



**HAL**  
open science

# Enantioselective Synthesis of Atropisomers by Oxidative Aromatization with Central-to-Axial Conversion of Chirality

Clément Lemaitre, Stefania Perulli, Ophélie Quinonero, Cyril Bressy, Jean Rodriguez, Thierry Constantieux, Olga García Mancheño, Xavier Bugaut

## ► To cite this version:

Clément Lemaitre, Stefania Perulli, Ophélie Quinonero, Cyril Bressy, Jean Rodriguez, et al.. Enantioselective Synthesis of Atropisomers by Oxidative Aromatization with Central-to-Axial Conversion of Chirality. *Molecules*, 2023, 28, 10.3390/molecules28073142 . hal-04410491

**HAL Id: hal-04410491**

**<https://hal.science/hal-04410491>**

Submitted on 22 Jan 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# Enantioselective Synthesis of Atropisomers by Oxidative Aromatization with Central-to-Axial Conversion of Chirality

Clément Lemaitre <sup>1</sup>, Stefania Perulli <sup>2</sup>, Ophélie Quinonero <sup>1</sup>, Cyril Bressy <sup>1</sup>, Jean Rodriguez <sup>1</sup>, Thierry Constantieux <sup>1</sup>, Olga García Mancheño <sup>2,\*</sup>  and Xavier Bugaut <sup>1,3,\*</sup>

<sup>1</sup> Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, 13397 Marseille, France; c.lemaitre13@gmail.com (C.L.); ophelie.quinonero@gmail.com (O.Q.); cyril.bressy@univ-amu.fr (C.B.); jean.rodriguez@univ-amu.fr (J.R.); thierry.constantieux@univ-amu.fr (T.C.)

<sup>2</sup> Organic Chemistry Institute, University of Münster, Corrensstraße 36/40, 48149 Münster, Germany; perulli@uni-muenster.de

<sup>3</sup> Université de Strasbourg, Université de Haute-Alsace, CNRS, LIMA, UMR 7042, 67000 Strasbourg, France

\* Correspondence: olga.garcia@uni-muenster.de (O.G.M.); xbugaut@unistra.fr (X.B.)

**Abstract:** Atropisomers are fascinating objects of study by themselves for chemists but also find applications in various sub-fields of applied chemistry. Obtaining them in enantiopure form is far from being a solved challenge, and the past decades has seen a surge of methodological developments in that direction. Among these strategies, oxidative aromatization with central-to-axial conversion of chirality has gained increasing popularity. It consists of the oxidation of a cyclic non-aromatic precursors into the corresponding aromatic atropisomers. This review proposes a critical analysis of this research field by delineating it and discussing its historical background and its present state of the art to draw potential future development directions.

**Keywords:** aromatic compounds; atropisomers; conversion of chirality; enantioselectivity; oxidation

## 1. Introduction

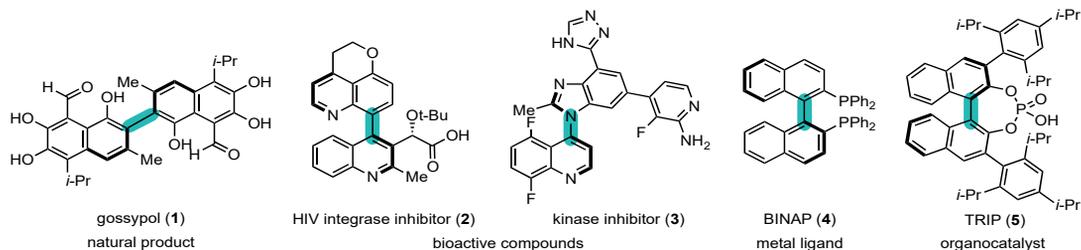
### 1.1. Interest of Atropisomers and Synthetic Methods to Prepare Them

Described for the first time 100 hundred years ago [1], atropisomers are conformers that gained enough stability because of the hindered rotation around a single bond. They are, thus, considered configurational stereoisomers [2], in which the bond with hindered rotation becomes a stereogenic axis. A half time life higher than  $10^3$  s is usually set as the limit to claim their existence, corresponding to a barrier to rotation of  $93 \text{ kJ}\cdot\text{mol}^{-1}$  at 300 K [2,3]. However, to be synthesized, stored, and used at ambient or biological temperature, higher barriers to rotation of  $\geq 105 \text{ kJ}\cdot\text{mol}^{-1}$  are generally required. The most frequently encountered atropisomers are biaryl compounds bearing *ortho* substituents to prevent the rotation around the biaryl bond. However, non-biaryl based atropisomers also exist [4–6].

In view of their unique properties, atropisomers have received much attention from researchers in all sub-fields of chemistry (Figure 1) [7–9]. They are present in natural products [10,11], such as gossypol (1) [12], and bioactive compounds [13–17], such as HIV integrase inhibitor (2) [18] and kinase inhibitor (3) [19], but they also find applications as metal ligands, such as BINAP (4) [20], organocatalysts, such as chiral phosphoric acid (5) [21], in polymer science [22,23], etc.

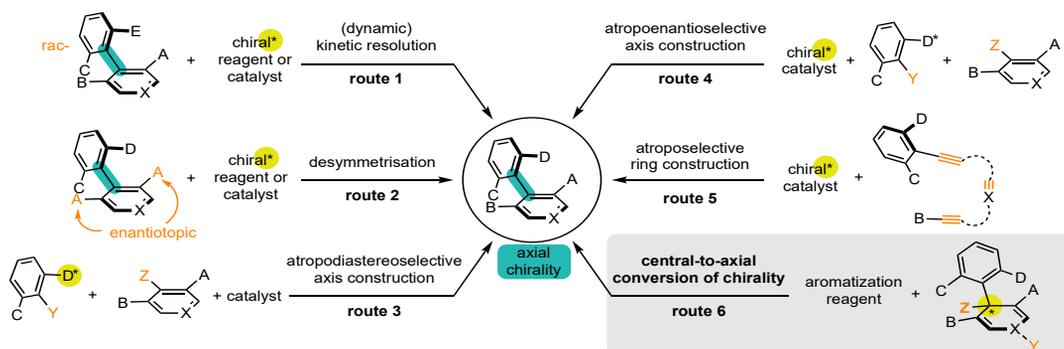
Considering the importance of atropisomers and the fact that the two enantiomers are likely to have different behaviors when placed in a chiral environment (as is the case for biological applications), methods to obtain them in enantioenriched form have been actively pursued. While resolution of the racemate is often used, the development of enantioselective synthetic methods can be highly appealing since (i) they obviate the

need to discard the unwanted enantiomer or recycle it by enantiomerization; and (ii) they stimulate the creativity of organic chemists.



**Figure 1.** Atropisomers: examples and their fields of application.

Enantioenriched atropisomers can be synthesized by a variety of methods, which can be classified into six main categories (Scheme 1): [24–30]



**Scheme 1.** Synthetic strategies to prepare atropisomers (presented on biaryl atropisomers for better readability).

- **Route 1:** Kinetic resolution based on the difference of reactivity of the two atropisomers with a chiral reagent or catalyst. Dynamic kinetic resolution can be envisaged if the two atropisomers are in fast equilibrium in the reaction conditions [31–33].
- **Route 2:** Desymmetrization relying on the selective reaction of one enantiotopic group of the prochiral precursor [34–36].
- **Route 3:** Atropodistereoselective construction of the stereogenic axis, for example, by cross-coupling or C–H activation, relying on preexistent stereocenter(s) at the periphery of the aromatic rings [37–40].
- **Route 4:** Atropoenantioselective construction of the stereogenic axis using a chiral catalyst [41–43].
- **Route 5:** Atroposelective ring construction, notably using [2+2+2] cycloaddition or alkyne hydroarylation reactions [44,45].
- **Route 6:** Control of central chirality followed by central-to-axial *conversion of chirality* during aromatization [46–49].

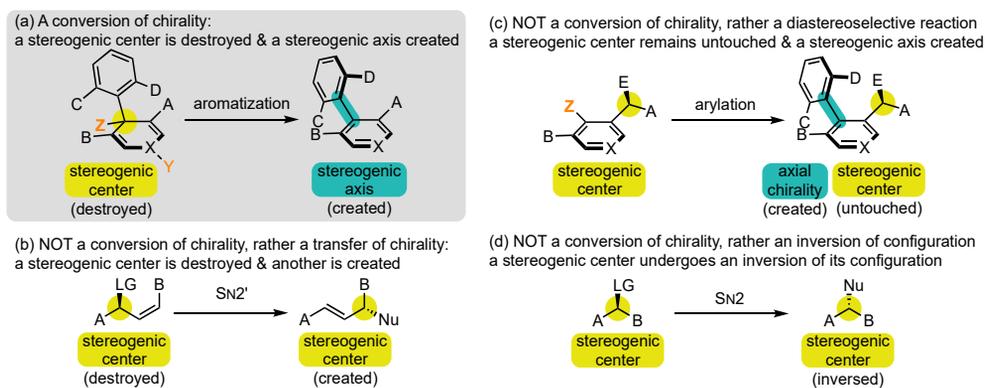
It should be noted that routes 1 and 2 start from substrates where the bond of the stereogenic axis and the two aromatic rings already preexist. On the contrary, substrates where the bond does not exist are involved in routes 3 and 4, whereas routes 5 and 6 involve substrates where at least one aromatic ring has to be constructed.

Despite the high potential of the central-to-axial conversion of chirality approach [50], no critical survey on the use of this strategy through oxidative aromatization exist in the literature, and we aim to fill this gap with the present review.

### 1.2. Defining Conversion of Chirality

We wish to define as *conversions of chirality* [51] all synthetic operations where a stereogenic element is forged in a molecule concomitantly with the destruction of a stereogenic element of a different type (Scheme 2a). The selection of this name requires an in-depth explanation:

1. At first, chirality is used in a quite improper sense, as it is normally applied to a molecule or an object in its entirety, while the process discussed here falls within local stereochemistry discussions [52]. *Conversion of stereogenicity* should, in fact, be recommended, but it seems completely absent from the literature and perhaps more difficult to comprehend for those who are not specialists of this field.
2. *Conversions of chirality* are also referred to in the literature by several other denominations, which all appear to us as less suited. *Transfer* has long been the most frequently used term [53–55], but it brings the idea of relocation rather than transformation. For us, it should be restricted to reactions where the stereogenic element that is destroyed and the one that is created are of the same nature, such as in  $S_N2'$  reactions with allylic leaving groups (Scheme 2b) [56]. *Exchange* [49,57] and *interconversion* [47] can also be encountered, but they evoke the idea of reversibility, which is generally not the case in those transformations.



**Scheme 2.** What is and is NOT a conversion of chirality?

Having defined the conversion of chirality, we now wish to point out which type of phenomenon should NOT be called so. Indeed, all the terms presented above are often misused to describe phenomena that are fundamentally different from conversion of chirality. *Conversions/transfers/interconversions/exchanges of chirality* are by nature potentially stereospecific processes and should be clearly distinguished from diastereoselective reactions. We can, for example, cite those where the configuration of a stereogenic axis is controlled thanks to the presence of one or several stereogenic centers in the surroundings, which remain completely untouched during the transformation (Scheme 2c) [58–62]. Rather, they belong to the strategy exposed in *Route 3* above. Sometimes these terms are even used for reactions that involve only an inversion of configuration, such as in a  $S_N2$  reaction (Scheme 2d) [63].

Being a phenomenon of enantiospecific nature, the efficiency of a conversion of chirality should be evaluated by comparing the relative enantioenrichment of the product and the substrate. In order to normalize this evaluation, Bressy, Bugaut, and Rodriguez

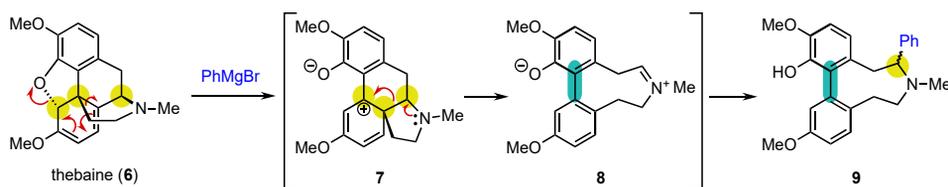
introduced the notion of conversion percentage (*cp*) [64], which can be calculated as such and will be used throughout this review:

$$cp = \frac{ee(\text{product}) \times 100}{ee(\text{substrate})}$$

## 2. Historical Background

### 2.1. A Surprisingly Early First Example!

From an historical point of view, it is quite amusing to realize that the first central-to-axial conversion of chirality was achieved in 1905 by Freund, even before the description of axial chirality, during reactivity studies on the natural product thebaine (**6**) (Scheme 3) [65]. Of course, it could not be identified at that moment, and it took almost half a century before the real explanation of what happened could be given by Robinson and Berson [66–68]. Treatment of **6** with phenylmagnesium bromide resulted in a complex rearrangement with aromatization to deliver biaryl atropisomer **9** as a mixture of two diastereomers. The reaction proceeds through the opening of the oxa-bridge with rearrangement of the carbon skeleton to afford **7**, which can aromatize to **8**. At this stage, the three initially present stereogenic centers have been destroyed with the concomitant installation of the stereogenic axis. The reaction terminates with trapping of the iminium ion by the Grignard reagent, giving rise to the formation of **9** as two diastereomers, which complicated the understanding of the transformation.



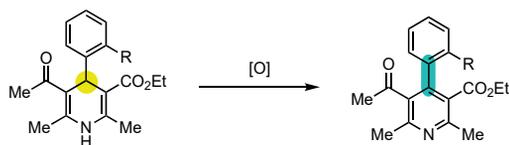
**Scheme 3.** Rearrangement of thebaine: the first example of central-to-axial conversion of chirality during aromatization.

### 2.2. Formulating Research Hypotheses to Achieve Conversion of Chirality

With the understanding of this phenomenon, Berson formulated three fundamental conditions that must be satisfied to allow the synthesis of atropisomers with central-to-axial conversion of chirality [51]:

1. Centrally chiral non-aromatic precursors should be accessible in enantioenriched form;
2. Steric hindrance around the stereogenic axis should be sufficient to ensure its configurational stability;
3. Aromatization should occur with a preservation of the enantiopurity.

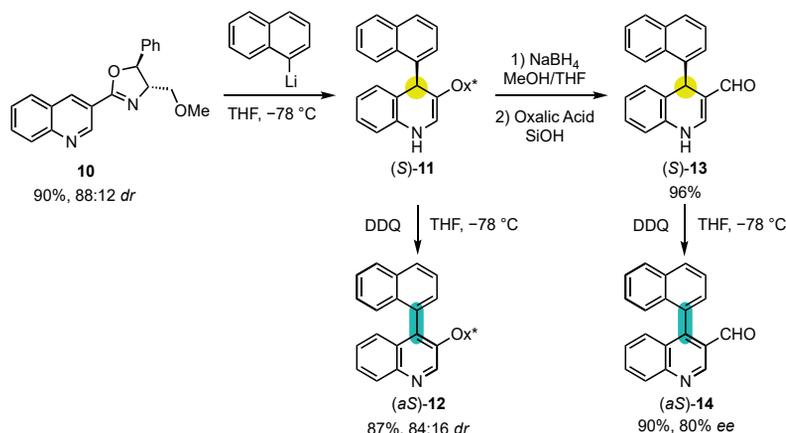
At that time, Berson could not design a suitable enantioenriched precursor (Scheme 4) and, apart from some other degradation studies in natural product chemistry [69–71], the situation remained as such for almost thirty additional years.



**Scheme 4.** Model proposed by Berson to study aromatization with central-to-axial conversion of chirality.

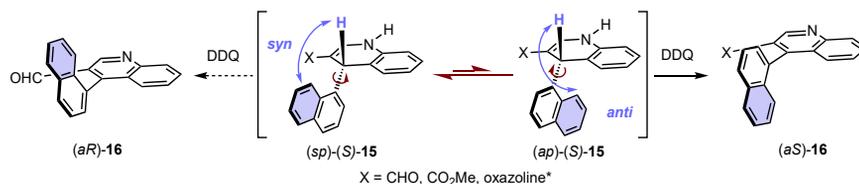
### 2.3. Verification of Berson's Hypotheses by Meyers

Berson's hypotheses were first confirmed by the explicitly designed central-to-axial conversion of chirality during aromatization proposed by the group of Meyers in 1984 (Scheme 5) [53]. Chiral oxazoline containing quinoline **10** underwent an efficient dearomatization by addition of naphthyllithium to obtain the corresponding dihydropyridine (*S*)-**11** with a diastereomeric ratio of 88:12. The sequence went on with an oxidative rearomatization with DDQ, yielding 4-arylquinoline atropisomer (*aS*)-**12** with a 84:16 *dr*, indicating a conversion percentage of 90%. In order to confirm that the enantioselectivity was not induced by the chiral oxazoline, it was deprotected to afford aldehyde (*S*)-**13**, which was oxidized in the same condition to obtain the pyridine (*aS*)-**14** with an enantiomeric excess of 80%. Those experiments brought the first definitive evidence that central-to-axial conversion of chirality can be an efficient strategy for the preparation of enantioenriched atropisomers.



**Scheme 5.** First explicitly designed example of central-to-axial conversion of chirality during aromatization.

In this seminal work, Meyers also proposed a stereochemical model inspired by Curtin–Hammett principle, which can be applied to all examples that will be discussed in this review [53]. 1,4-Dihydropyridines (DHP) adopt very flat boat conformations [72], with the bulkiest substituent at position 4 on pseudo-axial position to escape gauche interactions with adjacent substituents. On the basis of analyses of the 1,4-dihydroquinoline (*S*)-**15** by X-ray diffraction and NMR, two stable conformers with a rotation barrier below 75 kJ·mol<sup>-1</sup> could be identified, allowing for a rapid interconversion at room temperature. One conformer is the *anti*-periplanar (*ap*)-(*S*)-**15** in which the non-connective benzene of the naphthyl group is below the 1,4-dihydroquinoline core and *anti* to the hydrogen atom, and the other one is the *syn*-periplanar (*sp*)-(*S*)-**15** in which this benzene unit points towards to the hydrogen atom (Scheme 6). Despite the fact that the (*sp*)-(*S*)-**15** conformation is more stable [73], the configuration of the final product (*aS*)-**16** indicated that the (*ap*)-(*S*)-**15** *anti*-periplanar conformation, with the bulky group as far as possible from the hydride to be abstracted, was reacting. This result could be explained by the less important hindrance around the abstracted hydride in this conformation.



**Scheme 6.** Curtin–Hammett-type description of the stereochemical model during oxidative aromatization with central-to-axial conversion of chirality.

#### 2.4. Transformations Other Than Oxidations for Conversion of Chirality

Beyond oxidation reactions, such as the one used in the seminal example by Meyers and which will be the focus of this review, other mechanistic pathways are available to achieve conversions of chirality and have been discussed in more general reviews [46–50,74–82]. We can notably cite eliminations [83–88], retro-cycloadditions [89,90], opening of strained rings [91], and tautomerizations and isomerizations [57,92,93]. To really appreciate the impact of central-to-axial conversion of chirality during aromatization for the synthesis of enantioenriched atropisomers, and the importance of understanding it, one must also realize that in addition to the *explicit* examples presented here, many reactions actually proceed via an *implicit* conversion of chirality [47]. In those transformations, a non-isolable (or non-isolated) reaction intermediate with central chirality undergoes direct aromatization in the reaction mixture to afford an atropisomer. To cite just a few examples, this scenario is present in the enantioselective oxidative coupling of naphtha-2-ols [10,94,95], atroposelective nucleophilic aromatic substitutions [95–100], and many recent organocatalyzed transformations [32,101–109].

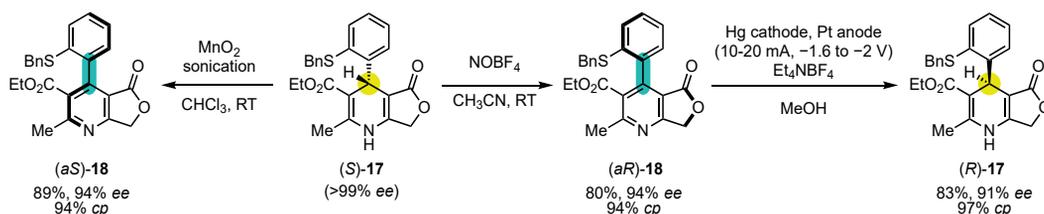
In addition to the previously described examples of oxidative central-to-axial conversion relying on the substrates bearing a chiral auxiliary or derivatives from the chiral pool, recently the attention has been turned towards enantioselective approaches. Among them, the combination of asymmetric catalysis with conversion of chirality has become very popular. In the next sections, we will focus only on enantioselective catalysis–oxidative aromatization with conversion of chirality sequential reactions, and they will be divided considering the type of (hetero)cyclic atropisomer.

### 3. Synthesis of Pyridine Atropisomers

#### 3.1. 4-Arylpyridine atropisomers

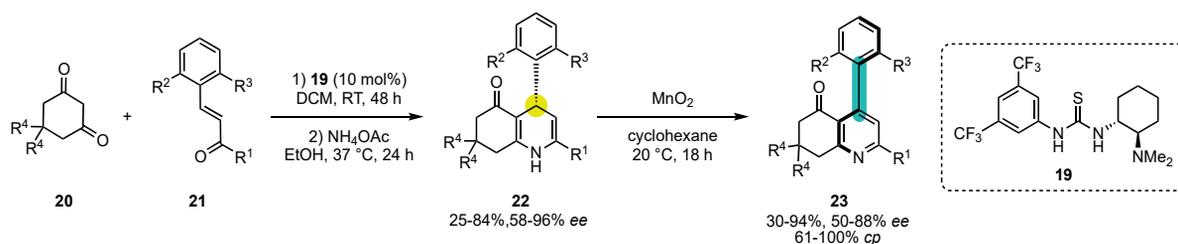
Following Meyer's initial achievement, other research groups applied similar strategies to the synthesis of pyridine atropisomers. The group of Straub was the first one to expose the strong dependence of conversion of chirality's efficiency on the choice of the oxidant in 1996 (Scheme 7) [110]. Indeed, starting from enantiopure (*S*)-**17**, obtained by preparative chiral HPLC on chiral stationary phase, they could convert it either to (*aS*)-**18** with 94% *ee* using  $\text{MnO}_2$  or into its antipode (*aR*)-**18**, also with 94% *ee* using  $\text{NOBF}_4$  as the oxidant. This enantiodivergence is likely to arise from the difference in mechanisms and steric requirements between the two oxidants. It should also be noted that other oxidants gave moderately or poorly efficient conversion of chirality (for example: 83% *ee* in favor of the (*aR*) enantiomer for  $\text{KMnO}_4$  or 18% *ee* in favor of the (*aS*) enantiomer for  $\text{Cu}(\text{NO}_3)_2$ ). Interestingly, electrochemical reduction of (*aR*)-**18** with axial-to-central conversion of chirality could turn it into (*R*)-**17** with 91% *ee*, achieving a formal inversion of configuration of the 1,4-dihydropyridine.

In this case, the two conformers of the DHP could be observed, and the X-ray structure confirmed that the *syn*-periplanar (*sp*)-(*S*) conformer is the most stable one. The calculation carried out a few years later showed an energy difference of  $15 \text{ kJ}\cdot\text{mol}^{-1}$  between the two conformations [111]. This follow-up study also disclosed that  $N$ -oxoammonium salt  $\text{TEMPO}^+\text{BF}_4^-$  is an appealing oxidant for such processes.



**Scheme 7.** Enantiodivergent oxidation of a 4-aryl-1,4-dihydropyridine to 4-arylpyridine atropisomer and subsequent inversion of configuration of the 1,4-dihydropyridine.

A strong limitation for the implementation of oxidative aromatization with central-to-axial conversion of chirality has long been the preparation of enantioenriched substrates. The key to force this lock was the strategy introduced by Bressy, Bugaut, and Rodriguez in 2016, which combined the organocatalyzed enantioselective synthesis of non-aromatic heterocycles with oxidative aromatization with central-to-axial conversion of chirality [64]. This first example consisted of an enantioselective pyridine Hantzsch synthesis (Scheme 8). Takemoto thiourea catalyst **19** was used to perform the enantioselective Michael addition between cyclic 1,3-diketones **20** and highly congested enones **21**, followed by cyclodehydration in the presence of  $\text{NH}_4\text{OAc}$  to afford the 4-aryl-1,4-dihydropyridines **22** with good to excellent yields and enantiomeric excesses. Screening of numerous oxidants revealed that only  $\text{MnO}_2$  was efficient at converting the stereochemical information. Cyclohexane was selected as the best solvent to perform the oxidation, and the corresponding 4-arylpyridine atropisomers **23** were obtained with good to excellent *ee* and *cp*. The difficulties in finding an oxidant that delivers high stereospecificities can be ascribed to the fact that **23** possesses one *ortho* substituent on the pyridine ring and two on the other ring, whereas it is the opposite for other systems presented previously.

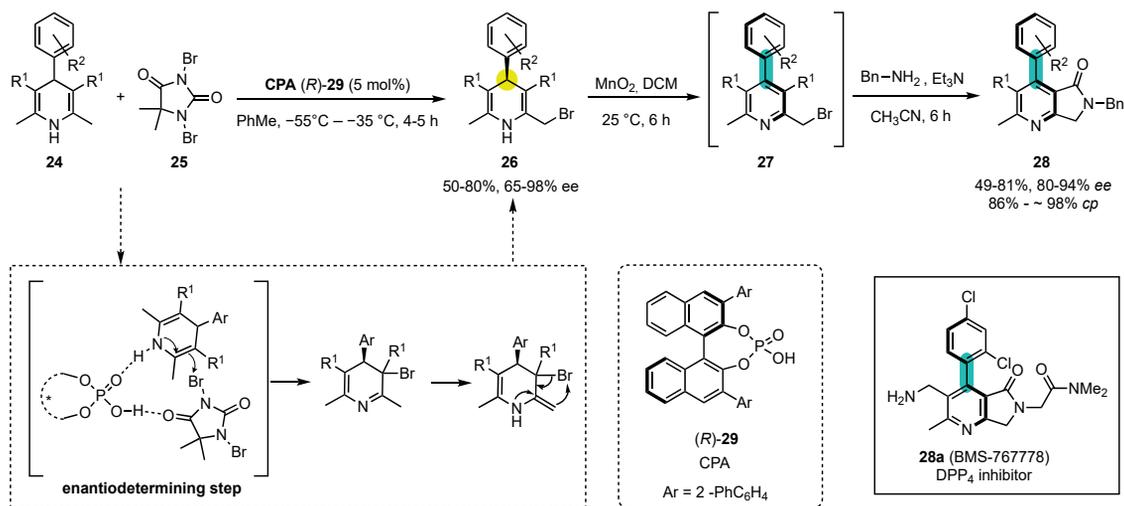


**Scheme 8.** Atroposelective Hantzsch pyridine synthesis by Takemoto's thiourea catalysis to build chiral 1,4-dihydropyridines/oxidation sequence.

More recently, a different approach for the synthesis of axial chiral 4-arylpyridines was developed by Li and Tang from commercially available symmetrical 1,4-dihydropyridines **24** (Scheme 9) [112]. The first step of this synthesis relies on an enantioselective desymmetrization by mono-substitution at one of the methyl groups of the 2,6-dimethyl 1,4-dihydropyridines **24** by C3-bromination—[1,3]-Br atom shift. 1,3-Dibromo-5,5-dimethyl hydantoin (**25**) was used as the brominating reagent, while the presence of the chiral phosphoric acid catalyst **29** allowed for an efficient transfer of chirality to a remote position from the bromination site.

After achieving moderate to excellent yields and enantiomeric excesses (up to 98% ee) in the first bromination reaction, they focused on the following oxidation step to obtain the axial chiral 4-arylpyridines **27** by central-to-axial chirality conversion. As in the previous work,  $\text{MnO}_2$  was selected as the oxidizing agent and DCM as the most suitable solvent for the reaction.

Finally, the subsequent functionalization of **27** by a  $\text{S}_\text{N}2$ /cyclization sequence using different nucleophiles was performed. Thus, when employing amines such as  $\text{BnNH}_2$ , the corresponding lactams **28** were obtained in moderate yields (49–81%) and good to high enantioselectivities (80–94% ee) and chiral conversion percentages (86–98% cp). It should also be noted that this strategy opens a route toward the enantioselective synthesis of BMS-767778, a potent DPP4 inhibitor.



**Scheme 9.** Atroposelective synthesis of 4-arylpiperidines from commercially available, symmetric 1,4-dihydropyridines by enantioselective phosphoric acid catalyzed desymmetrization–oxidation–substitution sequence.

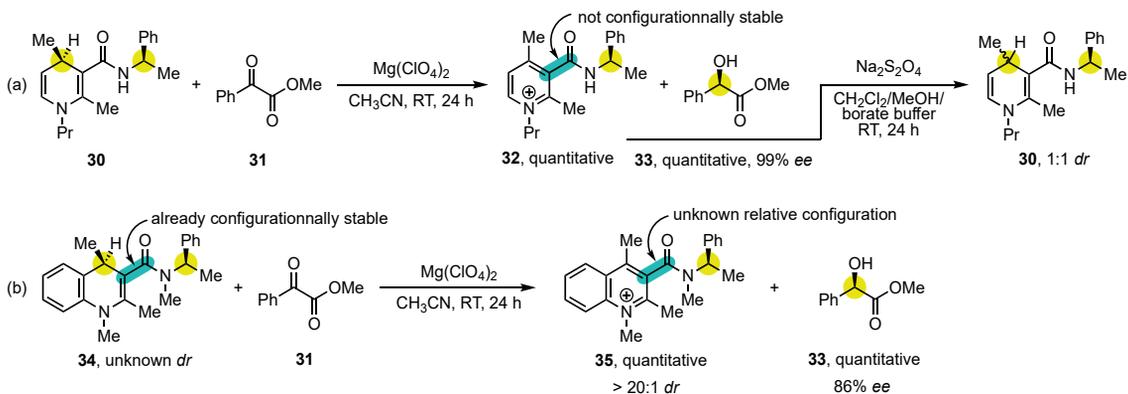
### 3.2. Nicotinamide Atropisomers

In addition to 4-arylpiperidine atropisomers, 3-carbamoylpyridine congeners, also known as nicotinamides, have also been the center of an intense attention, notably because of their structural similarity to NAD(P)H. Numerous contributions came from the research group of Ohno (Scheme 10). In 1986, they reported the synthesis of the enantioenriched 3-carbamoyl-1,4-dihydropyridine **30** containing a stereogenic center on the amide chain to facilitate analysis by the formation of diastereomers [113]. This substrate was oxidized using methyl phenylglyoxylate (**31**) as a hydride acceptor in presence of Mg(ClO<sub>4</sub>)<sub>2</sub>, delivering highly enantioenriched methyl (*R*)-mandelate (**33**) but with no diastereocontrol of the atropisomeric pyridinium salt **32** (Scheme 10a). This disappointing result was interpreted in terms of low configurational stability, which was confirmed by the fact that the subsequent reduction with Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> afforded 3-carbamoyl-1,4-dihydropyridine **30** with 1:1 *dr*.

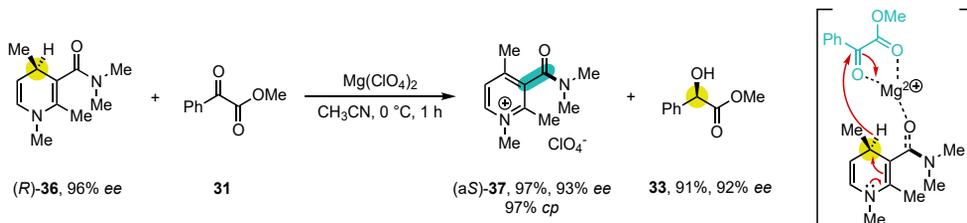
To solve this issue, tertiary 3-carbamoyl-1,4-dihydroquinoline **34** was synthesized, and it exhibited a substantial configurational stability at the stereogenic axis, even before oxidation (Scheme 10b). The two diastereomers could be separated by flash chromatography and characterized, even though the relative configurations and the barriers to rotation could not be determined. Treated under the same reaction conditions, it delivered the 3-carbamoylquinolinium salt **35** with >20:1 *dr*. This transformation does not exactly match the definition of the conversion of chirality since the stereogenic axis was already present in the substrate and could, instead, be seen as a stereoablative process [114]. Subsequent studies evaluated the effect of different reaction parameters, such as the nature of the organic oxidant and the metal ion on the reaction outcome, sometimes leading to an inversion of the stereoselectivity [115,116]. Alternative substrates and oxidation methods (Fe(III) or Co(III) anions, electrochemistry) could also be used [117–120].

In 1989, Vekemans and co-workers reported similar studies, but on enantiomeric instead of the diastereomeric systems used by Ohno, simplifying the stereochemical description of the transformation (Scheme 11) [121]. Enantioenriched 3-carbamoyl-1,4-dihydroquinoline (*R*)-**36** was obtained by repeated flash chromatography on chiral stationary phase (cellulose triacetate) until reaching 96% *ee*. Its oxidation by methyl phenylglyoxylate (**31**) delivered configurationally stable pyridinium salt (*aS*)-**37** with an enantiomeric excess of 93%, corresponding to a *cp* of 97%. Its absolute configuration could be determined, which allowed proposing a mechanism where the magnesium salt is complexed

by the carbonyl groups of both reaction partners, forcing the C=O of the amide function to point towards the oxidizing reaction partner. Oxidation then proceeds by hydride transfer from position 4 to the *si* face of the activated ketone function. A large diversity of electrophilic compounds were evaluated as hydride acceptors, enabling low (*p*-quinone, acetone), moderate (acetonitrile), or high (benzoin, activation ketones and imines) stereospecificities [121–124].



**Scheme 10.** Initial studies on the stereospecific oxidation of NAD(P)H mimics: (a) without diastereocontrol of atropisomeric salt **32**, and (b) by employment of a configurationally stable substrate.



**Scheme 11.** Studies on the enantiospecific oxidation of NAD(P)H mimics.

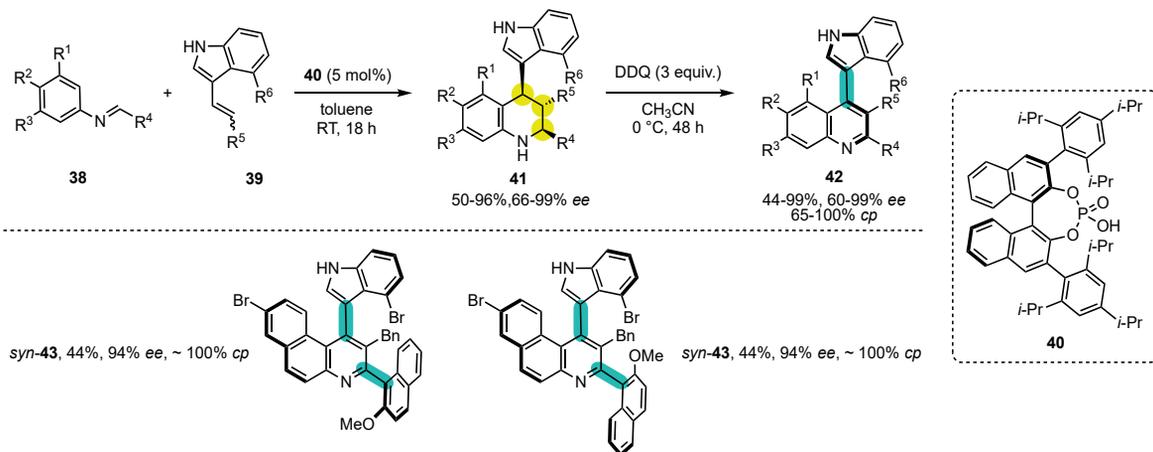
#### 4. Synthesis of 4-Arylquinoline Atropisomers

On the basis of this seminal report of Bressy, Bugaut, and Rodriguez on the combination of organocatalysis and conversion of chirality [64], the group of Bertuzzi and Corti described the two-step synthesis of chiral indole–quinoline systems (Scheme 12) [125]. The first step consisted of a Povarov reaction between *N*-arylimines **38** and 3-alkenylindoles **39** catalyzed by the chiral phosphoric acid **40** to obtain 1,2,3,4-tetrahydroquinolines **41**, which were then oxidized to the corresponding atropisomeric quinolines **42** using DDQ as oxidant. Good to excellent yields, *ee*, and *cp* were obtained for all examples. In the cases where R<sup>4</sup> is a bulky aromatic ring, molecules, such as **43**, containing two stereogenic axes, were obtained as separable diastereomers, with good enantioselectivities for both of them.

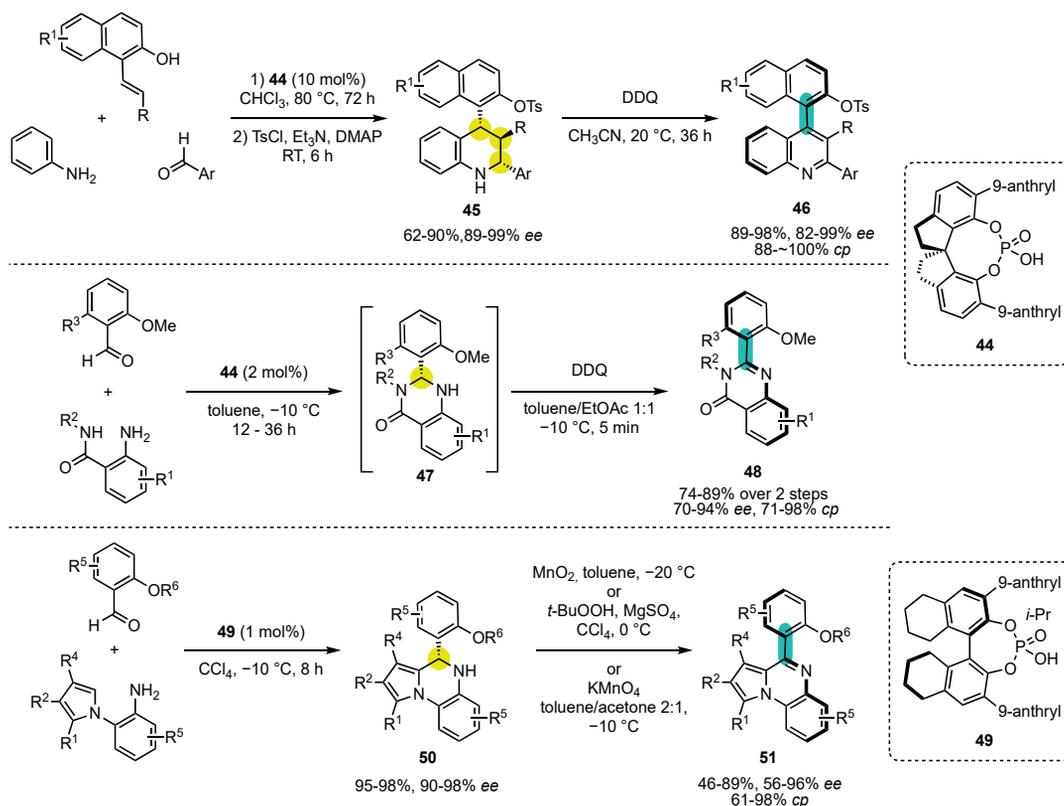
Closely related follow-up studies applied this strategy to the synthesis of other families of nitrogen-containing heterocycles, including 4-naphthylquinolines **46** [126], quinazolines **48** [127], and quinoxalines **51** (Scheme 13) [128].

All the non-aromatic precursors **45**, **47**, and **50** were obtained by a chiral phosphoric acid-catalyzed annulation or cyclization on in situ formed imines. In the first two cases, the conversion of chirality proceeded smoothly with DDQ as the oxidant with high levels of *cp*. A few examples of the 4-naphthylquinoline series also exhibited two stereogenic axes. However, for the last family of compounds, not only DDQ but also other oxidants, such as *m*-CPBA or PhI(OAc)<sub>2</sub>, were not suitable, leading the authors to develop three sets of reaction conditions which showed strongly different efficiencies depending on the

substrates: (i)  $\text{MnO}_2$ , toluene,  $-20\text{ }^\circ\text{C}$ ; (ii)  $t\text{-BuOOH}$ ,  $\text{MgSO}_4$ ,  $\text{CCl}_4$ ,  $0\text{ }^\circ\text{C}$ ; and (iii)  $\text{KMnO}_4$ , toluene/acetone 2:1,  $-10\text{ }^\circ\text{C}$ . For some examples, changing the oxidation conditions inverted the absolute configuration of the major enantiomer of the final product.



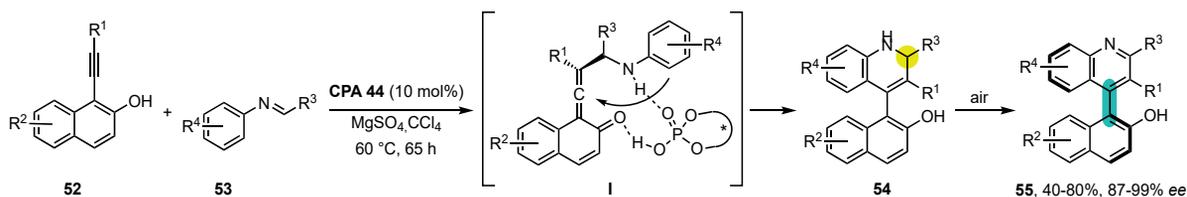
**Scheme 12.** Atroposelective synthesis of indole–quinoline double heterocyclic motives.



**Scheme 13.** Atroposelective synthesis of 4-naphthylquinolines, quinazolinones, and quinoxalines.

In 2022, the group of Zhou designed an elegant alternative approach for the preparation of atropisomeric 4-naphthylquinolines by chiral phosphoric acid (CPA) catalyzed asymmetric

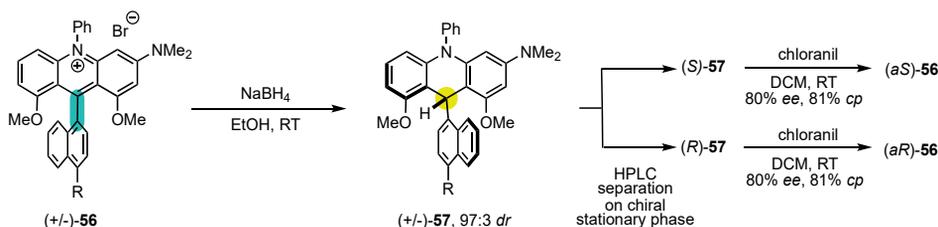
intramolecular cycloaddition of in situ formed vinylidene–quinone methines (VQM) from alkynyl naphthols **52** and isolated or one-pot-generated imines **53** (Scheme 14) [129]. A dual hydrogen-bonding activation by the catalyst **44** was proposed, allowing for a subsequent [2+4]-cycloaddition of VQM **I** to **54** and final auto-oxidation under air to build the desired atropisomers **55** in moderate to good yields and high enantioselectivities (up to 99% *ee*).



**Scheme 14.** Construction of chiral 4-naphthylquinolines via in situ generated vinylidene–quinone methine intermediates.

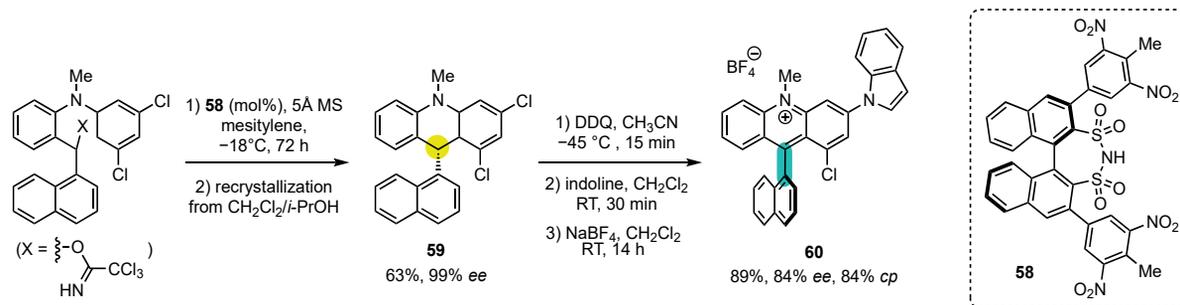
### 5. Synthesis of 4-Arylacridinium Atropisomers

Although the enantioselective synthesis of ionic heterocyclic atropisomers have been much less studied, in 2018, the group of Sparr showed that a similar oxidative approach to the one described for dihydropyridines could be used to prepare cationic atropisomers, namely acridinium salts (Scheme 15) [130]. Racemic 9-arylacridinium salt **56** could be reduced with  $\text{NaBH}_4$  to afford the leuco-form **57**. In this case, both conformers were stable enough to be observed by NMR, and the reduced acridinium was obtained as a racemate with an excellent 97:3 *dr*. Once again, the *syn*-periplanar conformation was the most stable one. The two enantiomers were separated by HPLC on chiral stationary phase and then oxidized with chloranil to yield the enantioenriched 9-arylacridinium salts (*aS*)- and (*aR*)-**56** with an 80% *ee*, corresponding to a *cp* of 81%.



**Scheme 15.** Preparation of enantioenriched 9-arylacridinium salts.

Recently, the same group disclosed an enantioselective synthesis of enantioenriched the 9-arylacridinium **60** combining enantioselective organocatalysis and central-to-axial conversion of chirality (Scheme 16) [131]. The reaction sequence consists of a  $6\pi$  electrocyclic cyclization catalyzed by disulfonimide **58**, followed by in situ oxidation with DDQ. For two examples (one of them presented in Scheme 15), the non-aromatic intermediate **59** was isolated and recrystallized, which allowed evaluating the efficiency of the conversion of chirality. The sequence could even be completed by a regioselective nucleophilic aromatic substitution of one of the chlorine atoms.



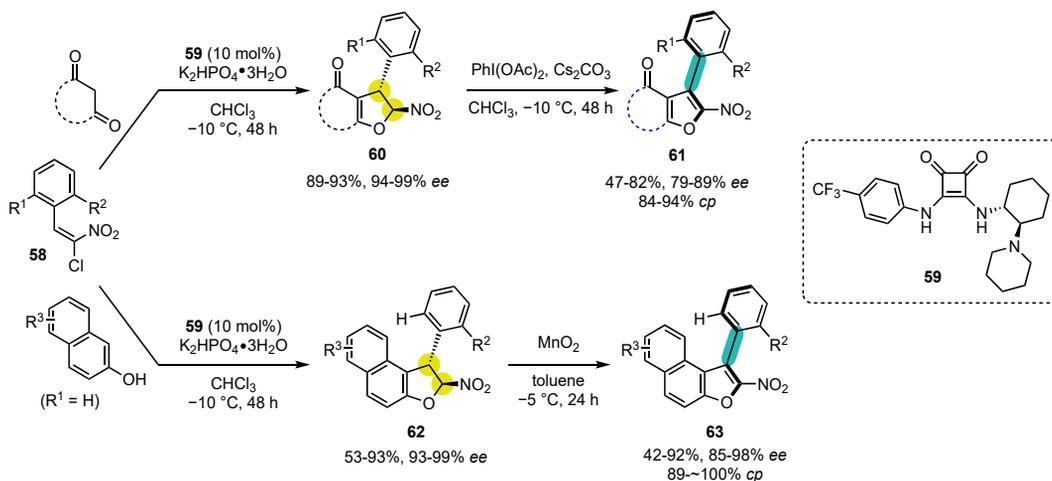
**Scheme 16.** Enantioselective synthesis of atropisomeric 9-arylacridinium salts.

## 6. Synthesis of Five-Membered Heterocyclic Atropisomers

Preparing enantioenriched five-membered heterocyclic atropisomers represent a very complicated synthetic challenge because reactivity and selectivity issues are also accompanied by questions on the configurational stability, which is lower than for six-membered congeners.

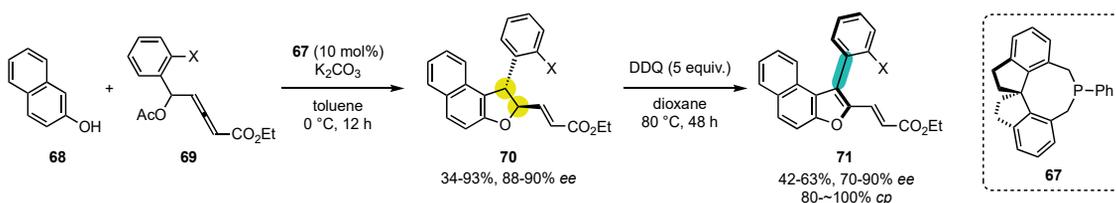
### 6.1. Oxygen-Containing Heterocycles

In 2017, Bonne and Rodriguez reported the first enantioselective synthesis of two series of arylfuran atropisomers (Scheme 17) [132]. Using  $\alpha$ -chloronitroolefins **61** as Michael acceptors in combination with cyclic diketones or  $\beta$ -naphthols in the presence of squaramide catalyst **62**, two families of dihydrofurans **63** and **65** could be prepared. The reaction consists of an enantioselective Michael addition followed by nucleophilic displacement of the chloride by the oxygen atom. The first family of furan atropisomers **64** was obtained using hypervalent iodine as the oxidant in basic media. For the second family, the best condition for the oxidation of this type of substrate to obtain furan atropisomers **66** was the use of  $\text{MnO}_2$  in toluene.



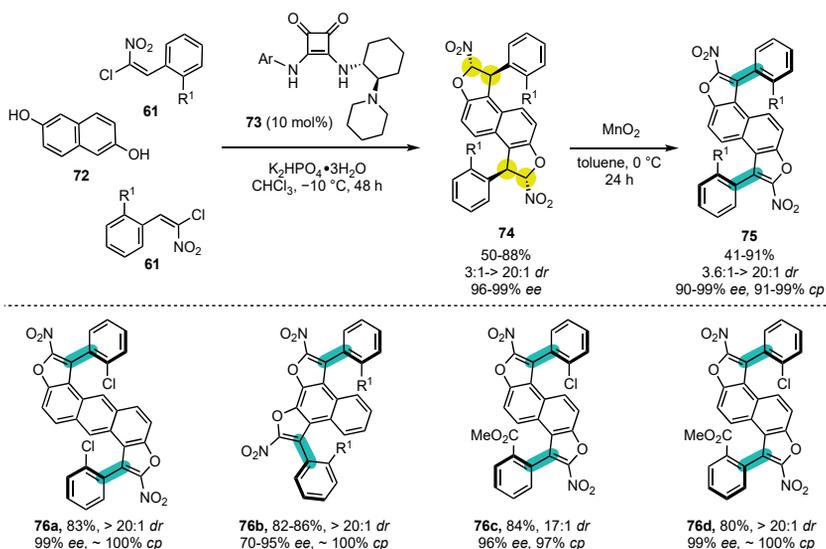
**Scheme 17.** Enantioselective synthesis of atropisomeric 3-arylfurans.

Similarly, fused furan atropisomers **71** could also be prepared by using a different approach for the organocatalyzed step (Scheme 18) [133]. In this case, allenenes **69** react with  $\beta$ -naphthols **68** in the presence of a chiral phosphine catalyst **67** to afford fused dihydrofurans **71**.



**Scheme 18.** Enantioselective synthesis of atropisomeric 3-arylfurans using a phosphine-catalyzed annulation step.

Subsequently, Bonne and Rodriguez implemented their two-step strategy from  $\alpha$ -chloronitroolefins for the bidirectional construction of atropisomeric bis-benzofurans bearing two stereogenic axes (Scheme 19) [134]. Dihydrofurans **74** were obtained in good to very good yields and with good stereoselectivities by enantioselective domino Friedel–Crafts–O-alkylation reaction between 2,6-dihydroxynaphthalene (**72**), and various  $\alpha$ -chloronitroolefins **61** catalyzed a bifunctional thiourea **73**. In the case of low diastereoselectivity, the two diastereomers could be separated. The conversion of chirality was then achieved with  $\text{MnO}_2$  in toluene, and the corresponding bis-benzofurans **75** were obtained with good yields and excellent *cp*, higher than 91%. Interestingly, the double axis could be synthesized stepwise to obtain the non-symmetrically functionalized S-shaped oligoarenes **76**. For the second organocatalyzed step, both enantiomers of the catalyst were used to obtain both diastereomers (a*S*,a*S*) and (a*S*,a*R*).

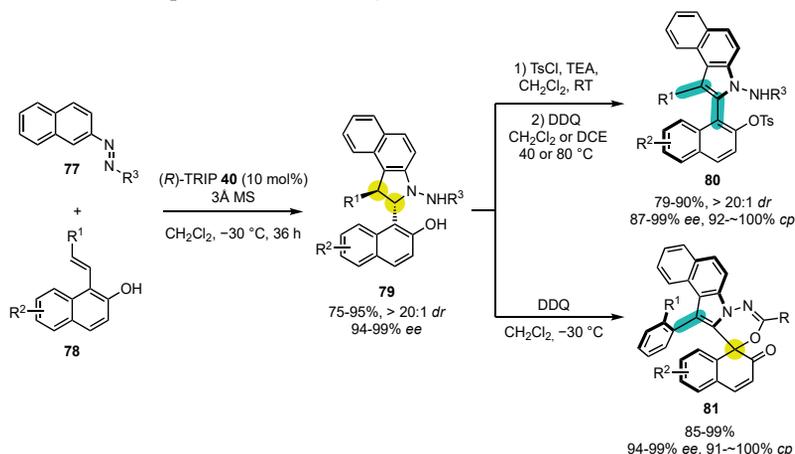


**Scheme 19.** Bidirectional synthesis of bis-benzofuran atropisomers with two distal stereogenic axes.

## 6.2. Nitrogen-Containing Heterocycles

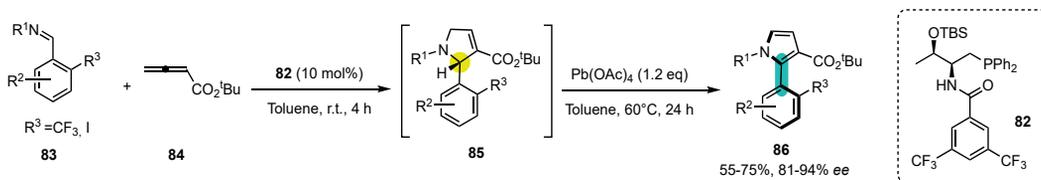
In 2019, the group of Zhou described the synthesis of 2,3-diarylbenzoindoles containing one or two stereogenic axis (Scheme 20) [135]. The authors used Brønsted acid organocatalysis, using (*R*)-TRIP (**40**) to promote the [3+2] annulation between azonaphthalenes **77** and 1-styrylnaphthtols **78** to obtain dihydropyrroles **79** in good yield and excellent diastereo- and enantioselectivities. To avoid possible dearomatization side reactions that would lead to erosion of the stereoselectivity, a sulfonylation of the naphthol moiety was conducted prior to oxidation to the corresponding benzoindole. Initially, a triflate substitution showed a poor enantioselectivity. This was then notably improved by tosylation, leading to the benzoindoles **80** with high enantioselectivities and with *cp* between 92% and 100% upon

oxidation using DDQ in DCE at 40 °C. In the case of R<sup>1</sup> being an *ortho*-substituted aryl ring, the oxidation proceeded at 80 °C, and molecules with two stereogenic axes were obtained with the same range of *cp* and high diastereoselectivities. DFT calculations carried out on the substrate highlighted the importance of the steric hindrance around the hydride for both conformers to explain the efficiency of the conversion of chirality. Subsequently, the same group utilized directly the free naphthols to undergo a simultaneous central-to-spiro transfer and central-to-axial conversion by exploiting intramolecular hydrogen-bonding interactions between the hydroxy and hydrazine groups to achieve **81** within high levels of enantiocontrol (up to 99% *ee* and 100 *cp*) [136].



**Scheme 20.** Enantioselective synthesis of atropisomeric 2-arylbenzoindoles.

In 2022, Ullah and Lu reported an approach for the synthesis of CF<sub>3</sub>-substituted 2-arylpyrroles by sequential asymmetric catalytic [3+2] annulation and oxidative central-to-axial chirality transfer (Scheme 21) [137]. To this purpose, a chiral bifunctional amide-phosphine organocatalyst **82** was employed, which allowed the construction of the five-membered N-heterocyclic moiety by reaction between an imine **83** and the allene **84**. Finally, the pyrrole group was built upon oxidation of **85** with Pb(OAc)<sub>4</sub>, which proved superior in terms of chirality transfer to other more commonly used oxidants in chiral-to-axial conversion processes. Following this method, both 2-CF<sub>3</sub> and 2-iodo-arylpyrroles **86** were prepared in up to 94% *ee*.

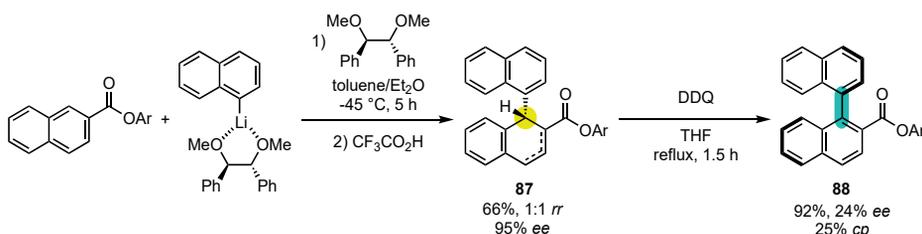


**Scheme 21.** Synthesis of enantioenriched 2-arylpyrrol-based atropisomers.

## 7. Synthesis of Carbocyclic Atropisomers

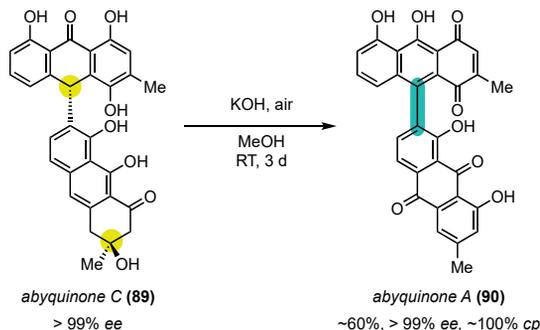
### 7.1. Seminal Results

As presented in the previous sections, the major part of the literature on oxidative aromatization with conversion of chirality focuses on heterocyclic systems. The first recognized historical example in the carbocyclic series reported by the group of Tomioka in 2009 was disappointing, with a conversion percentage of 25% when oxidizing dihydronaphthalene **87** (existing as two regioisomers) into naphthalene **88** (Scheme 22) [138]. In contrast, the corresponding S<sub>N</sub>Ar process, where the aromatization occurs by elimination and not oxidation, was far more efficient [98].



**Scheme 22.** First example of applying oxidative aromatization with central-to-axial conversion of chirality to carbocycles.

On the contrary, efficient conversion of chirality was previously observed by the group of Bringmann when studying a family of natural products called abyquinones (Scheme 23) [139]. Both family members abyquinone C **89** and abyquinone A **90** could be isolated in enantiopure form, the first one bearing central chirality and the second one axial chirality. Their structural resemblance leads to questions about the possibility to oxidize **89** into **90** with central-to-axial conversion of chirality. Aerobic oxidation was indeed observed in basic methanolic solution, with perfect *cp*. Semi-empirical calculations reveal that hydrogen bonding between the phenolic group could lead to conformational blockage on the precursor, explaining the stereospecificity.

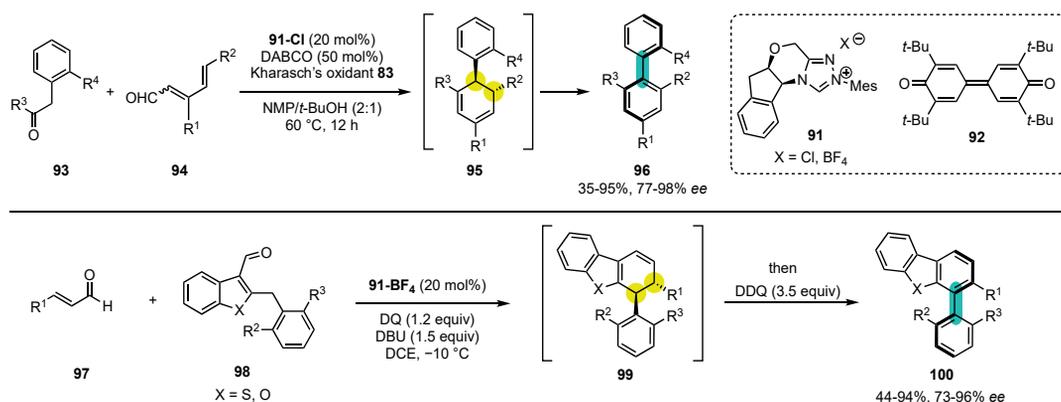


**Scheme 23.** Studies on the aerobic oxidative conversion in the abyquinone family, with central-to-axial conversion of chirality.

### 7.2. Combining Enantioselective Organocatalysis with Conversion of Chirality

It is the use of organocatalysis to prepare enantioenriched non-aromatic precursors that allowed the first general efficient strategies for the synthesis of carbocycles to be designed, even though examples remain scarce compared with heterocycles.

In 2019, the group of Zhu made use of enantioselective oxidative NHC organocatalysis with catalyst **91** to prepare chiral cyclohexadienes **95** from carbonyls **93** and  $\alpha,\beta$ -unsaturated aldehydes **94**. These intermediates **95** were readily oxidized into the corresponding atropisomers **96**, with implicit conversion of chirality (Scheme 24, top) [140]. The fact that the intermediate could not be isolated precluded the precise estimation of conversion of chirality efficiency. Interestingly, the stoichiometric Kharasch's oxidant **92** could be replaced by electrochemical oxidation.



**Scheme 24.** Implicit central-to-axial conversion of chirality during NHC-catalyzed benzannulations by Zhu (**top**) and Zhang and Ye (**bottom**).

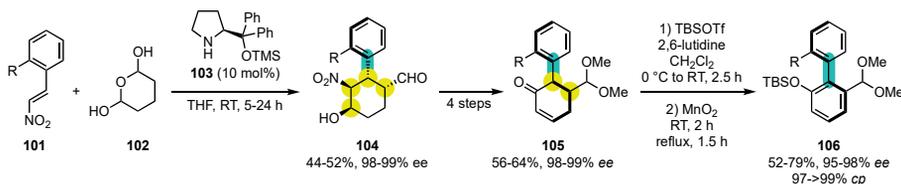
More recently, Zhang and Ye employed a similar approach for the synthesis of axial chiral benzothiophene and benzofuran-fused biaryls **100** (Scheme 24, bottom) [141]. They employed the chiral NHC catalyst precursor **91** as  $\text{BF}_4$  salt for the cyclization between an enal **97** and a 2-benzyl benzoheteroaryl 3-carbaldehyde **98**, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base and diquat (DQ) as the oxidant, followed by treatment of intermediate **99** with DDQ for the final oxidative aromatization step. The chiral atropisomer products **100** were then obtained in moderate to excellent yields and enantioselectivities (up to 96% *ee*).

For the synthesis of carbocyclic atropisomers, the group of Hayashi developed a method relying on enantioselective aminocatalysis (Scheme 25) [142]. It started with a domino reaction of aqueous glutaraldehyde **102** (occurring in its hemiacetal form) with nitroolefins **101**, affording polysubstituted cyclohexane derivatives **104** with four stereogenic centers. These were processed in six steps over intermediate enone **105** to the final biaryl atropisomers **106**. Due to the fact that they could not observe the existence of several conformers for **104**, the authors claimed that the stereogenic axis already exists in the very first chiral product and remains configurationally stable all along the synthesis, hence explaining the very high enantiomeric excess. This scenario appears unlikely, and we believe, instead, that the conformers cannot be observed because they interconvert too rapidly. In this case, the oxidative aromatization would occur with a standard central-to-axial conversion of chirality at the final oxidation step. Further studies on the conformational dynamics of **104** are required to distinguish between the two scenarios. Subsequently, the same group published a related work, where the final aromatization step occurred by tautomerization with, once again, a rather convoluted stereochemical description [143].

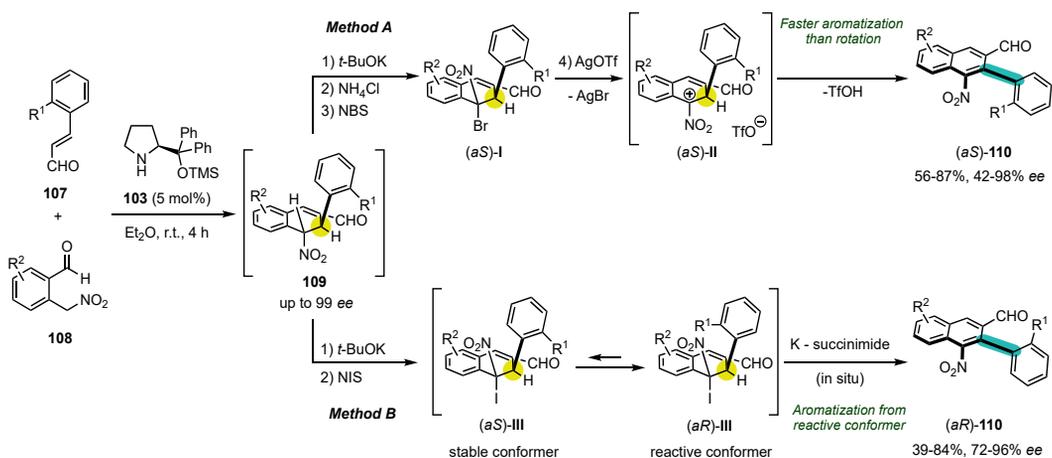
In 2021, Hayashi's group reported an enantiodivergent synthesis of axially chiral biaryls (Scheme 26) [144]. This one-pot synthesis incorporates a multiple-step strategy, starting with an aminocatalyzed one-pot enantioselective Michael reaction and aldol condensation domino reaction between 2-(nitromethyl)benzaldehydes **108** and substituted cinnamaldehydes **107** to give the chiral intermediate **109** in up to 99% *ee*. Later, depending on the halogenating agent and additive used, the synthesis of either one or the other axial conformer could be attained. To achieve the (*aS*)-atropisomer **110**, the intermediate **109** was treated with *t*-BuOK and  $\text{NH}_4\text{Cl}$  prior halogenation at the C4-position with NBS, followed by reaction with  $\text{AgOTf}$ . The cationic intermediate **II** is then formed by  $\text{S}_{\text{N}}1$ -type elimination, which is further aromatized by hydrogen atom extraction to build the desired conformers (*aS*)-**110** in good yields (56–87%) and enantiomeric excess up to 98% *ee*.

Alternatively, the (*aR*)-atropisomer **110** could be selectively obtained when reacting **109** with NIS in the presence of the *t*-BuOK, followed by deprotonation with the in situ formed potassium succinimide. DFT calculations showed that, in this case, the conversion

of axial chirality in the intermediate **III** is favored toward the reactive species (*aR*)-**III** because the steric hindrance around the acidic H-atom of the initially formed most stable conformer (*aS*)-**III** does not promote the deprotonation. The corresponding atropisomer (*aR*)-**110** was then achieved in moderate to good yields (39–84%) and enantioselectivities up to 96% *ee*.

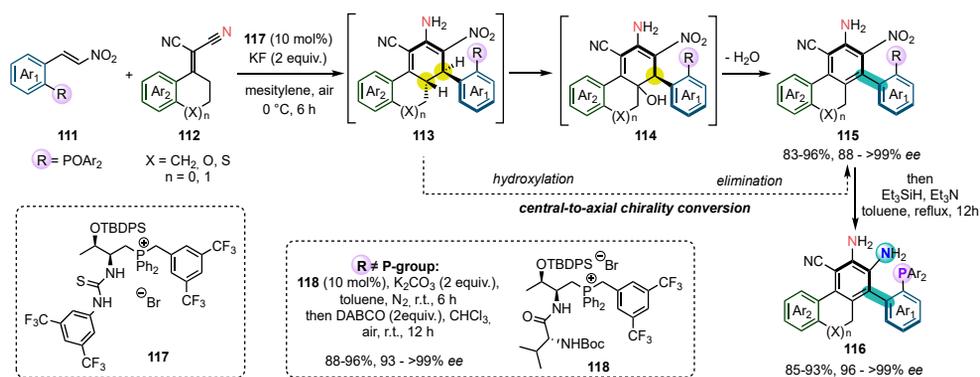


**Scheme 25.** Synthesis of carbocyclic atropisomers by combining aminocatalysis with central-to-axial conversion of chirality.



**Scheme 26.** Enantiodivergent multi-step synthesis of atropisomers by Hayashi et al.

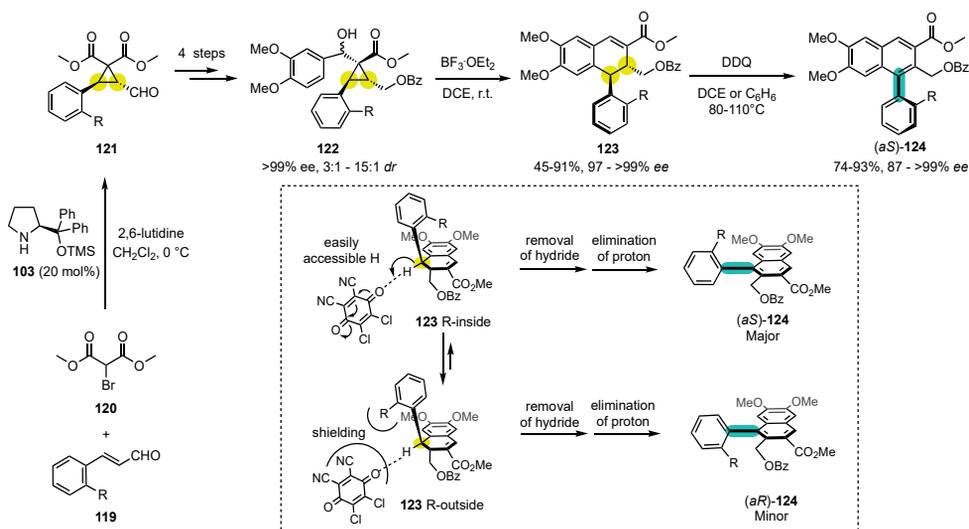
Recently, in 2022, Wang and co-workers employed an asymmetric thiourea-based phosphonium salt dual catalyst **117** in a cascade procedure for the atroposelective synthesis of aminophosphine-type ligands **116** (Scheme 27) [145]. This represents the first report on the use of such a dual catalyst in a central-to-axial chirality conversion, although the same group already employed it in other catalytic cyclizations [146] as well as for the synthesis of atropisomeric biaryls via kinetic resolution [147]. In this case, the reaction between a nitroolefin **111** and a substituted 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **112** provided a chiral intermediate **113** containing four rings. Such an intermediate can undergo a mild hydroxylation with air as the oxidant of choice in the presence of KF to achieve the intermediate **114**, which further undergoes dehydration to build the atropisomer **115**. Thus, the compounds **115** were achieved with remarkable yields (86–99%) and enantioselectivities (88–99% *ee*), which could be then transformed into the *N,P*-ligands **116** upon concomitant reduction of the nitro and phosphine oxide groups with  $\text{Et}_3\text{SiH}$ . A similar procedure for other substitution than phosphorus ( $\text{R} \neq \text{P}$ -group) was also developed, in which the ligand **118** and subsequent use of  $\text{K}_2\text{CO}_3$  and DABCO as bases were required for attaining the same high levels of central-to-axial chirality transfer.



**Scheme 27.** Atroposelective cascade synthesis towards aminophosphine-type ligands.

### 7.3. Miscellaneous

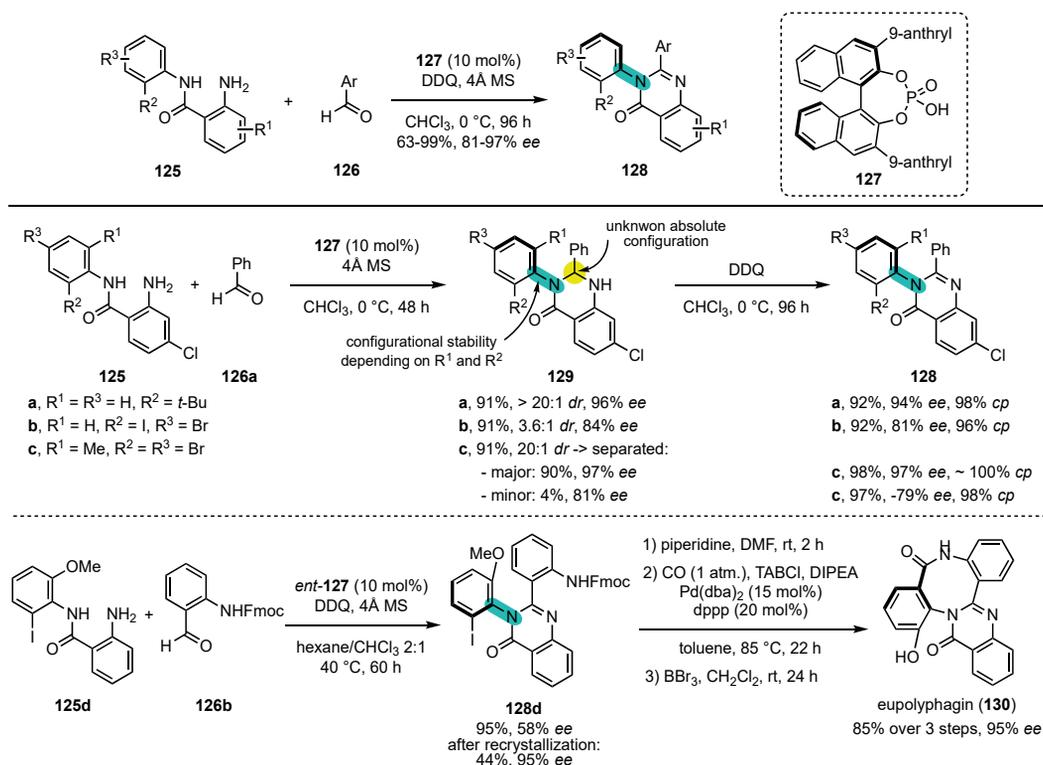
In 2022, Nishii and co-workers developed a seven-step procedure to synthesize the (a*S*)-atropisomers **123** from chiral cyclopropylcarbinols, implying central-to-axial chiral conversion (Scheme 28) [148]. In this first step, the Hayashi-Jørgensen amino catalyst **103** promoted Wang's asymmetric cyclopropanation between a cinnamaldehyde derivative **119** and dimethyl  $\alpha$ -bromomalonate (**120**). The enantiomeric configuration of the formed cyclopropane diester **121** was preserved during the next four synthetic steps to achieve the desired cyclopropylcarbinols **122**. These intermediates undergo a one-pot ring-opening/cyclization in the presence of BF<sub>3</sub>·OEt<sub>2</sub> to access with a nearly complete stereoreinduction the chiral dihydronaphthalenes **123**. The last step implies a central-to-axial chirality exchange by oxidative dehydrogenation of **123** using DDQ as the oxidant, providing the atropisomers (a*S*)-**124** with moderate to excellent enantioselectivities (87–99% ee) depending on the substituent R on the aromatic ring. The thermodynamically most stable conformer with the ortho-substituent pointing outside the naphthyl ring (R-outside) was, again, not the one favoring the last oxidation reaction step due to steric hindrance. Hence, in the intermediate **123** with the R-inside conformation, the hydrogen atom is more accessible and easier to extract, allowing for the oxidative dehydrogenation to take place.



**Scheme 28.** Central-to-axial conversion from chiral cyclopropylcarbinols via dihydronaphthalene intermediates.

## 8. Control of C-N Atropisomerism

In addition to the above-presented arylquinazolinones **48** bearing a C-C stereogenic axis (Scheme 13), conversion of chirality was also efficiently applied by the group of Tan for the preparation of enantioenriched related compounds **128** with a C-N stereogenic axis (Scheme 29) [149]. The reaction was carried out in the presence of chiral phosphoric acid catalyst **127** and the oxidant DDQ from the start, precluding the isolation of the non-aromatic intermediate. However, for three examples, the reaction was carried out in a sequential fashion with treatment by DDQ after the isolation of the intermediate **129**. The fact that the absolute configuration of the stereogenic center could not be determined complicates that mechanistic description. However, it appeared clearly that the stereocontrol of the final C-N atropisomerism arose from the initial enantioselectivity obtained during the cyclization step.



**Scheme 29.** Atroposelective synthesis of quinazolinones with a C-N stereogenic axis.

Interestingly, three different scenarios could be observed depending on the steric hindrance brought by the *ortho* substituents:

1. With a very bulky *tert*-butyl group in *ortho* position (**128a**), the rotation around the C-N bond is already restricted before oxidative aromatization with very high diastereocontrol, so that this step is not really a conversion of chirality but rather a stereoablative process [114];
2. With a smaller iodine atom (**128b**), the rotation is still possible around the C-N bond before aromatization, resulting in the production of equilibrating diastereomeric conformers, so that the oxidative aromatization fully meets the criteria to be considered a conversion of chirality;
3. When a second *ortho* substituent is present (**128c**), the two diastereomers could be isolated, and each of them was oxidized separately, leading to the two enantiomers of the final atropisomeric product.

Last but not least, compound **128d** could be derivatized in just three steps to afford natural product eupolyphagin **130** in 95% *ee*. It is a very rare example of applying central-to-axial conversion of chirality to the synthesis of atropisomeric natural and/or bioactive products.

## 9. Conclusions and Perspective

Oxidative aromatization with central-to-axial conversion of chirality has a rather special story among strategies that have been elaborated to achieve stereoselective synthesis. Indeed, the first example could be found in the literature even before axial chirality was recognized, even though its understanding was, of course, not possible at that time. Then, its theoretical possibility was hypothesized already in the 1950's, but it was only three decades later that the experimental realization could be achieved. A decade of rather intense research in this field followed this initial discovery before it slowly went to sleep. Revival arrived approximately 5 years ago with the discovery that enantioselective organocatalysis could act as a very efficient toolbox to prepare cyclic non-aromatic precursors, which could then be aromatized to deliver the corresponding enantioenriched atropisomers. Since then, this strategy was applied to the preparation of diverse families of heterocycles, and less widely to carbocycles.

Our opinion is that oxidative aromatization with central-to-axial conversion of chirality has still not reached the limits of its potential and could be applied to many more atropisomeric structural motives. A current limitation to a broader applicability of central-to-axial conversion of chirality is the little understanding and rationalization of this phenomenon. Indeed, from one publication to the other, a variety of oxidants are used, and even if some of them seem to be privileged (DDQ, MnO<sub>2</sub>), no rather general rule could be drawn. Thus, a trial-and-error approach has to be applied for each new family of precursors. Moreover, there is also a lack of understanding of how the steric and/or electronic properties of the substituents present on the non-aromatic precursor to finely influence the efficiency of the conversion of chirality.

From a preparative point of view, it should also be noted that (super)stoichiometric oxidants have been used in almost every case, and sometimes also highly toxic and/or carcinogenic solvents (for example CCl<sub>4</sub>), limiting the eco-compatibility of this strategy. Future methodologies should target more benign oxidizing conditions, notably catalytic ones. To conclude, research efforts should also be devoted not only to methodological developments but also to its implementation in target-oriented organic synthesis of natural and/or bioactive products.

**Acknowledgments:** The German Academic Exchange Service (DAAD) within the grant number 57660401\_PPP-Procope program and the French Ministries for Europe and Foreign Affairs (MEAE) and Higher Education, Research and Innovation (MESRI) within the PHC Procope Grant 49553PK are gratefully acknowledged for generous support. Financial support from Aix-Marseille Université, Centrale Marseille, the CNRS, and the Agence Nationale de la Recherche (ANR-13-BS07-0005, PhD scholarship for O.Q.) is acknowledged. Moreover, the project leading to this publication has received funding from Excellence Initiative of Aix-Marseille University—A\*MIDEX, a French “Investissements d’Avenir” programme (scholarship for C.L.).

## References

1. Christie, G.H.; Kenner, J. LX.—The molecular configurations of polynuclear aromatic compounds. Part V. The identity of the nitration products derived from 2:7- and 4:5-dinitrophenanthraquinones. *J. Chem. Soc. Trans.* **1922**, *121*, 614–620. [[CrossRef](#)]
2. Ōki, M. Recent Advances in Atropisomerism. In *Topics in Stereochemistry*; Allinger, N.L., Eliel, E.L., Wilen, S.H., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2007; Volume 14, pp. 1–81. [[CrossRef](#)]
3. Entropic factors are generally small for rotations around a bond, and can be neglected. As a consequence, barriers to rotation can be seen as temperature-independent.
4. Kumarasamy, E.; Raghunathan, R.; Sibi, M.P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **2015**, *115*, 11239–11300. [[CrossRef](#)]
5. Bonne, D.; Rodriguez, J. Enantioselective syntheses of atropisomers featuring a five-membered ring. *Chem. Commun.* **2017**, *53*, 12385–12393. [[CrossRef](#)] [[PubMed](#)]
6. Bonne, D.; Rodriguez, J. A Bird's Eye View of Atropisomers Featuring a Five-Membered Ring. *Eur. J. Org. Chem.* **2018**, *2018*, 2417–2431. [[CrossRef](#)]
7. Lassaletta, J.M. *Atropoisomerism and Axial Chirality*; World Scientific: Singapore, 2019.
8. Siegel, J.S. Prologue: Atropisomerism. *Synlett* **2018**, *29*, 2122–2125. [[CrossRef](#)]
9. Mancinelli, M.; Bencivenni, G.; Pecorari, D.; Mazzanti, A. Stereochemistry and Recent Applications of Axially Chiral Organic Molecules. *Eur. J. Org. Chem.* **2020**, *2020*, 4070–4086. [[CrossRef](#)]
10. Kozłowski, M.C.; Morgan, B.J.; Linton, E.C. Total synthesis of chiral biaryl natural products by asymmetric biaryl coupling. *Chem. Soc. Rev.* **2009**, *38*, 3193–3207. [[CrossRef](#)]
11. Bringmann, G.; Gulder, T.; Gulder, T.A.M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products. *Chem. Rev.* **2011**, *111*, 563–639. [[CrossRef](#)]
12. Heinstein, P.F.; Herman, D.L.; Tove, S.B.; Smith, F.H. Biosynthesis of Gossypol. *J. Biol. Chem.* **1970**, *245*, 4658–4665. [[CrossRef](#)]
13. Clayden, J.; Moran, W.J.; Edwards, P.J.; LaPlante, S.R. The Challenge of Atropisomerism in Drug Discovery. *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401. [[CrossRef](#)]
14. LaPlante, S.R.; Fader, L.D.; Fandrick, K.R.; Fandrick, D.R.; Hucke, O.; Kemper, R.; Miller, S.P.F.; Edwards, P.J. Assessing Atropisomer Axial Chirality in Drug Discovery and Development. *J. Med. Chem.* **2011**, *54*, 7005–7022. [[CrossRef](#)] [[PubMed](#)]
15. Zask, A.; Murphy, J.; Ellestad, G.A. Biological Stereoselectivity of Atropisomeric Natural Products and Drugs. *Chirality* **2013**, *25*, 265–274. [[CrossRef](#)] [[PubMed](#)]
16. Smyth, J.E.; Butler, N.M.; Keller, P.A. A twist of nature—The significance of atropisomers in biological systems. *Nat. Prod. Rep.* **2015**, *32*, 1562–1583. [[CrossRef](#)] [[PubMed](#)]
17. Toenjes, S.T.; Gustafson, J.L. Atropisomerism in medicinal chemistry: Challenges and opportunities. *Future Med. Chem.* **2018**, *10*, 409–422. [[CrossRef](#)]
18. Fandrick, K.R.; Li, W.; Zhang, Y.; Tang, W.; Gao, J.; Rodriguez, S.; Patel, N.D.; Reeves, D.C.; Wu, J.-P.; Sanyal, S.; et al. Concise and Practical Asymmetric Synthesis of a Challenging Atropisomeric HIV Integrase Inhibitor. *Angew. Chem. Int. Ed.* **2015**, *54*, 7144–7148. [[CrossRef](#)]
19. Chandrasekhar, J.; Dick, R.; Van Veldhuizen, J.; Koditek, D.; Lepist, E.-I.; McGrath, M.E.; Patel, L.; Phillips, G.; Sedillo, K.; Somoza, J.R.; et al. Atropisomerism by Design: Discovery of a Selective and Stable Phosphoinositide 3-Kinase (PI3K)  $\beta$  Inhibitor. *J. Med. Chem.* **2018**, *61*, 6858–6868. [[CrossRef](#)]
20. Noyori, R.; Takaya, H. BINAP: An efficient chiral element for asymmetric catalysis. *Acc. Chem. Res.* **1990**, *23*, 345–350. [[CrossRef](#)]
21. Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047–9153. [[CrossRef](#)]
22. Kamer, P.C.J.; Cleij, M.C.; Nolte, R.J.M.; Harada, T.; Hezemans, A.M.F.; Drenth, W. Atropisomerism in polymers. Screw-sense selective polymerization of isocyanides by inhibiting the growth of one enantiomer of a racemic pair of helices. *J. Am. Chem. Soc.* **1988**, *110*, 1581–1587. [[CrossRef](#)]
23. Lee, J.; Kalin, A.J.; Wang, C.; Early, J.T.; Al-Hashimi, M.; Fang, L. Donor-acceptor conjugated ladder polymer via aromatization-driven thermodynamic annulation. *Polym. Chem.* **2018**, *9*, 1603–1609. [[CrossRef](#)]
24. Bringmann, G.; Price Mortimer, A.J.; Keller, P.A.; Gresser, M.J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427. [[CrossRef](#)] [[PubMed](#)]
25. Wallace, T.W. Biaryl synthesis with control of axial chirality. *Org. Biomol. Chem.* **2006**, *4*, 3197–3210. [[CrossRef](#)] [[PubMed](#)]
26. Bencivenni, G. Organocatalytic Strategies for the Synthesis of Axially Chiral Compounds. *Synlett* **2015**, *26*, 1915–1922. [[CrossRef](#)]
27. Wencel-Delord, J.; Panossian, A.; Leroux, F.R.; Colobert, F. Recent advances and new concepts for the synthesis of axially stereoenriched biaryls. *Chem. Soc. Rev.* **2015**, *44*, 3418–3430. [[CrossRef](#)] [[PubMed](#)]
28. Renzi, P. Organocatalytic synthesis of axially chiral atropisomers. *Org. Biomol. Chem.* **2017**, *15*, 4506–4516. [[CrossRef](#)]
29. Zilate, B.; Castrogiovanni, A.; Sparr, C. Catalyst-Controlled Stereoselective Synthesis of Atropisomers. *ACS Catal.* **2018**, *8*, 2981–2988. [[CrossRef](#)]
30. Link, A.; Sparr, C. Stereoselective arene formation. *Chem. Soc. Rev.* **2018**, *47*, 3804–3815. [[CrossRef](#)]
31. Bringmann, G.; Breuning, M.; Tasler, S. The Lactone Concept: An Efficient Pathway to Axially Chiral Natural Products and Useful Reagents. *Synthesis* **1999**, *1999*, 525–558. [[CrossRef](#)]

32. Gustafson, J.L.; Lim, D.; Miller, S.J. Dynamic Kinetic Resolution of Biaryl Atropisomers via Peptide-Catalyzed Asymmetric Bromination. *Science* **2010**, *328*, 1251–1255. [CrossRef]
33. Ma, G.; Sibi, M.P. Catalytic Kinetic Resolution of Biaryl Compounds. *Chem. Eur. J.* **2015**, *21*, 11644–11657. [CrossRef]
34. Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. Catalytic asymmetric synthesis of axially chiral biaryls by palladium-catalyzed enantioselective cross-coupling. *J. Am. Chem. Soc.* **1995**, *117*, 9101–9102. [CrossRef]
35. Di Iorio, N.; Crotti, S.; Bencivenni, G. Organocatalytic Desymmetrization Reactions for the Synthesis of Axially Chiral Compounds. *Chem. Rec.* **2019**, *19*, 2095–2104. [CrossRef] [PubMed]
36. Yang, G.; Guo, D.; Meng, D.; Wang, J. NHC-catalyzed atropenantioselective synthesis of axially chiral biaryl amino alcohols via a cooperative strategy. *Nat. Commun.* **2019**, *10*, 3062. [CrossRef] [PubMed]
37. Lipshutz, B.H.; Kayser, F.; Liu, Z.-P. Asymmetric Synthesis of Biaryls by Intramolecular Oxidative Couplings of Cyanocuprate Intermediates. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1842–1844. [CrossRef]
38. Leermann, T.; Broutin, P.-E.; Leroux, F.R.; Colobert, F. Construction of the biaryl-part of vancomycin aglycon via atropo-diastereoselective Suzuki-Miyaura coupling. *Org. Biomol. Chem.* **2012**, *10*, 4095–4102. [CrossRef]
39. Baudoin, O.; Décor, A.; Cesario, M.; Guéritte, F. A Novel 1,3-Central-to-Axial Chirality Induction Approach to Cyclooctadiene Lignans. *Synlett* **2003**, *2003*, 2009–2012. [CrossRef]
40. Dherbassy, Q.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. Two Stereoiduction Events in One C-H Activation Step: A Route towards Terphenyl Ligands with Two Atropisomeric Axes. *Angew. Chem. Int. Ed.* **2018**, *57*, 4668–4672. [CrossRef]
41. Baudoin, O. The Asymmetric Suzuki Coupling Route to Axially Chiral Biaryls. *Eur. J. Org. Chem.* **2005**, *2005*, 4223–4229. [CrossRef]
42. Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. Synthesis of axially chiral biaryl compounds by asymmetric catalytic reactions with transition metals. *Coord. Chem. Rev.* **2016**, *308 Pt 2*, 131–190. [CrossRef]
43. Zhan, B.-B.; Wang, L.; Luo, J.; Lin, X.-F.; Shi, B.-F. Synthesis of Axially Chiral Biaryl-2-amines by PdII-Catalyzed Free-Amine-Directed Atroposelective C-H Olefination. *Angew. Chem. Int. Ed.* **2020**, *59*, 3568–3572. [CrossRef]
44. Tanaka, K. Cationic Rhodium(I)/BINAP-Type Bisphosphine Complexes: Versatile New Catalysts for Highly Chemo-, Regio-, and Enantioselective [2+2+2] Cycloadditions. *Synlett* **2007**, *2007*, 1977–1993. [CrossRef]
45. Zhang, J.; Simon, M.; Golz, C.; Alcarazo, M. Gold-Catalyzed Atroposelective Synthesis of 1,1'-Binaphthalene-2,3'-diols. *Angew. Chem. Int. Ed.* **2020**, *59*, 5647–5650. [CrossRef] [PubMed]
46. Wolf, C. *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*; RSC: Cambridge, UK, 2008; pp. 204–330.
47. Quinonero, O.; Bressy, C.; Bugaut, X. Organocatalytic Enantioselective Construction of Polyaromatic Architectures. *Angew. Chem. Int. Ed.* **2014**, *53*, 10861–10863. [CrossRef] [PubMed]
48. Pantaine, L.; Moreau, X.; Coeffard, V.; Greck, C. The impact of asymmetric organocatalysis in dearomatization and aromatization of carbocycles: Increasing molecular complexity and diversity. *Tetrahedron Lett.* **2016**, *57*, 2567–2574. [CrossRef]
49. Nguyen, T.T. Traceless point-to-axial chirality exchange in the atropselective synthesis of biaryls/heterobiaryls. *Org. Biomol. Chem.* **2019**, *17*, 6952–6963. [CrossRef]
50. Yang, H.; Chen, J.; Zhou, L. Construction of Axially Chiral Compounds via Central-to-Axial Chirality Conversion. *Chem. Asian J.* **2020**, *15*, 2939. [CrossRef]
51. Berson, J.A.; Brown, E. Studies on Dihydropyridines. III. An Absolute Asymmetric Synthesis and an Attempted Conversion of Carbon Atom Asymmetry to Biphenyl Asymmetry. *J. Am. Chem. Soc.* **1955**, *77*, 450–453. [CrossRef]
52. Mislow, K.; Siegel, J. Stereoisomerism and local chirality. *J. Am. Chem. Soc.* **1984**, *106*, 3319–3328. [CrossRef]
53. Meyers, A.I.; Wettlaufer, D.G. The complete intramolecular transfer of a central chiral element to an axial chiral element. Oxidation of (S)-4-naphthylidihydroquinolines to (S)-4-naphthylquinolines. *J. Am. Chem. Soc.* **1984**, *106*, 1135–1136. [CrossRef]
54. Baker, R.W.; Kyasnoor, R.V.; Sargent, M.V.; Skelton, B.W.; White, A.H. Formal Synthesis of Both Atropomers of Desertorin C and an Example of Chirality Transfer from a Biphenyl Axis to a Spiro Centre and its Reverse. *Aust. J. Chem.* **2000**, *53*, 487–506. [CrossRef]
55. Campolo, D.; Gastaldi, S.; Roussel, C.; Bertrand, M.P.; Nechab, M. Axial-to-central chirality transfer in cyclization processes. *Chem. Soc. Rev.* **2013**, *42*, 8434–8466. [CrossRef] [PubMed]
56. Alexakis, A.; Bäckvall, J.E.; Krause, N.; Pàmies, O.; Diéguez, M. Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions. *Chem. Rev.* **2008**, *108*, 2796–2823. [CrossRef] [PubMed]
57. Guo, F.; Konkol, L.C.; Thomson, R.J. Enantioselective Synthesis of Biphenols from 1,4-Diketones by Traceless Central-to-Axial Chirality Exchange. *J. Am. Chem. Soc.* **2011**, *133*, 18–20. [CrossRef] [PubMed]
58. Vorogushin, A.V.; Wulff, W.D.; Hansen, H.-J. Stereoselectivity of the Benzannulation Reaction: Efficient Central-to-Axial Chirality Transfer. *J. Am. Chem. Soc.* **2002**, *124*, 6512–6513. [CrossRef]
59. Qin, T.; Skrabala-Joiner, S.L.; Khalil, Z.G.; Johnson, R.P.; Capon, R.J.; Porco, J.A., Jr. Atropselective Syntheses of (–) and (+) Rugulotrosin A Utilizing Point-to-Axial Chirality Transfer. *Nat. Chem.* **2015**, *7*, 234–240. [CrossRef]
60. Pizzolato, S.F.; Štacko, P.; Kistemaker, J.C.M.; van Leeuwen, T.; Otten, E.; Feringa, B.L. Central-to-Helical-to-Axial-to-Central Transfer of Chirality with a Photoresponsive Catalyst. *J. Am. Chem. Soc.* **2018**, *140*, 17278–17289. [CrossRef]
61. Forkosh, H.; Vershinin, V.; Reiss, H.; Pappo, D. Stereoselective Synthesis of Optically Pure 2-Amino-2'-hydroxy-1,1'-binaphthyls. *Org. Lett.* **2018**, *20*, 2459–2463. [CrossRef]

62. Bai, H.-Y.; Tan, F.-X.; Liu, T.-Q.; Zhu, G.-D.; Tian, J.-M.; Ding, T.-M.; Chen, Z.-M.; Zhang, S.-Y. Highly atroposelective synthesis of nonbiaryl naphthalene-1,2-diamine N-C atropisomers through direct enantioselective C-H amination. *Nat. Commun.* **2019**, *10*, 3063. [CrossRef]
63. Watile, R.A.; Bunrit, A.; Margalef, J.; Akkarasamiyo, S.; Ayub, R.; Lagerspets, E.; Biswas, S.; Repo, T.; Samec, J.S.M. Intramolecular substitutions of secondary and tertiary alcohols with chirality transfer by an iron(III) catalyst. *Nat. Commun.* **2019**, *10*, 3826. [CrossRef]
64. Quinonero, O.; Jean, M.; Vanthuyne, N.; Roussel, C.; Bonne, D.; Constantieux, T.; Bressy, C.; Bugaut, X.; Rodriguez, J. Combining Organocatalysis with Central-to-Axial Chirality Conversion: Atroposelective Hantzsch-Type Synthesis of 4-Arylpyridines. *Angew. Chem. Int. Ed.* **2016**, *55*, 1401–1405. [CrossRef]
65. Freund, M. Untersuchungen über das Thebain. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 3234–3256. [CrossRef]
66. Small, L.; Sargent, L.J.; Bralley, J.A. The Phenylhydrothebaines. *J. Org. Chem.* **1947**, *12*, 839–868. [CrossRef]
67. Robinson, R. An Essay in Correlation Arising from Alkaloid Chemistry. *Nature* **1947**, *160*, 815–817. [CrossRef] [PubMed]
68. Berson, J.A. A Standard of Absolute Configuration for Optically Active Biphenyls. *J. Am. Chem. Soc.* **1956**, *78*, 4170. [CrossRef]
69. Davidson, T.A.; Hollands, T.R.; Mayo, P.D.; Nisbet, M. Terpenoids: XII. The Structure of Chaparrin. *Can. J. Chem.* **1965**, *43*, 2996–3007. [CrossRef]
70. Hollands, T.R.; Mayo, P.D.; Nisbet, M.; Crabbé, P. Terpenoids: XIII. The Stereochemistry of Chaparrin, Chaparrol, and Related Compounds. *Can. J. Chem.* **1965**, *43*, 3008–3017. [CrossRef]
71. Warnhoff, E.W.; Lopez, S.V. A one-step conversion of carbon atom asymmetry into biphenyl asymmetry and its relation to the absolute configuration of caranine. *Tetrahedron Lett.* **1967**, *8*, 2723–2727. [CrossRef]
72. Hofmann, H.J.; Cimiriaglia, R. Conformation of 1,4-dihydropyridine—Planar or boat-like? *FEBS Lett.* **1988**, *241*, 38–40. [CrossRef] [PubMed]
73. Straub, A.; Goehrt, A.; Born, L. 4-Biaryl-substituted dihydropyridines with an unusual antiperiplanar conformation. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2519–2522. [CrossRef]
74. Bao, X.; Rodriguez, J.; Bonne, D. Enantioselective Synthesis of Atropisomers with Multiple Stereogenic Axes. *Angew. Chem. Int. Ed.* **2020**, *59*, 12623–12634. [CrossRef]
75. Chenga, D.-J.; Shao, Y.-D. Advances in the Catalytic Asymmetric Synthesis of Atropisomeric Hexatomic N-Heterobiaryls. *Adv. Synth. Catal.* **2020**, *362*, 3081–3099. [CrossRef]
76. Li, T.-Z.; Liu, S.-J.; Tan, W.; Shi, F. Catalytic Asymmetric Construction of Axially Chiral Indole-Based Frameworks: An Emerging Area. *Chem. Eur. J.* **2020**, *26*, 15779–15792. [CrossRef]
77. Wencil-Delord, J.; Colobert, F. Challenging Atroposelective C–H Arylation. *SynOpen* **2020**, *4*, 107–115. [CrossRef]
78. Corti, V.; Bertuzzi, G. Organocatalytic Asymmetric Methodologies towards the Synthesis of Atropisomeric N-Heterocycles. *Synthesis* **2020**, *52*, 2450–2468. [CrossRef]
79. Wang, J.; Zhao, C.; Wang, J. Recent progress toward the construction of axially chiral molecules catalyzed by an N-heterocyclic carbene. *ACS Catal.* **2021**, *11*, 12520–12531. [CrossRef]
80. Cheng, J.K.; Xiang, S.-H.; Li, S.; Ye, L.; Tan, B. Recent Advances in Catalytic Asymmetric Construction of Atropisomers. *Chem. Rev.* **2021**, *121*, 4805–4902. [CrossRef] [PubMed]
81. Xu, K.; Wang, Z.; Zhu, T. Recent Progress towards Organocatalyzed Asymmetric (Hetero)-Arene Formation. *Synthesis* **2021**, *53*, 636–652. [CrossRef]
82. Min, X.-L.; Zhang, X.-L.; Shen, R.; Zhang, Q.; He, Y. Recent advances in the catalytic asymmetric construction of atropisomers by central-to-axial chirality transfer. *Org. Chem. Front.* **2022**, *9*, 2280–2292. [CrossRef]
83. Baker, R.W.; Kyasnoor, R.V.; Sargent, M.V. Chirality transfer from a biphenyl axis to a spiro centre and its reverse: Sequential self-immolation. *Tetrahedron Lett.* **1999**, *40*, 3475–3478. [CrossRef]
84. Hattori, T.; Date, M.; Sakurai, K.; Morohashi, N.; Kosugi, H.; Miyano, S. Highly stereospecific conversion of C-centrochirality of a 3,4-dihydro-2H-1,1'-binaphthalen-1-ol into axial chirality of a 3,4-dihydro-1,1'-binaphthalene. *Tetrahedron Lett.* **2001**, *42*, 8035–8038. [CrossRef]
85. Koyama, Y.; Kataoka, H.; Suzuki, K.; Matsumoto, T. Regioselective Remote Functionalization of Biaryl Framework via Tethered ortho-Quinol Intermediate. *Chem. Asian J.* **2011**, *6*, 355–358. [CrossRef] [PubMed]
86. Link, A.; Sparr, C. Remote Central-to-Axial Chirality Conversion: Direct Atroposelective Ester to Biaryl Transformation. *Angew. Chem. Int. Ed.* **2018**, *57*, 7136–7139. [CrossRef]
87. Zheng, S.-C.; Wang, Q.; Zhu, J. Catalytic Kinetic Resolution by Enantioselective Aromatization: Conversion of Racemic Intermediates of the Barton–Zard Reaction into Enantioenriched 3-Arylpyrroles. *Angew. Chem. Int. Ed.* **2019**, *58*, 9215–9219. [CrossRef] [PubMed]
88. Xu, W.-L.; Zhao, W.-M.; Zhang, R.-X.; Chen, J.; Zhou, L. Organocatalytic cycloaddition–elimination cascade for atroposelective construction of heterobiaryls. *Chem. Sci.* **2021**, *12*, 14920–14926. [CrossRef] [PubMed]
89. Liu, Y.; Lu, K.; Dai, M.; Wang, K.; Wu, W.; Chen, J.; Quan, J.; Yang, Z. An Efficient One-Pot Asymmetric Synthesis of Biaryl Compounds via Diels–Alder/Retro-Diels–Alder Cascade Reactions. *Org. Lett.* **2007**, *9*, 805–808. [CrossRef]
90. Zhao, C.; Guo, D.; Munkerup, K.; Huang, K.-W.; Li, F.; Wang, J. Enantioselective [3+3] atroposelective annulation catalyzed by N-heterocyclic carbenes. *Nat. Commun.* **2018**, *9*, 611. [CrossRef]

91. Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. Chirality Exchange from  $sp^3$  Central Chirality to Axial Chirality: Benzannulation of Optically Active Diaryl-2,2-dichlorocyclopropylmethanols to Axially Chiral  $\alpha$ -Arylnaphthalenes. *J. Am. Chem. Soc.* **2004**, *126*, 5358–5359. [[CrossRef](#)]
92. Konkol, L.C.; Guo, F.; Sarjeant, A.A.; Thomson, R.J. Enantioselective Total Synthesis and Studies into the Configurational Stability of Bismurrayaquinone A. *Angew. Chem. Int. Ed.* **2011**, *50*, 9931–9934. [[CrossRef](#)]
93. Candish, L.; Levens, A.; Lupton, D.W. N-Heterocyclic carbene catalysed redox isomerisation of esters to functionalised benzaldehydes. *Chem. Sci.* **2015**, *6*, 2366–2370. [[CrossRef](#)]
94. Feringa, B.; Wynberg, H. Biomimetic asymmetric oxidative coupling of phenols. *Bioorg. Chem.* **1978**, *7*, 397–408. [[CrossRef](#)]
95. Brussee, J.; Jansen, A.C.A. A highly stereoselective synthesis of s(-)-[1,1'-binaphthalene]-2,2'-diol. *Tetrahedron Lett.* **1983**, *24*, 3261–3262. [[CrossRef](#)]
96. Meyers, A.I.; Lutomski, K.A. Enantioselective synthesis of binaphthyls via nucleophilic aromatic substitution on chiral oxazolines. *J. Am. Chem. Soc.* **1982**, *104*, 879–881. [[CrossRef](#)]
97. Wilson, J.M.; Cram, D.J. Chiral leaving groups induce asymmetry in syntheses of binaphthyls in nucleophilic aromatic substitution reactions. *J. Am. Chem. Soc.* **1982**, *104*, 881–884. [[CrossRef](#)]
98. Shindo, M.; Koga, K.; Tomioka, K. A catalytic method for asymmetric nucleophilic aromatic substitution giving binaphthyls. *J. Am. Chem. Soc.* **1992**, *114*, 8732–8733. [[CrossRef](#)]
99. Armstrong, R.J.; Smith, M.D. Catalytic Enantioselective Synthesis of Atropisomeric Biaryls: A Cation-Directed Nucleophilic Aromatic Substitution Reaction. *Angew. Chem. Int. Ed.* **2014**, *53*, 12822–12826. [[CrossRef](#)]
100. Castanet, A.-S.; Boussonniere, A.; Mortier, J. Asymmetric Nucleophilic Aromatic Substitution. In *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*; Mortier, J., Ed.; John Wiley & Sons: Hoboken, NJ, USA, 2015; pp. 195–217.
101. Brandes, S.; Bella, M.; Kjærsgaard, A.; Jørgensen, K.A. Chirally Aminated 2-Naphthols—Organocatalytic Synthesis of Non-Biaryl Atropisomers by Asymmetric Friedel–Crafts Amination. *Angew. Chem. Int. Ed.* **2006**, *45*, 1147–1151. [[CrossRef](#)] [[PubMed](#)]
102. Terada, M.; Dan, K. Synthesis of unsymmetrically substituted 2,2'-dihydroxy-1,1'-biaryl derivatives using organic-base-catalyzed Ferrier-type rearrangement as the key step. *Chem. Commun.* **2012**, *48*, 5781–5783. [[CrossRef](#)]
103. De, C.K.; Pescioli, F.; List, B. Catalytic Asymmetric Benzidine Rearrangement. *Angew. Chem. Int. Ed.* **2013**, *52*, 9293–9295. [[CrossRef](#)]
104. Li, G.-Q.; Gao, H.; Keene, C.; Devonas, M.; Ess, D.H.; Kürti, L. Organocatalytic Aryl-Aryl Bond Formation: An Atroposelective [3,3]-Rearrangement Approach to BINAM Derivatives. *J. Am. Chem. Soc.* **2013**, *135*, 7414–7417. [[CrossRef](#)]
105. Link, A.; Sparr, C. Organocatalytic Atroposelective Aldol Condensation: Synthesis of Axially Chiral Biaryls by Arene Formation. *Angew. Chem. Int. Ed.* **2014**, *53*, 5458–5461. [[CrossRef](#)]
106. Moliterno, M.; Cari, R.; Puglisi, A.; Antenucci, A.; Sperandio, C.; Moretti, E.; Di Sabato, A.; Salvio, R.; Bella, M. Quinine-Catalyzed Asymmetric Synthesis of 2,2'-Binaphthol-Type Biaryls under Mild Reaction Conditions. *Angew. Chem. Int. Ed.* **2016**, *55*, 6525–6529. [[CrossRef](#)] [[PubMed](#)]
107. Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B. Highly Atroposelective Synthesis of Arylpyrroles by Catalytic Asymmetric Paal-Knorr Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 1714–1717. [[CrossRef](#)] [[PubMed](#)]
108. Qi, L.-W.; Mao, J.-H.; Zhang, J.; Tan, B. Organocatalytic asymmetric arylation of indoles enabled by azo groups. *Nat. Chem.* **2018**, *10*, 58–64. [[CrossRef](#)] [[PubMed](#)]
109. Witzig, R.M.; Fäseke, V.C.; Häussinger, D.; Sparr, C. Atroposelective synthesis of tetra-ortho-substituted biaryls by catalyst-controlled non-canonical polyketide cyclizations. *Nat. Catal.* **2019**, *2*, 925–930. [[CrossRef](#)]
110. Straub, A.; Goehrt, A. Inversion of Optically Active Dihydropyridines by Oxidation and Electroreduction. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2662–2664. [[CrossRef](#)]
111. Koop, B.; Straub, A.; Schäfer, H.J. Stereoselective oxidation of 4-aryl-1,4-dihydropyridines to axially chiral 4-arylpyridines with 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate (TEMPO+BF<sub>4</sub><sup>-</sup>). *Tetrahedron Asymmetry* **2001**, *12*, 341–345. [[CrossRef](#)]
112. Han, M.; Zhang, S.-q.; Cui, X.; Wang, Q.-w.; Li, G.-x.; Tang, Z. Chiral Phosphoric Acid Catalyzed Enantioselective Desymmetrization of 1,4-Dihydropyridines by C(sp<sup>3</sup>)-H Bromination. *Angew. Chem. Int. Ed.* **2022**, *61*, e202201418. [[CrossRef](#)]
113. Ohno, A.; Kashiwagi, M.; Ishihara, Y.; Ushida, S.; Oka, S. NAD(P)<sup>+</sup>-NAD(P)h models. 57: Stereochemistry in (net) hydride transfer from and to nad(p)<sup>+</sup>-nad(p)h models: Chirality sink. *Tetrahedron* **1986**, *42*, 961–973. [[CrossRef](#)]
114. Mohr, J.T.; Ebner, D.C.; Stoltz, B.M. Catalytic enantioselective stereoblatant reactions: An unexploited approach to enantioselective catalysis. *Org. Biomol. Chem.* **2007**, *5*, 3571–3576. [[CrossRef](#)]
115. Ohno, A.; Ohara, M.; Oka, S. NAD(P)<sup>+</sup>-NAD(P)H models. 61. An interconversion between central and axial chiralities as evidence for a functional model of chemical evolution of an enzyme. *J. Am. Chem. Soc.* **1986**, *108*, 6438–6440. [[CrossRef](#)]
116. Ohno, A.; Ogawa, M.; Oka, S. NAD(P)<sup>+</sup>-NAD(P)H models. 67. Stereospecific conversion of central chirality into axial chirality as a model for chemical evolution of a dehydrogenase. *Tetrahedron Lett.* **1988**, *29*, 3079–3082. [[CrossRef](#)]
117. Ohno, A.; Ogawa, M.; Mikata, Y.; Goto, M. NAD(P)<sup>+</sup>-NAD(P)H Models. 69. Mechanism of Stereospecific (NET) Hydride Transfer Controlled by Electronic Effect. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 813–818. [[CrossRef](#)]
118. Ohno, A.; Mikata, Y.; Goto, M.; Kashiwagi, T.; Tanaka, T.; Sawada, M. NAD(P)H-NAD(P)<sup>+</sup> Models. 73. Structure-Stereochemistry Relationship in the Reaction of NAD Analog. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 81–86. [[CrossRef](#)]
119. Okamura, M.; Kashiwagi, T.; Mikata, Y.; Maruyama, T.; Ohno, A. Stereospecificity observed in base-catalyzed electrochemical oxidation. *Tetrahedron Lett.* **1991**, *32*, 1475–1478. [[CrossRef](#)]

120. Mikata, Y.; Mizukami, K.; Hayashi, K.; Matsumoto, S.; Yano, S.; Yamazaki, N.; Ohno, A. NAD/NADH Models with Axial/Central Chiralities: Superiority of the Quinoline Ring System. *J. Org. Chem.* **2001**, *66*, 1590–1599. [[CrossRef](#)]
121. De Kok, P.M.T.; Bastiaansen, L.A.M.; Van Lier, P.M.; Vekemans, J.A.J.M.; Buck, H.M. Highly reactive and stereoselective (R)- and (S)-3-(N,N-dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridines for NADH-NAD<sup>+</sup> mimicry. *J. Org. Chem.* **1989**, *54*, 1313–1320. [[CrossRef](#)]
122. Beijer, N.A.; Vekemans, J.A.J.M.; Buck, H.M. Stereoselective reduction of benzoin by the NADH model 3-(dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 434–436. [[CrossRef](#)]
123. Vekemans, J.A.J.M.; Versleijen, J.P.G.; Buck, H.M. NADH model mediated reduction of C=N substrates: Enantioselective synthesis of D- and L-phenylglycinates. *Tetrahedron Asymmetry* **1991**, *2*, 949–952. [[CrossRef](#)]
124. Versleijen, J.P.; Sanders-Hovens, M.S.; Vanhommerig, S.A.; Vekemans, J.A.; Meijer, E.M. Enantioselective reduction of C=O and C=N compounds with NADH model N,N,1,2,4-pentamethyl-1,4-dihydrnicotinamide. *Tetrahedron* **1993**, *49*, 7793–7802. [[CrossRef](#)]
125. Bisag, G.D.; Pecorari, D.; Mazzanti, A.; Bernardi, L.; Fochi, M.; Bencivenni, G.; Bertuzzi, G.; Corti, V. Central-to-Axial Chirality Conversion Approach Designed on Organocatalytic Enantioselective Povarov Cycloadditions: First Access to Configurationally Stable Indole-Quinoline Atropisomers. *Chem. Eur. J.* **2019**, *25*, 15694–15701. [[CrossRef](#)]
126. Wang, S.-J.; Wang, Z.; Tang, Y.; Chen, J.; Zhou, L. Asymmetric Synthesis of Quinoline-Naphthalene Atropisomers by Central-to-Axial Chirality Conversion. *Org. Lett.* **2020**, *22*, 8894–8898. [[CrossRef](#)] [[PubMed](#)]
127. Gao, Z.; Qian, J.; Yang, H.; Zhang, J.; Jiang, G. Enantioselective Construction of C-C Axially Chiral Quinazolinones via Chirality Exchange and Phase-Transfer Catalysis. *Org. Lett.* **2021**, *23*, 1731–1737. [[CrossRef](#)]
128. Gao, Z.; Wang, F.; Qian, J.; Yang, H.; Xia, C.; Zhang, J.; Jiang, G. Enantioselective Construction of Quinoxaline-Based Heterobiaryls and P,N-Ligands via Chirality Transfer Strategy. *Org. Lett.* **2021**, *23*, 1181–1187. [[CrossRef](#)] [[PubMed](#)]
129. Gou, B.-B.; Tang, Y.; Lin, Y.-H.; Yu, L.; Jian, Q.-S.; Sun, H.-R.; Chen, J.; Zhou, L. Modular Construction of Heterobiaryl Atropisomers and Axially Chiral Styrenes via All-Carbon Tetrasubstituted VQMs. *Angew. Chem. Int. Ed.* **2022**, *61*, e202208174. [[CrossRef](#)] [[PubMed](#)]
130. Fischer, C.; Sparr, C. Configurationally Stable Atropisomeric Acridinium Fluorophores. *Synlett* **2018**, *29*, 2176–2180. [[CrossRef](#)]
131. Wu, X.; Sparr, C. Stereoselective Synthesis of Atropisomeric Acridinium Salts by the Catalyst-Controlled Cyclization of *ortho*-Quinone Methide Iminiums. *Angew. Chem. Int. Ed.* **2022**, *61*, e202201424. [[CrossRef](#)]
132. Raut, V.S.; Jean, M.; Vanthuyne, N.; Roussel, C.; Constantieux, T.; Bressy, C.; Bugaut, X.; Bonne, D.; Rodriguez, J. Enantioselective Syntheses of Furan Atropisomers by an Oxidative Central-to-Axial Chirality Conversion Strategy. *J. Am. Chem. Soc.* **2017**, *139*, 2140–2143. [[CrossRef](#)]
133. Wang, D.; Tong, X. Phosphine-Catalyzed Asymmetric (3+2) Annulations of  $\delta$ -Acetoxy Allenates with 2-Naphthols. *Org. Lett.* **2017**, *19*, 6392–6395. [[CrossRef](#)]
134. Bao, X.; Rodriguez, J.; Bonne, D. Bidirectional enantioselective synthesis of bis-benzofuran atropisomeric oligoarenes featuring two distal C-C stereogenic axes. *Chem. Sci.* **2020**, *11*, 403–408. [[CrossRef](#)]
135. Hu, Y.-L.; Wang, Z.; Yang, H.; Chen, J.; Wu, Z.-B.; Lei, Y.; Zhou, L. Conversion of two stereocenters to one or two chiral axes: Atroposelective synthesis of 2,3-diarylbenzoindoles. *Chem. Sci.* **2019**, *10*, 6777–6784. [[CrossRef](#)]
136. Yang, H.; Xu, W.-L.; Zeng, X.-Y.; Chen, J.; Yu, L.; Zhou, L. Hydrogen Bond Assisted Central-to-Spiro Chirality Transfer and Central-to-Axial Chirality Conversion: Asymmetric Synthesis of Spirocycles. *Org. Lett.* **2021**, *23*, 9315–9320. [[CrossRef](#)] [[PubMed](#)]
137. Xiang Alvin Tan, C.; Li, R.; Zhang, F.; Dai, L.; Ullah, N.; Lu, Y. Synthesis of Axially Chiral CF<sub>3</sub>-Substituted 2-Arylpyrroles by Sequential Phosphine-Catalyzed Asymmetric [3+2] Annulation and Oxidative Central-to-Axial Chirality Transfer. *Angew. Chem. Int. Ed.* **2022**, *61*, e202209494. [[CrossRef](#)] [[PubMed](#)]
138. Shindo, M.; Yamamoto, Y.; Yamada, K.-i.; Tomioka, K. Asymmetric Construction of Binaphthyl by the Chiral Diether-Mediated Conjugate Addition of Naphthyllithium to Naphthalenecarboxylic Acid 2,6-Di-*t*-butyl-4-methoxyphenyl Ester. *Chem. Pharm. Bull.* **2009**, *57*, 752–754. [[CrossRef](#)] [[PubMed](#)]
139. Wanjohi, J.M.; Yenesew, A.; Midiwo, J.O.; Heydenreich, M.; Peter, M.G.; Dreyer, M.; Reichert, M.; Bringmann, G. Three dimeric anthracene derivatives from the fruits of *Bulbine abyssinica*. *Tetrahedron* **2005**, *61*, 2667–2674. [[CrossRef](#)]
140. Xu, K.; Li, W.; Zhu, S.; Zhu, T. Atroposelective Arene Formation by Carbene-Catalyzed Formal [4+2] Cycloaddition. *Angew. Chem. Int. Ed.* **2019**, *58*, 17625–17630. [[CrossRef](#)]
141. Zhang, C.-L.; Gao, Y.-Y.; Wang, H.-Y.; Zhou, B.-A.; Ye, S. Enantioselective Synthesis of Axially Chiral Benzothiophene/Benzofuran-Fused Biaryls by N-Heterocyclic Carbene Catalyzed Arene Formation. *Angew. Chem. Int. Ed.* **2021**, *60*, 13918. [[CrossRef](#)]
142. Hayashi, Y.; Takikawa, A.; Koshino, S.; Ishida, K. Asymmetric Synthesis of Biaryl Atropisomers Using an Organocatalyst-Mediated Domino Reaction as the Key Step. *Chem. Eur. J.* **2019**, *25*, 10319–10322. [[CrossRef](#)]
143. Koshino, S.; Takikawa, A.; Ishida, K.; Taniguchi, T.; Monde, K.; Kwon, E.; Umemiya, S.; Hayashi, Y. Inversion of the Axial Information during Oxidative Aromatization in the Synthesis of Axially Chiral Biaryls with Organocatalysis as a Key Step. *Chem. Eur. J.* **2020**, *26*, 4524–4530. [[CrossRef](#)]
144. Koshino, S.; Taniguchi, T.; Monde, K.; Kwon, E.; Hayashi, Y. Enantiodivergent One-Pot Synthesis of Axially Chiral Biaryls Using Organocatalyst-Mediated Enantioselective Domino Reaction and Central-to-Axial Chirality Conversion. *Chem. Eur. J.* **2021**, *27*, 15786–15794. [[CrossRef](#)]

145. Zhu, L.; Peng, H.; Guo, Y.; Che, J.; Wu, J.-H.; Su, Z.; Wang, T. Enantioselective Synthesis of Atropisomeric Biaryl Phosphorus Compounds by Chiral-Phosphonium-Salt-Enabled Cascade Arene Formation. *Angew. Chem. Int. Ed.* **2022**, *61*, e202202467. [[CrossRef](#)]
146. Tan, J.-P.; Li, K.; Shen, B.; Zhuang, C.; Liu, Z.; Xiao, K.; Yu, P.; Yi, B.; Ren, X.; Wang, T. Asymmetric synthesis of N-bridged [3.3.1] ring systems by phosphonium salt/Lewis acid relay catalysis. *Nat. Commun.* **2022**, *13*, 357. [[CrossRef](#)] [[PubMed](#)]
147. Fang, S.; Tan, J.-P.; Pan, J.; Zhang, H.; Chen, Y.; Ren, X.; Wang, T. Enantiodivergent Kinetic Resolution of 1,1'-Biaryl-2,2'-Diols and Amino Alcohols by Dipeptide-Phosphonium Salt Catalysis Inspired by the Atherton–Todd Reaction. *Angew. Chem. Int. Ed.* **2021**, *60*, 14921–14930. [[CrossRef](#)] [[PubMed](#)]
148. Saito, T.; Shimizu, Y.; Araki, Y.; Ohgami, Y.; Kitazawa, Y.; Nishii, Y. From Enantioenriched Donor-Acceptor Cyclopropylcarbinols to Axially Chiral Arylnaphthalenes through Aryldihydronaphthalenes: Central-to-Axial Chirality Exchange. *Eur. J. Org. Chem.* **2022**, *2022*, e202101213. [[CrossRef](#)]
149. Wang, Y.-B.; Zheng, S.-C.; Hu, Y.-M.; Tan, B. Brønsted acid-catalysed enantioselective construction of axially chiral arylquinazolines. *Nat. Commun.* **2017**, *8*, 15489. [[CrossRef](#)] [[PubMed](#)]