Catalyst-Controlled Stereoselective Synthesis of Atropisomers

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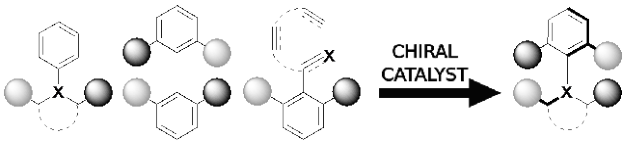
ABSTRACT: Owing to their favorable molecular topology, atropisomers represent particularly valuable chiral scaffolds for numerous applications throughout academic research and industry. Nevertheless, whereas various well-established catalyst-controlled methodologies allow addressing stereocenter configuration, efficient procedures to prepare axially chiral compounds in high isomeric purity are still scarce. Complementary to the comprehensive reviews in the area, this perspective article features representative advances for the catalyst-stereocontrolled synthesis of atropisomeric scaffolds. With a focus on axially chiral motifs frequently utilized in catalysis or medicinal chemistry, selected recent examples encompassing unique stereoselective transition metal, hydrogen bond, ion pairing, chiral phosphoric acid, and amine catalysis are highlighted.



KEYWORDS: atroposelective synthesis, axial chirality, stereoselective catalysis, atropisomer, *ortho*-substituted biaryls

Controlling the spatial arrangement of substituents within a molecular framework is of fundamental importance not only to affect the intrinsic properties of a specific molecule, but also to influence intermolecular interactions, for instance with substrates in catalytic processes or biological systems.[1]

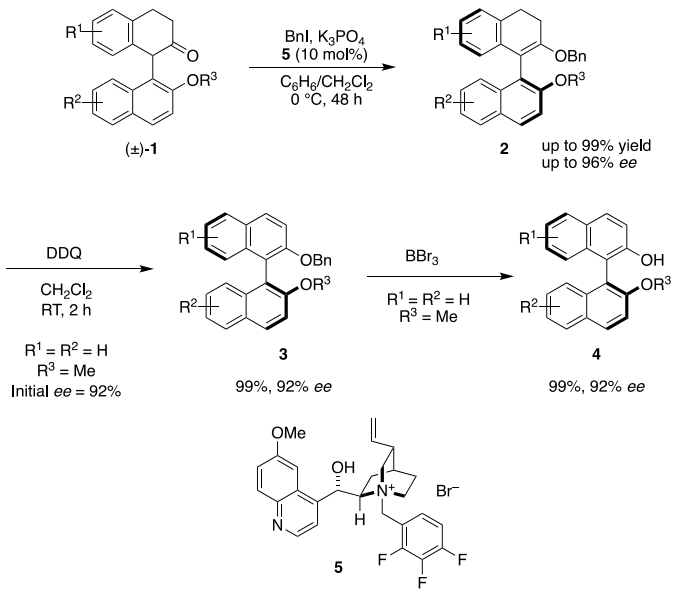
Atropisomers, stereoisomers arising from a restricted rotation about a single bond, are structurally particularly well defined and allow a predictable and precise alignment of relevant residues. The hallmarks of atropisomers are well established in catalyst design and are also increasingly recognized in medicinal chemistry.[2] While the structural diversity of atropisomers is remarkable, the prototypical biaryls had an extraordinary impact in the field of homogeneous catalysis.[3] In contrast, methods to prepare isomerically enriched atropisomers by stereoselective catalysis are still limited to selected structural entities.

Nevertheless, various elegant strategies were recently developed to address the constraints of the catalyst-controlled stereoselective synthesis of atropisomers, which are typically based on atroposelective cross-coupling, the *de novo* construction of arenes, desymmetrization, or the conversion of a stereodynamic system.[4] These different approaches offer an increasing structural diversity of atropisomers, for instance to provide a means to impart stereochemical information in catalytic processes or to allow the development of stereochemically complex atropisomeric pharmaceuticals. Herein, we highlight a selection of examples concerning the stereoselective syntheses of axially chiral compounds, which enable the preparation of a plethora of novel atropisomeric compounds with application in catalysis and medicinal chemistry. For a comprehensive overview on axial chirality, we refer to excellent review articles in the field.[4]

1. ATROPISOMERIC CATALYSTS

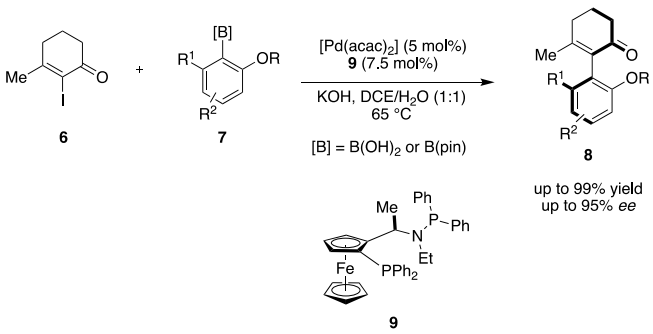
Since racemic 1,1'-bi-2-naphthol (BINOL) can be obtained in bulk amounts from the oxidative dimerization of 2-naphthol[5] and the enantiomers resolved by various methods,[6] the binaphthol scaffold is a frequently utilized motif in homogeneous catalysis and the starting material for various derivatives. Furthermore, the (S_a)-1,1'-bi-2-naphthol can be prepared selectively by a copper-catalyzed dimerization in presence of (*S*)-amphetamine as ligand.[7]

However, synthetic strategies that allow for more structural variability are highly desirable. An elegant approach was recently shown by Smith and co-workers, where treatment of racemic 1-aryl-2-tetralones (**1**) with benzyl iodide in the presence of a base and a chiral cinchona-derived ammonium salt (**5**) affords the corresponding benzylated enol ether (**2**) with excellent stereoselectivity (**Scheme 1**).[8] Controlled by the ion-pairing catalyst **5**, a base-promoted formation of rotationally restricted enolates is followed by atroposelective *O*-alkylation with benzyl iodide by means of a dynamic kinetic resolution of the starting material. To diversify the obtained scaffold, the obtained products were oxidized with DDQ, giving the corresponding protected aromatic diol (**3**) in excellent yields and with retention of optical purity. Furthermore, deprotection with BBr_3 affords both C_1- and C_2-symmetric binaphthols (**4**), which grant access to catalysts whose steric and electronic properties differ from typical BINOL derivatives.



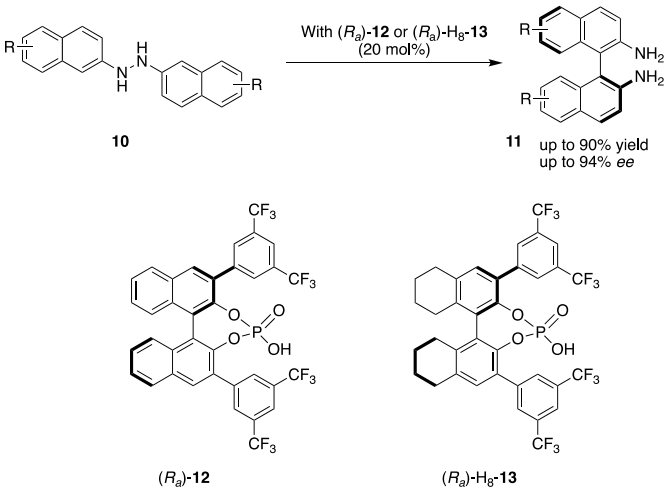
Scheme 1. Atroposelective *O*-Alkylation

To further extend the scope of axially chiral biaryl diol synthesis beyond binaphthyl systems, Gu and co-workers recently reported a palladium-catalyzed atroposelective synthesis of 2-aryl-2-cyclohexenones (**8**) through a Suzuki cross-coupling of 2-iodo-2,3-unsaturated enones (**6**) with trisubstituted aromatic boronic acids or boronic esters (**7**) (**Scheme 2**).[9] The transfer of the stereochemical information was achieved by the employment of a bidentate ferrocenyl aminophosphine ligand (**9**). The obtained axially chiral enones are configurationally stable precursors of the 2,2'-biphenol scaffolds and of other biaryl and non-biaryl structures, such as carbazoles, quinones or haloarenes, which are accessible without diminishing the enantiomeric excess of the starting enone (**8**).



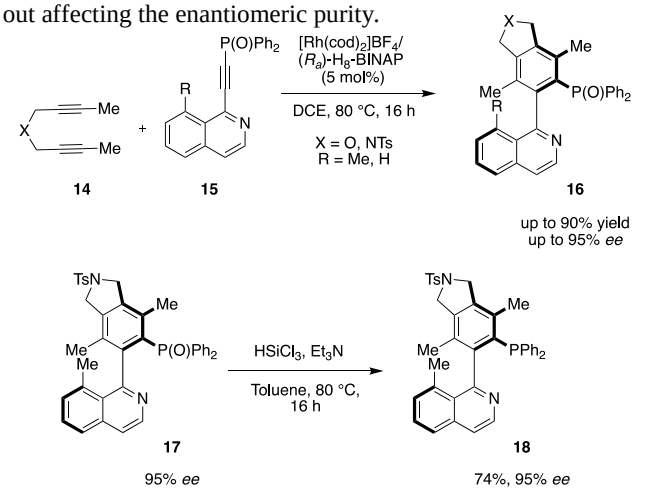
Scheme 2. Selective Synthesis of Arylcyclohexenones

By substitution of the hydroxy with amino groups, the BINAM scaffold with widespread application in catalysis is obtained.[10] The classical synthesis of BINAM relies on the oxidative homocoupling of 2-naphthylamine and subsequent separation of the enantiomers.[11] The development of stereoselective methods that give access to BINAM and related substituted 1,1'-binaphthyl-2,2'-diamines with high enantiomeric purity would thus be highly desirable. An elegant solution to this problem was reported by the groups of List and Kürti, disclosing a chiral phosphoric acid-catalyzed atroposelective rearrangement of symmetric benzidines (**10**). The procedure allows the preparation of C_2-symmetric BINAM derivatives (**11**, **Scheme 3**) with excellent selectivity and catalytic amount of chiral phosphoric acids, while the original work by Sannicolò employed an excess of camphor sulphonic acid.[12] Furthermore, the use of axially chiral phosphoric acids also proved to be a particularly effective catalyst for the conversion of quinones and iminoquinones to form axially chiral biaryl diols, which in turn enriches the scope of the selective synthesis of atropisomeric diols.[13]



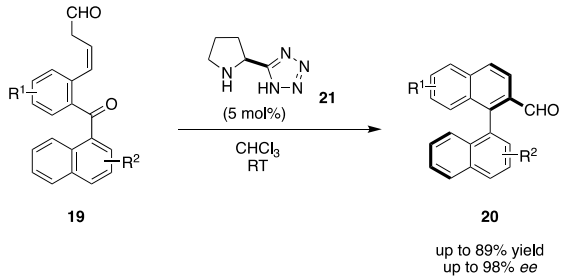
Scheme 3. Atroposelective Benzidine Rearrangement

Since the discovery of BINAP by Noyori, axially chiral bi- and monodentate phosphines have found widespread application in asymmetric catalysis.[14] Binaphthyl phosphines are frequently prepared from BINOL, which however limits the structural variability of the catalysts. Methods that allow to directly obtain unsymmetrical ligands with different degree of substitution in a selective reaction are thus especially valuable. By considering a *de novo* ring construction approach, Tanaka reported a highly enantioselective [2+2+2]-cycloaddition of alkynyl phosphine oxides (**15**) and symmetrical 1,6-diynes (**14**) (**Scheme 4**).[15] The reaction is catalyzed by a rhodium/H_8-BINAP complex and proceeds under mild conditions, affording the target QUINAP-type phosphine oxide (**16**) in high yields and selectivity. Subsequent reduction of the phosphine oxides affords the QUINAP-type ligand, as shown by the reaction of (**17**) with $HSiCl_3$, which yields the target P,N-ligand (**18**) without affecting the enantiomeric purity.



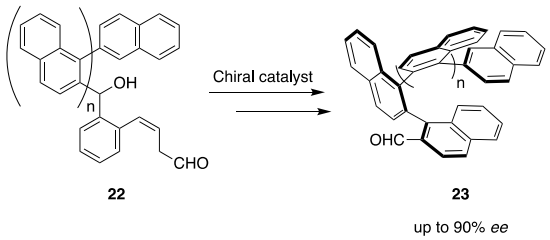
Scheme 4. *De novo* Synthesis of Substituted QUINAPs and their application

Fascinated by the biosynthesis of aromatic polyketides, our group developed a stereoselective arene-forming aldol condensation of ketoaldehydes (**19**) with a proline-derived catalyst (**21**) (**Scheme 5**).[16] The reaction proceeds under mild conditions, affording the corresponding atropisomeric biaryl (**20**) in high yields and enantiomeric excess.



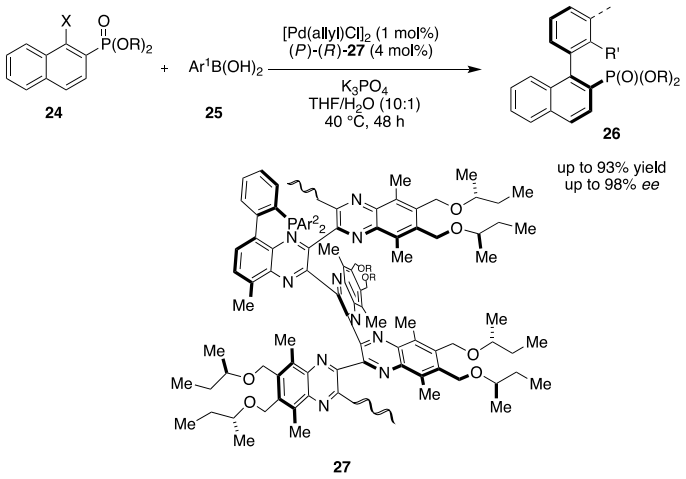
Scheme 5. Biomimetic atroposelective aldol condensation

We further expanded the scope of the atroposelective aldol condensation by studying the synthesis of configurationally stable oligo-1,2-naphthylenes with multiple stereogenic axes (**Scheme 6**).[17] The procedure relies on the iterative addition of a building block, oxidation of the diol to the corresponding ketoaldehyde (**22**) and a catalyst- or substrate-controlled stereoselective aldol condensation. The configurational stability of the products (**23**) provides particularly well-defined molecular scaffolds.



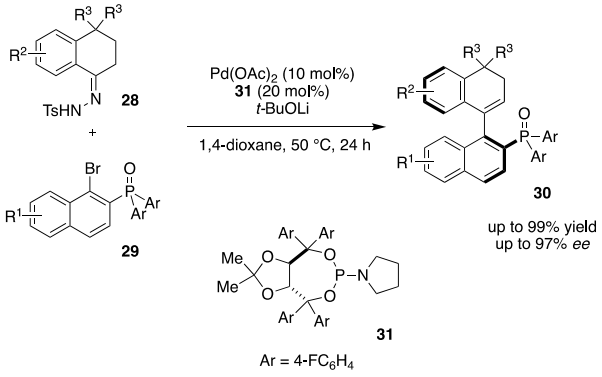
Scheme 6. Diastereoselective synthesis of oligo-1,2-naphthylenes

The Suzuki cross-coupling has seen great progress in the stereoselective synthesis of atropisomers.[18] In a seminal study by Buchwald, a catalyst-controlled atropoenantioselective synthesis of phosphonates was reported, where the employment of an axially chiral aminophosphine ligand afforded the biaryl phosphine precursor in high yields and selectivity.[19] Taking advantage of the substrate tolerance of the Suzuki reaction, Suginome and co-workers recently illustrated that 1-bromo-2-naphthylphosphonates (**24**) can be successfully coupled with a variety of substituted arylboronic acids (**25**).[20] Intriguingly, chiral polymeric quinoxaline with a covalently bound biarylphosphine (**27**) (PQXphos) could be employed, whose configuration is induced by the helicity of the polymer itself (**Scheme 7**). Interestingly, the helicity of PQXphos can be switched by heating of the catalyst, which allows an inversion of selectivity (98% *ee*) for the same cross-coupling reaction. The obtained biaryl phosphonates can be further converted to different C_1-symmetric phosphines, which can be used as novel ligands.



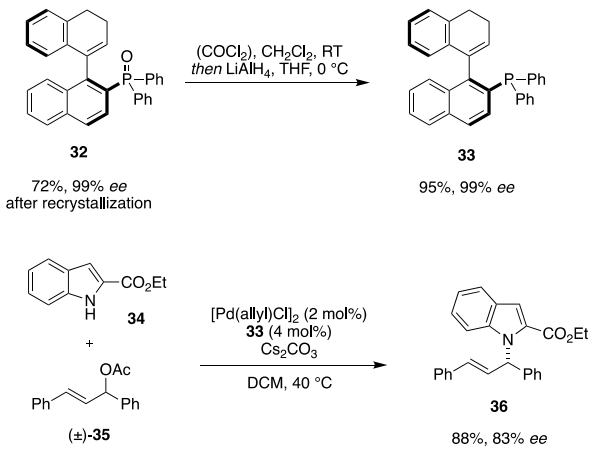
Scheme 7. Atroposelective Suzuki Reaction Catalyzed by Helically Chiral Phosphines

Gu and co-workers took advantage of the properties of palladium carbenes and illustrated an elegant procedure for the enantioselective synthesis of axially chiral vinyl arenes.[21] The reaction involves the coupling of 1-bromo-2-naphthylphosphine oxides (**29**) with tetralone-derived tosylhydrazones (**28**) in the presence of palladium acetate and a chiral phosphoramidite ligand (**31**) (**Scheme 8**). Under these conditions, the hydrazone was converted to the corresponding diazo compound that is able to form a palladium carbene with the oxidative addition complex. Migration and subsequent β-hydride elimination thus affords the target axially chiral phosphine oxides (**30**) in high yields and enantiomeric excess.



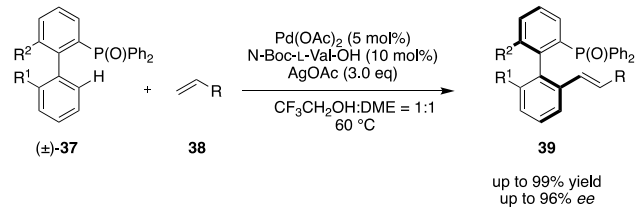
Scheme 8. Palladium-catalyzed Atroposelective Synthesis of Vinylaryl-Phosphine Oxides

To demonstrate the utility of the obtained compounds, the phosphine oxide (**32**) was reduced to the corresponding phosphine (**33**) in almost quantitative yields and with retention of enantiomeric excess. The newly synthesized ligand was employed in the palladium-catalyzed asymmetric allylic alkylation between 1,3-diphenylallyl acetate (**35**) and an indole-derived substrate (**34**). The resulting *N*-allylated indole (**36**) was obtained in 88% yield with 83% *ee*, corroborating the utility of this new class of axially chiral olefins (**Scheme 9**).



Scheme 9. Synthesis of Chiral P,Olefin Ligand and Application in the Asymmetric Allylic Alkylation

An alternative approach to obtain axially chiral phosphine–olefin ligands was shown by Yang.[22] The reaction takes advantage of the low rotational barrier of biaryl phosphine oxides (**37**), which are prone to undergo a dynamic kinetic resolution in the presence of a terminal olefin (**38**), $Pd(OAc)_2$ and Boc-protected valine as the ligand, giving the corresponding biaryl phosphine oxide (**39**) with up to 99% yield and up to 96% *ee* (**Scheme 10**).

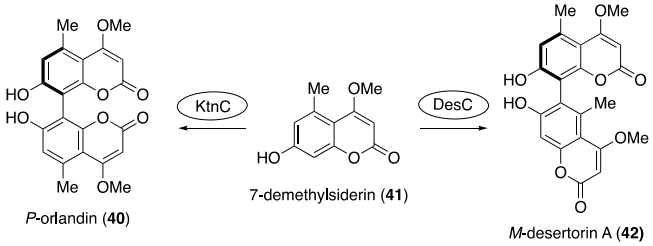


Scheme 10. Palladium-catalyzed atroposelective C-H olefination

2. BIOACTIVE ATROPISOMERS

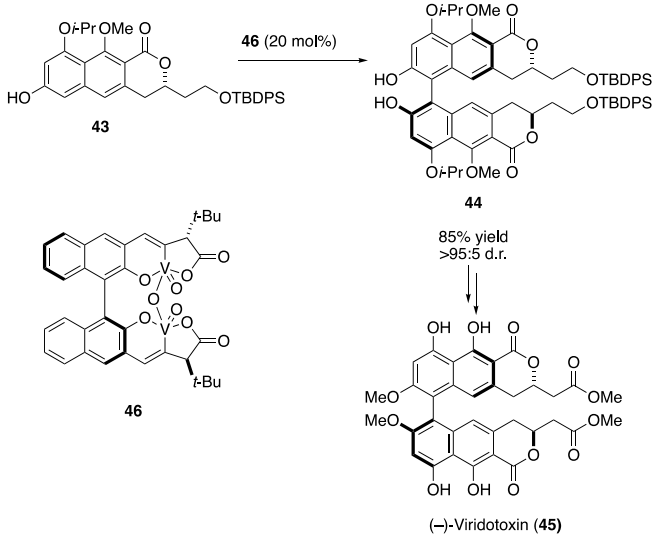
Initially targeting the synthesis of bioactive compounds as racemic mixtures, medicinal chemistry evolved towards the synthesis of single stereoisomers. In this context, atropisomers received increasing interest due to their unique properties and importance in natural product chemistry. Because of their structural complexity, the development of efficient processes to selectively obtain bioactive atropisomers nevertheless remained challenging. Furthermore, depending on steric interactions of the groups that hinder rotation, the degree of configurational stability of atropisomer drugs needs to be carefully considered throughout their preparation and under physiological conditions. Clayden and LaPlante classified atropisomers in drug discovery into three categories according to their rotational energy barrier and half-life of racemization at room temperature.[2, 23] Class 1 compounds exhibit a half-life of racemization of seconds and a $\Delta E_{rot} < 20$ kcal.mol^{-1}. These atropisomers are hence equilibrating rapidly under physiological conditions. On the other end, class 3 entities with a $\Delta E_{rot} \geq 30$ kcal.mol^{-1} are stable for years and can be produced as single atropisomers. Compounds within class 2 are however critical in their handling, as their half-life of racemization ranges from seconds to years. Therefore, class 2 structures are usually modified to obtain either class 1 or class 3 compounds, mostly by modulating the size of interacting groups.

In the biosynthesis of atropisomeric natural products, an enzyme-catalyzed assembly of two molecular moieties frequently results in the stereoselective construction of a C–C or C–N bond. These oxidative biaryl couplings are typically catalyzed by laccases, cytochrome P450 or peroxidases and in most cases, the enzymes impart stereoselectivity.[24] Müller demonstrated that certain cytochrome P450 enzymes are able to catalyze an atroposelective oxidative biaryl coupling of fungal natural products.[25] This study highlighted the fundamental implication of cytochrome P450 enzyme KtnC, from *Aspergillus niger*, in the dimerization process of the coumarin 7-demethylsiderin to produce a single enantiomer of *P*-orlandin. Similarly, cytochrome P450 enzyme DesC from *Emetricella desertorum* efficiently converts the same precursor into another isomer, *M*-desertorin A (**Scheme 11**). The catalytic activity of KtnC and DesC, holds great promises for future applications.



Scheme 11. Biosynthesis of *P*-orlandin and *M*-desertorin A by cytochrome P450 enzymes

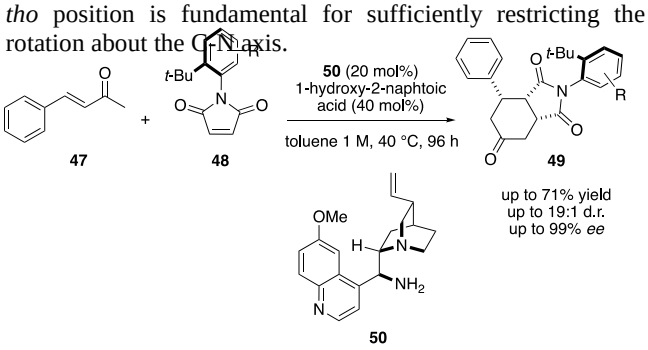
As alternative to the design of promiscuous enzymes, robust processes involving small molecule catalysts have received considerable attention. For instance, Shaw utilized a *tert*-leucine-BINOL derived vanadium complex for a related coupling of two naphthylpyranone units in the total synthesis of (–)-viridotoxin.[26] This efficient reaction led to the tetra-*ortho* substituted biaryl intermediate with excellent diastereoselectivity (95:5) (**Scheme 12**).



Scheme 12. Total Synthesis of (–)-Viridotoxin

For scaffolds with restricted rotation about a C–N bond, Bencivenni, studied a new class of succinimides, a type of compounds well-known for their anti-seizure properties (**Scheme**

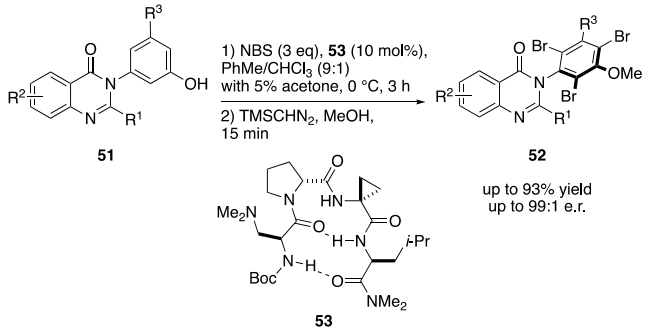
13).[27] An atroposelective Diels-Alder reaction catalyzed by a chiral primary amine allowed the successful desymmetrization of *N*-arylmaleimides, giving rise to a large range of heteroaryls displaying three stereocenters as well as a stereogenic axis. Notably, the sterically demanding *tert*-butyl substituent in the *ortho* position is fundamental for sufficiently restricting the rotation about the C–N axis.



Scheme 13

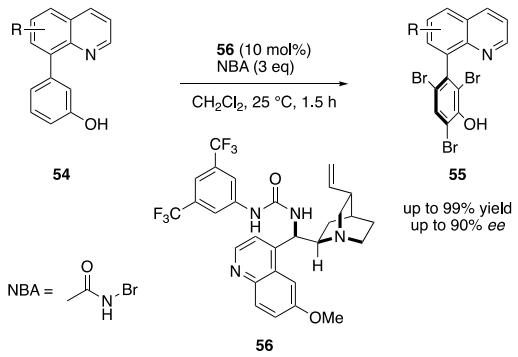
Scheme 13. Stereoselective desymmetrization of *N*-arylmaleimides

In a seminal atroposelective bromination of 3-arylquinazolin-4(3*H*)-ones, Miller and co-worker describe a concept for the synthesis of a large variety of potentially bioactive scaffolds (**Scheme 14**).[28] The approach consisting of a short peptide-catalyzed halogenation allowed the selective introduction of bulky bromine substituents in both *ortho* positions of the phenyl moiety, thus restricting the rotation about the C–N bond. A broad scope of quinazolinone derivatives was thus obtained with excellent yield and enantioselectivity. Furthermore, some of these precursors were functionalized by different cross-coupling reactions to give multiple drug-like molecules without loss of enantiomeric purity. The quinazolinone ring is a motif widely spread among compounds exhibiting various biological properties, these scaffolds could have intriguing applications in medicinal chemistry.[29]



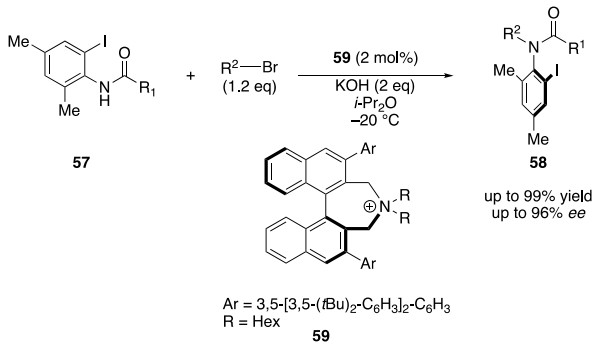
Scheme 14. Atroposelective bromination of 3-arylquinazolin-4(3*H*)-ones

Furthermore, Asano and Matsubara disclosed the synthesis of halogenated axially chiral 8-arylquinolines (**Scheme 15**).[30] Catalyzed by a bifunctional quinidine-urea derivative (**56**), the atroposelective bromination provided arylquinoline derivatives with excellent yield and enantioselectivity, thus potentially allowing further functionalization into complex bioactive atropisomers.



Scheme 15. Atroposelective halogenation of 8-arylquinolines

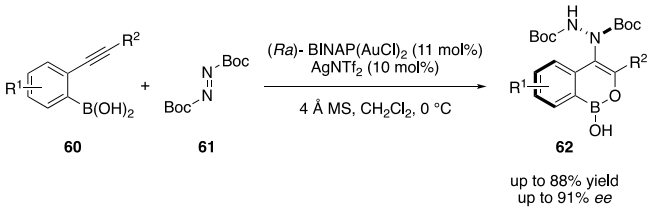
Starting from di-*ortho*-substituted aromatic anilides, Maruoka reported an enantioselective synthesis of anilides by introducing a substituent directly at the nitrogen.[31] An alkylation catalyzed by a chiral tetraalkylammonium bromide salt allowed the conversion of secondary into tertiary anilides, that suitably prevents the rotation about the Ar–N bond (**Scheme 16**). With a low catalyst loading, a large variety of axially chiral anilides could be prepared with excellent yields and enantioselectivity. Those scaffolds were further derivatized, without erosion of enantiomeric purity and are of potential use in medicinal chemistry.



Scheme 16. Synthesis of axially chiral anilides

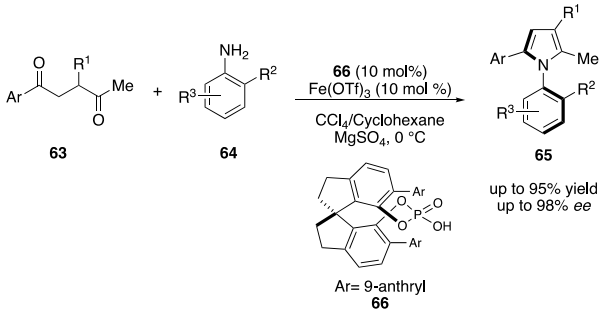
The *de novo* construction of a rotationally restricted structure often allows for a convergent synthesis of atropisomers, a strategy that Gong explored for the atroposelective synthesis of boron-based heteroaryls (**Scheme 17**).[32] A gold-catalyzed cycloisomerization-amination cascade reaction allowed the stereoselective construction of a variety of heteroaryls. The protecting groups on the diazene are thus responsible for the restricted rotation about the C–N bond of the corresponding hydrazide. The postulated mechanism involves an initial coordination of the Au(I) complex to the alkyne to form a vinylgold intermediate. The latter is added to the diazene, itself coordinated to a chiral gold complex, giving rise to a configurationally stable axially chiral compound.

Due to their unique properties, boron-containing compounds have been studied in medicinal chemistry as new class of bioactive molecules.[33] Their reversible interaction with proteins and the adjustability of their Lewis acidity make them an interesting target in drug discovery.



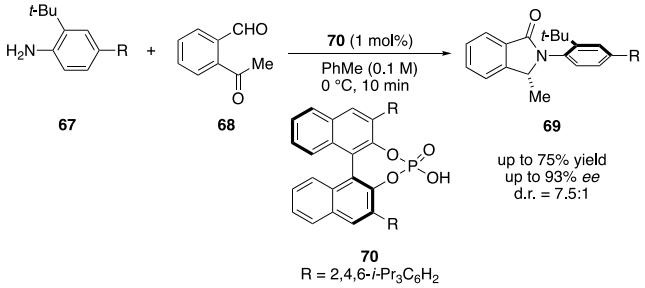
Scheme 17. Gold-catalyzed atroposelective synthesis of amino-oxaborininol dervivatives

By using an earth abundant metal combined with an organocatalyst, Tan developed an atroposelective synthesis of arylpyrroles, a motif largely found among natural products (**Scheme 18**).[34] A Paal-Knorr reaction catalyzed by a chiral phosphoric acid, with iron (III) triflate as a Lewis acid, led to a diversity of axially chiral arylpyrroles with excellent yields and enantioselectivity. After the formation of a key enamine intermediate, the chiral phosphoric acid catalyzes the dehydrative cyclization resulting in the formation of the atropisomer. The rotation about the C–N bond was sufficiently suppressed by the *ortho* substituents on the pyrrole moiety and the aryl ring.



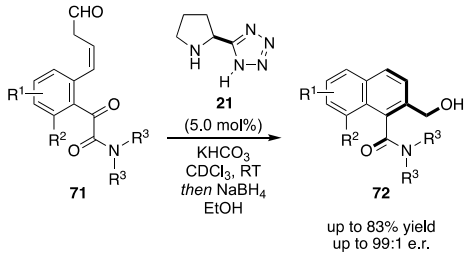
Scheme 18. Atroposelective Paal-Knorr for the synthesis of arylpyrrole derivatives

Seidel disclosed a biomimetic approach for the synthesis of isoindolinones cores and mariline A (**Scheme 19**).[35] A particularly low catalyst loading of chiral phosphoric acid promoted the intramolecular condensation between 2-acyl-benzaldehyde derivatives and anilines, enabling the construction of several isoindolinones with excellent enantioselectivity. The steric interactions of the *ortho*-*tert*-butyl *ortho*-group with the isoindolinone substituents provided sufficient rotational restriction about the stereogenic C–N bond.



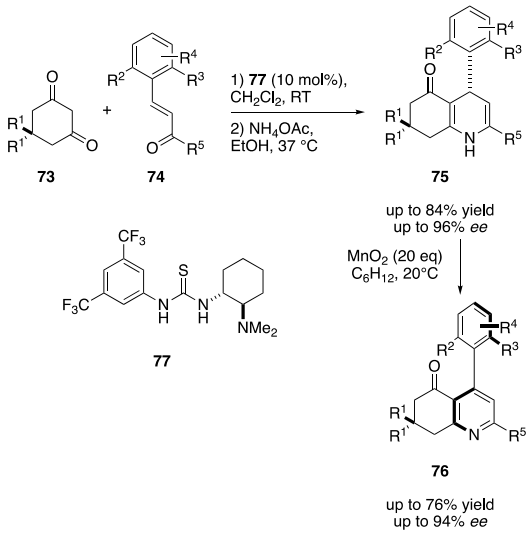
Scheme 19. Axially chiral synthesis of indolinones

Catalyzed by pyrrolidinyl tetrazole **21**, our group elaborated a stereoselective synthesis of axially chiral aromatic amides by the stereoselective arene-forming aldol condensation (**Scheme 20**).[36] Aryl amides are frequently utilized motifs in drug development[2] and axially chiral congeners with restricted rotation about the Ar–CO bond were obtained in enantioenriched form.



Scheme 20. Stereoselective synthesis of axially chiral aromatic amides

An elegant Hantzsch-type reaction for the atroposelective synthesis of 4-arylpyridines was recently described by Bressy, Bugaut and Rodriguez **(Scheme 21**).[37] The enantioselective Michael addition catalyzed by a chiral thiourea derivative was followed by the condensation with an ammonium acetate salt, giving rise to 1,4-dihydropyridines. By central-to-axial chirality conversion during the MnO_2 oxidation, a variety of axially chiral 4-arylpyridine derivatives where obtained, a general scaffold comprising members with anti-tumor and antiviral properties.[38]



Scheme 21. Atroposelective Hantzsch-type synthesis of 4-arylpyridines

4. CONCLUSION

Various conceptually distinct methods for the catalyst-controlled, stereoselective synthesis of atropisomers are emerging, making an increasing range of axially chiral scaffolds available. Elegant strategies that allow the transfer of the stereochemical information of readily available catalysts into important atropisomeric structures have been elaborated. As atropisomers allow a predictable relative arrangement of groups in space, their utility as structurally well-defined scaffold has been corroborated. For catalyst design and in medicinal chemistry, chiral atropisomeric motifs are therefore receiving a privileged position. It can be concluded, that with methods becoming available for their synthesis, that the various types of atropisomers will find widespread applications in several research fields.

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Notes

The authors declare no competing financial interest.

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