Asymmetric Synthesis of Axially Chiral C–N Atropisomers

Patricia Rodríguez-Salamanca,[a] Rosario Fernández,*[b] Valentín Hornillos,*[a, b] and José M. Lassaletta*^[a]

Dedicated to Professor Joan Bosch on the occasion of his 75th birthday
Abstract: Molecules with restricted rotation around a single bond or atropisomers are found in a wide number of natural products and bioactive molecules as well as in chiral ligands for asymmetric catalysis and smart materials. Although most of these compounds are biaryl and heterobiaryls displaying a C—C stereogenic axis, there is a growing interest in less common and more challenging axially chiral C—N atropisomers. This review offers an overview of the various methodologies available for their asymmetric synthesis. A brief introduction is initially given to contextualize these axially chiral skeletons, including a historical background and examples of natural products containing axially chiral C—N axes. The preparation of different families of C—N based atropisomers is then presented from anilides to chiral five- and six-membered ring heterocycles. Special emphasis has been given to modern catalytic asymmetric strategies over the past decade for the synthesis of these chiral scaffolds. Applications of these methods to the preparation of natural products and biologically active molecules will be highlighted along the text.

1. Introduction

Atropisomers, the most recognized class of compounds featuring axial chirality, comprise conformers with restricted rotation around a single bond that allow their isolation in a stable form. The configurational stability of these compounds depends on the rotational energy barrier and is generally determined by the number and size of substituents at the ortho, ortho positions relative to the stereogenic axis. The presence of larger substituents led to higher energy barriers and thus more configurationally stable products. In order to isolate atropisomers by analytical methods, a half-life for their interconversion of at least 1000 s is required, which is equivalent to a barrier of rotation of 90–100 kJ mol\(^{-1}\).\(^{[1,1]}\)

Atropisomerism was first reported in 1922 by Christie and Kenner after their isolation of 6,6′-dinitro-[1,1′-biphenyl]-2,2′-dicarboxylic acid atropisomers by using brucine as a resolution agent.\(^{[2]}\) Nonetheless, the importance of axial chirality in organic synthesis began to be widely recognized after 1980, when BINAP was implemented as a highly efficient ligand in catalysis with long-winded application as organocatalysts and desirable synthetic targets and tools in the field of asymmetric catalysis with long-winded application as organocatalysts and ligands for enantioselective transition-metal-catalyzed transformations.\(^{[3]}\) Furthermore, axially chiral biaryl scaffolds are present in numerous natural products and biologically active molecules in which the configuration of each enantiomer plays an important role in determining the final biological activity.\(^{[4]}\)

A family of nonbiaryl atropisomers that have attracted considerable attention in recent years comprises those with restricted rotation around a C(sp\(^2\))–N(sp\(^2\)) axis.\(^{[5]}\) These chiral scaffolds are also present as key motifs in biologically active compounds (Figure 1A). In 1931, Adams described the first example of a compound with C—N axial chirality, a pyrrole derivative that could be obtained in enantiomerically pure form by resolution with brucine (compound I).\(^{[6]}\) More recently, the groups of Curran and Clayden set the bases for the study, synthesis, and applications of C—N atropisomers\(^{[7,8]}\) and, in recent years, a growing number of members of this family have been described. Many of them are natural products or present varied biological activities.\(^{[9]}\) For example, quinazolinone derivative methaqualone II has sedative and hypnotic properties and has also been illegally used as a recreational drug,\(^{[10]}\) while aniline derivative metolachlor III is one of the most important grass herbicides for use in maize.\(^{[11]}\) Other relevant representatives include ancisheynine IV, a naphthylisoquinoline alkaloid isolated from Ancistrocladus heyneanus,\(^{[12]}\) or murrastifoline A, B and F alkaloids, extracted from the root of Murraya koenigii plants, which constitute a family of axially chiral carbazole-derived C—N compounds,\(^{[13,14]}\) whose configurational properties were studied by Bringmann in 2001 (compoundVI).\(^{[14]}\) More recently, axially chiral metabolites (–)-marinopyrrole Via and (–)-marinopyrrole Vb were isolated by cultivation of an obligate marine Streptomyces strain and have shown excellent antibiotic activity against methicillin-resistant staphylococcus aureus.\(^{[15]}\) Particularly relevant is the axially chiral quinazolinone derivative AMG S10 (Sotorasib) VII, a potent KRAS\(^{[16]}\) inhibitor that has been recently approved as an anti-cancer medication for the treatment of non-small-cell lung cancer (NSCLC). Remarkably, several types of axially chiral heterobiaryls show activity as kinase inhibitors. Selected representatives are quinazolinedione VIII, a reversible inhibitor of Bruton’s tyrosine kinase (BTK),\(^{[17]}\) benzimidazole IX, a phosphoinositide 3-kinase P13 K\(^{\beta}\) inhibitor,\(^{[18]}\) and pyrroline X, a potent p38 kinase inhibitor.\(^{[19]}\) Interesting bioactivities have also been found in axially chiral N-aryl triazole derivatives. For example Lenisurad X is a hURAD1 inhibitor used for the treatment of goiter,\(^{[20]}\) while analogue XII is a glycin transporter GlyT1 inhibitor.\(^{[21]}\) These types of compounds have also demonstrated their potential as

\(^{[a]}\) P. Rodríguez-Salamanca, Dr. V. Hornillos, Prof. J. M. Lasaletta
 Instituto de Investigaciones Químicas (CSIC-US) and Centro de Innovación en Química Avanzada (ORFEO-CINQA)
 C/ Americo Vespucio, 49, 41092 Sevilla (Spain)
 E-mail: jmlassa@iq.csic.es
 vhornillos@us.es

\(^{[b]}\) Prof. R. Fernández, Dr. V. Hornillos
 Departamento de Química Orgánica (Universidad de Sevilla) and Centro de Innovación en Química Avanzada (ORFEO-CINQA)
 C/ Prof. García González, 1, 41012 Sevilla (Spain)
 E-mail: ffernan@us.es

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chiral ligands for asymmetric catalysis, as exemplified by the selected examples VIII–XI shown in Figure 1(B).\[22\]

While the synthesis of axially chiral biaryls has been widely explored, the enantioselective construction of C–N heterobiar-
yls and other axially chiral compounds featuring a C–N stereo-
genic axis has been much less investigated and remains as a quite challenging task.\[23\] Their rotational stability generally relies on the steric factors of the substituents around the C–N axis as well as the structure of the nitrogen moiety. Thus, most of these axially chiral C–N atropisomers contain substituents in the ortho position of the aromatic unit attached to nitrogen. The structural properties of the C–N axis often led to a decrease in the configurational stability, which increases the difficulty of their enantioselective synthesis.

The aim of the present review is to provide an updated outline of the different strategies and methodologies developed for the asymmetric synthesis of compounds with restricted rotation around a C–N bond, with special emphasis on catalytic asymmetric methodologies. The manuscript includes methods for the synthesis of axially chiral anilides XII, indole and carbazole derivatives XIII, pyrroles and triazoles XIV, benzimidazo-
les XV, imides XVI, six-membered lactam derivatives XVII, quinazolinones XVIII, and thiazinones XIX, among others (Fig-
ure 2).

Early contributions based on diastereoselective approaches using auxiliaries from the chiral pool, classical resolutions, co-
crystallizations or chromatographic separations are presented for each group of compounds, but then the review emphasizes the different strategies developed for their catalytic asymmetric synthesis. These can be roughly classified according to the retrosynthetic pathways shown in Figure 3. Thus, target products featuring a C–N stereogenic axis can be accessed by N-
functionalization of aniline derivatives, either intramolecularly (Figure 3A) or by cyclization (Figure 3B). There are also method-
ologies involving atroposelective de novo construction of heterocyclic (Figure 3C) or aromatic (Figure 3D) moieties of the final product. Modern C–N activation/functionabilization stra-
tegies (Figure 3E) are also suitable tools for the atroposelective synthesis of these compounds. Alternatively, there are also approaches that focus on the direct generation of the C–N stereogenic axis (Figure 3F). Finally, examples of desymmetriz-
ation strategies based on transformations in either the aromatic (Figure 3G) or the heterocyclic (Figure 3H) part of heterobiaryls are also presented and discussed.

Patricia Rodríguez-Salamanca received in 2017 her Master in Organic Chemistry from the Autonomous Un-
iversity of Madrid, where she worked on iron-catalyzed hydroborylative cycliza-
tion of enynes. She commenced her PhD studies in the group of Asymmetric Catalysis at the Instituto de Investigaciones Químicas (CSIC-US) in 2018, exploring novel methodologies for the atroposelective synthesis of axially chiral biaryls involving dynamization proc-
esses.

Felix Serratosa

José María Lassaletta received his Ph. D. in 1990 at the University of Seville. He then performed postdoctoral stages at the Instituto de la Grasa y sus Deriva-
dos (CSIC) and the University of Kon-
stanz, (Germany), with Prof. R. R. Schmidt. In 1995 he moved to the Instituto de Investigaciones Químicas (CSIC, Seville), where he was promoted to Associate Professor. In 2008 she became a Full Professor at the same University. She has been recognized with the Excelen-
cia Investigadora’ Award from the Royal Society of Chemistry (2019). Her current research interests include asymmetric synthesis and enantioselective catalysis, in both aspects, asymmetric metal catalysis and organocatalysis.

Valentin Hornillos (Toledo, 1978) ob-
tained his Ph.D. from the University Complutense de Madrid in 2009, work-
ing on the synthesis of fluorescent lipid drugs. In 2007, he also spent four months in the Novartis laboratories in Vienna. From 2010 until 2015, he was a postdoctoral fellow in the group of Professor Ben Feringa at the University of Groningen and in 2015 he moved to the IIQ, CSIC in Seville as a Talent Hub Fellow. Since 2019, he has been a Ramón y Cajal researcher at the Uni-
versity of Seville. His research interests include the development of new transition metal-catalyzed enantioselective processes.

Ignacio Ribas (2009). He has been recognized with the ‘Exce-
lecencia Investigadora’ Award from the Royal Society of Chemistry (2019). Her current research interests include asymmetric synthesis and enantioselective catalysis, in both aspects, asymmetric metal catalysis and organocatalysis.
Figure 1. A) Naturally occurring and bioactive C–N-bonded axially chiral compounds. B) Selected ligands and complexes featuring C–N axially chirality.
Figure 2. Representative families of atropisomers featuring a C–N chiral axis.

Figure 3. Strategies for the catalytic asymmetric synthesis of axially chiral C–N atropisomers.
2. Atropisomeric cyclic derivatives: anilides and related analogues.

2.1. Early examples and conventional resolution approaches

In the case of anilides, a bulky ortho substituent, such as the tert-butyl group, is frequently used to attain configurational stability. In 1994, Curran et al.\(^\text{[24]}\) advanced the requirement of using large ortho substituents next to the C–N axis to increase their rotational barrier and thus prevent racemization at room temperature. Initially, they focused on the study of the configurational stability of racemic anilides 1 and their subsequent derivatization reactions, such as the 1,3 dipolar cycloaddition with benzonitrile oxide to afford a mixture of diastereomers 2a and 2b in a 97:3 ratio (Scheme 1).

These preliminary results fixed the bases for the development of a range of approaches for the synthesis of these compounds in enantiomerically pure form. Thus, Simpkins and co-workers\(^\text{[25]}\) performed a kinetic resolution (KR) of racemate 3 to obtain enantioenriched α-methylated product 4 together with unreacted 2-(tert-butyl)anilide (-)-3 in 88% ee. The reaction proceeds through the generation of an enolate using substoichiometric amounts of a chiral lithium amide base, followed by quenching with MeI (Scheme 2). Although the kinetic resolution was not optimized, the strategy paved the way for the development of more efficient methods to obtain highly enantioenriched axially chiral anilides.

Taguchi and co-workers\(^\text{[26]}\) employed a chiral pool approach to obtain enantiomerically pure anilide derivatives. Thus, the reaction of N-allyl-α-(tert-butyl)aniline 6 with 2 equivalents of lactic acid derivative 5 afforded a 3:1 separable mixture of diastereomeric carboxamides 7a and 7b. Subsequently, the former was easily transformed into anilide 8, obtained in 97% enantiomeric excess, as shown in scheme 3.

Following a related strategy, Simpkins and co-workers\(^\text{[27]}\) also used a chiral pool approach based on lactic acid. Starting from α-acetoxy anilide 9, readily available after condensation of acetate 5 with α-(tert-butyl)aniline, alkylation with MEMCl afforded a mixture of stereoisomeric anilides 10a and 10b in 41% and 25% yield, respectively. Subsequently, these products were reduced using a SmI\(_2\)-LiCl system to afford enantioenriched products 11 with a slight loss of stereochemical integrity. This reaction was general for a wide variety of acetates and the method was also effective for the removal of α-bromo and α-benzyloxy functionalities (Scheme 4).

Furthermore, Taguchi co-workers\(^\text{[28]}\) developed a chiral pool approach to access highly enantioenriched atropisomeric anilides based on the resolution of amide esters 13a and 13b, readily available from oxalyl chloride, (R)-pantolactone alkoxide 12 and N-allyl-(ortho-tert-butyl)aniline 6 (Scheme 5). Noteworthy, the chiral pantolactone 12 could be recovered and reused, and the efficient resolution of 13a and 13b by recrystallization makes large-scale preparation possible. The authors further performed the synthesis of enantiomerically pure α-ketoamides 14 and α,β-unsaturated anilides 15 from amide ester 13a, without loss of stereochemical integrity.

In 2000, Uemura and co-workers\(^\text{[29]}\) reported the asymmetric synthesis of atropisomeric anilides through a kinetically controlled enantiotopic lithiation of prochiral chromium arene complex 16 (Scheme 6). Deprotonation with chiral lithium amide base 17, followed by quenching with an electrophile (alkyl halides or carbonyl compounds) afforded axially chiral amides 18 with selectivities up to 97% ee. The high stereoselectivity could be associated with the conformal orientation of the prochiral chromium complex, where the amido carbonyl...
oxygen is oriented trans to the chromium atom in the complexed aryl group. Exposure of complex 18 to sunlight resulted in the removal of the ligand from the coordination sphere of chromium, providing pure anilides 19 without loss of optical purity.

Building upon the above findings of Simpkins and Taguchi, the group of Curran[30] described an efficient method to obtain axially chiral enantiopure anilides based on a crystallization-induced asymmetric transformation (Scheme 7). Upon reaction with dimethyl-L-tartrate, racemic anilide 20 was converted into a 1:1.1 mixture of diastereomeric ketals 21. Further selective recrystallization increased the diastereomeric ratio to 20:1. The enantiomeric excess of the final product 20 obtained after cleavage with SmI₂ or hydrolysis under basic conditions was determined by the diastereomeric ratio of 21, assuming that these transformations proceed faster than the interconversion of the rotamers (racemization). On the other hand, the diastereomeric ratio drops when the crystallization occurs too rapidly. In these compounds, the nitrogen atom exhibits a pyramidal structure, with the ortho-tert-butyl group adopting a syn orientation relative to the vicinal N lone pair.

In 2009, Clayden et al. reported a kinetic resolution for the synthesis of atropisomeric ureas 23 based on the vanadium-catalyzed enantioselective oxidation of ortho-thiophenethyl precursors 22 (Scheme 8).[31] Sulfoxidation proceeds with moderate enantioselectivities (up to 78% ee for ligand L1 and R₁=Bu, R₂=C₆H₁₃ and low selectivity factors except for one substrate (R₁=Bu, R₂=Me, S=300). The half-life for racemization of the substrates was determined to be between 8 weeks (R₁=CH-
2.2. Atroposelective N-functionalization of aniline derivatives

The groups of Taguchi[32] and Curran[33] independently described the catalytic asymmetric synthesis of atropoisomeric anilides 25
and 27 by palladium-catalyzed allylation of achiral precursors 24 and 26, using diphosphine ligands (S)-Tol-BINAP L2 and (S)-BINAP L3, respectively (Scheme 9). Excellent yields were observed in both cases, but the enantioselectivities were rather low, a fact that was attributed to poor facial discrimination during the nucleophilic attack of the soft anilide anion on the \( \pi \)-allyl system, which occurs from the opposite side of the coordinated chiral ligand.

Aiming to overcome these difficulties, Taguchi et al.\[34\] described the synthesis of optically active atropoisomeric anilide derivatives 29 through a catalytic asymmetric inter- and intramolecular \( N \)-arylation of achiral anilides 24, using in this

$$\text{Scheme 8. Kinetic resolution of sulfanyl ureas.}$$

$$\text{Scheme 9. Palladium-catalyzed asymmetric allylic alkylation for the synthesis of atropoisomeric anilides.}$$

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case (R)-DTBM-SEGPHOS L4 (Scheme 10). In this case, the anilide N atom attacks the Pd center instead of the allylic carbon in the stereodetermining step, so that the N-aryl bond lies in the proximity of the chiral ligand, making it therefore possible to reach high enantioselectivities. The absence of racemization under the reaction conditions was further confirmed by heating the product at 80°C. On the other hand, a limited scope was shown for the method: the reaction was performed with 1- iodo-4-nitrobenzene as a unique electrophile.

Kitagawa and co-workers reported more recently the enantioselective synthesis of C–N axially chiral sulfonamides 31, achieved through Pd-catalyzed N-allylation of precursors 30 with allyl acetate (Scheme 11). Using Trost’s ligand L5, good yields and high enantiomeric excesses were observed, especially for hindered substrates (R’=t-Bu).

Very recently, Feng and co-workers reported a methodology for the asymmetric acylation of N-sulfonyl anilides 32 using α,β-unsaturated carbonic anhydrides 33 as acyl transfer reagents and chiral isothiourea C1 as the catalyst, yielding axially chiral N-acyl sulfonamides 34 (Scheme 12). The reaction takes place under mild conditions using nonpolar solvents, and the use of a neutral base such as DIPEA was found to be key to obtain high enantioselectivities. Under the optimized conditions, a broad variety of carbonates were shown to be suitable substrates, although electron-poor derivatives gave better yields than electron-rich ones. Regarding the sulfonamide substrate, the

Scheme 10. N-arylation of achiral anilides.

Scheme 11. Atroposelective N-allylation of sulfonamides.
size of the ortho R' group directly correlates with the enantioselectivity. In the proposed enantiodetermining transition state model, the sulfonamide anion approaches from the opposite side of the phenyl group to avoid steric repulsion. Furthermore, the bulky o-tert-butyl group reduced the π-π interactions between the substrate and catalyst, while the interaction between the oxygen of the sulfonyl moiety and the positive electronic charge on the imidazolium salt side was proposed to play an important role.

A late strategy developed to access axially chiral sulfonamides makes use of a Pd-catalyzed atroposelective hydroamination of allenes with substituted aryl sulfonamides (Scheme 13). Excellent enantio- and diastereoselectivities, as well as a perfect branched-to-linear ratio were achieved by using Pd₂(dba)₃ as the precatalyst and multidentate Trost type ligand L₆. Moreover, the method benefits from wide functional group tolerance and, interestingly, substrates bearing uncommon ortho R groups such as ester, ketone, nitro, Cl, F, or OMe are well tolerated.

More recently, Maruoka et al. described an efficient asymmetric synthesis of axially chiral o-iodoanilides via phase-transfer catalyzed N-alkylation of precursors with alkyl bromides (Scheme 14). The key to obtaining high enantioselectivity relies on the ability of the chiral tetraalkylammonium bromide phase-transfer catalyst C₂ to discriminate between the ortho substituents in the anilide, a fact further supported by the
study of the crystal structure of the chiral ammonium/anilide anion complex.

In 2015, Feng and Du[39] studied the use of phosphoramidite-olefin L7 as the ligand for the Pd-catalyzed asymmetric allylic alkylation of ortho-substituted anilides 41 with carbonate derivatives 42 to obtain axially chiral anilides 43 (Scheme 15). The choice of the base was found to have a strong impact on enantioselectivity, and KOEt was found to provide the best results. Importantly, the catalyst loading could be reduced to 1.25 mol% without affecting reactivity or enantioselectivity. A wide range of allyl carbonates were tolerated to give the corresponding axially chiral anilide product with moderate to good enantioselectivities and yields.

Few years later, Li and co-workers[40] reported an efficient Lewis base organocatalyzed allylic alkylation of similar anilides 44 to access axially chiral anilides 46. Good yields and excellent enantioselectivities (up to 98% ee) were obtained using a biscinchona alkaloid catalyst C3 in combination with Morita-Baylis-Hillman carbonates 45 (Scheme 16). A large influence of the solvents in reactivity and enantioselectivity was observed with MeCN giving the best results. The size of the substituents on the aromatic ring of the anilides also has a strong influence on selectivity. Thus, it was found that bulky groups, such as Bu and i, in ortho position afforded the highest enantioselectivities. It should be mentioned that for aliphatic amides (R1=Et), the chiral anilines were obtained with lower yield, probably due to the lower acidity of the NH group. It was also found that the configurational stability of products bearing electron-withdrawing groups in the aromatic benzoyl ring (R1) was higher than that with electron-donating groups. At all, most of the products showed high configurational stability at 25 °C in the solid state.

More recently, the same group described an efficient protocol for the construction of axially chiral phosphamides 49 via atroposelective allylic N-alkylation reaction of precursors 47 with Morita-Baylis-Hillman carbonates 48 using hydroquinidine C4 as the catalyst.[41] Ortho-iodo-substituted anilide derivatives were selected as substrates considering the potential application of the resulting iodobenzene products as chiral hypervalent iodine catalysts (Scheme 17). It was found that the sterically hindered diphenyl phosphoryl group was beneficial for stability and stereoselectivity control. Phosphamides bearing different substitution patterns in combination with a wide range of carbonates resulted in a broad range of products, obtained in moderate to excellent yields and excellent enantioselectivities. As above, more crowded substrates gave better enantioselectivities. For example, the change of iodine to smaller halides, such as Br or Cl, led to lower enantiomeric excesses. The method also allows for the synthesis of compounds with both C–N axial chirality and P-stereogenic chirality.
2.3. Atroposelective construction of the aromatic ring

A different strategy for the atroposelective synthesis of axially chiral anilides was developed by Tanaka and co-workers. In this case, a rhodium-catalyzed enantioselective intermolecular [2 + 2 + 2] cycloaddition of 1,6-diynes with trimethylsilylynamides (Scheme 18) was accomplished under mild conditions to afford enantioenriched products in high enantioselectivity although in low-to-moderate yield. The enantioselectivity was determined by the preferential coordination of the carbonyl group of to a rhodacyclopentadiene intermediate and by the steric interactions between substituent R3 and the PAr2 group of the (S)-DM-BINAP ligand L8.

2.4. Atroposelective C–H activation/functionalization

Axially chiral anilides have also been prepared by Shi and co-workers using a PdII-catalyzed C–H olefination of racemic N-aryl picolinamides (Scheme 19A). Using L-pyroglutamate L9 as a chiral ligand, the reaction with alkenes proceeds via dynamic kinetic resolution to afford the coupling products in excellent yields and enantioselectivities. Both electron-donating and electron-withdrawn groups on the pyridine ring (R1) are tolerated, but the size of the ortho-substituents on the aryl ring (R2) plays an important role in the enantiocontrol, with the smallest groups such as methoxy leading to racemic products. Additionally, a variety of Z substituents were well tolerated. Finally, a broad range of electronically different olefins proved to be suitable reaction partners. As a particular case, simple aliphatic alkenes provide formal C–H allylation products (after double bond migration) in moderate yields and high ee’s. Mechanistically, the concerted metalation-deprotonation event was determined to be the enantiodetermining step. Further analysis revealed that a distortion provoked by the amino acid ligand is responsible for the chiral induction during the C–H bond activation event.

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Very recently, Gustafson and co-workers\cite{45} reported an elegant approach for the synthesis of a family of N-aryl quinoids 60, which exist as configurationally stable atropisomers. The strategy exploits the presence of a strong intramolecular N–H⋯O hydrogen bond that locks the ‘exo’ conformation in the parent quinoids 59 (Scheme 20). Direct C–H halogenation using phosphoric acid catalyst C5 provides configurational stability to the C(aryl)–N axis of the products, which were
obtained in excellent yields and enantioselectivities when a bulky $R_1$ group (such as tert-butyl) is installed in the ortho position. The reaction worked well for a variety of aryl substitutions, although a poorer enantiocontrol was observed when the aryl groups in the aniline moiety are replaced by methyl groups, suggesting that an interaction between the ortho-aryl group and the catalyst is key for the enantioselectivity. Additional studies revealed that the products were configurationally stable under thermal and acidic conditions.

2.5 Atroposelective direct formation of the stereogenic C–N bond

The group of Jørgensen also reported a highly regio- and enantioselective synthesis of unprecedented C–N atropisomers 62 through a cinchona-alkaloid organocatalyzed asymmetric Friedel-Crafts amination of 2-naphthols 61 with azodicarboxylates (Scheme 21). After screening a large number of catalysts, the quinidine and quinine derivatives $C_6$ and $C_6'$ were initially identified as promising candidates, reaching ee's up to 88%. Remarkably, selective amination took place selectively on substrate 61, although the cinchona-alkaloid catalyst $C_6$ is also susceptible to amination under the reaction conditions. In fact, these catalysts also react under forcing conditions to afford derivatives $C_7$ and $C_7'$, thus generating atroposomerism in cinchona alkaloids. Interestingly, these pseudo-enantiomeric derivatives proved to be better catalysts, efficiently affording 1,8-diamino-2-naphthol derivatives in excellent yields and enantioselectivities. The X-ray structure of $C_7$ showed a hydrogen bond between the quinuclidine nitrogen and the hydrogen atom bound to hydrazine, which blocks the basic site of this alkaloid.

In 2019, Zhang’s group reported a related approach for the atroposelective synthesis of axially chiral arylhydrazine derivatives 64 by intermolecular enantioselective C–H amination of N-aryl-2-naphthylamides 63 with azodicarboxylates using a chiral phosphoric acid (CPA) catalyst $C_8$ (Scheme 22A). The control of selectivity is provided by a π-π stacking interaction between the N-phenyl substituent of the substrate and the phenanthryl group of the catalyst, in combination with a dual H-bonding interaction. The reaction failed for N,N-disubstituted naphthylamines, demonstrating the key role of the N–H bond on reactivity. On the other hand, the introduction of protecting groups such as benzyl or tert-butyl on nitrogen led to low enantioselectivities, indicating the importance of the synergistic control by π–π and dual H-bonding interactions. The enantioselectivity of the reaction was also sensitive to the size of the azodicarboxylate reagent, with di-tert-butyl azodicarboxylate giving the best results. This methodology was later extended by Yang and co-workers to the synthesis of related hydrazines 66. In this case, a very similar chiral phosphoric acid catalyst $C_9$...
was used in the enantioselective amination of 1,3-benzenedi- 
amines 65 with azodicarboxylate derivatives (Scheme 22B). A 
wide variety of substrates with different acyl, aryl, sulfonyl and 
alkoxycarbonyl protecting groups in the secondary amine were 
well tolerated. However, the enantioselectivity drops when 
benzoyl groups are incorporated at this position. Importantly, 
the use of different azodicarboxylates as the aminating reagents 
afforded the corresponding product in excellent yields and 
enantioselectivities. The obtained axially chiral anilides 66 
presented the highest configurational stabilities reported to 
date.

3. N-Aryl Five-Membered Heterocycles

3.1. Pyrrole, indole/indoline, and carbazole derivatives

The enantioselective synthesis of N-aryl pyrrole, indole/ 
indoline, and carbazole atropisomers has received increasing attention in 
recent years, for potential applications as chiral ligands and 
intermediates in natural product synthesis. In these systems, the rotation about the C–N axis becomes easier than in biaryl 
compounds because of the relatively larger CNC angles 
associated with a five-membered heterocyclic ring.

3.1.1. Early examples

In 2001, Bringmann et al. reported the first total synthesis of the natural product Murrastifoline-F 68 through an oxidative 
C–N homocoupling of carbazole precursor 67 with Pb(OAc)₂. 
Due to the restricted rotation around the C–N bond, the two enantiomers of the coupling product were observed through liquid chromatography-circular dichroism (LC-CD). After cleav- 
age of the methoxy groups and further derivatization with Mosher’s acid, the resulting diastereomers 69 were separated 
by preparative thin-layer chromatography, allowing the deter- 
mination of their absolute configurations with the M-isomer 
being the major product (Scheme 23). Comparison with the Murrastifoline-F natural product isolated from the root extract 
of the curry leaf plant Murraya koenigii (Rutaceae), allowed to 
determine the presence of a 56:44 mixture in favor of the M- 
enantiomer in the natural source mixture.

Few years later, Uemura and co-workers reported the 
stereoselective synthesis of axially chiral N-aryl indoles 72 
through a nucleophilic substitution reaction of haloarene 
chromium complexes 71, featuring planar chirality, with 
indoles 70 (Scheme 24, A). The stereochemistry of the C–N axis was determined by the position of the substituent R₁. When the indole ring was unsubstituted or 3-methyl substituted, the
resulting chromium moiety was oriented anti with respect to the indole aryl ring, whereas when it was 2-methyl substituted, the benzene ring of the indole was oriented syn toward the chromium tricarbonyl group, even for sterically hindered indole compounds. It was also found that in product 72b containing a 1,3-dioxolanyl group, the chromium tricarbonyl group migrated from the N-aryl to the indole arene ring to yield complex 73 after heating in toluene (Scheme 24, B). When the 1,3-dioxolane group was changed to a methyl group, migration did not occur. X-Ray analysis revealed that the 1,3-dioxolane was oriented toward the chromium tricarbonyl group in the migrated product, suggesting that the former might play a role in assisting the transfer of the tricarbonyl chromium group by coordination.

3.1.2. Atroposelective cyclization

In 2017, Tan and co-workers described the first catalytic asymmetric Paal-Knorr reaction between functionalized 1,4-diketones 74 and anilines 75 to obtain axially chiral N-arylpyrroles 76. High enantiomeric excesses were observed by using again BINOL-derived phosphoric acid C10 as the catalyst (Scheme 25). Based on previous knowledge on the Paal-Knorr
reaction mechanism, the authors envisaged the ability of the chiral phosphoric acid to assist in the intramolecular nucleophilic addition step. It was also found that the reaction could be further speeded up by adding Fe(OTf)₃ as a Lewis acid cocatalyst. Remarkably, the ortho Z group in anilines 75 was not restricted to tert-butyl: iodine, bromo, and phenyl groups could also be employed, giving the expected products in good to excellent enantiomeric excesses. Mechanistically, the formation of an enamine key intermediate was proposed to control the stereoinduction. Finally, the authors also observed an unexpected solvent-dependent inversion of the enantioselectivity.

Kitagawa et al. reported in 2010 and further expanded in 2016 a Pd-catalyzed 5-endo-hydroaminocyclization of ortho-alkylanilines 77 for the synthesis of axially chiral indoles 78, obtained in moderate to good enantioselectivities by using (R)-SEGPHOS L10 as the chiral ligand (Scheme 26). This transformation represents the first transition metal-catalyzed asymmetric synthesis of such a structural motif. The reaction works well for aromatic alkynes but was sluggish for highly deactivated (R=2-NO₂C₆H₄) and aliphatic derivatives (R=n-C₄H₉). In these cases, the addition of AgOTf was necessary to increase the reactivity by generating more active cationic palladium species. It was also found that the presence of an ortho-substituent in the aromatic alkyne is important to improve the enantioselectivity (60% ee for R=Ph, 80–83% ee for ortho-substituted substrates). The authors attributed this observation to the dynamic axial chirality generated around the C-(alkynyl)–C(phenyl) bond. Because chirality transfer occurs during the N–C bond formation step, substrates with a bulky ortho-substituent transferred more effectively the chiral information from the ligand through the C(alkynyl)–C(phenyl) bond.

In 2015, Nakazaki and co-workers developed a methodology to access N-arylisatins with C–N axial chirality by means of an enantioselective intramolecular N-arylation reaction (Scheme 27). Cyclization of amide 79 using Pd(OAc)₂/(S)-DM-SEGPHOS L11 as the catalyst afforded N-aryloxindole 80 in 81% ee. This product was transformed into dibrominated derivative 81, which was enantoenriched to >99% ee by recrystallization and subsequently transformed into N-arylisatin 82 under mild conditions without erosion of the enantiomeric purity. Finally, this material was subjected to a diastereoselective 1,2-addition of MeLi, which took place from the less hindered face of the isatin, the one opposite to the tert-butyl group, to afford the 3,3-disubstituted oxindole scaffold 83, in good yield and high diastereoselectivity.

The group of Lin described the first three-component cascade heteroannulation reaction of 2,3-diketoesters 84, ortho-substituted aryl anilines 85 and 1,3-cyclohexanediones 86 using a chiral spirocyclic phosphoric acid organocatalyst C11 (Scheme 28). Under optimal conditions, substrates with different electronic properties in the aromatic ring of the 2,3-diketoesters were tolerated, giving axially chiral N-arylindoles 87 in excellent yields and enantioselectivities. The reaction also tolerates structural modifications in anilines (R’), thus expanding the scope of the method.
Very recently, Wang, Lan, Li and coworkers also reported an interesting approach to axially chiral N-isoquinolyl indole derivatives.\(^{90}\) Using the isoquinoline N atom as a directing group, a Rh\(^{III}\)-catalyzed C–H activation of anilines was used for an oxidative [3 + 2] annulation with alkynes (Scheme 29). Using Cramer’s Cp\(^{OMe}\)Rh\(^{III}\)/AgSbF\(_6\) catalyst and Ag(I) salts as the oxidant, the reaction proceeds under mild conditions with high enantioselectivity and high functional group tolerance. Interestingly, good to excellent regioselectivities were observed for alkyl-aryl alkynes and substituted 1,3-enynes when AgOPiv or MeSO\(_3\)Ag were used as the oxidants, respectively.

Finally, Yan and co-workers have recently reported on the synthesis of complex azepine derivatives featuring a C–N stereogenic axis incorporated into a bridged heterobiaryl skeleton.\(^{56}\) Starting from alkylnyl naphthol substrates bearing a carbazole moiety, reaction with N-bromosuccinimide (NBS) in the presence of squaramide organocatalyst afforded the products in good yields and with excellent enantio- and diastereoselectivities (Scheme 30). The bifunc-

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**Scheme 26.** Pd-Catalyzed enantioselective synthesis of axially chiral indoles.

**Scheme 27.** Palladium-catalyzed intramolecular N-arylation for the synthesis of enantioenriched N-aryloxindoles.
tional activation by the catalyst facilitates a highly stereo-controlled electrophilic bromination to generate reactive bromo-functionalized tetrasubstituted chiral vinylidene ortho-quinone methide (VQM) intermediates. Subsequently, intramolecular electrophilic aromatic substitution at the C1 position of the carbazole moiety affords the final products, which exhibited interesting optical properties and Ru$^{3+}$-induced fluorescence responses that suggest potential applications in optoelectronic materials and heavy metal ion detection.

3.1.3. Atroposelective C–H activation/functionalization

In 2019, Shi and co-workers described a palladium-catalyzed C–H alkynylation of aryl pyrroles 93 with bromoalkynes 94 for the synthesis of pyrrole derivatives 95 displaying axial chirality (Scheme 31). This elegant approach, inspired by the seminal work by the group of Yu, and applied previously to the resolution of biaryls, is based on the transient directing group formed by condensation of the formyl group of 93 with L-tert-leucine L12, thus enabling a regio- and atroposelective C–H activation to afford the alkynylated products in excellent yields and enantioselectivities up to $>99\%$ ee. These products exhibit high configurational stability, as no erosion of ee values was observed, even after heating at $120^\circ$C. Nevertheless, sterically bulky substituents in the ortho position to the axis are needed to maintain the configurational stability and to ensure good enantioselectivities.

Xie, Zhang and co-workers developed later a similar Pd$^0$-catalyzed atroposelective C–H olefination of N-aryl indoles 96 with electron-poor alkenes 97 (Scheme 32A). The authors reported on three different situations depending on the substitution pattern of the starting material: For atroposelective C–H olefination/desymmetrization reactions \([Z=H, R^2(\text{meta})=R^2(\text{meta'})]\), a wide variety of alkenylated products 98a could be prepared in good yields and high enantioselectivities using Pd(OAc)$_2$ as the precatalyst, L-valine L13 as the ligand and benzoquinone (BQ) as an external oxidant. Similar results were also obtained in the catalytic C–H olefination/dynamic kinetic resolution of configurationally labile N-aryl indoles. Finally, for
racemic, configurationally stable substrates with more sterically demanding substituents, a catalytic C–H alkenylation via kinetic resolution was developed. In this last case, the alkenylated N-aryl indoles 98b were obtained with excellent selectivity factors of up to 459 by using tert-leucine L12 as the ligand and AgTFA as the oxidant. All synthesized products present high configurational stability at rt. Very recently, Ackermann and co-workers recently reported developed a similar kinetic resolution of N-naphthyl indole carbaldehydes 99 into alkenylated products 100, but an electrocatalytic approach was used to avoid the need of an external oxidant (Scheme 32B). Excellent selectivity factors of up to $S = 355$ were achieve in the reaction with a variety of electron-poor olefins, including, acrylates, vinyl phosphonates, vinyl sulfones, maleimides and fluorinated alkenes. Interestingly, an unprecedented allylic selectivity was observed with 1,1-disubstituted alkenes, and the atroposelective allylation could also be performed to obtain products 101 with excellent selectivity factors of up to $S = 169$.

Subsequently, Wang et al. presented an alternative method to construct C–N axial chirality through a Rh$^{III}$-catalyzed Satoh-Miura-type reaction of N-aryloxindoles 102 and alkynes 103. Using catalyst C14 with a spirocyclic cyclopentadienyl ligand, chiral N-aryloxindoles 104 were obtained with high yields and enantioselectivities (Scheme 33). This dual C–H activation reaction tolerates both electron withdrawing and electron donating groups in the N-phenyl ring and in the diaryl alkyne. Mechanistic studies revealed that the C–H activation step proceeds by a carboxylate-assisted concerted metalation-deprotonation mechanism affording a six-membered rhodacyclic intermediate in which the bulky isobutyrate additive helps to better differentiate the two enantiotopic C–H bonds.

Very recently, Kwon and co-workers reported a Pictet-Spengler reaction of N-aryl indoles 105 with paraformaldehyde for the atroposelective synthesis of N-aryl-tetrahydro-β-carboline 107 (R=H, Scheme 34). Previous studies on acid-catalyzed atroposelective C-2 functionalization of unprotected indoles indicated the need for a bifunctional activation that includes acidic activation of the electrophile and interaction between the phosphate counterion and the indole N–H. The absence of a N–H group in these substrates, however, was addressed by
introducing an ortho-amino hydrogen bond donor (R₃) into the bottom aromatic ring. Thus, the use of chiral phosphoric acid C₁₅ afforded excellent yields and enantioselectivities with a variety of substrates that contain electron-donating or electron-withdrawing groups. In addition to paraformaldehyde, the reaction also works with different activated benzaldehydes, which additionally allows to control both central and axial chirality elements (4:1 to 10:1 d.r., >99 % ee).

Very recently, Meggers and co-workers described an atroposelective alkylation of N-arylpyrroles achieved by nucleophilic addition to N-acryloyl-1H-pyrazoles using a chiral-at-rhodium Lewis acid catalyst C₁₆ possessing a unique helical (chiral-at-rhodium) chirality (Scheme 35).₆⁴ Different substitution patterns were tolerated in the coupling partners affording structurally diverse axially chiral N-arylpyrroles in high yields and excellent atroposelectivities (up to >99 % ee). N-arylpyrroles with different R₃ groups on the phenyl ring could be used with excellent results. Thus, halogen-containing substrates and those with free hydroxy, amino, or strong deactivating nitro groups were tolerated. The thermal configurational stability was analyzed in products with the smaller R₃ substituents. Even in these cases, no erosion of the enantiomeric excess was observed after heating at 80 °C for 18 h.

3.1.4. Atroposelective construction of the C–N stereogenic axis

Direct N–C coupling in hindered systems usually requires harsh reaction conditions that compromise the configurational stability of the C–N axis. Looking for a synthetic solution to this
Scheme 33. Satoh-Miura-type reaction of N aryloxindoles and alkynes.

Scheme 34. Atroposelective synthesis of N-aryl-tetrahydro-β-carbolines.

Scheme 35. Atroposelective alkylation using a chiral at-rhodium catalyst.
problem, the group of Colobert, Wencel-Delord and co-workers introduced in 2018 the use of hypervalent iodine reagents as highly electrophilic coupling partners for the distereoselective synthesis of axially chiral N-arylated indolines 113 via Cu-catalyzed Ullmann coupling (Scheme 36A). Taking advantage of the high reactivity of sterically encumbered chiral iodanes 111, the reaction with indolines 112 could be performed at low temperature furnishing these axially chiral C–N motifs in a highly atroposelective manner. A traceless sulfoxide auxiliary placed in the ortho-position of the iodine substituent was chosen to control the stereochemical course of the reaction. It was found that CuI salts performed better than CuII salts, and that the nature of the iodane counteranion had a minor impact on selectivity. Structurally diverse iodane and indolines worked well under the optimized conditions, leading to higher selectivities for the more sterically hindered substrates. A proposed mechanism suggested that the chemoselectivity was controlled by a π,π-stabilizing interaction between the p-tolyl group of the chiral auxiliary and the aromatic part of the indoline. More recently, the same group reported on the development of a catalytic asymmetric version of the same reaction (Scheme 36B). Thus, the reaction between indolines 115 and dissymmetric mesityl-aryl iodanes 114 bearing an unsubstituted primary amide was efficiently catalyzed by a Cu(I)/bisoxazoline L14 chiral complex, leading to N-aryl indolines 116. The reaction tolerates both Br and F substituents at different positions of the indoline ring, which is important for further functionalization and biological applications. The nature of the R1 group in the hypervalent iodine reagent is of critical importance: substrates with reduced steric hindrance deliver nearly racemic products. On the other hand, halogen-substituted iodanes are suitable reaction partners, affording the corresponding indolines in good yields and enantioselectivities. The crystal structure of one of the products (R1 = R2 = OMe, R3 = 7-Br, R4 = H) showed an intermolecular hydrogen bond between the N atom of the indoline and the amide motif, which highlights the importance of the latter in the efficiency of the reaction. Moreover, preliminary mechanistic studies revealed the occurrence of a nonlinear amplification involving multi-metallic copper species, together with a very fast initial rate of the reaction.

Conversely, Tan et al. reported an acid-catalyzed atroposelective C–H amination of azonaphthalenes 117 with carbazoles 118 for the synthesis of axially chiral N-arylcarbazoles 119, reaching good to excellent enantioselectivities by using spinol-derived chiral phosphoric acid C10 as the catalyst (Scheme 37A). This was the first organocatalytic method for the synthesis of such chiral motifs and represents an alternative to metal-catalyzed cross-coupling reactions for C–N bond formation. Since this reaction is redox neutral, no external

Scheme 36. Axially chiral N-arylated indolines by Cu-catalyzed Ullmann coupling.
oxidant was needed. A sterically hindered group at the C2 position of the carbazole substrate ensures configurational stability on the resulting products. Replacement of the R² group in the ester functionality consistently gave the desired products in excellent yields and with a similar high enantiocontrol. The electronic nature and position of the R¹ groups also had a limited effect on enantioselectivity. The authors propose a CPA-assisted central to axial chirality transfer process through H-bond activation and rearomatization. Indoles were also effective in this transformation, although a bulky R³ substituent at C3 was required to generate the desired products and a different catalyst was required to obtain optimal results (Scheme 37, B). Furthermore, it was found that the introduction of a methyl group at C3 of the azonaphthalene significantly increased the yield and also had a positive impact on the enantioselectivity.

More recently, Wang and co-workers reported on a highly atroposelective synthesis of axially chiral N-arylindolocarbazoles. To this end, the authors developed a Rh(II)-catalyzed intermolecular N–H insertion of diazaphthoquinone-derived carbenes into indolocarbazole precursors. The reaction proceeds under mild conditions to afford moderate to good yields and excellent enantioselectivities by using phthalimido-derived dirhodium catalyst Rh₃(S-PTAD)₂, C18 (Scheme 38). The reaction exhibits a wide substrate scope, providing satisfactory results for a variety of diazaphthoquinones and indolocarbazoles, regardless of the electronic and steric nature of the substituents. Moreover, the methodology can be used for late-stage functionalization of natural products and bioactive molecules and for the synthesis of novel chiral phosphoric acids (CPAs).

3.1.5. Atroposelective desymmetrization of achiral heterobiaryls

Kamikawa and co-workers reported the desymmetrization of planar-prochiral (π-arene)chromium complexes via an enantioselective ring-closing metathesis catalyzed by (R)-Mo-alkylidene catalyst C10, generating N-arylindoles with both planar and axial chirality (Scheme 39). These substrates contain η²-disopropenyl-2-N-indolyl ligands, in which the orientation of the aryl ring of the indole is anti with respect to the Cr(CO)$_2$ group. The presence of electron-donating groups on the phosphine moiety was crucial to obtain good reactivity and high enantioselectivity. For substrates with poorer electron-donating groups on the allylphosphine, the reaction did not occur. The proximal isopropenyl groups slow down the rotation around the (π-arene)-indolyl single bond, and their orientation is therefore fixed in the anti-configuration. Mechanistically, the first metathesis takes place between the catalyst and the P-allyl group, which is the less sterically hindered olefin. The ring-closing metathesis is then favored because the more electron-donating PR$_2$ group increases the electron density at the two isopropenyl groups through the chromium atom. As ligation of
a π-aromatic moiety in (arene)chromium complexes is electronically neutral, the π-aromatic can be detached under mild conditions (exposure of the chloroform solution to sunlight under air) giving axially chiral N-arylindoles 126 with complete retention of the enantiomeric purity. Elemental sulfur was used to trap the released phosphine. It was also determined that the geometry of the internal olefin formed was exclusively cis.

### 3.2. Axially chiral triazole derivatives

Triazoles, prominent representatives of heterocyclic compounds, are key structural motifs in a plethora of biologically active compounds and useful building blocks in the synthesis of natural products. As is the case with axially chiral pyrroles and indoles, the wider angles next to the axis in these five-membered ring compounds are responsible for their limited configurational stability with respect to biaryl derivatives.

Sugane and co-workers were the first to report a method to resolve phenyl triazole derivatives 127 via diastereomeric salt formation, identifying (1R,2S)-2-amino-1,2-diphenylethanol [(1R,2S)-ADPE] 128 as the most suitable and effective resolving agent (Scheme 40).[70] Salt formation was afforded after stirring for 4 h, and the resulting precipitate was recrystallized to afford the desired product (R)-127 in excellent yield and enantioselectivity. The resolving agent was further removed in acidic media and the undesired (S)-127 was almost quantitatively recycled to racemate by heating in DMA and then reused to prepare additional (R)-127. Finally, the carboxyl group was transformed into a cyano group to obtain an important GlyT1 inhibitor.

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**Scheme 38.** Asymmetric Rh-catalyzed carbene insertion reaction for the synthesis of axially chiral N-arylindolocarbazoles.

**Scheme 39.** Enantioselective ring-closing metathesis for the synthesis of N-arylindoles.
inhibitor (R)-129 in good yield and in enantiomerically pure form.

In 2016, Tan and co-workers described an organocatalytic asymmetric approach to an interesting class of axially chiral N-arylurazole derivatives 132 (Scheme 41A). The authors used a bifunctional thiourea-based organocatalyst C20 for the desymmetrization of the triazole diones 131 in Friedel-Crafts type amination of phenols/naphthols 130, transferring central and axial chirality from the catalyst into a stereogenic axis located far from the reaction site. A variety of phenols and 2-naphtols...
were tolerated, with limited influence of the electronic properties of the aromatic ring substituents on stereoselectivity. Similar conclusions were also drawn from the effect of substitution on the aromatic ring of triazolediones 131. Additionally, the ortho-substituent on ary lurazole was not only restricted to tert-butyl group. Thus, iodo, bromo, or phenyl groups at the ortho position also afford excellent enantioselectivities. The use of indoles 133 as nucleophiles needed further optimization, resulting in the identification of spirocyclic phosphoric acid C10 as the optimal catalyst to obtain N-ary lurazole derivatives 135 from triazolediones 134 (Scheme 41B). The electronic nature, size, or substitution pattern of the triazoledione and substituted indoles have only minimal effects on yields and enantioselectivities. All products 132 and 135 presented high thermal stability and both reactivity and stereoselectivity were retained in large-scale production.

Very recently, Chi and co-workers reported on the synthesis of related axially chiral pyrazolo[1,2-a]triazole derivatives 139. In this case, the products are formed via an atroposelective [3 + 2] annulation/desymmetrization of urazoles 136 in their reaction with ynals 137. Optimal enantioselectivities were achieved using the triazolium NHC catalyst C21 in the presence of quinone 138 as an external oxidant (Scheme 42). The C–N stereogenic axis is generated by atroposelective addition of a nitrogen atom of the urazole to the acylazolium intermediate formed upon activation of ynal 137 with the catalyst and subsequent oxidation.

### 3.3. Axially chiral benzimidazole derivatives

Recently, Toste, Miller and co-workers presented a comparative study of two distinct catalyst C22 and C23 that are effective for the atroposelective cyclodehydration of ortho-substituted aniline derivatives 140 to afford N-aryl benzimidazoles 141 (Scheme 43A). Catalyst C22 is a C₂-symmetric chiral phosphoric acid, while catalyst C23 is a peptide-based phosphoric acid in which standard variations of the peptide sequence led to significant improvements in selectivity. Both catalysts gave similar results with several substrates bearing electron-donating and electron-withdrawing groups. However, for compounds that presented substitution at C7 (R₂=7-Me, 7-Et, 7-iPr, 7-Ph, 7-OMe), phosphoric acid C22 was a less selective catalyst (44–83 % ee). On the other hand, both catalysts showed low enantioselectivities with ortho, ortho'-disubstituted substrates. Mechanistic DFT studies and experimental results suggested that the cyclization was the rate- and stereodetermining step. Steric effects on both the catalyst and the substrate dictate the enantioselectivity for catalyst C22. For catalyst C23, conformational adjustments minimize repulsive interactions. Similar benzimidazoles 143 have also been synthesized in a simple manner using an intramolecular Buchwald-Hartwigamination of amidines 142 (Scheme 43B). Excellent yields and enantioselectivities were achieved using the common combination of Pd(OAc)₂ as the precatalyst and (S)-BINAP L₂ as the ligand. It is noteworthy that the stereochemical result strongly depends on the nature of the amidine substituent in C1. Excellent enantioselectivities were achieved for trifluoromethylated substrates (R₂=CF₃) and slightly lower ee’s were observed for other fluorinated derivatives (R₂=CF₂Cl or

### Scheme 42. NHC-catalyzed atroposelective desymmetrization of urazoles.
However, the enantioselectivity drops substantially when simple alkyl- or aryl-substituted amidine substrates are used instead.

An alternative methodology for the atroposelective synthesis of axially chiral N-aryl benzimidazoles has recently been reported by Fu and co-workers. In this approach, the reaction of N-(aryl)benzene-1,2-diamines with dicarbonyl compounds proceeds with C–C bond cleavage of the latter, yielding products and , respectively. In both cases, hindered phosphoric acid was identified as the best catalyst, affording both types of products with moderate to good yields and excellent enantioselectivities (Scheme 44).

Furthermore, an atroposelective synthesis of axially chiral N-arylbenzimidazoles have also been very recently reported by Tan and co-workers. The strategy relies on the use of chiral phosphoric acid (CPA) catalysis for the C–N bond formation between 2- naphthylamine derivatives and nitrosoarenes as the electrophilic amination reagent (Scheme 45). Best results were collected with the previously developed spirocyclic catalysts . The reaction proceeds by dehydration of the initially formed addition intermediate, followed by isomerization of the resulting diimine (either by two consecutive reduction and oxidation steps of by a direct [1,5]-H migration), a second C–N bond formation in the stereodetermining step (SDS), and a final oxidative aromatization. Remarkably, the nitroso group acts as both an electrophilic and nucleophilic site in the two C–N bond-forming events.

3.4. Axially chiral cyclic imides

Simpinks and co-workers reported the asymmetric synthesis of axially chiral imides by enantioselective deprotonation of succinimide with a chiral lithium amide base (Scheme 46). In this way, the anti-isomer of the desired monoalkylated product was obtained with moderate yields but excellent enantioselectivities. A kinetic resolution via double alkylation of the minor enantiomer is responsible for the high enantiomeric excesses observed. The reaction provides straightforward access to a range of target molecules and could be applied to the total synthesis of (+)-hinokinin, whose enantiomer is present in a lignin natural product.

In 2007, Hayashi and co-workers developed a highly enantio- and diastereoselective construction of axially chiral N-arylsuccinimides by a rhodium-catalyzed asymmetric 1,4-addition reaction of aryl boronic acids to N-aryl succinimides (Scheme 47). Optimal results were obtained by using chiral diene ligand , thus reaching high yields, good diastereoselectivity and excellent enantioselectivities for a wide range of boronic acids. Different R1 and R2 substituents were tolerated, with the best results obtained for the more hindered....
Scheme 44. Atroposelective construction of axially chiral N-aryl benzimidazoles involving carbon–carbon bond cleavage.

Scheme 45. Atroposelective construction of axially chiral N-aryl benzimidazoles involving carbon–carbon bond cleavage.
derivatives. It was also found that the stereochemical information of the C–N axis could be efficiently transferred in subsequent transformations. This was exemplified by a diasteroselective alkylation of 156 that led to derivative 157 featuring an all-carbon quaternary stereogenic center.

Later, Tan et al. described a thia-Michael addition/enantioselective protonation sequence of N-substituted itaconimides 158 with thiols 159 to obtain a 1:1 atropisomeric mixture of anti- and syn- N-arylsuccinimides 160a and 160b (Scheme 48). Using tert-butylthiol and chiral guanidine C25 as the catalyst, a higher ee value was observed for the anti-diastereomer (89%) relative to the syn-diastereomer (72%). The atropisomerization rate was experimentally measured to be 32.4 kcal mol$^{-1}$ (R=^t^Bu), in good agreement with the value of 30.9 kcal mol$^{-1}$ at 298 K obtained from DFT calculations.

A Michael addition of unprotected 3-substituted-2-oxindoles 162 to N-arylmaleimide derivatives 161 was reported by Feng et al. in 2015 (Scheme 49A). Using a Sc(OTf)$_3$/N,N'-dioxide catalytic system based on ligand L16, adducts 163 were obtained in excellent yields and enantioselectivities. The addition of K$_2$HPO$_4$ as the base accelerates the reaction and allows to obtain only one of the possible isomers. A broad scope was demonstrated, with oxindole and maleimide derivatives with different substituents, including halogens, being suitable reaction partners. Later, Bencivenni et al. also demonstrated the ability of a squaramide-functionalized cinchonidine derivative C26 to promote the reaction of the same
maleimides 161 with N-Boc protected oxindoles 164 for the synthesis of adducts 165 (Scheme 49B). The bifunctional character of the catalyst containing a tertiary amine was essential to interact with the acidic proton at C3 of the oxindole and simultaneously as H-bond donor to coordinate the imide carbonyl, ensuring in this way a well-defined geometry in the transition state. Under optimal conditions, it was shown that the presence of diverse electron-withdrawing and electron-donating groups at the oxindole core did not affect the reactivity of the system. Furthermore, no loss of reactivity or stereoselectivity was observed with para or meta substituents in the maleimide. On the other hand, excellent results were obtained with halogenated maleimides, although a lower reactivity was observed for the larger ones.

A related strategy for the atroposelective synthesis of spirocyclic N-aryl succinimides 167 has also been recently reported.34 The method is also based on a desymmetrization of maleimides 161, making use in this case of a NHC-catalyzed Stetter-aldol/oxidation sequence from dialdehydes 166 (Scheme 50). Using triazolium salt C27 as the carbene precursor in the presence of DIPEA as the base and thiourea as an additive, a variety of products were obtained in good yields and enantioselectivities.

Lastly, axially chiral N-aryl succinimides 170 have been prepared from N-aryl 5-norbornene-2,3-dicarboximides 168 using a nickel-catalyzed enantioselective hydrocyanation with cyanohydrin 169 as a hydrogen cyanide surrogate (Scheme 51).35 The desymmetrization process proceeds with generation of central and remote N–C axial chirality, reaching high levels of enantioselectivity by using (R)-DM-SEGPHOS ligand ent-L11. The absence of a nonlinear effect (NLE) suggests that a monomeric [NiL11] complex is the catalytically active species, and control experiments confirmed the key role of the carbonyl groups of the substrate. Finally, computational DFT studies revealed that reductive elimination is the enantiodetermining step.

Scheme 49. A: Scandium-catalyzed Michael addition of 3-substituted-2-oxindoles to arylmaleimide derivatives. B: Organocatalytic atroposelective desymmetrization of maleimides.
4. N-Aryl/Vinyl Six-Membered Heterocycles

4.1. Axially chiral lactams

The above-mentioned intermolecular anilide N-arylation by Taguchi and co-workers (Scheme 10) could also be applied in an intermolecular fashion to anilide derivatives 171 for the atroposelective synthesis of cyclic products 172. Good ee's and excellent yields were observed by using a modified catalyst system comprising Pd(OAc)$_2$/(S)-BINAP L2 (Scheme 52A). This methodology was later applied by the authors to the synthesis of dihydroquinolinone derivatives 173 using a Pd(OAc)$_2$/(R)-SEGPHOS L10 catalyst (Scheme 52B). The synthesis of 174 precursor of a norepinephrine transporter (NET) inhibitor, was then carried out by diastereoselective $\alpha$-alkylation of the corresponding lactam enolate, where the attack of the electrophile occurs preferentially from the opposite side or the ortho-tert-butyl group, generating finally a quaternary carbon. anti-Markovnikov hydration of the allyl group followed by trans-tert-butylation was then performed under mild conditions to afford the target product.

In 2010, Tan and co-workers described an intramolecular hetero-Michael reaction of alkynylamide 175 for the synthesis of axially chiral lactam 176. Using Brønsted base-catalyst C28, this transformation proceeds via isomerization into chiral allene intermediates followed by cyclization (Scheme 53). Limitations in the preparation of related atropoisomeric six-membered lactams were encountered due to difficulties in the synthesis of suitable alkyne substrates.

Tanaka and co-workers have also described an atroposelective Rh(I)-catalyzed $\left[2+2+2\right]$ cycloaddition reaction of diynes 177 with ortho-substituted phenyl isocyanates 178 for the synthesis of axially chiral N-aryl-2-pyridones 179 (Scheme 54A). The optimal cationic catalyst was generated in situ from [Rh(cod)$_2$l]BF$_4$ and (R)-BINAP ent-L2. Under the optimized conditions, it was observed that an increase of the steric hindrance of the alkyl substituent at the 2-position of substrates 178 led to higher ee values but at expenses of yield. Conversely, substituents such as 2-OMe and 2-Cl afforded good yields but moderate ee’s. On the other hand, malonate-derived diynes, 1,3-diol-derived diynes, 1,6-diynes and ethylene-linked 1,7-diynes could all participate in the reaction although moderate enantioselectivities were reached.

Using the same approach, Takeuchi et al. later described that the alternative catalyst formed in situ from [Ir(cod)Cl]$_2$ and chiral diphosphines can also be used in the same transformation, reaching optimal enantioselectivities by using L17 as the ligand (Scheme 54B). The use of iridium instead of
rhodium or nickel has advantages, as the catalyst does not require preactivation. Under optimized conditions, the reaction worked well for a wide range of isocyanates 178. As in the precedent case, the higher the steric hindrance of R, the lower the observed yield. The reaction tolerates ortho-halophenyl isocyanates, with the bromo derivative giving a yield lower than that of the chlorine, although good enantioselectivities were observed in both cases. Alternatively, Ollivier and co-workers used in the same reaction an anion metathesis between the rhodium catalyst [Rh(cod)Cl]₂ and a chiral silver phosphate \( \text{C}_2\text{H}_3\text{O}_2 \) in order to generate in situ a catalytically active [Rh-(I)]-[phosphate] chiral complex (Scheme 54C). An H₂ atmosphere was initially used to accelerate decoordination of the cyclooctadiene ligand, but similar results were also obtained without H₂ premix, although a higher temperature was required to generate the catalytically active species. The presence of bulky R substituents in 178 provided better ee's under optimized conditions, but the use of halogenated derivatives (R = Cl, Br) was detrimental to both yield and enantioselectivity. Regarding the scope of the diynes 177, good results were obtained when Z was a diester, cyclic acetal, and N-tosyl group, but lower yields and selectivities were observed for an unsubstituted tether, indicating the underlying positive gem-dialkyl effect on the reaction.

Gu and co-workers developed a copper-catalyzed enantioselective Ullmann-type amination reaction for the construction of C–N atropisomers (Scheme 55). Using diamide L₁₈ as the optimal ligand, a series of biaryl bromo anilides 180 afforded the corresponding lactams 181 in excellent selectivities. Different substitution patterns in the biaryl skeleton and in the aniline fragment were well tolerated. Ortho-substituted alkyl substrates (R₃) in the latter, however, afforded lower yields due to steric hindrance, but the enantioselectivities remained excellent. Racemization studies indicated the need to work under mild conditions (below 60°C), to avoid racemization.

In 2016, Kitagawa et al.[90] reported on the atroposelective synthesis of C–N axially chiral N-aryl phenanthridin-6-ones 183 via Pd-catalyzed intramolecular Buchwald-Hartwig amination from bromo amides 182 (Scheme 56). Using (R)-DTBM-SEGPHOS L₄ as ligand, ortho-ethyl and ortho-methyl substituted products...
were obtained with moderate yield and enantioselectivity (25 and 68% ee respectively) although racemization of the products was also observed. Surprisingly, the use of bulky ortho-tert-butyl substituents led to poor yield and enantioselectivity, although these results could be improved by heating the reaction at 130 °C. This behavior was attributed to a high rotational barrier around the C–N chiral axis in the Pd-amine diastereomeric intermediates.

Very recently, Hong, Zhou and co-workers have developed an elegant approach for the synthesis of axially chiral N-arylphenanthridinones. The strategy relies on cooperative palladium/chiral norbornene (Pd/NBE*) catalysis, in what can be
considered as a variant of the Catellani reaction with an intramolecular amidation as the termination event. Thus, starting from ortho-substituted iodoarenes 184 and ortho-bromoanilides 185, an optimized catalyst formed by Pd(OAc)$_2$, tri(2-furyl)phosphine (TFP) and 2-ethyl ester-substituted norbornene C30 provided the desired products 186 in good yields and excellent enantioselectivities (Scheme 57). The process, supported by DFT calculations, starts with the oxidative addition of the Pd$^0$ catalyst to iodoarene 184, NBE$^*$ C30 insertion, and C–H activation leading to palladacycle intermediate A. Oxidative addition to 185 followed by reductive elimination and extrusion of the NBE transient mediator C30 affords the key Pd$^I$ intermediate B, featuring a transient C–C stereogenic axis from which the final C–N stereogenic axis originates with high levels of stereoselectivity during the final intramolecular amidation step via intermediate C and the final axial-to-axial chirality transfer to the N–C axis.

Very recently, He and co-workers$^{[92]}$ described the synthesis of axially chiral pyridones 189 through an iridium-catalyzed enantioselective allylic amination of cinnamyl carbonates 187 with the unsubstituted precursors 188, followed by a stereospecific central-to-axial chirality transfer process (Scheme 58). As a remarkable singularity, the C–N bond is built on an N-styryl moiety instead of the common N-aryl unit. The reaction proceeds smoothly using an iridacycle catalyst generated in situ with a chiral phosphoramidite ligand L19. The C–H amination procedure tolerates different para- and meta-substituted carbonates bearing electron-neutral, electron-donating, and electron-withdrawing groups, as well as difunctionalized derivatives, affording the corresponding products in excellent yields and enantioselectivities. Bulky substituents and heterocyclic rings were also tolerated, but a lower ee was obtained with ortho-substituted derivatives. Remarkably, the electronic properties of substituents on 2-quinolinol substrates have an important impact on enantioselectivity with electron-withdrawing groups...
at C4, resulting in a decrease in enantiocontrol. Density functional theory (DFT) studies revealed that the stereospecificity during the central-to-axial chirality transfer ([1,3]-H transfer) can be explained by the stabilizing H-bonding interaction between the base and the amide carbonyl group in the favored transition structure.

4.2. Quinazolinone derivatives

*N*-Aryl quinazolinone derivatives are privileged heterocyclic structures in medicinal chemistry as they possess a wide spectrum of biological activities. Their high rotational barrier compared to other axially chiral C–N compounds also makes them good chiral ligands candidates for asymmetric catalysis. Until 2006, quinazolinone derivatives could only be obtained in enantiomerically pure form after chromatographic separation in chiral stationary phases or classical resolution with chiral resolving agents. For example, Virgil and co-workers described in 1998 the synthesis of different racemic quinazolinone ligands from 2-chloroanilines (Scheme 59) and the resolution of the former, which was accomplished by means of chiral palladium dimer, a conventional resolving agent for monophosphines. Enantiomerically pure quinazoline complex and unreacted were obtained with high enantioselectivities. A more convenient strategy for larger-scale synthesis was applied to the resolution of analogue with (+)-camphorsulfonic acid (benzenesulfonyl)hydrazone as the resolving agent.

In 2006, Natsugari and co-workers reported a method for the atroposelective synthesis of quinazolinone derivatives through an atroposelective tribromination reaction of precursors into a wide range of substituted 3-arylquinazolin-4(3H)-ones through an atroposelective tribromination reaction of precursors (Scheme 61). High enantioselectivities were achieved by using a tertiary amine-embedded β-turn peptide catalyst. Even in the absence of ortho-substituents in the phenol ring, quinazolinones present a modest rotational barrier around the C–N axis (18.8 kcal/mol for R<sub>1</sub>=Me, R<sub>3</sub>=H). Therefore, the slow addition of NBS over 2.5 h was necessary for an efficient DKR to occur. A screening of truncated peptide catalysts provided evidenced that the β-turn secondary structure is important to achieve high levels of enantioinduction in this reaction. Under optimized conditions, it was possible to achieve good yields and high enantioselectivities for substrates possessing alkyl substituents at the 2-position (R<sub>1</sub>) or electron-donating and withdrawing groups at the phenol ring (R<sub>3</sub>), suggesting a weak effect of distal substitution on enantioselectivity. However, electron-withdrawing groups or lack of substitution at the 2-position (R<sub>1</sub>) led to products with a lower rotational barrier around the chiral axis, resulting in lower levels of enantioselectivity. Mechanistically, the chiral axis is set after the first bromination reaction at ortho-position.

Based on the results previously described by Miller, Kitagawa et al. reported in the following year a reductive desymmetrization of chiral quinazolinone derivatives into...
Scheme 59. Classical resolution of racemic quinazolinones.

Scheme 60. Diastereoselective dehydrative cyclization for the synthesis of quinazolinone derivatives.
debrominated derivatives 203 using palladium catalysts based on (R)-DTBM-SEGPHOS L4 as the ligand (Scheme 62). As an important strategic advance, the presence of an hydroxyl group at the C3 position of the phenyl ring, which hampered the synthesis of bioactive quinazolinone products in the previous method, is not required. During the optimization of the reaction, it was found that the enantioselectivity could be improved by decreasing the reaction temperature to 0 °C. Furthermore, reducing the amount of NaBH4 resulted in a considerable increase in the chemical yield of 203 at the expense of that of the fully dibrominated byproduct 204, although lower enantioselectivities were achieved. This result suggests that the enantioselectivity is determined not only by the desymmetrization process (the first dehydrodebromination), but also by a kinetic resolution of 203 (the second dehydrodebromination). The outcome of the reaction was significantly influenced by the R2 substituent, with alkyl groups affording a remarkable increase in enantioselectivity. However, the presence of methoxy or chlorine groups in R2 was found to decrease enantioselectivity due to the influence of inductive effects. Later, the same research group developed a diastereoselective α-alkylation reaction of lithium enamines, prepared from mebroqualone derivatives 203 (R1 = Et). Under optimized conditions, the resulting α-alkylation products 205 were obtained in good yields and diastereomeric ratios (up to 99 % yield and up to d.r. = 26:1.) The diastereoselectivity was found to be strongly dependent on the bulkiness of the R2 group. Thus, bulky alkyl halides, in particular isopropyl iodide, afforded

Scheme 61. Atroposelective tribromination of N-arylquinazolinones.

Scheme 62. Reductive desymmetrization of chiral quinazolinones.
the best results. The relative (R,S)-configuration of the major diastereomer could be explained by the steric repulsion between the R and the ortho-bromo groups.

4.3. Other six-membered heterocycles

The synthesis of biaryls compounds featuring both C–C and C–N axial chirality were reported by Hsung et al. in 2007. These products were obtained by a Rh(I)-catalyzed asymmetric [2 + 2 + 2] cycloaddition of ynamines 206 with 1,6-diynes 207 (Scheme 63).[106] Using (S)-DM-BINAP L8 as the ligand, cycloadditions of achiral 6-membered 2-oxazinone rings \( n = 1 \) afforded products with good yields and enantioselectivities, with the diastereomer 208b being formed preferentially (d.r. up to 8:1). In the case of ynamides containing 5-membered 2-oxazolidinones \( n = 0 \), the resulting chiral biaryl were also obtained in good yields and good to excellent enantioselectivities (82 to 99% ee), but with moderate diastereoselectivity (d.r. 1:1 to 1:6). The key step of the reaction is the chelation of the Rh metal by both the methoxy and carbonyl groups and the following cycloaddition yielding the major stereoisomer.

Kitagawa and co-workers described the enantioselective synthesis of C–N axially chiral quinolinone derivatives 211 by a palladium-catalyzed amination/cyclization of yrones 209 with ortho-tert-butyl aniline 210 (Scheme 64).[101] Low enantioselectivities and yields were observed when bidentate phosphines were used as ligands, while monodentate derivatives such as (R)-MOP L20 provided better results. As a limitation, ethynyl ketones with nonaromatic substituents were unproductive in the reaction.

Murata and co-workers developed a cyclization reaction of ureas 212 for the synthesis of axially chiral uracil derivatives 213 through the combined use of (R)-ALBO as a chiral auxiliary and quinidine C32 as a chiral organic base catalyst (Scheme 65).[102] The chiral auxiliary was placed in the ortho-position of the substituted N-phenyl group to effectively control the enantioselective cyclization. It was also found that the absolute configuration of the stereocenter at C9 of the catalyst C32 is crucial to achieve high diastereoselectivity due to the formation of an intermolecular hydrogen bond between the hydroxy group and the urea carbonyl group. Finally, removal of the (R)-ALBO auxiliary was successfully achieved to obtain the corresponding phenol derivative 214 under mild acidic conditions without significant racemization.

Finally, NHC catalysis has been exploited by Jin and co-workers[103] for the atroposelective cycloaddition of trioureas 215 with ynals 216 for the synthesis of axially chiral N-aryl thiadiazines 217 (Scheme 66). Moderate yields, but excellent enantioselectivities were achieved using triazolium salt C33 as the NHC precatalyst, DMAP as the base and furan as the solvent in the presence of Sc(O\(_2\)F\(_2\)) and 5 Å MS as beneficial additives to improve the yield of the thiadiazine product. The reaction involves NHC-catalyzed addition of 215 to acylazolium intermediate I,
leading to key intermediate II, which undergoes a face-selective intramolecular lactam formation. The reaction tolerates various functionalities, and it was found that the size of substituent $R_2$ on the $N$-phenyl moieties of the thiazine products plays a significant role in both chirality induction and stereochemical stability. As a limitation, aliphatic ynals are not suitable substrates in this reaction, leading to complex reaction mixtures.

In conclusion, the development of new synthetic methods for accessing axially chiral C–N atropisomers has emerged as a relevant goal in asymmetric catalysis. A minor number of these strategies have nonetheless been reported when compared with those for the synthesis of axially chiral biaryl scaffolds. Reasons for this difference include the lower configurational stability of the formers due to the high degree of freedom of their conformers and the reduced steric congestion around the C–N axis, in particular for the more challenging 5-membered ring atropisomers. This review has covered enantioselective strategies for the synthesis of atropisomers that display a stereogenic C–N bond, starting from the seminal work of Curran and Simpkins, and putting emphasis on catalytic asymmetric methods. The preparation of new families of atropisomers,
products and biologically active molecules, and as chiral ligands methods have found applications in the synthesis of natural stereogenic axis have been revised. Interestingly, many of these perspectives of the state-of-the-art in this fast-growing field and new innovative strategies need clearly to be developed. We expect that this review will help researchers to have an updated
discussion of the state-of-the-art in this fast-growing field and will stimulate the development of new approaches for the synthesis of this important family of compounds.

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Conflict of Interest

The authors declare no conflict of interest.
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