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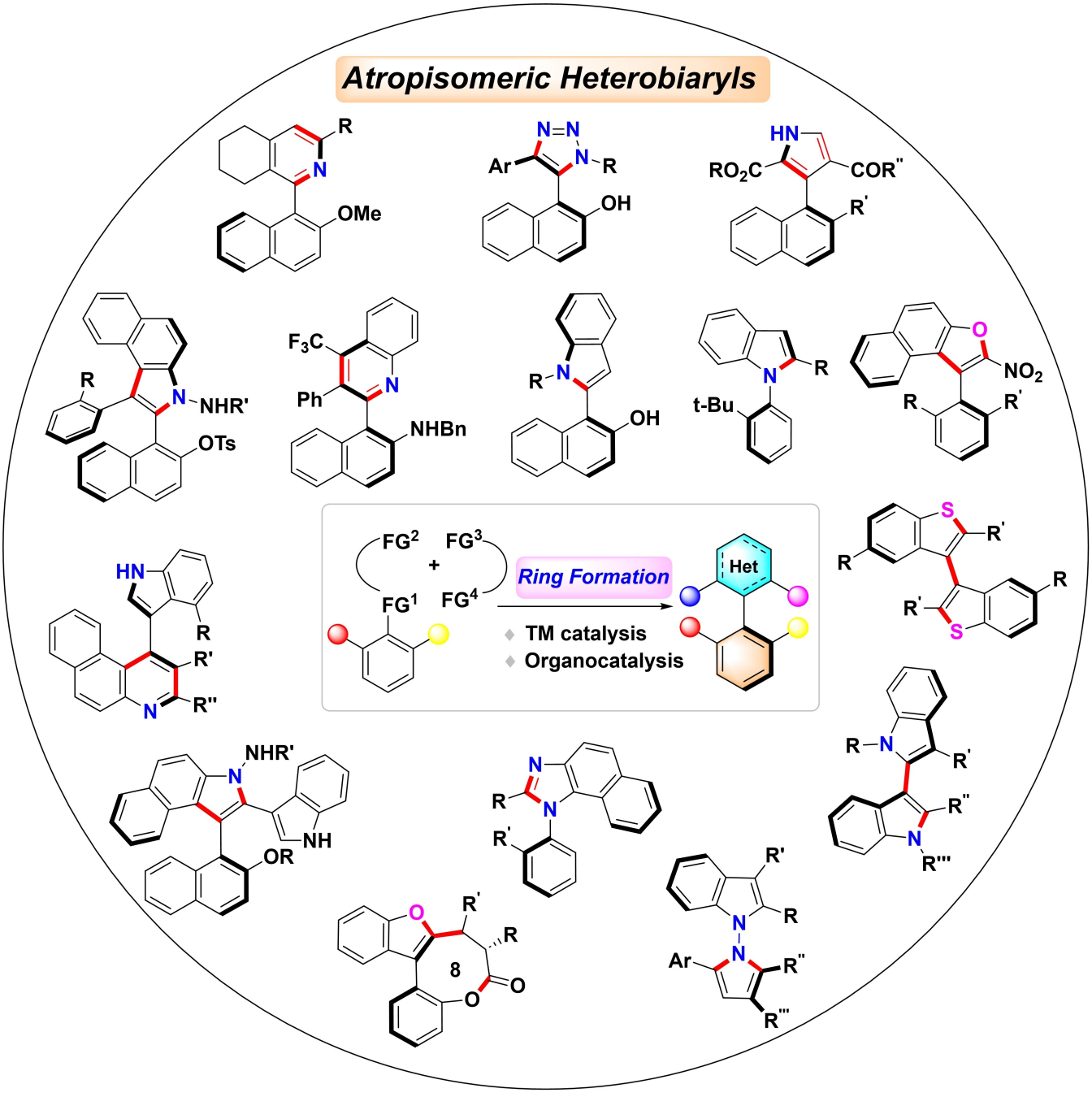
Atroposelective Synthesis of Heterobiaryls through Ring Formation

Huai-Ri Sun[+],[a] Atif Sharif[+],[a] Jie Chen,*[a] and Ling Zhou*[a]



Abstract: Atropisomeric heterobiaryls play a vital role in natural products, chiral ligands, organocatalysts, and other research fields, which have aroused great interest from chemists in recent years. Until now, a growing number of optically active heterobiaryls based on indole, quinoline, isoquinoline, pyridine, pyrrole, azole, and benzofuran skeletons have been successfully synthesized through metal or organic catalytic cross-coupling, functionalization of prochiral or racemic heterobiaryls, and ring formation. Among different strategies for the atroposelective synthesis of heterobiaryls, the strategy of ring formation has become a vital tool toward this goal. In this review, we summarize the enantioselective synthesis of axially chiral heterobiaryls through ring formation approaches, such as cycloaddition, cyclization, and chirality conversion. Meanwhile, the reaction mechanism and the corresponding applications of the chiral heterobiaryls are also discussed.

1. Introduction

Since the first report by Christie and Kenner in 1922,[1] enantiopure atropisomers have found wide applications in asymmetric catalysis,[2] chiral ligands,[3] complex natural products,[4] and drug discovery.[5] Heterobiaryls, like other axially chiral compounds, are useful skeletons in asymmetric catalysis and have potential biological activities, such as QUINAP, BIMINAP, *N*-methyl pyridoxal, Murrastifoline-F, and Marinopyrrole (Figure 1).[2–5] Despite the advances made in this field to date, the construction of heterobiaryl atropisomers has been studied to a lesser extent historically, which may be due to the difficulty in controlling the axial stability of the heterobiaryls, especially the axially chiral compounds bearing five-membered heterocycles or *ortho* nitrogen-containing six-membered aza-heterocycles.[6] In the past few years, a range of catalytic atroposelective approaches for the synthesis of heterobiaryls has been developed, which have witnessed a progressive advancement in this area. Up to present, there are three major approaches to synthesizing axially chiral heterobiaryl structures: (i) formation of axial bonds via cross-coupling of aryl heterocyclic compounds; (ii) functionalization of prochiral or racemic heterobiaryls, such as dynamic kinetic resolution, kinetic resolution, and desymmetrization; (iii) formation of a new ring segment or aromatic unit, such as the construction of N, O, and S containing rings utilizing direct cycloaddition, cyclization, and other cascade reactions.

As we know, one of the most important ways to get axially chiral biaryls is through enantioselective Ar–Ar couplings that are sped up by transition metals.[7a–c] However, the preparation of axially chiral heterobiaryls via a transition metal-catalyzed coupling reaction is more difficult in terms of stereoselectivity, and greater efforts are still needed.[7d–g] Fortunately, organocatalytic asymmetric cross-coupling or arylation has achieved the construction of heterobiaryls, as reported by Shi,[8a] Tan,[8b,d] Miller[8c] and other groups. Additionally, functionalization of racemic heterobiaryls via dynamic kinetic resolution[7a–c] is mainly reported by Miller,[9a,j] You,[9b–d] Li,[9e] Lassaletta,[9f,g] Stoltz and Virgil,[9h] Turner and Clayden[9i] neatly illustrate the great potential of this method in building heterobiaryl skeletons. On the other hand, cycloaddition and cyclization reactions are one of the most powerful synthetic methods for the rapid construction of cyclic frameworks, owing to their high atom economy and convergent nature.[10] Over the past decades, organocatalytic ring formation strategies have been developed for the efficient construction of furan, pyran, quinoline, and other central chiral compounds.[10] However, compared with the number of centrally chiral products, the enantioselective cycloaddition and cyclization synthesis of atropisomeric biaryls or heterobiaryls still have great potential, although Sparr,[11] Tanaka,[12] Shibata,[13] and other groups[14] have reported many elegant works to access the atropisomeric biaryls using arene-forming routes.

Although various reviews regarding the asymmetric synthesis and application of axially chiral molecules have been published,[15] there is no detailed review on the atroposelective synthesis of heterobiaryls via ring formation methods. Here, we comprehensively summarized the recent developments of axially chiral heterobiaryls catalyzed by transition metal and organic catalysts using ring formation strategies, such as cycloaddition, cyclization, and chirality conversion cascade reactions (Figure 2).

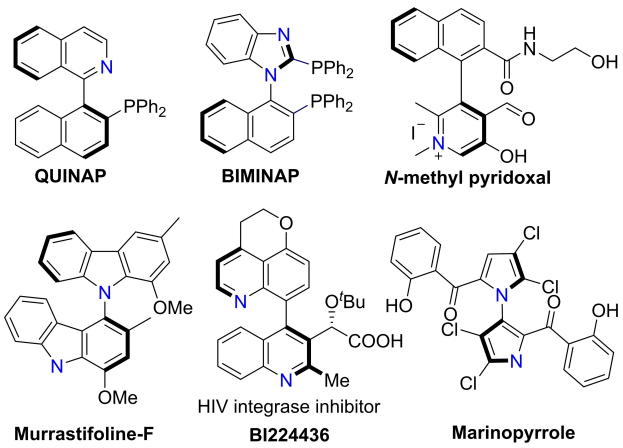


Figure 1. Selected chiral ligands and pharmaceuticals containing heterobiaryls.

[a] *H.-R. Sun,[+] A. Sharif,[+] Prof. Dr. J. Chen, Prof. Dr. L. Zhou*
Key Laboratory of Synthetic and Natural Functional Molecule of the Ministry of Education
College of Chemistry & Materials Science
Northwest University,
Xi'an 710127 (P. R. China)
E-mail: chmchenj@nwu.edu.cn
zhoul@nwu.edu.cn

[+] *These authors contributed equally to this work.*

2. Transition-Metal-Catalyzed Enantioselective Cycloaddition Synthesis of Heterobiaryls

2.1. [2+2+2] Cycloaddition

Transition-metal-catalyzed [2+2+2] cycloaddition of alkynes has received much attention for the synthesis of substituted benzenes.[15a,16] Even though many enantioselective [2+2+2] cycloaddition of alkynes have been used to access axially chiral biaryls and non-biaryls with axial chirality, only a few have been used to make heterobiaryls.

The [2+2+2] cycloaddition of alkynes and nitriles is allowing easy access to pyridine derivatives in one step. In 2004, Gutnov, Heller, and co-workers discovered the first asymmetric approach to build axially chiral 2-arylpyridines **3** by the cobalt(I)-catalyzed [2+2+2] cycloaddition of alkynes **1** and nitriles **2** (Scheme 1a).[17a] On the other hand, in 2010, Hapke and co-workers continuously developed the reaction of 1-naphthyl diynes with a range of differently functionalized nitriles that contained 2-furyl, substituted benzene, and piperidine, giving the corresponding atropisomers **6** with good to excellent yields and ee values (Scheme 1b).[17b] In the two methods for the synthesis of atropisomeric heterobiaryls **3** and **6**, the aryl-substituted terminal alkyne **4** outperformed the alkyl-substituted alkynes **1**. In general, although there are not many examples of these reactions, this strategy still opens up an advanced and convenient way for the construction of axially chiral heterobiaryls.

Tanaka and colleagues demonstrated in 2006 the synthesis of C2-symmetric axially chiral heterobiaryls **9** via rhodium(I)/**L1**

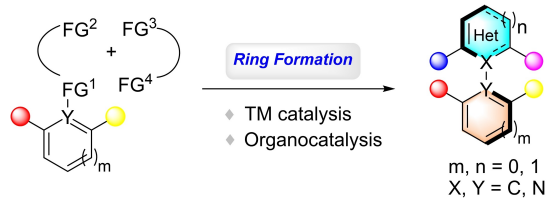
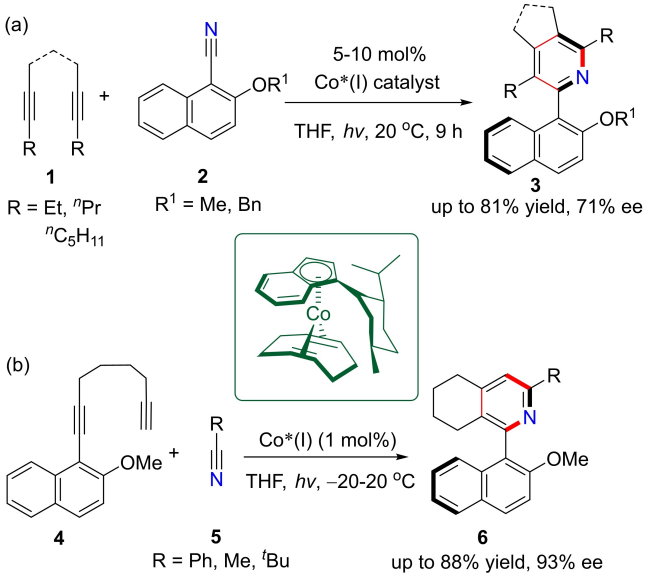


Figure 2. Ring formation strategy for the synthesis of atropisomeric heterobiaryls.



Scheme 1. Cobalt(I)-catalyzed atroposelective [2+2+2] cycloaddition between diynes and nitriles.[17a,b]

Huai-Ri Sun was born in Shandong Province, the People's Republic of China, in 1994. He graduated in Chemical Engineering and Technology from Heze University in 2017. Currently, he is a Ph.D. candidate under the supervision of Prof. Ling Zhou in the Department of Chemistry and Material Science at Northwest University. He is currently working on developing new methodologies with chiral phosphoric acid catalysis.

Atif Sharif was born in Punjab Province, Lahore, Pakistan. He graduated with an MPhil in Chemistry from the University of Engineering & Technology (UET) Lahore in 2019. Currently, he is a Ph.D. candidate under the supervision of Prof. Ling Zhou in the Department of Chemistry and Material Sciences at Northwest University. His research is focused on the development of cycloaddition reactions.

Jie Chen received her PhD from Lanzhou University in 2009. After postdoctoral studies with Prof. Choon-Hong Tan at Nanyang Technological University, and with Prof. Yeung Ying-Yeung at the National University of Singapore, she started her independent career at Northwest University in 2012. Her research interests are focused on asymmetry catalysis and natural product synthesis.

Ling Zhou received his B.S. (2002) and PhD (2007) from Lanzhou University under the supervision of Prof. Xiao-Ping Cao and Prof. Xinshan Ye. He joined Basilea Pharmaceutica China Ltd. as a group leader (2007-2009). He worked as a postdoc at the National University of Singapore with Prof. Yeung Ying-Yeung (2009-2011). In 2012, he began his independent career at Northwest University. His research interest includes the development of new methodologies of organocatalysis and their application to the synthesis of natural products and bioactive compounds.

catalyzed double [2+2+2] cycloadditions, which provides an attractive route to enantioenriched *tetra-ortho*-substituted molecules from readily available alkynes.[18] In this case, activated nitrile **8a** reacts with electron-rich tetraynes **7** to produce the corresponding axially chiral pyridines with 98% ee, accompanying 38% yield due to the formation of other regioisomers (Scheme 2).

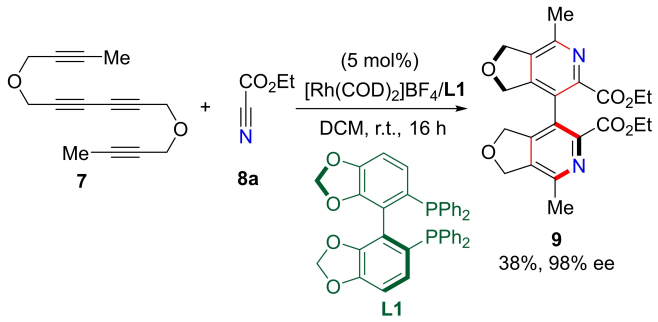
Tanaka discovered in 2011 that cationic Rh(I)/**L2** had exceptional catalytic activity for enantioselective [2+2+2] cycloaddition of *O*/*N*-linked 1,6-diynes **10** with $SiPh_3$/$P(O)PPh_2$-substituted 1-ethynylisoquinolines **11**, which furnished axially chiral 1-arylisoquinolines **12** in high yields with high enantioselectivity (up to 99% ee) (Scheme 3).[19] Furthermore, the newly synthesized $P(O)PPh_2$-substituted heterobiaryls were successfully derivatized to the corresponding Lewis base catalyst **12a** and *P,N*-ligand **12b**.

In 2016, Tanaka and co-workers achieved the enantioselective synthesis of axially chiral 3-(2-halophenyl)pyridines and achiral 6-aryl pyridines by a rhodium/**L3** complex-catalyzed regio- and enantioselective [2+2+2] cycloaddition of *ortho*-substituted phenyl diynes **13** with nitriles **8**.[20] The scope of diynes shows that the regioselectivity and enantioselectivity closely depend on the *ortho*-substituents (R^1) of diynes: (i) the R^1 group consisted of Br, Cl, and axially chiral 3-aryl pyridines that were obtained in good yields with high enantioselectivities, such as **14a** and **14b**; (ii) the R^1 group consisted of OMe and CO_2Me, axially chiral compounds that were also major products while the ee values were extremely reduced (**14c**); (iii) the R^1 group consisted of Me, CF_3 and CH_2OMe to give achiral 6-aryl pyridines in excellent yields, such as **14d′** and **14e′** (Scheme 4).

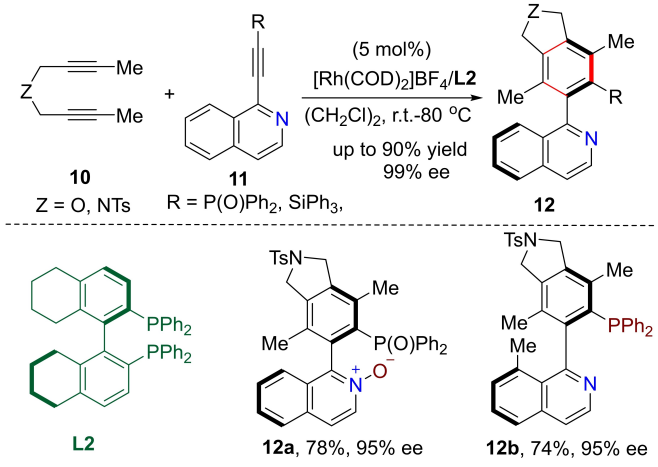
A possible explanation of the effect of the R^1 groups is shown in Scheme 5. When R^1 is a coordinating group (Cl, Br, OMe, CO_2Me), axially chiral products **14** were formed via a process of coordination (**TS-1**), oxidative cyclization (**Int-1**), insertion of nitrile (**Int-2**), and reductive elimination. The reason why the methoxy or methoxycarbonyl substituted substrates returned lower enantioselectivity may be due to the generation of intermediate **Int-1′**, in which strong coordination between R^1 and Rh was proposed. On the other hand, when R^1 is a less coordinating group (Me, CF_3, CH_2OMe), **TS-2** was proposed as a result of weak coordination between R^1 and Rh. Oxidative cyclization gave rhodacycle **Int-3**, and the corresponding **Int-3′** was believed unfavorable due to the steric repulsion. Thus, achiral 6-aryl pyridines **14′** would be formed via **Int-4**.

2.2. Click reactions

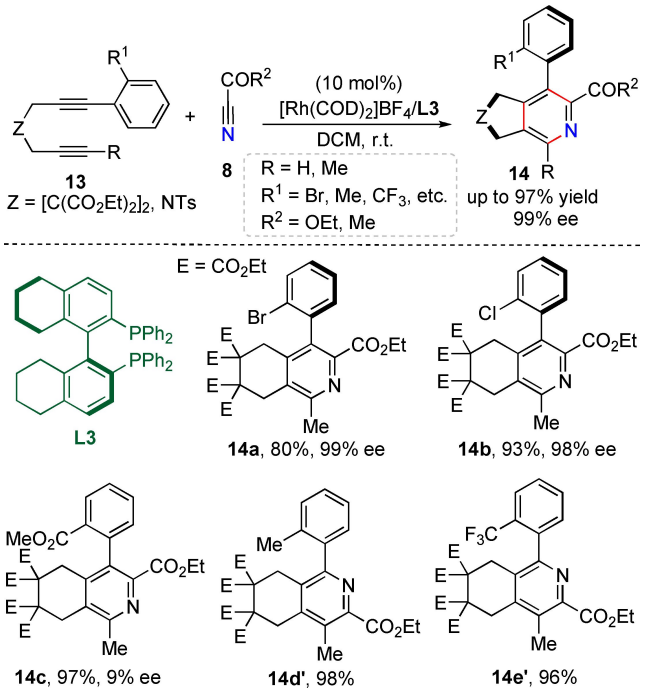
Click chemistry, which was originally described by Sharpless and co-workers in 2001, is widely used in chemistry, material science, biology, and other fields. It is recognized as an ideal synthesis approach because it uses easily available starting materials and simple reaction conditions to develop promising constructs. However, the enantioselective synthesis and applica-



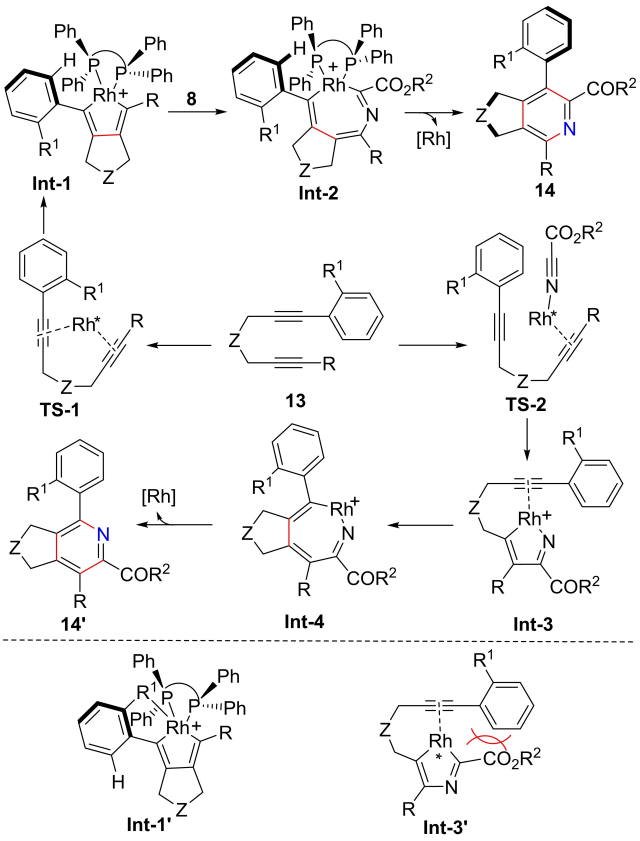
Scheme 2. Rhodium(I)-catalyzed atroposelective double [2+2+2] cycloaddition of tetrayne with nitrile.[18]



Scheme 3. Rhodium(I)-catalyzed atroposelective [2+2+2] cycloaddition of diynes with alkynes.[19]



Scheme 4. Atroposelective [2+2+2] cycloaddition of *ortho*-substituted phenyl diynes with nitriles.[20]



Scheme 5. Proposed mechanism of [2 + 2 + 2] cycloaddition of *ortho*-substituted phenyl diynes with nitriles.[20]

tion of click chemistry are rarely studied, possibly due to the lack of efficient synthetic methods and the difficulty to achieve excellent stereoselectivity as well.[21]

The azide–alkyne cycloaddition (AAC) is one of the signs of click chemistry due to the facile modification and the rapid click process. Asymmetric Cu-catalyzed azide–alkyne cycloaddition has achieved high chemoselectivity and stereoselectivity, producing point-chiral triazoles efficiently.[21] Noteworthily, the azide–alkyne cycloaddition has great potential to construct axially chiral heterobiaryls. However, utilizing the click methodology to synthesize these compounds remains unexplored. Until 2022, Xu and co-workers disclosed an unprecedented Ir(I)/squaramide **C1** cooperative catalytic azide–alkyne cycloaddition reaction for the atroposelective synthesis of axially chiral aryl triazoles from internal 2-alkynylnaphthols **15** and azides **16**, which cannot be accessed by traditional click reactions (Scheme 6a).[22] A wide range of heterobiaryls **17a** were synthesized in good yields with excellent enantioselectivities. Meanwhile, the initial terminal group (R^1 = Ph) could be replaced by the methyl (72% ee), cyclopropyl (91% ee), 2-thiophenyl (85% ee), ferrocenyl (84% ee) and trimethylsilyl (92% ee) groups without loss of obvious efficiency and enantioselectivity. In this way, a new monophosphine ligand of **18a** could be easily synthesized and successfully promoted allylic alkylation with 40% yield and 36% ee through preliminary attempts (Scheme 6d, left). Additionally, a preliminary cooperative catalytic mechanism of Ir(I)/squaramide was proposed in Scheme 7a. First, the activated cooperative catalyst reacted with 2-alkynylnaphthol in situ, forming a vinylidene *ortho*-quinone methide (VQM) via 1,5-hydrogen migration. Subsequently, VQM with Ir(I) coordinated azide undergo enantioselective cycloaddition, following stereospecific [1,5]-H migration to obtain heterobiaryl products. It is worth emphasizing that the formation of the new C–N bond determines the stereoselectivity.

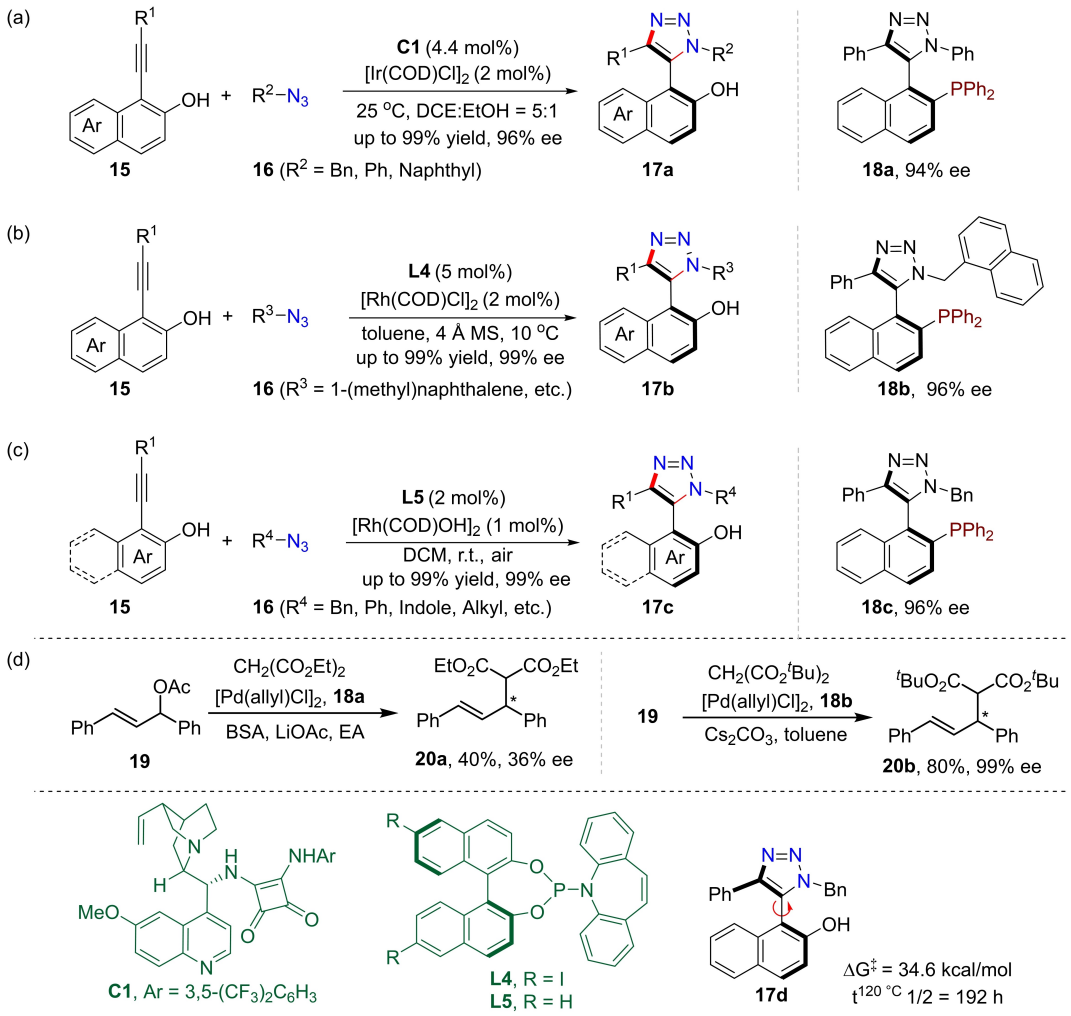
The same year, Li, Deng, Qian, and co-workers also reported a Rh/**L4**-catalyzed azide–alkyne cycloaddition (E-RhAAC), via the catalytic asymmetric [3 + 2] process, to construct five-membered axially chiral 1,4,5-trisubstituted 1,2,3-triazoles **17b** with excellent regio- and enantiocontrol, mild conditions, simple operation, and broad substrate scope (Scheme 6b).[23] This approach also successfully provides an avenue for the synthesis of chiral ligand **18b** and offers the allylic alkylation product in 80% yield and 99% ee (Scheme 6d, right). Importantly, the DFT calculations and racemization experiments sufficiently demonstrated the positive correlation relationship between rotation barrier and enantioselectivity by comparison of the internal alkyne bulkiness (R^1 = methyl (60% ee, 30.9 kcal/mol), cyclopropyl (65% ee, 31.2 kcal/mol), *n*-butyl (69% ee, 32.2 kcal/mol), and trimethylsilyl (97% ee, 34.1 kcal/mol)).

According to experimental observations and DFT calculations, the most favorable mechanism is described in Scheme 7b. First, the triple bond and Rh(I) catalyst via the H–Cl bond coordination to afford complex **TS-5**, which is then trapped by **16** to form **TS-6** and **TS-6′**, respectively. Subsequently, **TS-6** and **TS-6′** undergo cycloaddition, reductive elimination, and catalyst regeneration to generate *rac*-**17b** and *rac*-**17b′**. The DFT shows that **TS-A1** (−62.6 kcal/mol) is lower than **TS-B1′** (−55.8 kcal/mol), *rac*-**17b** (−42.9 kcal/mol) is lower than *rac*-**17b′** (−41.6 kcal/mol). Moreover, when chiral ligands are employed in DFT, they also obtain similar results, which is consistent with the experimental conclusions. The hydrogen bond H–Cl in **Int-6** (bond length 2.06 Å) and steric effects are most likely responsible for enantioselectivity.

Nearly at the same time, Cui and co-workers reported the highly enantioselective synthesis of atropisomeric triazoles **17c** via a robust Rh/**L5**-catalyzed enantioselective click cycloaddition of azides and alkynes in excellent results under mild reaction conditions as well (Scheme 6c).[24] In comparison to the E-RhAAC reaction reported by Li et al., this methodology features a much broader substrate scope (> 80 examples), lower catalyst loading, remarkable efficiency, and more practical manipulation. In addition, the racemization experiments to study the thermal stability of the axially chiral triazole product **17d** presented good results. The $\Delta G^{\ddagger}$ was calculated as 34.6 kcal/mol, and the half-life at 120 °C was 192 h, giving good synthetic potential to click chemistry.

2.3. Other forms of cycloaddition

In 2018, Zhu and co-workers reported an efficient silver oxide/Dixon-type amino phosphine ligand **C2** catalyzed asymmetric



Scheme 6. Atroposelective synthesis of axially chiral aryl triazoles via click cycloaddition.[22–24]

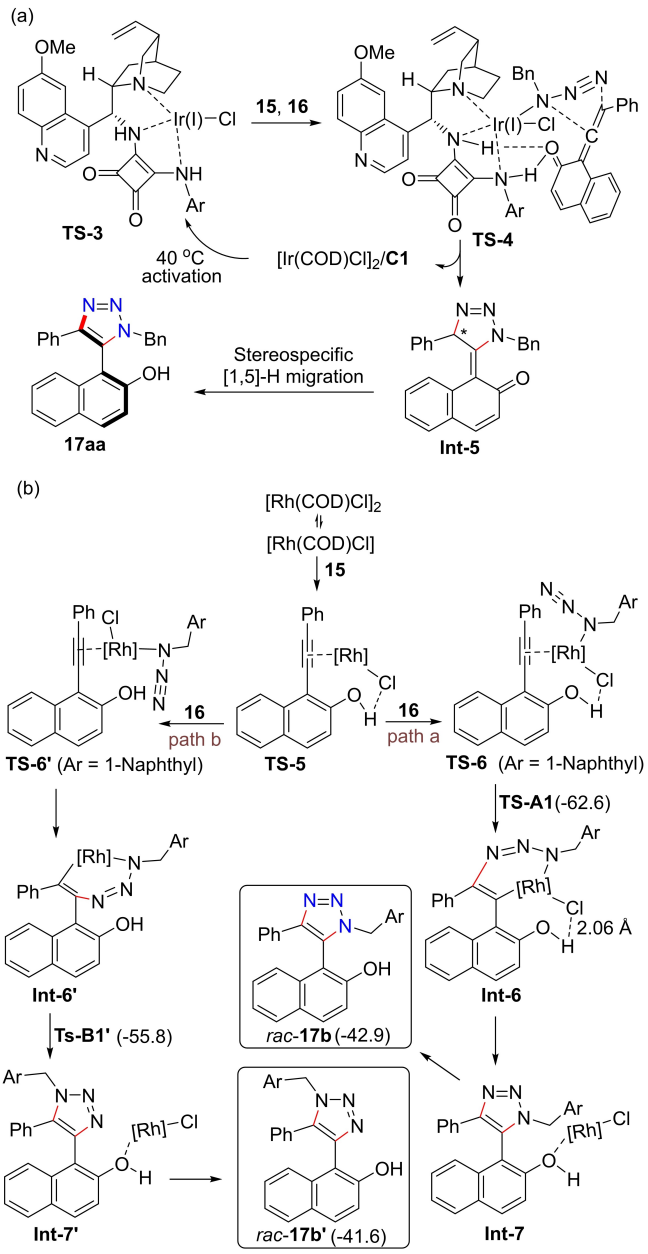
heteroannulation of α-isocyanoacetates **22** with alkynyl ketones **21**, providing axially chiral 3-arylpyrroles **23** in good yields with excellent enantiomeric excesses. Moreover, the strategy represented the first examples of asymmetric synthesis of arylpyrroles bearing a chiral C–C axis (Scheme 8).[25] First, the coordination of isocyanoacetate, carbonyl oxygen, phosphine ligand, and silver forms the transition state **TS-7**, in which the additional hydrogen bond between the protonated quinuclidine and the carbonyl oxygen could further improve the stereoselectivity. Then, due to the steric hindrance effect, the alkyne would approach the enolate from the backside to give intermediate **Int-8**, followed by an intramolecular addition, protonation, and a 1,5-hydrogen shift that afforded the final axially chiral arylpyrroles. Importantly, in 2019, they also developed an efficient asymmetric synthesis of axially chiral 3-arylpyrroles via kinetic resolution of racemization-prone 3-aryl 3H-pyrrole for the first time.[26]

In 2022, Shao, Peng, and co-workers reported a cycloaddition isomerization strategy for the enantioselective synthesis of axially chiral indole-based biaryls in the presence of two chiral phosphoric acids (CPAs) **C3** and **C4**, and $AgNO_3$.[27] A range of valuable heterobiaryls with C–N axes (**26**) was achieved with good yields and ee values. In this process, the centrally chiral propargylic intermediate **25′** was first formed. Subsequently, a kinetic resolution occurred in the presence of metal-coordination and hydrogen-bonding dual interactions through a 5-*exo*-selective cyclization process to offer the intermediate **Int-11**, followed by protodemetalation and olefin isomerization to give the final axially chiral compounds (Scheme 9).

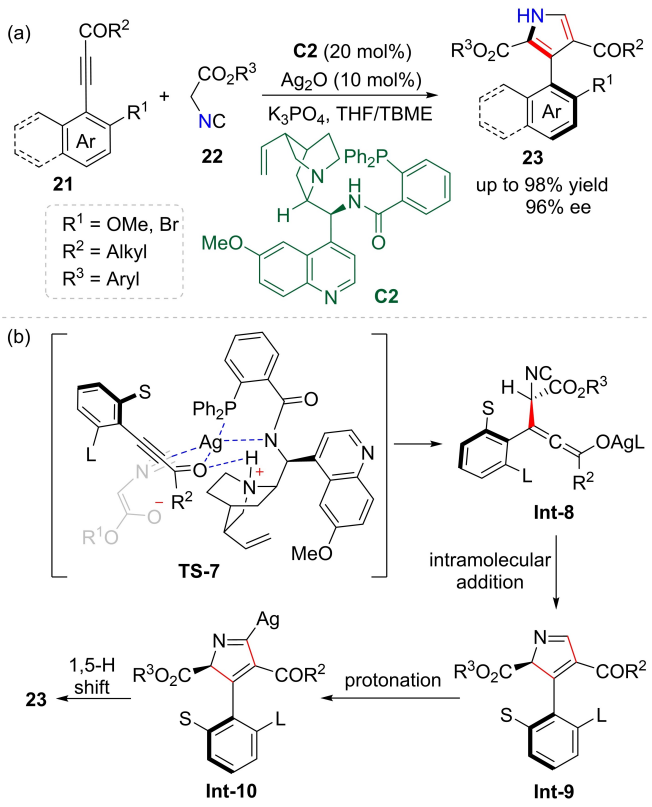
3. Organocatalytic Asymmetric Cycloaddition Synthesis of Heterobiaryls

3.1. Cycloaddition reaction of alkenes

Central-to-axial chirality conversion represents an appealing strategy for the construction of axially chiral compounds, including biaryls, heterobiaryls, allenes, and so on.[28] Here, we selected some examples of cycloaddition involving alkenes and



Scheme 7. Proposed mechanism of azide–alkyne cycloaddition.[22,23]



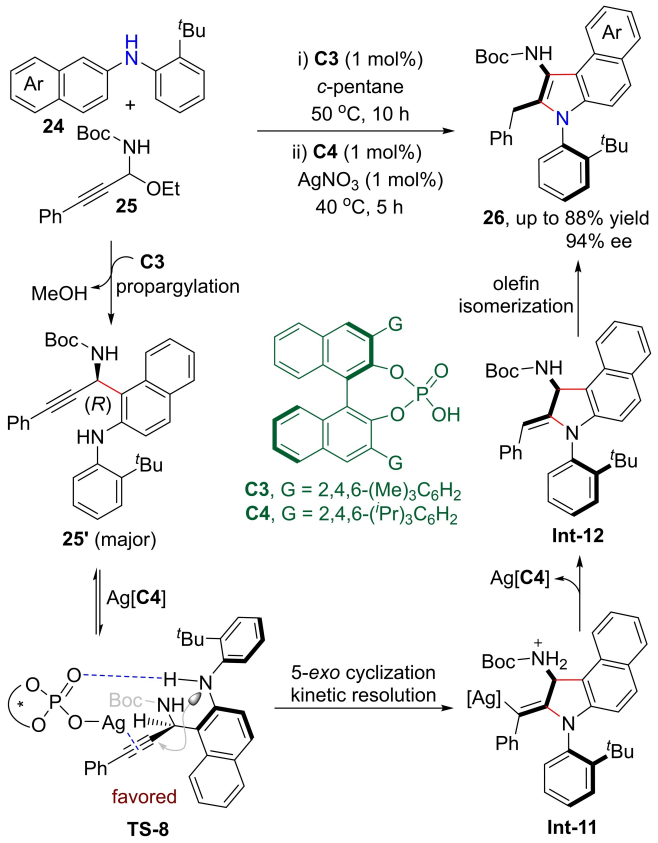
Scheme 8. Enantioselective synthesis of axially chiral 3-arylpyrroles.[25]

chirality conversion cascade reactions to introduce the trends in the preparation of atropisomeric heterobiaryls.

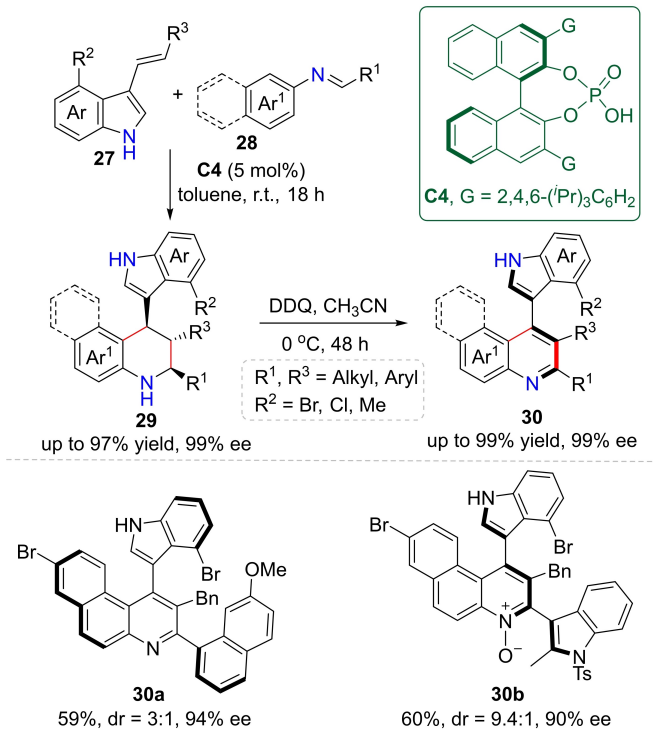
In 2019, Corti, Bertuzzi, and co-workers developed the stereoselective synthesis of axially chiral indole-quinoline biaryls via an asymmetric Povarov reaction and chirality conversion cascade process for the first time.[29] The organocatalytic cycloaddition of alkenylindoles **27** and *N*-arylimines **28** produces tetrahydroquinolines **29** with three consecutive stereocenters in excellent yields and ee values, despite the high steric demand required to produce stable atropisomeric 4-(indol-3-yl)quinolines **30** after DDQ oxidation. Additionally, the challenging compounds exhibiting two chirality axes (**30a** and **30b**) followed two different approaches that were implemented in this methodology (Scheme 10). Moreover, the unconventional behavior of the central-to-axial chirality conversion is illustrated by the DFT calculations.

In 2019, our group reported a CPA-catalyzed [2+3] formal cycloaddition reaction of 1-styrylnaphthols **31** with azonaphthaenes **32** to afford 2,3-diarylbenzoindoles **33** with two adjacent stereocenters and excellent results under mild conditions.[30] Subsequently, we achieved the conversion of two stereocenters to one or two chiral axes for the first time via the protection of the OH group and the DDQ oxidation strategy. A series of atropisomeric heterobiaryls **34** were obtained without loss of enantiomeric purity (Scheme 11). Moreover, DFT calculations and mechanistic studies sufficiently revealed a speculative model of the central-to-axial chirality conversion. In addition, a new benzoindolenaphthyl phosphine ligand **35** (99% ee) can be synthesized smoothly via six-step transformations.

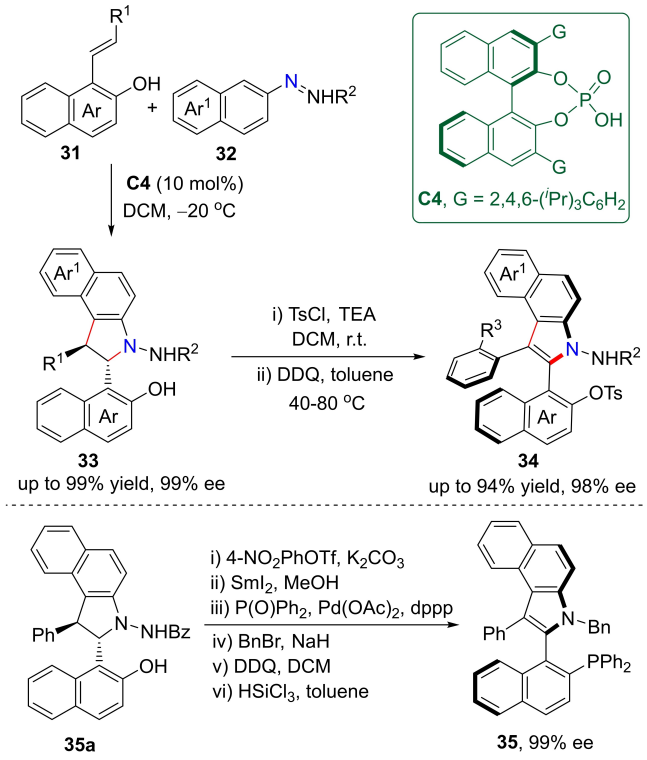
In 2020, Feng, Liu, and co-workers discovered a chiral *N,N'*-dioxide-metal complexes catalyzed asymmetric [3+2] cycloaddition and central-to-axial chirality conversion cascade reaction to obtain axially chiral 3-arylindolizines **38** in moderate to good enantioselectivities (Scheme 12).[31] An experimental study found that four-carbon centers tetrahydroindolinzines **Int-13** generated by the initial cyclization of enones **36** and pyridinium ylides **37** were unstable. On the other hand, by introducing a light source, intermediate **Int-13** could be converted into chiral



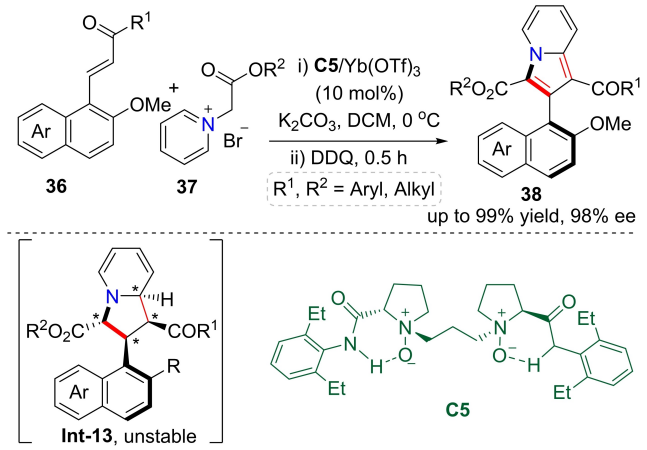
Scheme 9. Cycloaddition-isomerization strategy for the enantioselective synthesis of axially chiral indole-based biaryls.[27]



Scheme 10. Atroposelective synthesis of indole-quinoline skeletons via Povarov cycloaddition and chirality conversion process.[29]



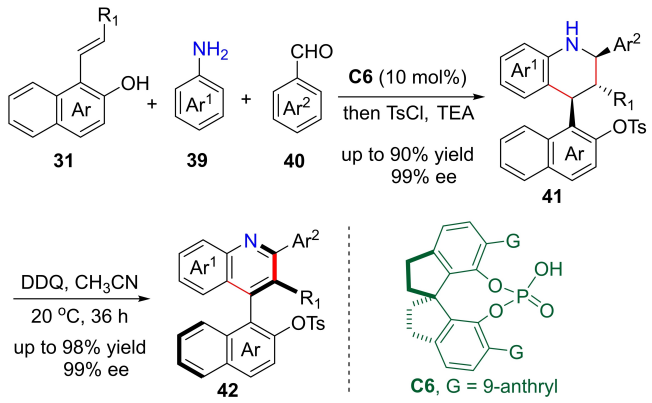
Scheme 11. Atroposelective synthesis of 2,3-diarylbenzoindoles via [3 + 2] cycloaddition and chirality conversion.[30]



Scheme 12. Asymmetric [3 + 2] cycloaddition synthesis of axially chiral 3-arylindolizines.[31]

dicarbon-functionalized 1,5-diketones with good to excellent stereoselectivities via aza-Norrish II rearrangement.

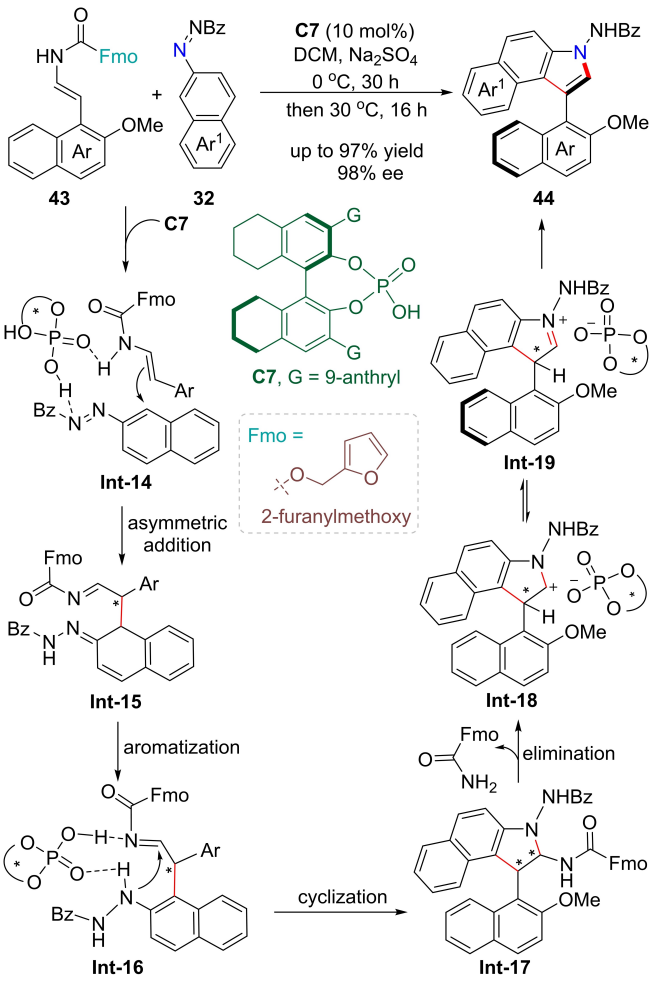
In 2021, we reported an enantioselective [4 + 2] annulation of 1-styrylnaphthols **31** with in situ-generated aryl imines from compounds **39** and **40**.[32] Next, the Povarov reaction products **41** bearing two adjacent stereocenters can be efficiently converted to diverse functionalized quinolone-naphthalene atropisomers **42** via the central-to-axial chirality conversion in excellent yields and excellent enantioselectivities, including one or two chiral axes (Scheme 13). As expected, a new chiral



Scheme 13. Atroposelective synthesis of quinolone-naphthalene frameworks via Povarov cycloaddition and chirality conversion.[32]

phosphine ligand can be synthesized smoothly through a four-step derivatization from the corresponding heterobiaryls.

In the same year, we also developed the enantioselective synthesis of axially chiral naphthyl-C3-benzoindoles or phenyl-C3-benzoindoles through CPA-catalyzed phenol-derived enecarbamates **43** with azonaphthalenes **32**.[33] A series of atropisomeric heterobiaryls **44** were generated in high yields and enantioselectivities (up to 97% yield, 98%ee) using this approach. The key to the success of these reactions is the chiral phosphoric acid catalyzed asymmetric formal [2+3] cycloaddition (**Int-14** to **Int-17**) and subsequent central-to-axial chirality conversion by CPA catalyzed elimination (**Int-17** to **Int-18**) of a carbamate (Scheme 14). Moreover, the synthetic utility of this methodology is illustrated by further conversion to varieties of functionalized atropisomers.

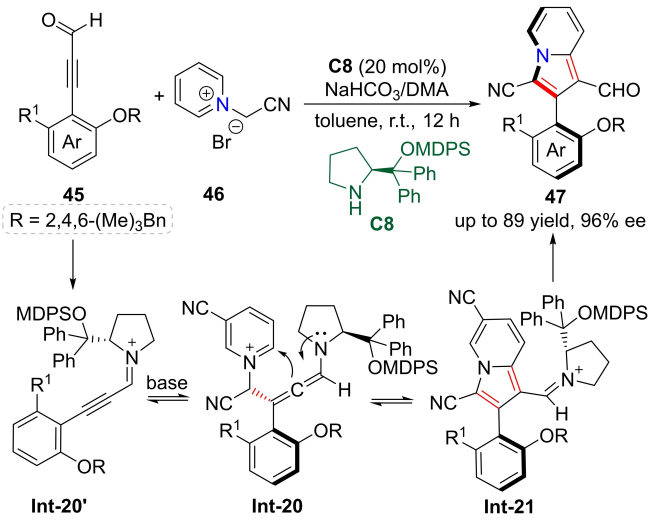


Scheme 14. Atroposelective construction of heterobiaryls via cycloaddition-elimination cascade reactions.[33]

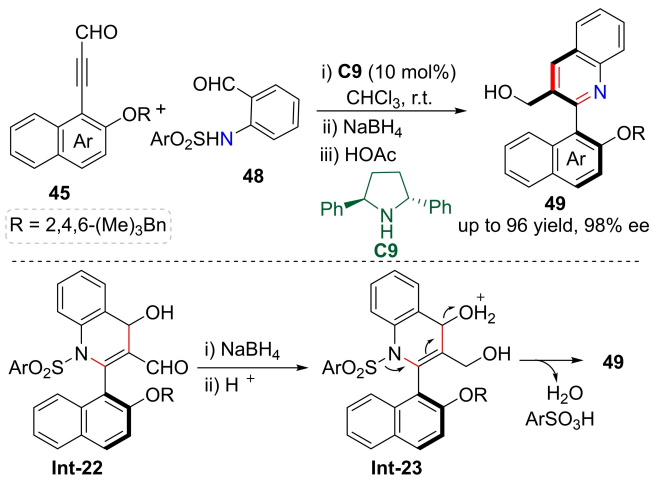
3.2. Cycloaddition reaction of alkynes

In 2021, Wang and co-workers reported the asymmetric synthesis of a new type of axially chiral 3-arylindolizines **47** through chiral amine catalyzed [8+2] cycloaddition reactions of pyridinium/isoquinolinium ylides **46** and ynals **45** (Scheme 15).[34] It is worth noting that this method represents a new type of organocatalytic higher-order cycloaddition reaction (**Int-20**), providing various heterobiaryls in good yields with excellent ee values, which provide more possibilities for potential pharmaceutical research and synthetic transformations. In the same year, they also disclosed a chiral amine-catalyzed atroposelective cycloaddition reaction of alkynes **45** with *N*-protected *o*-aminoarylaldehyde **48** via the formation of an axially chiral styrene intermediate (**Int-22**) to afford an axially chiral 2-arylquinoline framework **49** with excellent yields and high enantioselectivities.[35] Additionally, further conversion to axially chiral QUINOX and isoquinoline skeletons serve to illustrate the synthetic utility of this methodology (Scheme 16).

In 2022, we reported a CPA-catalyzed intermolecular asymmetric [2+3] cycloaddition of 3-alkynylindoles **50** with azonaphthalenes **32**. A series of axially chiral indole-based



Scheme 15. Synthesis of axial chiral 3-arylindolizines via [8+2] cycloaddition.[34]

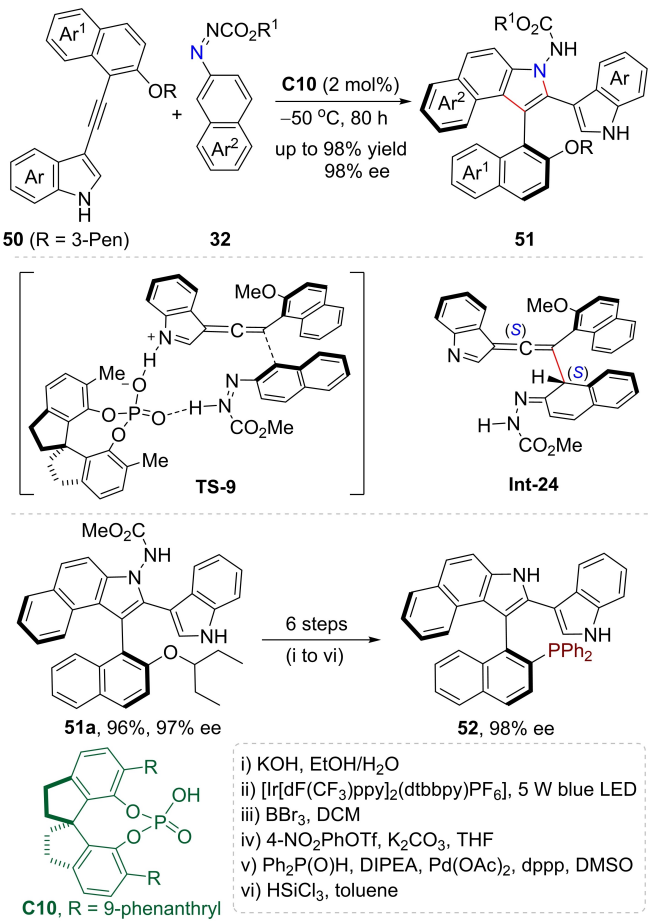


Scheme 16. Synthesis of axially chiral 2-arylquinoline frameworks.[35]

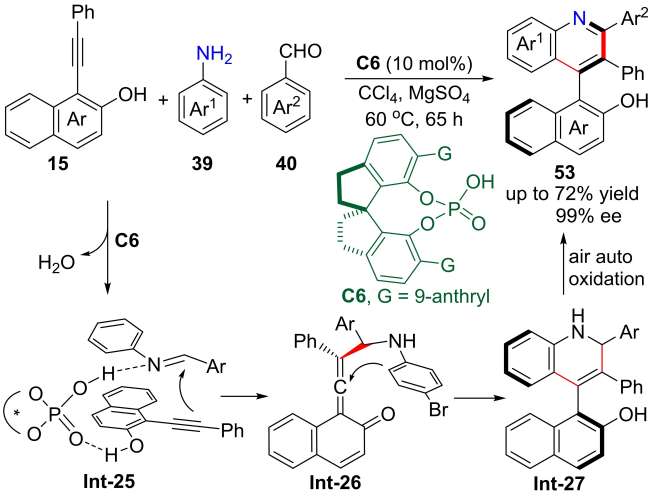
atropisomers **51** were afforded efficiently with excellent yields and excellent stereoselectivities (up to 98% yield and 98% ee).[36] The control experiment and DFT calculations revealed that a dearomatization of indole occurred to initiate the cycloaddition (**TS-9**), followed by an intramolecular Michael addition with an in-situ generated allene-iminium intermediate (**Int-24**). Additionally, a new type of monophosphine ligand **52** can be efficiently prepared through a six-step derivation and transformation (Scheme 17). Furthermore, this approach not only provides a convergent synthetic strategy for the atroposelective synthesis of indole-base derivatives but also advances the development of asymmetric chemistry involving alkynylindoles.

In the same year, a CPA-catalyzed enantioselective cycloaddition of alkynylnaphthols **15** with imines from **39** and **40** was disclosed.[37] This method provides facile access to functionalized axially chiral quinone-naphthols **53** with excellent yields and enantioselectivities under mild reaction conditions (up to 72% yield, 99% ee). Mechanistic studies revealed that a new type of chiral all-carbon tetrasubstituted VQM was smoothly generated in the reaction process for the first time. Then, an intramolecular [2 + 4] cycloaddition and auto-oxidation cascade process occurred to produce the final axially chiral heterobiaryls. It is worth noting that this strategy is more efficient and simpler than the construction of atropisomers by the Povalov reaction involving olefins (Scheme 18 vs 13). Moreover, the newly generated all-carbon tetrasubstituted VQMs will provide more possibilities for other transformations.

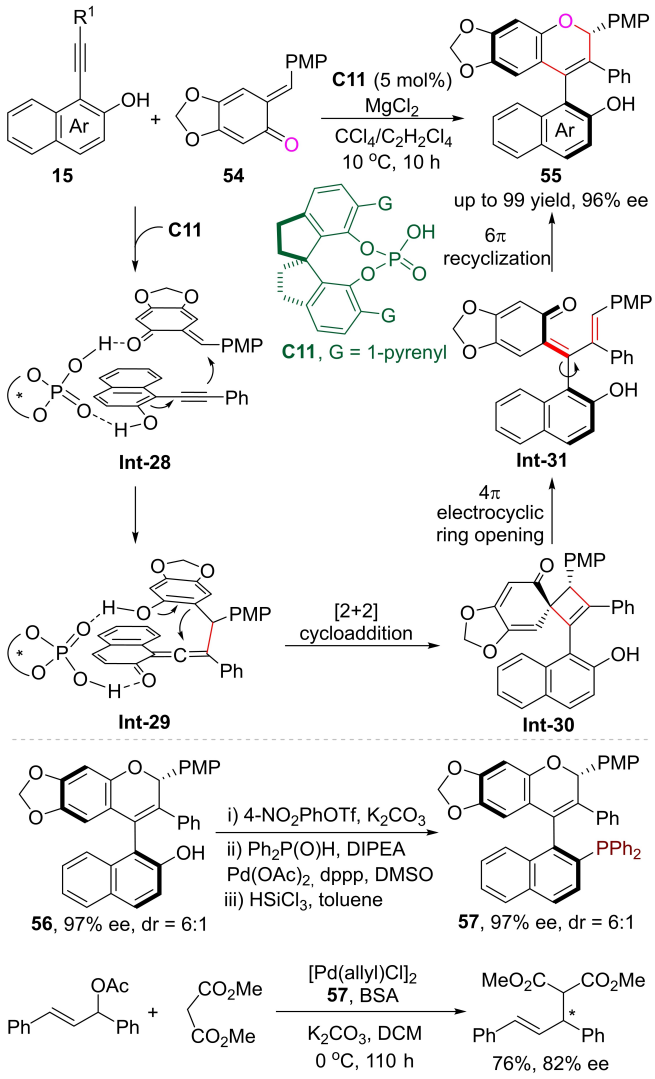
Meanwhile, the enantioselective cycloaddition of alkynylnaphthols **15** with *o*-quinone methides **54** was also developed.[37] A wide range of functionalized naphthyl-2H-chromenes **55** bearing axially and centrally chiral elements with excellent yields, diastereo- and enantioselectivities were successfully prepared (up to 99% yield, 96% ee, >20:1 dr) (Scheme 19). Similarly, all-carbon tetrasubstituted VQMs were generated smoothly at the beginning of the reaction. Then, the asymmetric cycloaddition of alkynylnaphthols with *o*-quinone methides proceeded via a [2 + 2] cycloaddition (**Int-29** to **Int-30**), 4π-electrocyclic ring opening (**Int-30** to **Int-31**), and 6π re-cyclization (**Int-31** to **55**) cascade process to generate the target products. In addition, the new type of axially chiral heterobiaryls



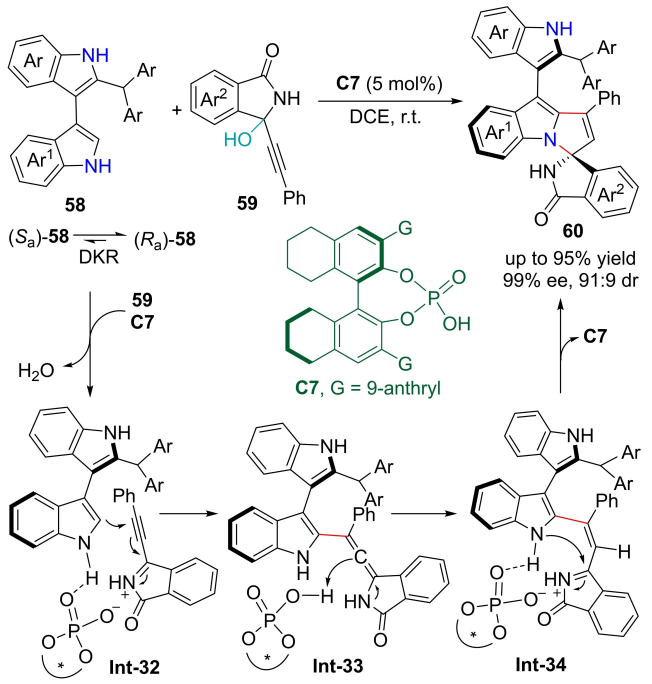
Scheme 17. Atroposelective intermolecular [2 + 3] cycloaddition of 3-alkynylindoles and azonaphthalenes.[36]



Scheme 18. Synthesis of axially chiral quinone-naphthols via [2 + 4] cycloaddition.[37]



Scheme 19. Synthesis of naphthyl-2H-chromenes bearing both axial and central chirality.[37]



Scheme 20. Atroposelective synthesis of indolyl-pyrroloindoles skeletons via [2 + 3] cycloaddition.[38]

can be converted into phosphine ligand **57** and other chiral molecules.

In 2022, Shi and co-workers reported a CPA-catalyzed enantioselective [2 + 3] cycloaddition of racemic 3,3′-bisindoles **58** with isoindolinone-based propargylic alcohols **59**. A range of axially chiral indolyl-pyrroloindole scaffolds **60** bearing both axial and central chirality were synthesized with excellent results (up to 95% yield, 99% ee, 91:9 dr).[38a] At room temperature, the two enantiomers (R_a)-**58** and (S_a)-**58** can rapidly transform into each other, where (R_a)-**58** reacts faster with the alkynyliminium cation from the dehydration of **59** than (S_a)-**58**, resulting in the allene intermediate **Int-33** via a dynamic kinetic resolution process. Then proton transfer and intramolecular cyclization give the final axially chiral products. The hydrogen-bonding and ion-pairing interactions between chiral phosphoric acid, substrates, and intermediates are the key factors to control the stereoselectivity (Scheme 20). In addition, axially chiral aryl-alkene-indole skeletons also made an elegant presentation in their group recently.[38b]

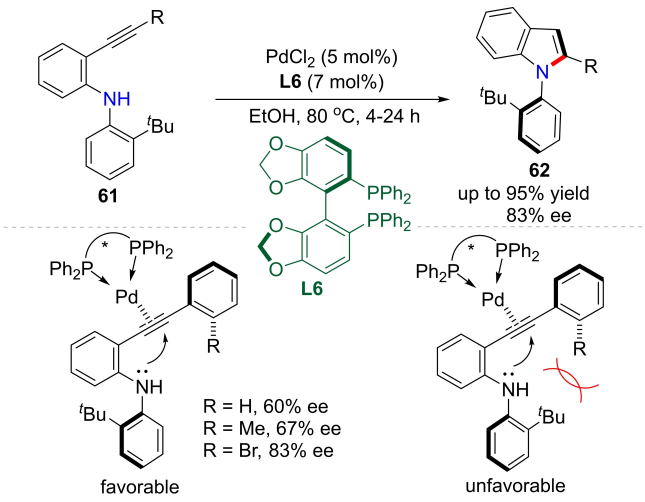
4. Asymmetric Cyclization Synthesis of Heterobiaryls

In addition to the cycloaddition reaction, the cyclization (annulation) strategy also makes great contributions to the synthesis of atropisomeric heterobiaryls. In this part, we mainly summarize the intramolecular and intermolecular cyclization for the synthesis of heterobiaryls bearing chiral C–C, C–N, and N–N axes.

4.1. Intramolecular cyclization

In 2010, Kitagawa's group reported making atropisomeric indole derivatives **62** by using $PdCl_2$ and **L6** to speed up the 5-*endo*-hydroaminocyclization of *ortho*-alkynylanilines **61**. A possible mechanism for the increase in the enantioselectivity caused by the *ortho*-substituent is also disclosed in the reaction (Scheme 21). Despite achieving moderate to good enantioselectivities, it was the first reported work to create N–C axially chiral compounds in a catalytic asymmetric manner.[39]

In 2019, Yan and co-workers established the quinine-derived thiourea **C12** catalyzed asymmetric annulation of *ortho*-alkynylanilines **63** to access chiral aryl-C2-indole frameworks **64** with excellent enantioselectivities and a wide scope of application.

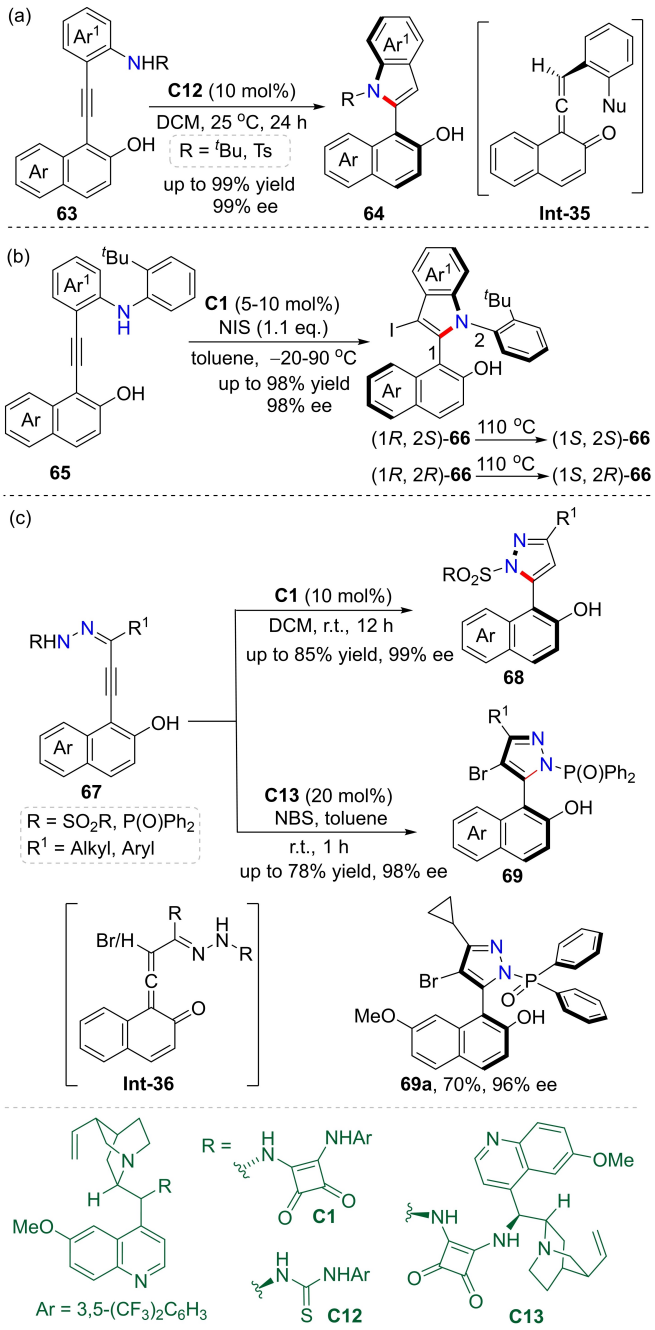


Scheme 21. Atroposelective 5-*endo*-aminocyclization of *ortho*-alkynylanilines.[39]

The present reaction was applied to a 50.0 g scale preparation, along with the catalyst being recovered without significant loss of catalytic performance. In the reaction process, the VQM intermediate **Int-35** was involved and played a key role in stereoselectivity (Scheme 22a).[40] In 2021, through modified VQM intermediates, they also achieved the synthesis of axially chiral heterobiaryls **66** (bearing both C–C and C–N axes)[41] and two types of axially chiral 1,2-azoles **68** and **69**,[42] respectively (Scheme 22b and c). Control experiments show that the C–N axis of (1*R*, 2*S*)-**66** and (1*R*, 2*R*)-**66** was more thermodynamically stable than the C–C axis, which could be converted when heated at 110 °C in toluene for 24 h (Scheme 22b). Moreover, a wide range of atropisomeric heterobiaryls bearing other heteroatoms (such as Si, O, and B) with different ring sizes (five to seven-membered rings) was smoothly prepared with excellent results as well. On the other hand, 1,2-azole plays an important role in natural products and medicines. For example, *N*,*N*-1,2-azoles **69a** proved to be effective antiproliferation agents and induced apoptosis in A375 cells. Synthesis of 1,2-azoles was achieved efficiently via **Int-36**, and compound **69a** was prepared in 70% yield with 96% ee.

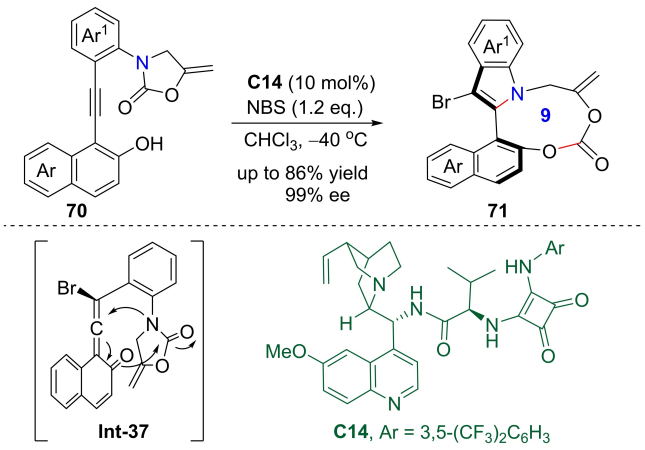
In particular, Yan's group also developed some molecular structures with multiple-stereogenic elements[43] or bridged biaryls[44] through VQM intermediates. For instance, in 2022, they disclosed an efficient method to access nine-membered carbonate-bridged biaryls **71** via VQM intermediate **Int-37** under the catalysis of **C14**. A wide range of axially chiral products was synthesized with excellent yields and enantioselectivities. Moreover, these compounds also have potential pharmaceutical properties (Scheme 23).

In 2018, Miller's group found a catalyst-controlled stereodivergent synthesis of *N*-arylbenzimidazole **73a** which contained a N–C stereogenic axis and a remote stereocenter (Scheme 24a).[45a] In addition to CPA, peptide catalysts also showed similar catalytic results. Concerning the comparable enantioselectivity catalyzed by both catalyst classes, in 2019,

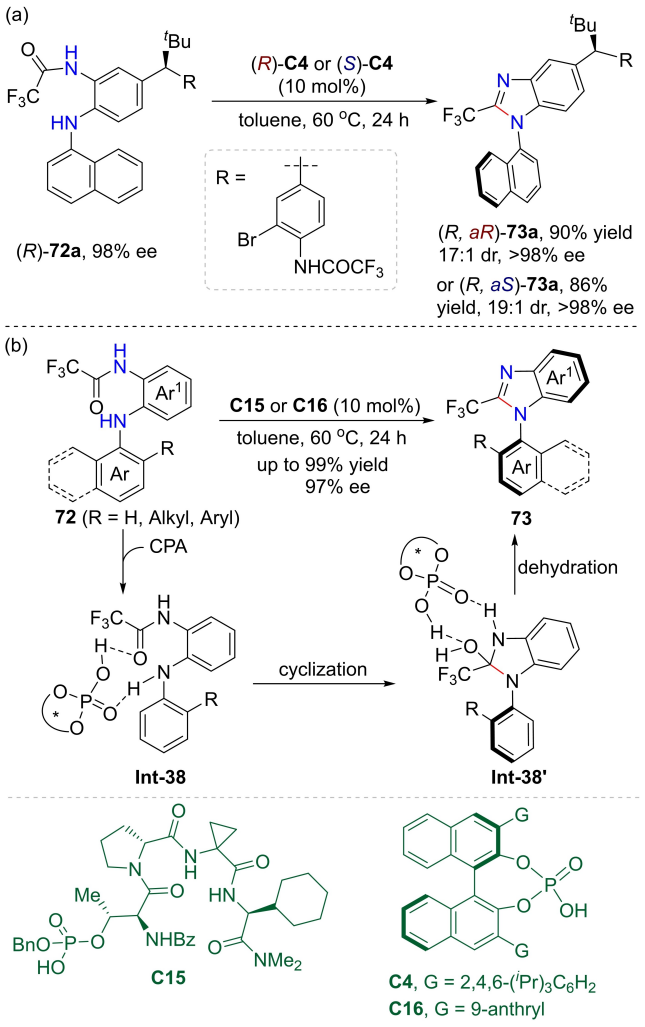


Scheme 22. Atroposelective construction of heterobiaryls via VQM intermediates.[40–42]

Miller, Toste, Sigman, and co-workers revealed an unusually atroposelective cyclodehydration of **72** under the catalysis of **C15** and **C16** (Scheme 24b).[45b] Although most of the target products **73** have similar enantioselectivity results, this was not the case for substrates **72** with C7-substitution, which exposed the unique mechanistic attributes related to the two catalysts. In this reaction, the enantioselectivity of **C16** seems to be determined by the steric effects between the catalyst and substrate. However, **C15** acts in the form of an alternative mode of enantioinduction, where conformational adaptation probably



Scheme 23. Atroposelective construction of carbonate-bridged biaryls via VQM intermediates.[44]



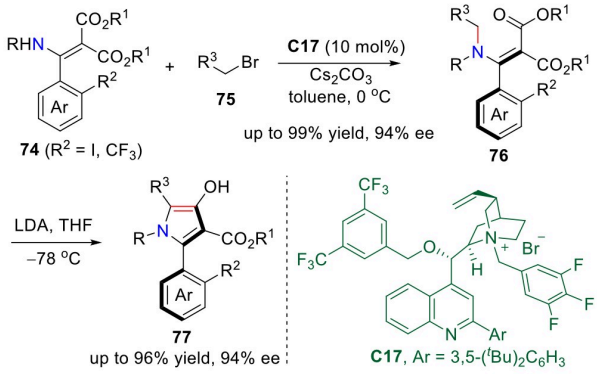
Scheme 24. Intramolecular atropisomer-selective cyclodehydration.[45]

limits repulsive interactions. These interesting works show that different kinds of catalysts could provide complementarity to accelerate the extensive exploration of chirality compounds. For these N–C biaryl atropisomer skeletons **73**, Liu, Lu, and co-workers also developed a Pd-catalyzed asymmetric Buchwald–Hartwig amination strategy, resulting in a series of enantioenriched 1,4- and 1,5-dibenzimidazoles bearing two chiral N–C axes.[46]

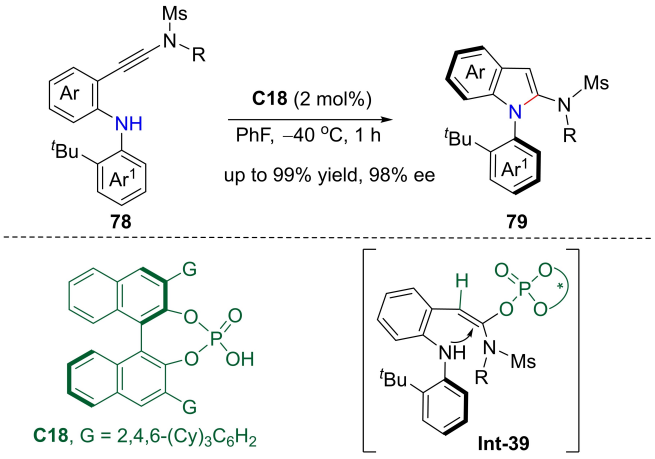
In the same year, Tan and co-workers developed the asymmetric synthesis of axially chiral 2-arylpyrroles **77** through the cyclization of enantioenriched atropisomeric alkenes **74** for the first time. Under the catalysis of the classical cinchonine-derived organocatalyst **C17**, a series of enantioenriched atropisomeric alkenes **76** were synthesized via *N*-alkylation reactions. Treatment with lithium diisopropylamide (LDA) then promoted intramolecular cyclization, yielding fully substituted atropisomeric pyrroles with high yields and ee values (Scheme 25).[47]

In 2022, Ye, Hong, and co-workers developed a CPA-catalyzed 5-*endo*-dig cyclization of ynamides that gave access to axially chiral *N*-heterocycles **79** in excellent yields with excellent enantioselectivities (up to 99% yield, 98% ee). Mechanistic study shows that the intermediate **Int-39** produced by ynamide hydrophosphorylation was critical in the reaction process. Furthermore, novel monophosphine ligands and thiourea-derived organocatalysts with *N*-arylindole skeletons were demonstrated to be suitable for asymmetric catalysis. Additionally, the present work represents the first metal-free protocol for the construction of heterobiaryls from ynamides (Scheme 26).[48]

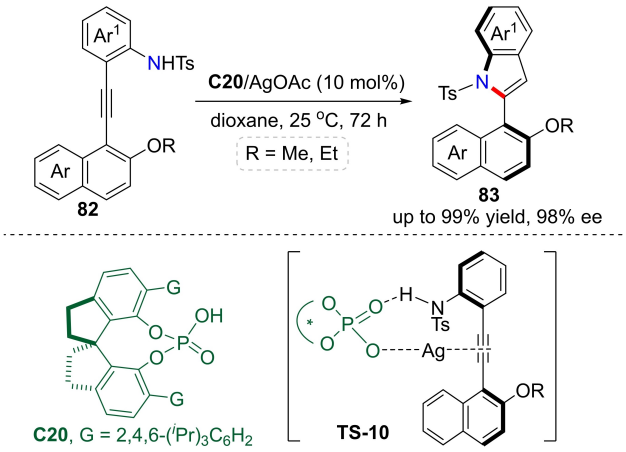
In 2022, Sparr's group developed a catalyst-controlled Friedel–Crafts 6π electrocyclization of *ortho*-quinone methide iminiums to synthesize axially chiral acridinium salts with good results (up to 86% ee) (Scheme 27).[49a] More specifically, the disulfonimide catalyst **C19** activates racemic trichloroacetimidate substrates with a benzylic leaving group in situ to generate *ortho*-quinone methide iminiums that lead to the chiral ion pair intermediate **Int-40**. Then, the final atropisomeric heterobiaryls **81** were obtained through intramolecular cyclization and the DDQ oxidation cascade process. Additionally, the method of



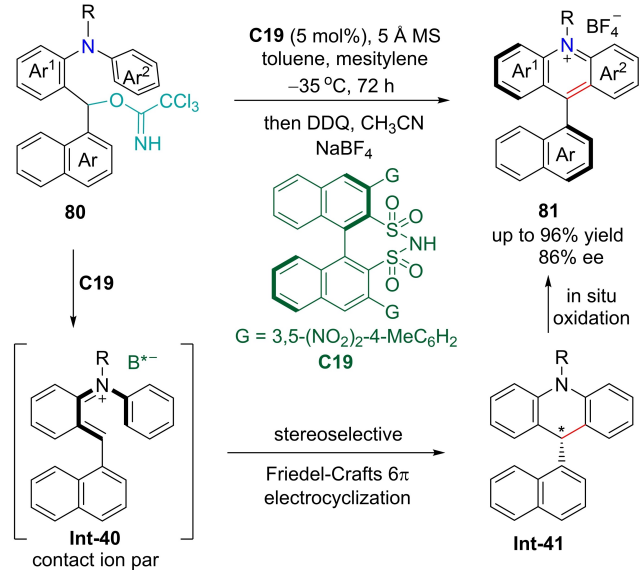
Scheme 25. Synthesis of axially chiral 2-arylpyrroles via intramolecular cyclization.[47]



Scheme 26. Synthesis of axially chiral *N*-arylindoles via atroposelective cyclization of ynamides.[48]]



Scheme 28. Enantioselective de novo synthesis of axially chiral 2-arylindoles.[50]



Scheme 27. Synthesis of atropisomeric acridinium salts via asymmetric intramolecular cyclization reaction.[49a]

obtaining axially chiral biaryls through a remote central-to-axial chirality conversion has also been realized in their group.[49b]

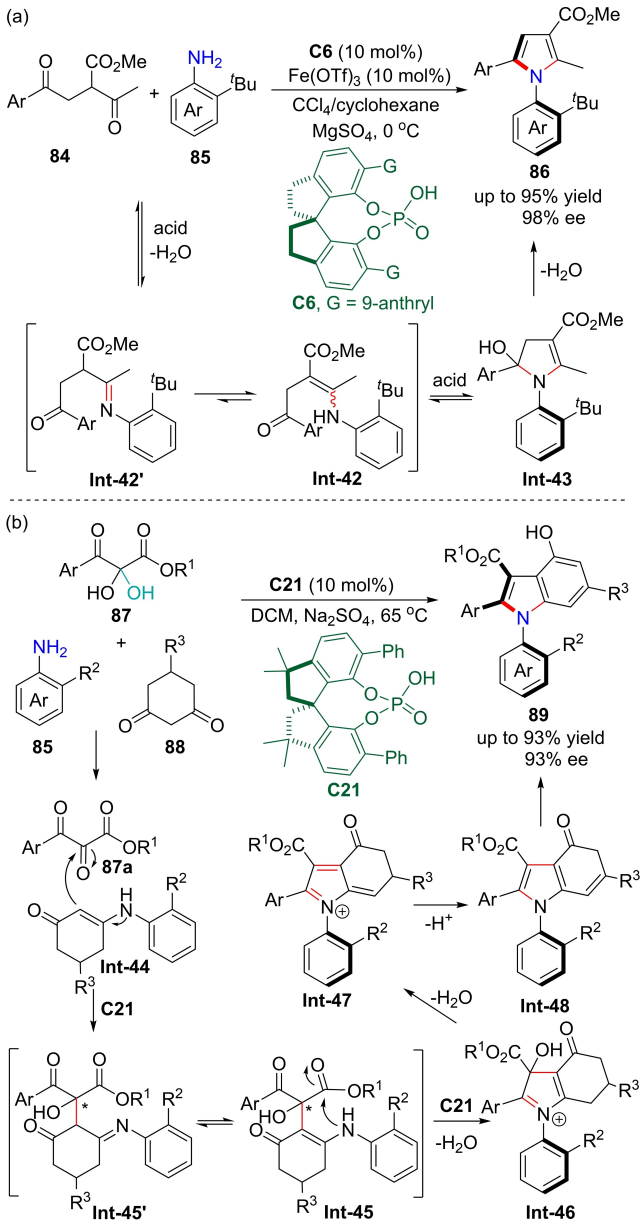
In 2023, Zhao and co-workers developed a chiral silver phosphate-catalyzed direct 5-*endo*-dig cyclization of 2-alkynylanilins **82**, providing a range of axially chiral 2-arylindoles **83** in high yields and excellent enantioselectivities under mild conditions (up to 99% yield, 98% ee). Control experiments implied the possibility of cooperative catalysis (**TS-10**), in which AgOAc accelerated the required conversion while CPA improved the enantioselectivity (Scheme 28).[50]

4.2. Intermolecular cyclization

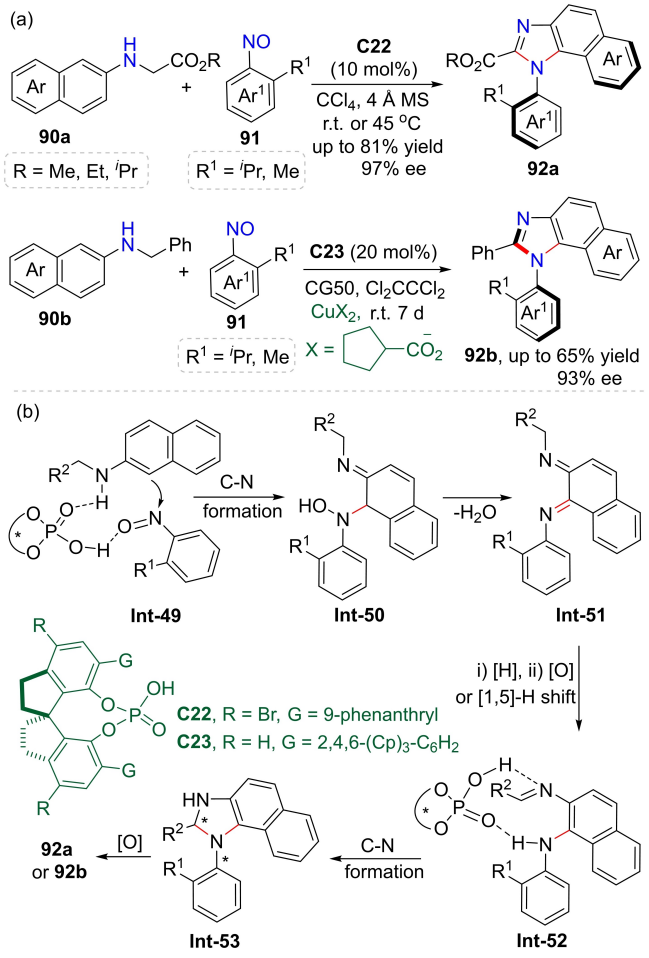
In 2016, Tan and co-workers established the first highly atroposelective construction of axially chiral arylpyrroles via the asymmetric Paal–Knorr reaction, which afforded a wide scope of heterobiaryls **86** in high yields and good to excellent enantioselectivities (Scheme 29a).[51] In the present reaction, the combined-acid catalytic system involving a Lewis acid $Fe(OTf)_3$ and a chiral phosphoric acid **C6** was the key factor in achieving high enantioselectivity. Interestingly, the key enamine intermediate **Int-42** was isolated and confirmed by NMR and HRMS. These observations suggested that the final pyrrole formation might be through **Int-42** followed by acid-catalyzed dehydrative cyclization, which is not completely consistent with the recognized Paal–Knorr reaction.

In 2019, Lin and co-workers also reported an effective method for the asymmetric construction of *N*-arylindoles **89** via a CPA-catalyzed three-component cascade heteroannulation reaction (Scheme 29b).[52] Feasible reaction mechanisms were proposed based on some control experiments and literature research. First, the key intermediate enamine **Int-44** was generated from aromatic amines **85** and 1,3-cyclohexanediones **88**, followed by CPA-catalyzed aldol condensation with the dehydrated 2,3-diketoester **87a** to afford intermediate **Int-45**. Following that, dehydrative cyclization, dehydration by 1,4-elimination, and tautomerization all took place under the catalysis of CPA to produce the final axially chiral products.

In 2021, Tan, Zhong, and co-workers reported two kinds of CPA-catalyzed asymmetric synthesis of axially chiral *N*-arylbenzimidazoles **92a** and **92b** via an imidazole ring formation strategy from 2-naphthylamines **90a** or **90b** and nitrosobenzenes **91** (Scheme 30a).[53] A series of *N*-arylbenzimidazole atropisomers can be easily prepared with excellent chemo-, regio-, and stereoselectivity (up to 97% ee). As shown in Scheme 30b, in the presence of CPA as a bifunctional catalyst, the chemo- and regioselective nucleophilic addition of the 2-naphthylamine derivatives to nitrosobenzenes **91** gives the intermediate **Int-50**, where a C–N bond is formed for the first



Scheme 29. Enantioselective synthesis of axially chiral *N*-arylpyrroles and *N*-arylindoles.[51,52]

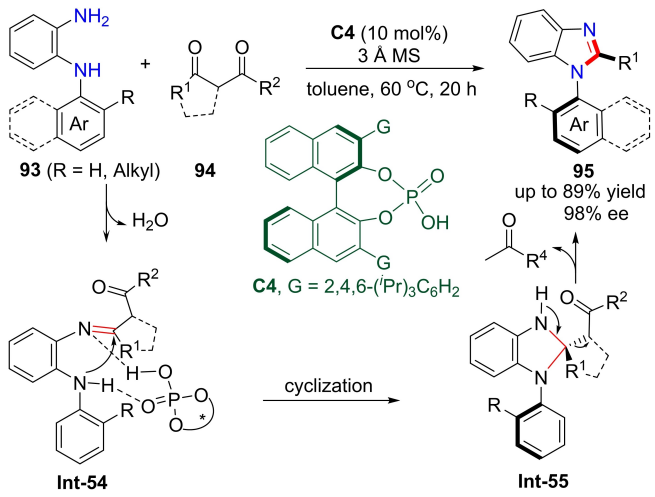


Scheme 30. Synthesis of axially chiral *N*-arylbenzimidazoles of naphthylamine derivatives and nitrosobenzene.[53]

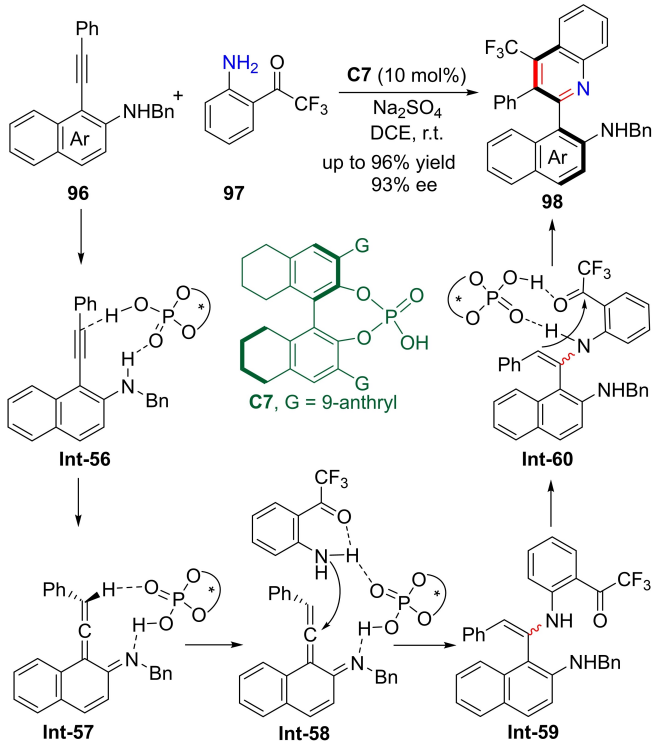
time. Then, vicinal diimine intermediate **Int-51** is generated by releasing a molecule of water. Next, the intermediate **Int-52** are generated by successive reduction and oxidation cascade process or a direct [1,5]-H migration of **Int-51**. Subsequently, under the catalysis of CPA, amines, and imines undergo intramolecular addition reactions to provide the intermediate **Int-53**, which forms the C–N bond for the second time and is also the stereoselectivity determination step. It is worth emphasizing that the nitroso group acts as both an electrophilic site, nucleophilic site, and oxidant, which plays a unique role in this domino reaction.

In 2020, Fu's group reported a CPA-catalyzed asymmetric cyclization reaction to construct axially chiral *N*-aryl benzimidazoles **95** via the reaction of *N*-(aryl)benzene-1,2-diamines **93** with (multi)carbonyl compounds **94**. The present reaction provided the target heterobiaryls with up to 89% yield and 98% ee. In addition, as shown in Scheme 31, **Int-54**, and **Int-55** are two important intermediates in the reaction process that play a vital role in stereoselectivity.[54]

In 2020, Tan and colleagues developed an efficient method for accessing axially chiral isoquinoline-naphthylamine skeletons in the presence of CPA by using alkynes with *ortho*-aminophenones in a cascade heteroannulation reaction. A wide range of axially chiral heterobiaryls **98** were obtained in high yields with excellent enantioselectivities under mild reaction conditions (Scheme 32).[55] During this reaction, CPA plays an important role in the asymmetric induction by creating a suitable chiral environment. First, the dual hydrogen bonding between **96** and CPA was the key factor in forming the complex **Int-56**, which promotes the subsequent 1,5-H transfer process, thus forming the key VQM intermediate **Int-57**. Subsequently, **97** forms the complex **Int-58** with CPA through additional hydrogen bonding and attacks the VQM intermediate, leading to the formation of enamine intermediate **Int-59**. Next, the intramolecular aldol reaction and dehydration reaction were carried out successively to obtain the final axially chiral



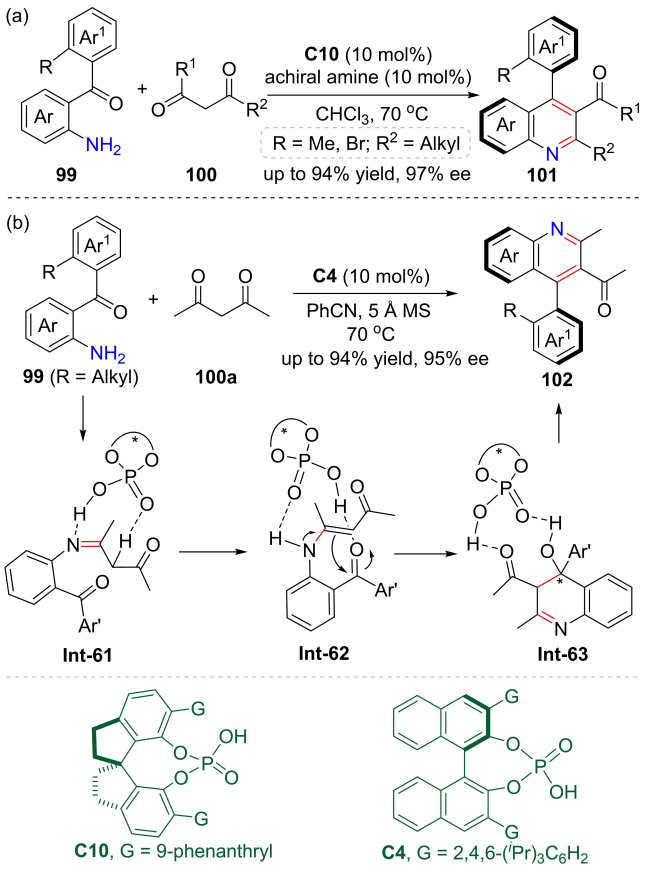
Scheme 31. Synthesis of axially chiral *N*-aryl benzimidazoles via C–C bond cleavage.[54]



Scheme 32. Asymmetric heteroannulation of alkynes to construct axially chiral isoquinoline-naphthylamine skeletons.[55]

products and release the CPA catalyst. This method could also be used on a larger scale without losing enantioselectivity. It could also be used with a new type of ligand and an axially chiral thiourea.

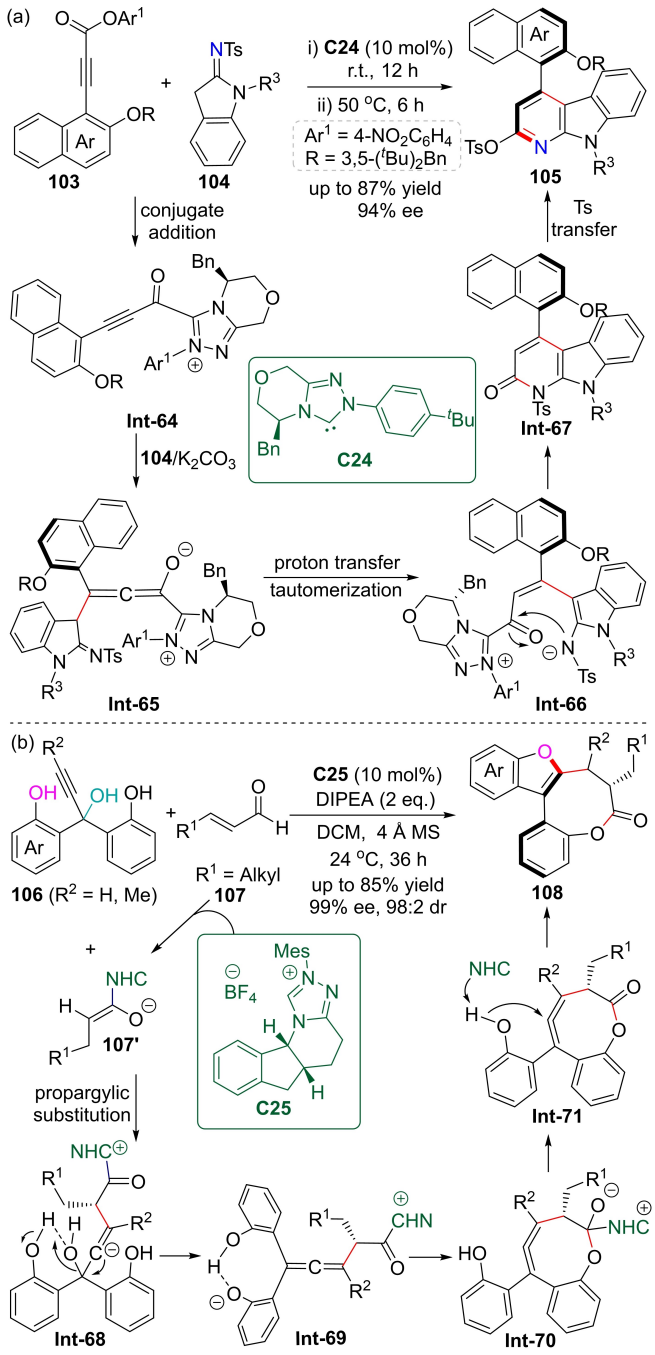
In 2019, Cheng and colleagues reported a chiral phosphoric acid-catalyzed atroposelective Friedländer heteroannulation reaction of 2-aminoaryl ketones **99** with α-methylene carbonyl derivatives **100** for the first time (Scheme 33a).[56a] A wide range of axially chiral polysubstituted 4-arylquinoline scaffolds **101**



Scheme 33. Synthesis of atropisomeric quinolines by Friedländer reaction.[56a,57]

were prepared with good to excellent results (up to 94% yield, 97% ee). At the same time, Jiang's group also developed an asymmetric Friedländer reaction to give a series of optically active biaryl quinolones **102** (up to 95% ee), which hold great potential in drug discovery and biological studies as well (Scheme 33b).[57] In both reactions, the following processes were mainly proposed: (i) the condensation reaction of amine and ketone to form **Int-61**; (ii) the intramolecular aldol reaction to produce **Int-62**; and (iii) elimination of a molecule of H_2O from the **Int-63** to obtain the final products. Interestingly, in 2021, Cheng's group also envisaged a chiral amine-catalyzed Michael/aldol/aromatization sequence between 2-aminoaryl ketones and alkynals for the asymmetric synthesis of axially chiral quinoline-3-carbaldehydes.[56b]

In 2021, Du, Wei, and co-workers disclosed an *N*-heterocyclic carbene (NHC) catalyzed atropoenantioselective [3 + 3] annulation reaction for the first time by employing 4-nitrophenyl 3-arylpropiolates **103** with 2-sulfonamidoindolines **104**, providing an efficient approach to construct axially chiral 4-aryl α-carboline atropisomers **105** with high enantioselectivities (Scheme 34a).[58] First, catalyst **C24**, substrates **103** and **104** undergo conjugate addition to forming the allenolate intermediate **Int-65** through the alkynyl acylazolium intermediate **Int-64** under the basic condition. Then sequential proton transfer, tautomerization, and tosyl transfer (from N to O) form



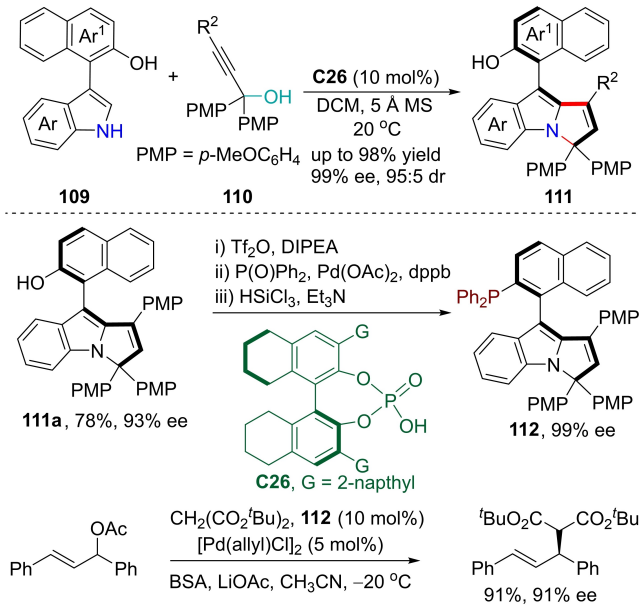
Scheme 34. Synthesis of axially chiral heterobiaryls via NHC catalysis.[58,59]

the more stable aromatized products. The DFT calculations show that the energy barrier of the *R* isomer is 1.8 kcal/mol lower than that of the *S* isomer, which is consistent with the experimental observation.

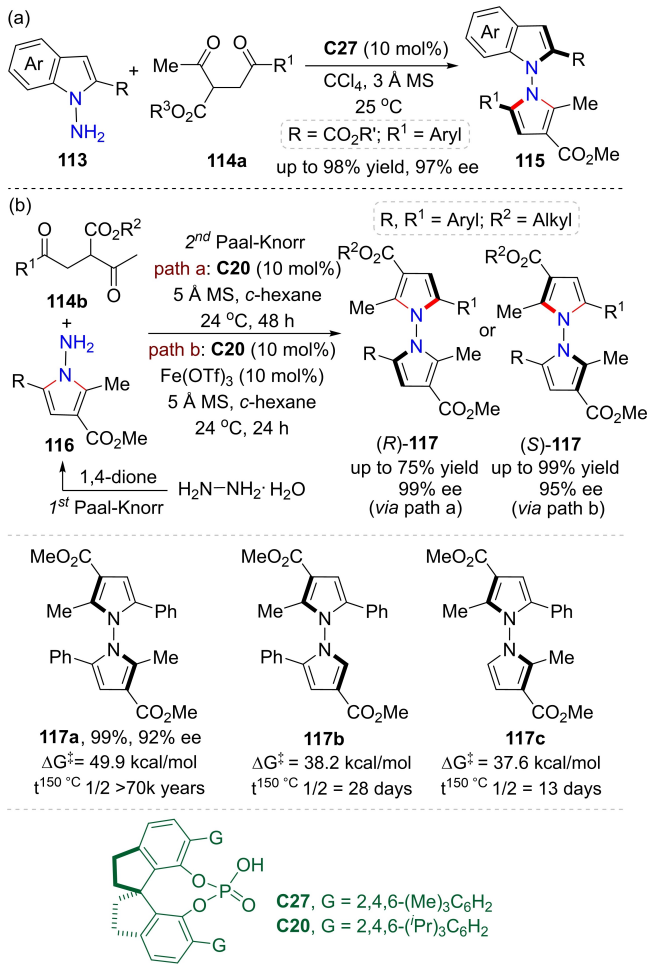
In the same year, Zhao, Wong, and co-workers also developed an NHC-catalyzed stereoselective synthesis of bridged biaryls bearing an eight-membered lactone from readily available starting materials. A wide range of benzofuran or indole-derived biaryls **108** bearing both axial and central chirality were prepared with excellent results (up to 99% ee, >98:2 dr) (Scheme 34b).[59] The mechanistic study and DFT calculation showed that the reaction proceeds through a propargylic substitution (**Int-68**) and a two-directional cyclization cascade (**Int-70** and **Int-71**).

In 2022, Shi and co-workers accomplished the highly atroposelective synthesis of axially chiral aryl-pyrroloindole scaffolds **111** via a CPA-catalyzed asymmetric [2+3] cyclization of 3-arylindoles **109** with propargylic alcohols **110** under mild reaction conditions (up to 98% yield, 99% ee, >95:5 dr). Meanwhile, theoretical calculations indicate that the reaction undergoes a dynamic kinetic resolution process (Scheme 35 vs 20).[60] More importantly, a new class of axially chiral phosphine ligand **112** was synthesized in three steps and successfully applied to palladium-catalyzed asymmetric reactions.

Nitrogen-nitrogen axially chiral molecules are present in an array of natural products, chiral ligands, and medicinal chemistry.[61] In 2022, Shi, Zhang, and co-workers established an unprecedented catalytic atroposelective synthesis of N–N axially chiral indole scaffolds via the strategy of de novo ring formation from well-designed *N*-aminoindoles **113** and readily available 1,4-diketones **114a** (Scheme 36a).[62] Under the catalysis of chiral phosphoric acid **C27**, a wide scope of *N*-pyrrolylindoles (up to 98% yield, 96% ee) and N–N axially chiral bispyrroles (up to 98% yield, 97% ee) were prepared in high yields with excellent atroposelectivities. More importantly, some N–N axially chiral molecules have anticancer properties. Almost at the same time, Zhao and co-workers achieved the highly atroposelective construction of N–N axially chiral bispyrroles **117** from simple hydrazine and 1,4-diones as well (Scheme 36b).[63] In addition, for this CPA-catalyzed double Paal–Knorr reaction, an intriguing enantiodivergence was also observed: (*R*)-**117** are obtained in the absence of $Fe(OTf)_3$ (path a), and (*S*)-**117** are generated in the presence of $Fe(OTf)_3$ (path



Scheme 35. Synthesis of axially chiral aryl-pyrroloindoles via [2+3] cyclization.[60]

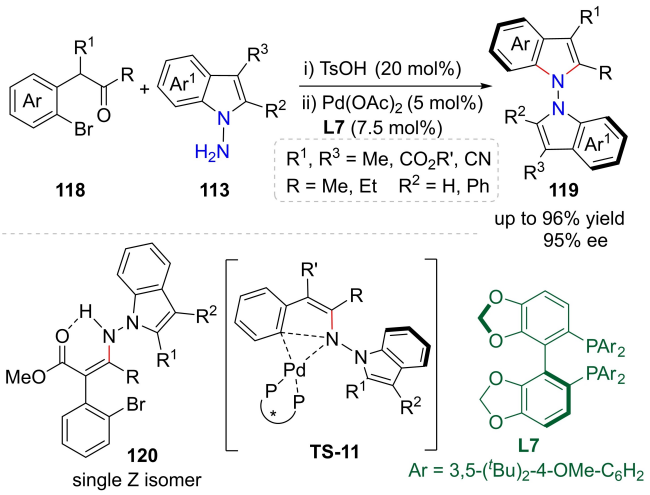


Scheme 36. Synthesis of N–N axially chiral indoles and pyrroles via CPA catalysis.[62,63]

b). Moreover, the configurational stability of N–N axially chiral compounds (selected heteroaryls **117a–c**) was also investigated. The experimental results show that the rotation energy of **117a** was determined to be 49.9 kcal/mol in ^{i}PrOH at 150 °C ($t_{1/2} > 70$k years). In comparison, the rotation energy barrier and stability of **117b** and **117c** are greatly reduced after removing one of the *ortho*-substituents, which also shows the tricky problem in the construction of chiral five-five biaryl skeletons.

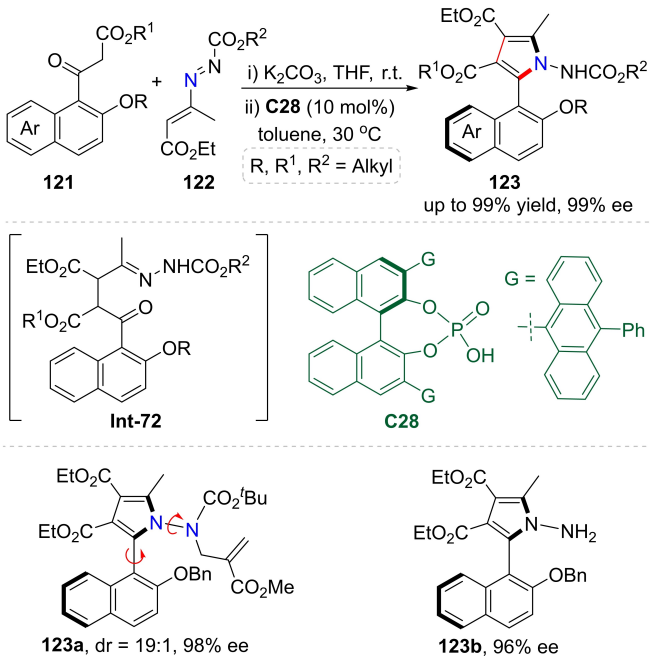
In 2022, Liu, Li, and co-workers developed the palladium-catalyzed enantioselective intramolecular arylation of enamines **120** (generated from **118** and **113**) to construct N–N bisindole atropisomers **119**. A wide range of axially chiral bisindoles was accessed in good yields with excellent enantioselectivities via the de novo construction of one indole ring. Meanwhile, the diverse atropisomers of indole-pyrrole, indole-carbazole, and non-biaryl-indole-bearing N–N axes were smoothly prepared. Moreover, the possibility of **TS-11** and other key intermediates was revealed through DFT calculations (Scheme 37).[64]

In 2022, Mei, Xu, Wang, and co-workers developed a CPA-catalyzed intramolecular asymmetric Attanasi reaction of **Int-72** to access axially chiral C2-arylpyrrole-derived amino alcohols **123** for the first time (up to 89% yield, 99% ee). The

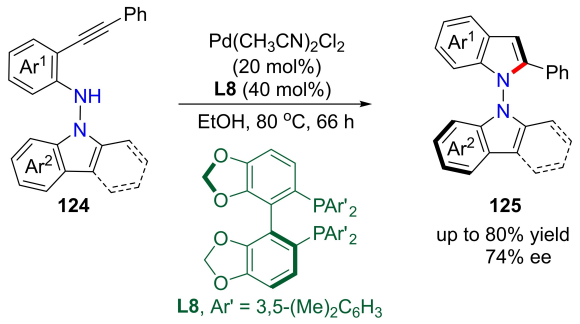


Scheme 37. Atroposelective synthesis of N–N bisindole via Pd-catalyzed intermolecular reaction.[64]

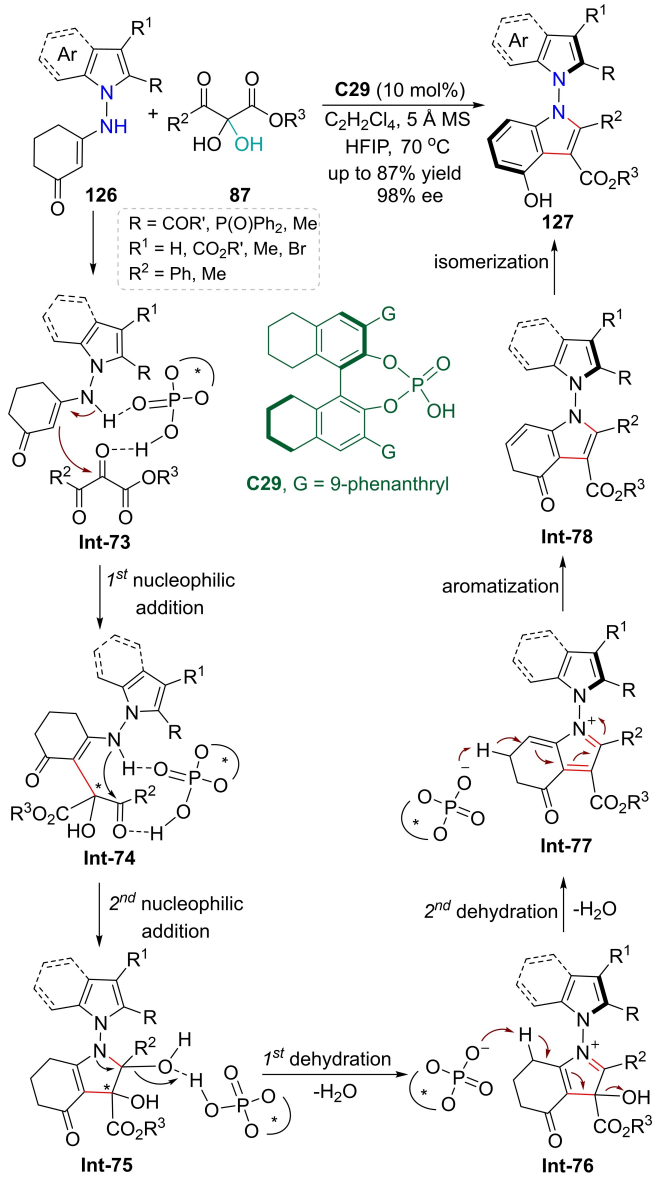
intermediate **Int-72** was formed by the reaction of azoalkenes **122** and 1,3-dicarbonyl compounds **121** promoted by K_2CO_3 (Scheme 38).[65] In this reaction, compound **123a** with two stereogenic axes was obtained through simple *N*-allylic alkylation. Moreover, the axially chiral C2-arylpyrrole derivative **123b** can be easily converted into organocatalysts/ligands, and their preliminary applications in asymmetric catalytic reactions demonstrated the promising utility of the method. DFT calculations were performed to reveal the reaction mechanism and the origins of the enantioselectivity.



Scheme 38. Atroposelective synthesis of axially chiral C2-arylpyrrole-derived amino alcohols.[65]



Scheme 39. Atroposelective synthesis of N–N bisindole via Pd-catalyzed intramolecular reaction.[66]



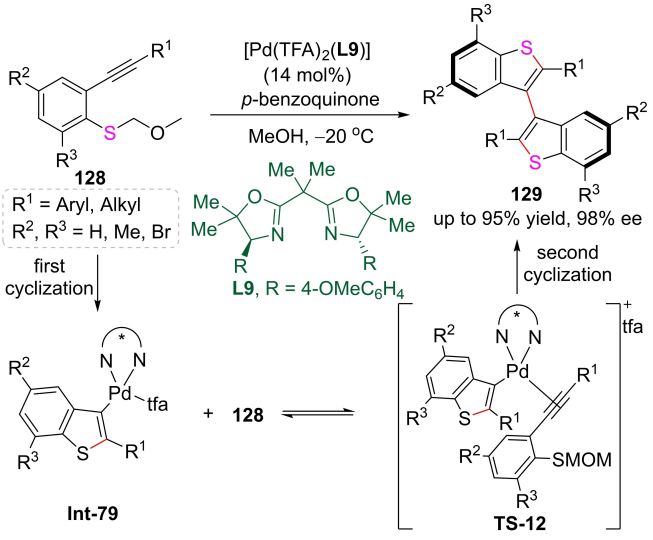
Scheme 40. Atroposelective synthesis of N–N bisindole via de novo indole-ring formation.[67]

In 2023, Sparr's group also developed a novel approach to construct N–N atropisomeric compounds via a Pd/**L8**-catalyzed 5-*endo*-hydroaminocyclization. Under mild conditions, a wide range of N–N-linked bisindoles **125** were prepared with up to 90% yield and 74% ee (Scheme 39).[66]

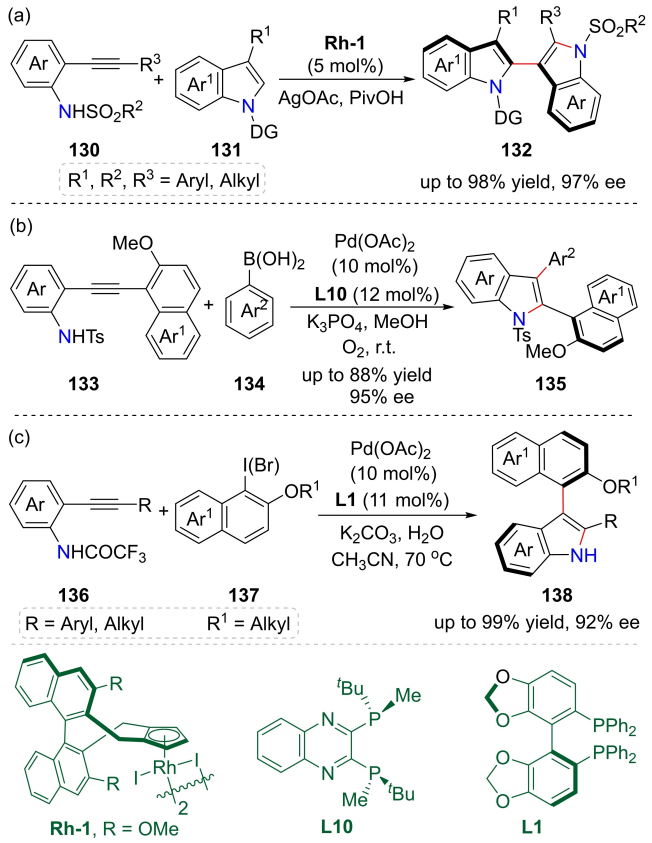
In 2023, Shi, Zhang, and co-workers performed CPA-catalyzed enantioselective [2+3] cycloaddition of 2,3- diketoesters **87** and indole-based enaminones **126** (Scheme 40).[67] A wide range of axially chiral *N,N'*-bisindoles and *N,N'*-pyrrolylindoles **127** were synthesized in excellent enantioselectivities (up to 98% ee) via de novo indole-ring formation process involving two nucleophilic addition (**Int-73** to **Int-75**), two dehydration (**Int-75** to **Int-77**), aromatization, and isomerization. In addition, they could obtain *N,N'*-pyrrolylindoles in moderate yields with good enantioselectivities through three-component reactions. More importantly, they also synthesized and investigated the potential applications of N–N axially chiral bisindole ligands and catalysts in asymmetric catalysis and medicinal chemistry.

In 2018, Kato and co-workers developed a Pd/**L9**-catalyzed asymmetric cyclization-dimerization of *ortho*-alkynyl phenyl methoxymethyl sulfides **128**, affording axially chiral dibenzothiophenes **129** with good to excellent results (up to 95% yield and 98% ee). A mechanistic study shows that the box ligand **L9** enhances the alkynophilicity of intermediate **TS-12** thus promoting the coordination of the second alkyne substrate, resulting in good stereoselectivity (Scheme 41).[68]

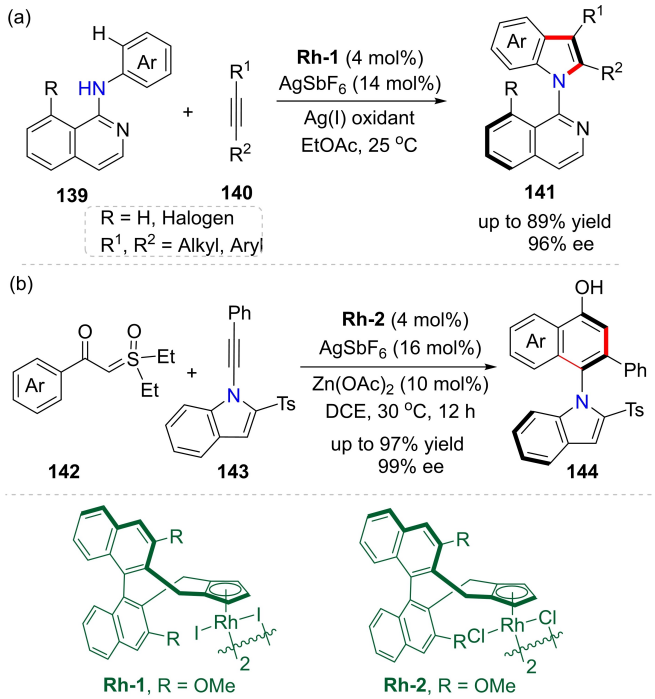
In 2019, Li and co-workers realized the oxidative coupling of *o*-alkynylanilines/phenols **130** and indoles **131** to the asymmetric synthesis of 2,3′-biindolyls **132** via highly active Rh-catalyzed C–H activation and nucleophilic cyclization cascade reactions. Importantly, a chiral rhodacyclic intermediate was separated from the stoichiometric reaction, which provided a direct insight into the mechanistic process (Scheme 42a).[69] In the same year, Zhu and co-workers developed the first examples of $Pd(OAc)_2$ and **L10** ligand-catalyzed asymmetric Cacchi reactions.



Scheme 41. Asymmetric cyclization dimerization of sulfides to access axially chiral bibenzothiophenes.[68]



Scheme 42. Metal catalyzed asymmetric cyclization synthesis of axially chiral 2,3-disubstituted indoles.[69–72]



Scheme 43. Rhodium-catalyzed annulation to construct C–N axially chiral molecules.[74]

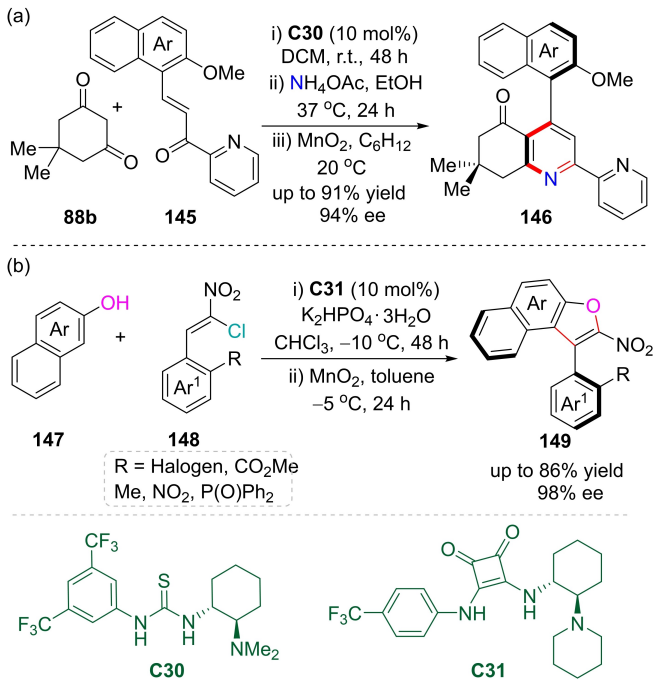
In the presence of oxygen, a wide range of *N*-sulfonyl-2-alkynylanilides **133** and arylboronic acids **134** react to form axially chiral 2,3-disubstituted indoles **135** with high yields and enantioselectivities (Scheme 42b).[70] In the present reaction, complexation-induced chirality transfer was proposed to explain the chirality transfer from the ligand to the product. In 2021, after the Li group reported an asymmetric Cacchi reaction,[71] Wang and co-workers achieved a Pd/**L1**-catalyzed enantioselective Cacchi reaction of 2-alkynylanilines **136** with naphthyl halides **137**, which afforded a series of enantioenriched axial naphthyl-C3-indoles **138** with excellent results (up to 99% yield, 92% ee). Moreover, the extra water and the modulation of the manipulation procedure by premixing the palladium complex and the naphthyl halides were key to the smooth operation of the reaction (Scheme 42c).[72] Besides, Xu and co-workers also performed a Pd-catalyzed asymmetric tandem C–C bond activation and Cacchi reaction, leading to indanone-substituted indoles with both axial and central chirality.[73]

Recently, Li and his colleagues also demonstrated the C–H activation strategy for rhodium(III)-catalyzed intermolecular atroposelective [3+2] or [4+2] annulation to access axially chiral heterobiaryls (Scheme 43).[74] In the two reactions, internal alkynes **140** or **143** react with anilines **139** and sulfoxonium ylides **142**, respectively, to obtain a series of *N*-isoquinolylindoles **141** or 4-functionalized 1-naphthols **144** under mild conditions with high regio- and enantioselectivity. These two elegant works also reflect the great application potential of Rh-complex catalysts in the construction of axially chiral frameworks.

4.3. Cyclization and chiral conversion cascade reaction

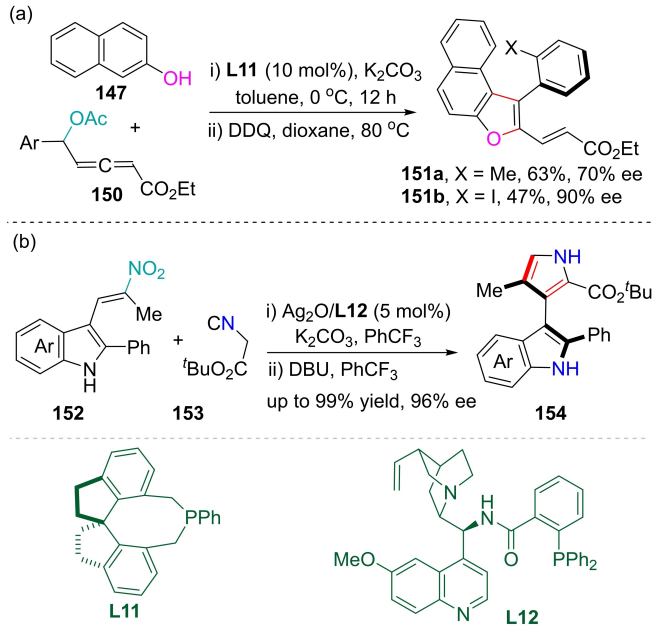
In 2016, Rodriguez, Bugaut, Bressy, and co-workers realized the atroposelective synthesis of 4-arylpyridines via a [4+2] cyclization and a central-to-axial chirality conversion cascade reaction (Scheme 44a).[75] In 2017, Rodriguez, Bonne, and colleagues developed an asymmetric synthesis of axially chiral *O*-heteroatropisomers with up to 98% ee. The synthetic route combines a [3+2] cyclization synthesis of *trans*-dihydrofurans with a central-to-axial chirality conversion strategy. First, under the catalysis of squaramide catalyst **C31**, the cyclization reaction of β-naphthols **147** and bulky β-substituted nitroolefins **148** yields the target products with central chirality. Next, the final axially chiral furans were obtained under oxidation with MnO_2 (Scheme 44b).[76] In addition, dimedone also showed good reaction performance in this methodology. In 2020, they also realized the synthesis of chiral compounds containing two distal C–C stereogenic axes based on chiral transformation strategies.[77]

In 2017, Tong and co-workers reported a chiral phosphine-catalyzed asymmetric [3+2] annulation of 2-naphthols **147** with δ-acetoxy allenoates **150**, which provides a facile method for the synthesis of 1,2-dihydronaphtho[2,1-b]furans with good



Scheme 44. Chiral amine catalyzed cyclization and chirality conversion to construct axially chiral skeletons.[75,76]

results under mild reaction conditions. Inspired by the report of Bonne and Rodriguez, they also attempted to synthesize the furan atropisomers through a central-to-axial chirality conversion strategy. Finally, two examples of axially chiral furans **151a** (70% ee) and **151b** (90% ee) were successfully obtained under the oxidation of DDQ (Scheme 45a).[78]

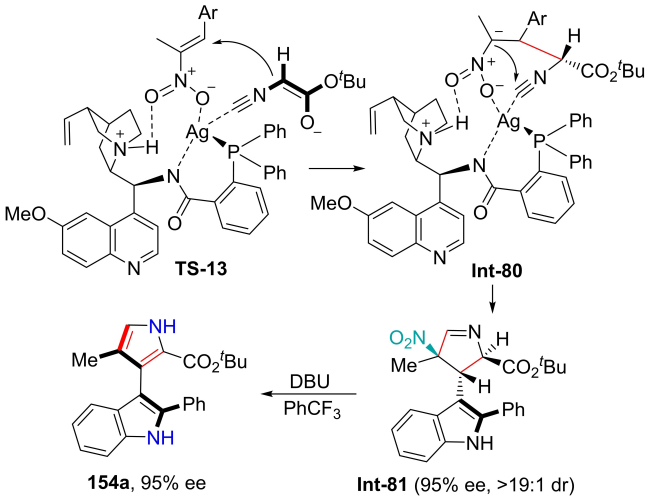


Scheme 45. Asymmetric cyclization and oxidation strategy to construct axially chiral molecules.[78,79]

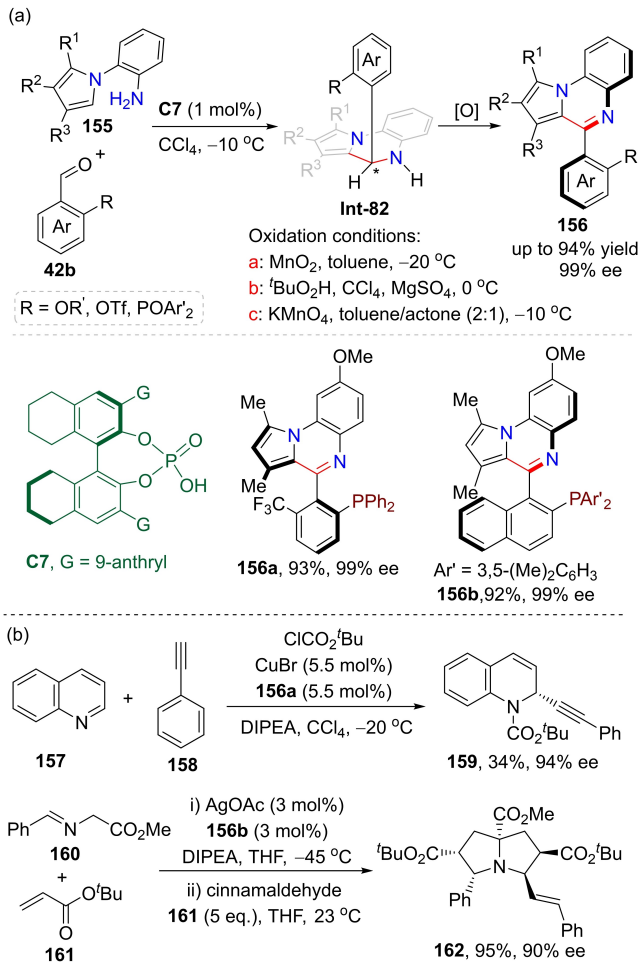
In 2019, Chen, Du, and co-workers established an Ag_2O/cinchona-derived phosphine ligand (**L12**) catalyzed asymmetric Barton–Zard reaction to construct 3-pyrrole-containing axially chiral skeletons in excellent yields and enantioselectivities (Scheme 45b).[79] First, under the action of silver oxide and phosphine ligand, the [3+2] cyclization reaction of α,β-disubstituted nitroolefins **152** and α-isocyanic **153** successfully provides centrally chiral intermediate **Int-81** (Scheme 46). Fortunately, the [3+2] intermediate **Int-81** was successfully isolated with a moderate yield and excellent stereoselectivity (95% ee, >19:1 dr). Subsequently, the final axially chiral pyrrole **154a** was obtained in 95% ee by aromatization via treatment with DBU in $PhCF_3$. Moreover, no additional DBU was required for this reaction to be compatible with α-substituted nitroolefins with a β-*ortho*-substituted naphthyl group.

In 2020, Jiang, Zhang, Xia, and co-workers reported a highly enantioselective synthesis of atropisomeric quinoxaline-based heterobiaryls **156** by condensation, cyclization, and chirality transfer cascade reactions (Scheme 47a).[80] In the present reaction, through different oxidation conditions, two atropisomers of *P,N*-ligands could be easily obtained from the same precursor enantiomer. Meanwhile, the preliminary application of newly synthesized ligands found that they have great application potential in asymmetric catalytic reactions (Scheme 47b), such as CuBr/**156a** catalyzed conjugate addition and AgOAc/**156b** catalyzed glycinate imine [3+2] cyclization. Moreover, in 2021, they also developed an efficient method for enantioselective construction of axially chiral azepines bearing seven-membered cyclic *P,N*-ligands from L-Alanine.[81]

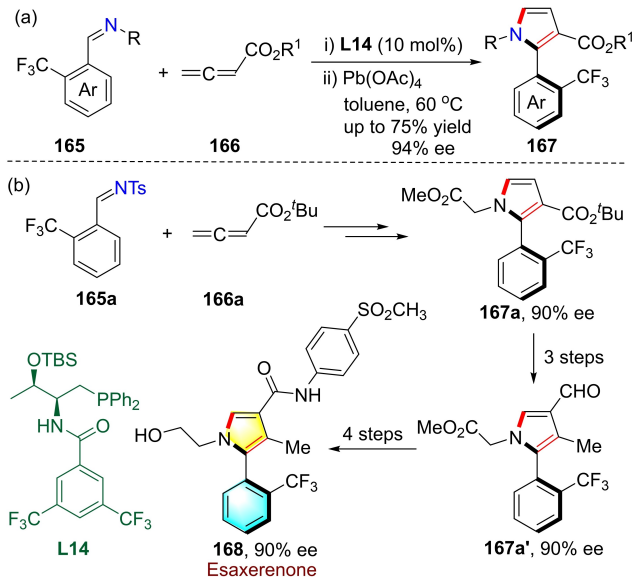
In 2022, Wang and co-workers reported a central-to-axial chirality conversion strategy for the synthesis of axially chiral *N*-arylpyrroles **164** from amino acid derivatives **163**. Through a gold-catalyzed 5-*endo*-dig cyclization and dehydration cascade process, providing a range of heterobiaryls with excellent results (up to 99% ee). DFT calculations suggest that the stability of the conformations of an amino alcohol and the



Scheme 46. Proposed mechanism of asymmetric Barton–Zard reaction.[79]



Scheme 47. Asymmetric construction of axially chiral quinoxalines.[80]

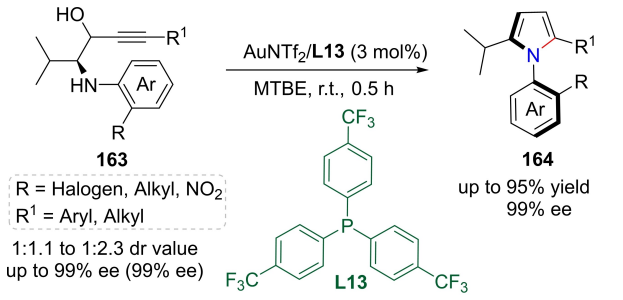


Scheme 49. Asymmetric synthesis of axially chiral iodo-containing arylpyrroles and esaxerenone.[83]

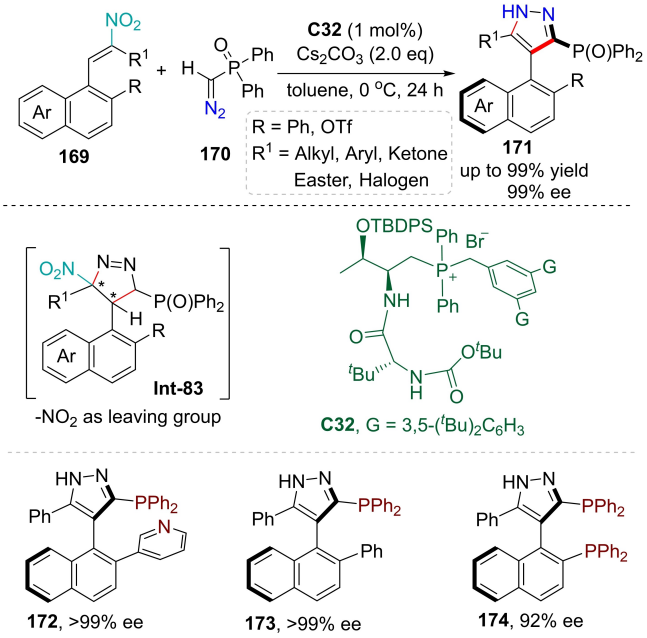
corresponding low barrier transition state are the keys to stereoselectivity (Scheme 48).[82]

In 2022, Lu, Ullah, and co-workers developed a phosphine catalyzed stereoselective [3 + 2] annulation of 2-CF_3 substituted *N*-tosylaldimines **165** and allenoates **166**, followed by oxidative central-to-axial chirality transfer to access a range of axially chiral 2-arylpyrroles **167** in excellent yields and enantioselectivities (Scheme 49a).[83] Interestingly, enantiopure esaxerenone **168**, used to treat hypertension, can be successfully synthesized using this methodology (Scheme 49b).

In 2023, Wang, Song, and co-workers developed a dipeptide-phosphonium salt-catalyzed asymmetric cascade reaction involving Huisgen-type cycloaddition of olefins **169** and diazophosphonates **170** and central-to-axial chirality conversion of **Int-83** (Scheme 50).[84] Under mild conditions and low catalyst loading, a great diversity of axially chiral phosphine compounds **171** was prepared efficiently (up to 99% yield, 99% ee). The



Scheme 48. Synthesis of axially chiral arylpyrroles via chirality conversion strategy.[82]



Scheme 50. Enantioselective synthesis of axially chiral pyrazole-based phosphine compounds.[84]

derivatization synthesis and application of novel axial chiral *P,N*-ligand **172**, mono- or bisphosphine ligands **173** or **174** were effectively demonstrated the practicality of this elegant method.

5. Summary and Outlook

Axially chiral heterobiaryls have been recognized as a class of important chiral molecules that play a vital role in many research fields, such as natural product synthesis, chiral ligands, and organocatalysts in asymmetric catalysis. Therefore, the atroposelective synthesis of heterobiaryls has aroused great interest in the chemistry community. Among various strategies for the catalytic enantioselective synthesis of axially chiral heterobiaryls, the heterocycle formation strategy has become a vital tool to achieve this goal. In this review, we comprehensively summarized the recent progress in the synthesis of axially chiral heterobiaryls through ring formation. We can conclude that transition-metal-catalyzed [2+2+2] cycloaddition of alkynes, click reaction of azides with alkynes, and the organocatalyzed intermolecular [3+2], [4+2], and [8+2] cycloadditions of alkynes provide numerous possibilities for the synthesis of axially chiral compounds. Furthermore, the intramolecular cyclization of alkynylnaphthol or alkynylaniline derivatives has made significant contributions to the development of indole-based axially chiral heterobiaryls with C–C or C–N axis, many interesting works using VQM intermediates have been reported by Yan and other groups, various chiral molecules with multiple-stereogenic elements[43] and chiral helicenes[14e,85] were prepared efficiently. On the other hand, many name reactions, such as Paal–Knorr, Friedländer, Cacchi, Barton–Zard, and the Attanasi reaction have become useful tools to construct atropisomeric heterobiaryls via transition-metal- and organocatalyzed intermolecular cyclization.

Despite certain achievements, there are still various challenges in this field of catalytic enantioselective synthesis of heterobiaryls, which are likely to be addressed in future studies. As described above, significant progress has been made in the development of the atroposelective synthesis of heterobiaryls through the cycloaddition of alkynes. However, most of the reported transition-metal-catalyzed methodologies used precious noble metals (such as Rh, Ir, and Au), and the development of new methods utilizing more sustainable earth-abundant metals is highly anticipated. Moreover, the organocatalytic cycloaddition of alkynes for the formation of heterobiaryls is still lacking, only polarized alkynes with electron-rich aromatic substituents or electron-poor carbonyl group are suitable for the atroposelective ring formation. Therefore, looking for other nucleophilic or electrophilic reagents that can react smoothly with such polarized alkynes to create more interesting and complex chiral molecules is highly desirable. Furthermore, we believe that the discovery of new organocatalysts containing new functionalities to active readily available alkynes via new activation modes is an important aim in this area. Additionally, the development of novel synthetic strategies or catalytic systems for the synthesis of axially chiral heterobiaryls containing other heteroatoms or chiral elements is another goal in this field. Overall, with the development of new strategies and methods for enantioselective construction of heterobiaryls, we can readily synthesize various valuable chiral ligands, catalysts, and bioactive molecules, and have more opportunities to tackle the pending challenges. Finally, we hope that the chemistry of axially chiral compounds would be forthcoming and blooming in the near future, taking up an important position in the fields of chemistry, industry, and medicine.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: cycloaddition · enantioselective · heterobiaryls · organocatalysis · transition-metal catalysis

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