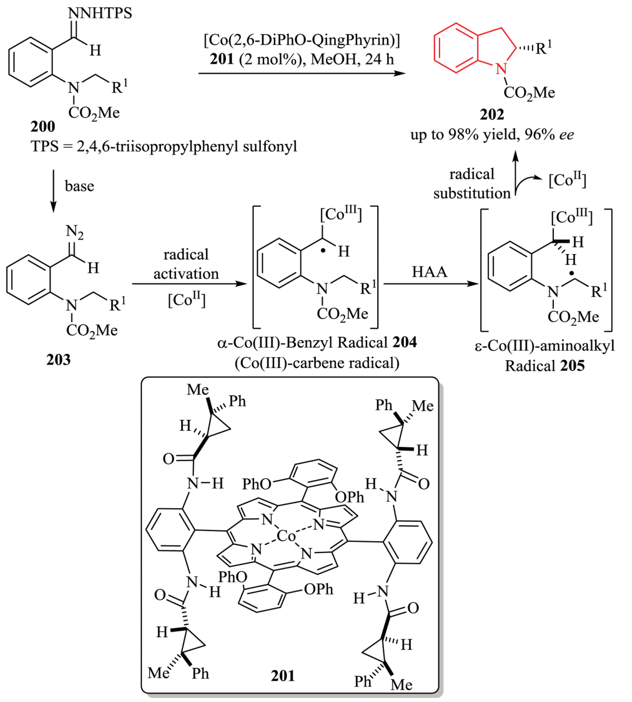
Scheme 39. Chiral dirhodium-catalyzed C-H insertion reaction of donor/donor carbene from hydrazones.



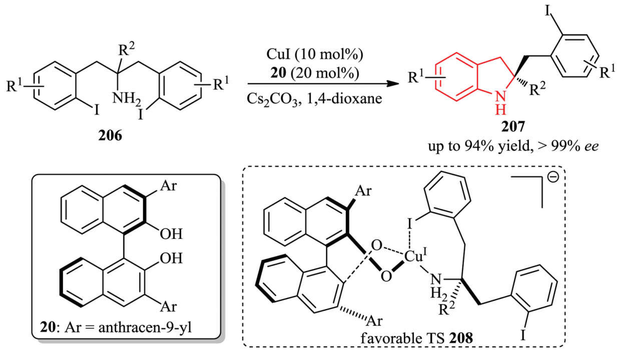
Scheme 40. Chiral dirhodium-catalyzed C-H insertion of donor/donor carbene by a nondiazo approach.

The metal-catalyzed C-H insertion of diazo compounds has been widely investigated for C-C bond formation and also applicable for the synthesis of diverse heterocycles [66]. In 2017, the Wirth group reported an efficient enantioselective synthesis of *trans*-2,3-disubstituted indolines **185** with good yield and enantioselectivity through Rh(II) catalyzed C-H insertion from α-diazo carbonyl compounds **183** (Scheme 37) [70]. In this process, donor/acceptor carbene **186** was involved.

In 2018, Doyle, Xu and their co-workers disclosed that a novel chiral dirhodium complex **189** catalyzed an asymmetric cascade carbene/alkyne metathesis (CAM) reaction of propargyl diazoacetates **187** to give intermediate **188** (Scheme 38) [71]. Then, highly site-selective intramolecular C(sp^3)-H bond insertion provided a general access to chiral indolines in high yield with excellent enantiocontrol. Experimental and DFT studies suggested that the regioselectivity was determined by the competition between electronically favored carbocation stability and sterically demanding catalyst and substrates. The chiral dirhodium catalysts



Scheme 41. Enantioselective synthesis of chiral indolines *via* radical C-H alkylation by Co(II)-MRC.



Scheme 42. Cu(I)-catalyzed desymmetric intramolecular Ullmann C-N coupling reaction of 1,3-bis(2-iodoaryl)propan-2-amines.

promoted both the carbene/alkyne metathesis process and the observed asymmetric induction of the terminating C-H insertion reaction. The donor/donor carbene intermediate **188** was generated *in situ via* carbene/alkyne metathesis with reduced reactivity compared to donor/acceptor carbene, which would enable high site-selectivity and enantioselectivity.

Almost at the same time, the Shaw group expanded the C-H insertion protocol of donor/donor carbene to the asymmetric synthesis of indolines. Oxidation of hydrazones **194** provided the corresponding requisite diazo precursor *in situ* for donor/donor carbene, which avoided the potential explosiveness and practical problems associated with diazo compounds (Scheme 39). They also studied the impact of sterics and electronics in C-H insertion of donor/donor carbene on the regiochemistry [72].

Zhang, Zhu, and co-workers continued their efforts to develop more safe and practical carbene chemistry based on enynones **197** as efficient carbene precursors for intramolecular C-H insertion (Scheme 40) [73]. The reaction gave rise to a range of enantioenriched indolines **199** in a one-pot manner and slow addition of reagent was not necessary.

Radical chemistry offers a potentially powerful approach for the construction of organic molecules with unique reactivity and selectivity, which are complementary to the ionic chemistry. However, the control of stereoselectivity, particularly the enantioselectivity of radical reactions is typically difficult. To solve the inherent disadvantages of radical reactions, a more promising trend has been moved to metalloradical catalysis (MRC), which has emerged as a conceptually new approach involving the catalytic generation of metal-centered radical for the development of stereoselective radical processes [74]. In 2018, Zhang and co-workers developed a novel Co(II)-based metalloradical system for enantioselective radical alkylation of C(sp^3)-H bonds towards the synthesis of chiral indolines **202** in high yield with excellent enantioselectivity (Scheme 41) [75]. Using the new catalyst 2,6-DiPhO-QingPhyrin **201**, the Co(II)-catalyzed system enables the activation of *in situ* generated *ortho*-aminoaryldiazomethanes **203** as radical precursors at room temperature. The *in situ*-formed *α*-Co(III)-benzyl radical intermediate **204** (also known a Co(III)-carbene radical) underwent intramolecular hydrogen atom abstraction (HAA) of C-H bond, followed by 5-*exo-tet* radical cyclization. Donor-type carbene was firstly involved in the asymmetric construction of 2-substituted indolines **202** through C2(sp^3)-C3(sp^3) bond formation. Mechanistic studies were conducted to provide evidences for the stepwise radical pathway.

4.3.6. Ullmann C-N coupling

Ullmann C-N Coupling has offered a classic and powerful method for C-N bond formation [76]. In this context, the Cai group has devoted a great deal of efforts towards developing asymmetric aryl C-N couplings by asymmetric desymmetrization strategy [77]. In 2012, they developed an asymmetric Cu-catalyzed desymmetric intramolecular Ullmann C-N coupling reaction of 1,3-bis(2-iodoaryl)propan-2-amines **206**, which led to the enantioselective preparation of indolines **207** in both high yield and *ee* value (Scheme 42) [78]. The transition state **208** for the chirality induction was proposed. The favorable model implied that the deformation of the substrate and the oxygen-copper interaction attribute to the excellent enantioselectivity.

5. Conclusion and outlook

In this review, a number of recent approaches to the construction of chiral 2-substituted indolines were described. Among these reported examples, the indole functionalization and metal-catalyzed de novo construction were the most straightforward and widely used methodologies. It goes without saying that this research field has emerged as one of the fast growing fields in heterocycle synthesis, and will continue to be flourishing in the future. We hope that this review will provide researchers a comprehensive updated overview of the efforts devoted to assembly of chiral 2-substituted indolines. It is likely that more and more powerful and mild approaches to enantioenriched 2-substituted indolines will thus be developed. In addition, it can be anticipated that there will be more versatile synthetic transformations of optically active 2-substituted indolines to other more complex molecules such as natural products or pharmaceuticals in the near future.

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