Construction of Non-Biaryl Atropisomeric Amide Scaffolds Bearing a C–N Axis via Enantioselective Catalysis

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Abstract: The significant scaffold offered by atropisomeric amides with a C–N chiral axis has been extensively utilized for pharmaceuticals, agricultural science, and organic syntheses. As a result, the field of atropisomer synthesis has attracted considerable interest within chemistry communities. To date, a range of catalytic atroposelective approaches has been reported for the efficient construction of these challenging scaffolds. However, greatly concise and highly useful methodologies for the synthesis of these atropisomeric compounds, focusing on transition-metal, chiral amine, and phosphoric acid catalysis reactions, etc., are still desirable. Hence, it is indispensable to succinctly and systematically present all such reports by means of disclosing the mechanistic analysis and application, as well as the challenges and issues associated with the establishment of these atropisomers. In this review, we summarize the development of catalytic asymmetric synthetic strategies to access non-biaryl atropomers rotating around a C–N chiral axis, including the reaction methods, mechanism, late-stage transformations, and applications.

Keywords: non-biaryl atropisomers; C–N chiral axis; atroposelectivity; catalytic asymmetric synthesis

1. Introduction

Atropisomerism, a form of chirality caused by restricted rotation around a bond axis, has been of the utmost interest to chemists since its discovery in 1922 [1]. One particular category of non-biaryl atropisomeric amide scaffolds containing axial chirality along a C–N bond axis, comprising tertiary anilides, sulfonamides, sulfinamides, and phosphamide, has received more attention in the past few decades due to the discovery of their crucial roles in the pharmaceutical industry [2–6], agricultural science [7–9], and organic chemistry [10–13]. To date, the C–N axially chiral units have presented a series of significant natural products and bioactive molecules, which usually exhibit different pharmacological activities and metabolic processes, both in vivo and in vitro (Scheme 1a) [4]. Telenzepine is a selective muscarinic antagonist assisting in the therapy of peptic ulcers [2]. When it comes to the field of agricultural science, S-metolachlor, a significant herbicide, features a C–N chiral axis structure [8,9]. Numerous efficient ligands and catalysts bearing C–N axially chiral backbones have also been synthesized and extensively utilized in organocatalysis and transition-metal-mediated asymmetric catalysis (Scheme 1b) [10–13].

The conventional methods for preparing these optically active C–N axially chiral compounds generally relied on the optical resolution of the racemate, utilizing chiral column chromatography or chiral resolution agents [14,15]. Over the past few decades, our
expanding knowledge of asymmetric catalysis has paved the way toward pioneering work on enantioselective synthesis. The catalytic synthesis of C–N axially chiral amides has now been established, via both asymmetric transition-metal catalysis and organocatalysis [16–21]. The atropisomeric amide scaffolds cover the acyclic and cyclic C–N axially chiral amides, including the anilides, sulfonamides, sulfinamides, phosphamides, hydrazides, succinimides, urazoles, aryl-2-pyridones, arylquinazolinones, etc. (Figure 1). As such, the structures that bear a C–N chiral axis without −(R)C=S, −(R)C=O, −(R)SOx, or −(R)2P=O bonds linking to the nitrogen atom will not be included. As elaborated at the beginning of this introduction, these frameworks have various utilities that highlight the necessity of discussing the enantioselective construction of these structures in a review.

In this mini-review, we aim to summarize the breakthroughs and recent advances in asymmetric catalyzed functionalization for the construction of C–N axially chiral amide scaffolds, enabled by both metal catalysis and organocatalysis strategies. We hope that this mini-review will highlight the great potential of these strategies in asymmetric syntheses and inspire further developments in this emerging field. For clarification, this mini-review is organized into two sections, according to the generation of different types of chiral products, including acyclic C–N, axially chiral amide, and cyclic C–N axially chiral amide. In the following part, the detailed performance of these scenarios will be depicted using specific examples.
2. Enantioselective Synthesis of Acyclic C–N Axially Chiral Amides

This section covers the most pertinent examples of synthesizing acyclic atropisomeric anilides, sulfonamides, sulfonamides, and phosphamides via transition-metal catalysis, phase-transfer catalysis, and nucleophilic catalysis.

2.1. Synthetic Strategies for Acyclic C–N Axially Chiral (Thio)anilides

2.1.1. Atropisomeric (Thio)anilide Syntheses via Transition-Metal Catalysis

The transition metal-catalyzed cross-coupling reaction has emerged as one of the most effective methods for the construction of C–C and C–Heteroatom bonds from readily available feedstocks and has also found extensive utilization in organic synthesis [22–26]. The booming demand for chiral compounds in the chemical and pharmaceutical industries has continued to facilitate the advancement of practical catalytic methods for asymmetric transformation. As a significant research area in asymmetric catalysis, the enantioselective transition-metal-catalyzed cross-coupling reaction has attracted increasing scientific attention, offering a general and direct technique for preparing enantiopure molecules [27–29]. In 2002, Kitagawa and co-workers generalized the first catalytic asymmetric N-alkylation strategy to afford atropisomeric anilide 3 from amide 1 and diallyl carbonate 2 (Scheme 2) [30].

In this palladium-catalyzed alkylation, (S)-tol-BINAP (L1) served as the optimized ligand, to enable the efficient formation of the enantiopure axially chiral anilides 3 in high yields with low enantioselectivities (up to 96% yield and 44% ee). Although this method was inefficient for realizing the high enantioselective synthesis of atropisomeric amides by the limitation of ligands, it could illuminate the future of this cutting-edge area by providing novel and high-efficiency synthetic methodologies. Almost simultaneously, a similar
method was then reported by Curran’s group, who achieved the catalytic asymmetric synthesis of axially chiral anilides with chiral palladium catalysts, up to about 50% ee [31].

![Scheme 2. The formation of atropisomeric anilides via Pd-catalyzed asymmetric allylic N-alkylation.](image)

Selected examples:

- **3a** (94% yield, 40% ee)
- **3b** (93% yield, 36% ee)
- **3c** (93% yield, 36% ee)
- **3d** (95% yield, 35% ee)
- **3e** (92% yield, 44% ee)
- **3f** (92% yield, 35% ee)

On the basis of the earlier works by Kitagawa et al., Du and co-workers exploited a palladium catalytic system to gain access to axially chiral anilides via the Tsuji–Trost reaction (Scheme 3) [32]. With the development of ligand design and formation, these asymmetric syntheses achieved dramatic improvements. Under the conditions of allylic substitutions, the process allowed the construction of atropisomeric amides with moderate enantioselectivity (up to 92% yield and 84% ee). The key to success in promoting enantioselectivity was the utilization of the P/olefin hybrid ligand **L2**. In contrast to the previous alkylation strategies, Du’s work would further improve the substrate scopes and enantioselectivities of the desired products.

Building on the previous study, Kitagawa’s group generalized a novel asymmetric arylation strategy to afford atropisomeric N-arylamides **9** (Scheme 4) [33,34]. In this palladium-catalyzed arylation of amides **7** with aryl iodides **8**, 1-iodo-4-nitrobenzene served as the optimized substrate to enable an efficient formation of the enantiopure axially chiral anilides **9** in high yields, with excellent enantioselectivities (up to 92% yield and 94% ee). In contrast to the synthetic yields and enantioselectivities of **9a–9d**, the reactivity of the amides **7** might be rationalized on the basis of the nucleophilicity of the corresponding amide anions. That is, the yields of the desired products **9** were increased with the enhancement in the nucleophilicity of the related amide anions (the decrease in the acidity of NH-hydrogen).

The asymmetric [2 + 2 + 2] annulation is a highly effective protocol for the construction of axially chiral biaryls [35–41]. As illuminated by the previous works, a Rh(I)-catalyzed asymmetric enantioselective aromatization of trimethylsilylamides **10** and 1,6-diynes **11** via [2 + 2 + 2] cycloaddition was reported independently by Tanaka and co-workers in 2006 (Scheme 5) [42,43]. This method furnished enantioenriched axially chiral anilides with poor to good yields, with good to excellent enantioselectivity. It is worth mentioning that the preferential formation of **Int-1** determined the enantioselectivity of this cyclization, due to the coordination of the carbonyl group of **11** to rhodium and the steric interaction...
between the PAr$_2$ group of (S)-xyl-BINAP and the benzyl group of 11. The reductive elimination of rhodium species releases the rhodium catalyst and forms the desired product (S)-12. Notably, the carbonyl group on trimethylsilylamides might serve a supporting role in gaining high ee values by its coordination with rhodium. The 1,6-diyne bearing a methoxycarbonyl group sharply decreased the enantioselectivity of the corresponding product, probably owing to the electronic repulsion between the carbonyl group of trimethylsilylamides and 1,6-diyne (12f).

Scheme 3. Formation of atropisomeric anilides via Pd-catalyzed asymmetric allylic N-alkylation.

Building on the previous study, Kitagawa’s group generalized a novel asymmetric arylation strategy to afford atropisomeric N-arylamides 9 (Scheme 4) [33,34]. In this palladium-catalyzed arylation of amides 7 with aryl iodides 8, 1-iodo-4-nitrobenzene served as the optimized substrate to enable an efficient formation of the enantiopure axially chiral anilides 9 in high yields, with excellent enantioselectivities (up to 84% yield and 94% ee). In contrast to the synthetic yields and enantioselectivities of 9a–9d, the reactivity of the amides 7 might be rationalized on the basis of the nucleophilicity of the corresponding amide anions. That is, the yields of the desired products 9 were increased with the enhancement in the nucleophilicity of the related amide anions (the decrease in the acidity of NH-hydrogen).

Scheme 4. Pd-catalyzed enantioselective N-arylation for the construction of atropisomeric anilides.
The above-mentioned enantioselective protocols were limited to conventional transition metal-catalyzed cross-coupling reactions. An asymmetric C–H functionalization has become one of the most efficient strategies in the formation of enantioselective structures [44–49]. As a significant research field in asymmetric catalysis, atroposelective C–H functionalization has attracted increasing attention, furnishing a novel technique for generating chiral molecules in a step- and atom-economical manner. The utilization of a C–H activation strategy by which to construct atropisomeric anilides was underdeveloped. To fill this gap, in 2020, Shi and co-workers described the first formal Pd(II)-catalyzed atroposelective C–H olefination to access a highly efficient synthesis of atropisomeric anilides 15 via using readily available L-pyroglutamic acid (L5) as the chiral ligand (Scheme 6) [50]. This reaction underwent both an asymmetric C–H functionalization and a dynamic kinetic resolution process. Striving toward making this straightforward access a success, it should not only overcome the relatively complicated rotational freedom to fulfill the excellent enantioselective induction needed during the C–H activation step but also maintain the chirality that is forming, due to the relatively low atropostability of the resulting products, respectively. Notably, the utilization of the readily available and inexpensive ligand (L-pGlu-OH) to form the key intermediate Int-2 and the development of the mild reaction conditions were essential for an elegant transformation. In terms of substrate scope, a wide range of anilides could be transferred to the anilide atropomers, giving excellent yields and enantioselectivities (50 examples, with up to 99% yield and > 99% ee). Furthermore, a double C–H olefination of 14a and a kinetic resolution of 14b were completed with high efficiency. The scaffolds were then introduced to act as both an olefin-pyridine-type ligand (e.g., 15l) with N–C axial chirality in the Rh-catalyzed asymmetric conjugate addition and a chiral Lewis base catalyst (e.g., 15j) in the asymmetric allylation of aldehydes. Experimental studies were conducted to investigate the N–Ar rotational barriers (AG°) and the negative correlation between δCO and the rotational barriers. These demonstrated that the atropostability of those atropisomeric anilides toward racemization depended on the electronic effects of both the aromatic ring and the picolinamide. Computational investigations were executed to reveal the mechanistic process and the asymmetric induction model of the atroposelective C–H olefination, leading to the brilliant access of synthetic applications by utilizing the axially chiral anilides to form bioactive molecules and develop asymmetric reactions.
Scheme 6. Pd(II)-catalyzed asymmetric C–H olefination to form atropisomeric anilides via an asymmetric C–H functionalization/dynamic kinetic resolution (DKR).
Very recently, a similar Pd-catalyzed atroposelective C–H allylation with 1,1-di-substituted alkenes 23 was disclosed by the same group, leading to the formation of chiral N-aryl peptoid atropisomers 24 via β–H elimination, utilizing commercially available and inexpensive L-pGlu-OH L5 as the chiral ligand (Scheme 7) [51]. In this transformation, exclusive allylic selectivity was easily obtained, and numerous enantioenriched N-aryl peptoid products were generated in good yields, with high enantioselectivities (up to 90% yield and 97% ee).

Scheme 7. Construction of enantioenriched N-aryl peptoid atropisomers via Pd(II)-catalyzed atroposelective C–H allylation.

In a similar vein, the concept of atroposelective C–H functionalization was focused on the construction of a wide variety of N-aryl peptoid atropisomers 27 in high yields, with excellent enantioselectivities as well (Scheme 8) [52]. The Pd(II)-catalyzed asymmetric C–H alkynylation utilized the inexpensive L-pyroglutamic acid as a ligand. In this conversion, pyridine was indispensable; it served as the coordination site to accelerate the C–H activation rather than the carbonyl group or peptoid backbone. Moreover, the steric hindrance on the pyridine group would inhibit the coordination ability of palladium. Density functional theory (DFT) calculations identified that Int-4, leading to the formation of (R)-axial chirality, is more favorable than Int-3. When product 27b was oxidized by m-CPBA, the corresponding pyridine N-oxide was furnished with the retention of enantioselectivity. These significant scaffolds could also be scalably formed and transformed in high fidelity into chiral aryl acetylene 27bb, which is frequently applied in the Sonogashira cross-coupling and click reactions.

Kinetic resolution (KR), as one of the most traditional and fundamental approaches, has been extensively employed in asymmetric catalysis and synthesis, in which racemic substrates are resolved to furnish enantiomerically pure chiral complexes [53]. This general strategy was also concerned and applied to the synthesis of C–N axially chiral substances. In 2021, the Gong group developed a unique atroposelective C(sp3)–H coupling reaction and successfully achieved the kinetic resolution of thioanilides 28 (Scheme 9) [54]. Under the catalysis of a hybrid palladium catalyst encompassing a phosphoramidite ligand L6 and an anionic chiral cobalt complex L7, both atropisomeric arylated thioanilides 30 and N-methyl atropisomeric thioanilides (R)-28 were readily obtained with excellent enantioselectivities via the kinetic resolution of atropisomeric thioanilides 28.
ilides and N-methyl atropisomeric thioanilides (R)-28 were readily obtained with excellent enantioselectivities via the kinetic resolution of atropisomeric thioanilides 28.

Scheme 8. Pd(II)-catalyzed asymmetric C–H alkynylation to form N-aryl peptoid atropisomers.
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Scheme 9. Atroposelective C(sp^3)–H coupling for the kinetic resolution of thioanilide atropisomers.

2.1.2. Atropisomeric Anilides Syntheses via Phase-Transfer Catalysis (PTC)

Phase-transfer catalysis (PTC) has long been identified as a versatile strategy for organic synthesis in both academic and industrial laboratories, characterizing its concise experimental operations, mild reaction conditions, environmentally benign and inexpensive reagents and solvents, and promising potential for accessing large-scale applications [55–59]. Hence, a broad avenue can be provided to obtain a highly selective methodology for the formation of enantioenriched axially chiral anilides.

In 2012, the first example of phase-transfer-catalyzed N-alkylations for the asymmetric synthesis of axially chiral o-iodoanilides 33 was reported independently by Maruoka and co-workers (Scheme 10) [60]. Under the catalysis of chiral quaternary ammonium salt Cat-1, a highly enantioselective S_N2 attack of anilides 31 to a range of bromides 32 was realized, leading to the generation of atropisomeric anilides at high yields, with moderate to excellent atroposelectivity. To verify the utility of these atropisomers, transformation operations were conducted. The axially chiral phosphine oxides 34 were obtained from o-iodoanilide 33a with the full maintenance of stereoinformation, which acted as a dramatic forerunner for the design of novel chiral ligands and catalysts. The intramolecular radical cyclization of axially chiral N-allyl-o-iodoanilide 33d was then carried out to form 3-methyl indoline.
with high chirality transfer from axial chirality to C-centered chirality. Furthermore, the XRD analysis from the structure of (S)-36, prepared from a chiral ammonium bromide, and o-iodoanilide 31a was performed to obtain insight into the transition-state structure for the present asymmetric synthesis of axially chiral anilides. The information of crystal structure (S)-36 indicated that the negative charge of the iodoanilide anion was delocalized, while the transition state Int-6 was probably more favorable than Int-7 for the prevention of steric repulsion between aryl groups (Ar) on phase-transfer catalyst and iodide on the anilide anion. The transition state, Int-6, could finally react with a bromide 32 to obtain axially chiral anilide 33 with the observed absolute configuration.

**Scheme 10.** Phase-transfer catalyzed N-alkylations for the generation of axially chiral o-iodoanilides.

Building on the success in N-alkylation to form axially chiral o-iodoanilides 39, Maruoka and coworkers then achieved the construction of axially chiral o-tert-butylanilides, possessing lower rotational energy barrier, with high yield and enantioselectivity by using piperidine-derived catalyst Cat-2 (Scheme 11) [61]. These fantastic scaffolds could
be readily transformed to both sulfone products through Michael addition and chiral alcohol via the sequence of $S_N^2$ substitution and reduction. In the application process, the substrates' enantioselectivity could be retained without erosion using steps.

\[
\begin{align*}
\text{37} + \text{38} & \xrightarrow{\text{Cat-2 (2 mol%), KOH (2–20 equiv.), } \delta\text{Pr}_2} \text{39} \\
\text{82–95% ee} & \quad \text{51–99% yields}
\end{align*}
\]

**Selected examples:**

- 39j (97%, 95% ee) (98%, 76% ee) (Cat-1 as catalyst)
- 39k (99%, 92% ee)
- 39l (70%, 91% ee)
- 39m (99%, 86% ee)
- 39n (70%, 91% ee)
- 39o (84%, 85% ee)
- 39p (91%, 93% ee)
- 39p (51%, 86% ee) (Ar' = 4-MeC₆H₄)

**Synthetic applications:**

\[
\begin{align*}
\text{39m} & \xrightarrow{\text{PhCH₂Br, KO}^\text{Bu, THF, } -40^\circ C} \text{41} \\
\text{86% ee} & \quad \text{(63%, } d.r. = >20:1, 85% ee)
\end{align*}
\]

Scheme 11. Phase-transfer-catalyzed construction of axially chiral anilides.

2.1.3. Atropisomeric Anilides Syntheses via Organocatalysis

Organocatalysis, designed to mimic biomimetic catalysis, is a powerful instrument by which to fulfill fascinating transformations. To date, nucleophilic catalysis has experienced a range of developments regarding the construction of C–N axially chiral compounds by utilizing chiral amines or isothioureas as catalysts. The first exquisite amine-catalyzed asymmetric allylic alkylation (AAA) reaction to access C–N axially chiral scaffolds was reported by Li and coworkers, which employed anilides and Morita–Baylis–Hillman carbonates as substrates, with the biscinchona alkaloid Cat-3 as the catalyst (Scheme 12). In this transformation, the axially chiral anilides were obtained in moderate to high yields with good enantioselectivities, stereoselectivities, and cis/trans selectivities. The stereochemical stability of the chiral anilides was proven to
be regulated by electronics (45a–c), substitution pattern (45c–d), steric effects (45e–f), and solvents. These significant entities were easily transformed into the α-amino acid derivative 51 and indoline alkaloid scaffold 49, with high chirality transfer.

Scheme 12. Catalytic asymmetric allylic alkylation reaction for axially chiral anilides with achiral Morita–Baylis–Hillman carbonates. * represents a chiral center.
2.2. Synthetic Strategies for Acyclic C–N Axially Chiral Sulfonamide and Sulfinamide

2.2.1. Atropisomeric Sulfonamide Syntheses via Transition-Metal Catalysis

Recently, palladium-catalyzed allylation was also established to construct atropisomeric sulfonamide 52 in good yields, with the enantioselectivities satisfied (Scheme 13) [77]. A chiral π-allyl Pd intermediate was formed in this approach; the highly asymmetric transformation was arduous as a result of the sulfonamide anion attacking the π-allyl carbon on the opposite site of the Pd atom (as shown in Int-8). The key to achieving the atroposelective N-allylation was the suitable basicity of the sulfonamide anion, which was incapable of abstracting the amide hydrogen of the ligand to form the inactive catalyst, Cat-4.

![Scheme 13. Chiral palladium-catalyzed N-allylation to access axially chiral sulfonamides.](image)

To date, the integrated methods for constructing highly diastereoselective amides containing an N–C chiral axis and vicinal stereogenic center have been extremely scarce. The challenge in the synthesis of those compounds would be increased by introducing the stereogenic center in an adjacent position, which enhanced the steric effect and decreased the substrate reactivity. The product possessed more than one chiral center, thereby also leading to the difficulty of achieving high diastereoselectivity. As a workaround for challenging the synthesis of these complicated scaffolds, the alkyloxyallenes acted as convenient synthons by which to access the novel amide entities bearing a N–C chiral axis and stereogenic center. Jiang et al. performed a direct atroposelective hydroamination of sulfonamides 55 with alkyloxyallenes 56, utilizing Pd-catalysis to give the unique scaffolds 57 in good yields, with excellent enantioselectivities and diastereoselectivities under mild reaction conditions (Scheme 14) [78]. The electron-withdrawing and large steric hindrance groups in the sulfonyl unit provided the desired product with high diastereoselectivity. Besides this, the ortho substituents in the N-phenyl ring bearing bulky steric hindrance also led to accessing the atropisomers in terms of high dr values. The continued oxidation process successfully approached the axially chiral anilide analogs 58, while the atropoisomeric iminium-ion-mediated conversion enhanced the synthetic potential of this method.
Moreover, the γ-addition adduct 59b from product 57 and TMSN₃ could transfer to an eight-membered cyclic sulfonamide 60 with 78% ee for four steps.

Scheme 14. Atroposelective hydroamination of allenes to approach axially chiral sulfonamides.

2.2.2. Synthetic Strategies for Acyclic C–N Axially Chiral Sulfonamide and Sulfinamide via Nucleophilic Catalysis

Recently, Zhao and coworkers disclosed an elegant asymmetric allylic alkylation reaction to approaching the chiral sulfonamide 62 bearing an allyl scaffold, by the utilization of sulfonamide 61 and Morita–Baylis–Hillman (MBH) carbonates 44 as substrates (Scheme 15) [71]. This method showed excellent efficiency and enantioselectivity in the formation of axially chiral N-aryl sulfonamides. In this note, the chiral compound, bearing
a mono-ortho-tert-butyl substituent on the aryl group, possessed a low rotation barrier, while its enantiopurity decreased rapidly during the reaction process, which could be a significant guidance point for the chemists who were designing reactions. The desired product 62 was value scaffolds, which could easily be transformed into indoles 63, 64, and 65, with the retention of enantiopurity. Furthermore, the catalytic kinetic resolution of the NOBIN analogs was achieved smoothly by this method. This led chemists to furnish various valuable chiral catalyst precursors.

Scheme 15. Practical access to axially chiral sulfonamides via organocatalytic atroposelective N-alkylation.

Very recently, the Xiao and Chen groups reported a practical and concise organocatalytic atroposelective N-alkylation to efficiently approach sulfonamides bearing both an alene [79–81], and an allyl entity, with high enantioselectivity (Scheme 16) [72]. Significantly, this methodology also enabled selective N–H activation in the subsequent transformation toward functionalized sulfonamides and achieved the kinetic resolution of NOBIN analogs to obtain a series of chiral catalyst precursors. In this article, the racemization experiments
demonstrated that substituted allenoate-sulfonamides presented higher rotational barriers than the related acrylate-sulfonamides. Notably, the universal synthetic transformation could be readily scaled up, which boded well for its wide applications in chiral molecular syntheses via ozonization and reduction.

Scheme 16. Divergent construction of axially chiral sulfonamides via organocatalytic atroposelective N-alkylation.

In 2020, Dong disclosed a highly atroposelective N-acylation reaction of aniline-derived sulfonamides with \( \alpha,\beta \)-unsaturated carbonic anhydride, using chiral isothiourea as the catalyst (Scheme 17) [75]. This approach provided a facile and efficient avenue for the formation of atropoisomeric sulfonyl-substituted anilides in good yields, with high to excellent enantioselectivities. Two types of intermediates would be generated in this transformation process. The Int-10 was preferred for constructing the chiral product (R)-74 than the Int-11 because of the presence of the bulk o-tert-butyl group on the phenyl ring, which affected not only steric repulsion but also the \( \pi-\pi \) interaction between the substrates and the skeleton of the catalyst.

On a similar note, the isothiourea-catalyzed atroposelective N-acylation of sulfonamides by employing the ent-Cat-6 was delineated by Zhao and co-workers (Scheme 18) [76]. This method offered a facile and efficient process by which to access an array of atropoisomeric sulfonyl-substituted anilide products in good yields, with high to excellent enantioselectivities. It should be noted that the diminished size difference between the two
ortho-substituents would inhibit the enantioselectivity (77b vs. 77a). Moreover, these desired products possessed the potential to be aryl iodide catalysts.

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\text{Scheme 17. Organocatalytic atroposelective } N\text{-acylation of axially chiral sulfonamides.}
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Selected examples:

- 74a R = H (88%, 95% ee)
- 74b R = OMe (63%, 95% ee)
- 74c R = NO₂ (>95%, 93% ee)
- 74d X = S (70%, 96% ee)
- 74e X = O (74%, 95% ee)
- 74f R = iPr (61%, 98% ee)
- 74g R = Et (95%, 94% ee)
- 74h R = NO₂ (88%, 87% ee)
- 74i R = I (63%, 92% ee)
- 74j R = Ph (80%, 94% ee)
- 74k R = Me (82%, 81% ee)
- 74l R = Br (81%, 73% ee)
- 74m R³ = Ph (67%, 87% ee)
- 74n R³ = Bn (80%, 94% ee)

Plausible transition-state models
Further results on cinchona alkaloid-based catalysis and the formation of complex C–N axially chiral and sulfoxide chiral compounds were reported by Li and coworkers, wherein they proposed the utilization of sulfinamides \( \text{(80)} \) and MBH carbonates \( \text{(81)} \) to achieve this transformation via an asymmetric allylic alkylation (Scheme 19) [73]. Excellent enantioselectivity and suitability for high diastereoselectivity were obtained in this reaction. The results of stereochemical stability showed that the new atropoisomeric scaffold possessed a higher rotation barrier \( \text{(82a)} \) than the other reported axially chiral anilines’ rotation barriers \( \text{(83a–83e)} \) [16]. This demonstrated that the large steric hindrance of tert-butyl on the C–N axis was crucial for the stabilization effect.
Scheme 19. Synthesis of axially and centrally chiral sulfinamides via asymmetric allylic alkylation.

2.3. Synthetic Strategies for Acyclic C–N Axially Chiral Phosphamide via Nucleophilic Catalysis

In a similar vein, Li extended chiral amine catalysis to the atroposelective N-allylic alkylation of phosphonamides 84 and MBH carbonates 44 to obtain axially chiral phosphamides 85 with hydroquinidine catalyst Cat-7 (Scheme 20) [74]. Apart from the sterically crowded diaryl phosphoryl unit, the bulkier ortho-substituents were essential for stereochanical stability (85a–c). The ortho-halogen group performed a pivotal role in terms of excellent stereocontrol (85e), in which the group would be predisposed to generate favorable noncovalent interactions with the hydrogen atoms in Int-12. In the transition state Int-13, the methyl group triggered steric repulsion instead.

When the diphenyl phenylphosphoramidate was employed in this transformation, only moderate yield and bad enantioselectivity were obtained (85f). It might be that the weak hydrogen bond interaction was difficult to initiate. A kinetic resolution process was easily achieved by utilizing a disymmetric phosphamide 84g as the substrate. As effective catalysts (85g and 85a), these products were applied to the asymmetric catalysis. Notably, the iodine-bearing phosphoryl anilide 85a was more practical than benzoyl and sulfonyl analogs, as well as the previously reported spiro chiral diiodide entity, in the enantioselective oxidative spirolactonization of phenolic compounds 88.
Scheme 20. Asymmetric formation of axially chiral phosphamides via atroposelective N-allylic alkylation. * represents a chiral center.
2.4. Synthetic Strategies for Acyclic C–N Axially Chiral Hydrazide via Enantioselective Amination

The concept of making use of azodicarboxylates as an electrophilic amino source has been well established. This section will cover examples of the formation of acyclic C–N axially chiral hydrazides from azodicarboxylates.

2.4.1. Atropisomeric Hydrazide Synthesis via Asymmetric C–H Amination

Jørgensen et al. pioneered the innovative cinchona–alkaloid-based organocatalytic atroposelective amination of naphthamides 90 and carboxamides 91 via the asymmetric Friedel–Crafts reaction (Scheme 21) [10,11]. This process was conducted through an activated naphthoxide that generated a chiral ion pair with azodicarboxylate 91 by using a cinchona-alkaloid catalyst that subsequently transformed, so as to access naphthamides 92 with excellent stereo- and regioselectivity. Significantly, the cinchona-alkaloid catalysts, Cat-8, themselves occurred with the Friedel–Crafts reaction, leading to the formation of a new class of cinchona-alkaloids Cat-9 and Cat-10 that promoted the atroposelective amination more efficiently, generating product 92 with high enantioselectivities and enabling an approach to both enantiomers of the products. The modified cinchona-alkaloid catalyst also successfully achieved an asymmetric Michael addition. Interestingly, the axially chiral catalyst 92a was smoothly employed in the high-efficiency fluorination, giving rise to the desired product 95, with high optical purity.

![Scheme 21. Asymmetric Friedel–Crafts amination for the synthesis of non-biaryl atropisomers.](image)

Selected examples:

- 92a: 90% yield, 88% ee
- 92b: 95% yield, 80% ee
- 92c: 95% yield, 98% ee
- 92d: 98% yield, 48% ee

Cat-8b as Catalyst, b) Cat-8b as catalyst, c) Cat-10b as catalyst.

Catalyst synthesis:

- Cat-8a (DHQD) Cat-8b (DHQ)
- Cat-9a (from DHQD) Cat-10a (from DHQ)
- "Upper isomer" Cat-9b (from DHQD) Cat-10b (from DHQ)
- "Lower isomer"

Synthetic application:

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{Me}} \text{93} \\
\text{PhOS} & \xrightarrow{\text{N-SO}_{2}\text{Ph}} \text{94} \\
\text{92a} & \xrightarrow{\text{(5 mol%)}} \text{95} \\
& (95\% \text{ yield, } 88\% \text{ ee})
\end{align*}
\]

Chiral phosphoric acids (CPAs) have been widely employed in atropisomer synthesis [17,19,82,83]. In this context, Zhang and coworkers reported the CPA-catalyzed
enantioselective C–H amination of N-aryl-2-naphthylamines 96, with azodicarboxylates 97, which directly furnished a broad range of substituted C–N atropisomers 98 with excellent enantioselectivity (Scheme 22) [84]. This method could easily be applied to achieve the late-stage modification of the estrone analog. The stereo-stability study demonstrated that the intramolecular H-bonding interaction of the carbonyl group with the N-H bond was pivotal to the stereo-stability of these C–N axially chiral products. The putative reaction pathway was commenced on a simultaneous dual H-bonding activation from a self-assembly combination of CPA Cat-11, N-phenyl-2-naphthylamine 96 and azodicarboxylate 97, leading to the formation of intermediate Int-15. The nucleophilic addition of N-phenyl-2-naphthylamine to the azodicarboxylate then occurred, resulting in the generation of intermediate Int-16. An efficient central-to-axial chirality conversion was easily realized via rearomatization, followed by the generation of product 98. Notably, the π-π interaction in Int-15 and Int-16 was essential for the enantioselectivity control.

![Scheme 22. Atroposelective synthesis of non-biaryl naphthalene-1,2-diamine C–N atropisomers through direct enantioselective C–H amination.](image-url)
2.4.2. Atropisomeric Hydrazide Synthesis via an Au-Catalyzed Cycloisomerization–Amination Cascade Reaction

Another characteristic example was reported by Gong and coworkers and showcased chiral gold(I) complex catalysis for enabling the enantioselective cycloisomerization–amination of 2-(alkynyl)phenyl boronic acids 99 and azodicarboxylates 100, to furnish the atropisomeric hydrazide 101 (Scheme 23) [85]. A wide scope of substrates possessing various functional groups was tolerated to form axially chiral hydrazide derivatives in high yields and fairly good enantioselectivities. The probable reaction pathway was initiated from the coordination of Au(I) complex to the C-C triple bond of 2-(alkynyl)phenyl boronic acids 99, leading to the formation of vinyl-gold intermediate Int-17. A stereoselective attack of Int-17 to gold-activated azodicarboxylates subsequently occurred to generate the species Int-18, followed by a proton transfer to obtain the desired product 101 and release the Au(I) complex for the next catalytic cycle.

Scheme 23. Gold-catalyzed cycloisomerization–amination cascade reaction to construct heteroaryl atropisomers.

3. Enantioselective Synthesis of Cyclic C–N Axially Chiral Amides

This section covers the most pertinent examples of synthesizing acyclic C–N axially chiral amides from prochiral precursors, such as the arylmaleimides, atropisomeric urazoles, spirobenzazepinones, arylpyridones, arylquinazolinones, and the other types of atropisomeric anilides.

3.1. Synthetic Strategies for C–N Axially Chiral N-Aryl Succinimides via the Desymmetrization of N-Arylmaleimides

The dominant method to assemble cyclic C–N axially atropisomeric amides is generalized by desymmetrization of N-arylmaleimides and triazodiones, atroposelective
N-annulation, and atroposelective functionalization on preformed nonbiaryl C–N scaffolds. In this part, the catalytic asymmetric desymmetrization of N-aryl prochiral precursors requires a remote stereochemical control; undoubtedly, it is more difficult to enable excellent stereochemical controls of two chiral units via the desymmetrization process.

3.1.1. Synthetic Strategies for C–N Axially Chiral N-Aryl Succinimides via Transition-metal Catalyzed Desymmetrization of N-Arylmaleimides

The first rhodium-catalyzed desymmetrization of N-arylmaleimides was reported by Hayashi and coworkers, wherein the asymmetric 1,4-addition reaction of phenylboronic acids 29 to maleimides 102 was employed to form atroposelective N-aryl succinimides 103 with high enantioselectivity and diastereoselectivity (Scheme 24) [86]. Moreover, the desired product 103a could be smoothly transformed to the complex 104, bearing a quaternary carbon stereocenter via S_N2 substitution, leading to the access of a chiral substituted succinic acid 105. In addition, a subsequence of oxidation and Diels–Alder reaction easily followed, giving a chiral cycloadduct 107 in a high diastereomeric ratio.

Scheme 24. Rhodium-catalyzed 1,4-addition for syntheses of chiral C–N Axes from N-Arylmaleimides.

Subsequently, Feng and co-workers disclosed an elegant catalytic enantioselective Michael addition/desymmetrization reaction of N-(2-t-butylphenyl)maleimides 109 with unprotected 3-substituted-2-oxindoles 108, creating oxindole-succinimides 110 containing a
C–N axis in good yields with good to excellent diastereo- and enantio-selectivities by using a chiral N,N'-dioxide-Sc(III) complex as catalyst (Scheme 25) [87]. In this transformation, the various functionalized oxindoles 108 were well tolerated, while the scope of N-aryl prochiral precursors 109 was limited.

In 2016, Wang et al. further developed a highly efficient Ag(I)-catalyzed atroposelective desymmetrization of N-(2-t-butylphenyl)maleimide 109, through the 1,3-dipolar cycloaddition of in situ-generated azomethine ylides from readily available imino esters 111, leading to a facile generation of numerous biologically important and enantioenriched octahydropyrrolo [3,4-c]pyrrole derivatives 112 in high yields and with excellent levels of diastereo-/enantio-selectivities (Scheme 26) [88]. The further oxidative transformations were successfully achieved by utilizing DDQ as oxidant, leading to the formation of fascinating 2H-pyrrole 113a and poly-substituted pyrrole 113b, respectively.

**Scheme 25.** The chiral N,N'-dioxide-Sc(III)-catalyzed enantioselective desymmetrization of N-arylmaleimides.

---

**Selected examples:**

110a (94% yield, 96% ee, >19:1 dr)  
110b (99% yield, 97% ee, >19:1 dr)  
110c (1.37 g, 95% yield, 99% ee, >19:1 dr)  
110d (99% yield, 97% ee, >19:1 dr)  
110e (99% yield, 98% ee, >19:1 dr)
Scheme 26. The Ag-catalyzed atroposelective desymmetrization of N-arylmaleimide through 1,3-cylic cycloaddition of azomethine ylides.

Recently, Xu and coworkers developed the palladium-catalyzed atroposelective hydrosilylation of N-maleimides 114 with hydrosilanes 115, via remote control of the axial chirality strategy, giving a series of silyl succinimides 3 bearing a C–N axis in good yields, with good diastereo- and enantio-selectivities (Scheme 27) [89]. The key to success with the perfect and remote control of axial chirality lay in the influence of bulky substitutions on the aryl ring. Moreover, this process possessed high functional group compatibilities.

More recently, Li and coworkers successfully created N-aryl succinimides 119, containing an axially chiral axis and a central chirality via a single stereo-determining step, in which the rhodium-catalyzed C–H alkylation of benzamides 117 was utilized, with N-arylmaleimides 118 as the alkylating reagent (Scheme 28) [90]. This transformation featured mild reaction conditions, broad functional group tolerance, and excellent enantio- and diastereo-selectivity. The key to the installment of the distally disposed axial and central chirality lay in the judicious choice of the chiral rhodium cyclopentadienyl catalysts, which enabled researchers to control both the orientation of the olefin element and the prochiral C–N bond.
Scheme 27. The palladium-catalyzed atroposelective hydrosilylation of maleimides.

Selected examples:

\[
\begin{align*}
116a & \quad \text{(80% yield, 99% ee, dr = 92:8)} \\
116b & \quad \text{(77% yield, 94% ee, dr = 99:1)} \\
116c & \quad \text{(90% yield, 93% ee, dr = 99:1)} \\
116d & \quad \text{(82% yield, 95% ee, dr = 95:5)} \\
116e & \quad \text{(87% yield, 95% ee, dr = 92:8)} \\
116f & \quad \text{(85% yield, 92% ee, dr = 95:5)}
\end{align*}
\]

Scheme 28. Rhodium-catalyzed C–H alkylation for the syntheses of chiral C–N axes from N-acrylmaleimides.

Subsequently, Cheng, Fang and co-workers achieved the nickel-catalyzed enantioselective hydrocyanation of N-aryl 5-norbornene-endocis-2,3-dicarboximides 120, leading to the fabrication of N-aryl succinimides 121, bearing both five contiguous stereogenic carbon centers and one remote C–N axial axis, with excellent enantioselectivities (Scheme 29) [91]. Mechanism studies indicated that the rigid structure of the cyclic imide was crucial for
stereoselective control, and the existence of the imide carbonyl group was necessary for
this transformation.

Scheme 29. The nickel-catalyzed asymmetric hydrocyanative desymmetrization of maleimides
derivatives.

3.1.2. Synthetic Strategies for C–N Axially Chiral N-Aryl Succinimides via the
Organo-Catalyzed Desymmetrization of N-Arylmaleimides

To date, hindered imides, acting as prochiral precursors, are widely applied in con-
struction of C–N atropisomers. The representative works were disclosed by Bencivenni’s
group, in which a series of organocatalytic nucleophilic desymmetrization reactions of
\( \text{N-(2-tert-butylphenyl)} \)-maleimides were well developed. In this case, the hindered rotation
of bulky \( ^{1} \text{Bu} \) group on the aryl ring achieved this atropostability. Mechanistically, the \( \text{Re} \) or
\( \text{Si} \) atropodopic face of maleimide substrates could be recognized by an organocatalyst to
conduct a direct facial selective nucleophilic attack, away from the steric hindrance on the
favorable side away from the \( ^{1} \text{Bu} \) group, leading to the construction of the distal C–N axis
stereogenic and concomitantly forming stereocenters (Scheme 30) [92–96].

Scheme 30. Aminocatalytic desymmetrization of \( N \)-arylmaleimides via Michael addition. * represents
a chiral center.

The first organocatalyzed desymmetrization of \( N \)-(2-t-butylphenyl)succinimides 123 to
furnish remote C–N atropisomers 124/125 was reported by Bencivenni and coworkers via
the vinylogous Michael addition of 3-substituted cyclohexenones 122 to \( N \)-arylmaleimides 123, in 2014 (Scheme 31) [93]. In this transformation, the combination of 9-amino(9-
deoxy)epi-quinine Cat-12 and the acid, Cat-13, facilitated enantioselective desymmetrization,
leading to the access of atropisomeric succinimides with two adjacent stereocenters in the
required enantioselectivities. Regrettably, the catalyst system ineffectively controlled the
diastereoselectivities. When the cooperative catalyst system was loaded to separate the
solutions of pure 124a and 125a; after 24 h, the same 70:30 ratio of 124a and 125a in both
mixtures was found, which demonstrated that catalyst-promoted dynamic epimerization
was occurring at the exocyclic stereocenter, allowing the assignment of the ratio of epimers
124a and 125a. As shown in Int-22, the configuration of 124f might be formed by the
\( \text{Si-face-selective nucleophilic attack.} \)
Scheme 31. Aminocatalytic desymmetrization of N-arylmaleimides via a vinylogous Michael addition.

Another desymmetrization example of the organocatalytic atroposelective formal Diels–Alder reaction with 3-substituted cyclohexanones 109 and enones 126 was realized with the identical 9-amino(9-deoxy)-epi-quinine catalyst Cat-12 to access new succinimide atropisomer scaffolds 127 containing a chiral axis and three stereogenic centers (Scheme 32) [94]. Except for ortho-bromo-substituted phenyl, alkyl, or ester enones, enones bearing both electronically differentiated phenyl and thiophenyl moieties obtained endo-diastereomers under excellent control of atroposelectivities and diastereoselectivities. In the more favored transition state, the H-bond interaction with the carbonyl group of maleimide was produced. Subsequently, the tert-butyl group crucially controlling an enamine addition
from the less-crowded bottom plane led to access the desired products in 127. Interestingly, inversed configurations at the three stereogenic centers resulted when only the tert-butyl group was absent. Notably, the scaffolds ent-127 were smoothly afforded by utilizing the Cat-14 as an organocatalyst. Moreover, this cinchonidine-catalyzed desymmetrization strategy was further utilized for the Michael additions of active carbon nucleophiles, such as α-acetylcyclopentanones, α-acylbutyrolactones, 2-cyano-2-phenylacetates, and oxindoles [95,96]}

Scheme 32. The desymmetrization of N-aryl maleimides via an organocatalytic atroposelective formal Diels–Alder reaction.

The N-heterocyclic carbene (NHC)-catalyzed transformation has emerged as a powerful strategy for the construction of significant scaffolds in the field of organic synthesis [97–102]. Recently, Biju and coworkers reported an NHC-catalyzed atroposelective desymmetrization of prochiral N-aryl maleimides 123 to access C–N axially chiral compounds 129 bearing a spiral ring skeleton (Scheme 33) [103]. This elegant process underwent an intermolecular Stetter-aldol cascade of dialdehydes 128 with N-aryl maleimides 123 followed by one-pot oxidation, leading to approach the C–N axially chiral N-aryl succinimides 129 in good yields with excellent ee values. This transformation featured remote axial chirality control, broad scope, and mild conditions. The proposed mechanism commenced on the generation of a free carbene Int-24 from the chiral triazolium salt Cat-16. A nucleophilic addition of the dialdehyde 128a and the subsequent intramolecular proton transfer would smoothly afford the Breslow intermediate Int-26. The Re-face nucleophile addition of species Int-26 to the electron-poor double bond of the maleimide 123a generated the enolate intermediate Int-27, followed by a proton transfer as the enantio-determining step to obtain the amide enolate Int-28. The intermediate Int-28 could be converted to carbinol Int-29 in two routes. In the first scenario, the intramolecular aldol process took
place before the dissociation of NHC, leading to the generation of the complex \textbf{Int-29}. In the alternative pathway II, the aldol reaction occurred in the absence of NHC, and \textbf{Int-30} was subsequently formed, followed by a final proton transfer to afford the carbinol \textbf{Int-29}. The DFT computational calculations revealed that the aldol process was likely to occur after the dissociation of NHC. Ultimately, the oxidation of carbinol \textbf{Int-29} could furnish the desired product \textbf{129a} by utilizing PDC as oxidant.

\begin{center}
\textbf{Scheme 33.} NHC-Catalyzed Desymmetrization of N-Aryl Maleimides to Access the Atropisomeric N-Aryl Succinimides.
\end{center}
3.1.3. Synthetic Strategies for C–N Axially Chiral N-Aryl Succinimides through Miscellaneous Strategies

In 2009, Tan and coworkers disclosed a conjugate addition/enantioselective protonation cascade reaction of N-substituted itaconimides 130 with thiols to obtain the axially chiral N-phenyl-itaconimides by using chiral bicyclic guanidine Cat-17 as catalyst (Scheme 34) [104]. In this transformation, two atropisomers 131 and 132 were formed in high yields. These compounds possessed high energy barriers, providing a potential means for onward chirality transfer to some charming scaffolds.

![Scheme 34. Enantioselective protonation of Itaconimides with thiols to Form Atropisomeric N-Arylamides.](image)

In yet another report, Li et al. disclosed a brand-new palladium-catalyzed atroposelective construction of amides 134 with high efficiency through the carbonylative process (Scheme 35) [105]. By interacting with aryl iodides 133 and carbon monoxide (CO), a series of cyclic axially chiral amides 134 were furnished in good yields, offering excellent enantioselectivities. Notably, this reaction can be employed to synthesize the drug candidates for inhibiting NF-κB activation in HeLa cells.
3.2. Synthetic Strategies for C–N Axially Chiral Urazoles via Desymmetrization

The N-arylmaleimide analogs, 4-aryl-1,2,4-triazole-3,5-diones (ATADs), have been widely applied as part of an asymmetric desymmetrization strategy for the establishment of C–N axial chirality. Recently, the Tan group developed a desymmetrization reaction to achieve the synthesis of urazole-type molecules encompassing axial chirality through the organocatalytic asymmetric tyrosine click-like addition of triazolediones 135 (Scheme 36) [12]. The reaction was very compatible with the 2-substituted indoles 136 and 2-naphthols 137 by the utilization of the catalysis of chiral phosphoric acid (CPA) Cat-18 and bifunctional thiourea-tertiary amine catalyst Cat-19, respectively. Excellent remote axial chirality control resulted from the efficient recognition of the two reactive sites in triazoledione, and the transfer of stereochemical information into the prochiral axis, far from the site of addition, was realized.

Based on the electrophilicity and a low N=N π-bond dissociation energy of prochiral ATADs, a three-component ene reaction of substrates 135 with in situ-generated stereo-defined spirooxindoles 143 from the bisthiourea-catalyzed Diels–Alder reaction between methyleneindolinones 140 and 3-vinyl-indoles 141 was efficiently developed to approach spirooxindole–urazoles 142 in high yields with configurationally defined with the C–N axis and carbon centers (Scheme 37) [106]. In the Diels–Alder reaction, the spatial configuration of intermediates 143 was determined by the bifunctional bisthiourea catalyst, through the proposed intermediate Int-31. Moreover, the aromaticity-driven ene reaction, proceeded with substrate-controlled enantioselectivity and led to forming the chiral spirooxindole–urazole 142, in which ATAD access to the alkene from the opposite face of sterically hindered ester group and the bicyclic moiety was the favored process.
Scheme 36. The organocatalytic tyrosine click reaction forming axially chiral urazoles from indoles/phenols and triazodiones.
Very recently, the Chi group reported an NHC-catalyzed desymmetrization of a prochiral urazoles 145 for an atroposelective construction of the urazole 146 bearing a chiral C–N axis (Scheme 38) [107]. An Enantioselective Michael addition of a nitrogen atom on the N-arylurazole 145 to an ynac-derived acetylenic acylazolium species Int-32 was the pivotal
process and yielded the intermediate Int-33, thereby the C–N axially chiral \( N \)-arylurazole 146 was furnished in excellent yields and with high \( ee \) values. Furthermore, these useful scaffolds could not only be obtained in gram scales but also readily achieve the synthetic applications, such as a sequence of reduction and amidation to access the urea 148e.

Very recently, the Chi group reported an NHC-catalyzed desymmetrization of a prochiral urazoles 145 for an atroposelective construction of the urazole 146 bearing a chiral C–N axis (Scheme 38) [107]. An Enantioselective Michael addition of a nitrogen atom on the \( N \)-arylurazole 145 to an ynacetylenic acylazolium species Int-32 was the pivotal process and yielded the intermediate Int-33, thereby the C–N axially chiral \( N \)-arylurazole 146 was furnished in excellent yields and with high \( ee \) values. Furthermore, these useful scaffolds could not only be obtained in gram scales but also readily achieve the synthetic applications, such as a sequence of reduction and amidation to access the urea 148e.

Scheme 38. NHC-catalyzed atroposelective annulation and desymmetrization of urazoles.

3.3. Synthetic Strategies to Access Atropisomeric (iso-)Indolinone

Isoindolinones are significant pharmacophores, and they also extensively exist in various natural products. Nevertheless, catalytic atroposelective formation of \( N \)-arylisoindolinones bearing a C–N axial chirality remained to be unexplored until very recently. In 2017, Seidel et al. disclosed a catalytic atroposelective synthesis of isoindolinones 151 (Scheme 39) [108]. A highly efficient enantioselective biomimetic transformation between 2-acylbenzaldehydes 149 and anilines 150 gave rise to approach C–N axially chiral \( N \)-arylisoindolinones 151 containing a central chirality with the help of CPA Cat-22. The catalytic reaction occurred by the generation of the cyclic bis-hemiaminal Int-34 in the presence of CPA, followed by a sequence of dehydration and tautomerization, leading to the formation of active \( 2H \)-isoindole Int-35. A subsequent stereoselective-control tautomerization
proceeded to give the desired products 151. Moreover, the methodology was successfully utilized for creating the first generation of mariline A.

Scheme 39. A biomimetic approach to accessing atropisomeric isoindolinones via CPA catalysis.

The C–H activation of arenes to fabricate C–N axially chiral elements represents a promising approach and remains highly desired and sought after. In 2019, Wang and co-workers developed the first example of employing C–H functionalization strategy to access a variety of C–N axially chiral N-aryloxindoles 154 in high yields with excellent enantioselectivities, in which an asymmetric Satoh–Miura-type process involving dual C–H activation proceeded (Scheme 40) [109]. Mechanistically, the reaction began with oxidization to access CpRhIII from the chiral CpRhI by using AgNTf2 as the oxidant. The subsequent coordination of the oxygen atom of 152a to the RhIII catalyst promoting the first C–H bond activation occurred through a concerted metalation-deprotonation (CMD) mechanism, leading to the formation of the six-membered rhodacyclic intermediate Int-36. The subsequent insertion of aryl alkyne 153 to Int-36 occurred, resulting in the formation of the complex Int-37. Subsequently, the cleavage of the second C–H bond successfully managed to yield the species Int-38. Another equivalent of 153 inserted into the intermediate Int-38 then generated the intermediate Int-39 or Int-39′, followed by reductive elimination to furnish the product 154a and release the CpRhI species. Ultimately, to close the catalytic cycle, the real catalyst, CpRhIII, was regenerated from CpRhI with the assistance of the oxidant (Ag2O). Preliminary mechanistic studies figured out that the C–H cleavage step was not the turnover-determining step.
Scheme 40. Asymmetric Synthesis of C–N Axially Chiral N-Aryloxindoles by Enantioselective Rhodium-Catalyzed Dual C–H Activation.
3.4. Synthetic Strategies to Access Cyclic C–N Axially Chiral N-Aryl Piperidinone/Pyridones/Quinolinone/Phenanthridinone

3.4.1. Construction of Cyclic C–N Axially Chiral N-Aryl-Piperidinone via Brønsted Base Catalysis

Azacycles and oxacycles are significant scaffolds that are widely employed in numerous natural products and valuable fine chemicals. In 2010, Tan and coworkers disclosed an efficient process to access oxacycles and azacycles through a Brønsted base-catalyzed tandem alkyne [110] isomerization–Michael reaction sequence (Scheme 41) [111]. In this transformation, one of the modified alkylnyl amides 155 was employed in an intramolecular aza-Michael reaction on an in situ-generated allene (Int-40) via chiral guanidine catalysis, leading them to approach an axially chiral lactam with high enantioselectivity.

![Scheme 41. Guanidine-catalyzed tandem isomerization of the Michael reactions of alkynes.](image)

3.4.2. Construction of Cyclic C–N Axially Chiral N-Aryl-Piperidinone via Brønsted Base Catalysis

The scaffold of 2-pyridone is a significant heterocycle, one that is more commonly found in pharmaceuticals and agrochemicals [112,113]. In this context, Tanaka and coworkers realized the enantioselective synthesis of the N-aryl-2-pyridone 158, bearing a C–N chiral axis through cationic rhodium(I)–catalyzed asymmetric [2 + 2 + 2] annulation reaction of the 2-substituted phenyl isocyanate 157 with the alkyne 11 (Scheme 42) [114]. A probable mechanism for the rhodium-catalyzed atroposelective [2 + 2 + 2] cycloaddition began with the cyclometallation of isocyanate 157 and alkyne 11 with rhodium, leading to accessing the intermediate Int-41 or Int-42, depending on the structure of the substrates. The cycloaddition of less-coordinating diynes and/or more-coordinating isocyanates with rhodium showed a preference to form the intermediate Int-43. On the contrary, the reactions of more coordinating diynes and/or less coordinating isocyanates with rhodium led to the generation of species Int-42. Due to the steric effect between the aryl group of 11 and the chiral ligand, the formation of Int-41 gave rise to higher enantioselectivity than that of Int-42. Insertion of alkyne or isocyanate would obtain intermediate Int-43 and the subsequent reductive elimination of rhodium formed the atropisomeric pyridone 158.

Later on, a similar strategy for the [2 + 2 + 2] cycloaddition was also successfully achieved by the Takeuchi group, via the catalytic system of [Ir(cod)Cl]2/BNAP, in which α,ω-diyne 159, cyclized with the isocyanate 160 to give the C–N axially chiral 2-pyridone 161 in high efficiency. Both aliphatic and aromatic isocyanates were well tolerant of this transformation (Scheme 43) [115]. Moreover, aromatic isocyanates were less reactive than aliphatic isocyanates due to its electronic properties. Mechanistically, an iridium active species reacted with the diyne 159 to obtain the iridacyclopentadiene Int-44 via an oxidative cyclization. An isocyanate 160 then interacted with iridacyclopentadiene Int-44 to form Int-45, and finally transformed it to the 2-pyridone 161.
Scheme 42. The rhodium-catalyzed \([2 + 2 + 2]\) cycloaddition of alkynes with isocyanates for the synthesis of axially chiral \(N\)-aryl-2-pyridones. * represents a chiral axis.
Scheme 43. Iridium-catalyzed [2 + 2 + 2] annulation of isocyanates with α,ω-diynes.

3.4.3. Atropisomeric Quinolinone/Phenanthridinone Syntheses via Transition Metal Catalysis

In the above-mentioned strategy of synthesizing acyclic atropisomeric anilides, Kitagawa et al. also applied this Pd-catalyzed intramolecular atroposelective N-arylation to construct the cyclic atropisomeric products 163 from substituted amides 162, with high enantioselectivities (Scheme 44) [33,34]. This pioneering work provided a promising orientation by which to access atropisomeric arylheterocycles.

Scheme 44. Catalytic asymmetric N-arylation reaction for the synthesis of optically active atropisomeric quinolinone.

Shortly after, Kitagawa et al. reported another perfect example of the palladium-catalyzed enantioselective synthesis of C–N axially chiral phenanthridin-6-one derivatives 165 bearing numerous ortho-substituted phenyl groups on the nitrogen atom through the palladium-catalyzed intramolecular Buchwald–Hartwig amination from the amide 164.
The enantioselectivity of this transformation was extremely reliant on bases, solvents, and reaction temperature, as well as on the steric hindrance of ortho-substituents.

Scheme 45. Asymmetric synthesis of C–N axially chiral phenanthridin-6-one derivatives via intramolecular C–N cross-coupling.

Copper-catalyzed enantioselective coupling reactions have attracted considerable attention from the chemistry communities over the past few years. In particular, these coupling strategies have become a very powerful tool for the construction of C–C, C–N, C–O, and other carbon–hetero-atom bonds, as well as for the synthesis of heteroatom-containing ring systems \[117–121\]. Whereas there are rare reports making use of heteroatom-containing coupling systems, Gu and coworkers disclosed a novel Cu/N,N-(cyclohexane 1,2-diyl) dipicolinamide catalyst system, in which an intramolecular atroposelective Ullmann-type amination was successfully achieved for the generation of C–N atropisomers 167 from acyclic amides 166 (Scheme 46) \[122\]. This process could obtain the desired compounds 166 in high yields, with excellent enantioselectivities. Notably, selected C(sp\(^2\))–Br bond cleavage and Gram-scale operations were easily achieved, providing access to bromo-substituted products 167g and 167h with high efficiency. In addition, further transformation was readily applied to form the potential chiral phosphine ligand 170. The catalytic process commenced with the formation of complex Int-47 in the presence of NaOH, the copper catalyst Cat-23, and substance 166. A subsequent intramolecular oxidative addition of Int-47 furnished the Cu(III) intermediate Int-48 or Int-49. Alternatively, the directed oxidative addition of Cu(I) Cat-23 to the bromide 166 perhaps underwent the generation of Cu(III) species Int-50, followed by a ligand substitution from bromide to amide to form Int-48 or Int-49. Less steric repulsion was produced in Int-48 because of the picolinamide group located in the downward position. Conversely, the ortho group in the aniline moiety of Int-49 possessed a strongly steric repulsion with the upward picolinamide unit. Ultimately, the reductive elimination of Int-48 constructed a new axial C–N bond to obtain the atropisomer 167 with an R absolute configuration.
Scheme 46. Cu-catalyzed intramolecular-adjacent C–N coupling to form enantioselective atropisomeric anilides.
Very recently, Zhou and coworkers disclosed a highly efficient synthetic strategy to access C–N axially chiral phenanthridin-6-one derivatives 173 from widely available substrates 171 and 172 (Scheme 47) [123]. In this process, an exquisite palladium/chirla NBE* cooperative catalysis (Catellani reaction) was employed [124]. Logically, a sequence of C–H activation, oxidative addition, and reductive elimination proceeded to yield the key axially chiral palladium(II) species \textbf{Int-51}, followed by intramolecular amidation (\textbf{Int-52}) and the crucial axial-to-axial chirality transfer, to eventually produce C–N axially chiral phenanthridinones 173 with high fidelity. The proposed mechanistic routes were confirmed by the DFT’s computational calculations. Interestingly, further transformation studies were realized, giving access to the medium-sized lactone 174.

Scheme 47. An axial-to-axial chirality transfer strategy for the atroposelective construction of C–N axial chirality. * represents a chirality.
In yet another example from He and coworkers, the first atroposelective establishment of C–N axially chiral enamides from substituted cinnamyl carbonates and 2-quinolinols was disclosed via Ir-catalyzed asymmetric allylic substitution-isomerization, in which elegant hydrogen-bonding promoted central-to-axial chirality transfer. This was easy to achieve and provided entry to a great variety of quinolone- and pyridone-derived axially chiral enamides in high yields, with excellent enantioselectivities (Scheme 48) [125]. Mechanistically, substrates 175 and 176 underwent an Ir-catalyzed asymmetric allylic amination to obtain the preponderant products 178, followed by H-bonding interaction with 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) to form the complex. Subsequent isomerization occurred via a hydrogen bonding interaction and promoted [1,3]-H transfer, giving rise to the enantioselective formation of the desired enamides with high fidelity. Significantly, hydrogen bonding interaction was essential for reactivity and stereospecificity during central-to-axial chirality transfer, which not only played a key role in the stabilization of the deprotonation transition state and the chiral ion-pair species but also suppressed the intramolecular steric repulsion of the intermediate stage, to greatly inhibit the generation of the undesired enantiomer. Furthermore, a valuable approach was employed to synthesize the chiral epoxide derivatives through the epoxidation of axially chiral enamides.

Scheme 48. Asymmetric allylic substitution-isomerization to access axially chiral enamides via hydrogen bonding-promoted central-to-axial chirality transfer.
3.4.4. Synthetic Strategies to Access Cyclic C–N Axially Chiral N-Aryl-Quinazolinones/Thiazines

Whereas the catalytic asymmetric desymmetrization of N-arylmaleimides was widely applied to atroposelectively construct atropisomers bearing C–N axes, there are scarce reports that other prochiral axial compounds are employed as substrates. In 2016, Kitagawa and coworkers developed the palladium-catalyzed reductive enantioselective desymmetrization of quinazolinones 179 for direct access to axially chiral mebroqualone derivatives 180 (Scheme 49) [127]. The reductive efficiency of this enantioselective mono-hydrode bromination was not particularly high, due to the formation of byproducts 181 via over-reduction. Moreover, a Pd-catalyzed transformation was readily achieved to obtain the bioactive methaqualone in low ee, which was the GABA receptor agonist.

Scheme 49. Reductive Asymmetric Desymmetrization to Generate N–C Axially Chiral Mebroqualone.

By taking advantage of the de novo construction strategy, Tan and coworkers reported the first catalytic atroposelective formation of C–N axially chiral N-arylquinazolinones 186 (Scheme 50) [128]. This novel one-pot transformation was commenced on a CPA-promoted hemiaminal formation, followed by an oxidative dehydrogenation to furnish numerous aryl-quinazolinones bearing a C–N axis. When 4-methoxypentenones 185 were utilized as condensation partners, and more acidic N-triflylphosphoramide Cat-25 was employed as catalyst, a carbon–carbon bond cleavage strategy was also realized to synthesize the axially chiral arylquinazolinones. Significantly, the practicability of this methodology was
presented in the easy total atroposelective synthesis of the natural product, eupolyphagin, in high enantioselectivity.

\[
\begin{align*}
\text{Cat-24 (Ar = 9-anthryl)} & \quad \text{Cat-25 (Ar = 9-anthryl)} \\
\end{align*}
\]

Scheme 50. Brønsted acid-catalyzed enantioselective transformation of axially chiral arylquinazolinones.

Enantioselective aryl functionalization of C–N-containing prochiral synthons is a significant strategy to the atroposelective construction of an axially chiral C–N bond. However, the key to success in the elegant reaction process lies in: (1) taking full advantage of existing structural scaffolds; (2) effective creation of the structural complexity of the desired products; (3) introduction of the C–N axial chirality in high efficiency. In 2015, Miller et al. developed a pioneering investigation on the asymmetric construction of 3-arylquinazolin-4(3H)-ones 193 via an atroposelective bromination process (Scheme 51) [129,130].
Enantioselective aryl functionalization of C–N-containing prochiral synthons is a significant strategy to the atroposelective construction of an axially chiral C–N bond. However, the key to success in the elegant reaction process lies in: (1) taking full advantage of existing structural scaffolds; (2) effective creation of the structural complexity of the desired products; (3) introduction of the C–N axial chirality in high efficiency. In 2015, Miller et al. developed a pioneering investigation on the asymmetric construction of 3-arylquinazolin-4(3H)-ones via an atroposelective bromination process (Scheme 51) [129,130].

With the assistance of the tertiary amine-substituted β-turn peptide catalyst Cat-26, the tribromination of quinazolinones 192 bearing a pre-existing C–N bond gave rise to the highly atroposelective synthesis of C–N axially chiral 3-arylquinazolinones 193. Comparing peptides catalyst Cat-26 to Cat-29, it was demonstrated that Cat-26, when substituted with aminocyclopropane carboxylic acid (Acpc) on the labeled position, possessed the highest catalytic activation. Moreover, the terminal tertiary amine was essential for this enantioselective process due to the enhanced hydrogen bond acceptor ability (for details, see Int-56). Finally, further elaborations of both a dehalogenation Suzuki–Miyaura cross-coupling sequence and a regioselective Buchwald–Hartwig amination fabricated the products 193a–g to obtain the complexes 194 and 195, respectively.

Thiazines are a valuable class of heterocyclic scaffolds that have been widely utilized in pharmaceuticals and agrochemicals. Very recently, Jin et al. disclosed an asym-

Scheme 51. Peptide-catalyzed atroposelective bromination to synthesizing atropisomeric 3-arylquinazolin-4(3H)-ones.
metric cyclization for the construction of thiazine derivatives 198 containing a C–N axis (Scheme 52) [131]. The keys to achievements in this process involved both a NHC-catalyzed addition of thiourea to ynal-derived acetylenic acylazolium species and the subsequent intramolecular lactamation, finally leading to approaching atropisomeric thiazines 198 with excellent enantioselectivities. Moreover, the Lewis acid Sc(OTf)₃ was essential for the catalytic transformation in both the enhancement of the reaction yield and retention of the enantioselectivity. Finally, this optical pure compound was easy to apply to the halogena-
tion reactions, giving access to the chloro-, bromo-, and alkynyl-substituted products 199, 200, and 202.

**Scheme 52.** Enantioselective protonation of itaconimides with thiols to form atropisomeric N-arylamides.
3.5. Synthetic Strategies to Access Miscellaneous Cyclic C–N Axially Chiral N-Arylamides

Ynamides are practical and valuable synthons employed in a variety of synthetic methodologies. In 2007, Hsung and co-workers disclosed a rhodium(I)-catalyzed enantioselective \([2 + 2 + 2]\) annulation of 1,6-diynes 11 with achiral ynamides 203, yielding enantiomerically enriched N,O-biaryls 204 and 205, bearing both the C–C and C–N axis via the intermediate \(\text{Int-55}\) (Scheme 53) [132]. This transformation offered a concise and useful synthetic method to access chiral N,O-biaryls and chiral anilides.

![Scheme 53](image)

Selected examples:

- **204a**: (93% yield, 99% ee, 1/6 dr)
- **204b**: (93% yield, 18% ee, 1/5 dr)
- **204c**: (92% yield, 91% ee, 1/5 dr)

Scheme 53. Synthesis of chiral N,O-biaryls via the stereochemical control of both C–C and C–N axial chirality.

The development of an efficient methodology to access medium-sized \(N\)-heterocycles remains a challenging goal in synthetic organic chemistry, due to the unfavorable entropy effect and transannular interactions. In 2016, Enders and coworkers reported an NHC-catalyzed enantioselective, formal \([3 + 4]\) annulation of isatin-derived enals 206 with \(N\)-(ortho-chloromethyl)arylamides 207 to construct a variety of spirobenzazepinones 208 bearing a quaternary all-carbon stereocenter and a C–N axial axis, offering good yields with excellent ee values (Scheme 54) [133]. By this route, the nucleophilic addition of activated NHC Cat-31 to the enal 206 formed a mesomeric azolium homoenolate, \(\text{Int-56}\). A subsequent attack of \(\text{Int-56}\) to the in situ-generated \(aza-o\)-quinonemethide 209 from the substrate 207 led to access the key intermediate acyl azolium \(\text{Int-57}\), followed by an intramolecular cyclization to afford the desired product 208. Subsequent reduction of the amide and tosyl fragments of product 208a led to the development of the sprio-compounds 210a and 210b, with the complete retention of the enantiopurity, respectively.
4. Conclusions and Perspectives

In summary, manifold catalytic atroposelective methodologies have been successfully achieved for the construction of atropisomeric C–N skeletons possessing diverse structures, such as acyclic/cyclic C–N axially chiral amides. Although rapid developments have been seen in this field, the methods for the enantioselective synthesis of C–N axially chirality are deficient, compared to the well-established strategies for biaryl atropisomers. Future efforts and advances need to be focused on the establishment of more robust, useful, general, concise, and efficient original catalytic asymmetric systems to synthesize these elegant entities. Furthermore, the merging of enabling and advanced techniques, such as flow chemistry, photochemistry, mechanochemistry, and electrochemistry, with the
atroposelective formation of C–N atropisomers would be highly desired and sought after. Last but not least, the employment of these optically pure axially chiral C–N units as novel types of chiral ligands, catalysts, and pharmaceuticals should be extensively conducted.

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