RECENT PROGRESS ON ATROPENANTIOSELECTIVE SYNTHESIS OF AXIALLY CHIRAL PYRROLES

DOI: http://dx.medra.org/10.17374/targets.2024.27.151

Yu-Jing Xi, Xiao-Ming Zhao,* Sheng-Cai Zheng*

School of Chemical Science and Engineering, Tongji University, 1239 Siping Road, Shanghai, 200092, P. R. China

(e-mail: xmzhao08@mail.tongji.edu.cn; zhengsc@tongji.edu.cn)

Abstract. *Optically active pyrroles appear as useful building blocks in materials science and natural products. Although the first reported axially chiral pyrroles were achieved early in 1930 through resolution, their catalytic atropenantioselective synthesis was not implemented until 2017 accompanying the tide of more strategies emerged for constructing axial chirality. This review intends to summarize recent progress on catalytic atropenantioselective synthesis of axially chiral N1-, C2- and C3-(hetero)arylpyrroles according to the developed strategies. Some corresponding mechanistic studies have been illustrated as well.*

Contents

1. Introduction

Axially chiral compounds, also known as atropisomers, are a class of stereoisomers that can be observed or separated due to spatial or electronic effects that limit the rotation of the σ-bonds in the molecule to form a stereogenic axis.[1] Oki[2] stated that the rotational energy barrier of an axially chiral compound should be higher than 23.3 kcal/mol^{-1} at room temperature, and the half-life at that temperature should be more than 1000 s to isolate the isomers. Although axial chirality has been characterized in 6,6'-dinitro-2,2'-diphenic acid by Christie and Kenner early back in 1922,[3] chemists' attention to atropisomerism was limited until 1980s when BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) was successfully applied in rhodium-catalyzed asymmetric hydrogenation.[4] Since then, the chemistry concerning axial chirality started to flourish due to more and more axially chiral compounds found in bioactive substances, chiral chemical catalysts, and ligands. Even reviews[5-22] on axially chiral compounds had to renew frequently because of the emerging literature reported not only on the accumulation of the synthesis strategies and applications but also for the accurate category of the subclasses.

On the other hand, pyrrole is one of important five membered heterocycles, which is also widespread in nature as a basic structural unit found in pigments essential for life such as chlorophyll and heme. Axially chiral pyrroles, as the core skeletons of a wide range of natural products,[23-25] pharmaceuticals,[26-28] ligands[29,30] and catalysts,[31] have attracted the attention of chemists over the years. First proposed and synthesized through resolution by Bock and Adams[32] in 1930, axially chiral pyrrole did not meet a rapid growth until Tan and co-workers reported a seminal work on the development of an elegant $Fe(OTf)_3$/chiral

phosphoric acid-catalyzed enantioselective Paal-Knorr reaction for the synthesis of enantioenriched *N*-aryl substituted pyrroles bearing a chiral C-N axis in 2017.[33] Since then, great attention has been paid to explore more strategies for atropenantioselective synthesis of axially chiral pyrroles. In this review, the available literature will be sorted into N1-, C2- and C3-pyrrole-aryl axis according to the atomic sites involved in chiral axis linkage in pyrroles (Figure 1), and the N1-axially chiral pyrroles are the most studied at present, which are more stable than the others mainly due to short average C−N(N−N) bond lengths (1.47 Å) compared to average C−C bond lengths (1.54 Å).

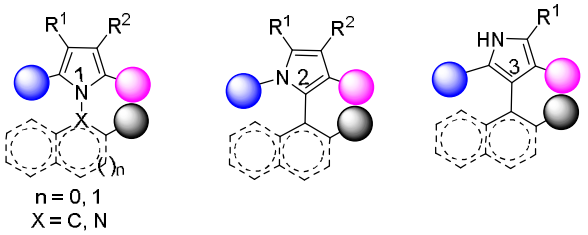


Figure 1. Axially chiral N1-, C2- and C3-(hetero)arylpyrroles.

Currently, the synthesis of this class of compounds mainly includes a total of four strategies: 1) *de novo* ring formation. From *Latin* "from the new", it refers to the synthesis of a ring from noncyclic starting material. For the axially compounds, it could be a newly formed ring connected to a (hetero)aryl ring or two newly formed rings to construct the axial chirality; 2) desymmetrization. An axially prochiral molecule turn into a chiral one by any reaction that result in the loss of one or more symmetry elements. For axially prochiral pyrrole, normally it easily destroys symmetry when the reaction take place the C3 position at pyrrole ring; 3) (dynamic) kinetic resolution. For kinetic resolution, two (potential) axial pyrrole enantiomers react with different reaction rates in a chemical reaction with a chiral catalyst or reagent, resulting in an enantioenriched sample of the less reactive enantiomer. For dynamic kinetic resolution, based on the principle of kinetic resolution, if two (potential) axial pyrrole enantiomers could convert to each other by heating or catalyst, 100% of a racemate can be converted into an enantiopure axial pyrrole; 4) central-to-axial chirality. Literally, it should construct a center chirality prior to the transfer of the chirality through the asymmetrical synthesis.

2. Axially chiral pyrroles bearing stereogenic axis at N1-position

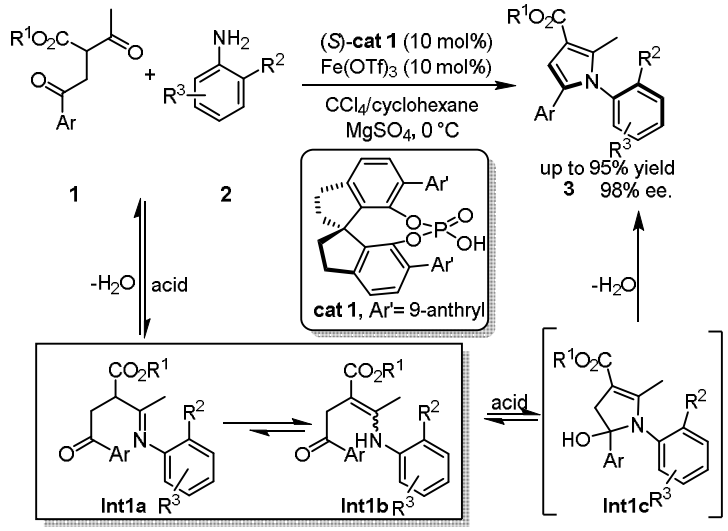
2.1. "*De novo* ring formation" strategy

In 2017, Tan's group[33] implemented the "*de novo* ring formation" strategy to give a seminal report concerning N1-axially chiral pyrrole compound synthesis by an asymmetric Paal-Knorr reaction catalyzed by chiral phosphoric acid. With the optimized chiral phosphoric acid (CPA) **cat 1** and Lewis acid $Fe(OTf)_3$, the reaction between compounds **1** and **2** yields product **3** bearing a stereogenic C−N axis up to 98% ee. Interestingly, if the solvent CCl_4 is replaced with CH_3OH, inversed product configuration could be observed. Mechanism study showed that the isolable enamine **Int1b** isomerized from **Int1a**, which is the key intermediate for enantiocontrol to form axially chiral **Int1c** by the CPA **cat 1** (Scheme 1).

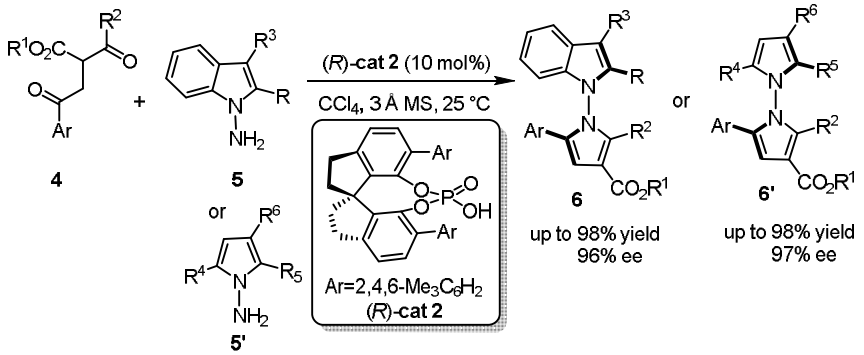
In 2022, based on the above-mentioned work of Tan's group, Shi's group[34] extended another asymmetric Paal-Knorr reaction to construct N1-axially chiral pyrroles. Instead of the aniline substrate **2**, Shi applied *N*-aminoindole **5** to react with **4**, and the *N*-pyrrolyl indole product **6** was obtained with a N−N chiral axis up to 98% yield and 96% ee in the precence of catalyst **cat 2**. The axially chiral *N*,*N*'-bispyrroles **6'** could be obtained as well by appropriately designing the amine part to *N*-amino pyrrole **5'** using the same catalytic system (Scheme 2). It is worth noting that the reaction needs to be carried out at room temperature and the addition of 3 Å MS significantly improves the enantioselectivity.

"*De novo* ring formation" chemistry was further enriched by double Paal-Knorr reactions of hydrazine and 1,4-diketone in Zhao's group[35] to successfully construct the N1-axially chiral bipyrrole skeleton (Scheme 3). The first Paal-Knorr reaction occurred between hydrazine **7** and 1,4-diketone **8** in the presence of catalytic trifluoracetic acid (TFA) furnishing *N*-aminopyrrole **9** which is used as a substrate for a second

Paal-Knorr reaction with 1,4-diketone **8'** in the presence of CPA **cat 3** to access the N−N axially chiral bipyrrole skeleton **10**. Interestingly, the addition of Lewis acid $Fe(OTf)_3$ here, which is different from Tan's reports where it serves an additive only to improve the reaction efficiency, leads to a inversed product configuration (***ent*-10**) while maintaining a high enantioselectivity.



Scheme 1. Asymmetric synthesis of axially chiral N1-arylpyrroles *via* the Paal-Knorr reaction.



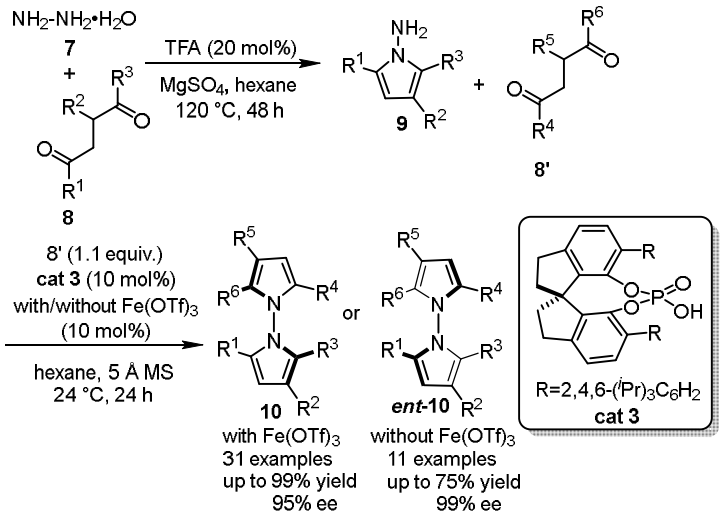
Scheme 2. Asymmetric Paal-Knorr reaction to axially chiral *N*,*N*'-indolylpyrroles/bispyrroles.

2.2. "Desymmetrization" strategy

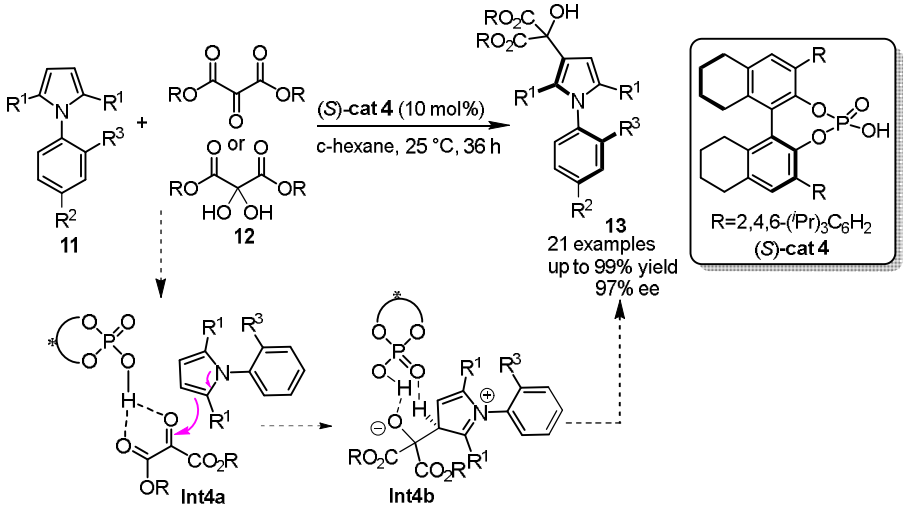
In 2019, Tan's group[36] acutualized the concept of desymmetrization to efficiently prepare N1-axially chiral pyrroles under the catalysis of (*S*)-**cat 4** by asymmetric addition with ketomalonates **12** at C3-site of pre-axiallychiral pyrrole **11** (Scheme 4). A monofunctional activation mode was proposed in which hydrogen bonding to CPA **cat 4** with both carbonyl moieties of ketomalonates create a rigid chiral pocket **Int4a**. After asymmetric addition, the hydrogen at C3-site pyrrole **11** of pyrrole was shuttled to alkoxide anion **Int4b** through CPA **cat 4** to furnish product **13** bearing a stereogenic N−C axis. In addition, highly efficient kinetic resolution was achieved when R^1 groups are different on each side of pyrrole.

In 2021, Liu's group[37] desymmetrized *N*,*N*'-bispyrroles **14** through Friedel-Crafts alkylation of ketomalonate derivatives 1**2** using the catalytic system **Int5a** consisting of $Cu(OTf)_2$ and ^{t}BuBOX ligand **L1** (Scheme 5). A wide range of axially chiral *N*-*N* bispyrroles atropisomers **15** could be efficiently obtained in

high yields with excellent enantioselectivities. Furthermore, two examples applying kinetic resolution as two R^1 groups differentiated from each other were illustrated as well. Aside from *N*,*N*'-bispyrroles, other axially chiral pyrroles where skeletal diversity was represented by indole **15a**, 2-thioxo-thiazolidin-4-one **15b**, pyrimidin-4(3*H*)-one **15c** or 1,2,4-triazin-5(4*H*)-one **15d** core were obtained with reduced enantioselectivities.



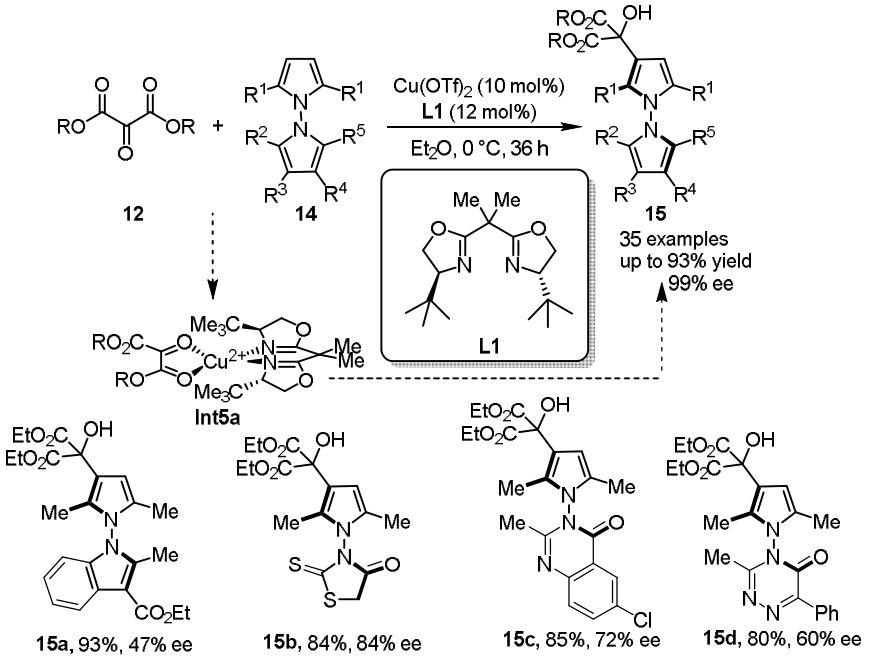
Scheme 3. Axially chiral *N*,*N*'-bispyrroles *via* double Paal-Knorr reactions.



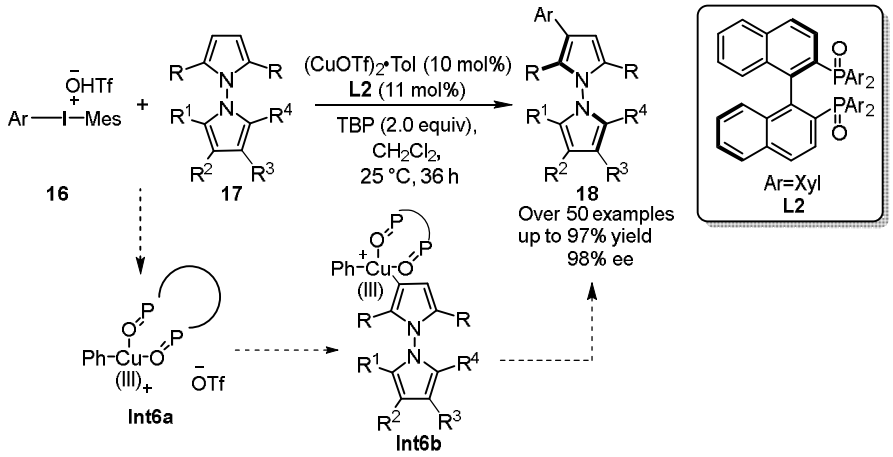
Scheme 4. CPA-Catalyzed desymmetrization toward axially chiral N1-arylpyrroles.

In 2022, Liu's group[38] continued to explore the synthesis of N1-axially chiral bipyrroles using a desymmetrized arylation reaction (Scheme 6). The reaction employed a catalytic system of in situ formed Cu(I) complex from $(CuOTf)_2$•Tol and chiral bisphosphine oxide ligand **L2**, which in proposed mechanism undergoes oxidative insertion by diaryl iodonium salt **16** to generate the highly electrophilic Cu(III) intermediate **Int6a** followed by asymmetric electrophilic arylation with **17** to form the intermediate **Int6b**

via π-facial discrimination, aromatization and reductive elimination to obtain the products. A wide range of bipyrroles could be desymmetrized furnishing 3-aryl *N*,*N*'-bispyrroles **18** in good to excellent yields with excellent enantioselectivities. On the other hand, numerous aryliodonium salts could be used with a limitation for those bearing an *ortho*-substituted aryl group that did not react due to steric hindrance.



Scheme 5. Desymmetrization toward axially chiral *N*,*N*'-bispyrroles/heteroarylpyrroles. **5a**

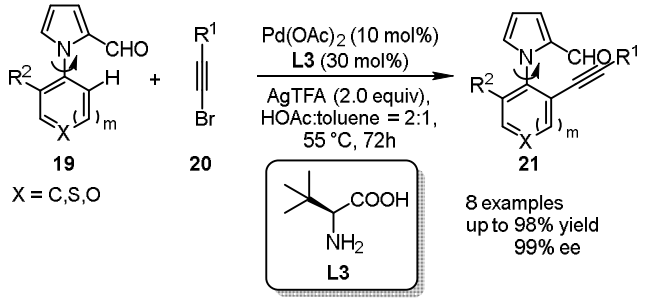


Scheme 6. Axially chiral *N*,*N*'-bispyrroles from "desymmetrization" strategy.

2.3. "(Dynamic) kinetic resolution" strategy

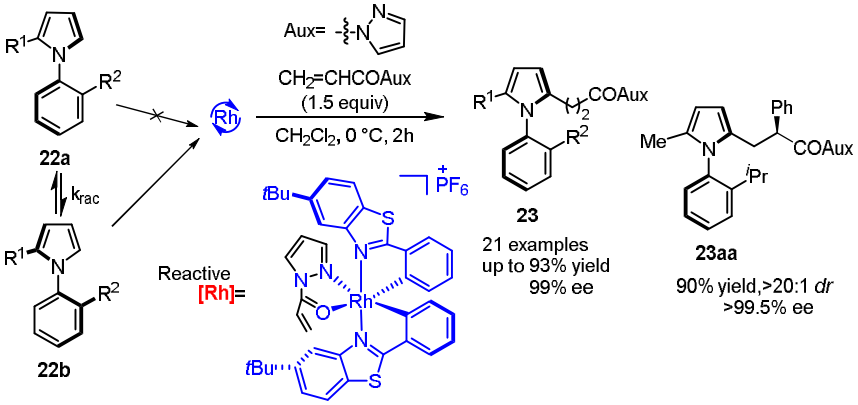
For the synthetic formed racemic N1-axially chiral pyrroles especially with low rotation barrier energy, as the atropisomers could be converted to each other easily, dynamic kinetic resolution is a pivotal

method to prepare the axially chiral pyrrole derivatives. In 2019, Shi[39] reported a palladium-catalyzed alkynylation with **20** through C−H activation directed by 2-pyrrolyl aldehyde **19** to enhance the rotation barrier energy to construct axially chiral N1-arylpyrroles (Scheme 7). L-*tert*-leucoamino acids **L3** as transient chiral auxiliary which coordinated to Pd complex to accelerate the the C−H activation on one atropisomers specifically brought the dynamic kinetic resolution process in high efficiency obtaining **21** with a high enantioselectivity of up to 98% ee.



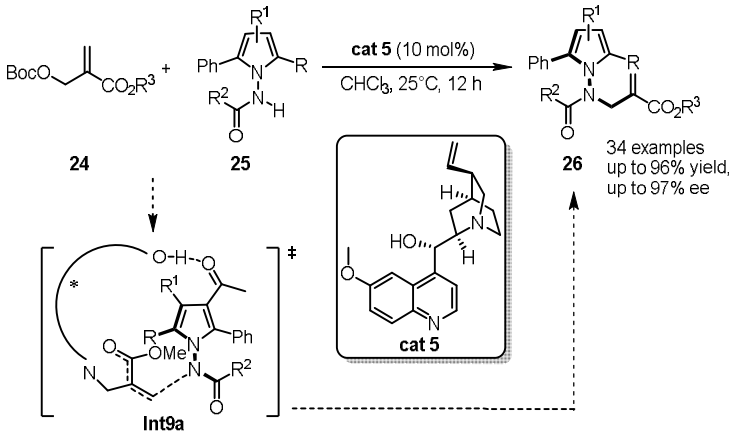
Scheme 7. C−H Alkynylation toward axially chiral N1-arylpyrroles.

In 2020, Meggers group[40] used the unique in situ chiral-at-metal of rhodium complex catalysts to construct N1-axially chiral pyrroles with C−N chiral axes. Two atropisomers **22a** and **22b** could rapidly interconvert even at low temperature such as 0 °C, one of which can be utilized for dynamic kinetic resolution to react with in situ formed reactive chiral-at-metal of rhodium complex (Scheme 8), rendering fluxional *N*-arylpyrroles **23** with *N*-acryloyl-1*H*-pyrazole at C5 site of pyrrole in high yields with excellent enantioselectivities. It is worth noting that when 2-phenyl-1-(1*H*-pyrazol-1-yl)-propenone was employed as coordination partner to Rh complex, product **23aa** was obtained with very high stereoselectivity of >20:1 dr and >99.5% ee.



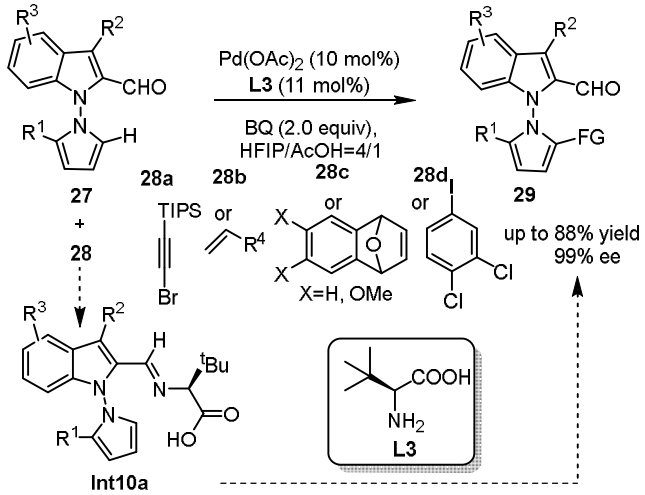
Scheme 8. Axially chiral N1-arylpyrroles through rhodium catalyzed DKR reaction.

The first construction of non-biaryl N1-pyrroles **26** bearing N–N chiral axes was realized by the groups of Lu and Houk[41] in 2021 through a Morita-Bayliss-Hillman reaction with **24** and **25** under **cat 5** finishing N-allyl alkylation which dramatically brought a high stability of the new stereogenic axis (Scheme 9). The axial chirality is controlled not only by the steric effect of neighboring substituents close to the chiral axis but the more distant functional groups (see **Int9a**) at the C3- or C4-positions of pyrrole. DFT calculations further explained that the axial chirality is determined by a combination of spatial site resistance and hydrogen bonding between the chiral catalyst and the substrate.



Scheme 9. Morita-Bayliss-Hillman reaction toward axially chiral *N,N*-amidylpyrroles.

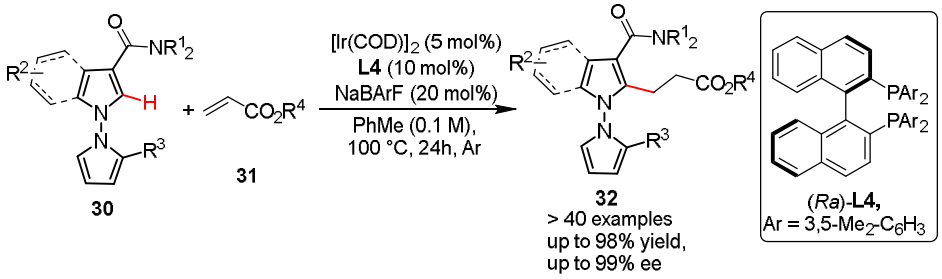
Recently, Liu's group[42] devised a palladium-catalyzed C−H functionalization at C5-positon of pyrroles directed by 2-indolyl aldehyde **27** which later transformed to transient chiral auxiliary **Int10a** by L-*tert*-leucoamino acids **L3** as well, providing axially chiral *N,N*-indolylpyrroles **29** with high yields and enantioselectivities (Scheme 10). Complementary to the Shi report, this protocol not only could functionalize the C5-positon of pyrroles with alkynylation **28a**, but also with olefination **28b**, allylation **28c**, arylation **28d**, showing excellent generality to diverse axially N1-pyrrole with high enantioselectivities.



Scheme 10. C−H Functionalization toward axially chiral *N,N*-indolylpyrroles.

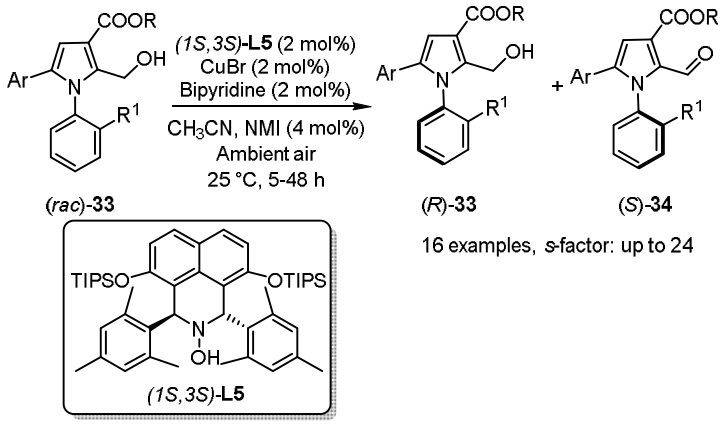
Very recently, structurally diverse N−N indole(pyrrole)-pyrrole atropisomers **32** were assembled by the You group[43] *via* a highly efficient iridium-catalyzed asymmetric C−H alkylation reaction in the presence of chiral phosphine ligand **L4** (Scheme 11). Different from other strategy, the directing group and the C−H alkylation site are on the same heterocycle ring in **30**, making the protocol very general for the asymmetrical induction. More than 40 examples were illustrated in good yields (up to 98 %) with excellent enantioselectivity (up to 99 % ee). Interestingly, the medicine or nature product derivatives either in the

directing groups R^1 or acrylation partners **31** were demonstrated to be compatible in the reaction, giving an opportunity for the post-modification in the drug discovery process.



Scheme 11. Iridium-catalyzed kinetic C−H alkylation reaction.

"Kinetic resolution" strategy was deployed for those racemic N1-axially chiral pyrroles with high rotation barrier energy, as the atropisomers could not be converted to each other for later chiral recognition. Only half of the substrates could react to further transformation and resulted in an enantioriched starting material. In 2022, Szpilman's group[44] realized a kinetic resolution by oxidation of *N*-arylpyrrolitols **33** under the catalyst CuBr and **L5** complex in ambient air, giving product **34** in a moderate resolution efficiency with *s*-factor up to 24 (Scheme 12).



Scheme 12. Kinetic resolution of *N*-arylpyrrolitols.

3. Axially chiral pyrroles bearing stereogenic axis at C2-position

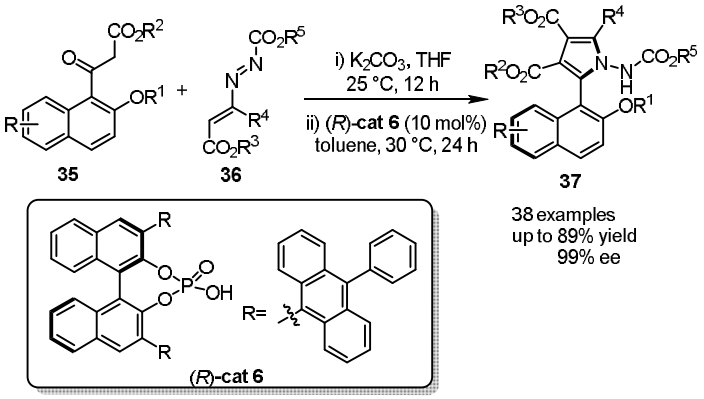
3.1. "*De novo* ring formation" strategy

In 2022, Mei's group[45] synthesized C2-axially chiral arylpyrrole skeletons (NPNOL) **37** by *de novo* ring formation through a cascade sequence. Chiral phosphoric acid **cat 6** was chosen to catalyze the asymmetric Attanasi's[46] reaction between 1,3-dicarbonyl compounds **35** and azo olefins **36** to achieve a high enantioselectivity up to 99% ee (Scheme 13). The calculations revealed that C−H--π interactions and spatial exclusion elaborated the origin of the enantioselectivity. Deprotection of ester (Boc) bind to N-amine and removal of R^1 group could forge the parent NPNOL scaffold, which is quite similar to NOBIN and having diverse applications in asymmetric synthesis.

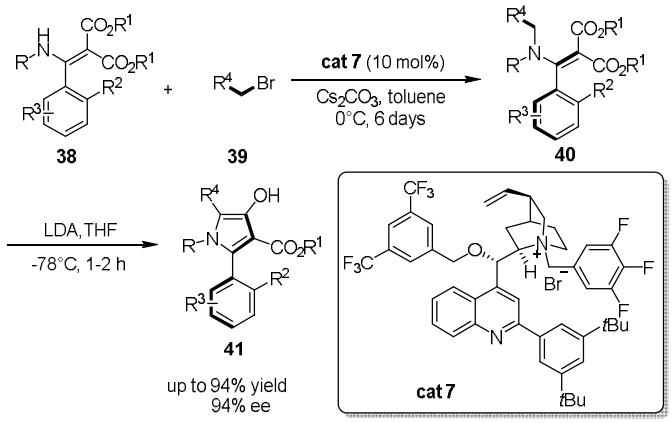
3.2. "Central-to-axial chirality" strategy

Early in 2019, the first axially chiral C2-arylpyrrole was synthesized by Tan's group[47] by a sequential reaction involving a central-to-axial chirality transfer (Scheme 14). Under the catalysis of **cat 7**, the

enamines **38** could undergo N-alkylation with **39** to obtain polysubstituted axially chiral styrenes **40**, which were later cyclized to construct C2-arylpyrroles **41** containing chiral C−C axes under the strong base LDA. The products had excellent yields and enantioselectivity showing an excellent chiral transfer efficiency.



Scheme 13. Asymmetric Attanasi's reaction between 1,3-dicarbonyl compounds and azo-olefins.



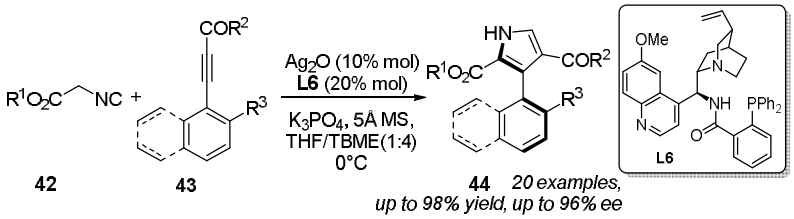
Scheme 14. Axially chiral C2-arylpyrroles *via* central-to-axial chirality conversion.

4. Axially chiral pyrroles bearing stereogenic axis at C3-position

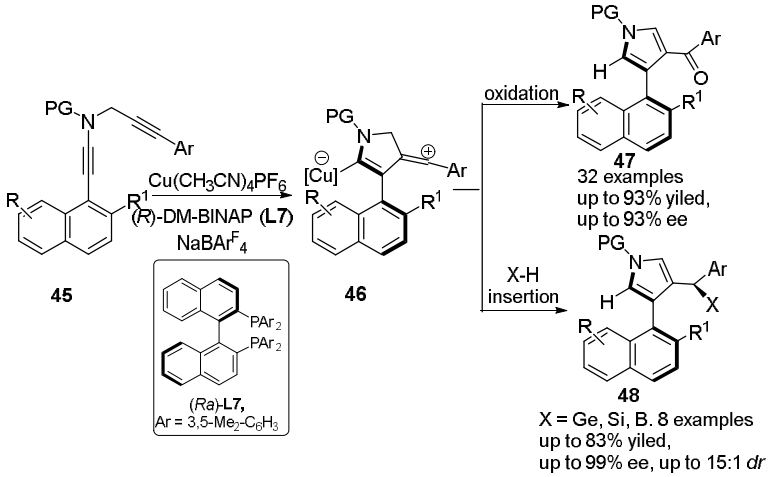
4.1. "*De novo* ring formation" strategy

In 2019, the first catalytic asymmetric synthesis of C3-axially chiral arylpyrroles **44** was realized by the group of Zhu[48] through heteroannulation between isocyanoacetates **42** and alkynyl ketones **43** in the presence of catalytic Ag_2O and Dixon-type chiral phosphine ligand **L6**, affording the axially chiral 3-arylpyrroles in good yields with excellent enantioselectivities (Scheme 15).

Very recently, Ye's group[49] exemplified the introduction of chiral C3-aryl axis in 3,4-disubstituted pyrroles **47** and **48** by enlisting catalytic $Cu(CH_3CN)_4PF_6$, (R)-DM-BINAP **L7** and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F_4$) in the asymmetric diyne cyclization of **45** (Scheme 16). A range of axially chiral arylpyrrole biaryls were assembled in good to excellent yields with generally excellent enantioselectivities *via* oxidation or X−H insertion of vinyl cations **46**. Notably, this protocol represents the first synthesis of mono-substituted 3-arylpyrrole atropisomers, which normally have a low rotation energy.



Scheme 15. Axially chiral C3-arylpyrrole from heteroanulation.



Scheme 16. Asymmetric diyne cyclization toward axially chiral C3-arylpyrrole.

4.2. "Kinetic resolution" strategy

In 2019, an interrupted Barton-Zard pyrrole synthesis was reported by Zhu's group[50] involving a kinetic resolution of isolated hypothetic intermediates **50** of the Barton-Zard reaction with **49** and **42** in the presence of a bifunctional thiourea-quinine catalyst **cat 8** (Scheme 17). A broad range of 3-arylpyrroles **51** were obtained with high enantioselectivities and excellent selectivity factors of up to 153. Additionally, the enantioriched (+)-**50** could be easily aromatized to ***ent*-51** in the presence of a bifunctional thiourea-quinidine **cat 9**. The authors rationalized the atroposelectivity through a nonconventional formal 1,2-elimination of the dihydro-2*H*-pyrrole intermediate **50**, in contrast to the broadly accepted mechanism.

4.3. "Central-to-axial chirality" strategy

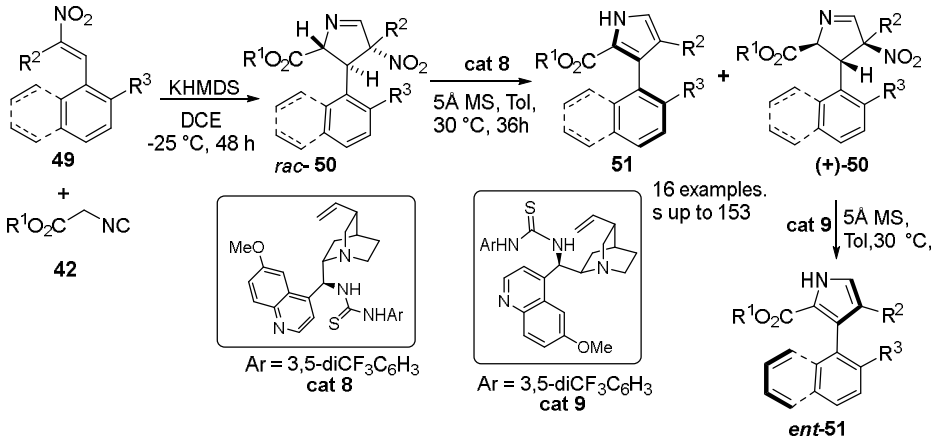
Asymmetric Barton-Zard reaction was realized under a catalytic system Ag_2O/**L6** by Chen and Du's group[51] in 2019 to construct moderately atropostable 3-(hetero)arylpyrrole **55** in high yields with excellent enantioselectivity from α-substituted nitroolefins tethered to *ortho*-substituted (hetero)aryl group **52** and α-isocyano substrates **53** bearing various electron withdrawing groups (Scheme 18). Interestingly, the enantioriched intermediates of the Barton-Zard **54** could also be isolated, which further aromatized to 3-(hetero)arylpyrrole **55** facilitated by DBU possessing a central-to-axial chirality conversion.

5. Conclusions

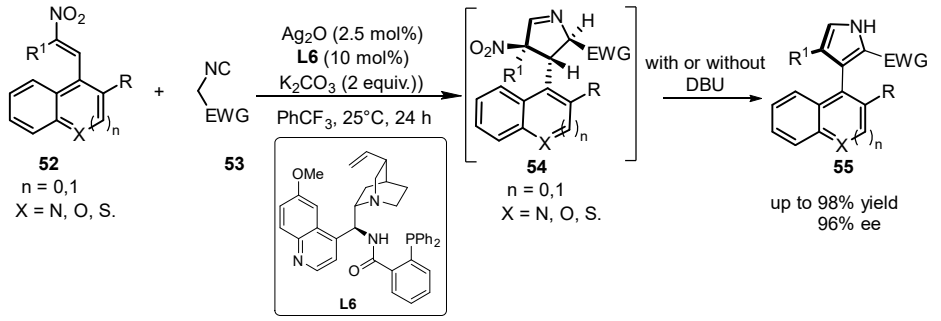
In summary, we have presented the latest research progress on the enantioselective synthesis of categorized by N1-, C2- or C3-pyrrole- (non)aryl chiral axes. Compared with prevalent axially chiral six-membered biaryls that have been extensively studied, methods of synthesis of these pyrroles are still rare and challenging to establish. The disadvantage in the low rotational barrier energy is gradually being

resolved with the innovative methodologies developed. By combing through these volumes of research and data, it may assist in the development of new strategies for asymmetrical synthesis of axially chiral pyrroles.

On the other hand, axially chiral pyrrole derivatives have great relevance in many fields of chemistry. For example, introduction of axial chirality in pyrrole makes possible for more potential diverse application in ligand and catalyst due to the unique bite angles and electronic properties of these optical active pyrroles. Furthermore, in the field of material chemistry, through cooperation of axial chirality, it may bring special function on the pyrrole-based materials such as BIDPY and polypyrroles. We hope that this review will serve to stimulate research in this fascinating and prominent area of chemistry.



Scheme 17. Axially chiral 3-(hetero)arylpyrroles through kinetic aromatization.



Scheme 18. Asymmetric Barton-Zard reaction toward axially chiral 3-(hetero)arylpyrroles.

Acknowledgements

We thank the National Natural Science Foundation of China (NSFC, grant number 21971193 and 22171213), Fundamental Research Funds for Central Universities for financial support.

References

1. Kuhn, R. in *Stereochemie*, Freudenberg, K., Ed.; Franz Deuticke: Leipzig, 1933.
2. Ōki, M. in *Topics in Stereochemistry*, Allinger, N.L., Eliel, E.L., Wilen, S.H., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 1983; Volume 14, 1-81.
3. Christie, G.H.; Kenner, J. *J. Chem. Soc. Trans.* **1922**, *121*, 614-620.
4. Miyashita, A.; Yasuda, A. *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934.
5. Bringmann, G.; Price Mortimer, A.J.; Keller, P.A.; Gresser, M.J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384-5427.

6. Kozlowski, M.C.; Morgan, B.J.; Linton, E.C. *Chem. Soc. Rev.* **2009**, *38*, 3193-3207.
7. Bringmann, G.; Gulder, T.; Gulder, T.A.M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563-639.
8. Wencel-Delord, J.; Panossian, A.; Leroux, F.R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44*, 3418-3430.
9. Bencivenni, G. *Synlett.* **2015**, *26*, 1915-1922.
10. Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. *Coordin. Chem. Rev.* **2016**, *308*, 131-190.
11. Bonne, D.; Rodriguez, J. *Chem. Commun.* **2017**, *53*, 12385-12393.
12. Bonne, D.; Rodriguez, J. A *Eur. J. Org. Chem.* **2018**, *2018*, 2417-2431.
13. Bao, X.; Rodriguez, J.; Bonne, D. *Angew. Chem. Int. Ed.* **2020**, *59*, 12623-12634.
14. Wang, J.; Zhao, C.; Wang, J. *ACS Catal.* **2021**, 12520-12531.
15. Wu, S.; Xiang, S.-H.; Cheng, J.K.; Tan, B. *Tetrahedron* **2022**, *1*, 100009.
16. Xiang, S.; Cheng, J.K.; Tan, B. in *Catalytic Asymmetric Synthesis*; Akiyama, T., Ojima, I., Eds.; Wiley, 2022; 727-768.
17. Cheng, J.K.; Xiang, S.-H.; Tan, B. *Acc. Chem. Res.* **2022**, *55*, 2920-2937.
18. Kumar, A.; Sasai, H.; Takizawa, S. *Acc. Chem. Res.* **2022**, *55*, 2949-2965.
19. Xiang, S.-H.; Cheng, J.K.; Tan, B. *Synlett.* **2022**, *33*, 1991-2003.
20. Li, Z.-H.; Li, Q.-Z.; Bai, H.-Y.; Zhang, S.-Y. *Chem. Catal.* **2023**, 100594.
21. Sun, H.; Sharif, A.; Chen, J.; Zhou, L. *Chem. Eur J.* **2023**, e202300183.
22. Centonze, G.; Portolani, C.; Righi, P.; Bencivenni, G. *Angew. Chem. Int. Ed.* **2023**, e202303966.
23. Ito, C.; Thoyama, Y.; Omura, M.; Kajiura, I.; Furukawa, H. *Chem. Pharm. Bull.* **1993**, *41*, 2096-2100.
24. Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. *J. Am. Chem. Soc.* **2001**, *123*, 2703-2711.
25. Hughes, C.C.; Prieto-Davo, A.; Jensen, P.R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629-631.
26. Cho, H.; Choi, M.-K.; Cho, D.-Y.; Yeo, C.-W.; Jeong, H.-E.; Shon, J.-H.; Lee, J.-Y.; Shin, J.-S.; Cho, M.; Kim, D.-Y.; Shin, J.-G. *J. Clinic. Pharm.* **2012**, *52*, 976-984.
27. Barbarino, M.; Cesari, D.; Intruglio, R.; Indovina, P.; Namagerdi, A.; Bertolino, F.M.; Bottaro, M.; Rahmani, D.; Bellan, C.; Giordano, A. *J Cell Physiol.* **2018**, *233*, 7391-7401.
28. Esumi, H.; Lu, J.; Kurashima, Y.; Hanaoka, T. *Cancer Sci.* **2004**, *95*, 685-690.
29. Faigl, F.; Mátravölgyi, B.; Szöllősy, Á.; Czugler, M.; Tárkányi, G.; Vékey, K.; Kubinyi, M. *Chirality* **2012**, *24*, 532-542.
30. Deák, S.; Mátravölgyi, B.; Feczku, G.; Erdélyi, Z.; Nyerges, M.; Faigl, F. *Tetrahedron: Asymmetry.* **2015**, *26*, 593-599.
31. Faigl, F.; Erdélyi, Z.; Holczbauer, T.; Mátravölgyi, B. *Arkivoc.* **2016**, *2016*, 242-261.
32. Bock, L.H.; Adams, R. *J. Am. Chem. Soc.* **1931**, *53*, 374-376.
33. Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B. *J. Am. Chem. Soc.* **2017**, *139*, 1714-1717.
34. Chen, K.; Chen, Z.; Yang, S.; Wu, S.; Zhang, Y.; Shi, F. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116829.
35. Gao, Y.; Wang, L.; Zhang, T.; Yang, B.; Zhao, Y. *Angew. Chem. Int. Ed.* **2022**, *61*, e202200371.
36. Zhang, L.; Xiang, S.-H.; Wang, J.; Xiao, J.; Wang, J.-Q.; Tan, B. *Nat. Commun.* **2019**, *10*, 566.
37. Wang, X.-M.; Zhang, P.; Xu, Q.; Guo, C.-Q.; Zhang, D.-B.; Lu, C.-J.; Liu, R.-R. *J. Am. Chem. Soc.* **2021**, *143*, 15005-15010.
38. Xu, Q.; Zhang, H.; Ge, F.-B.; Wang, X.-M.; Zhang, P.; Lu, C.-J.; Liu, R.-R. *Org. Lett.* **2022**, *24*, 3138-3143.
39. Zhang, S.; Yao, Q.-J.; Liao, G.; Li, X.; Li, H.; Chen, H.-M.; Hong, X.; Shi, B.-F. *ACS Catal.* **2019**, *9*, 1956-1961.
40. Ye, C.; Chen, S.; Han, F.; Xie, X.; Ivlev, S.; Houk, K.N.; Meggers, E. *Angew. Chem. Int. Ed.* **2020**, *59*, 13552-13556.
41. Mei, G.-J.; Wong, J.J.; Zheng, W.; Nangia, A.A.; Houk, K.N.; Lu, Y. *Chem.* **2021**, *7*, 2743-2757.
42. Yao, W.; Lu, C.; Zhan, L.; Wu, Y.; Feng, J.; Liu, R. *Angew. Chem. Int. Ed.* **2023**, *62*, e202218871.
43. Yin, S.; Zhou, Q.; Liu, C.; Gu, Q.; You, S. *Angew. Chem. Int. Ed.* **2023**, e202305067.
44. Verdhi, L.K.; Fridman, N.; Szpilman, A.M. *Org. Lett.* **2022**, *24*, 5078-5083.
45. Han, T.; Zhang, Z.; Wang, M.; Xu, L.; Mei, G. *Angew. Chem. Int. Ed.* **2022**, *61*, e202207517.
46. Attanasi, O.; Filippone, P. *Synlett* **1997**, *1997*, 1128-1140.
47. Wang, Y.; Wu, Q.; Zhou, Z.; Xiang, S.; Cui, Y.; Yu, P.; Tan, B. *Angew. Chem. Int. Ed.* **2019**, *58*, 13443-13447.

48. Zheng, S.-C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 1494-1498.
49. Chen, Y.; Liu, L.; Chen, C.; Liu, Y.; Zhou, B.; Lu, X.; Xu, Z.; Ye, L. *Angew. Chem. Int. Ed.* **2023**, e202303670.
50. Zheng, S.-C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 9215-9219.
51. He, X.-L.; Zhao, H.-R.; Song, X.; Jiang, B.; Du, W.; Chen, Y.-C. *ACS Catal.* **2019**, *9*, 4374-4381.