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Enantioselective Synthesis of Heteroatom-Linked Non-Biaryl Atropisomers

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Abstract: Atropisomers hold significant fascination, not only for their prevalence in natural compounds but also for their biological importance and wide-ranging applications as chiral materials, ligands, and organocatalysts. While biaryl and heterobiaryl atropisomers are commonly studied, the enantioselective synthesis of less abundant heteroatom-linked non-biaryl atropisomers presents a formidable challenge in modern organic synthesis. Unlike classical atropisomers, these molecules allow rotation around two bonds, resulting in low barriers to enantiomerization through concerted bond rotations. In recent years the discovery of new configurationally stable rare non-biaryl scaffolds such as aryl amines, aryl ethers and aryl sulfones as well as innovative methodologies to control their configuration have been disclosed in the literature and constitute the topic of this minireview.

1. Introduction

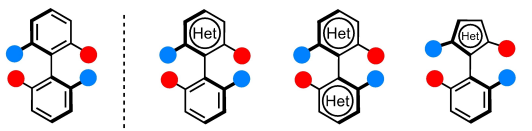
Atropisomers are of utmost interest due to their prevalence in natural products,^[1] but also for their biological relevance^[2] and their numerous applications as chiral materials,^[3] ligands^[4] and organocatalysts.^[5] Among them, biaryl and heterobiaryl atropisomers are the most common, and many synthetic approaches are available (Scheme 1a).^[6] Non-biaryl atropisomers constitutes another family of these axially chiral molecules with fewer synthetic approaches and consequently are less represented in the literature (Scheme 1b).^[7] Within this family, the highly challenging enantioselective construction of even less common heteroatom-linked atropisomeric structures such as aryl amines, -ethers or -sulfides still constitutes a daunting challenge of modern organic synthesis (Scheme 1c). This is mainly due to the fact that, unlike classical atropisomers, the rotation is possible around two $C(sp^2)$ -X bonds, which grants low barriers to enantiomerization via concerted bond rotations.^[8]

This crucial stereochemical feature was brought to light by the pioneering work of Fuji in 1998^[9] with diaryl ethers and studied in more detail by Clayden^[10] with both diaryl-ethers and amines clearly showing the need for bulky substituents around the two $C(sp^2)$ -X stereogenic axes to secure high enough barriers to enantiomerization (Scheme 1d, $\Delta G^\ddagger_{\text{enantiomerization}} > 93.3 \text{ kJ}\cdot\text{mol}^{-1}$ for Oki's definition,^[11] or $\Delta G^\ddagger_{\text{enantiomerization}} > 125.4 \text{ kJ}\cdot\text{mol}^{-1}$ for a class 3 atropisomer,^[12] according to LaPlante classification).

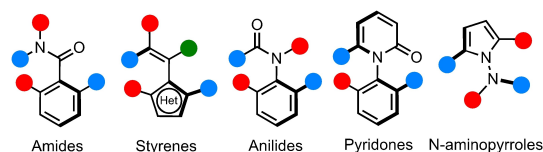
Such unusual stereogenic features are found in natural products such as vancomycin^[13] and bastadins,^[14] which contain two atropisomeric diaryl ether units (Scheme 2). Atropisomerism is also ubiquitous throughout modern drug discovery,^[15] but the potential axial chirality found in these rare families of heteroatom-linked non-biaryl atropisomers has been largely overlooked. Vandetanib, bosutinib and

tricyclazepam are three examples of such molecules with potential axial chirality. They are used in the treatment of chronic myelogenous leukemia (CML),^[16] as cell tumor proliferation inhibitor^[17] and as pesticide,^[18] respectively. In this domain, the irrelevant atropisomer contributes little to the desired activities^[19] and may even cause undesired side effects.^[20] Therefore, the discovery of new configurationally stable heteroatom-linked atropisomeric scaffolds as well as innovative methodologies to control their configuration, has started to emerge recently, justifying this review. Hence, it

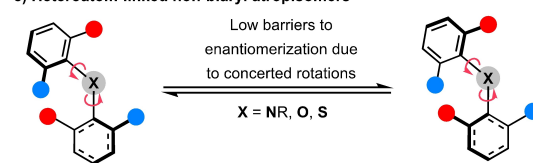
a) Biaryl and heterobiaryl atropisomers - Many examples



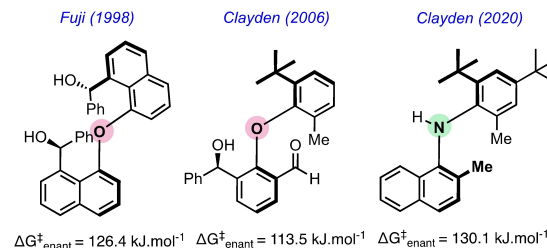
b) Non-biaryl atropisomers - Less represented



c) Heteroatom-linked non-biaryl atropisomers



d) Pioneer reports



Scheme 1. Heteroatom-linked non-biaryl atropisomers.

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will cover the history of the development in this field, based on a classification by heteroatom type.

2. Aryl Amines

Aryl amines play a crucial role in various biologically relevant targets, showcasing their widespread presence in medicinal chemistry and drug discovery.^[21] It is well known that they may exhibit atropisomerism if any structural element preventing the “concerted gearing” of the two C–N axes is present in the molecule (Scheme 1c). In this context, both intramolecular hydrogen-bonding interactions and steric repulsions have been proposed to secure configurational stabilization, allowing the enantioselective synthesis of aryl amines. These strategies will be presented in the two following subsections.

2.1. Configurational Stabilization by Hydrogen-Bonding

In 2020, Gustafson’s group reported the pioneering atroposelective synthesis of axially chiral diaryl amines **2**,^[22] building upon the concept previously described by Kawabata, which relies on the hydrogen-bonding enhancement of the barrier to enantiomerization.^[23] The pre-stereogenic C–N bond is already present in the substrate **1**, which undergoes a chiral phosphoric acid (CPA) **C1** catalyzed atroposelective electrophilic halogenation (Scheme 3a). This method results in a broad spectrum of stereochemically stable *N*-aryl quinoids **2**, thanks to an intramolecular hydrogen bond, with excellent yields and atroposelectivities, featuring barriers to enantiomerization of approximately 127 kJ.mol⁻¹. This initial instance paved the way for future strategies in the underexplored realm of enantioselective synthesis of axially chiral aryl amines. This atroposelective halogenation was later exploited by Chen and Li (Sche-



Abdelati Naghim studied chemistry at the University of Chouaib Doukkali (Morocco), where he obtained his bachelor's degree in 2018, followed by two master diplomas, with the most recent one in organic synthesis from the University of Poitiers. After completing his studies, he joined Aix-Marseille University, where he is currently undertaking a PhD under the supervision of Prof. Damien Bonne, Dr Gaëlle Chouraqui, and Dr Olivier Chuzel. His research interests focus on the enantioselective organocatalyzed synthesis of non-biaryl atropisomers.



Jean Rodriguez was born in Cieza (Spain) in 1958, and studied chemistry at the University of Aix-Marseille (France), he completed his Ph.D. in 1987, and his Habilitation in 1992. He is currently Professor and was appointed Director of the UMR-CNRS-7313-iSm2 until December 2023. His research interests include the development of multiple bond-forming transformations and their application in stereoselective organocatalyzed synthesis. In 2021 he was awarded the “Grand Prix Emile Jungfleisch from the French Academy of Sciences”.



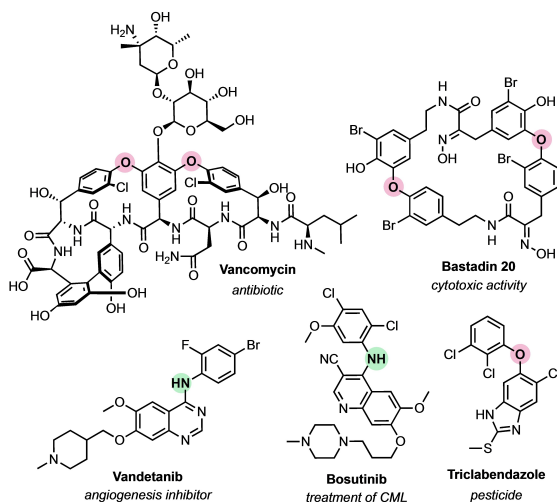
Olivier Chuzel obtained his PhD in 2006 from the Catholic University of Louvain (Belgium) under the supervision of Professor O. Riant. He then proceeded to complete two postdoctoral trainings in the laboratory of E. Schulz (ICCMO, Paris-Saclay University) and in the laboratory of V. Vidal (Chimie ParisTech—PSL). He was subsequently appointed as an Assistant Professor at Aix-Marseille University in 2008. His research interests encompass the development of novel catalytic and enantioselective processes, with a particular interest in boron chemistry and the chemistry-physics interface.



Gaëlle Chouraqui obtained her PhD in 2003, from Université Pierre et Marie Curie. After postdoctoral training at Wayne State University and the University of Cambridge, she was appointed CNRS Tenured-Researcher in 2007 at Aix-Marseille University. Her research interests are centered on: the development of novel methodologies to reach molecular complexity, the reactivity of donor-acceptor cyclopropanes, and main group catalysis.

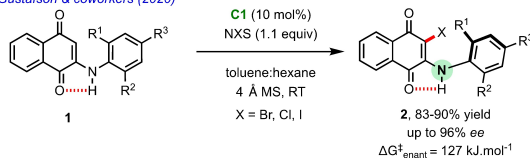


Damien Bonne obtained his PhD in 2006 from the ‘Institut de Chimie des Substances Naturelles’ (ICSN) under the direction of Prof. Jieping Zhu working on multicomponent reactions. After a postdoctoral training in the group of Prof. Varinder Aggarwal (Bristol), he was appointed Lecturer at Aix-Marseille University in 2007. He was promoted Full Professor in 2022 and in 2023, he became “Junior Distinguished Member” of the French Chemical Society. His research focuses on the development of enantioselective methodologies for the control of axial and helical chiralities.

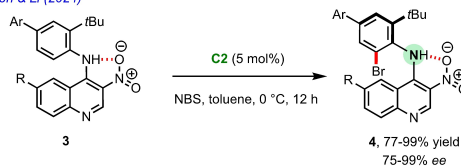


Scheme 2. Heteroatom-linked non-biaryl atropisomers in natural products and drugs.

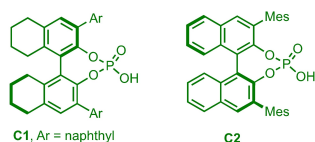
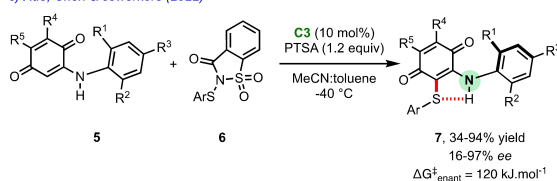
a) Gustafson & coworkers (2020)



b) Chen & Li (2024)



c) Xue, Chen & coworkers (2022)



Scheme 3. Chiral organocatalysts-mediated atroposelective electrophilic functionalization.

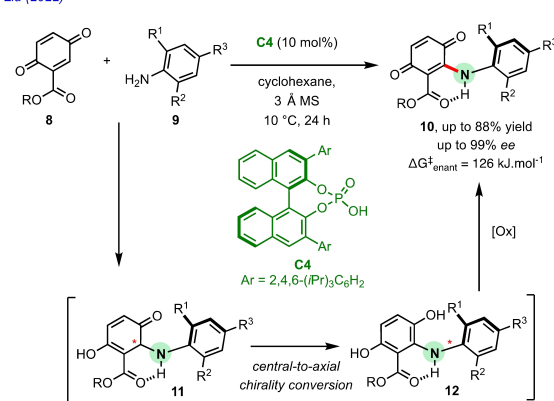
me 3b) from quinolines **3** already featuring an intramolecular $\text{NO}_2\cdots\text{H-N}$ bond but with low barriers to enantiomerization due to the lack of a second *ortho*-substituent on the *N*-aryl group.^[24] Hence, in the presence of *N*-bromosuccinimide

(NBS) and CPA catalyst **C2**, an enantioselective *ortho*-bromination occurred, delivering the desired atropostable aryl amines **4** with excellent yields and high enantiomeric excesses.

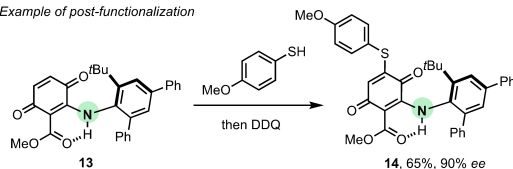
Xue & Chen^[25] also employed the “hydrogen-bonding” concept. The electrophilic sulfenylation of **5** with sulfenylating reagent **6** assisted by *para*-toluenesulfonic acid (PTSA) and in the presence of a chiral Lewis base such as the newly designed 6,6'-disubstituted SPINOL catalyst **C3**, afforded the corresponding sulfonyl quinones **7** in moderate to excellent yields and enantioselectivities (Scheme 3c). This strategy hinges on rigidifying the scaffold of the starting quinone through a $\text{N-H}\cdots\text{S}$ bond, effectively constraining the system and its environment from an atroposelective perspective. The latter assertion is supported by computational studies.

Liu and colleagues' method^[26] distinguishes itself from previous examples by facilitating direct C–N bond formation through a domino process via an enantioselective azamichael addition leading to centrally chiral intermediates **11** with a six-membered ring intramolecular $\text{N-H}\cdots\text{O}$ hydrogen bond interaction (Scheme 4). Subsequent tautomerization with central-to-axial chirality conversion^[27] and in situ oxidation of the resulting axially chiral hydroquinones **12** render a new family of *N*-aryl quinone atropisomers **10**. This direct **C4** CPA-catalyzed atroposelective coupling between quinone esters **8** and hindered anilines **9** proceeded in good yields and enantioselectivities (up to 88% yield and 99% *ee*, Scheme 4). The six-membered intramolecular $\text{N-H}\cdots\text{O}$ bond stabilizes the quinone in a planar conformation and prevents

Liu (2022)



Example of post-functionalization



Scheme 4. Enantioselective synthesis of *N*-arylated quinoid atropisomers via organocatalytic *N*-arylation/oxidation.

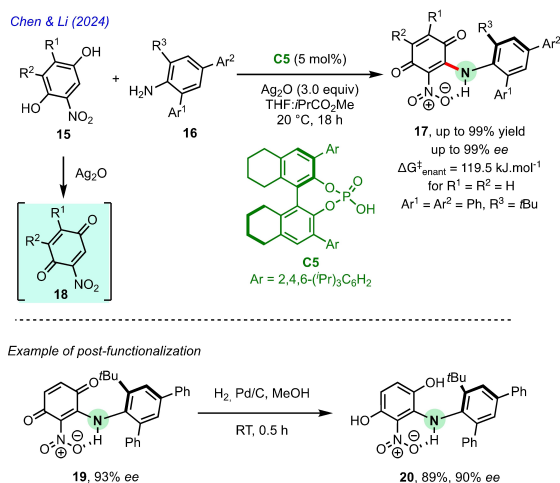
a complex conformational profile which would lead to racemization. Subsequently, the authors highlighted the synthetic potential of the obtained compounds through various post nucleophilic additions of thiophenols or indoles on the quinone Michael acceptor (e.g., **13**) and subsequent oxidation, which gave highly functionalized *N*-aryl quinones (e.g., **14**) with preserved enantiopurity.

Brønsted acid organocatalysis with **C5** could also successfully promote the atroposelective silver-mediated oxidative domino reaction of nitro-functionalized hydroquinones **15** with substituted anilines **16** (Scheme 5).^[24] Key to the success is the in situ generation of highly reactive nitroquinones **18** resulting in the formation of the aza-Michael addition products, which upon a second oxidation delivered the final atropisomeric anilines **17**. The resulting six-membered intramolecular NO₂⋯H–N hydrogen bond fixes one C–N axis of the aryl amine providing the desired adducts **17** in good yields and excellent enantioselectivities (up to 99 % yield, up to 99 % *ee*). This methodology proves to be a platform for the synthesis of structurally diverse optically active secondary amine atropisomers through further functionalization (e. g. **19** to **20**).

2.2. Configurational Stabilization by Steric Repulsion

Other recent strategies have emerged, standing out as they disclose atroposelective electrophilic amination without intramolecular H-bonding. In these approaches, the presence of highly bulky groups (R = *tert*-butyl, adamantyl) is therefore necessary to achieve sufficiently high barriers to enantiomerization by steric repulsion.

In the next approaches, the stereogenic C–N bond is created between an electrophilic nitrogen atom and a carbon centered nucleophile. Hence, Liao & Zhong disclosed a CPA-C6-catalyzed atroposelective electrophilic amination

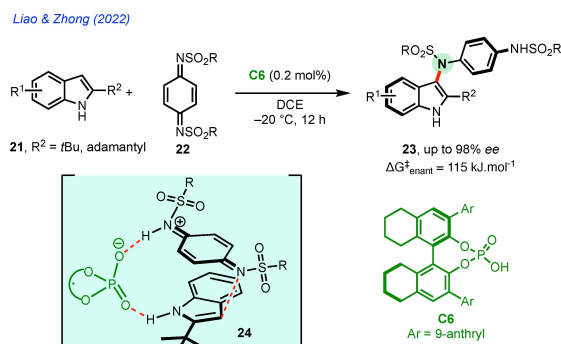


Scheme 5. Atroposelective domino reaction for the synthesis of *N*-aryl aminoquinones.

of 2-substituted indoles **21** via regioselective 1,6-addition to *p*-quinone sulfonyl dimines (QDI) **22** as highly electrophilic nitrogen source delivering the corresponding *N*-arylaminoindoles **23** in good yields, with excellent enantioselectivities (Scheme 6).^[28] The scope here is limited to tertiary sulfonyl heterodiaryl amines bearing a bulky R² substituent (*tert*-butyl, *tert*-pentyl, adamantyl) on the indole moiety. Control experiments and extensive computations allowed to propose an ionic nucleophilic process, with a more exergonic driving force for the regioselective C–N bond formation (versus C–C), rather than a radical pathway. The strong inductive sulfonyl group drastically enhanced the electrophilicity of the QDI imine nitrogen, which upon protonation by the CPA can evolve through transition state **24** featuring high degree of aromaticity and accounting for the observed stereoselectivity.

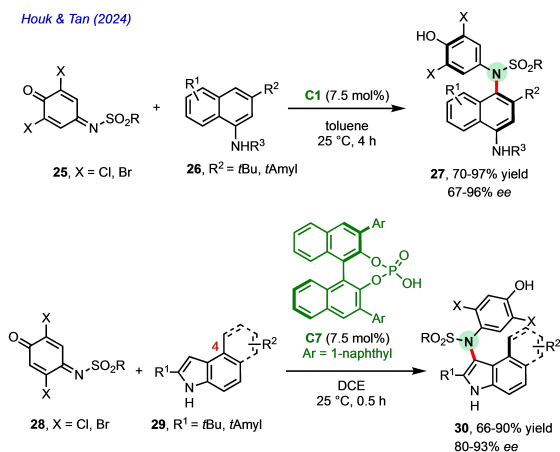
A closely related catalytic enantioselective umpolung reaction of *N*-sulfonyl iminoquinones **25** as *N*-electrophilic arenes has been developed with CPA catalyst **C1**, enabling the atroposelective amination of C3-substituted 1-naphthylamines **26** to access *N*-sulfonyl diaryl amine atropisomers **27** in good yields (up to 97 %) and high enantiomeric excesses (up to 96 %) (Scheme 7).^[29] As in the previous study (see, Scheme 6), the key feature is the polarity reversal of highly electrophilic imines, promoted by aromatization upon protonation. The method was also applicable to C2,C4-disubstituted indoles **29** as C-nucleophiles, with **C7** as CPA organocatalyst, which gave the corresponding heterodiaryl amines **30** in excellent yields and atroposelectivities, but failed to elucidate the origin of the enantioselectivity.

Finally, Yang started from diaryl amines **31** featuring a prosterogenic C–N bond,^[30] and developed a CPA-C4-catalyzed atroposelective electrophilic *ortho*-amination employing azodicarboxylates, which afforded a variety of axially chiral secondary diaryl amines **32** in good yields with high enantioselectivities (Scheme 8). Notably, the presence of an *ortho-tert*-butyl group is mandatory in this study to reach high enough barriers to enantiomerization.



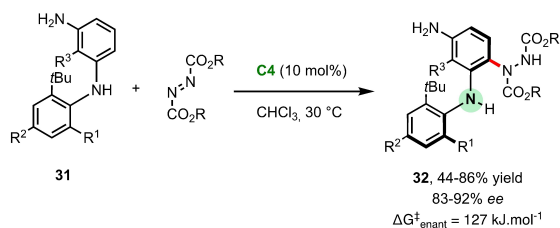
Scheme 6. Atroposelective access to *N*-sulfonyl-3-arylaminoindoles.

Houk & Tan (2024)



Scheme 7. Brønsted acids catalyzed enantioselective umpolung reaction of iminoquinones.

Yang (2024)



Scheme 8. Atroposelective synthesis of diaryl amines via organocatalyzed electrophilic amination.

3. Aryl Ethers

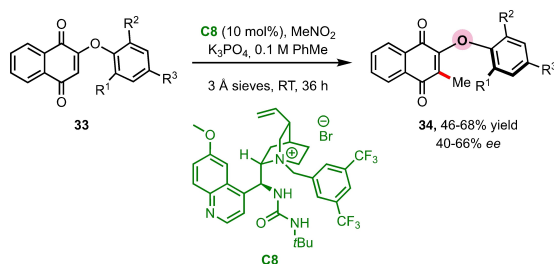
Controlling the axial chirality of aryl ethers holds significant importance due to their relevance in biologically active molecules such as the well-known vancomycin,^[13] their architectural significance in the development of novel ligands,^[31] and their applications in materials science.^[32] The control of axial chirality in aryl ethers is a complex endeavor due to lower barriers to rotation around the two C–O axes. The conformational freedom is therefore increased, leading to less spatial interactions between substituents. In addition, as compared to axially chiral aryl amines, which can incorporate a third substituent on the nitrogen atom to bring additional steric congestion, this is not possible with a divalent oxygen atom in aryl ethers. Relatively underexplored, synthetic strategies for achieving precise stereochemical control have recently gained significant attention, with a notable surge in publications on this subject over the past year. It is noteworthy that all strategies for achieving axial chirality in aryl ethers rely on the pre-existing C–O axis, which configurational stabilization is secure by steric repulsion.

The group of Gustafson capitalized on their previous methodology for the atropocontrol of C–N bond in aryl amines^[22] (see above) to develop an organocatalyzed atroposelective C(sp²)–H alkylation of functionalized naphthoquinone **33** via an addition/elimination process with nitromethane to access enantioenriched aryl ethers **34** under phase-transfer catalysis with **C8** (Scheme 9).^[33] Although this approach is limited in terms of substrate scope and enantioselectivity, this example stands alone as the only one not involving a desymmetrization reaction.

Apart from the previous still unique example, enantiomerically pure aryl ethers are typically produced through desymmetrization of prochiral substrates.

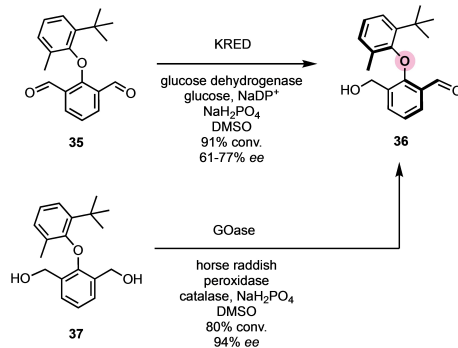
In this field, Clayden and Turner described the first catalytic atroposelective synthesis of axially chiral diaryl ethers **36** (Scheme 10). The enzyme-catalyzed desymmetrization of prochiral diaryl ether dicarboxaldehydes **35** occurs either via reduction with a ketoreductase (KRED) or through oxidation of prochiral diol **37** with a galactose oxidase (GOase).^[34] This process allowed to reach very high enantiomeric excesses (up to 94% *ee*). Despite a limited substrate scope, this example has paved the way for other desymmetrization approaches of various *o,o'*-difunctionalized diaryl ethers including alkynes or amines (see below).

Gustafson (2018)



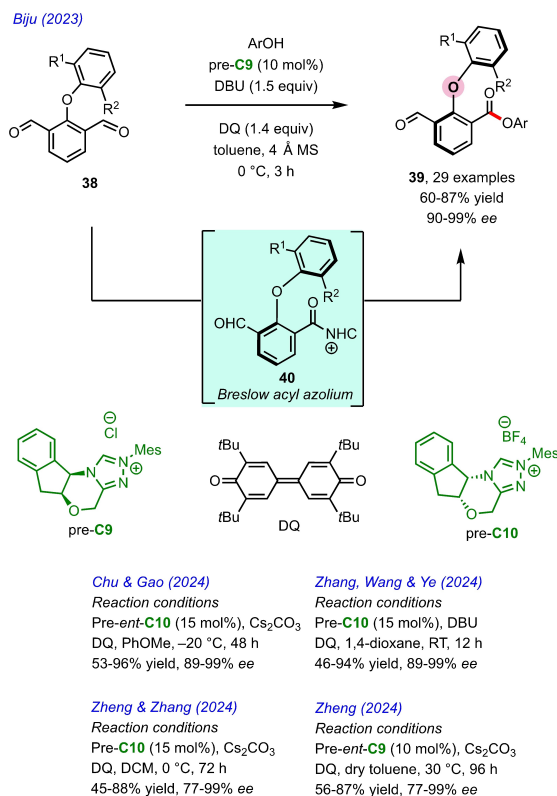
Scheme 9. Atroposelective C(sp²)-H alkylation of prostereogenic aryl ethers.

Clayden & Turner (2010)



Scheme 10. Biocatalyzed desymmetrization.

Recently, and independently, five different groups have reported the use of N-heterocyclic carbene (NHC) organocatalysts for the desymmetrization of pro-axially chiral dialdehydes.^[35] Activation of the carbonyl group thanks to the NHC pre-catalyst **C9** was first reported by Biju in 2023^[35a] and followed this year by four closely related complementary contributions^[35b-e] using structurally close NHC leading to the efficient desymmetrization of axially prochiral dialdehydes **38** (Scheme 11). From a mechanistic point of view, the reaction with pre-catalyst **C9** could generate the atropisomerically enriched Breslow acylazolium intermediates **40** under oxidative conditions using bisquinone (DQ) followed by a nucleophilic substitution with various (hetero)aromatic alcohols (ArOH). Preliminary studies aimed at explaining the origin of enantioselectivity, tend to suggest a preference for simple desymmetrization over background kinetic resolution. The authors have obtained a series of C–O axially chiral diaryl ethers **39** with good yields and excellent enantioselectivities. This reaction features a broad scope under mild conditions. Given that a major drawback in the development of C–O axially chiral ethers is the low rotational barrier of the C–O bonds, thermal racemization studies have been conducted and indicate that the isolated products possess high configura-



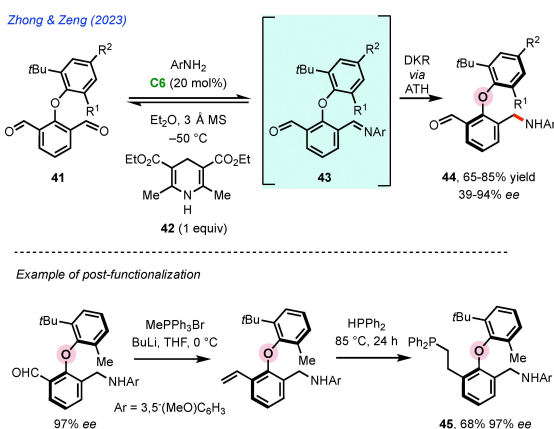
Scheme 11. NHC-catalyzed desymmetrization.

tional stability. This offers a versatile platform, enabling access to structural diversity.

Other organocatalysts have been involved in the atroposelective synthesis of axially chiral diaryl ethers, with several studies demonstrating the utilization of CPAs. Zhong and Zeng reported an elegant Dynamic Kinetic Resolution (DKR) approach involving a CPA-**C6**-catalyzed Atroposelective Transfer Hydrogenation (ATH) with Hantzsch ester **42** starting from dialdehydes **41** and simple anilines (ArNH₂) (Scheme 12).^[36] A plausible mechanism suggests that one of the two enantiomers of the in situ formed imine intermediates **43**, undergo faster ATH allowing a DKR process based on the reversible formation of the imine. This approach features good functional group tolerance, scale-up synthesis, and broad substrate scope (up to 79% yield and 95% ee). The synthetic value was further highlighted by late-stage functionalization, as for example a two-step olefination/1,2-hydrophosphination sequence for the access to stereocontrolled axially chiral phosphine **45**.

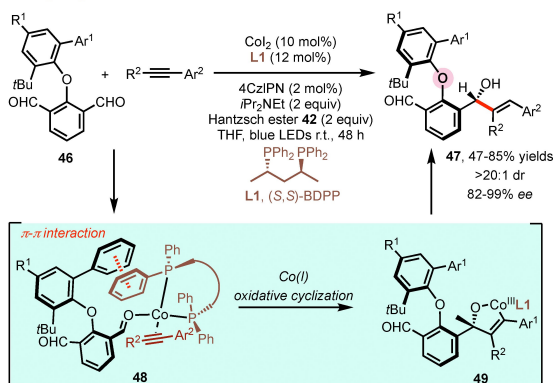
In a complementary organometallic approach, the group of Li and Yu developed a cobalt-catalyzed photoreductive desymmetrization of pro-axially chiral dialdehydes **46** for the expedient synthesis of axially and centrally chiral more challenging diaryl ethers **47**.^[37] This unique example of dual stereocontrol involves the reductive coupling with disubstituted alkynes in the presence of (*S,S*)-BDPP chiral diphosphine ligand **L1**, commercially available carbazoyl isophthalonitrile photocatalyst 4CzIPN and Hantzsch ester **42** as reducing agent gave the best results under blue LED irradiation. The reaction is triggered by a favorable π - π interaction in **48** between the bis-aldehyde **46** and the chiral phosphine ligand leading to a key cobaltacycle intermediate **49** by an oxidative cyclization considered to be both the enantio- and diastereo-determining step (Scheme 13). Interestingly, the resulting bulky secondary allylic alcohol fragment increase the configurational stability of the products.

In complement to the desymmetrization of dialdehydes, the group of Yang reported a CPA-catalyzed enantioselective



Scheme 12. CPA-catalyzed atroposelective ATH desymmetrization of dialdehydes.

Yu & Li (2024)

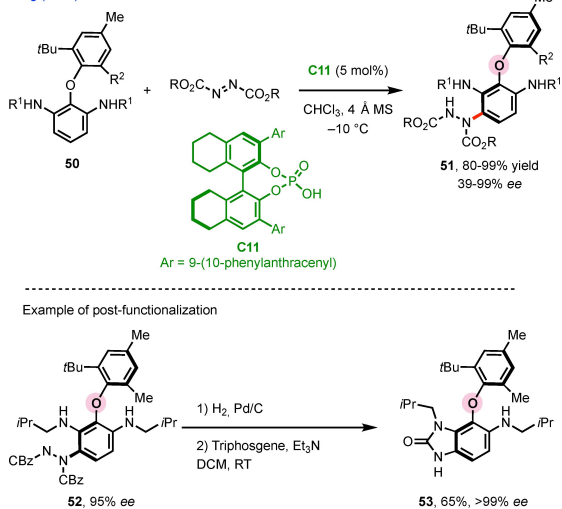


Scheme 13. Cobalt-mediated photoreductive desymmetrization.

tive electrophilic aromatic amination of symmetrical 1,3-benzenediamines **50** with **C11** to give diaryl ether atropisomers **51** in excellent yields and enantioselectivities (Scheme 14).^[38] Gram-scale synthesis and several post-transformations demonstrated the synthetic utility of this process, as for example the easy conversion of the product **52** to benzoimidazolone derivative **53**, demonstrating the synthetic usefulness of the electrophilic amination process.

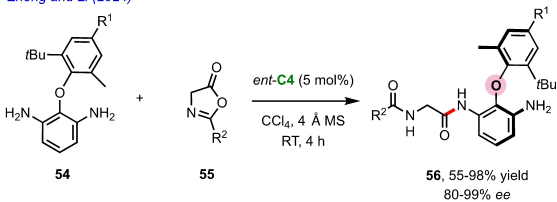
From related prochiral 1,3-benzenediamines **54**, Zheng and Li described an atroposelective acylation reaction using azlactones **55** as acylating reagents catalyzed by chiral phosphoric acid *ent*-**C4** (Scheme 15).^[39] Benzamide atropisomers **56** were obtained in moderate to excellent yields and high enantioselectivities. Kinetic of racemization experi-

Yang (2023)

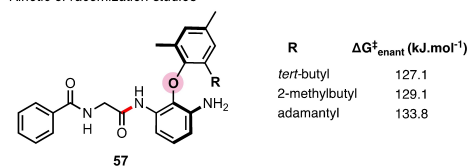


Scheme 14. CPA-catalyzed atroposelective electrophilic aromatic amination of prochiral 1,3-benzenediamines.

Zheng and Li (2024)



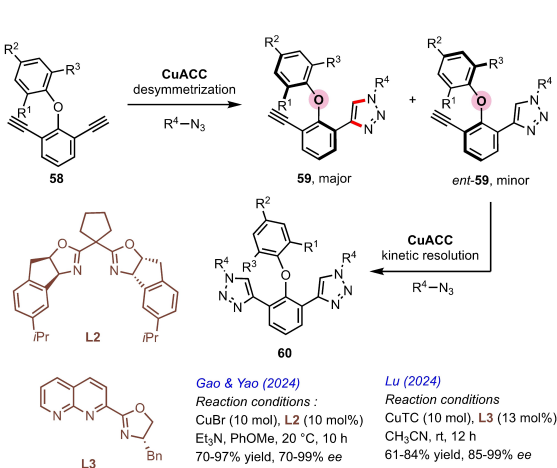
Kinetic of racemization studies



Scheme 15. CPA-catalyzed atroposelective acylation of prochiral 1,3-benzenediamines.

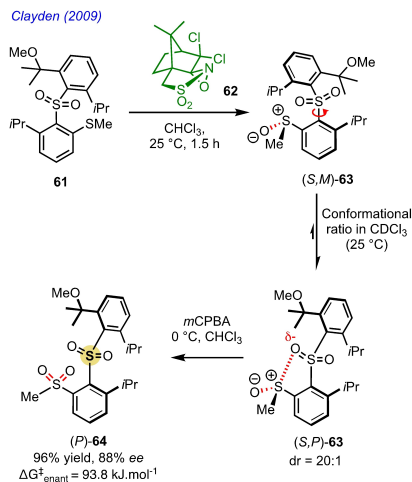
ments have allowed to determine barriers to enantiomerization of three benzamides ranging between 127.1 and 133.8 kJ.mol⁻¹, depending on the nature of the *ortho* substituent on the phenyl moiety.

In the competitive field of atroposelective synthesis of axially chiral diaryl ethers, Gao and Yao,^[40] on one hand, and Lu,^[41] on the other, have successively reported approaches starting from dialkynes **58** using the Copper Alkyne-Azide click Cycloaddition (CuAAC) strategy with simple azides in the presence of chiral oxazoline ligands **L2** or **L3** (Scheme 16).^[42] Mechanistically and in both cases, this reaction involves a sequential enantioselective desymmetrization-kinetic resolution leading to axially chiral triazolodiarylethers **59** in excellent yields and enantioselectivities when at least one *ortho*-substituent (R³) is a bulky *tert*-butyl or *tert*-pentyl group, while adamantyl or isopropyl gave much lower enantioselectivity and a racemic compound is

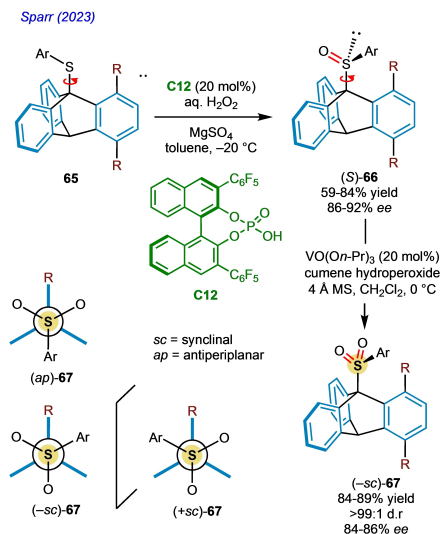


Scheme 16. Copper Alkyne-Azide click Cycloaddition (CuAAC) strategy.

obtained with an ethyl. The success of this transformation lies on the formation of the bis-triazole adduct **60** from the minor enantiomer, after the desymmetrization step. Experimental determination of the barrier to rotation indicates good configurational stability around the two C–O axes ($\Delta G^\ddagger_{\text{enant}} = 150 \text{ kJ}\cdot\text{mol}^{-1}$ for $R^1=\text{Me}$, $R^2=\text{H}$, $R^3=i\text{Pr}$, $R^4=\text{Bn}$), allowing diverse functionalization of products.



Scheme 17. First atroposelective synthesis of a diaryl sulfone by dynamic thermodynamic resolution.



Scheme 18. Stereoselective synthesis of triptycyl aryl sulfone atropisomers.

4. Aryl Sulfones

The stereogenic C–S bond is more challenging to obtain due to its longer length compared to C–O and C–N bonds (C–O=1.43 Å; C–N=1.48 Å; C–S=1.8 Å)^[43] and nowadays, no atroposelective synthesis of diaryl sulfides is known^[44] only two approaches have been reported to date dealing with sulfones and sulfoxides. In 2009, the Clayden group described one single example of atroposelective control of a C–SO₂ bond, leading to the formation of diaryl disulfone **64** with satisfactory yield and enantioselectivity (Scheme 17).^[45] Despite the low barrier to rotation, potentially related to the length of the C–S bond, a dynamic thermodynamic resolution could be observed by oxidizing the corresponding sulfanyl sulfone **63** obtained by oxidation of dimethyldisulfide **61** with oxaziridine **62**. A good to excellent diastereomeric ratio was observed, attributed to a dipole interaction between sulfone and sulfoxide, as well as steric repulsion between methyl and 2-*i*Pr-6-(2-methoxypropan-2-yl)phenyl substituents.

More recently, Sparr's group reported a stereoselective synthesis of threefold stereogenic triptycyl aryl sulfones **67**,^[46] governing C–S axis stereogenicity through a catalytic oxidative sequence of triptycyl thioethers **65** (Scheme 18). The (*S*)-sulfoxides **66** were obtained by CPA-**C12**-catalyzed sulfoxidation of thioethers **65** in good to excellent enantioselectivity. Subsequently, a second oxidation of the enantioenriched sulfoxides **66** with cumene hydroperoxide in the presence of vanadyl acetylacetonate provided a series of configurationally stable sulfone atropisomers (–*sc*)-**67** via a central-to-axial chirality conversion with remarkable enantiospecificity and diastereoselectivity, achieving stereoisomeric ratios of (–*sc*):(+*sc*):(*ap*) = 93:7:<1.

5. Conclusion

The atroposelective synthesis of heteroatom-linked non biaryl atropisomers stands as a remarkable achievement in organic chemistry. Through innovative strategies and meticulous optimization, chemists have succeeded in controlling the atroposelectivity of these reactions, paving the way for the synthesis of complex molecular architectures with tailored properties and functionalities.

The synthesis of compounds featuring two contiguous atropisomeric C–N axes poses a distinct set of obstacles owing to their inherent flexibility. However, researchers have adeptly navigated this complexity. One notable approach entails the formation of intramolecular hydrogen bonds, crucial for maintaining stable axial chirality and stabilizing one of the planar axial conformations. The field of aryl amine atroposelective synthesis has undergone a notable evolution over a short and prolific period. Strategies predominantly relied on electrophilic functionalization starting from a prosterogenic C–N bond, where chiral phosphoric acid (CPA) has emerged as a catalyst of choice.

The atroposelective synthesis of aryl ethers, with the exception of a single example, largely relies on the desymmetrization approach, starting from a preformed pro-

chiral C–O axis. Consequently, a significant challenge remains to be addressed: developing an approach capable of forging one of the C–O axis atroposelectively.

Methods for the stereocontrol of axially chiral aryl sulfides have yet to be discovered and atropisomeric aryl sulfones are the only ones currently synthetically available probably because of higher challenge to reach high enough barriers to rotation around the C–S bond. The elegant solutions disclosed until now in a very short period of time underscore the innovative strategies employed to advance atroposelective synthesis, ultimately contributing to the development of complex molecular architectures with promising properties and functionalities.

The construction of an axially chiral aryl phosphorous compounds has never been reported. One example of low C–P barrier to diastereomerization ($\Delta G^{\ddagger}_{\text{diast.}} = 60 \text{ kJ.mol}^{-1}$) in a chiral phosphine oxide, was described by Gasparrini and co-workers,^[47] which makes this goal highly challenging but nevertheless achievable.

Finally, the atroposelectivity around a C–B^[48] bond has been tackled very recently^[49] and compiled in a recent article,^[50] but unlike the different approaches detailed in the present review, the boron atom is included in a cycle and the enantiomerization of these compounds necessitates the rotation around on single C–B bond.

The progress made in atroposelective synthesis not only expands our synthetic toolbox but also enhances our understanding of molecular chirality and its role in shaping chemical reactivity and biological activity. Successfully tackling of the many remaining challenges could lead to groundbreaking advancements in atroposelective synthesis, offering new avenues for the creation of complex molecular architectures with precise control over stereochemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

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

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