Catalytic enantioselective synthesis of C–N atropisomeric heterobiaryls

Catalytic Enantioselective Synthesis of C-N Atropisomeric Heterobiaryls

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Abstract Molecules containing an atropisomeric C-N biaryl axis are gaining increasing attention in catalytic and medicinal chemistry. Despite this rising interest, relatively few approaches towards their catalytic enantioselective synthesis have been reported. Here we review these approaches, with a focus on the mechanism of asymmetric induction. Some common themes emerge: Bronsted acid catalysed cyclo-condensation and palladium-catalysed ring-closure are the most common and successful approaches. Meanwhile, the more direct but challenging axial C-N bond formation strategy remains in its infancy, with just two reports to date. We hope this review will inform and inspire other researchers to develop new creative approaches to this important chemical motif.

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Key words enantioselectivity, atropisomerism, asymmetric catalysis, axial chirality, heterocycles, heterobiaryls

1. Introduction

Isomerism arising from restricted rotation about a single bond – atropisomerism – was first proposed by Christie and Kenner for hindered 2,2',6,6'-tetrasubstituted biphenyl derivatives in 1922.1 Just nine years later the first example of a C-N heterobiaryl atropisomer was reported by Adams.2 In the years since, C-C atropoisomers have become central to synthetic organic chemistry, in particular due to the ubiquity of the 1,1'-binaphthyl motif at the core of numerous chiral ligands and organocatalysts. By contrast, C-N atropoisomerism has remained relatively overlooked. However, the importance of these molecules is increasingly emerging across chemistry and biology. New organocatalysts3 and ligands for metal-catalysed cross-coupling containing C-N chiral axes have recently been reported, hinting at the general utility of such molecules for asymmetric catalysis applications (Figure 1). The medical importance of C-N atropoisomers3 was recently highlighted by the FDA approval of Amgen’s first-in-class KRAS inhibitor Sotorasib,4 which contains an atropisomeric N-arylquinazolin-2-one linkage.

The heteroaromatic structure lends itself to many synthetic strategies not accessible to homobiaryl C-C atropoisomers, such as metal-catalysed C-N bond formation and organocatalytic condensation reactions. In the past 10 years there has been an explosion in catalytic enantioselective approaches towards C-N heterobiaryl atropoisomers. This review attempts to summarise and categorise these developments, with reactions are grouped by the strategic bond-forming approach taken to control axial stereochemistry. We have drawn particular attention to substrate-catalyst interactions (where such details have been provided by authors), in the hope that the reader may gain a greater understanding of the origins of enantiocontrol in the formation of C-N heterobiaryl atropoisomers, and be inspired to make new creative developments in this field. Readers are encouraged to consult the primary texts for further details of all mechanistic and stereochemical proposals provided and the evidence underpinning them. This review does not seek to discuss the numerous elegant approaches to non-heterobiaryl C-N
N atropisomers (where one or both termini of the axial C-N bond are not aromatic rings) and readers are referred to several excellent reviews for discussion of those aspects.7

2. Cyclo-Condensation

The classical approach to aza-heterocycle synthesis is through condensation chemistry (e.g. Paal-Knorr, Friedlander, Skraup etc.) and the majority of these processes are acid-catalysed. It is unsurprising therefore – with the advent of powerful chiral acidic organocatalysts – that this condensation approach has been brought to bear on the challenge of enantioselective synthesis of C-N atropoisomers. Bin Tan has been prolific in the use of chiral phosphoric acids (CPAs) for the enantioselective synthesis of heterobiaryls.8 In 2017 Tan et al. employed CPA catalysis when synthesising arylpyrroles via an enantioselective Paal-Knorr reaction (Scheme 1).8 1,4-Diketones (1) and 2-substituted anilines (2) successfully underwent dehydrative cyclisation in the presence of SPINOL-derived CPA 3 and Fe(OTf)₃ in CCl₄/cyclohexane at 0 °C. They reported excellent yields (up to 95%) and enantioselectivities (up to 98% ee) for a range of axially chiral arylpyrroles (4). An interesting solvent effect was observed in which the opposite arylpyrrole enantiomer could be obtained, albeit at lower ee values, by changing one solvent from the mixture of cyclohexane and non-polar CCl₄ (96% ee, (R)₄-4) to cyclohexane and polar protic EtOH (-75% ee, (S)₄-4), though the reasons for this stereodivergence are not further expounded. The isolation of intermediate 5 led the authors to propose the mechanism given, though it is not stated whether the reaction proceeds through centre-to-axis chirality transfer from the chiral semi-aminal, or by atroposelective elimination of water.

Lin et al. reported the synthesis of axially chiral N-aryl indoles through a three-component coupling approach (Scheme 2).4b When ortho-substituted anilines (8), 2,3-diketoester hydrates (6) and 1,3-cyclohexanediones (7) were combined in the presence of a SPINOL-type chiral phosphoric acid (9), chiral indole products (10) were obtained in up to 93% yield and 97% ee. The authors’ mechanistic proposal closely resembles that of Tan (Scheme 1), though specific substrate-catalyst interactions leading to the observed atropisomer are not discussed.

More recently benzimidazoles have been synthesised via acid-catalysed cyclo-condensation (Scheme 3). Fu et al. synthesised axially chiral C-N atropoisomeric benzimidazoles in excellent enantioselectivity (up to 98% ee) and in high yields (up to 89%) from ary 1,2-diamines (11) and 1,3-diketones or β-ketoesters (12) in the presence of CPA (R₉)-TRIP (13).8 The reaction is suggested to proceed via CPA-controlled aminal formation, followed by a retro-Mannich reaction to form the benzimidazole, similar to that previously reported by Tan19 (Scheme 1). The Brønsted acid is proposed to act in a bifunctional manner, through a dual hydrogen-bonded transition state with the presumed ortho-amino imine intermediate, though the precise interactions of the chiral catalyst backbone with the substrate are not further delineated.

Zhong, Tan et al. have also reported the synthesis of benzimidazoles through a catalyst-controlled Friedel-Crafts amination (Scheme 4).4c Nitrosobenzenes lie at the heart of this strategy, serving both as an electrophilic nitrogen source and oxidant. When a series of N-naphthylglycine and N-naphthylbenzylamine derivatives (15) were reacted with ortho-substituted nitrosobenzenes (16) in the presence of a chiral SPINOL-type CPA (17 or 18), N-arylbenzimidazole products (19,20) were obtained in up to 97% yield and 84% yield. An interesting stereochimical divergence was observed, where (R₉)-configured CPAs afforded the (R) products in the naphthylglycine series, and the (S) products for the naphthylbenzylamine derivatives, the latter requiring a copper(II)-based exogenous oxidant. This divergence is
attributed to different non-covalent substrate-catalyst interactions. The mechanism proceeds through initial acid-catalysed Friedel-Crafts reaction of the naphthalene with the nitrosoarene. The resulting ortho-dimine undergoes tautomerization to an amino-imine, followed by enanti-determining aminal formation, then by oxidation to afford the benzimidazole, with the nitrosoarene evidently a competent oxidant in this step for the glycine-derived series.

Miller et al. have also reported the synthesis of a benzimidazole, 22, using peptide-based organocatalysts (Scheme 5).11 Cyclo-condensation of phenylenediamine derivative 21 onto an electro-deficient trifluoroacetyl group afforded the axially chiral benzimidazole 22 in 92% ee and 99% conversion in the presence of (R)-TRIP (13), while similar results (88% ee, 99% conversion) were obtained when peptide-based phosphoric acid 23 was used. Use of alternative peptide catalysts 24 and 25 showed that both product enantiomers were accessible by inversion of the pThr phosphoric acid-containing amino acid residue alone, demonstrating the versatility of a peptide-based organocatalytic platform. In collaboration with Toste and Sigman, the same laboratory expanded the substrate scope, and further explored the factors influencing enantiocontrol in peptide-based versus BINOL-derived CPAs using DFT and multi-linear regression analysis.22 While the BINOL-derived CPAs largely operate under steric control due to clashes with the large 3,3'-aryl groups on the catalyst, the more flexible peptide-based acid was more accommodating of steric bulk in the substrate, highlighting the importance of greater catalyst scaffold diversity in new catalytic applications.

The sole example of catalytic enantioselective cyclo-condensation to form a C-N atropisomer six-membered nitrogen-containing heterocycle was reported by Tan et al. in 2017 (Scheme 6).10 By combining a series of N-aryl anthranilamides (26) and aromatic and cyclic aldehydes in the presence of a CPA and DDQ oxidant, the corresponding arylquinazolinones (27/28) were obtained in up to 98% yield and 97% ee. The Brønsted acid is presumed to initially catalyse formation of an imine, then to control stereochemistry in the cyclisation to afford an aminal intermediate, which is oxidized in situ to form the target molecule. Though clearly a powerful approach, the reaction did not proceed satisfactorily for linear aliphatic aldehydes. An alternative C-C bond cleavage approach was devised, where 4-methoxyphenylamine replaced the aldehyde reactant and undergoes acid-mediated formation of an enamino, followed by acid-catalysed aminal formation. In this case, a retro-Mannich-type reaction liberates acetone and generates the quinazolinone without the need for an exogenous oxidant. A stronger acid was required, with triflylphosphoramide 30 generating products in up to 97% yield and 96% ee. Control experiments demonstrated that the aminal intermediate undergoes fast C-N bond rotation and is functionally non-atropisomic. The enantipurity of the product is therefore suggested to be a consequence of centre-to-axis chirality transfer from the aminal stereogenic centre.

Scheme 4 Zhong and Tan’s nitrosoarene linchpin approach to benzimidazoles. R = cyclopentanecarboxylate.

Scheme 5 Miller’s peptide-based CPA approach to benzimidazole 22 and Sigman’s mechanistic proposal.

Scheme 6 Tan’s Brønsted acid-catalysed cyclo-condensation approach to arylquinazolinones.
The cyclo-condensation route to C-N atropisomers has seen an explosion of interest in recent years. This has largely been enabled by the development of powerful chiral Brønsted acids, including the peptide-based catalysts introduced by Miller, and by creative strategies such as the use of nitrosobenzenes and the retro-Mannich method used by both Tan and Fu. Through careful study of classical and contemporary condensation approaches to aromatic heterocycles, it is likely that many more enantioselective variants will be uncovered in the years to come.

3. Proximal C-N Bond Formation

While the above approach was generally to take classical heterocycle syntheses and render them enantioselective, an alternative strategy is to use the powerful metal-catalysed C-N cross-coupling reactions developed in recent years in the presence of chiral ligands. Steric hindrance hampers atroposelective direct intermolecular axial cross-couplings, but metal catalysed cyclisation of the pro-axial nitrogen onto a tethered coupling partner is an effective method to generate axial chirality under the directing effect of chiral ligands.

Osamu Kitagawa has been prolific in this approach.74 In 2006 Kitagawa, Taguchi et al. reported a series of inter- and intramolecular N-arylations under Buchwald–Hartwig conditions in the presence of chiral phosphine ligands, with (S,S)-BINAP proving most effective for the cyclisations, yielding products (32) in up to 95% yield and 98% ee (Scheme 7), with the reaction proceeding in the highest yield with aryl iodide coupling partners (31, X=I).15 While the products were non-biaryl, subsequent studies demonstrated that they could be efficiently oxidized to the corresponding arenes (quinolin-2-ones and quinazolin-2-ones), with no loss of stereochemical integrity.14 In fact, the oxidized products had significantly higher rotational barriers than the non-aromatic precursors (increases of 6.7-10.4 kcal mol⁻¹), a fact attributed to the ability of the non-aromatic heterocycles to twist in the enantiomerization transition state, lowering their overall strain energy.

In the same year, Kitagawa et al. reported the first atroposelective synthesis of quinolin-4-ones using palladium(0) catalysis (Scheme 8).15 Several ortho-substituted anilines (35) were reacted with a series of 2-bromophenyl arylethynyl ketones (34), producing the corresponding quinolin-4-ones (37) in up to 72% ee and 51% yield under the optimized conditions in the presence of monodentate phosphine ligand (R,R)-MOP (36). The authors note a curious “self-disproportionation of enantiomers” (SDE) effect under achiral chromatography conditions. When 72% ee sample was purified by medium-pressure liquid chromatography on silica gel, the less polar, faster-eluting material was found to be enantio-enriched (up to >99% ee), while the later fractions were enanto-depleted (54% ee). This provides a method to obtain highly enantiopure material even in the absence of a highly enantioselective catalytic method, and is further noted in subsequent work from the same laboratory.16

The reaction proceeds via an initial conjugate addition generating an enaminone intermediate, which undergoes palladium-catalysed ring-closure to afford the quinolin-4-one products.

Knipe et al. used a similar strategy to afford N-arylquinolin-4-ones en-route to cationic chiral N-arylquinolinium salts (Scheme 9).17 Using as substrates the enaminones (38) presumed as intermediates in the Kitagawa study above, they obtained a series of N-(2-tert-butylphenyl) and N-naphthyl quinolin-4-ones (39) under optimized conditions using palladium(ii) acetate and (R,R)-BINAP in high yields (up to 99%) and variable enantioselectivity (up to 82% ee). A curious enantidivergence was observed during optimization: use of (R,R)-BINAP led to opposite product enantiomers depending on the palladium source. This was attributed to the in-situ reduction of palladium(ii) sources by (R,R)-BINAP affording (R,R)-BINAP(0), a competent ligand that evidently favours the opposite product enantiomer to the parent diphosphine. Organometallic addition into the quinolin-4-ones (39) followed by re-aromatization afforded N-arylquinolinium salts (40) in up to 89% yield and 93% ee, with up to 100% retention of chirality of the parent quinolinone. The quinolinium salts were shown to exhibit solvatochromatic behaviour, and to possess rotational barriers of 40-51 kcal mol⁻¹.

**Scheme 7** Kitagawa’s atroposelective cyclisation-oxidation approach towards C-N heterobiaryl. Note that the oxidation procedure was conducted on the opposite product enantiomer (formed using (R,R)-BINAP) from that obtained in the initial cyclisation report.15

**Scheme 8** Kitagawa’s synthesis of N-arylquinolin-4-ones using a palladium-catalysed asymmetric ring-closure.
Kitagawa further extended the repertoire of palladium-catalysed atroposelective ring-closure to the synthesis of phenanthridine-6-ones (Scheme 10).\(^{16a}\) Cyclisation of bromo-anilides 41 with palladium(II) acetate in the presence of a chiral bidentate phosphine ligand 43 gave the products in up to 95% yield and 77% ee, with the products displaying the same SDE effect observed previously for quinolin-4-ones.\(^{15}\)

Most intramolecular C-N couplings to form lactam-type biaryl atropisomers operate through palladium-catalysed Buchwald-Hartwig-type reactivity modes, yet some exceptions exist. In 2019, Gu et al. reported the first such synthesis using copper-catalysed Ullmann-type coupling (Scheme 11).\(^{18}\) This approach significantly improved upon the substrate scope and enantioselectivity achieved above under palladium catalysis, suggesting that Ullmann-type coupling may be an under-utilized methodology in atroposelective C-N axis formation. The chiral copper(I) complex formed in situ from copper(I) thiophene-2-carboxylate and a \(C_2\)-symmetrical diaminoxyclohexane-derived ligand 46 serves as an effective catalyst in the ring-closure, affording the products (45) in consistently high yields (up to 99%) and ee (up to 99%). The substrate preference for formation of the phenanthridine-6-one product means additional C-Br bonds can remain unreacted under the optimized conditions, allowing subsequent derivatization via cross-coupling. The authors propose a Cu(I)/Cu(III) catalytic mechanism where steric clashing between the ortho-substituent on the N-aryl ring and the ligand picolinamide favours the observed diastereoisomer.

Structurally similar products have also been generated through a palladium-catalysed domino reaction recently reported by Hong, Zhou et al. (Scheme 12).\(^{19}\) The Catellani reaction between aryl iodides (47) and 2,6-disubstituted aryl bromides (48) catalysed by Pd(OAc)\(_2\) tri(2-furyl)phosphine (TFP), enantiopure norborene 49 and potassium carbonate afforded phenanthridine-6-one derivatives (50) in good to excellent yields (up to 98%) and excellent ee (up to 98%). DFT revealed that the reaction occurs via an axis-to-axis chirality transfer mechanism: the initial Catellani-type reaction proceeds through syn-carbometallation anti-to the ethylene bridge, followed by C-C biaryl axis formation with stereochemistry controlled by the norborne. This undergoes a subsequent Buchwald-Hartwig-type ring-closure under substrate control, where the existing C-C axis controls the C-N axis stereochemistry. The methodology is further extended to the formation of doubly atropisomeric product using diiodo-biphenyl and -naphthalene substrates.

Thus far reactions generating amide-type aromatic heterocycles (quinolinones, phenanthridinones etc.) have been discussed. However, metal-catalysed C-N coupling reactions have also provided access to other heterocyclic motifs. In 2010 Kitagawa et al. reported the synthesis of C-N atropisomerichydroxyindoles via palladium-catalysed intramolecular alkyne hydroamination (Scheme 13).\(^{20}\) Further substrate scope and mechanistic aspects were reported in a subsequent full paper in 2016.\(^{21}\) Cyclisation of the alkylnilamine (51) proceeds to form the indole product (52) with up to 99% product yield and 83% ee. A strong dependence on the substrate electronics was observed and quantified by Hammett plot, with electron-rich amines at the R1 position giving
poor enantioselectivities (p-OMe: 18% ee) while electron-poor arenes yielded much better selectivity (p-NO2: 79% ee). This observation led the authors to propose a mechanism with the enantio-determining intermediate existing on a continuum between an η1-allyne-palladium(II) complex and an allene σ-complex, with the former favoured by electron-poor and the latter by electron-rich substrates. The η1-allyne complex is said to exhibit "dynamic axial chirality" (since rotation about the alkyne is possible), allowing the ligand to efficiently transfer chirality to the substrate, whilst the allenyl complex is configurationally locked, preventing the relaying of chiral information from the ligand.

Quinine-derived squaramide catalyst 58 induces the substrate (56) to undergo a cascade bromination-cyclisation reaction generating products (57) containing C-N and C-N chiral axes, as well as a stereodefined tertiary amine and a helically chiral saddle-shaped 7-membered ring, proceeding in up to 92% yield and 97% ee and in >20:1 d.r. The authors’ mechanistic proposal is that catalyst-controlled bromination generates a chiral bromovinylidine ortho-quinone methide intermediate. The stereogenic C-N axis is then forged in the subsequent intramolecular electrophilic aromatic substitution on the prochiral carbazole under substrate control, which is suggested to be the overall rate-determining step. Where the carbazole was unsymmetrical a kinetic resolution was possible, or the reaction could be run to completion with a diastereoselectivity of 1:3.19:1. Preliminary data suggested that these azepines have potential applications as selective fluorescent sensors for RuIII.

Axially chiral C-N benzimidazoles have also been formed by proximal C-N cross coupling under palladium catalysis. In 2021 Lu, Liu et al. reported the asymmetric ring-closing Buchwald-Hartwig reaction of a series of amidines (Scheme 14). Treatment of the amidines (54) with palladium(II) acetate and chiral bidentate ligand (S)-BINAP gave the benzimidazole products (55) in up to 98% yield and 93% ee. The method was further extended to the synthesis of dibenzimidazoles from the corresponding diamidines formed from 1,4-diaminobenzene derivatives, which seemingly benefited from Hovey amplification giving products up to 99% ee. The mechanism is presumed to proceed through initial oxidative addition, followed by amidine deprotonation to form the diazaallyl anion, ligand exchange and reductive elimination. The authors propose a transition state model wherein the diazaallyl palladacycle is positioned in an unhindered quadrant, and the aniline ortho substituent is positioned away from the bulk of the ligand structure.

This final example notwithstanding, the synthesis of C-N atropisomers by intramolecular C-N bond formation is dominated by palladium-catalysed approaches. Despite this there remains little understanding of the catalyst-substrate interactions leading to the observed product atropisomers, and reaction discovery is largely a matter of laborious ligand screening. We hope that physical organic and quantum chemical approaches may be brought to bear on these systems to accelerate reaction development and inspire new ligand and catalyst systems.

In some substrates, restricted rotation may exist along a C-N axis where a symmetrical substitution pattern means the molecule is achiral. In such instances, desymmetrisation provides a viable route to enantio-enriched atropisomeric compounds. In 2015 Kamikawa, Takahashi and Ogasawara reported an interesting double desymmetrisation reaction involving (π-arene)chromium complex (59) through Mo-catalysed asymmetric ring-closing metathesis (Scheme 16). A transition state was proposed where after initial metathesis with the less hindered terminal alkene, intramolecular coordination of the metal to the pro-(R,R) alkene favours cyclisation to the observed planar and axial stereoisomer (60). Since the starting material aryl-chromium bond is
exclusively anti- relative to the indolyl group and these remain unchanged, the product is obtained as a single diastereoisomer. Decomplexation of the chromium complexes was achieved in 93-97% yield and with complete retention of stereochemistry, upon exposure to sunlight under air in the presence of elemental sulfur.

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Kitagawa used an asymmetric reductive desymmetrization approach to access axially chiral quinazolinones (Scheme 17).\textsuperscript{16b} Symmetrical N-(2,6-dibromophenyl)-quinazolin-4-ones (62) were treated with sodium borohydride in the presence of Pd(OAc)\textsubscript{2} and chiral phosphine ligand 43, affording a mixture of single (63) and double-reduced (achiral) products. The reaction requires a balance to be struck between yield and enantioselectivity: for example, when a substrate (R\textsubscript{1}=Me; R\textsubscript{2}=H) was treated with 1.5 equivalents of sodium borohydride the monobrominated product was obtained in 76% yield and 56% ee with just 7% over-reduction; with 2.0 equivalents of reductant the same product was obtained in just 48% yield, but with an increased 73% ee, and 27% over-reduced product. The monobrominated products could be kinetically resolved, albeit to just 38% ee. The products displayed the self-disproportionation of enantiomers effect discussed previously (Scheme 8). Lastly the monobrominated product was converted to methaqualone (64) through Suzuki cross-coupling, with a 52% loss in ee suggesting a lower barrier to rotation in the intermediate Pd(II) complex. While not discussed by the authors, this may indicate that a dynamic kinetic resolution could be achieved in this system if chiral ligands were present on the metal.

C-H functionalisation remote to the C-N chiral axis can also allow access to enantioenriched material, either through desymmetrization or kinetic resolution. Wang, Tan et al. recently disclosed a Brønsted acid-catalysed electrophilic aromatic substitution strategy (Scheme 18):\textsuperscript{4d} treatment of 2,5-disubstituted N-aryl pyrroles (65) with diethyl ketomalonate (66) in the presence of (S)-H\textsubscript{8}-TRIP (68) allowed the desymmetrization of prochiral substrates in up to 99% yield and 97% ee. Where the existing ortho-substituents were non-identical (69) a kinetic resolution gave s-factors of up to 69. A mechanism was proposed involving bifurcated hydrogen bonding between the catalyst and electrophile, though the precise reason why this favours reaction with the transient (R)-atropisomer of the starting material is not discussed. The utility of these compounds was demonstrated: ortho-diphenylphosphino N-aryl pyrrole (R\textsubscript{2}= PPh\textsubscript{2}) was a competent ligand for Pd-catalysed asymmetric allylic substitution, giving products in up to 97% ee.

Desymmetrization can be an elegant approach to C-N atropisomers as shown above, but does place rather stringent requirements on the products that may be obtained since they necessarily must derive from a symmetrical and suitably reactive precursor.
5. ortho-C-H Functionalisation

The rapid development of C-H functionalisation strategies in recent years has provided an alternative strategy towards C-N atropisomeric compounds. With the axis already in place, replacement of an adjacent ortho-C-H bond adjacent with a carbon or heteroatom generally leads to an increase in the rotational barrier. This approach has the potential to be extremely broad due to the ubiquity of such bonds. Miller et al. pioneered this strategy for quinazolines,25 Treatment of the substrate (71) with NBS in the presence of peptide-organocatalyst 73 afforded tribrominated products (72) in up to 98% ee and 93% yield (Scheme 19). The catalyst is proposed to adopt a type-II’-β-turn conformation through X-ray studies. By considering both the catalyst X-ray structure and solution-phase NOESY experiments, a transition state was proposed invoking dual substrate-catalyst hydrogen bond formation. After the initial bromination the chiral axis is sterically locked, and the subsequent two brominations proceed as expected. Subsequently Miller, Sigman et al. attempted to parametrize and modify the peptide catalyst in an effort to enhance selectivity.26 This study highlighted the importance of the cyclopropane-containing amino acid, and concluded that although the type-II’-β-turn is likely important, the true mechanism involves an ensemble of conformers acting simultaneously.

Unsurprisingly, palladium-catalysed C-H functionalisation has also been applied to C-N atropisomeric axes. In 2019 two groups independently reported the atroposelective C-H functionalisation of N-aryl-2-formyl indoles and pyrroles, with the aldehyde in both cases providing a handle to incorporate a transient imine-directed group. Hong, Shi et al. explored a series of pentatomic heteroaromatic biaryl where the aldehyde handle enabled enantioselective C-H alkenylation (Scheme 20).27 When the prochiral aldehyde substrate (74) was treated with silyl-protected bromoacetylene (75), catalytic Pd(OAc)2 and stoichiometric AgTFA, and in the presence of chiral transient director L-tert-leucine the pyrrole products (76) were obtained in up to 97% yield and >99% ee. The authors were unable to form axially chiral indoles through the same method, with the aldehyde positioned on the benzenoid ring.

Zhang, Xie et al. circumvented this problem in their Pd-catalysed oxidative Heck reaction by instead positioning the aldehyde on the indole 2-position (Scheme 21).28 When N-aryl-2-formylindoles (77) were treated with butyl acrylate (78) in the presence of Pd(OAc)2, L-valine and benzoquinone under air, the corresponding oxidative Heck products (79) were formed in good yields and up to 99% ee. Where the benzenoid ring in the starting material bears an ortho group the starting materials themselves are axially chiral. By replacing the benzoquinone/air oxidant with AgTFA and increasing the temperature to 60 °C, these compounds underwent kinetic resolution with s-factors up to 459.

Scheme 20 Hong, Shi et al.’s transient imine-directed C-H alkenylation.

Scheme 21 Zhang, Xie et al.’s transient imine-directed C-H alkenylation.

Given that both studies above involved similar 2-formyl heterocycles and used L-amino acid directing groups, it is unsurprising that the stereochemical outcome in both cases is the same, though neither group proposes a transition state model.

In 2021, Kwon et al. disclosed the enantioselective synthesis of N-aryl indoles via a chiral acid-catalysed Pictet-Spengler reaction (Scheme 22).29 When the substrate (80) is treated with paraformaldehyde in the presence of chiral phosphoric acid 83, the cyclisation onto the 2-position proceeds smoothly at 2 °C. Electron-deficient aldehydes (81) also reacted, but required an increase in temperature to 80 °C. Electron-neutral and electron-rich aryl aldehydes failed to react. Cyclisation onto the 2-position increases the rotational barrier sufficiently that the products can be obtained in high yield and enantiopurity. R2 was typically a hydrogen bond donor such as NHBn, and the importance of this is highlighted in the putative transition state, where this group participates in a hydrogen bond with the catalyst that reduces conformational flexibility in the transition state. Cyclisation is proposed to proceed via a chair-like transition state to afford the observed major (S)-stereoisomer. However, assuming the transient imine intermediate is (E)-configured, this does not fully account for the observed diastereoochemical outcome in the reaction involving electron-deficient aryl aldehydes.
Houk, Meggers et al. disclosed a related strategy using Lewis acid activation (Scheme 23).\(^{30}\) When N-aryl-pyroles (88) were treated with N-acryloyl pyrazoles (85) in the presence of d- configured chiral Lewis acid 87, the axially chiral products (86) were obtained in up to >99.5% ee and high yields. Quantum chemical calculations revealed that the (R)-stereochmical outcome is controlled by a steric clash between R\(^2\) and the tert-butyl substituent on the catalyst. The pyrazoles were necessary to achieve the required bidentate binding to the Lewis acid, but were easily removed by reduction to afford the corresponding aldehyde or alcohol, or by substitution to form ester, amide and cyclic ketone derivatives.

Research into C-H functionalisation in the context of C-N chiral axis remains in its infancy. However, given the growth of C-H functionalisation across synthetic chemistry in recent years, it is likely that this strategy will continue to develop. It is well-suited to this application, since it is almost inevitable that ortho-C-H functionalisation will lead to an increase in the rotational barrier around a chiral axis providing a window for dynamic kinetic resolution approaches.

6. Cycloaddition

Cycloaddition is an appealing strategy for the formation of C-N atropisomers, allowing the chiral axis to be forged in a convergent manner from simple, achiral precursors. This approach was first explored by Tanaka et al. in 2008 (Scheme 24).\(^{31}\) They reported the enantioselective synthesis of N-aryl-2-pyridones (90) via the rhodium-catalysed formal [2+2+2]-cycloaddition of ortho-substituted aryl isocyanates (89) with a series of symmetrical diynes (88), in the presence of a achiral (R)-BINAP ligand. Products were obtained in variable yield and enantiopurity. This variability was rationalized on the basis of two potential reaction pathways, with more coordinating isocyanates and less coordinating diynes expected to go via the more stereoselective pathway A, and vice-versa for pathway B. The change in the order-of-events renders the presumed stereodetermining step to be either intra- or inter-molecular, with the former proposed to give higher enantioselectivities. Though the absolute stereochemistry of products was not determined, we suggest products are (R)- by retrospective comparison of optical rotation data (R=OMe, Z=C(CO2Me)) with reference 32.

In 2011 Takeuchi et al. conducted a wide-ranging study into iridium-catalysed [2+2+2]-cycloadditions.\(^{32}\) They reported an improvement upon the stereoselectivity of the rhodium-catalysed reaction by using an iridium-based catalyst (Scheme 25). Furthermore, the use of reduced ligand (R)-H\(_3\)BINAP was found to be superior for some substrates, such as methoxy product 92-OMe.

In the rhodium-catalysed study by Tanaka et al. the cationic metal possesses an achiral tetrafluoroborate counter-ion. Aubert, Fensterbank, Ollivier et al. have explored whether a chiral counter-ion – both in the presence and absence of a chiral ligand on rhodium – can influence the absolute stereochemistry of the pyridone products. In 2013 they reported that pre-treatment of an achiral rhodium complex with an (S)-TRIP-derived chiral silver(I) phosphate afforded a catalytically-active ion pair which in many cases out-performed the chiral ligand approach of Tanaka (Scheme 26, top).\(^{33}\) The Z-pyridone products were
obtained in up to 88% yield and 82% ee. In an extension of this study, the case where both the ligand and counter-ion are homochiral was explored (Scheme 26, bottom).\textsuperscript{34} After re-optimizing the reaction with respect to the chiral ligand, the authors reported evidence of double-stereodifferentiation, where in some cases a matched combination of ligand ((R)\textsuperscript{-}DM-BINAP) and counter-ion ((S)\textsuperscript{-}TRIP-derived phosphate 93) allows product formation in higher ee than in the presence of either chiral species alone. The same substrate discussed previously (92-OMe) was formed in 88% yield and 92% ee under the optimized conditions, but when the chiral ligand alone was present (counter-ion: BF\textsubscript{4}\textsuperscript{-}) the ee dropped to 80%, and when the chiral counter-ion alone was present (ligand: dpbb) the ee further fell to 77%. The ligand appears to dominate stereocentre to a greater extent than the counter-ion: changing to (S)\textsuperscript{-}DM-BINAP led to an inversion of the product absolute stereochemistry, albeit with a reduction in ee to 79%.

\begin{center}
\textbf{Scheme 26} Aubert, Fensterbank and Olliver’s single and double-stereodifferentiation strategy using chiral phosphate counter-ions in the synthesis of Z-pyridones via [2+2+2]-cycloaddition.
\end{center}

Rhodium catalysis has also been used in formal [3+2]-cycloaddition to generate axially chiral N-aryl anilines by Wang, Lan, Li et al. (Scheme 27).\textsuperscript{35} When N-aryl isoquinoline derivatives (94) were subjected to alkynes (95) in the presence of a chiral rhodium-based catalyst and a silver oxidant, the corresponding N-isoquinolinyl indole products (96) were obtained in high enantioselectivity (up to 96%) and good yields. Where R\textsuperscript{1} ≠ R\textsuperscript{2} regioisomeric ratios of up to 20:1 were obtained. Kinetic isotope effects indicate that C-H bond breaking is involved in the turnover-limiting step, and based on this and DFT studies the authors tentatively propose a mechanism involving enantiodetermining reductive elimination of a rhodium(III) species. DFT indicated the atropisomeric outcome of this reductive elimination is controlled by repulsion between the N-phenyl group and the methoxy substituents on the binaphthyl ligand.

\begin{center}
\textbf{Scheme 27} Wang, Lan and Li’s [3+2]-cycloaddition approach to axially chiral N-aryl indoles.
\end{center}

Cycloaddition approaches to C-N biaryl atropoisomers are not the sole preserve of group 9 transition metal-catalysed reactions. In 2021 Jin et al. reported the first such synthesis of N-arylthiazines catalysed by a chiral N-heterocyclic carbene (NHC) organocatalyst (Scheme 28).\textsuperscript{36} Treatment of a series of ynals (98) with N-acylioureas (99) in the presence of NHC 101, DMAP, quinone 102 and Sc(OTf)\textsubscript{3}, additive led to a formal [3+3] cycloaddition, with furan the optimal (albeit unusual) solvent. The heterobiaryl N-aryl thiazine products (100) were obtained in moderate yield (up to 71%) and high enantioselectivity (up to 98% ee). The reaction is proposed to proceed through initial formation of the Breslow intermediate followed by its oxidation to the corresponding alkynyl acylazolium cation, which undergoes conjugate addition with the thiourea. The enantiodetermining step is the subsequent intramolecular N-acylation, templated by scandium(III) and with stereochemistry controlled by the chiral azolium species, though it is not clear specifically which interactions between R\textsuperscript{1} and the NHC scaffold control the torsional preference about the pro-axial C-N bond.

\begin{center}
\textbf{Scheme 28} Jin’s organocatalysed [3+3]-cycloaddition approach to thiazines.
\end{center}

In a synthetic approach primarily aimed at generating C-C atropisomeric quinazolinones, Luo, Zhu et al. recently reported a palladium-catalysed formal [5+1]-cycloaddition between amidoisocyanide (103) and aryl iodide (104) coupling partners (Scheme 29).\textsuperscript{37} In a single example a C-N atropisomeric axis was formed in 91% yield, 7:2 d.r. and 93% and 89% ee of the major and minor diastereomers of the product 105 respectively. Based on mechanistic control experiments the authors propose a
reaction sequence involving oxidative addition of palladium into the aryl iodide followed by carbene insertion and cyclosation-reductive elimination to forge the quinazolinone.

The cycloaddition approach is clearly an expedient method to synthesize axially chiral 2-pyridones. Prior to 2021 the strategy had not been expanded to encompass any substrate classes beyond those initially reported by Tanaka in 2008. There is clearly a dormant opportunity to exploit this elegant strategy for the synthesis of more diverse C-N atropisomeric scaffolds.

7. Axial C-N Bond Formation

From a retrosynthetic perspective, perhaps the most appealing strategy for the synthesis of C-N atropisomers is direct C-N bond formation where the bond being formed is the chiral axis itself. However, this approach is intrinsically challenging; by their very nature chiral axes are stericly encumbered, and this effect is may be even more pronounced for C-N atropisomers than their C-C counterparts due to the shorter bond. For example, there are no reported cases of intermolecular atroposelective Buchwald-Hartwig couplings (e.g., of pyridones, quinolones etc.) to form C-N axes. This challenging behaviour may in no small part contribute to the relative success of intramolecular approaches (see section 3), where the energetic penalty of bringing the reacting partners into close proximity is reduced. Nonetheless, in the last two years several atroposelective axial C-N bond-forming reactions have emerged. Li, Tan et al. disclosed a LUMO-lowering approach to organocatalytic axial C-N bond formation (Scheme 30). A series of azonaphthalenes (107) were treated with carbazoles (108) in the presence of a SPINOL-based chiral phosphoric acid (3); coordination of the azo group to the acid enhances the electrophilicity of the naphthyl 1-position sufficiently that nucleophilic attack of the carbazole occurs. The atropisomeric products (110) were obtained in up to 96% ee and 95% yield. Indoles (109) were also competent nucleophiles affording products (111) in up to 93% yield and 99% ee with a re-optimized catalyst (18) and protocol. The reaction is proposed to proceed via a dual hydrogen-bonded transition state to a point-chiral intermediate, the stereochemistry of which is efficiently transferred to the chiral axis upon re- aromatization, though a precise description of the transfer of chirality is not given. The products were converted to phosphine and thiourea derivatives whose potential in asymmetric catalysis applications was demonstrated. Diazonaphthalenes also formed 1,5-dicarbazole naphthalene derivatives containing two chiral axes in up to 98% ee, 57% yield and 4:1 d.r., though a third CPA catalyst was required.

The first metal-catalysed enantioselective axial amination was recently disclosed by Wang et al. (Scheme 31). Here, the steric repulsion intrinsic to axial C-N bond formation is overcome through the use of a reactive carbenoid intermediate. Diazonaphthoquinones (113) were reacted with indolocarbazoles (112) in the presence of a chiral rhodium-based catalyst (115), providing N-aryl carbazole products (114) in high enantioselectivity and good yield. Where R=Br, regioisomeric ratios varied between 1:1 to 19:1. Upon scale-up, catalyst turnover numbers of 200 were achieved. The authors demonstrated the utility of this method by conducting late-stage functionalisation of naturally occurring and bioactive molecules such as tijpanazole. However, the extremely hindered diazochrysenone failed to react under the optimized conditions, though the racemic reaction (with Rh(OAc)) did proceed. Lastly, the product phenols were converted to novel chiral phosphoric acids with potential applications in asymmetric organocatalysis.

Despite the elegance and convergency of the approach, direct catalytic axial C-N amination to form heterobiarylts remains in its infancy. However, inspired by these first few reports it seems likely that this approach will see rapid development in the very near future.
8. Atropisomeric N-N Axes: an Emerging Class of Heterobiaryls

The synthesis of atropisomeric molecules possessing N-N chiral axes was until recently, limited to resolution-based approaches. However, in 2021 Lu, Liu et al. disclosed the first catalytic asymmetric approach (Scheme 32).\(^{38}\) Their strategy resembles that of Wang, Tan et al. (Scheme 18),\(^{11}\) where catalytic activation of an electrophilic ketomalonate enables desymmetrization of a pre-formed axial bond. Treatment of pre-formed bipyrroles (116) with ketomalonates (117) resulted in alkylation at the 3-position of the more electron-rich and less hindered upper pyrrole (as drawn), and the presence of copper(II) trifluoromethanesulfonate and bisoxazoline ligand 119 led to the products (118) being formed in high yields and enantioselectivities. Kinetic resolution of racemic bipyrroles with \(s\)-factors up to 173 was demonstrated. Furthermore, other N-N bisazaaheterocycles (N-naphthyl, -rhodaninyl, -quinazolinyl and -triazinonyl pyrroles) were reactive under the optimized conditions, though enantioselectivities were generally lower (47-84%) than the bipyrrole series. Stereocontrol was found to be raised from coordination of the ketomalonate to the square-planar copper(II)-ligand complex. The bipyrrole then proceeds from beneath to avoid steric clash with the tert-butyl group, and its approach evidently favours the \(\text{pro-}(R)\) atropisomeric conformer.

![Scheme 32 Lu and Liu's enantioselective synthesis of axial N-N biaryl.](image)

The importance of chiral hydrazides is not purely esoteric: they have previously been employed as chiral catalysts in their own right.\(^{39}\) Whilst this reaction technically falls outside of the scope of this review, it paves the way for future developments in catalytic N-X axial atropisomer synthesis.

9. Conclusion and Outlook

There has been a recent and dramatic explosion in catalytic enantioselective approaches towards biaryl C-N atropisomers: despite reports as early as 2008\(^{12}\) over half of the primary literature reviewed was published in the years 2019-2021. This explosion has largely been fuelled by the use of CPAs for cyclocondensation, but an abundance of other catalytic strategies has emerged. Recently two approaches to the challenging direct axial C-N bond formation were disclosed, providing a new, more direct approach to these heterobaryl atropisomers. A deeper understanding of reaction mechanisms and the origin of asymmetric induction is still needed, so there is an opportunity for physical organic and computational chemists to have a significant impact on this field. A great many C-N heterobaryl motifs have not yet succumbed to the formation of atropisomeric congeners, but the current pace of development makes further progress a near-certainty.

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Conflict of Interest

The authors declare no conflict of interest.

References


Template for SYNTHESIS

Thieme
Biosketches

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