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A Bird's Eye View of Atropisomers Featuring a Five-Membered Ring

Damien Bonne*^[a] and Jean Rodriguez*^[a]

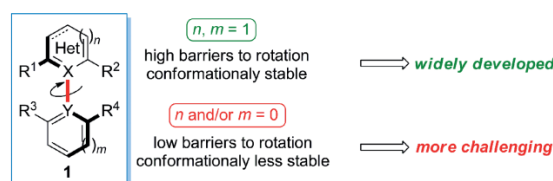
Abstract: An atropisomer is a member of a subclass of restricted rotational conformers – this restricted rotation giving rise to stereogenic sigma bonds – that can be isolated as separate chemical species. Most atropisomers are six-membered-ring biaryl or heterobiaryl derivatives. The aim of this microreview is to shed light on a less common class of atropisomers, those containing at least one five-membered hetero- or carbocycle and displaying variously a stereogenic C–N, C–C, or even N–N

chemical bond. After a short introduction, the occurrence of atropisomers in nature is presented, as well as the synthetic efforts – encompassing non-stereoselective and diastereoselective strategies, together with an update on very recent enantioselective approaches – devoted to such axially chiral compounds. Finally, a special focus is placed on their important utilization as original and efficient ligands for metal complexes.

1. Introduction

Nonracemic axially chiral systems of type **1**^[1] (Scheme 1) are recognized as central elements in many scientific domains, with notably numerous applications in catalyst design,^[2] drug discovery,^[3] and materials sciences,^[4] and are also widely represented in nature. Among them, six-membered carbocyclic – and, to lesser extent, heterocyclic – atropisomers^[5] have commanded huge attention over the years and still constitute a central topic of research worldwide, resulting in the development of many elegant synthetic approaches.^[6] In sharp contrast, atropisomeric species featuring one or even two five-membered rings connected variously through a C–C, C–N, or

N–N bond have received less attention.^[6i] This situation is basically due to the increased distance between the *ortho*-substituents (R¹ to R⁴) next to the axis, which is responsible for lower barriers to rotation, hampering the conformational stability (Scheme 1).



X, Y = carbon or heteroatom

\curvearrowright = barrier to rotation ΔG 93 kJ·mol⁻¹, half-life 1000 s at r.t.

Scheme 1. Situation of six- versus five-membered atropisomeric systems.

Pioneering observations and experimental determinations of barriers to rotation highlight the crucial effect of *ortho*-substituents. It has been proposed by Oki that a pair of atropisomers

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Damien Bonne was born in Epinal (France) in 1979. After studying chemistry at the Ecole Supérieure de Chimie de Lyon (CPE Lyon, France), he completed his Ph.D. in 2006 under the supervision of Prof. J. Zhu, working on isocyanide-based multicomponent reactions. He then moved to the University of Bristol (UK) to join the group of Prof. V. A. Aggarwal as a postdoctoral associate. Since 2007 he has been working as a "Maître de Conférences" (associate professor) at Aix-Marseille University (France). He passed his habilitation (HDR) in 2015 and his research interests include the development of new organocatalyzed methodologies and their application in stereoselective synthesis.



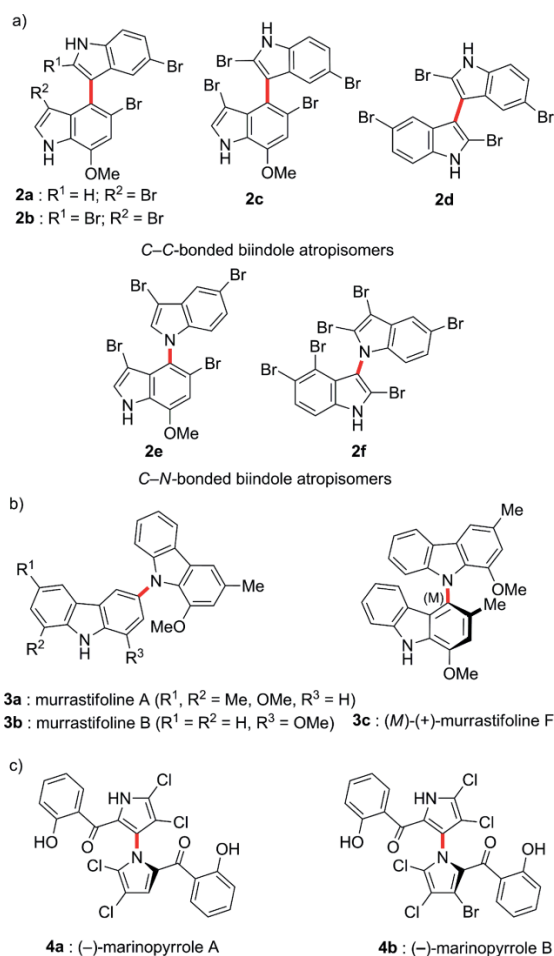
Jean Rodriguez was born in Cieza (Spain) in 1958, and in 1959 his family emigrated to France. After studying chemistry at the University of Aix-Marseille (France), he completed his Ph.D. as a CNRS researcher with Prof. B. Waegell and Prof. P. Brun in 1987. He completed his Habilitation in 1992, also at Marseille, where he is currently Professor and Director of the UMR-CNRS-7313-iSm2. His research interests include the development of multiple bond-forming transformations including domino and multicomponent reactions, and their application in stereoselective organocatalyzed synthesis. In 1998 he was awarded the ACROS prize in Organic Chemistry, in 2009 he was awarded the prize of the Division of Organic Chemistry from the French Chemical Society, and in 2013 he became a "Distinguished Member" of the French Chemical Society.

should exhibit a minimum energy barrier of 93 kJ mol⁻¹, to ensure a half-life of at least 1000 seconds at room temperature^[7] and to offer reasonable expectation of the convenient separation of the two enantiomeric atropisomers.^[8]

In this context, the aim of this microreview, after a brief historical background highlighting their natural occurrence, is to give an overview on the preparation of atropisomers from neglected pioneering achievements up to more contemporaneous selective approaches, including an update on very recent enantioselective syntheses. The last section is devoted to their utilization as efficient ligands for metal complexes, followed by their efficient utilization as ligands for metal complexes.

2. In Nature

Both axially chiral C–C- and C–N-bonded atropisomers containing five-membered rings exist in nature, essentially in three small, rare families featuring one or two five-membered rings from the indole, carbazole, or pyrrole series. However, their isolation and characterization were achieved only at the end of the last century (Scheme 2).



Scheme 2. Naturally occurring C–C- and C–N-bonded axially chiral arylazoles.

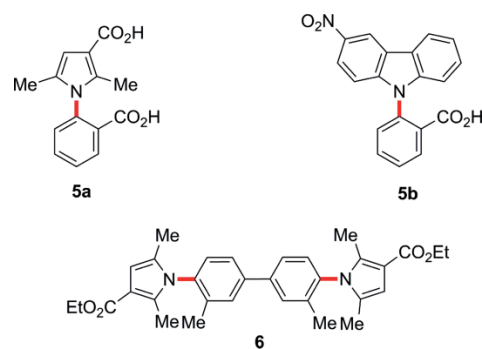
The first of these families is that of the optically pure polybrominated biindoles **2** from marine blue-green alga *Rivularia firma*, isolated in 1982 and including the four C–C-bonded congeners **2a–d** and the two C–N-bonded congeners **2e** and **2f** (Scheme 2a).^[9]

Another C–N-bonded carbazole alkaloid family, named murrastifolines A (**3a**), B (**3b**), and F (**3c**), was isolated eleven years later from the acetone extract of the root of the plant *Murraya koenigii* (Scheme 2b).^[10] From the substitution pattern of the axially chiral C–N-bonded phenyl ring of murrastifolines A and B, lacking any *ortho*-substituent, rapid rotation at the biaryl axis was suspected, whereas murrastifoline F, bearing four *ortho*-substituents next to the axis, was expected to be configurationally stable. This was established by Bringmann and collaborators in 2001, both through a very high calculated (AM1) atropisomerization barrier of 165 kJ mol⁻¹ and by the unique total synthesis of the F analogue, showing its presence in the root extract as a 56:44 mixture in favor of the *M* enantiomer.^[11]

More recently, the two new axially chiral metabolites (–)-marinopyrrole A (**4a**) and (–)-marinopyrrole B (**4b**) were isolated after cultivation of an obligate marine *Streptomyces* strain^[12] and showed potent antibiotic activities against methicillin-resistant *staphylococcus aureus* (Scheme 2c).^[13] Two years after their isolation, two different total syntheses of (±)-marinopyrrole A were reported contemporaneously by the groups of Li^[12c] and Sarli,^[12d] with nine steps and 30 % yield and six steps and 22 % yield, respectively.

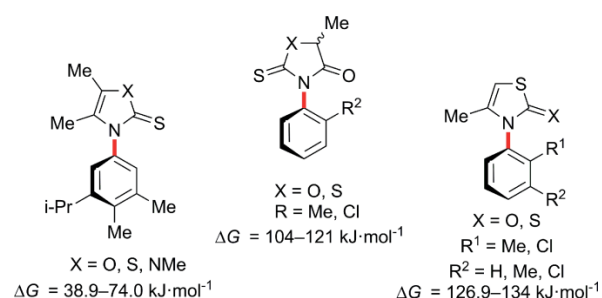
2. Non-Stereoselective Syntheses

The first synthesis of an axially chiral five-membered-ring compound was that of C–N-bonded^[14] arylpyrrole **5a**, reported back in 1931 by the group of Adams,^[15] followed by a series of papers dealing with the preparation of the related arylcarbazole^[16] **5b** and the dipyrrolyl biphenyl **6**^[17] (Scheme 3). In all these studies, the racemic atropisomers obtained from the required 1,5-diketones and anilines in a Paal–Knorr heterocyclization in the case of **5a** and **6** or through the Ullman-type coupling of *o*-iodobenzoic acid with 3-nitrocarbazole in that of **5b** were resolved by means of the corresponding brucine salts. Interestingly, for pyrrole **5a** and carbazole **5b** the two enantiomers were found to be relatively stable in boiling ethanol but to undergo total thermal racemization in the presence of NaOH.



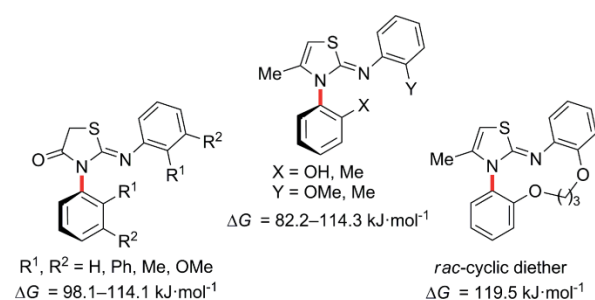
Scheme 3. First families of axially chiral N-arylpyrroles **5** and **6**.

After these pioneering contributions, the experimental determination of steric barriers in atropisomers containing five-membered rings became a central research domain of early conformational analysis. This was facilitated by the concomitant development of chiral liquid chromatography, allowing efficient separations of atropisomers as thoroughly studied by Roussel and collaborators, starting in 1985.^[18a–18d] This strategy was applied to *N*-arylthiazolinethione derivatives and their oxygen analogues, and later on by Pirkle's, Mannschreck's, and Doğan's groups, notably with related *N*-aryloxazolinones^[18e–18g] and *N*-arylthioxo-oxazolidinones or *N*-arylrhodanines.^[18h,18i] These comparative studies of large series of compounds clearly showed the crucial effect of *ortho*-substitution on the value of the barriers to rotation, which fluctuated from 38.9 kJ mol⁻¹ for *ortho*-unsubstituted derivatives up to ≥134 kJ mol⁻¹ (Scheme 4). Interestingly, some specifically functionalized *N*-arylthiazolinethione nuclei have been used either as enantioselective anion receptors for amino acid derivatives^[18j] or as new atropisomeric chiral probes to study supramolecular organization in porphyrin self-assemblies.^[18k]



Scheme 4. Variations of the barriers to rotation in *N*-arylthiazoline derivatives.

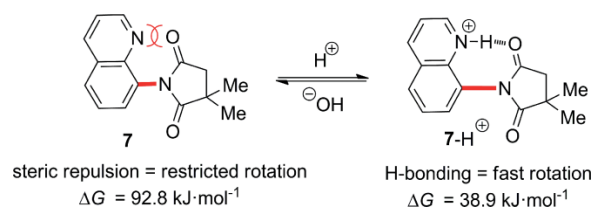
More recently, the groups of Doğan and Roussel independently reported complete experimental and theoretical studies relating to the synthesis of, and the evaluation of the barriers to rotation in, a series of original atropisomeric iminothiazolidinones and iminothiazolines, respectively (Scheme 5).^[19a–19c] In all of these studies the resolution of atropisomeric enantiomers was achieved by chromatography on chiral supports. In the case of *N*-aryliminothiazolines, it was found that the barriers significantly decrease when $X = \text{OH}$ through the creation of an internal hydrogen bond with the nitrogen atom of the imino group, as was corroborated by DFT calculations. The authors



Scheme 5. Variations of the barriers to rotation in *N*-aryliminothiazolidinone and -iminothiazoline derivatives.

also demonstrated the possibility of forming a rather stable 12-membered-ring diether atropisomer with a slightly higher barrier to rotation.

This unusual intramolecular hydrogen bond effect was exploited four years later by Shimizu's group for the design of original simple molecular rotors featuring compound **7**, a *N*-8-quinoliny succinimide framework (Scheme 6).^[19d,19e] The authors clearly established that protonation of the quinoline resulted in a dramatic lowering of the barrier to rotation, due to the stabilization of a planar transition state through the formation of an intramolecular hydrogen bond between the protonated nitrogen atom and the imide carbonyl group. Interestingly, the acceleration of the rotation is reversible and can be stopped by addition of base. The determining presence of the nitrogen atom in this specific 8-position was unambiguously established, with no effect being observed with the corresponding control rotors from both the 6-substituted quinoline and the naphthalene series. The same group, upon guest complexation of an acetate ion, observed a closely related effect on the barrier to rotation with *N*-arylsuccinimides containing a urea recognition group.^[19e]

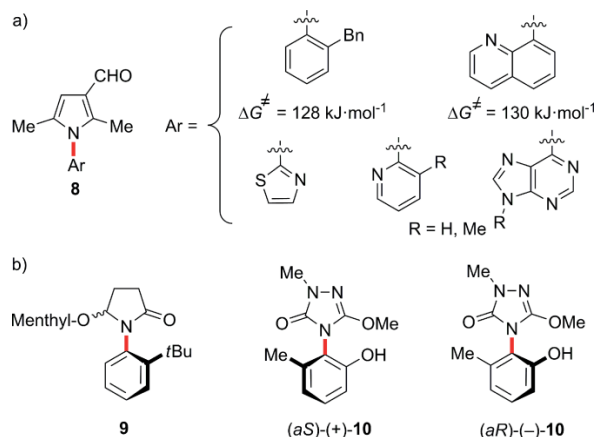


Scheme 6. Acid-accelerated *N*-8-quinoliny succinimide molecular rotor.

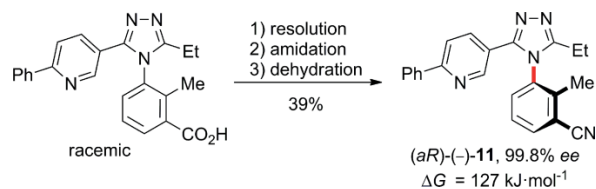
Mintas and collaborators also reported detailed pioneering studies dealing with the synthesis and chromatographic separation of compounds **8**, a series of *N*-aryl- and *N*-heteroaryl-2,5-dimethylpyrrole-3-carbaldehydes variously containing simple phenyl, quinoliny, thiazoly, pyridyl, and 6-puriny groups, and the determination of their barriers to racemization, either experimentally or by calculation (Scheme 7a).^[20] Here also, the crucial effect of steric factors next to the axis in reaching the required minimum of 100 kJ mol⁻¹ for the barrier to rotation was clearly highlighted. Accordingly, in this series only *N*-phenyl- and *N*-quinoliny pyrroles gave room-temperature-stable atropisomers with high calculated free enthalpies of activation: $\Delta G^\ddagger = 128$ and 130 kJ mol⁻¹, respectively. Related enantiopure axially chiral *N*-phenylpyrrolidones **9** and *N*-phenyltriazolones **10** were also obtained by resolution of the corresponding menthol and naproxen esters, respectively (Scheme 7b).^[21]

More recently, Sugane and co-workers proposed an efficient means of resolution using (1*R*,2*S*)-(-)-2-amino-1,2-diphenylethanol for the synthesis of the stable atropisomeric *N*-phenyl-1,2,4-triazole (*aR*)-(-)-**11**, which displayed a barrier to rotation of 127 kJ mol⁻¹ and exhibited interesting GlyT1-inhibiting properties (Scheme 8).^[21c]

In 2016, Ciogli, Mazzanti, and Perumal exploited a new domino reaction between aryl isocyanates **12** and commercially available 1,4-dithiane-2,5-diol for the synthesis of axially chiral *N*-arylthiazolinethione derivatives **14** (Scheme 9).^[22] A complete

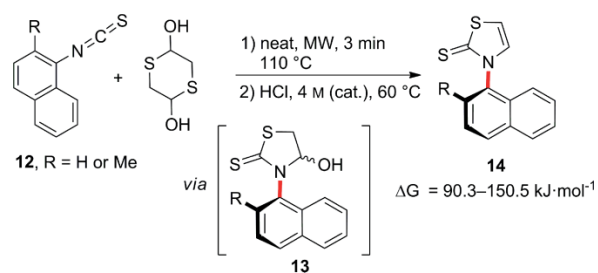


Scheme 7. *N*-Aryl and *N*-heteroaryl axially chiral atropisomers **8–10**.



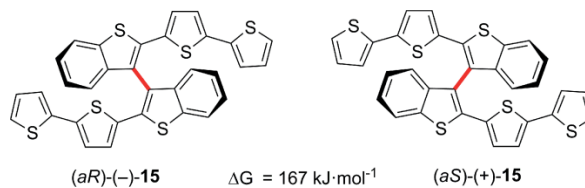
Scheme 8. Biologically active *N*-phenylthiazole **11**.

combined dynamic NMR and HPLC study both of the transient hemiaminal intermediates **13** and of the *N*-arylthiazolidinethiones **14** allowed the determination of a low barrier to rotation of 90.5 kJ mol⁻¹ for R = H, in agreement with fast atropisomerization at room temperature. In sharp contrast, for R = Me the barrier to rotation was estimated to be higher than 150.5 kJ mol⁻¹, allowing the separation of the two stable enantiomers by chiral HPLC.



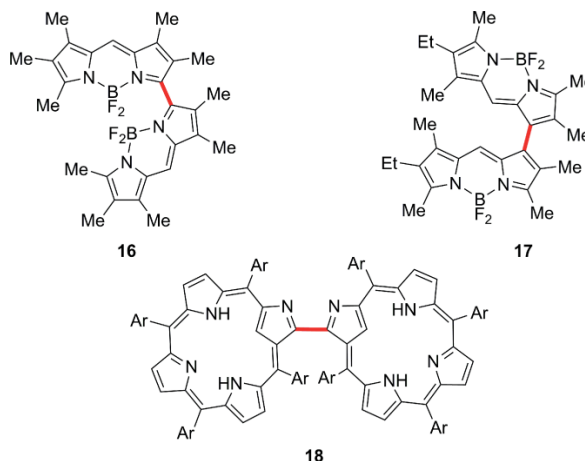
Scheme 9. One-pot synthesis of *N*-arylthiazolidinethiones **14**.

A new electroactive chiral polyheterocyclic organic film based on axially chiral C–C-bonded bithienyl assemblies was designed and synthesized by Sannicolò's group. The racemic material was obtained by Stille coupling, and the two monomeric optically pure atropisomers (*aR*)-(-)-**15** and (*aS*)-(+)-**15** were obtained by separation on chiral HPLC and present a very high barrier to rotation of 167 kJ mol⁻¹ (Scheme 10).^[23]



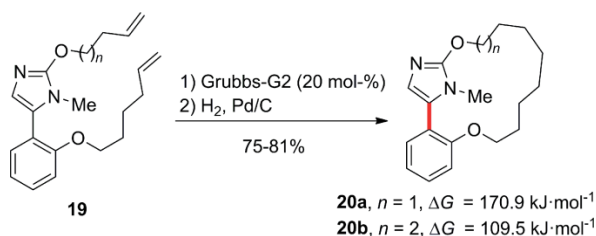
Scheme 10. C3–C3'-bonded chiral atropisomeric bithienyl derivatives (+)- and (-)-**15**.

Other recent examples of related C–C-bonded atropisomeric derivatives of the bis-pyrrole type have been proposed independently by Bringmann's and Chmielewski's groups for the design of axially chiral BODIPY dyes **16** and **17** or of bis(*N*-confused porphyrin) **18** as a semirigid receptor with memory of chirality, respectively (Scheme 11).^[24]



Scheme 11. C–C-bonded atropisomeric BODIPY derivatives **16** and **17** and porphyrin derivative **18**.

Finally, the imidazole nucleus has also been used to elaborate C–C-bonded atropisomeric 15- and 16-membered macrocycles **20a** and **20b** from precursor **19** by ring-closing metathesis followed by hydrogenation. These macrocycles **20a** and **20b** show high barriers to rotation of 170.9 and 109.5 kJ mol⁻¹, corresponding to half-lives of racemization at 25 °C of several trillion years and 40 days, respectively (Scheme 12).^[25]



Scheme 12. C–C-bonded atropisomeric 15- and 16-membered macrocycles **20a** and **20b**.

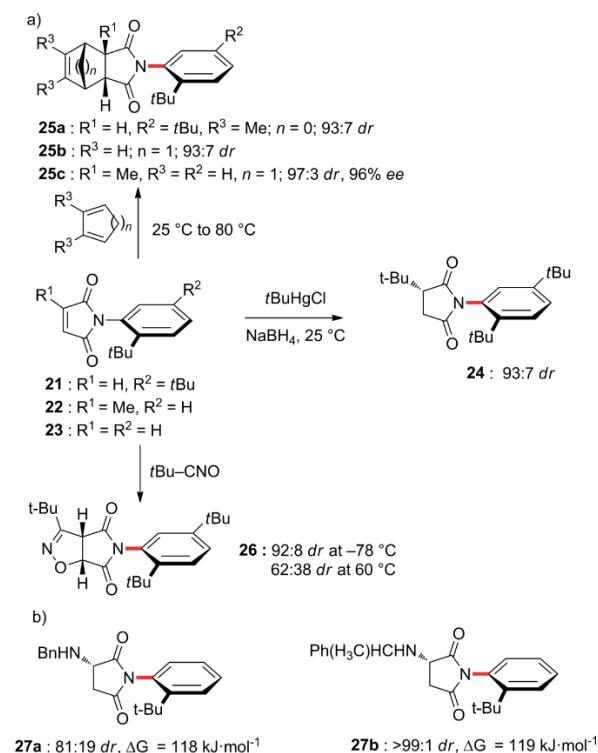
Since the first report of the axially chiral C–*N*-bonded arylpyrrole **5a** in 1931,^[15] the resolution of racemic mixtures either chemically or chromatographically has emerged as a central

tool for the production of enantiomerically pure atropisomers containing five-membered rings. These have found numerous applications, notably in the design of metal complexes. Complementarily to these robust techniques, original stereoselective synthetic approaches have appeared during the two last decades and are presented in the following sections together with some specific applications of the resulting atropisomers.

3. Stereoselective Syntheses

3.1. Diastereoselective Functionalizations of Axially Chiral Atropisomers

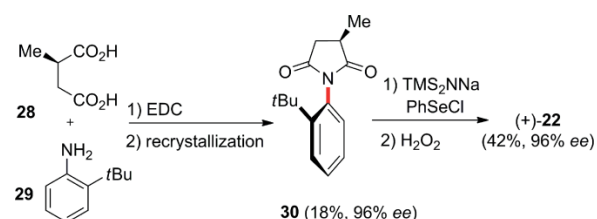
The first representative, based on atropodiastereoselective desymmetrization of prochiral *N*-arylmaleimide **21**, is that of Curran et al. in 1994.^[26b] They reasoned that the presence of a large *ortho*-*t*Bu substituent should provide a high enough barrier towards rotation around the C–N axis, for efficient stereoselective synthesis. Hence, the addition of a *t*Bu radical to **21** under the Giese conditions gave **24** with high diastereoselectivity (Scheme 13a, right). Alternatively, *endo*-selective Diels–Alder cycloaddition either with 2,3-dimethylbuta-1,3-diene at 80 °C or with cyclopentadiene at 25 °C afforded the cycloadducts **25a** and **25b** with the same high diastereoselectivity (Scheme 13a, top). In addition, the authors demonstrated similar efficiency in 1,3-dipolar cycloaddition with neopentane nitride oxide, although an important effect of the temperature on



Scheme 13. Atropodiastereoselective desymmetrizations of maleimides **21**–**23**.

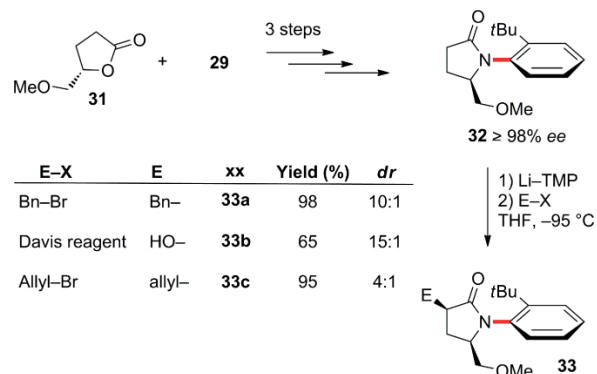
the diastereoselectivity was observed in the case of compound **26** (Scheme 13b, down arrow). Interestingly, and in agreement with their expectations, chiral compounds **24**, **25a**, and **26** were stable at room temperature and started to isomerize above 120 °C, whereas **25b** never isomerized even at 150 °C. At the same time, the Kishikawa group reported a related atropodiastereoselective amination of **23** affording the corresponding *N*-benzyl- and *N*-(1-phenylethyl)succinimides **27a** and **27b** with diastereoselectivity ranging from 81:19 to >99:1 *dr*.^[26d] The barriers to rotation were measured by ¹H NMR and were found to be around 120 kJ mol^{–1} for both atropisomers (Scheme 13b).

After these pioneering contributions with the prochiral *N*-arylmaleimides **21**–**23**, Taguchi and co-workers proposed a simple synthesis of axially chiral maleimide (+)-**22** with 96 % *ee* and a half-life for racemization of 15 h at 80 °C allowing its utilization in further stereoselective transformations (Scheme 14).^[27a] The synthesis started from (*R*)-2-methylsuccinic acid (**28**) and *ortho*-*t*Bu-aniline (**29**), followed by an oxidative selenoxide elimination from the resulting major diastereomer (1.3:1 *dr*) of succinimide **30** obtained with 96 % *ee* after recrystallization. As expected from Curran's work, the thermal or Lewis-acid-catalyzed *endo*-selective Diels–Alder reaction between (+)-**22** and cyclopentadiene proceeded with good yields and high diastereoselectivities to furnish **25c** with 97:3 *dr* and 96 % *ee* (Scheme 13a, top).



Scheme 14. Diastereoselective preparation of axially chiral maleimide (+)-**22**.

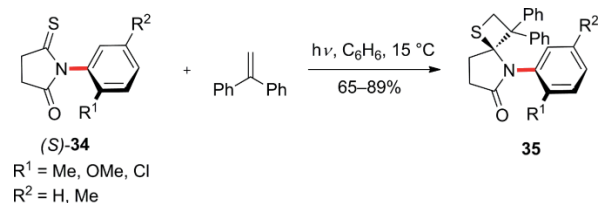
In a subsequent contribution, the same group disclosed an original three-step synthesis of **33**, a new optically active axially chiral *N*-arylpyrrolidone, with ≥98 % *ee* from (*S*)-5-(methoxymethyl)butyrolactone (**31**) and aniline **29** (Scheme 15).^[27b] Interestingly, the lithium enolate of **32** underwent diastereo-



Scheme 15. Diastereoselective axially chiral *N*-arylpyrrolidones **32** and **33**.

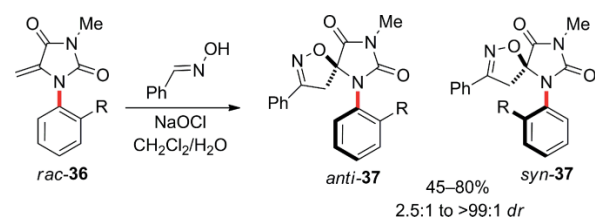
selective functionalization with various electrophiles, leading to unusual 3,5-*cis*-disubstituted 2-pyrrolidinone derivatives **33**. Here also, the *ortho*-*t*Bu group ensures a high barrier to rotation and shields the *Si* face of the enolate, resulting in the uncommon 3,5-*cis* selectivity. It is interesting to note that changing the *t*Bu- group to a -OBn or even a -OTBDPS group resulted in free rotation around the C–N axis at room temperature.

The usually high stereoselectivity found for cycloadditions has been exploited to access various families of original atropisomeric derivatives from easily accessible unsaturated precursors. For example, simple room-temperature-stable axially chiral *N*-aryl-substituted monothiosuccinimides **34** were proposed by Sakamoto and collaborators in 2003 as interesting partners in chemo-, regio-, and diastereoselective [2+2] photocycloaddition to 1,1-diphenylethylene, leading to spirothietanes **35** in good yields (Scheme 16).^[28] In this transformation, the steric hindrance of the *ortho*-substituent was crucial and perfectly controlled the addition to form **35** exclusively.



Scheme 16. Photocycloaddition of *N*-aryl-substituted monothiosuccinimides **34**.

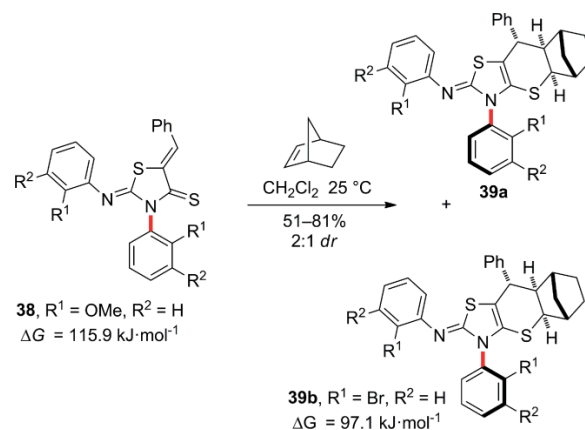
In 2011 Savage's group reported an interesting atropisomeric facial selectivity during regioselective (1,3)-dipolar cycloaddition between benzonitrile oxide and racemic axially chiral *N*-arylmethylenehydantoins **36** (Scheme 17).^[29] The nature of the *ortho*-substitution (*R* group) was crucial for the attainment of high diastereoselectivities, ranging from 2.5:1 to >99:1 ratios of *anti*-**37** to *syn*-**37**. Interestingly, the best result was obtained with *R* = NO₂, leading to *anti*-**37** only, probably due to additional electrostatic repulsion with the approaching nitrile oxide dipole.



Scheme 17. (1,3)-Dipolar cycloaddition to *N*-arylmethylenehydantoins **36**.

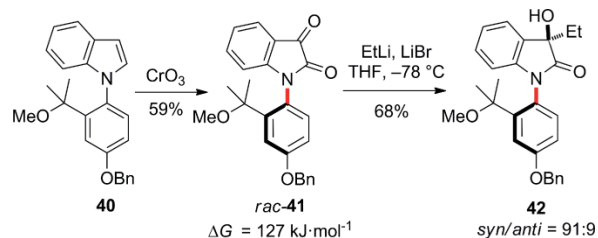
Also of interest is the reactivity of benzylidene *N*-arylthiazolidinethiones **38**, developed by Doğan's group as heterodiene partners in *exo*-selective inverse-electron-demand Diels–Alder cycloaddition with norbornene (Scheme 18).^[30] The cycloaddition proceeded smoothly to give the corresponding adducts **39a** and **39b** at room temperature with a transient kinetic atroposelectivity of 11:1 (*R*¹ = Br, *R*² = H), with equilibration after 24 h to the isolated thermodynamic ratio of 2:1 in favor of **39a**, regardless of the substitution patterns. This phenom-

non is due to a quite significantly lower barrier to rotation for the adducts **39** than for the starting heterodienes **38**, by about 20 kJ mol⁻¹.



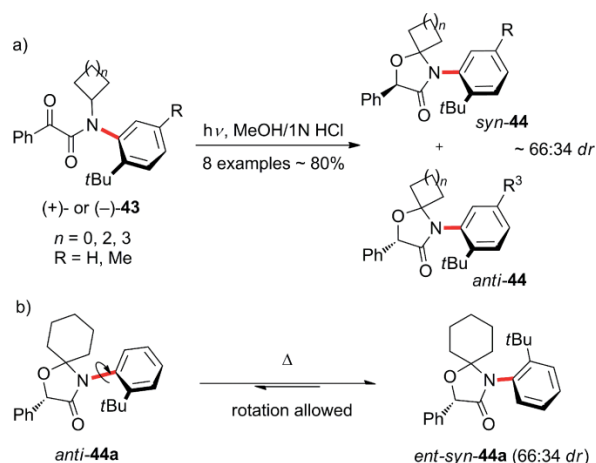
Scheme 18. *exo*-Selective hetero-Diels–Alder cycloaddition of *N*-arylthiazolidinethiones **38**.

Complementarily to cycloadditions, simple chemical transformation of *N*-arylindole **40** was used by Nakazaki and collaborators to prepare the stable chiral nonracemic *N*-arylisatin **41**, obtainable in optically pure form by chiral HPLC and featuring a barrier to rotation of 130 kJ mol⁻¹ (Scheme 19).^[31] The racemic **41** constituted an interesting synthetic starting material for obtaining functionalized *N*-aryloxindole derivatives **42** through diastereoselective nucleophile additions, alkylations, and cycloadditions.



Scheme 19. Axially chiral *N*-arylindole, -isatin and -oxindole atropisomers **40–42**.

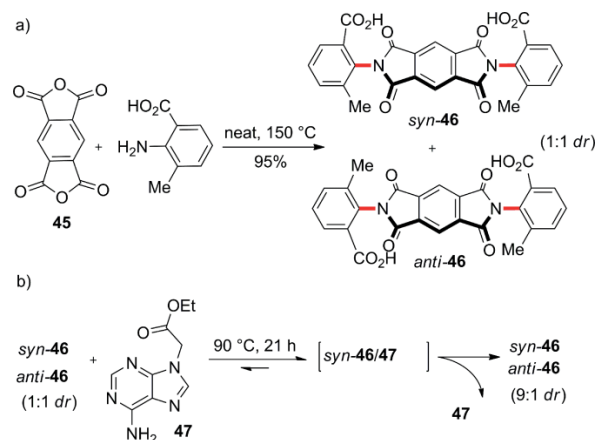
Utilization of enantiopure precursors was reported by Sivaguru's group in the photochemical type II cyclization of non-biaryl atropisomeric benzoylformamides **43** to afford *N*-aryl-oxazolidinones **44** (Scheme 20a).^[32] The cyclization proceeds with chiral memory, resulting in the preservation of the configuration of the C–N chiral axis with the concomitant creation of one stereogenic center with an average of 66:34 *dr* and ≥86 % *ee* for each *syn* and *anti* diastereomer. Their mechanistic experiments argue for lower barriers to rotation in *N*-aryloxazolidinones **44** than in the starting benzoylformamides **43**, as corroborated by the thermally induced atropisomerization of optically pure *anti*-**44** in favor of the corresponding *ent-syn*-**44** photoproduct without the C-5 stereogenic center being affected (Scheme 20b).



Scheme 20. Photochemical synthesis and atropisomerization of *N*-aryloxazolidinones **44**.

3.2. Diastereoselective Construction of the Stereogenic Chemical Bond

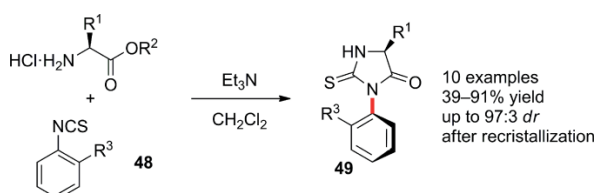
The direct stereoselective construction of the axially chiral bond constitutes a challenging synthetic task and only few examples have been proposed to date. A simple transamidation approach between pyromellitic dianhydride (**45**) and 2-amino-3-methylbenzoic acid, giving access to the expected atropisomeric diacids as a 1:1 mixture of *syn* and *anti* conformers **46**, was disclosed by Shimizu's group (Scheme 21a).^[33] Both atropisomers were found to be stable at room temperature, as illustrated by calculated ΔG^\ddagger values of 122.9 to 142.1 kJ mol⁻¹, and have different hydrogen-bonding affinities toward ethyl adenine-9-acetate (**47**) as a guest. This was exploited to devise new thermally induced conformationally imprinted receptors with "write, save, and erase" recognition properties. This is shown by selective H-bonding interactions between **47** and *syn*-**46** at 90 °C ("write") and release of the guest molecule upon cooling to room temperature, resulting in a large increase in the diastereomeric ratio (1:1 to 9:1 *dr*) in favor of *syn*-**46** ("save"), due to the restricted rotation around the C–N axes (Scheme 21b). Finally, the 1:1 *syn/anti* ratio can be restored by heating ("erase") the 9:1 mixture in the absence of the guest.



Scheme 21. Stable *syn*- and *anti*-atropisomeric diacids **46** as imprinted receptors.

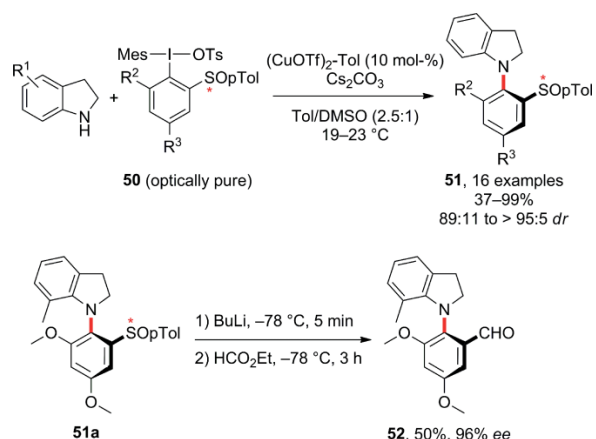
perature, resulting in a large increase in the diastereomeric ratio (1:1 to 9:1 *dr*) in favor of *syn*-**46** ("save"), due to the restricted rotation around the C–N axes (Scheme 21b). Finally, the 1:1 *syn/anti* ratio can be restored by heating ("erase") the 9:1 mixture in the absence of the guest.

More recently, Doğan reported the atropodistereoselective synthesis of axially chiral thiohydantoin derivatives **49** through the reaction between amino acid ester salts and *o*-arylisothiocyanates **48** in the presence of a base (Scheme 22).^[34] Moderate diastereoselectivities were achieved and could be increased by recrystallization. Bulky substituents R^3 were necessary to avoid racemization of the stereogenic center during the heterocyclization step.



Scheme 22. Atropodistereoselective synthesis of thiohydantoin **49**.

Very recently, Wencel-Delord and Colobert reported elegant intermolecular atropodistereoselective C–N bond cross-coupling between indolines and optically pure chiral sulfoxide iodanes **50** (Scheme 23).^[35] The use of these highly electrophilic coupling partners allowed this Cu^I-catalyzed C–N bond Ullmann-type coupling to be performed at low temperature, ensuring the configurational stability of atropisomers **51**. The use of the sulfoxide function as a traceless auxiliary is interesting because many post-functionalizations are available. As an example, the atropisomer **51a** was converted into axially chiral aldehyde **52** with complete retention of C–N bond stereogenicity.



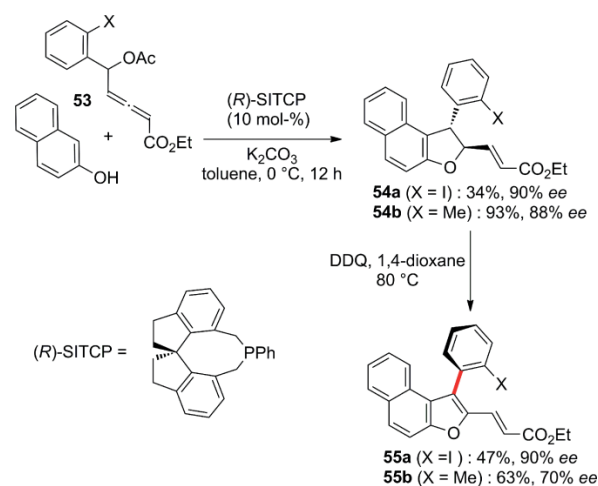
Scheme 23. Atropodistereoselective C–N bond cross-coupling reaction.

3.3. An Update on Enantioselective Approaches

This more appealing but highly challenging alternative emerged at the beginning of the last decade and has attracted

strong recent interest, notably with the development of organocatalytic transformations. It includes complementary strategies based on both stoichiometric and catalytic enantioselective methods, starting variously with simple achiral, prochiral, or racemic precursors, which have been comprehensively reviewed very recently.^[36] Therefore, the next section offers an update of this growing field, presenting the small number of very recent and elegant approaches that allow direct enantioselective access to axially chiral five-membered atropisomers.

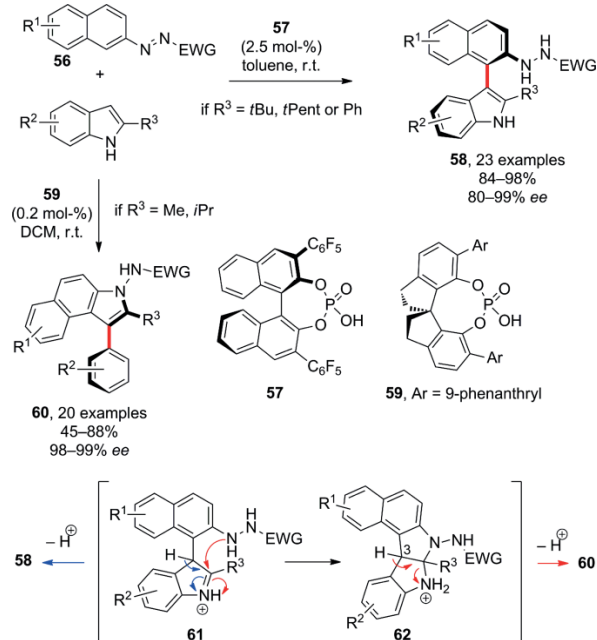
Tong and co-workers have recently proposed two complementary examples based on the strategy developed in our group^[37] for the enantioselective synthesis of furan atropisomers through oxidative central-to-axial chirality conversion (Scheme 24).^[38] The optically active dihydronaphthofuran precursors **54a** and **54b** were obtained by enantioselective phosphine-catalyzed (3+2) annulation of δ -acetoxy allenates **53** with 2-naphthols. Subsequent DDQ oxidation resulted in total conversion of chirality in the case of **55a**, whereas a slight enantiomeric erosion was observed with **55b**, probably due to its lower barrier to rotation and the relatively high temperature necessary for oxidation.



Scheme 24. Enantioselective synthesis of furan atropisomers **55** by a central-to-axial chirality conversion.

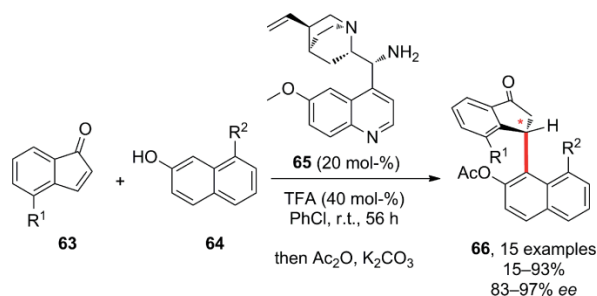
In their outstanding quest for new enantioselective atroposelective reactions, Tan and co-workers^[39] disclosed a particularly elegant and general organocatalytic method for arylation of indoles (Scheme 25). They found that the azo function acts both as a directing and as an activating group for the nucleophilic aromatic substitution of azobenzene derivatives **56** with indoles. When R^3 is a hindered alkyl group, the presence of chiral phosphoric acid **57** allows the synthesis of indole derivatives **58** with excellent yields and enantioselectivities, through the formation of intermediates **61** that quickly aromatize by proton elimination. The authors serendipitously discovered that when the R^3 substituent is less bulky (Me or *i*Pr), the intermediates **61** evolve differently and cyclize by intramolecular addition to the iminium ion to generate pentacyclic intermediates **62**. After β -H elimination and cleavage of the C–N bond, the atropisomers **60** are obtained in good yields and with excellent

enantioselectivities. Interestingly, in this last transformation, only 0.2 mol-% of chiral phosphoric acid **59** is necessary, showing the high efficiency of this catalyst in this case.



Scheme 25. Organocatalytic enantioselective arylation of indoles.

Finally, Bencivenni's group developed organocatalyzed enantioselective Friedel–Crafts alkylation between inden-1-ones **63** and 2-naphthols **64**, giving rise to a not so common class of atropisomers each displaying a stereogenic $C(sp^3)$ – $C(sp^2)$ bond (Scheme 26).^[40] Quinidine derivative **65** was used as the organocatalyst, and bulky R^2 substituent were necessary to achieve high enough barriers to rotation. In this transformation, the steric hindrance generated during the creation of the stereogenic bond, combined with the presence of the stereogenic carbon atom, govern the distribution in favor of the *ap*-diastereomeric conformer, through thermodynamic control.

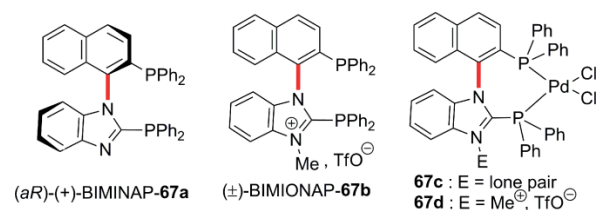


Scheme 26. Organocatalytic enantioselective construction of $C(sp^3)$ – $C(sp^2)$ atropisomers **66**.

4. As Ligands for Metal Complexes

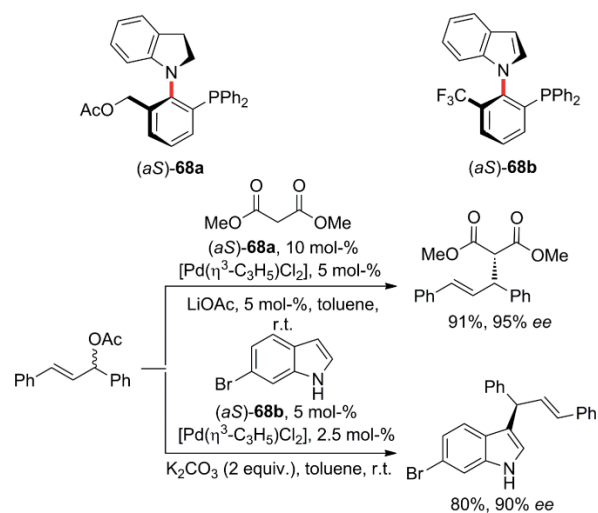
An important application for atropisomers displaying five-membered rings is their utilization as ligands for metals. This may

involve either axially chiral C–N- or C–C-bonded five-membered heterocyclic rings. Chauvin's group, for example, reported comprehensive studies on the synthesis, resolution, and applications in enantioselective catalysis of atropochiral C–N-bonded *N*-naphthylimidazolylphosphine BIMINAP-**67a** and its corresponding *N*-methylated cation BIMIONAP-**67b** as new diphosphane ligands with similar chelating properties for palladium, leading to the corresponding Pd^{II} complexes **67c** and **67d** (Scheme 27).^[41a,41b] Interestingly, (*aR*)-(+)-**67a**, obtained by fractional crystallization of the (*R*)- α -naphthylethylamine Pd^{II} complexes, proved to be an efficient ligand for the enantioselective Tsujii–Trost allylation of dimethyl malonate.^[41b]



Scheme 27. C–N-bonded atropisomeric *N*-naphthylimidazolylphosphine ligands **67a** and **67b** and their Pd^{II} complexes **67c** and **67d**.

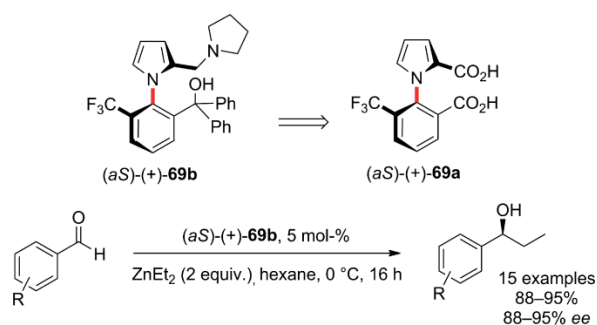
Interestingly, the related atropisomeric *N*-arylindoline-type aminophosphine **68a**, introduced by Mino and collaborators in 2006 and also obtained by optical resolution from their palladium(II) complexes, and the corresponding oxidized *N*-arylindole **68b** proved to be efficient ligands for enantioselective allylic alkylation catalyzed by Pd⁰ with either malonates or indoles as nucleophilic partners (Scheme 28).^[42]



Scheme 28. *N*-Arylindoline and *N*-arylindole chiral atropisomeric ligands **68a** and **68b**.

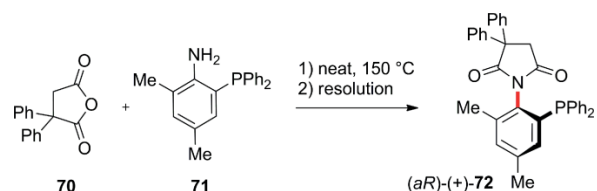
Complementary contributions in the field of organometallic catalysis appeared soon after and involve C–N-bonded atropisomeric 1-*N*-phenylpyrrole-derived amino alcohols of type **69b** proposed by Faigl's group for the efficient enantioselective addition of diethylzinc to arylaldehydes (Scheme 29).^[43] The optically active 1-phenylpyrrole-2-carboxylic acid precursor **69a**

was obtained by resolution with (*R*)-methylbenzylamine and also served both as a chiral discriminating agent in enantiomeric excess determination with different chiral amines and for derivatizations to other atropisomers.^[44] The presence of the pyrrolidine ring resulted in greatly improved *ee* values in relation to other previously developed *N*-alkyl ligand analogues of **69b**,^[43a–43d] ranging from 88% to 95%.^[43e]



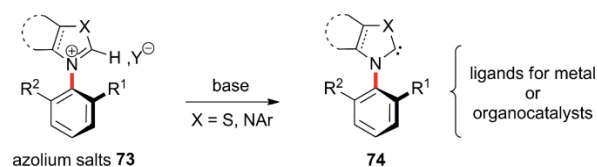
Scheme 29. Enantioselective addition of ZnEt₂ in the presence of 1-phenylpyrrole ligand **69b**.

Enantioenriched arylsuccinimide **72** was obtained by Shimizu and collaborators by means of a transamidation strategy with simple succinic anhydride **70** and aminophosphine **71** coupled with a chemical resolution. This new axially chiral phosphine ligand gave only moderate enantioselectivity in Pd⁰-catalyzed allylic alkylation (Scheme 30).^[45]



Scheme 30. Preparation of axially chiral *N*-arylphosphinosuccinimide ligand **72**.

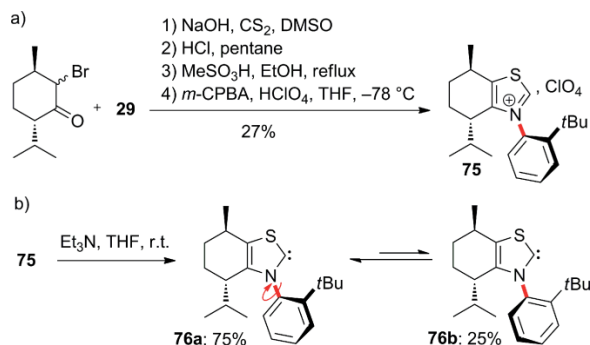
Another very important family of C–N-bonded non-biaryl atropisomers incorporating five-membered rings is that of *N*-arylazolium salts **73**, precursors of *N*-heterocyclic carbenes (NHCs) **74**, which have found many important applications in catalysis either as ligands or as catalysts (Scheme 31).^[46]



Scheme 31. Axially chiral *N*-arylazolium salts **73** and *N*-aryl-NHCs **74**.

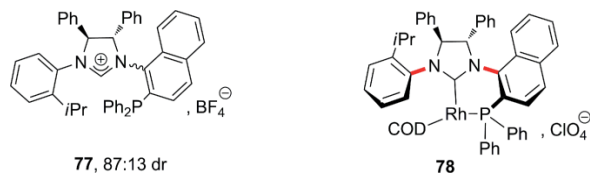
In this field, the independent pioneering contributions by the Grubbs and Hoveyda groups in designing new chiral nonracemic precatalysts for olefin metathesis have inspired further interesting developments.^[47] Their strategies are based on diastereoselective synthesis of optically pure Ru-NHC complexes, securing atropochiral stability of *ortho*-*N*-phenyl-

N-naphthyl substituents. However, because of relatively low barriers to rotation the situation becomes difficult to manage with the corresponding azolium salt precursors and even more so when the free carbene ligands are considered. In this context, the first insights into obtaining axially chiral azolium salts and their carbene analogues were reported in 2004 by Bach's group (Scheme 32).^[48] The most promising result involves the diastereoselective synthesis of optically pure *N*-phenylthiazolium salt **75**, a precursor of the corresponding thiazolylidene-NHCs **76** evaluated as catalysts in model benzoin and Setter condensations. The synthesis started with the condensation of *ortho*-*t*Bu-aniline (**29**) with α -bromomenthone in the presence of CS₂, followed by cyclodehydration and subsequent oxidation (Scheme 32a). Although **75** proved to be configurationally stable at room temperature, the modest 40% and 50% *ee* values obtained for benzoin and Stetter reactions, respectively, suggested substantial (75:25 *dr*) atropisomerization of the corresponding NHCs **76** generated in situ (Scheme 32b).



Scheme 32. Axially chiral *N*-phenylthiazolium salt **75** and *N*-phenyl-NHCs **76**.

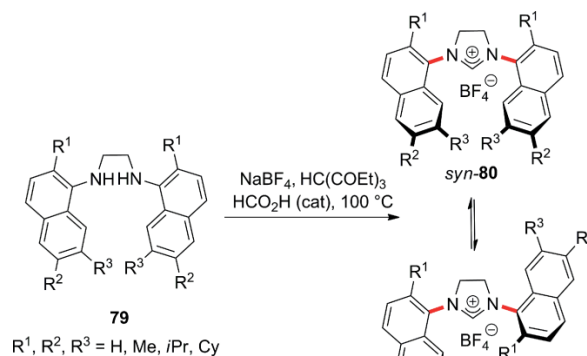
At the same time, Helmchen proposed **77**, an axially chiral *N*-naphthyl *ortho*-diphenylphosphinoimidazolium salt precursor of the chiral Rh complex **78**, which proved to be an efficient promoter of enantioselective catalytic hydrogenation of α,β -unsaturated esters, with up to 99% *ee* (Scheme 33).^[49] Interestingly, **77**, easily obtained in 87:13 *dr* from (*S,S*)-1,2-diphenylethylene-1,2-diamine, proved to be conformationally stable up to 135 °C, indicating a high barrier to rotation around the stereogenic C–N axis.



Scheme 33. Axially chiral *N*-naphthyl *ortho*-diphenylphosphinoimidazolium salt **77** and Rh complex **78**.

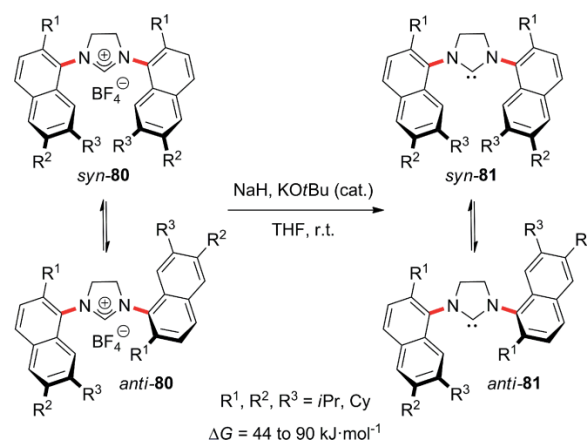
After those reports, Dorta and collaborators showed that the preparation of imidazolium salts **80** from the corresponding ethane-1,2-diamines **79**, bearing alkyl substituents (Me, *i*Pr, Cy) on the naphthyl moiety, resulted in the diastereoselective formation of (*anti*)-*C*₂-symmetric and (*syn*)-*meso* atropisomers in ratio ranging from 1.1:0.9 to 3:1 (Scheme 34).^[50] Whereas fast

rotation was observed for the unsubstituted imidazolium salt ($R^1 = R^2 = R^3 = H$) even at –90 °C, introduction of Me or *i*Pr substituents at the crucial R^1 position needed temperatures higher than 96 °C for interconversion to be observable. With $R^1 = Cy$, both diastereomers were found to be stable up to 126 °C.



Scheme 34. Axially chiral *N,N*-dinaphthylimidazolium salts **80**.

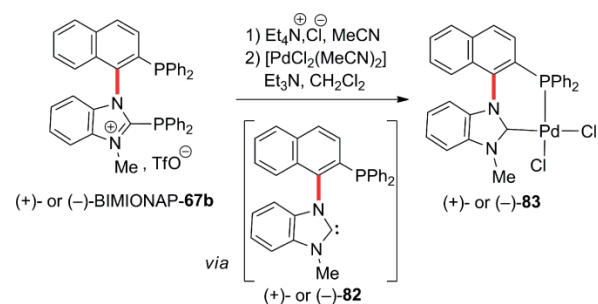
Interestingly, base-promoted deprotonation of **80** allowed the identification of **81**, a new family of stable free monomeric imidazolylidene NHCs incorporating two identical substituted naphthyl moieties on each nitrogen atom (Scheme 35). However, when $R^1 = Me$, the atroposelectivity was lost for **81** at room temperature, but it was totally maintained with $R^1 = iPr$ or Cy, rendering the same ratio of *anti*-**81** and *syn*-**81** atropisomeric NHCs. This result clearly argues for preserved high rotation barriers even after removal of the imidazolium proton. In all cases the activation free energies (ΔG^\ddagger) of atropisomerization for salts **80** and NHCs **81** were determined by variable-temperature NMR analyses, showing values from 44 to 90 kJ mol^{–1} and an average decrease of 20 kJ mol^{–1} after deprotonation.^[50b] Complementarily, the authors demonstrated the efficient ligand ability of this new family of NHCs, which was comparable with that of other widely used congeners, showing good catalytic



Scheme 35. Axially chiral *N,N*-dinaphthylimidazolylidene NHCs **81**.

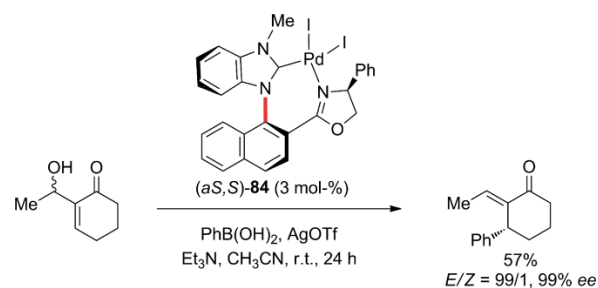
activities in Ru-, Pd-, or Al-catalyzed transformations such as ring-closing metathesis, Suzuki–Miyaura cross-coupling, Hartwig–Buchwald amination, and alkylative ring-opening of epoxides.

More recently, axially chiral NHCs of the *N*-naphthylbenzimidazole series have been the subject of detailed experimental and theoretical studies by Chauvin and collaborators (Scheme 36).^[51a,51b] They have clearly established that enantiopure axially chiral NHCs **82**, derived from the two enantiomers of imidazolium ions **67b** by dephosphorylation, are configurationally stable, leading to the isolation of the two corresponding enantiomeric Pd complexes **83**.



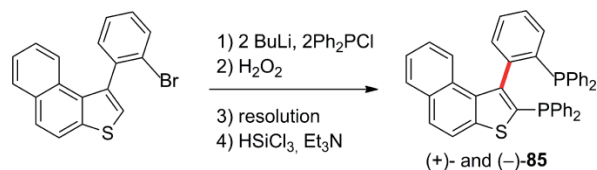
Scheme 36. Axially chiral *N*-naphthylbenzimidazolynilidene NHCs **82** and its Pd complex **83**.

Concurrently, the group of Wang and Shi designed the new related Pd complex (*aS,S*)-**84**, featuring a chiral nonracemic oxazoline ligand instead of the –PPh₂ one. It was found to be efficient for catalytic enantioselective allylic arylation, resulting in the kinetic resolution of Morita–Baylis–Hillman adducts (Scheme 37).^[51c]



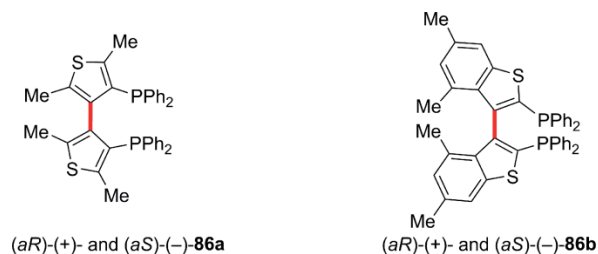
Scheme 37. Enantioselective allylic arylation with Pd complex **84**.

The resolution approach has also been exploited to obtain chiral nonracemic atropisomers featuring interesting properties as new ligands for transition-metal catalysis, intensively developed by the Sannicolò group at the end of the 1990s.^[52] An interesting example can be found in the straightforward synthesis of 3-arylbenzothiophene derivatives such as **85** by fractional crystallization of the diastereomeric adducts from (*R*)- or (*S*)-*O,O'*-dibenzoyltartaric acid (Scheme 38).^[53] The authors showed the excellent behavior of this atropisomeric diphosphine as ligand either for Ru-catalyzed enantioselective hydrogenation or for Pd-catalyzed Diels–Alder cycloaddition.



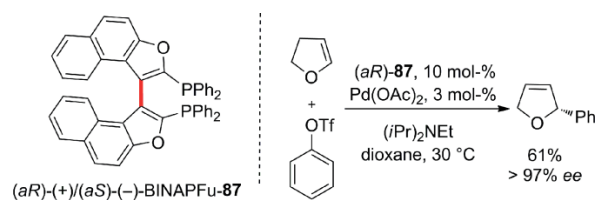
Scheme 38. Enantiomerically pure 3-phenylbenzothiophene diphosphines **85**.

Related atropisomeric diphosphine derivatives, each containing two axially chiral C–C-bonded five-membered heterocyclic rings, are also easily available by the same resolution protocol. This is exemplified by the preparation of the two stable enantiomers of bithiophene **86a** and of those of bibenzothiophene **86b** (Scheme 39). This new family of atropisomers proved to be efficient ligands for the enantioselective Ru-catalyzed hydrogenation of unsaturated esters and 1,3-dicarbonyl compounds^[54a–54c] or for inter- and intramolecular Heck reactions.^[55]



Scheme 39. Axially chiral bithiophene and bibenzothiophene ligands **86a** and **86b**, respectively.

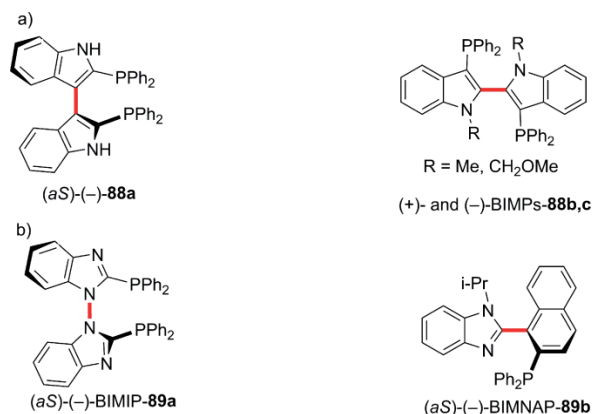
The benzofuran analogue was found to be configurationally unstable,^[54c] but the corresponding bis-diphenylphosphine binaphthofuran BINAPFu (**87**) could be successfully prepared and resolved with (*S*)-camphorsulfonyl azide through a Staudinger reaction.^[56] It was then found that this new ligand outperformed BINAP in the Heck reaction between phenyl triflate and 2,3-dihydrofuran (Scheme 40).



Scheme 40. Binenzofuranyl phosphine **87** as a chiral atropisomeric ligand.

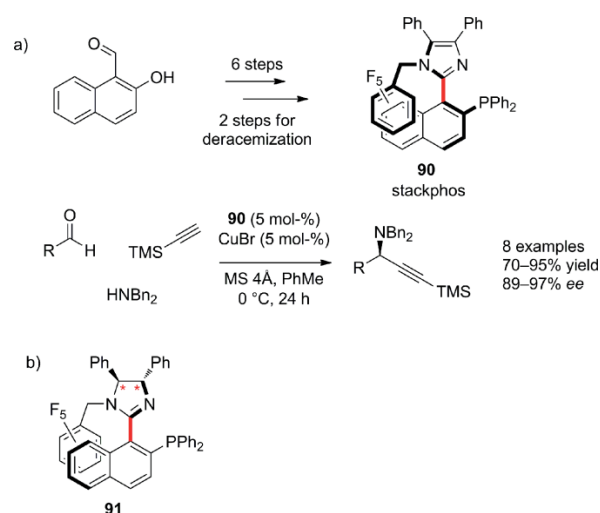
Complementarily to this new series of chiral atropisomeric phosphine ligands, the C3–C3-bonded *NH*-biindolyl analogue **88a**^[54d] and the corresponding C2–C2-bonded *N*-alkyl-biindoles BIMPs-**88b** and **88c**^[54e,54f] were obtained enantiomerically pure by resolution from chiral palladium complexes or tartaric acid adducts, respectively (Scheme 41a). Similarly, BIMIP-**89a**^[54e,54g] a unique example of an axially chiral *N*–*N*-bonded benzimidazole atropisomer, could be obtained in enantiomerically pure form by resolution of the corresponding (*R*)- or (*S*)-dimethyl naphthylethylamine palladium complexes or by

separation by chiral HPLC (Scheme 41b). All of these unconventional diphosphines have been evaluated as ligands, with variable efficiencies, in either Pd^{II}- or Pt^{II}-catalyzed Diels–Alder cycloadditions.^[54h] A similar resolution approach was used to prepare C-naphthylbenzimidazole *P,N*-bidentate ligand (a*S*)-(-)-BIMNAP-**89b**.^[54i]



Scheme 41. C3–C3- and C2–C2-bonded biindolyls **88a–c**, *N,N*-bonded bi-benzimidazolyl **89a**, and C-naphthyl-bonded benzimidazolyl **89b**.

An original design for a chiral biaryl *P,N*-ligand was introduced by Aponick's group in 2013 (Scheme 42a).^[57a] They prepared the imidazole-based biaryl *P,N*-ligand **90** in six steps from commercially available 2-hydroxy-1-naphthaldehyde. Two additional steps, including a highly diastereoselective complexation with a chiral palladium complex, followed by decomplexation with dppe, allowed its deracemization (isolated in 98 % ee). The barrier to rotation of **90** is increased by a favorable intramolecular π -stacking interaction that stabilizes the chiral ground-state conformation. This ligand, named Stackphos, was found to be particularly efficient not only in enantioselective copper-catalyzed aldehyde-alkyne-amine coupling (A3-coupling), but

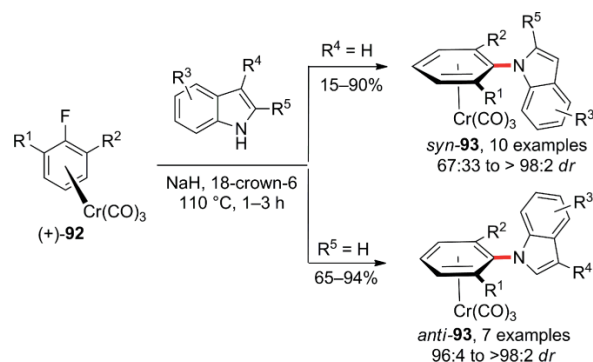


Scheme 42. Aponick's five-membered-ring-containing atropisomeric *P,N*-ligands **90** and **91**.

also in quinoline alkylation,^[57b] the synthesis of skipped diynes,^[57c] and the conjugate alkylation of Meldrum's acid acceptors.^[57d]

Building on this new strategy for increasing the barrier to rotation, the same group, as well as Guiry's group, introduced axially chiral phosphino-imidazoline ligands **91**, also featuring central chirality (Scheme 42b).^[58] The synthesis is more efficient, notably avoiding the use of stoichiometric amounts of chiral palladium complex for the deracemizing step. In this case, the resolution was achieved by fractional crystallization. This ligand was found also to be very efficient in enantioselective alkylation reactions, and interestingly both central and axial chiralities affect the selectivity of the reaction.

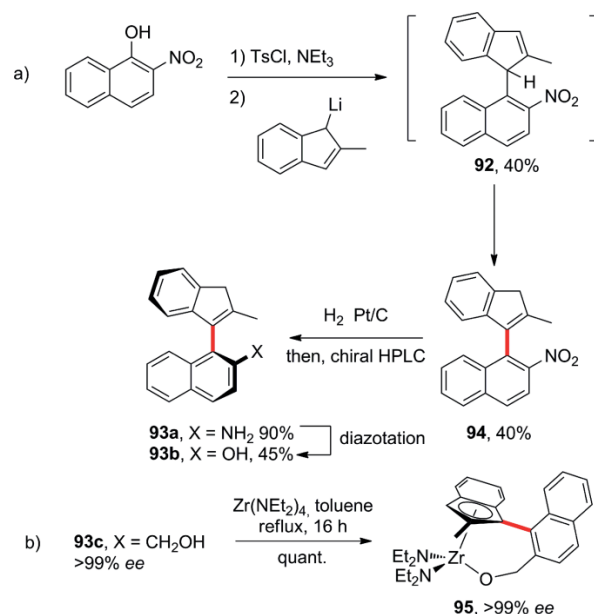
Kamikawa and Uemura elegantly exploited the planar chirality of enantiomerically pure fluoroarene-Cr(CO)₃ complexes **92** toward nucleophilic aromatic substitution with substituted indoles (Scheme 43).^[59] The reactions proceeded in the presence of NaH at relatively high temperature but with usually very good diastereoselectivities depending on the substitution at the 2-position of the indole. When 2-substituted indoles (R⁵ ≠ H) were used, *syn*-axially chiral *N*-arylidole-Cr(CO)₃ complexes **93** were obtained as major diastereomers (67:33 to >98:2 *dr*) whereas absence of substitution at C-2 resulted in the *anti* atropisomers **93**, also with excellent diastereoselectivities (96:4 to > 98:2 *dr*).



Scheme 43. From planar chirality to axially chiral *N*-arylidole-Cr(CO)₃ complexes *syn*- and *anti*-**93**.

All of the examples presented until now deal with atropisomers incorporating a five-membered heterocycle. It is quite surprising that only one single example, reported in 1996 by Baker's group, reports the synthesis of atropisomers with an axially chiral C–C-bonded five-membered carbocyclic ring. Thus, the synthesis of enantiomerically pure chiral 1-(3'-indenyl)-naphthalenes **94** was accomplished thanks to a central-to-axial chirality conversion process^[60] involving double bond migration (Scheme 44a).^[61a] The preparation of the ligands **93a** and **93b** starts with 2-nitro-1-naphthol, which is first converted into the corresponding tosylate. Then, nucleophilic aromatic substitution with 2-methylindenyllithium anion leads to the centrally chiral rotamer **92** in 40 % yield. This undergoes central-to-axial chirality conversion through double bond isomerization upon warming to room temperature to furnish axially chiral **94** in 40 % yield. The nitro function of **94** can be easily converted into

the corresponding amine by hydrogenation in the presence of platinum on carbon. Also, the amine **93a** can be converted into the corresponding axially chiral naphthol **93b** by diazotization. Resolution of the ligands is achieved by semipreparative chiral HPLC. Using a related strategy with a chiral sulfoxide auxiliary, the same team also showed the possibility of accessing enantiomerically pure axially chiral ligand **93c**, bearing a hydroxymethyl moiety on the naphthyl ring.^[61b] Treatment of **93c** with one equivalent of $Zr(NEt_2)_4$ enantiospecifically provides the planar chiral zirconium complex **95** in quantitative yield, thanks to a complete axial-to-planar chirality conversion step (Scheme 44b).^[61c]



Scheme 44. Synthesis of atropisomers with an axially chiral C–C-bonded five-membered carbocyclic ring.

5. Conclusion and Perspectives

The synthesis and isolation of stable atropisomers with one axially bonded five-membered cycle is far less developed than that of the more classical six-membered biaryl axially chiral compounds, which are also more widely represented in nature. The main reason for this is increased distances between the crucial *ortho*-substituents next to the axis, resulting in lower barriers to rotation and higher conformational mobility. Nevertheless, synthetic chemists took up this challenge quite a long time ago, with the first synthesis of a C–N-bonded arylpyrrole being described in 1931, opening important new synthetic opportunities. The less popular axially chiral C–C-bonded family was introduced at the end of the 1990s with only few examples and still constitutes a real synthetic challenge for modern organic chemistry. For more than 70 years the isolation of stable enantiomerically pure atropisomers has relied mainly on resolution of racemates or more recently on chromatographic separation on chiral phases, allowing access to new classes of ligands

for various metal catalysts and organocatalysts, sometimes also featuring interesting biological or physical properties. A significant synthetic breakthrough appeared with the desymmetrization of privileged structures such as *N*-arylmaleimides, -succinimides, and other related heterocycles, which has largely been developed in its diastereoselective version and to a lesser extent in some enantioselective transformations. This last point became a tantalizing challenge and has attracted increased interest in the last two years. Notably, thanks to the huge progress in organocatalytic activation methods, various complementary enantioselective approaches have been designed, allowing access to several new families of atropisomers each featuring an axially chiral C–N- or C–C-bonded five-membered heterocyclic ring of the succinimide, naphthylimide, urazole, indole, pyrrole, thiophene, or furan series. Surprisingly, only one example, reported back in 1996, describes the synthesis of atropisomers with an axially chiral $C(sp^2)$ – $C(sp^2)$ bonded five-membered carbocyclic ring, whereas an enantioselective synthesis of carbocyclic five-membered atropisomers featuring a stereogenic $C(sp^3)$ – $C(sp^2)$ chemical bond was disclosed very recently.

With this historical overview, we hope that readers will be convinced that the design of ingenious methodologies is still possible and should open the way to other strategies providing new answers to this important synthetic challenge. Moreover, this should produce hitherto unknown chiral molecular species with potential applications for a wide cross-section of chemistry including chiral ligands, organocatalysts, materials, and new biologically relevant compounds.

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Keywords: Atropisomerism · Five-membered ring atropisomers · Ligand design · Natural products · Organocatalysis · Rotational barriers

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