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Enantioselective syntheses of atropisomers featuring a five-membered ring†

Damien Bonne * and Jean Rodriguez*

Atropisomerism is a fundamental property of molecules featuring a hindered rotation around a chemical bond. If six-membered ring biaryl or heterobiaryl atropisomers are the most popular ones, the focus of this feature article will be put on less common and more challenging five-membered ring containing atropisomers displaying either a stereogenic C–N or C–C bond. After an historical background, a description of the latest flourishing enantioselective strategies for the construction of this attractive family of atropisomers will be presented.

Introduction

In 1884, when Bandrowski proposed for the first time the existence of a possible isomerism in 3,3'-dinitrobenzidine,¹ he could not have suspected the importance of this finding in modern synthetic organic chemistry. In 1912, and without any direct experimental evidence, Cain and collaborators²

rationalised this pioneer observation as a new form of isomerism of functionalised biphenyl derivatives that was later on supported by chemical transformations³ and unambiguously established nine years after by Kenner.⁴ He was the first to identify the existence of a common axis between two functionalised phenyl groups featuring a restricted rotation, which was evidenced by resolution of the two enantiomeric forms of 6,6'-dinitro-2,2'-diphenic acid (**1**) by fractional crystallisation of the corresponding brucine salts (Scheme 1).

This new fundamental stereochemical behaviour of biphenyl derivatives rapidly turned into a central research topic resulting as soon as in 1933 in a detailed compilation of this

Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France.

E-mail: damien.bonne@univ-amu.fr, jean.rodriguez@univ-amu.fr

† Dedicated to Professor Christian Roussel for his outstanding pioneering studies and still active contribution to the field.



Damien Bonne

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 PhD 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”

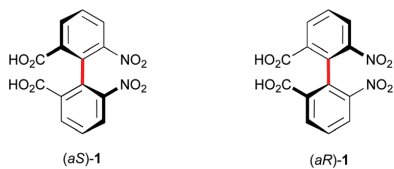
(associate professor) at Aix-Marseille University (France). He passed his habilitation (HDR) in 2015 and his research interests include the development of new enantioselective organocatalyzed methodologies and their application in stereoselective synthesis.



Jean Rodriguez

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 PhD 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 became “Distinguished member” of the French Chemical Society.



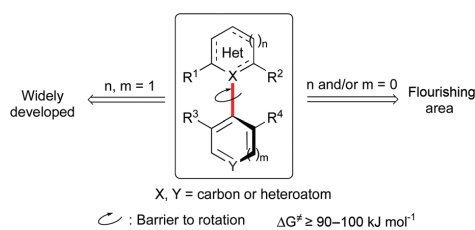
Scheme 1 The two enantiomers of 6,6'-dinitro-2,2'-diphenic acid (**1**).

emerging field.⁵ In the same year, Khun⁶ proposed the current name of atropisomerism to describe this peculiar conformational isomerism found in rotationally hindered chiral biaryl structures.

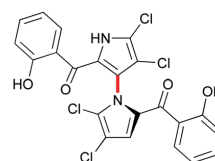
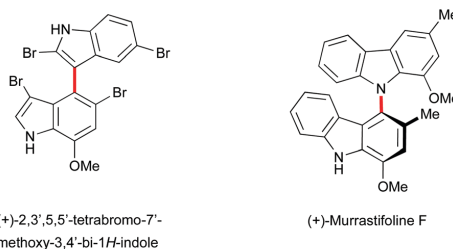
Nowadays non-racemic axially chiral systems, which are also widely represented in Nature,⁷ are recognised as central elements for many scientific domains with notably numerous applications in catalyst design,⁸ drug discovery⁹ and material sciences.¹⁰ Among them, six-membered carbocyclic and, to lesser extent, heterocyclic atropisomers¹¹ have retained a huge attention over the years and still constitute a central topic of research worldwide resulting in many elegant synthetic approaches.¹² In sharp contrast, atropisomeric species displaying one five-membered ring connected either by a C–N or C–C bond have been largely overlooked.¹² This situation is basically due to the increased distance between *ortho*-substituents (R^1 to R^4) next to the axis responsible of lower barriers to rotation hampering the conformational stability (Scheme 2). Pioneer observations and experimental determinations of barriers to rotation point out the crucial effect of *ortho*-substituents. It has been proposed by Oki that atropisomers should exhibit a half-life of at least 1000 seconds at room temperature,¹³ corresponding to a barrier to rotation of the order 90–100 kJ mol⁻¹, to expect a convenient separation of both enantiomeric atropisomers.¹⁴

Despite this inherent structural difficulty, both axially chiral C–N- and C–C-bonded atropisomers are present in nature, through essentially three rare small families featuring one or two five-membered ring of the indole,¹⁵ carbazole,¹⁶ or pyrrole series.¹⁷ However, their isolation and characterisation have been possible only by the end of the last century (Scheme 3).

The first synthetic axially chiral C–N-bonded¹⁸ arylpyrrole **2** was reported back to 1931 by the group of Adams¹⁹ followed by a series of papers dealing with the preparation of related arylcarbazole²⁰ **3** and dipyrrolyl biphenyl **4**²¹ derivatives (Scheme 4).

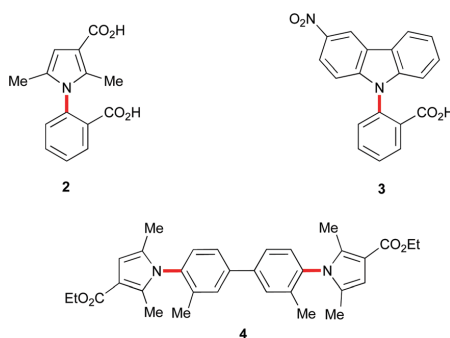


Scheme 2 Situation of six- versus five-membered atropisomeric systems.



(–)-Marinopyrrole A

Scheme 3 Examples of naturally occurring C–C- and C–N-bonded axially chiral arylazoles.



Scheme 4 First families of axially chiral *N*-arylpyrroles.

In all these studies, the racemic atropisomers were obtained from the required 1,5-diketones and anilines in a Paal–Knorr heterocyclisation for **2** and **4**, or from the Ullmann-type coupling of *o*-iodobenzoic acid with 3-nitrocarbazole for **3**. They were resolved by means of the corresponding brucine salts. Interestingly, for pyrrole **2** and carbazole **3** the two enantiomers were found relatively stable in boiling ethanol but suffer a total thermal racemisation in the presence of sodium hydroxide. Since then, together with the development of more efficient resolution technics, including chiral HPLC, many interesting diastereoselective approaches have been proposed over the past eighty years and compiled in 2012.^{11a} Meanwhile, the direct enantioselective access to this challenging target has been ignored up to the very beginning of this century and received an increasing interest these last two years that has not been covered to date.

The next section will present and comment the few elegant approaches reported to date allowing a direct enantioselective

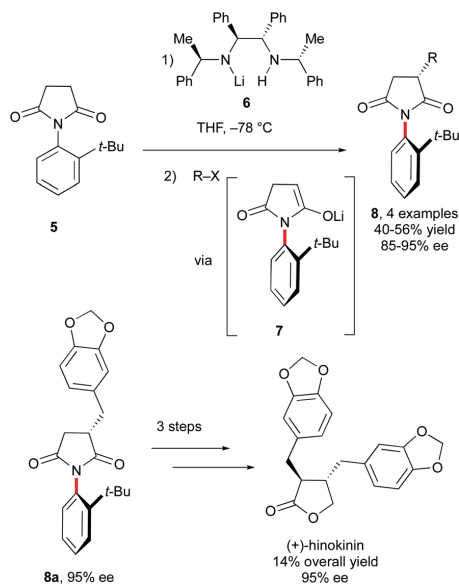
access to either axially chiral C-N- or C-C-bonded atropisomers for which the five-membered ring is already present in the starting substrate or formed concomitantly with the chiral axis.

Enantioselective syntheses of atropisomers featuring a five-membered ring

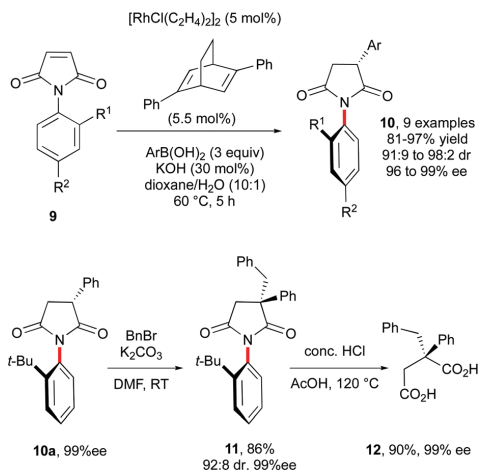
The recent advances in both organometallic and organic enantioselective catalyses have allowed the development of two main new strategies for the direct synthesis of optically active axially chiral C-N- and C-C-bonded atropisomers featuring a five-membered ring. The more popular is based on either the desymmetrisation of prochiral *N*-aryl derivatives or the enantioselective transformation of achiral precursors, both bearing a preformed five-membered ring. Alternatively, in the less common and more challenging approach the five-membered ring is forged during the reaction with concomitant formation of the chiral axis from simple acyclic and achiral substrates.

Axially chiral C-N-bonded atropisomers

The first example of enantioselective construction of an atropisomer incorporating a five-membered ring heterocycle has been disclosed by Simpkins and collaborators in 2004 by desymmetrisation of prochiral *N*-arylsuccinimides such as **5**.²² Hence, enantioselective deprotonation using enantiopure lithiated base **6** at low temperature generated the configurationally stable chiral lithium enolate **7** (Scheme 5). Subsequent diastereoselective alkylation with various alkyl halides afforded the *anti* isomers **8** in moderate yields and



Scheme 5 Enantioselective desymmetrisation of *N*-arylsuccinimide **5**.



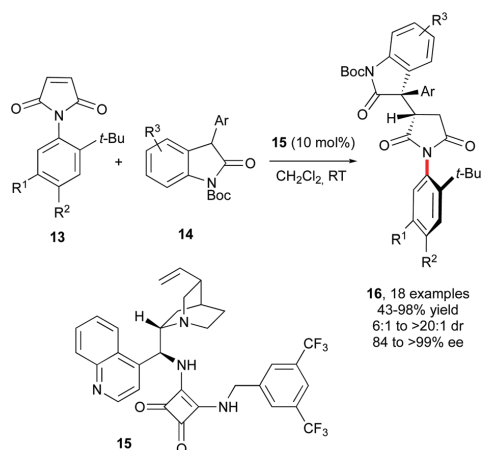
Scheme 6 Metal-catalysed desymmetrisation of *N*-arylmaleimides **9**.

generally excellent enantioselectivities, due to kinetic resolution by double alkylation of the minor enantiomer. Starting with the piperonyl functionalised derivative **8a** the method was then applied to the total synthesis of (+)-hinokinin, the enantiomer of a well-known lignin natural product.

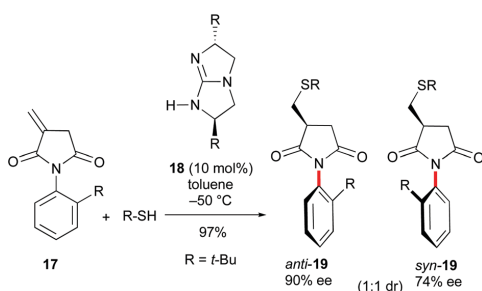
Related desymmetrisation of *N*-arylmaleimides **9** has been accomplished by Shintani and Hayashi in 2007 through a rhodium-catalysed enantioselective 1,4-addition reaction of arylboronic acids (Scheme 6).²³ Excellent diastereo- and enantioselectivities have been obtained for the final *N*-arylsuccinimides **10**. The authors shown that the stereochemical information of the C-N axis was a good template to control the stereochemistry in subsequent transformations. This is illustrated by alkylation of **10a** giving **11** with very good diastereoselectivity and maintained enantiomeric excess. Finally, the hydrolysis of **11** afforded the chiral dicarboxylic acid **12** displaying an all-carbon quaternary stereogenic centre.

More recently, the group of Bencivenni developed a series of related organocatalytic Michael addition promoted desymmetrisations of prochiral maleimides using primary amines derived from cinchona alkaloids as catalysts.²⁴ Their latest developments involve a squaramide cinchonidine organocatalyst **15** and *N*-Boc-3-aryloxindoles **14** as pronucleophiles towards *N*-arylmaleimides **13** (Scheme 7).²³ The transformation is efficient and accommodates various substitutions on the oxindole as well as on the aryl group of the maleimide, giving rise to the desired functionalised *N*-phenyl succinimides **16** with excellent stereoselectivities in most cases. Two stereogenic carbon atoms are created and controlled during this reaction while the stereogenic C-N bond is revealed. This desymmetrisation of *N*-arylmaleimides by Michael addition of oxindole derivatives has also been described by Feng using a chiral *N,N'*-dioxide/ $\text{Sc}(\text{OTf})_3$ complex.²⁵

In complement to succinimides and maleimides, related *N*-arylitacconimides **17** have been briefly studied by C.-H. Tan's



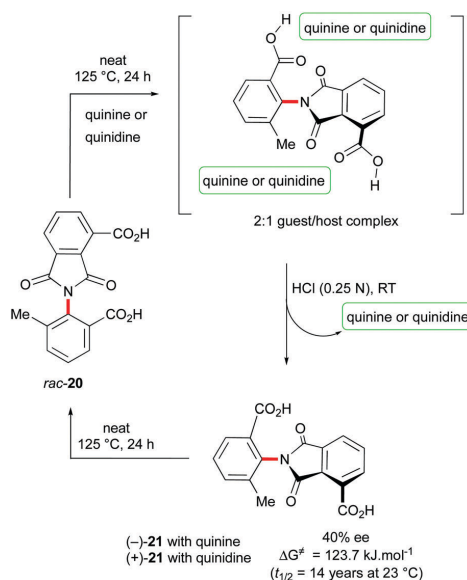
Scheme 7 Organocatalytic desymmetrisation of *N*-arylmaleimides **13**.



Scheme 8 Organocatalysed enantioselective protonation of itaconimide **17**.

group in 2009 (Scheme 8).²⁶ They proposed an organocatalysed thia- or phospho-Michael addition/enantioselective protonation sequence using chiral bicyclic guanidine **18** leading to a 1:1 mixture of *anti*- and *syn*-atropisomeric *N*-arylsuccinimides **19** bearing a functionalised stereogenic carbon centre with 90% and 74% ee, respectively. The two enantiomerically enriched diastereomers were easily separated by column chromatography allowing the experimental determination of a high barrier to rotation of 129.2 kJ mol⁻¹ corroborated by DFT calculation.

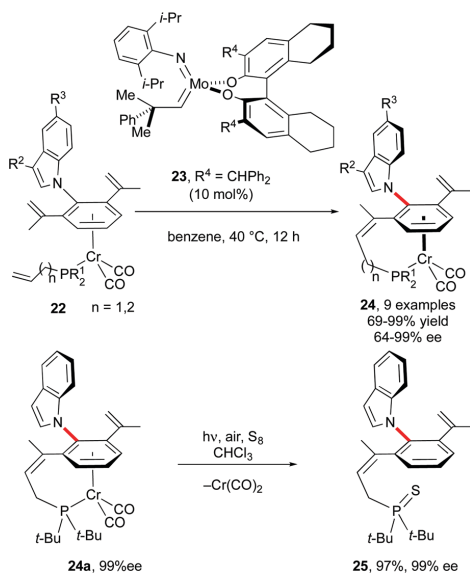
In parallel, Shimizu and collaborators design a very simple *N*-arylphthalimide carboxylic diacid **20** featuring interesting chiral memory based on restricted rotation around the C-N axis (Scheme 9).²⁷ Its high conformational stability with a barrier to rotation of 123.7 kJ mol⁻¹ allows a guest-induced enantiomeric enrichment of up to 40% ee after heating *rac*-**20** in the presence of optically pure quinine or quinidine followed by acidic release of the guest upon cooling to room temperature. Interestingly, the detailed study of the chirality transfer showed that quinine and quinidine templated the formation of opposite enantiomers (-)-**21** and (+)-**21**, respectively, through a 2:1 guest/host salt complex with each carboxylic acid function.



Scheme 9 Chiral memory of *N*-arylphthalimide dicarboxylic acid **20**.

In 2015, Kamikawa, Takahashi and Ogasawara reported an elegant strategy leading to axially chiral *N*-arylidole compounds **24** via an enantioselective desymmetrising ring-closing metathesis (Scheme 10).²⁸ They started from functionalised prochiral planar (π -arene)chromium complexes of type **22** bearing an indolyl substituent whose orientation is fixed in the *anti* configuration [Cr(CO)₂ group and the benzo moiety of the indolyl substituent are on opposite sides with respect to the π -arene plane]. The reactions were run in benzene at 40 °C with 10 mol% of *in situ* generated chiral molybdenum catalyst **23**. The presence of an electron-rich phosphine in **23** (R¹ = *t*-Bu, Cy or *i*-Pr) is crucial to obtain high yields and enantioselectivities. With these reaction conditions, chiral chromium complexes **24** were produced very efficiently and interestingly, both axial and planar chirality were simultaneously forged and controlled during this transformation. In addition, the authors showed the possibility of decomplexing **24a** under very soft reaction conditions, destroying the planar chirality and releasing the axially chiral *N*-arylidole **25** in excellent yield with retention of the enantiomeric purity.

Another interesting prochiral atropisomeric scaffold concerns the *N*-arylurazole series **26** elegantly exploited by B. Tan and co-workers very recently (Scheme 11a).²⁹ They identified two structurally different bifunctional organocatalysts **27** and **31** for the enantioselective desymmetrisation of **26** resulting in the efficient revelation of the stereogenicity of the C-N bond with usually high level of enantioselectivity (86–99% ee). The use of the bifunctional thiourea **27** allowed the fast Friedel-Crafts type amination of naphthol-(phenol) derivatives **28** to give **29**, while in sharp contrast, with indoles **30** only, chiral phosphoric acid **31**

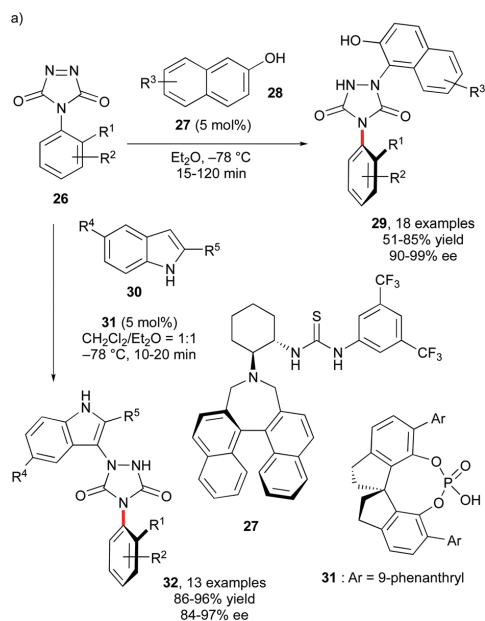


Scheme 10 Molybdenum-catalysed enantioselective ring-closing metathesis.

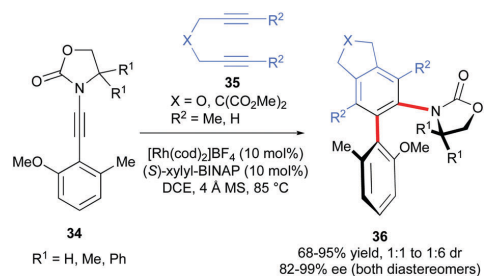
gave excellent results for the formation of **32**. Interestingly, the naphthol-urazole adduct **29a** ($R^1 = t\text{-Bu}$, $R^2 = R^3 = \text{H}$) was found configurationally stable for 12 h at 80 °C in CH_3CN accounting for a high rotation barrier opening potential applications in the field of enantioselective catalysis. This is illustrated by its use as chiral ligand for the enantioselective scandium-catalysed addition of *N*-methylindole to *N*-methylisatin affording adduct **33** with a promising 62% ee and an excellent 96% yield (Scheme 11b).

In complement with the desymmetrisation of simple prochiral *N*-aryl substrates, Hsung's team efficiently exploited the utilisation of an achiral starting material incorporating the five-membered ring that will reveal the C–N chiral axis by an enantioselective transformation. They proposed an elegant Rh(I)-catalysed enantioselective [2+2+2] cyclotrimerisation between achiral ynamides **34** and diynes **35** (Scheme 12).³⁰ Remarkably, two stereogenic bonds (one C–C and one C–N) are created and controlled during the reaction providing an attractive approach to chiral anilides **36**. Even if the diastereoselectivity was not very high (1:6 dr maximum), both diastereomers were obtained in high enantiomeric excesses. Replacement of the methoxyphenyl group in **34** by a 2-methoxynaphthyl moiety is possible affording the desired product in good yield and good enantiomeric excess for both diastereomers (1:3 dr in this case). However, the reaction of ynamide **34a** ($R^1 = \text{H}$) led to a mixture of rapidly interconverting atropisomers, highlighting the crucial effect of the substitution pattern on the barrier to rotation.

Forging the five-membered ring with concomitant creation of the chiral axis has been proposed for the first time in 2010 by the group of Kitagawa with a palladium-catalysed enantioselective 5-*endo*-aminocyclisation of *ortho*-alkynylanilines **37**

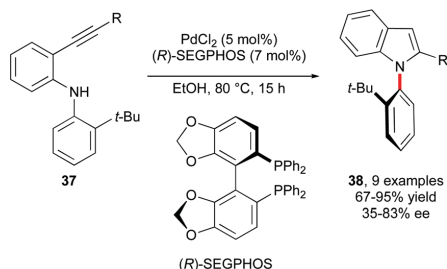


Scheme 11 Enantioselective desymmetrisation of arylurazoles **26** and ligand affinity of **29a**.



Scheme 12 Enantioselective [2+2+2] cyclotrimerisation for the synthesis of chiral anilide derivatives **36**.

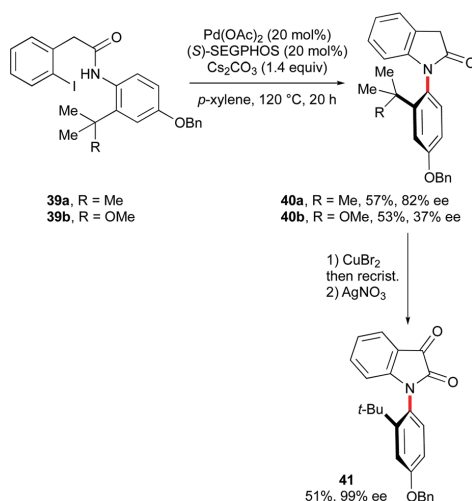
for the synthesis of axially chiral *N*-arylindoles **38** (Scheme 13).³¹ The use of PdCl_2 and chiral diphosphine (*R*)-SEGPHOS gave the desired indoles in good yields but moderate enantioselectivities. When less reactive substrates were employed ($R = \text{alkyl}, \text{NO}_2$), the



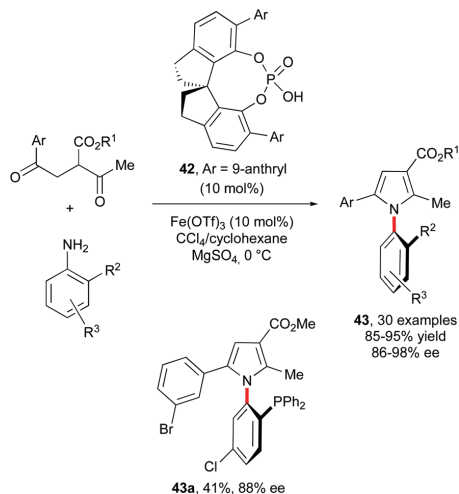
Scheme 13 Enantioselective 5-*endo*-aminocyclisation with various *ortho*-*t*-Bu-anilines **37**.

use of silver(I) triflate as an additive to generate more reactive cationic-Pd species was necessary to achieve good yields. The relatively high distance between the chiral ligand and the stereogenic axis being constructed could explain the modest enantiomeric excesses obtained.

Five years later, Nakazaki and co-workers reported the enantioselective access to C–N axially chiral *N*-aryloxindoles **40** from the corresponding *N*-arylamide precursors **39** by an enantioselective intramolecular Buchwald-Hartwig *N*-arylation (Scheme 14).³² The reaction was performed using palladium acetate and (*S*)-SEGPHOS as the chiral ligand on two substrates **39a** and **39b** bearing different *ortho*-substituents. Good enantioselectivity (82% ee) was obtained for **40a** with a *tert*-butyl group, while **40b**, bearing a 2-methoxypropan-2-yl group, was formed with only 37% ee. The authors showed the possibility of converting **40a** into synthetically valuable isatin derivative **41** by a two-step oxidative sequence including a recrystallisation to increase the final enantiopurity.



Scheme 14 Enantioselective intramolecular Buchwald-Hartwig *N*-arylation.



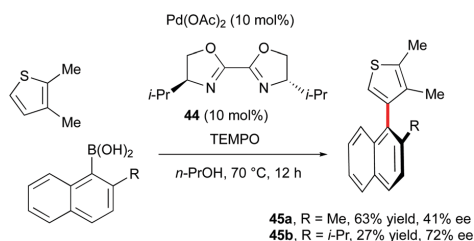
Scheme 15 Enantioselective synthesis of *N*-arylpyrrole atropisomers **43**.

Finally, a more efficient construction of arylpyrrole atropisomers **43** has been reported very recently by B. Tan and coworkers with the first organocatalysed enantioselective Paal-Knorr reaction between simple functionalised 1,4-diketones and anilines (Scheme 15).³³ Dual catalysis using a combination of spinol-derived chiral phosphoric acid **42** and Fe(OTf)₃ resulted in very good atroposelectivity rendering axially chiral *N*-arylpyrroles **43** with up to 98% ee. Moreover, the authors observed an intriguing and still non-rationalised solvent-dependent inversion of the enantioselectivity by addition of a protic solvent such as EtOH with somewhat lower enantioselectivities from 73% to 76% ee. Gram-scale synthesis maintained good yield and enantioselectivity and many functions were tolerated in this methodology, as for example the synthesis of the chiral monophosphine **43a** with 88% ee, a potential chiral ligand.

Axially chiral C–C-bonded atropisomers

This more challenging situation has been largely overlooked until recently and to our knowledge, only three complementary catalytic strategies are available in the thiophene, indole and furan series, respectively.³⁴

A pioneer contribution is due to Yamaguchi and Itami in 2012 with two isolated examples of the first enantioselective palladium-catalysed direct *C*4-regioselective C–H arylation of 2,3-dimethylthiophene with hindered arylboronic acids leading to C–C-bonded naphthylthiophenes **45a,b** (Scheme 16).³⁵ The key to this challenging reaction relies on a combined dramatic effect of chiral bisoxazoline ligand **44** and a protic source leading to the formation of the desired products albeit in moderate yields (27% and 63%) and enantiomeric excesses (41% and 72%). The barrier to rotation of the *C*4-naphthylthiophene **45a** (R = Me) was determined by DFT calculations to be > 138 kJ mol⁻¹ in agreement with a good configurational

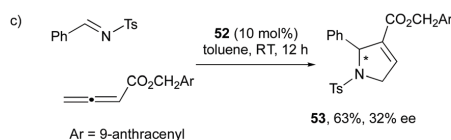
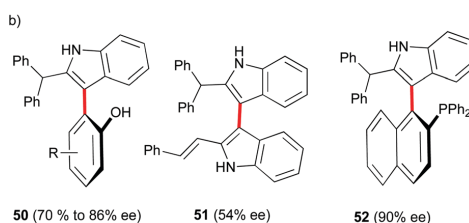
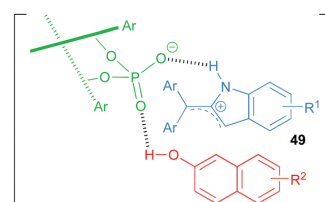
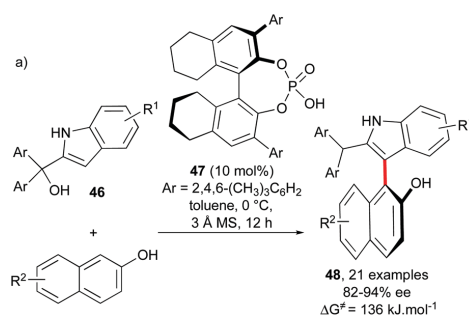


Scheme 16 Enantioselective C–H coupling for the synthesis of thiophene atropisomers **45a,b**.

stability at room temperature of this new family of atropisomeric compounds.

Five years later, Li and Shi proposed the first organocatalytic enantioselective construction of a new class of axially chiral C–C-bonded naphthylindole derivatives **48** using chiral phosphoric acid **47** catalysed coupling reaction between 2-indolylmethanols **46** and 2-naphthols (Scheme 17a).³⁶ The originality of this methodology lies on the peculiar reactivity of 2-indolylmethanols **46** displaying unusual electrophilicity at the C3-position that allows a dehydrative nucleophilic substitution *via* a strongly stabilised delocalised carbocation intermediate **49**. The use of substituted phenols instead of 2-naphthols is possible leading to **50** and the C3–C3-bonded *NH*-biindolyl analogue **51** is also available with a 2-substituted indole as nucleophile, albeit with lower enantioselectivities in both cases (Scheme 17b). This loss of efficiency in the control of the axial chirality is attributed to presumably lower barriers to rotation as corroborated by the calculated 115.8 kJ mol⁻¹ for biindole **51** compared to 136 kJ mol⁻¹ for indolynaphthol **48a** (R¹ = R² = H, Ar = Ph). Higher enantiopurities are obtained at low concentration (typically 0.01 M), which is necessary to favour the formation of a dual hydrogen-bonding interaction hypothesised in the transition state. This activation mode was supported by control experiments showing the necessary presence of both free OH and NH moieties to ensure good reactivity and high level of selectivity. The synthetic interest of these new axially chiral naphthylindoles was illustrated with the monophosphine **52** (98% ee after recrystallisation), obtained in three steps from **46a** (R¹ = H, Ar = Ph), that proved to be a potential organocatalyst in the (3+2) annulation of tosylimines with allenyl esters providing the corresponding pyrrolidines **53** with an encouraging 32% ee (Scheme 17c).

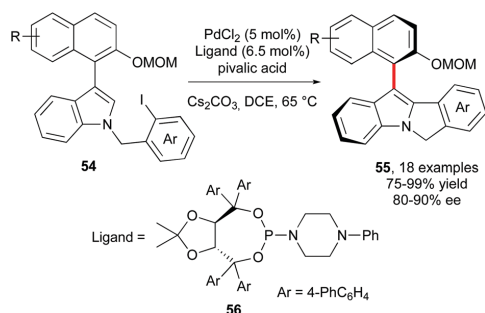
Very recently, an elegant approach to related indole-based atropisomers **55** was reported by Gu *via* enantioselective palladium-catalysed intramolecular dynamic kinetic C–H cyclisation of 3-naphthylindoles **54** (Scheme 18).³⁷ The relatively long distance between the reactive site and the chiral axis might explain the difficulties in reaching very high enantioselectivities. Nevertheless, the TADDOL-based phosphoramidite ligand **56** was found to give the desired product with up to 90% ee. The value of the barrier to rotation was experimentally determined to 130 kJ mol⁻¹ for this class of compounds. The authors also demonstrated the possibility of removing the MOM group, which



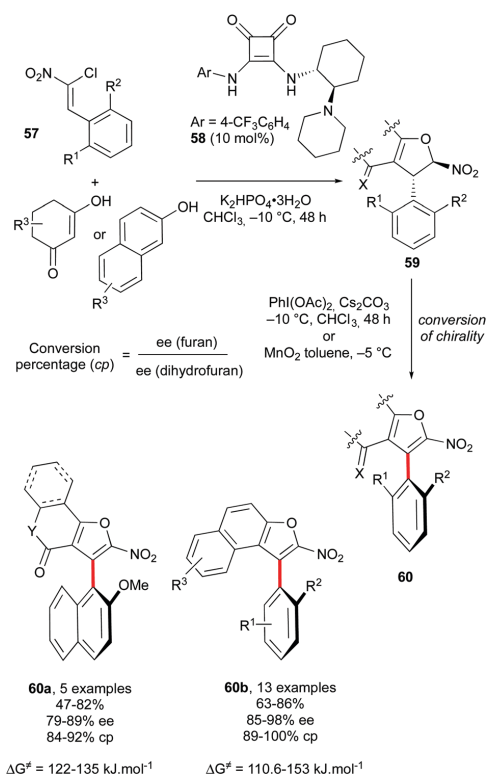
Scheme 17 Enantioselective construction of axially chiral C–C-bonded arylindole atropisomers **48**, **50**, **51** and organocatalytic activity of **52**.

necessitates prior oxidation to oxo-isoindoline derivative, without affecting the optical purity.

Alongside these recent achievements, our group developed the first enantioselective synthesis of furan atropisomers **60** using a central-to-axial chirality conversion strategy (Scheme 19).³⁸ The central chirality in the dihydrofuran precursor **59** is controlled by the bifunctional squaramide organocatalyst **58** triggering an enantioselective domino Michael/*O*-alkylation sequence between the chloronitroalkene **57** and a *C/O*-bisnucleophile (1,3-diketone or 2-naphthol derivatives). The chiral axis is revealed with good to excellent conversion percentages (cp) by an oxidative dehydrogenation with either $\text{PhI}(\text{OAc})_2$ or MnO_2 . Two different mechanisms, with respect to the oxidising agent, have been proposed to explain the observed stereochemistry. Depending on



Scheme 18 Enantioselective palladium-catalysed dynamic kinetic intramolecular cyclisation of **54**.



Scheme 19 Enantioselective syntheses of furan atropisomers **60** by an oxidative central-to-axial chirality conversion strategy.

the nature of the bis-nucleophilic partner, we could efficiently access two structurally different optically active heteroatropisomeric families displaying very good conformational stabilities with experimentally determined barriers to rotation from 122 to 135 kJ mol⁻¹ for **60a** and from 110.6 to 153 kJ mol⁻¹ for **60b**.

Conclusions

The synthesis and isolation of stable atropisomers with one axially bonded five-membered cycle is far less developed compared to the more classical six-membered biaryl axially chiral molecules, which are also more represented in Nature. The main reason for this is an increased distance 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 described in 1931 opening important new synthetic opportunities. The less popular axially chiral C–C-bonded family has been introduced by the end of the 1990s with only few examples and still constitutes a real synthetic challenge for modern organic chemistry. From the pioneer contribution of Kenner in 1922 and for more than 70 years, the isolation of stable enantiomerically pure atropisomers has relied mainly on resolution of racemic mixtures or more recently on chromatographic separations on chiral phases allowing access to new classes of ligands for various metal, organocatalysts and sometimes featuring interesting biological or physical properties. A significant synthetic breakthrough appeared with the desymmetrisation of privileged structures such as *N*-aryl-maleimides, -succinimides and other related heterocycles, which has been largely developed firstly in its diastereoselective version and to lesser extent in enantioselective transformations. This last point became a daunting challenge for the C–N- and even more for the C–C-bonded series, which has been taken in consideration only in 2004 and received an increasing interest these last two years. Notably, thanks to the huge progresses of organocatalytic activation methods various complementary enantioselective approaches have been designed allowing access to several new families of atropisomers featuring an axially chiral C–N- or C–C- bonded five-membered heterocyclic ring of the succinimide, naphthylimide, urazole, indole, pyrrole, thiophene, and furan series.

With this feature article, we hope that the 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 will produce hitherto unseen chiral molecular species with potential applications for a wide cross-section of chemistry including chiral ligands, organocatalysts, materials and new biologically relevant molecules.

Conflicts of interest

There are no conflicts to declare.

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