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Chem Catalysis

Review

Enantioselective synthesis of indoles through catalytic indolization

Bin-Miao Yang,[1,*] Xiao Qian Ng,[2,3] and Yu Zhao[1,2,*]

SUMMARY

A variety of chiral indole-containing functional molecules are of great importance in chemistry and medicine. These compounds have traditionally been prepared by enantioselective functionalization of simple indole substrates. Although diverse indolization methods are established for the construction of indoles, achieving enantioselectivity directly in these transformations remained elusive until the past decade or so. In this review, we summarize various catalytic indolization strategies for the enantioselective construction of chiral substituted indoles or novel indole-based backbones bearing an axial or helical chirality. The cyclization of 2-alkynylanilines either in a direct atroposelective fashion or in cascade with another enantiodetermining transformation will be described. Subsequently, the development of enantioselective Fischer indolization, Doyle indolization, and chiral indole synthesis via a formal cycloaddition will also be reviewed.

INTRODUCTION

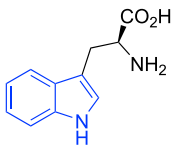
Indole is one of the most widely present heteroarenes in chemistry and medicine. A variety of chiral indole-containing functional molecules are of great importance (Figure 1). For the case of natural products, indole-based examples include proteinogenic amino acid L-tryptophan (**1**), the *Aspidosperma* alkaloid goniomitine (**2**) isolated from the root bark of *Gonioma malagasy*[1] and the pentacyclic monoterpenoid alkaloid andranginine (**3**)[2] isolated from *Craspidospermum verticillatum*. Numerous indole-based pharmaceuticals are also of great importance, which include the powerful antimigraine medicine frovatriptan (**4**),[3] statin-based blood cholesterol drug fluvastatin (**5**)[4] and the receptor antagonist pharmaceutical tropisetron (**6**).[5] Last but not least, indole-based backbones also find applications as chiral ligands in asymmetric catalysis, as exemplified by axially chiral indole-fused phosphine ligands BISCAP (**7**),[6] N-Me-2-BINPO (**8**),[7] and INDOLPhos (**9**).[8]

Due to the importance of chiral indole-containing compounds, development of efficient strategies for the construction of enantioenriched indoles remains an important research topic in chemical synthesis. Toward this goal, the majority of established methods have focused on asymmetric functionalization of simple indoles, using strategies such as Friedel-Crafts reaction and nucleophilic addition.[9–12] Although extensive development of indolization methods have been documented in the literature,[13,14] realization of stereocontrol in indolization reactions was not practiced for decades due to the absence of intrinsic chirality in the indole moiety. Only in the past decade or so, catalytic asymmetric indolization has caught much interest, by the design and development of novel indole-containing backbones as well as new cascade transformations. In this review, we summarize various catalytic indolization strategies for the enantioselective construction of chiral substituted indoles

THE BIGGER PICTURE

Indolization, the process of indole construction from acyclic precursors, has been extensively explored in synthetic chemistry for the delivery of diversely substituted indoles. The introduction of chirality into indole-containing compounds, however, has traditionally been limited to functionalization of indole substrates. This review summarizes the new trends and strategies in the enantioselective construction of indole-based compounds, including (1) catalytic indolization/functionalization cascades for facile access to diverse enantioenriched indole-based compounds and (2) the delivery of novel indole-based backbones bearing an axial or helical chirality.

Natural products:



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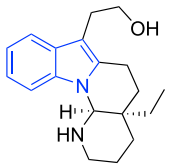
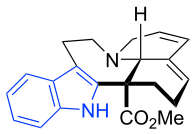
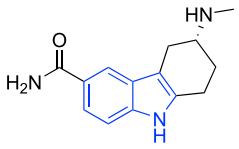


(-)-Goniomitine (2)

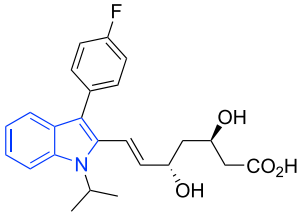


Andranginine (3)

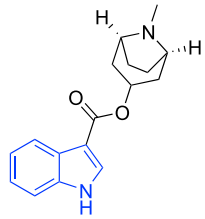
Pharmaceuticals:



Frovatripten (Frova™) (4)

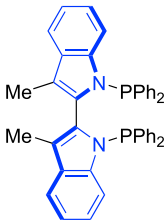


Fluvastatin (5)

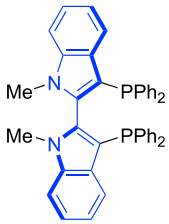


Tropisetron (Navoban™) (6)

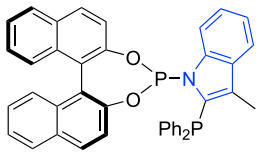
Chiral ligands:



BISCAP (7)



N-Me-2-BINPO (8)



INDOLPhos (9)

Figure 1. Representative natural products, pharmaceuticals, and chiral ligands containing indole skeletons

or novel indole-based backbones bearing an axial or helical chirality. These examples are categorized into the following sections based on the type of transformations and operating mechanisms:

1. Atroposelective indolization of 2-alkynylanilines (Schemes 1–6)
2. Cascade indolization of 2-alkynylanilines with another enantioselective bond formation
   - 2.1. Indolization of 2-alkynylanilines followed by asymmetric nucleophilic addition (Schemes 7–12)
   - 2.2. Indolization of 2-alkynylanilines/Heck cascade (Schemes 13–17)
   - 2.3. Indolization of 2-alkynylanilines/borrowing hydrogen cascade (Scheme 18)
   - 2.4. Asymmetric cyclization of aniline to allene (Scheme 19)
3. Asymmetric Fischer indolization
   - 3.1. Enantioselective aza-[3.3]-sigmatropic rearrangement (Schemes 20–22)
   - 3.2. Enantioselective hydrazone condensation (Scheme 23)
4. Asymmetric Doyle indolization (Scheme 24)
5. Asymmetric indolization involving a formal [3 + 2] cycloaddition (Schemes 25–29)

It is noteworthy that some of these methods entail the indolization step as the enantiodetermining event to construct novel chiral indoles (e.g., those bearing an axial or

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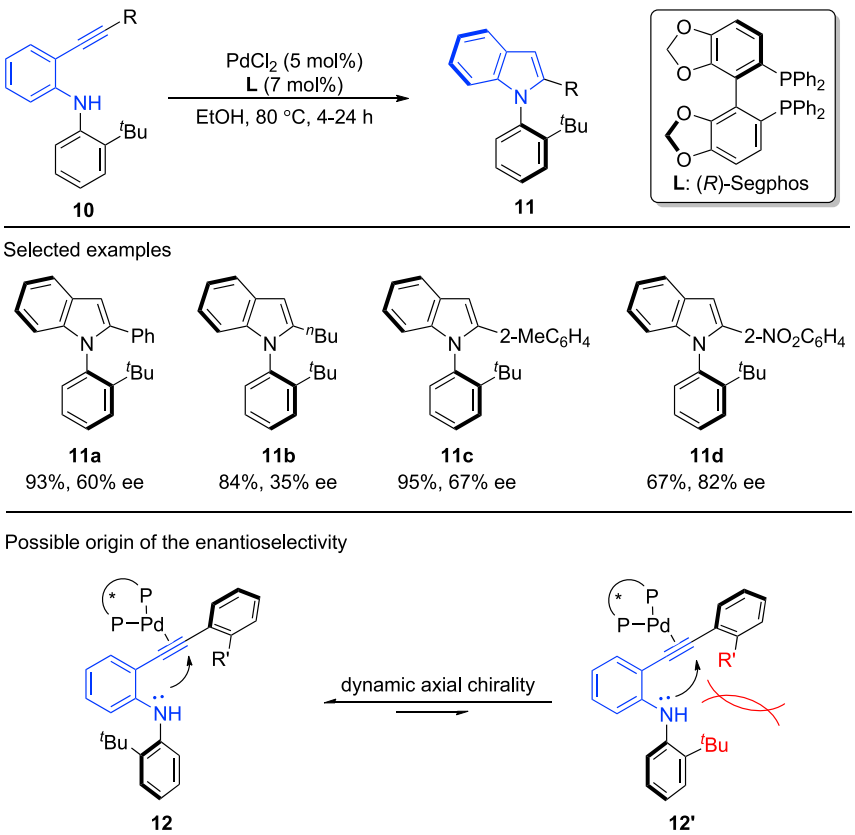
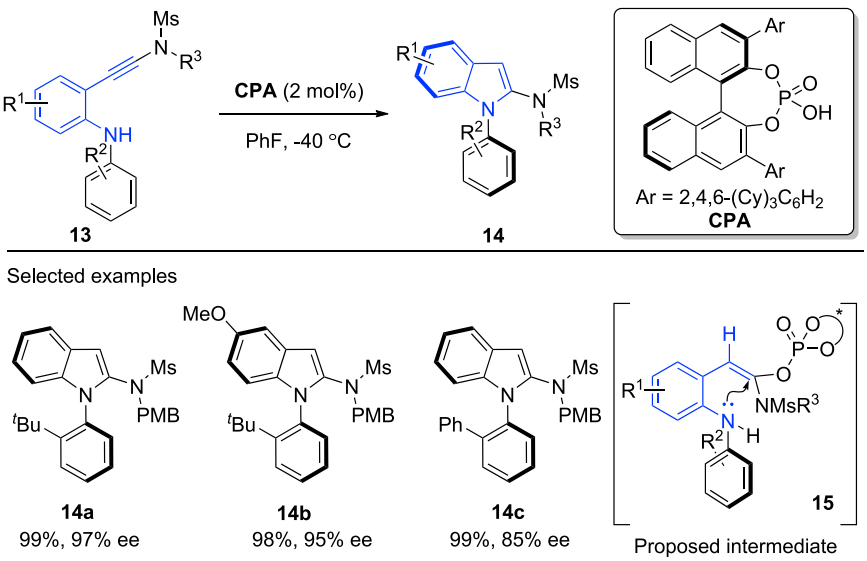
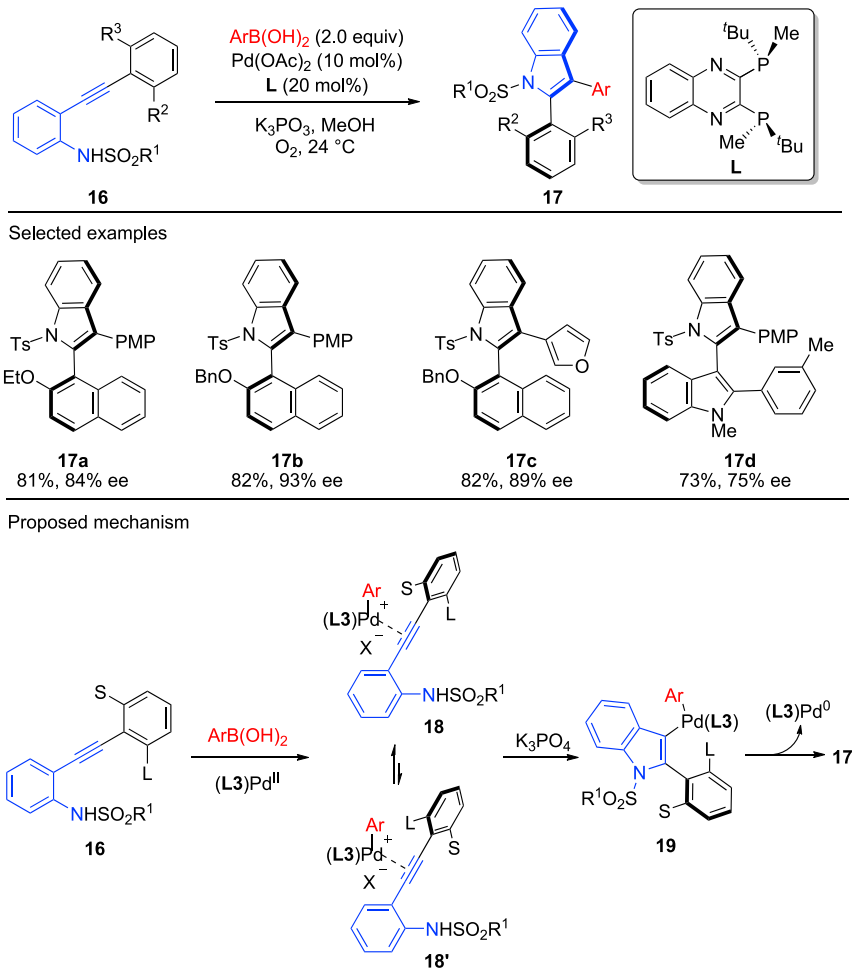


Scheme 1. Palladium-catalyzed atroposelective indolization to access axially chiral *N*-aryl indoles

helical chirality). In other cases, indolization is achieved in cascade with another enantioselective step, leading to direct construction of enantioenriched indole-containing compounds from simple substrates.



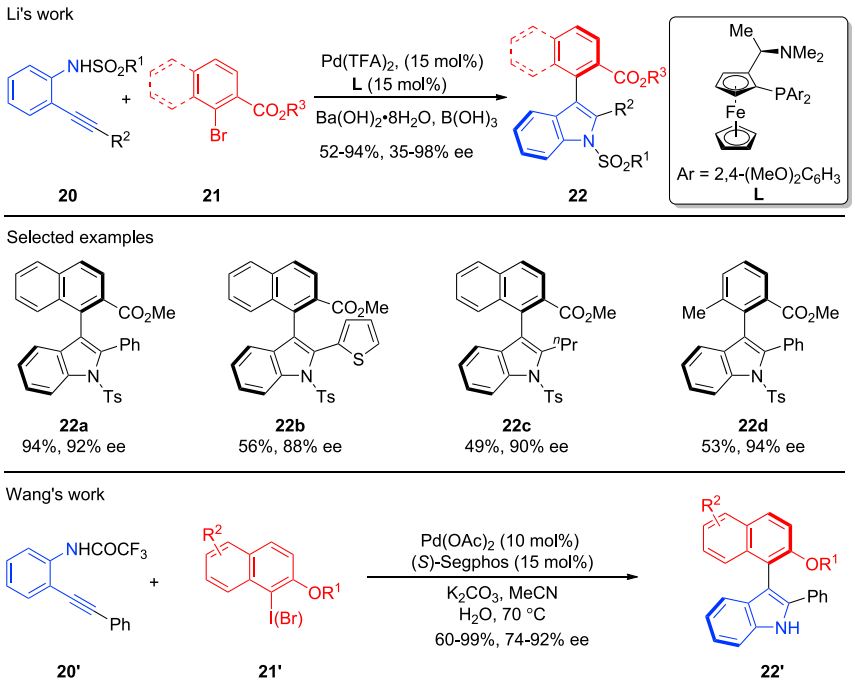
Scheme 2. Organocatalytic atroposelective indolization of ynamides to access axially chiral *N*-aryl indoles



Scheme 3. Pd-Catalyzed enantioselective oxidative Cacchi reaction for the synthesis of indoles bearing a chiral C_2-aryl axis

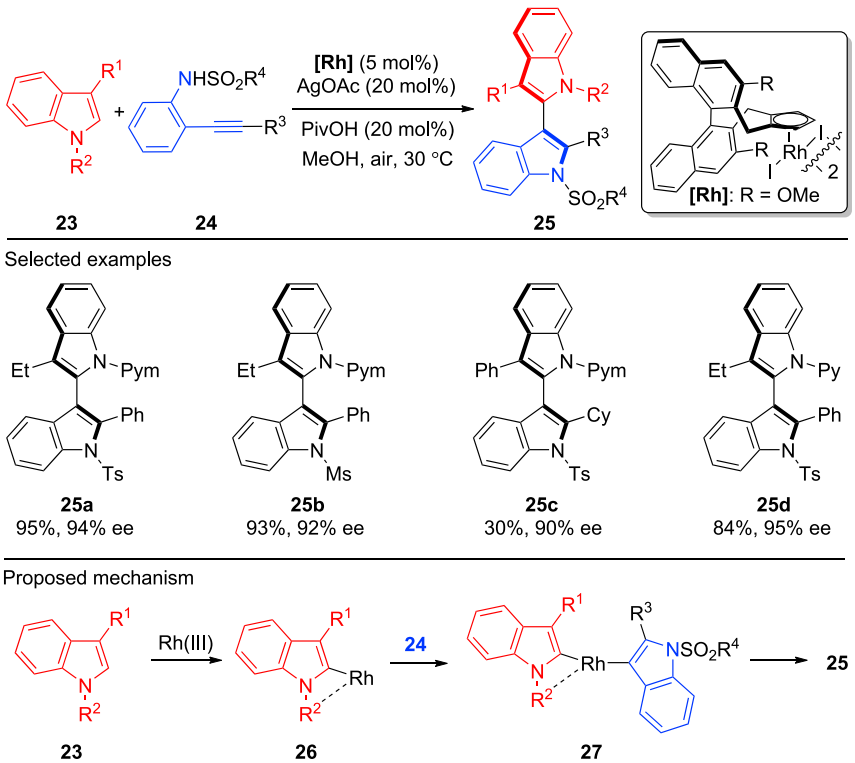
1. ATROPOSELECTIVE INDOLIZATION OF 2-ALKYNYLANILINES

2-Alkynylanilines, which are easily accessible from simple starting materials, can serve as a valuable precursor for the construction of indoles through cyclization.[15–21] In 1985, Taylor, Mckillop and co-workers reported the first example of Pd-catalyzed cyclization of 2-alkynylanilines to afford indoles.[22] Subsequently, a series of methodologies have been reported to access indoles using 2-alkynylanilines as the substrate. Despite these significant achievements, achieving enantio-control in indolization of 2-alkynylanilines remained elusive due to the absence of intrinsic chirality of the indole unit. In 2010, Kitagawa and co-workers reported a catalytic atroposelective indolization of 2-alkynylanilines for the construction of axially chiral indoles bearing a carbon-nitrogen chiral axis (Scheme 1).[23] Under conditions utilizing $PdCl_2$/(*R*)-Segphos as the catalyst, indolization of a series of N-aryl-2-alkynylanilines **10** yielded axially chiral indoles **11** in good yields with moderate to good enantioselectivities. The results demonstrated that the enantioselectivity of this transformation was influenced by the substituent R on the alkyne moiety. While the presence of aromatic substituents gave better enantioselectivity than aliphatic ones (**11a** vs. **11b**), the presence of *ortho*-substituent in the aryl unit on the alkyne

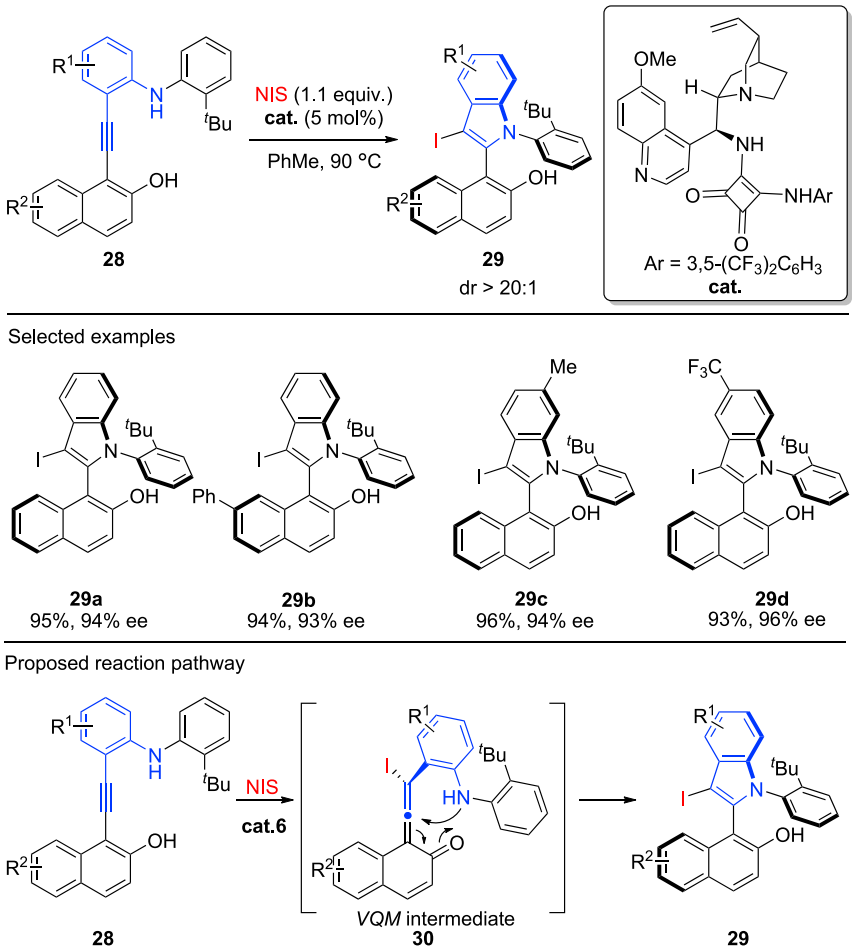


Scheme 4. Pd-Catalyzed enantioselective Cacchi reaction for the synthesis of indoles bearing a chiral C3-aryl axis

led to further improved enantioselectivity (**11c** and **11d** vs. **11a**). The authors proposed that the enhanced enantioselectivity with *ortho*-substituted products is likely due to chiral relay through the dynamic axial chirality of the $C_{alkynyl}$-C_{aryl}



Scheme 5. Rh(III)-Catalyzed oxidative coupling of indoles and 2-alkynylanilines

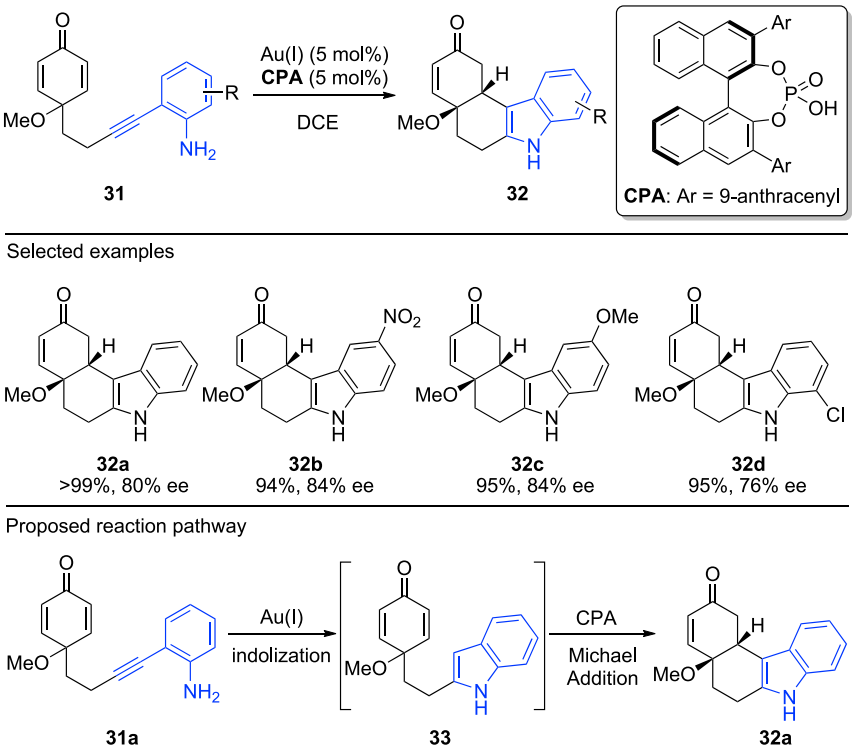


Scheme 6. Organocatalytic asymmetric formal iodoaminocyclization of alkynes via vinylidene *ortho*-quinone methide intermediate

bond.[24] As shown in Scheme 1, indolization in transition station **12** is more favored than that in **12′** that involves more steric repulsion in the two substituents (^{t}Bu and R′).

It is worth noting that this elegant work represents the first example of catalytic enantioselective indolization. Following this work, 2-alkynylaniline has become a versatile substrate for the preparation of enantioenriched indoles through either enantiodetermining indolization or indolization-containing enantioselective cascade transformations.

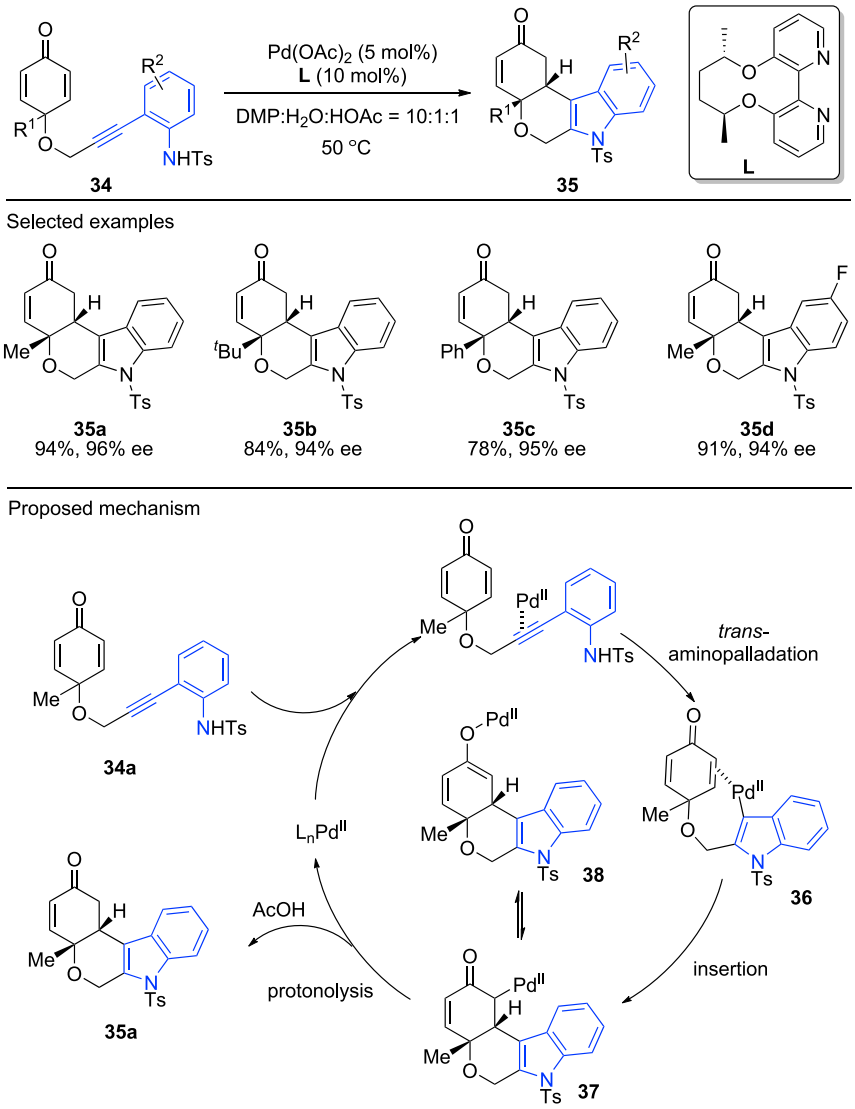
Very recently, Ye and co-workers reported a chiral phosphoric acid-catalyzed direct indolization of 2-ynamide-substituted anilines **13**, forming axially chiral 2-amino-indoles **14** with a C-N linkage in excellent yields and enantioselectivities (Scheme 2).[25] Substituent R^1 can tolerate both electron-donating and electron-withdrawing groups, while only benzyl-type substituents are suitable as the R^3 group. Based on the mechanistic studies, the authors proposed the mechanism with chiral phosphoric acid addition to the ynamide unit, forming the key intermediate **15** that undergoes an intramolecular nucleophilic substitution via the amino unit to afford axially chiral indole products **14**.



Scheme 7. Au-catalyzed indolization followed by CPA-catalyzed asymmetric Michael addition

In 1992, Cacchi and co-workers reported a palladium-catalyzed cascade indolization/cross-coupling of 2-alkynylanilines with aryl halides or vinyl triflates for the preparation of functionalized indoles. This strategy enables a highly efficient access to diverse 2,3-disubstitited indoles and is later referred to as the Cacchi reaction.[26,27] Although this reaction has been widely used in the synthesis of indole derivatives, an enantioselective variant remained elusive until the recent report on an asymmetric oxidative Cacchi reaction by Zhu and co-workers in 2020 (Scheme 3).[28] This work introduced a highly efficient and versatile construction of axially chiral 2,3-diarylindoles bearing a chiral axis at the C2 position, by the reaction of N-sulfonyl-2-alkynylanilines **16** with aryl boronic acids under oxidative palladium catalysis. Mechanistic studies indicated that the reaction is initiated by transmetallation of palladium (II) with the borate species derived from the aryl boronic acid substrate. The resultant Pd species then coordinates with the triple bond in **16** as a π-acid to form the key intermediate **18** (favored over the diastereomeric **18′** due to steric interaction between substituents on the aryl group at the alkyne moiety with the catalyst). Subsequent indolization produces **19** in an atroposelective manner, which is followed by reductive elimination to afford the desired 2,3-diaryl indole **17**. Oxidation of Pd(0) back to Pd(II) then completes the catalytic cycle.

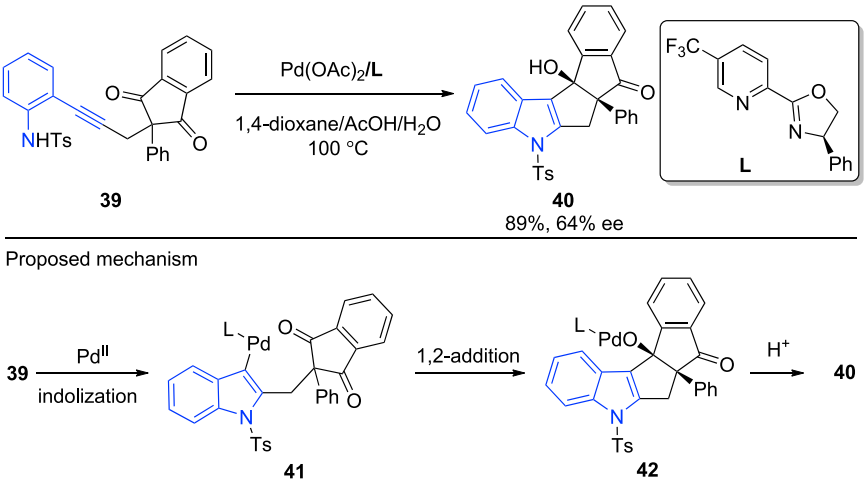
Following the previous work on the preparation of indoles bearing a chiral axis at the C2 position, the Li group[29] and the Wang group[30] reported, independently in 2021, the Pd-catalyzed enantioselective Cacchi reaction between 2-alkynylailines **20**/**20′** and aryl halides **21**/**21′**. Notably enantioenriched indoles bearing a chiral axis at the C3 position were produced in these reactions with good yields and excellent enantioselectivities (Scheme 4). The Li group used sulfonyl-protected **20** and an ester-substituent **21** to produce biaryls **22** containing the N-Ts unit. In contrast,



Scheme 8. Palladium (II)-catalyzed cascade aminopalladation and desymmetrizing 1,4-addition

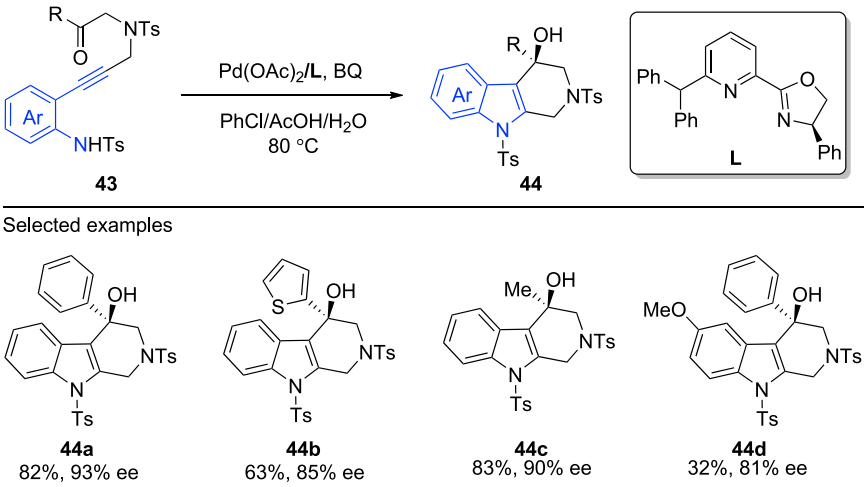
the Wang group adopted trifluoroacetyl-protected **20′** and an electron-rich **21′** as the substrates, the reaction of which yielded alkoxide-substituted biaryl **22′** with a free N-H indole.

Using a C-H functionalization strategy, Li and co-workers disclosed in 2019 a Rh(III)-catalyzed oxidative coupling of indole **23** with 2-alkynylanilines **24** to produce axially chiral 2,3′-bisindoles **25** in good yields with excellent enantioselectivities (Scheme 5).[31] Notably the rotational barrier for these bisindole atropisomers connected by two five-membered rings is lower than that of the analogous biphenyl or indole-arene compounds. As a result, it is more challenging to construct these bisindoles in an atroposelective manner. The mechanism of this Rh-catalyzed system involves C-H activation of indole **23** to form intermediate **26**, which subsequently activates the alkyne moiety in **24** to promote indolization leading to intermediate **27**. Finally, reductive elimination, which is likely the enantiodetermining step, affords the 2,3′-bisindole product **25**. Re-oxidation of Rh(I) to Rh(III) is affected by running the reaction in air.

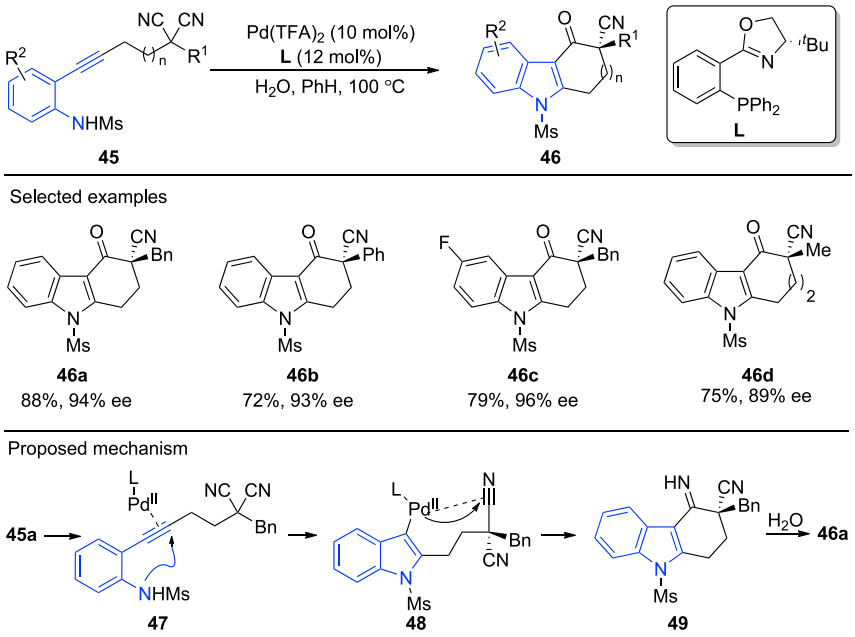


Scheme 9. Palladium (II)-catalyzed cascade aminopalladation and desymmetrizing 1,2-addition to ketone

In addition to the above examples of metal-catalyzed atroposelective indolization, organocatalytic methods have also been documented. In 2021, Yan and co-workers reported an organocatalytic formal iodoaminocyclization of 2-alkynylanilines **28** bearing a 2-naphthol unit for the construction of axially chiral 3-iodo-2-aryl indoles **29** with excellent yields and stereoselectivities (Scheme 6).[32] This reaction is proposed to proceed via atroposelective formation of the key iodo-substituted vinylidene-quinone methide (VQM) intermediate **30** by organocatalytic electrophilic substitution of **28** with NIS (N-iodosuccinimide). Subsequent trapping of the vinylidene unit in **30** with the aniline motif affords the enantioenriched 3-iodo-2-aryl indoles **29** with transfer of the axially chirality of allene to the biaryl unit. High diastereoselectivity is also obtained for the C-N axis bearing the *ortho*-^{t}Bu-substituted arene. Notably VQM has been applied as a powerful and versatile electrophilic intermediate in many asymmetric catalytic systems in recent years.[33,34]



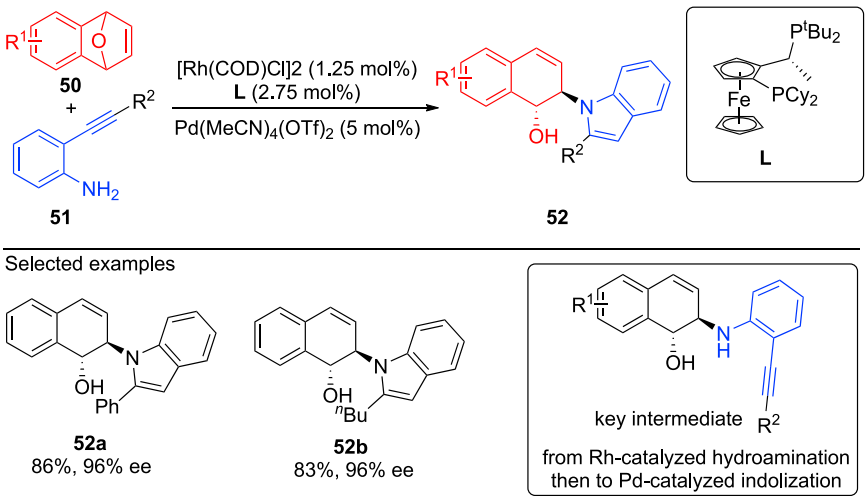
Scheme 10. Palladium (II)-catalyzed cascade aminopalladation and asymmetric 1,2-addition to ketone



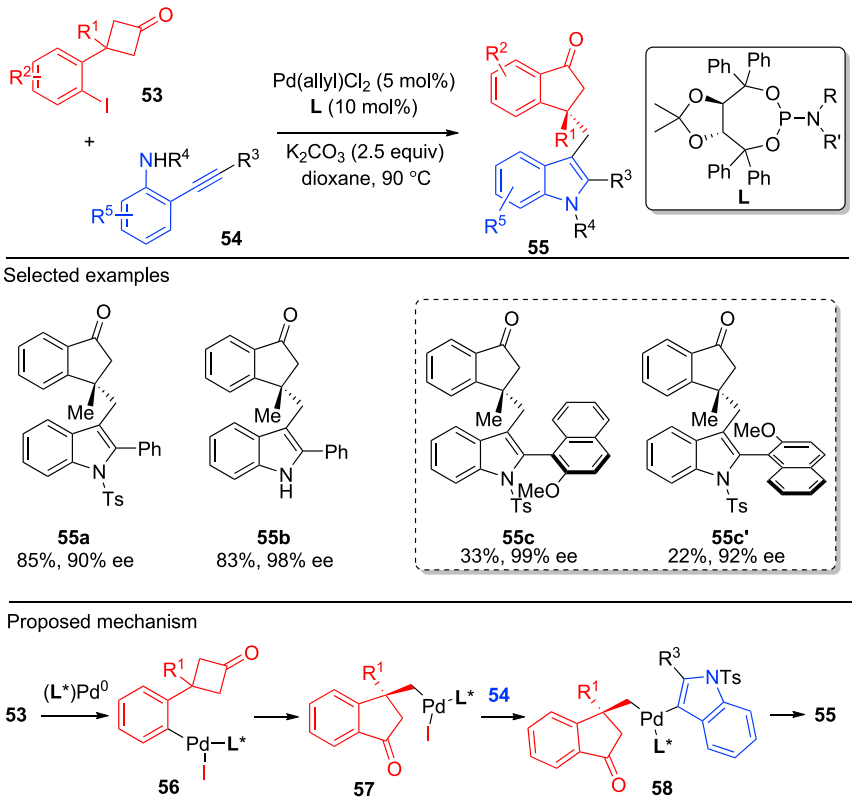
Scheme 11. Palladium (II)-catalyzed cascade aminopalladation and desymmetrizing 1,2-addition to cyanide

2. CASCADE INDOLIZATION OF 2-ALKYNYLANILINES WITH ANOTHER ENANTIOSELECTIVE BOND FORMATION

The strategy of enantioselective tandem or cascade reactions has shown significant utility in chemical synthesis over the past few decades. Higher efficiency and economy in stereoselective synthesis can be achieved by facile construction of molecular complexity in a one-pot fashion. Novel transformations that are not possible using stepwise approach can also be realized, where unstable, active intermediates can be adopted to achieve multiple bond formation without the need for difficult isolation.[35–42] Using this strategy, indolization of 2-alkynylanilines has been combined

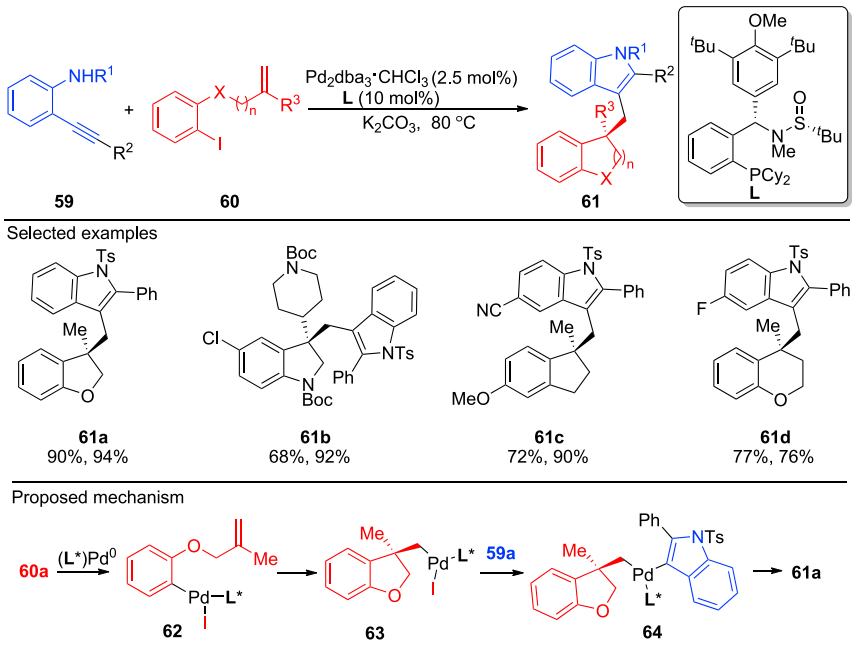


Scheme 12. Rh/Pd relay catalysis asymmetric hydroamination of oxabenzonorbornadiene then indolization

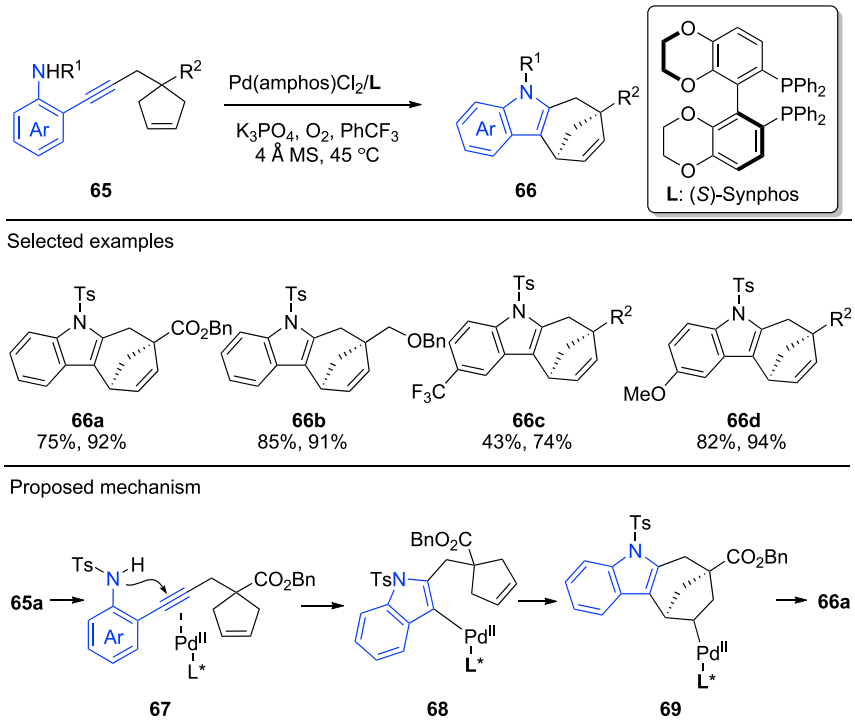


Scheme 13. Pd-catalyzed cascade enantioselective C-C bond activation/Cacchi reaction

with various enantioselective transformations to achieve an overall efficient and enantioselective construction of indoles. Different approaches along these lines are discussed in the following sections.



Scheme 14. Pd-catalyzed cascade enantioselective Heck/Cacchi reaction



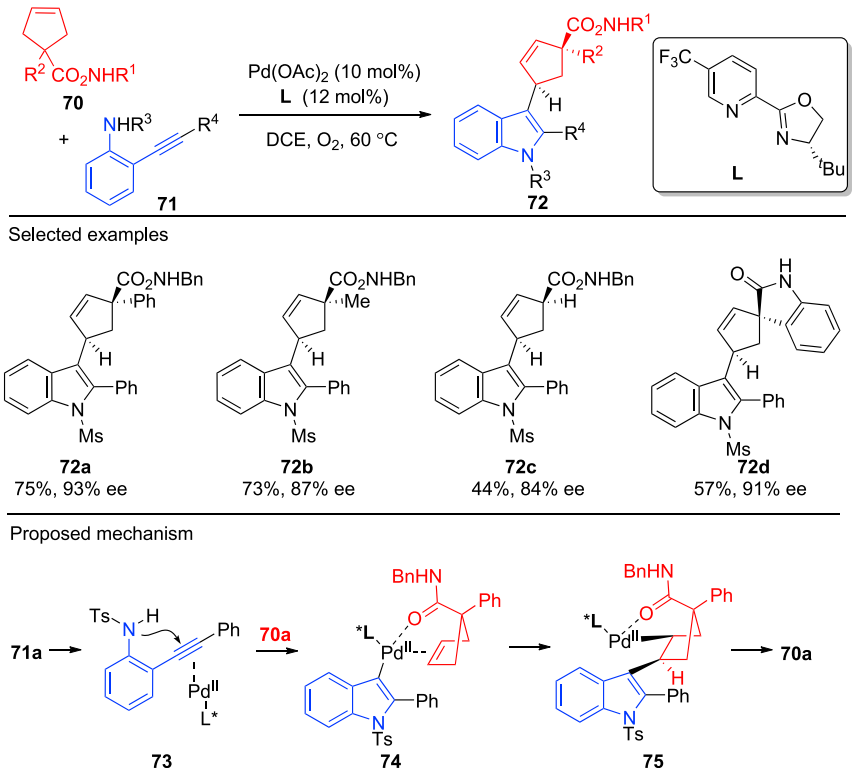
Scheme 15. Pd-Catalyzed intramolecular cascade Cacchi/enantioselective Heck-type reaction

2.1. Indolization of 2-alkynylanilines followed by asymmetric nucleophilic addition

In 2016, Han and co-workers reported an intramolecular indolization/Michael addition cascade reaction under relay catalysis of Au(I) complex and chiral phosphoric acid. Starting from cyclohexadienone-fused 2-alkynylainlines (**31**), tetrahydrocarbazoles (**32**) bearing two stereogenic centers were afforded in excellent yields with good enantioselectivities (Scheme 7).[43] Mechanistic studies indicated that Au(I) complex promotes the indolization step to form indole intermediate (**33**) that is too reactive to isolate. Subsequent chiral phosphoric acid-catalyzed enantioselective Michael addition then generates the desired chiral product **32**.

In 2017, Lu and co-workers achieved the efficient synthesis of enantioenriched 1,3,4.9-tetrahydropyrano[3,4-*b*]indoles **35** using similar substrates **34** (Scheme 8).[44] The reactions were proposed to proceed through a palladium-catalyzed tandem indolization/1,4-addition of cyclohexadienone-fused 2-alkynylainlines **34** to afford **35** in high yields with excellent enantioselectivities. This reaction tolerated a wide scope of alkyl and aryl groups as the R^1 substituent, but the electron-withdrawing Ts-group was needed as the amino protecting group.

The authors proposed that the reaction mechanism involves the activation of the triple bond in the substrate **34a** by the chiral palladium (II) complex as a π-acid. A *trans*-aminopalladation takes place to deliver the indole-Pd species **36**, which undergoes a subsequent desymmetrizing insertion to the electron-deficient C=C bond to deliver intermediate **37**. Protonolysis of this palladium enolate then furnishes the desired product **35a** with the regeneration of the Pd (II) catalyst.

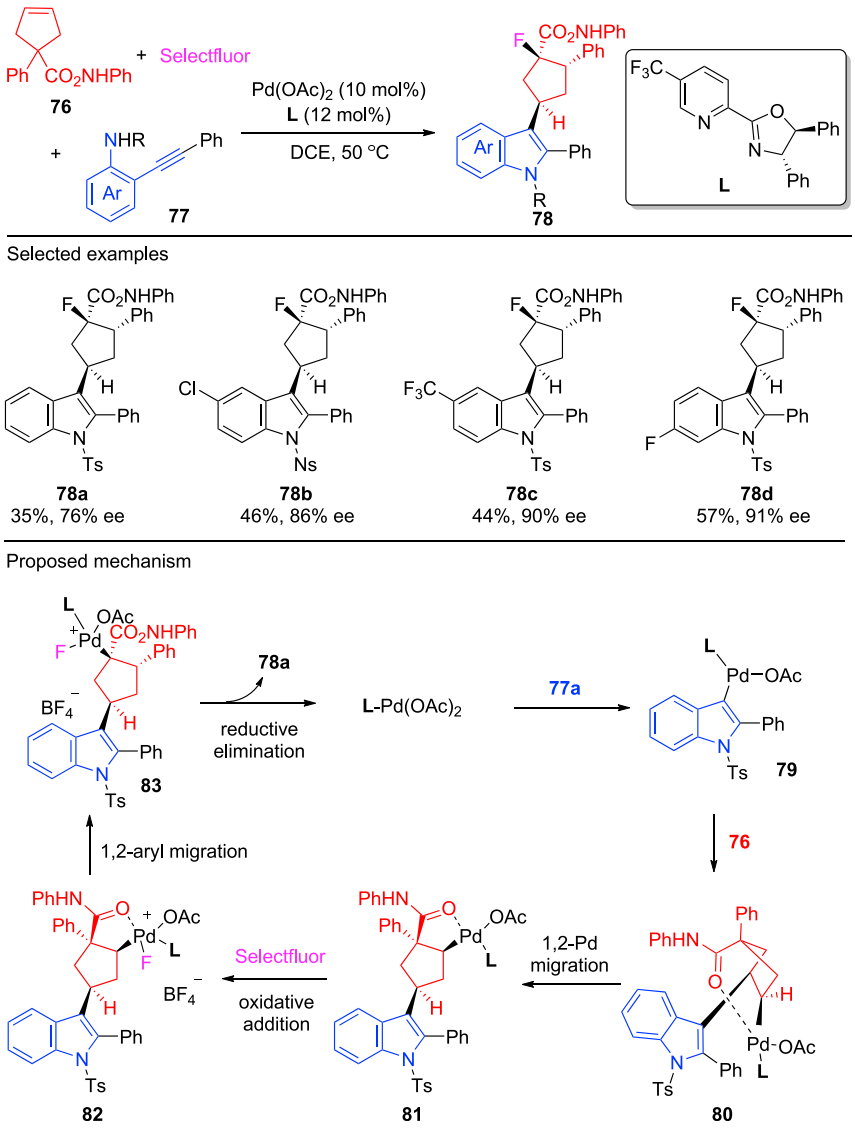


Scheme 16. Pd-Catalyzed intermolecular cascade Cacchi/enantioselective Heck-type reaction

In addition to C=C insertion of the indole intermediate generated *in situ*, it is also possible for such insertion to occur for other types of unsaturated bonds. In 2017, the Lu group also reported a palladium-catalyzed intramolecular indolization in tandem with insertion of the indole-palladium intermediate to a C=O bond (Scheme 9) to prepare chiral indoles **40** via desymmetrization of the diketone substrate **39**.[45] The chiral palladium complex coordinates with the triple bond in **39** to induce indolization, generating intermediate **41**. The desired product **42** is then furnished by subsequent C=O bond insertion of the palladium intermediate followed by protonolysis. The level of enantioselectivity for this catalytic system, however, was only moderate.

Continuing the above work, the same group developed an efficient approach for the construction of 1,2,3,4-tetrahydro-β-carbolines **44** bearing a tertiary alcohol stereocenter from a ketone-containing 2-alkynylanilines **43**. The same catalytic strategy using $Pd(OAc)_2$ and a chiral pyridine-oxazoline ligand was adopted to deliver products **44** in moderate to good yields and good to excellent enantioselectivities (Scheme 10).[46] In this system, the addition of 1,4-benzoquinone as an additive was shown to be beneficial for the reactivity of this catalytic system.

In 2021, Liu and co-workers demonstrated a highly enantioselective palladium-catalyzed indolization/desymmetrizing nitrile addition cascade reaction for the synthesis of enantioenriched carbazolones **46** from the gem-dinitriles **45** (Scheme 11).[47] A variety of **46** bearing an all-carbon quaternary center were efficiently prepared in good yields with excellent levels of enantioselectivity. This reaction tolerated a wide scope of R^1 and R^2, but the N-Ms group was crucial for the enantioselectivity and reactivity of this system. The proposed mechanism involves Pd-catalyzed indolization of **45a**



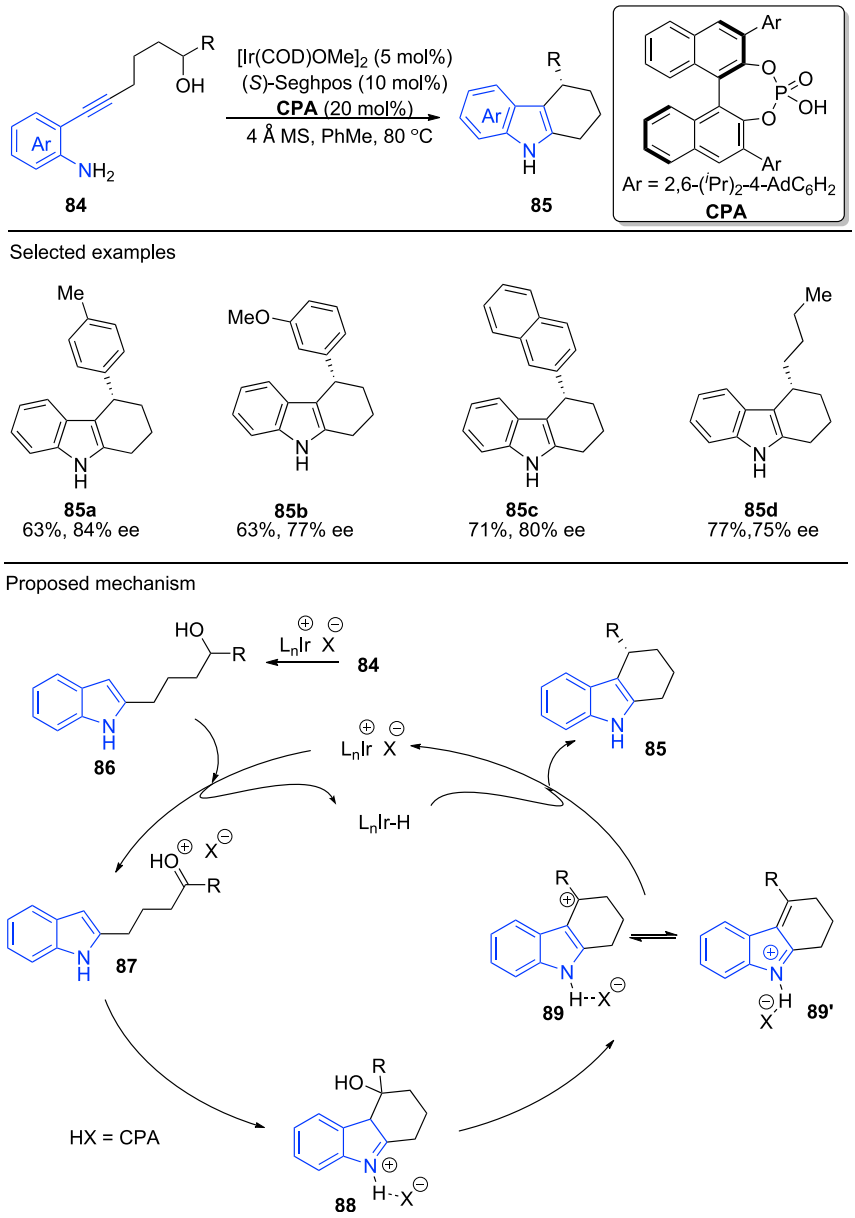
Scheme 17. Pd-catalyzed enantioselective cyclative cross-coupling of 2-alkynylanilines, cyclopentenes, and Selectfluor

via **47** to afford intermediate **48**. Subsequently, desymmetrizing insertion of the Pd intermediate to one of the cyanides delivers intermediate **49** that undergoes protonation and hydrolysis with acid to give the product **46a**.

The Wang group reported in 2020 an Rh/Pd relay catalytic system for the ring opening of oxabicycle **50** with 2-alkynylanilines **51** followed by indolization (Scheme 12).[48] Notably in this example the amine in **51** served as a nucleophile for the enantioselective Rd-catalyzed hydroamination of **50**, producing the key alkyne-containing amino alcohol intermediate as shown below. Pd-catalyzed indolization then followed to yield the N-substituted indoles **52** in high yield and enantioselectivity.

2.2. Indolization of 2-alkynylanilines/Heck cascade

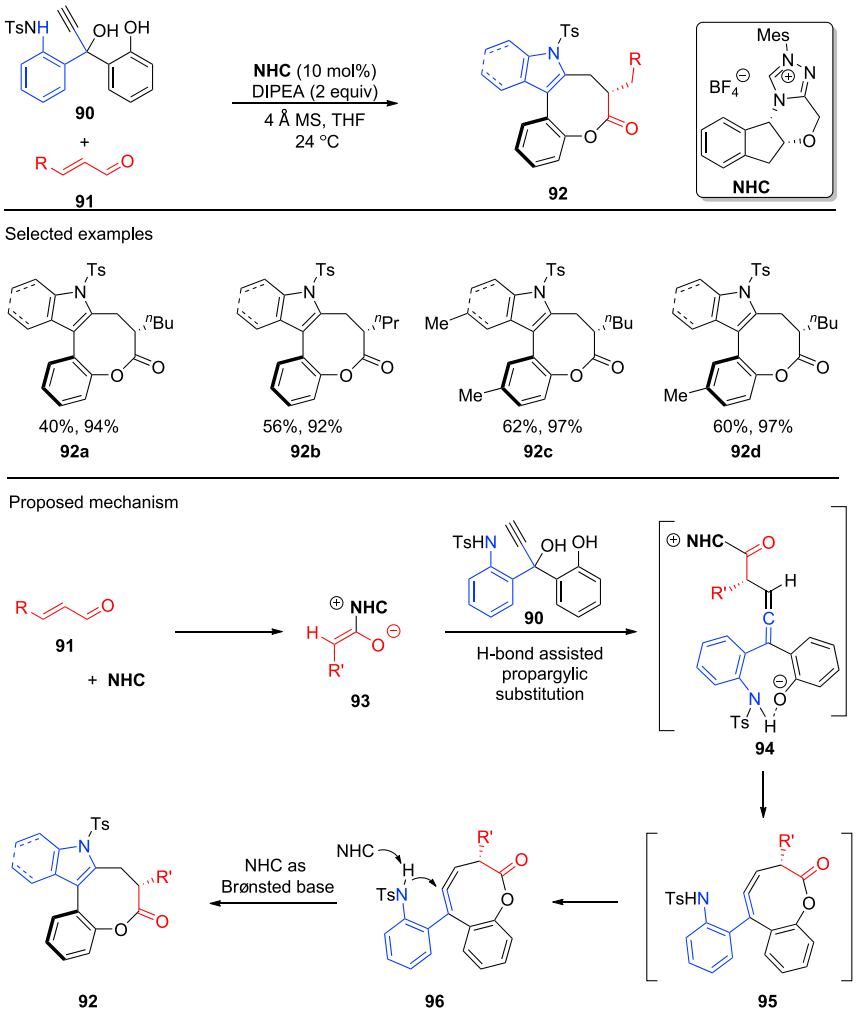
In 2021, Xu and co-workers reported a palladium-catalyzed asymmetric tandem C-C bond activation/Cacchi reaction of cyclobutanone-fused indobenzene **53** with



Scheme 18. Tandem catalytic indolization/enantioconvergent substitution of alcohols by borrowing hydrogen

2-alkynylanilines **54**, providing a series of indoles **55** bearing an indanone motif (Scheme 13).[49] A broad scope of both substrates were well-tolerated to deliver the desired products in moderate to good yields with excellent enantioselectivities. In addition, by the use of substrate **54** with a bulky aryl R^3 substituent, the methodology is also suitable for the construction of enantioenriched products with both central and axial chirality (**55c** and **55c'**), albeit with a low diastereoselectivity (dr 1.1 to 1.5).

The proposed reaction pathway is shown in Scheme 13.[49,50] Oxidative addition of Pd (0) to the aryl iodide unit in **53** forms intermediate **56**, which undergoes a desymmetrizing C-C bond activation of the cyclobutanone unit to form alkylpalladium

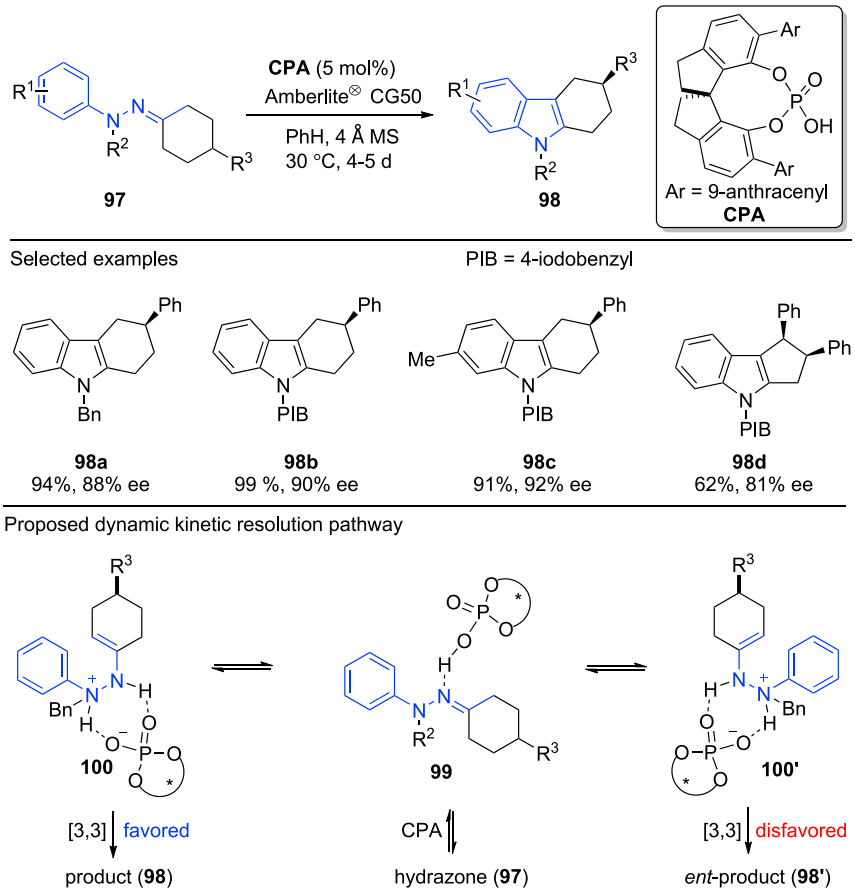


Scheme 19. Organocatalytic cascade to bridged biaryls with defined axial and central chirality

intermediate **57**. Subsequent coordination of Pd (II) in intermediate **57** with 2-alkynylaniline substrate **54** promotes indolization to deliver intermediate **58**. Finally, reductive elimination affords the final product **55**.

In the same year, Lautens and co-workers reported a palladium-catalyzed asymmetric tandem Heck/aminopalladation reaction of 2-alkynylanilines **59** and alkenyl-fused aryl iodides **60**, providing a series of enantioenriched indoles **61** bearing an all-carbon quaternary center in moderate to good yields and excellent enantioselectivities (Scheme 14).[51] The authors proposed that oxidative addition of palladium to the C-I bond in **60a** forms intermediate **62**, migratory insertion of which then generates the alkylpalladium (II) intermediate **63** that cannot undergo β-hydride elimination. This step serves as the enantiodetermining step of this sequence. Coordination of palladium (II) in **63** with the triple bond of 2-alkynyaniline **59a** promotes indolization through *trans*-aminopalladation to form **64**, reductive elimination of which finally affords the final product **61a**.

In 2021, Ye and co-workers developed a palladium-catalyzed intramolecular enantioselective indolization/Heck reaction of cyclopentene-containing **65** for

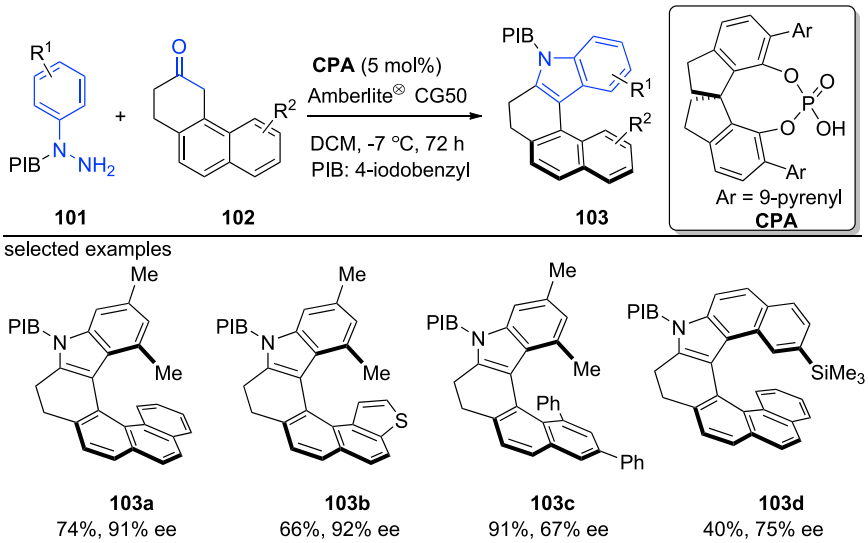


Scheme 20. Catalytic asymmetric Fischer indolization to access chiral 3-substituted tetrahydrocarbazoles

the synthesis of indole-fused bicyclo[3.2.1]octanes **66** bearing a [3,2,1] bicyclic unit with excellent enantioselectivities (Scheme 15).[52] The proposed mechanism involves the coordination of the chiral palladium complex with the triple bond of substrate **65a** to promote the following indolization, affording indole-palladium intermediate **68**. Subsequently, intramolecular arylpalladation furnishes intermediate **69** in an enantioselective fashion, which undergoes β-hydride elimination to afford the desired product **66a**. Oxidation of Pd (0) back to Pd (II) by oxygen then regenerates the catalyst.

In the same year, Zhu and co-workers independently reported a more challenging intermolecular palladium-catalyzed stereoselective tandem indolization/Heck reaction of prochiral cyclopentenes **70** and 2-alkynylanilines **71**, generating enantioenriched indoles **72** with moderate to good yields and good to excellent diastereo- and enantioselectivities (Scheme 16).[53] The mechanism of this catalytic system is similar to that in Scheme 16. In addition, mechanistic studies carried out in this work suggested that the amide group on the cyclopentene substrate **70a** is crucial for the control of the enantioselectivity and the reactivity by effective coordination with the palladium center in the postulated intermediate **74**.

Following the above work, the Zhu group further advanced this methodology by achieving a palladium-catalyzed highly stereoselective three-component reaction



Scheme 21. Catalytic asymmetric Fischer indolization to construct chiral helicenes

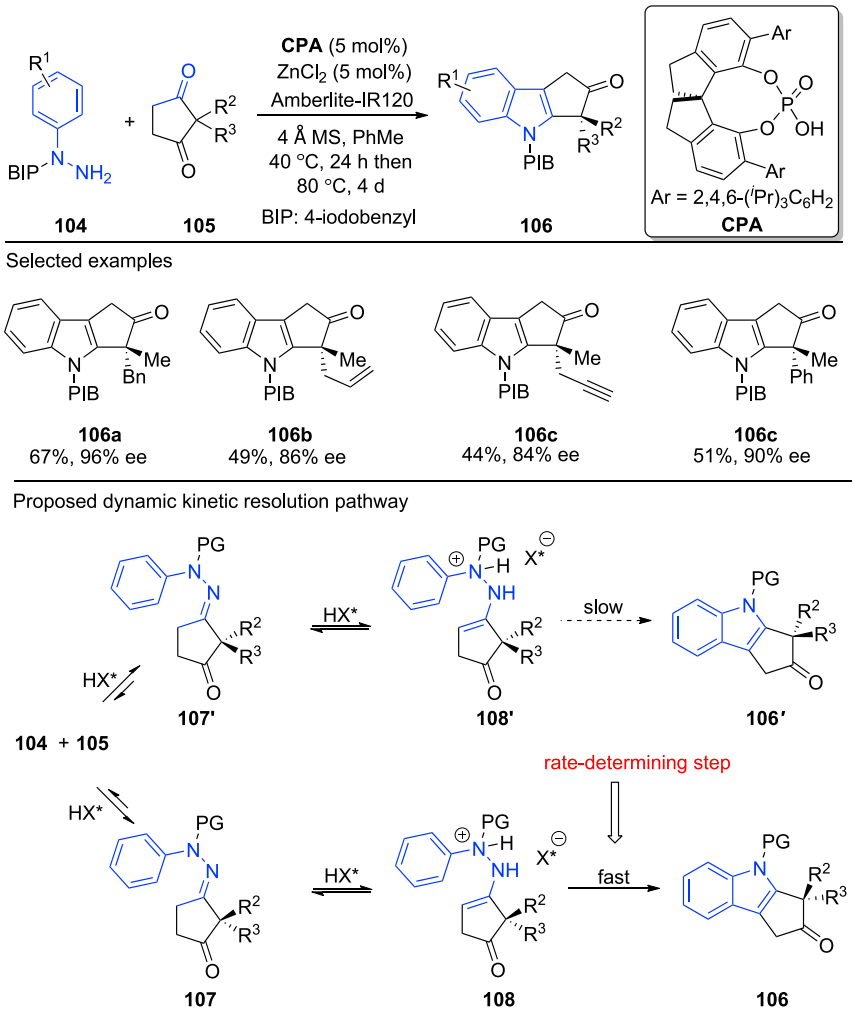
of cyclopentenes **76**, 2-alkynylanilines **77** and Selectfluor (Scheme 17).[54] Using this method, a range of indole-substituted cyclopentanes **78** bearing three stereogenic centers can be obtained as single stereoisomers in moderate yields with good to excellent enantioselectivities. As shown by the proposed mechanism, Pd (II)-catalyzed indolization of **77a** yields **79**, which engages amide-substituted cyclopentene **76** to undergo arylpalladation en route to **80** in high stereoselectivities. At this stage, instead of direct β-hydride elimination, an intriguing 1,2-palladium migration takes place, which is followed by oxidation addition using Selectfluor to produce Pd (IV) species **82** via **81** 1,2-aryl migration of this key intermediate, and reductive elimination of the resultant **83** then produces the final product **78a**.

2.3. Indolization of 2-alkynylanilines/borrowing hydrogen cascade

In 2021, our group established an efficient iridium/chiral phosphoric acid-catalyzed enantioconvergent borrowing hydrogen strategy for the formal Friedel-Crafts alkylation of electron-rich heteroarenes such as pyrroles using simple racemic alcohols as the alkylating agent.[55] Following this work, we also reported the construction of enantioenriched tricyclic indoles **85** from alcohol-fused 2-alkynylanilines **84** through a cascade process of indolization of 2-alkynylaniline followed by intramolecular indole alkylation via borrowing hydrogen (Scheme 18).[56] Based on the mechanistic studies and our previous reports,[57–60] we proposed the reaction mechanism as shown below. Firstly, the formation of cationic iridium species is essential for the activation of alkyne in **84** to undergo indolization, yielding indole intermediate **86**. Subsequently a borrowing hydrogen process takes place, including iridium-catalyzed dehydrogenation and acid-catalyzed Friedel-Crafts ketone addition and dehydration to produce the α,β-unsaturated ketimine intermediate **89′**. Finally, reduction of this intermediate by the iridium-hydride species yields tricyclic indole products **85** in an overall redox-neutral enantioconvergent fashion with the regeneration of catalysts.

2.4. Asymmetric cyclization of aniline to allene

In our group's exploration of *N*-heterocyclic carbene (NHC)-catalyzed enantioselective acylation of phenols,[61–63] we became interested in bisphenol or aniline phenol substrates that bear a tertiary alcohol unit such as **90** (Scheme 19). To our surprise,

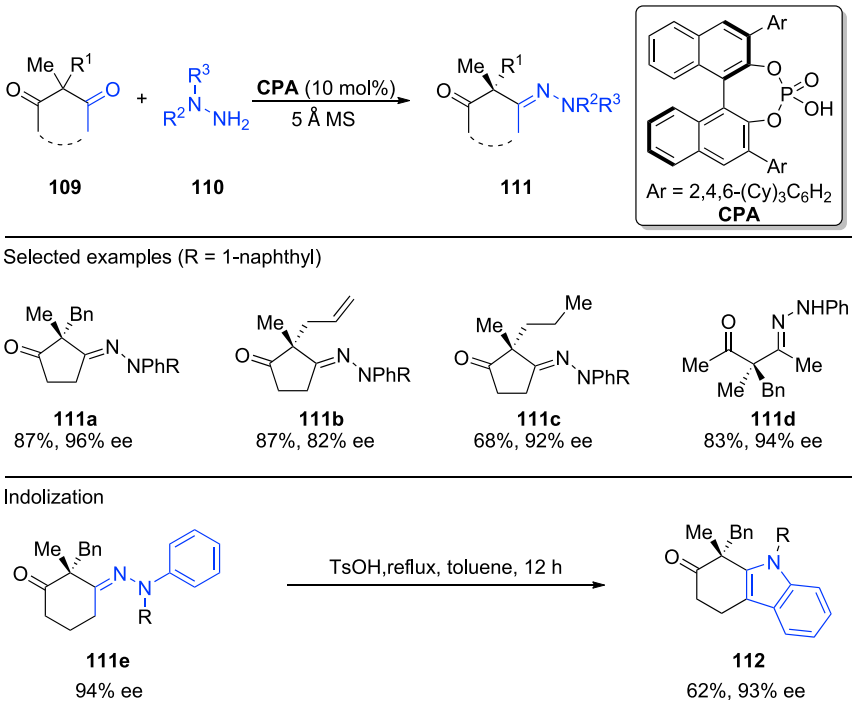


Scheme 22. Enantioselective desymmetrizing Fischer indolization through dynamic kinetic resolution

these substrates worked out with a completely different mechanism: the alternative azolium enolate intermediate **93** is generated, which undergoes a facile propargylic substitution onto **90** to produce allene intermediate **94**. Lactone formation then produces **95** possessing an endocyclic allene moiety. At this stage, NHC also serves as a BrØnsted base to activate the sulfonamide to undergo cyclization onto the allene to produce bridged biaryls **92** bearing an indole unit. This represents a rare example of indolization via allene insertion and a straightforward access to bridged biaryls in a stereoselective fashion. Using this catalytic procedure, a wide range of chiral indoles **92** possessing both axial and central chirality can be produced in an excellent enantioselectivity as a single atropoisomer.[64]

3. ASYMMETRIC FISCHER INDOLIZATION

Since its discovery as early as 1883, Fischer indolization has been extensively utilized for the construction of indoles.[65–67] However, catalytic enantioselective Fischer indolization remained elusive for decades due to the lack of intrinsic chirality in indoles and the necessity to use stoichiometric acid under harsh conditions. Some related exploration of interrupted Fischer rindolization to deliver chiral indolines also met with limited success.[68] Achieving enantiocontrol in a



Scheme 23. Desymmetrization of 1,3-diones by catalytic enantioselective condensation with hydrazine and derivatization by Fischer indolization

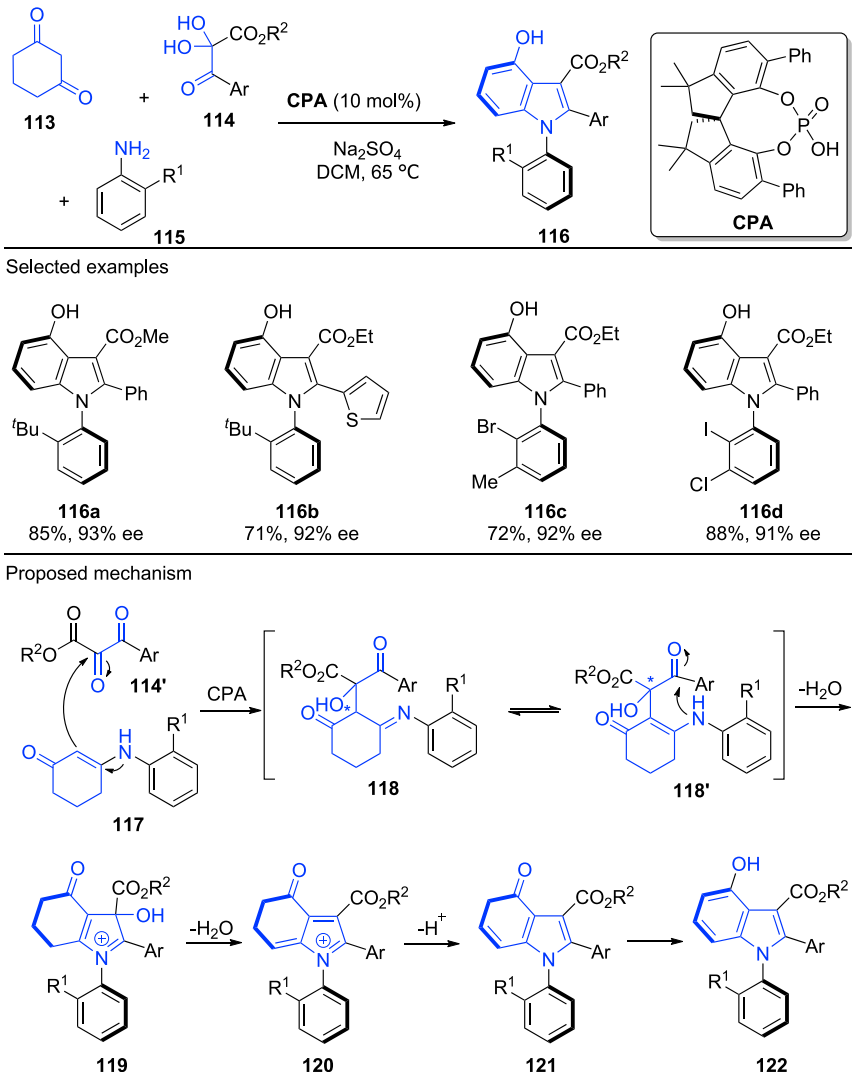
sigmatropic rearrangement process has also remained a significant challenge in asymmetric synthesis.[69]

3.1. Enantioselective aza-[3.3]-sigmatropic rearrangement

In 2011, List and co-workers reported the first catalytic asymmetric Fischer indolization in the form of enantioselective desymmetrization of 4-substituted cyclohexane-derived phenylhydrazones **97** (Scheme 20).[70] This process uses chiral phosphoric acid (CPA) as the catalyst, with the addition of cation exchange resin of CG50 to remove the ammonia side-product. Using this methodology, a variety of chiral 3-substituted tetrahydrocarbazoles **98** are obtained in high yields with good to excellent enantioselectivities. With comparison to the classical Fischer indolization mechanism, the authors proposed that the initial substrate-CPA adduct **99** can be converted to both diastereomeric enamines **100** and **100′** as an ion pair with CPA, with one of them undergoing a more favored irreversible aza-[3.3]-sigmatropic rearrangement. This dynamic kinetic resolution eventually produces the final product **98** with high enantioselectivity. The ammonium-CPA salt generated in this process is regenerated by the cation exchange resin CG50.

Three years later, the List group reported another elegant example of chiral phosphoric acid-catalyzed enantioselective Fischer indolization, for the synthesis of indole-fused chiral helicences **103** from the reactions of hydrazine **101** and tricyclic ketone **102** (Scheme 21).[71] This represents a rare example of chiral helicene synthesis.[72–74]

In 2021, Jindal, Mukherjee and co-workers reported the desymmetrization of prochiral 2,2-disubstituted cyclopentane-1,3-diones **105** by reacting it with

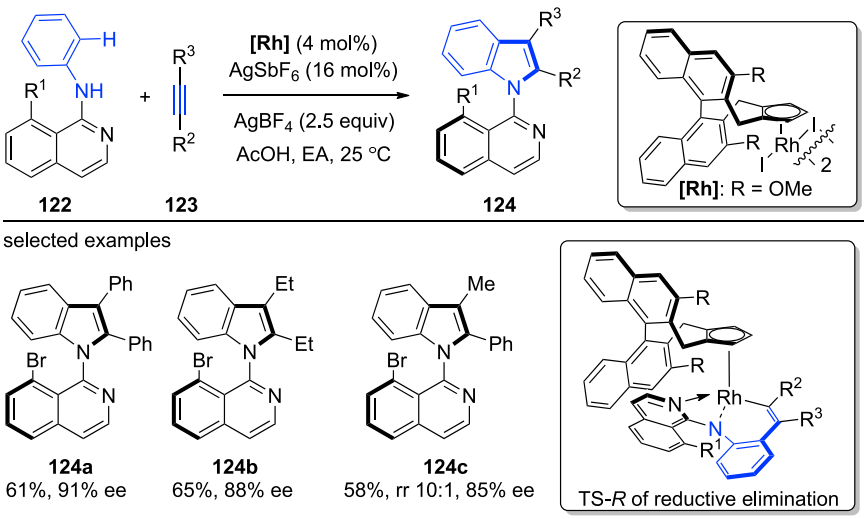


Scheme 24. CPA-catalyzed enantioselective Doyle indolization to access axially chiral *N*-arylindoles

arylhydrazines **104** through enantioselective Fischer indolization under the co-catalysis of a chiral phosphoric acid and $ZnCl_2$ (Scheme 22).[75] A variety of ketone-containing indole derivatives **106** were produced with moderate yields and good to excellent enantioselectivities. Mechanistic studies suggested that the initial condensation between dione **105** and hydrazine **104** is a reversible process, generating interconvertible hydrazone intermediates **107** and **107′**. The hydrazones are subsequently tautomerized to the corresponding ene-hydrazine intermediates **108** and **108′**, one of which preferentially undergoes the following indolization to afford the desired product, achieving an overall effective dynamic kinetic resolution. The rate- and enantiodetermining step in this transformation, similar to that in Scheme 19, is the aza-[3,3]-sigmatropic rearrangement.

3.2. Enantioselective hydrazone condensation

The reaction pathway of Fischer indolization generally involves two steps: hydrazone condensation between ketone and hydrazine followed by

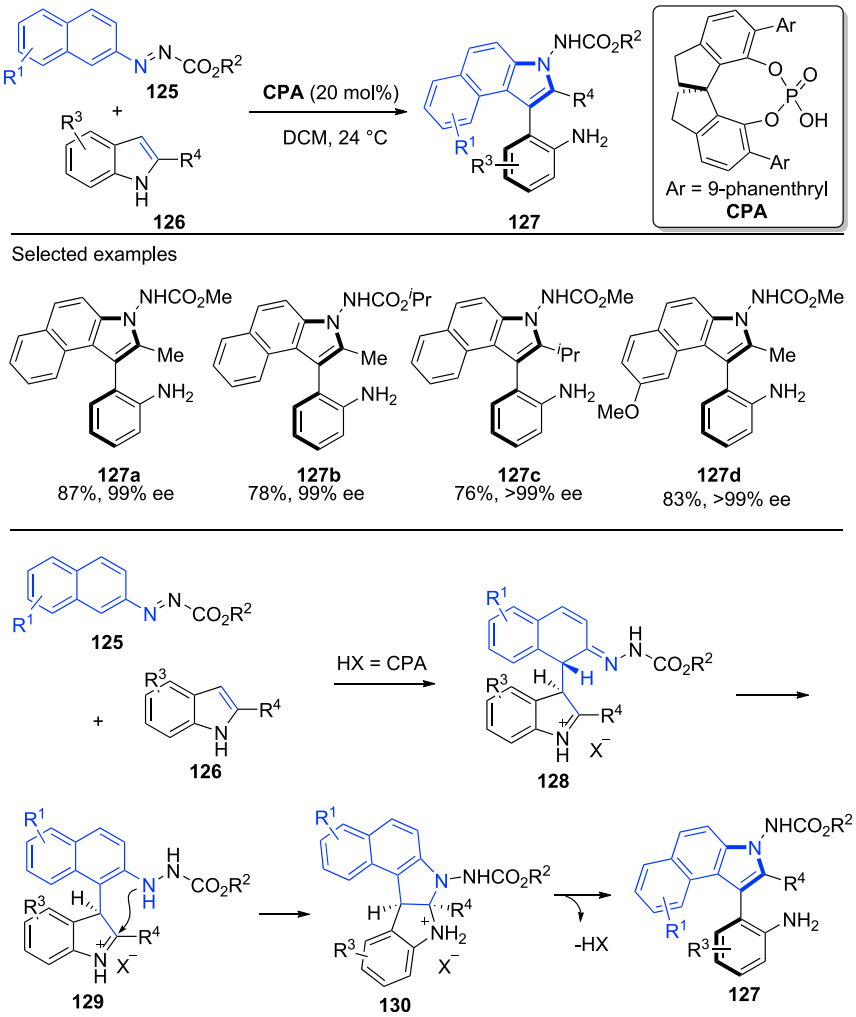


Scheme 25. Rh-catalyzed oxidative [3 + 2] cycloaddition of anilines with internal alkynes

rearrangement/cyclization to form the indole product. The few examples shown above involved the latter step as the enantiodetermining one. In contrast, achieving enantiocontrol in a simple hydrazone condensation step remained elusive until our recent work.[76] In 2021, our group reported the first example of enantioselective desymmetrization of 2,2-disubstituted diones **109** via condensation with hydrazines **110** under chiral phosphoric acid catalysis (Scheme 23).[77] This enantioselective desymmetrizing condensation is applicable to a wide range of 1,3-diones, delivering the desired chiral keto-hydrazones **111** in good yields with good to excellent enantioselectivities. Five- and six-membered cyclic and acyclic 1,3-diones, together with a range of R^1 substituents (benzyl, allyl, propyl, phenyl, etc.) were all well-tolerated in this system. Notably, the enantioenriched hydrazone product can be conveniently converted to the corresponding indole derivatives **112** by simply refluxing **111e** in toluene in the presence of TsOH.

4. ASYMMETRIC DOYLE INDOLIZATION

In 2015, Doyle and co-workers developed a TFA-catalyzed three-component cascade reaction between cyclohexane-1,3-diones, amines and 2,3-diketoesters for the construction of indoles. This transformation is later referred to as the Doyle indole synthesis.[78] In 2019, Lin and co-workers achieved the first catalytic enantioselective variant of this transformation for the synthesis of axially chiral *N*-aryl-indoles (Scheme 24).[79] Using a newly developed chiral spirocyclic phosphoric acid as the catalyst, the reaction between cyclohexane-1,3-diones **113**, 2,3-diketoesters **114**, and *ortho*-substituted aryl amines **115** provided the corresponding enantioenriched indoles **116** in good yields with good to excellent enantioselectivities. The mechanism of this transformation involves the initial formation of enamine intermediate **117** between **113** and **115** followed by aldol addition to the most activated ketone in **114** to form imine **118** that are in equilibrium with enamine **118′**. Intramolecular imine condensation (yielding **119**) followed by dehydration (yielding **120**) and aromatization produces **121** with regeneration of the acid catalyst. At last, tautomerization of **121** to phenol generates the N-aryl indole product **116**.

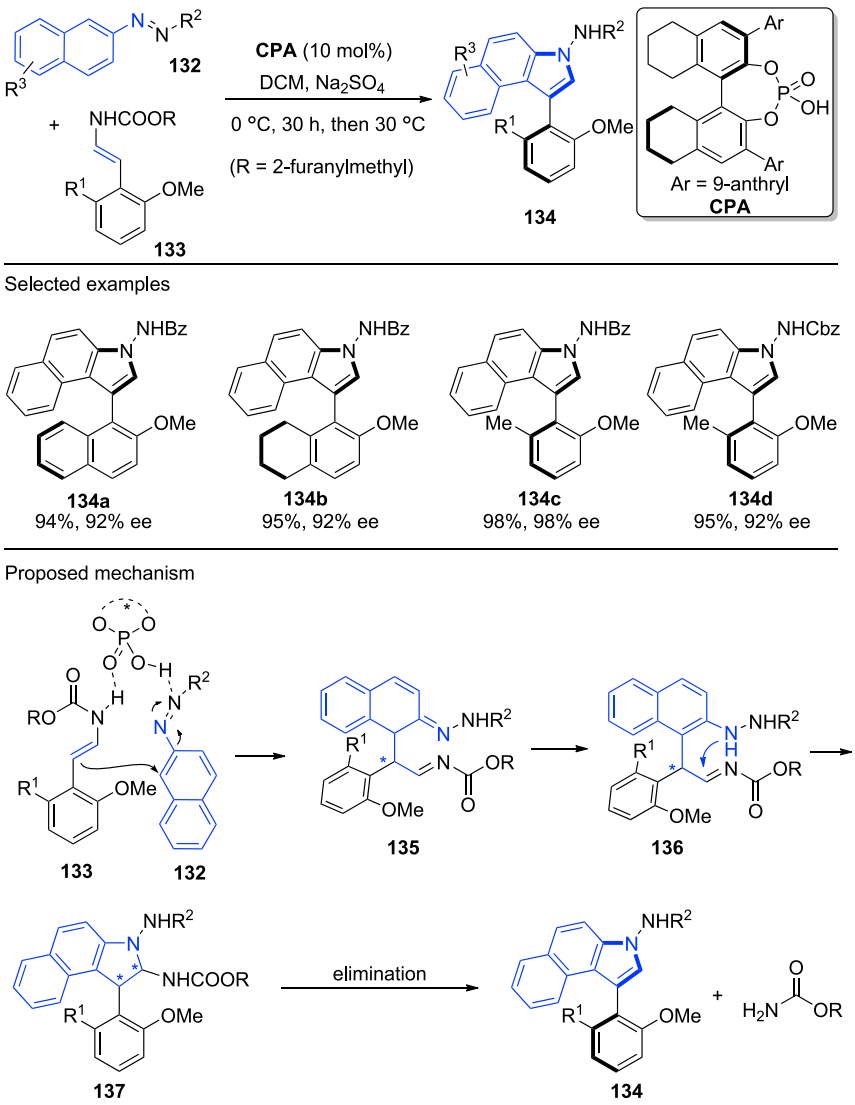


Scheme 26. Organocatalytic asymmetric arylation of indoles enabled by azo groups

5. ASYMMETRIC INDOLIZATION INVOLVING A FORMAL [3 + 2] CYCLOADDITION

Formal [3 + 2] dipolar cycloaddition represents one of the most efficient strategies to construct five-membered heterocycles from simple precursors, and this strategy has also been successfully applied to the synthesis of indoles using either transition metal- or organocatalytic approaches.[13]

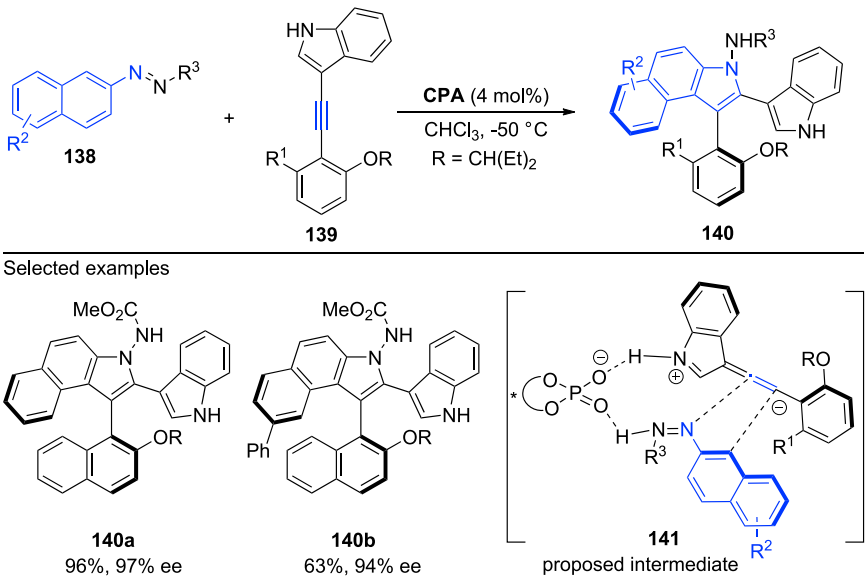
In 2021, Wang, Lan, Li, and co-workers reported a rhodium-catalyzed formal oxidative [3 + 2] cycloaddition of *N*-isoquinolylanilines **122** with internal alkynes **123** for the synthesis of axially chiral *N*-isoquinoline indoles **124** (Scheme 25).[80] The reaction proceeds through C-H activation of **122**, migratory insertion to alkyne **123** followed by C-N bond formation via reductive elimination, and it delivers enantioenriched indoles **124** using $AgBF_4$ as the terminal oxidant. A wide range of internal alkynes and *N*-isoquinoylanilines are suitable substrates in this catalytic system, affording axially chiral indoles **124** in good yields with high regio- and atroposelectivities. The reaction was proposed to proceed through Rh-catalyzed C-H activation directed by the amine/quinoline nitrogens, which then engage the alkyne by migratory insertion



Scheme 27. Organocatalytic cycloaddition–elimination cascade reaction of phenol-derived enecarbamates with azonaphthalenes

followed by C-N bond formation via reductive elimination. In the key enantiodetermining reductive elimination step, DFT studies showed that the formation of *R*-product through TS-*R* was 5.8 kcal/mol lower in energy compared with that of the corresponding *S*.

In 2018, Tan and co-workers reported an intriguing CPA-catalyzed reaction between azonaphthalenes **125** and indoles **126** to yield a variety of axially chiral aniline-indoles **127** in good yields with excellent enantioselectivities (Scheme 26).[81] In this work, azonaphthalenes **125** is identified as a highly effective Michael acceptor for formal nucleophilic aromatic substitution, and the resultant hydrazine intermediate then serves as a nucleophile to induce ring cyclization. For this transformation, CPA is proposed to serve as a bifunctional catalyst to activate both the N=N bond in **125** by BrØnsted acid catalysis and the indole N-H by H-bond interaction. Intermediate **124** formed by the formal nucleophilic aromatic substitution undergoes rearomatization to yield **129**, the enamine nitrogen of



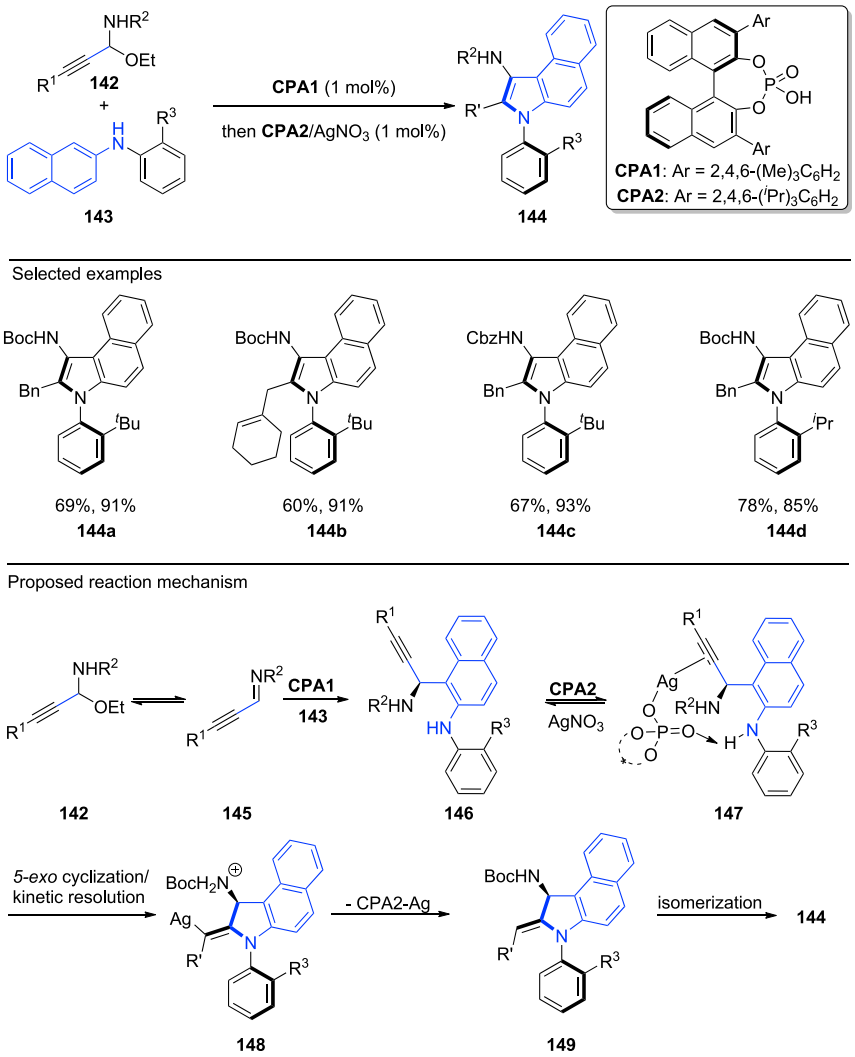
Scheme 28. Organocatalytic cycloaddition of alkynylindoles with azonaphthalenes

which then attacks the iminium ion to generate intermediate **130**. Finally, collapse of the aminal moiety then generates product **127** with regeneration of the acid catalyst.

In 2021, Zhou and co-workers reported a CPA-catalyzed cycloaddition/elimination cascade reaction between aryl-derived enecarbamates **133** and azonaphthalenes **132**, producing axially chiral indole derivatives **134** in excellent yields with excellent enantioselectivities (Scheme 27).[82] A similar mechanism with that in Scheme 25 was proposed, with CPA acting as a bifunctional catalyst to activate both substrates for the asymmetric addition to form **135**. Subsequent aromatization forms intermediate **136**, which undergoes cyclization to form **137** with central chirality. Lastly, elimination of the carbamate results in aromatization with central-to-axial chirality transfer to deliver enantioenriched product **134**.

More recently, Zhou and co-workers reported a chiral spirocyclic phosphoric acid-catalyzed intermolecular formal [3 + 2] cycloaddition of 3-alkynylindoles **139** and azonaphthalenes **138** for the atroposelective construction of axially chiral indole derivatives **140** in high yields with excellent enantioselectivities (Scheme 28).[83] Due to conjugation with the indole substituent, the alkyne moiety in **139** can serve as a nucleophile to undergo addition to azonaphthalenes **138** through the proposed allene anion in **141**. Compared with previous studies in Schemes 26 and 27, this work presents an interesting substrate design in **139**, enabling the electron-rich alkyne to serve as an effective partner to undergo formal [3 + 2] cycloaddition with **138**.

Very recently, Wang, Peng, Shao, and co-workers reported a chiral phosphoric acid and silver sequential catalyzed formal [3 + 2] cycloaddition-isomerization of C-alkynyl N,O-acetals **142** and 2-naphthylamines **143**, producing C-N axially chiral indole derivatives **144** in good yields and enantioselectivities (Scheme 29).[84] Mechanistic studies suggested that enantioselective propargylation of imine intermediate **145** and **143** affords chiral propargylic amine intermediate **146**



Scheme 29. CPA and silver sequential catalytic cycloaddition-isomerization of C-alkynyl N,O-acetals and 2-naphthylamines

catalyzed by CPA1. Subsequently, the intermediate **146** transfers to the corresponding intermediate **148** through 5-exo cyclization/kinetic resolution. Protodemetalation of **148** followed by olefin isomerization gives enantioenriched axially chiral indole **144**.

CONCLUSIONS AND OUTLOOK

With the increasing awareness of the importance of enantioenriched indole derivatives in pharmaceuticals, catalysis, and material sciences, catalytic asymmetric construction of indoles has gained significant progress over the past few decades. By incorporating enantiocontrol in various classical indolization methods, novel catalytic processes have been achieved that enable the facile conversion of simple linear substrates to enantioenriched indole derivatives including structurally novel ones bearing an axial or helical chirality. Strategies such as indolization of 2-alkynylanilines, Fischer indolization, Doyle indole synthesis, and formal [3 + 2] cycloaddition have all been applied to efficient and enantioselective indole synthesis. These endeavors have also served as an effective platform for the development

of new chiral catalysts, new cascade catalysis concepts, and enantioselective synthetic methods. Considering the vast diversity of classical approaches established for indole synthesis, we anticipate that the subject of enantioselective indolization will witness even more exciting developments in the near future.

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AUTHOR CONTRIBUTIONS

B.M.Y. and Y.Z. wrote the manuscript with help from X.Q.N.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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