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Recent advances & new concepts for the synthesis of axially stereoenriched biaryls

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TUTORIAL REVIEW

Recent advances & new concepts for the synthesis of axially stereoenriched biaryls

J. Wencel-Delord,*[a] A. Panossian,[b] F. R. Leroux[b] and F. Colobert[a]

Axial chirality is a key feature of many important organic molecules, such as biologically active compounds, stereogenic ligands and optically pure materials. Significant efforts in the field of the atropisomeric synthesis of biaryls have hence been undertaken over the past decade. Several major improvements of the already known methods to build up such chiral backbones (e.g. oxidative couplings and stereoselective Suzuki-Miyaura arylations) have been achieved and, in parallel, novel concepts have emerged enabling unprecedented synthetic routes toward molecules of this kind. These outstanding steps forward unlocked the door to the preparation of previously difficult-to-access precursors of privileged ligands like BINOL, BINAM, QUINAP and many others molecules of interest.

Key learning points

(1) Principal synthetic approaches toward axially chiral biaryls.

(2) Recent advances in stereoselective Ar-Ar couplings *via* Suzuki-Miyaura coupling and direct arylation.

(3) Use of organocatalysis for the synthesis of chiral biaryls.

(4) Synthetic approaches enabling conversion of racemic/prochiral biaryls into atropisomerically enriched scaffolds.

(5) The most efficient pathways for the preparation of biaryls with an expected specific substitution pattern.

Introduction

Vancomycin, korupensamin, (-)-steganacin, gossypol, cavicularin, are only selected examples of well known, biologically active compounds exhibiting an axis of chirality (Figure 1).[1] Moreover, stereogenic ligands such as BINOL or BINAP are undeniably privileged chiral inductors. In the case of both families of compounds their unique features may be attributed to their atropisomerism (or axial chirality), i.e. restricted rotation around the biaryl linkage. Also certain modern materials, like liquid crystals,[2] are characterised by atropisomeric architectures. Consequently, the synthesis of asymmetric compounds containing such a stereogenic element has been attracting increasing scientific interest. Historically, atropisomerically enriched backbones were prepared by resolution of racemic mixtures. However, the end of the 20th and the beginning of the 21st centuries have been marked by major advances as conceptually distinct approaches have been devised to access such high value-added molecules. The expanding knowledge on transition metal-catalyzed cross-couplings paved the way toward pioneering work on asymmetric aryl-aryl couplings. The atropoenrichment has also been achieved *via* selective functionalization of prostereogenic biaryls. Another elegant approach concerns Bringmann's

"lactone strategy" i.e. the stereoselective opening of configurationally unstable biaryl lactones. These different synthetic strategies enabling atroposelective synthesis were discussed in details in 2005 in an excellent review[1a] and few more specialized articles focusing on one type of synthetic routes have been published since that date.[1b-g]

However, as the last decade has witnessed major progress in this field, we feel that a general update of this research is of
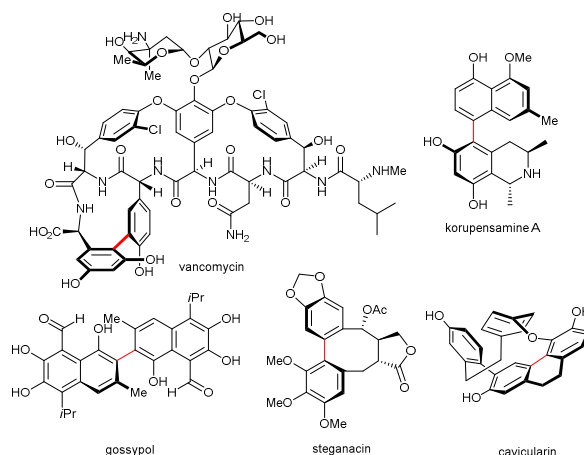

Figure 1

interest. Consequently, the aim of this tutorial review is to showcase and discuss these recent major improvements achieved since 2005. To guide the reader in the field of atroposelective synthesis this review is divided into four major sections (**Scheme 1**): Section I covers the stereoselective construction of biaryl linkages whereas Section II concerns the access to chiral biaryls *via* construction of (an) aromatic ring(s). Section III deals with stereoselective transformations of prochiral or racemic biaryls. Finally section IV presents an interesting example of synthesis of optically enriched biaryls relying on a central-to-axial chirality transfer. As our target is to present the concepts rather than furnish an exhaustive list of publications, selected contributions are discussed in this article.
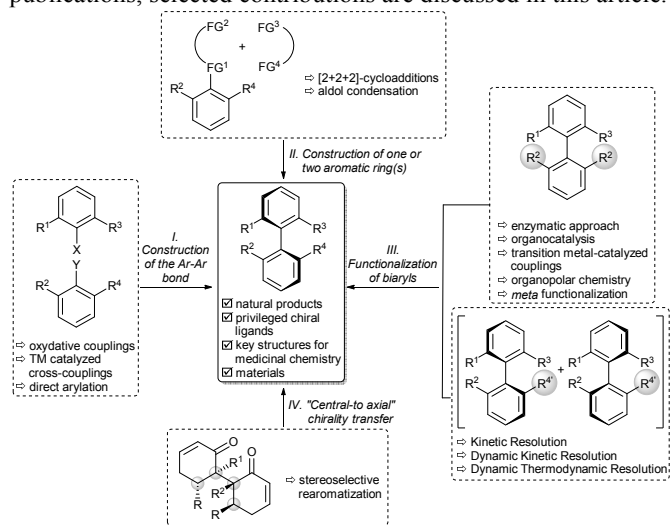
Scheme 1 Modern approaches toward atropisomeric biaryls.

# I Stereoselective construction of biaryl scaffolds

Ar-Ar couplings are transformations of key importance for both academia and industry and therefore many diverse approaches have been considered to access biaryl scaffolds. However, achieving asymmetric induction during the coupling is substantially more difficult. Indeed, the steric congestion around the Ar-Ar axis of biaryls is essential to ensure their configurational stability (generally 3 substituents in *ortho-*, *ortho'*-positions are required) but such important hindrance hampers the C-C coupling. To obviate this obstacle more powerful asymmetric catalytic systems have been designed and innovative coupling strategies have been imagined.

I. A Transition metal-catalyzed couplings.

I.A.1 ADVANCES IN INTERMOLECULAR OXIDATIVE COUPLINGS.
Chemists often draw their inspiration from the biosynthesis of natural products. Therefore it is not surprising that the asymmetric oxidative couplings of phenols have rapidly emerged as one of the reliable and atom-economical routes toward atropisomeric biaryls. Several efficient Cu, V and Ru – based chiral catalytic systems performing homocouplings of naphthols have been reported at the end of the 20th and early

21st.1[d] More recently, further attempts have been undertaken to improve these catalytic systems and a particular attention has been paid to the development of aerobic transformations compatible with the use of air as terminal, green and widespread oxidant (**Scheme 2**). Following this goal, Luo and Gong designed a new generation of H_8-BINOL-based bimetallic oxovanadium complexes **1**.[3] Good chemical yields, excellent enantioselectivity and high tolerance for substituents at either C7 or at both C7 and C6 positions are the additional advantages of this catalytic system. In 2009 Katsuki reported a complementary strategy based on the use of a Fe(salan) catalyst **2** and compatible with 2-naphthols bearing a non-coordinating substituent at the C3-position.[4] Finally, the homocoupling of 2-naphthols bearing carbonyl-substituents at the C3-position using molecular oxygen as terminal oxidant and a catalytic amount of TEMPO (2,2,6,6-tetramethylpiperidin-1-yl oxyl) as a co-catalyst was promoted with a moderate to good atroposelectivity by the Cu/BINAM **3** catalytic system.[5] Importantly, the Cu-catalyzed synthesis of (*S*)-bisoranjidiol[6a] and V-catalyzed synthesis of pigmentosin A and talaroderxines A and B6[b] illustrate the synthetic utility of such asymmetric oxidative homocouplings.
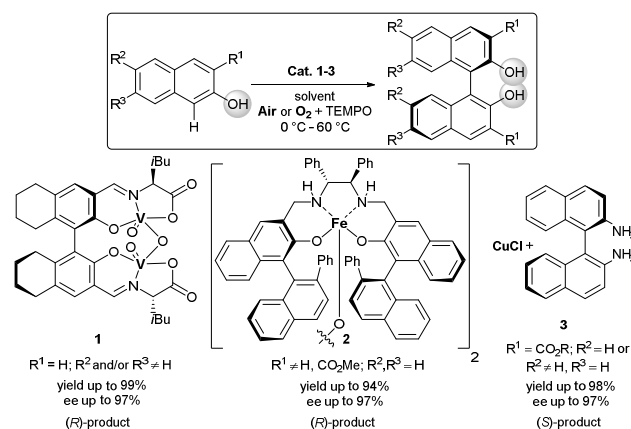
Scheme 2 Asymmetric oxidative homocoupling of 2-naphthols.

An original example of a diastereoselective oxidative homocoupling was discovered by Zhou and Li.[7] The authors used a chiral sulfoxide moiety as both an *ortho*-directing group and a chiral inductor, to promote the DoM (directed *ortho*-metallation) of aryl sulfoxides followed by an iron-catalyzed C-C coupling. This radical coupling straightforwardly furnished axially chiral bis-sulfoxides with high stereoinduction (**Scheme 3**).

Finally, we would like to draw the readers' attention to the intramolecular oxidative and reductive couplings which have also been widely explored. The chiral information is generally introduced by applying stereogenic tethers prefixing two aryl units. As such transformations have already been presented in other reviews,[1] they will not be covered in this article.[8]
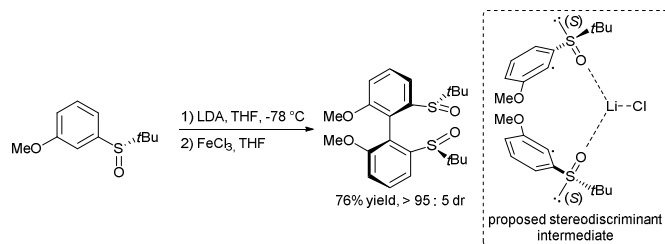
Scheme 3 Diastereoselective oxidative homocoupling of aryl sulfoxides.

I.A.2 ADVANCES IN ATROPOSELECTIVE SUZUKI-MIYAURA COUPLINGS. Regarding the chief improvements in the field of Suzuki-Miyaura couplings, the development of the asymmetric version of these cross-couplings appeared, in the late 1990s, as an attractive route toward axially chiral biaryls.[1b,g] Initially, diastereoselective transformations were performed, using one chiral coupling partner bearing a motif such as a planar-chiral chromium complex or a carbon-stereogenic center.[1b,g] In this context, stereogenic moieties, such as benzylic alcohols or β–hydroxy sulfoxides, appeared as highly promising auxiliaries (**Scheme 4A**). In recent years this strategy has been applied to the total synthesis of natural compounds, namely dibenzoxepine derivatives,[9] (-)-steganone[10] and the biaryl part of vancomycin.[10c] In addition, *tert*-butyl sulfinyl moiety was devised in 2009 as an additional chiral auxiliary (**Scheme 4B**).[11] The key advantage of this atroposelective Suzuki-Miyaura coupling lies in both its important functional group tolerance and its efficiency in terms of chemical yield and diastereoselectivity (up to 97:3). The chiral induction is probably achieved *via* coordination between the chiral sulfoxide moiety and the Pd-catalyst thus enabling either stereocontroled transmetallation or a stereodiscriminant reductive elimination.

A conceptually distinct approach to transfer chiral information during the Ar-Ar coupling was elaborated by Lipshutz *et al.* for the total synthesis of (+)-korupensamine B (**Scheme 4C**).[12] Despite the natural presence of two stereogenic carbons in the final product, these chiral elements are too distal from the biaryl linkage to efficiently control the cross coupling. The high level of atroposelectivity could however be reached *via* intramolecular π–stacking interactions between the electron-rich tetrahydroisoquinoline motif and a temporarily installed aryl ester moiety, hindering one face of the aryliodide.

In addition, the diastereoselective intramolecular Suzuki coupling may also be employed as a key step in the synthesis of axially chiral macromolecules. If a chiral linker, like a peptidic moiety, is installed between two aromatic units, an efficient atroposelection during the cross-coupling macrocyclization is expected as illustrated by the synthesis of arylomycins A$_2$ and B$_2$, disclosed by Neuville and Zhu.[13]

A highly enantioselective metal-catalyzed Ar-Ar cross-coupling was achieved for the first time in 1988 by Hayashi and Ito who developed a Ni/ferrocenyl monophosphines-catalyzed Kumada reaction between two naphthalene derivatives.[14] Quite surprisingly, the development of a related enantioselective Suzuki-Miyaura C-C bond formation remained unexplored for more than a decade, until the seminal, independent reports by Buchwald and Cammidge.[15] In spite of their relatively limited substrate scopes and efficiencies, these pioneering works rapidly instigated a veritable rush in this new field. Due to the inherent difficulty of such cross-couplings resulting from the required considerable steric crowding of both coupling partners (haloarene and boronic acid), the design of novel, chiral ligands was a cornerstone of this research. Such ligands should insure at once optimal electronic properties of the Pd-catalyst and a sufficient steric hindrance to facilitate a generally difficult reductive elimination step. Following these requirements, different classes of both mono- and bidentate ligands and Pd-complexes (**4-13**, **Scheme 5**) have been designed.[16,17,18,19,20,21,22,23,24,25] Despite these foremost advances, the current substrate scope of the enantioselective Suzuki-Miyaura coupling still remains somewhat restricted, mainly to tri-substituted (benzo-ring is considered as substituent) binaphthyl, phenyl-naphthyl and, more sporadically, biphenyl compounds. In several cases, an optimal stereoinduction is enhanced by the "anchoring effect" of a coordinating group (CG), e.g. an aldehyde or a dialkyl phosphonate, present at the 2-position of the haloarene. In clear contrast, the synthesis of either tetra-*ortho*-substituted cores or heterobiaryls continues to be an almost unmet goal.

Apart from homogeneous catalysis, heterogeneous catalytic systems provide additional opportunities toward enantioselective arylations. In this spirit, in 2009 Uozumi reported a PEG-supported imidazoindole dicyclohexyl-phosphine copolymer **13**. This resin-supported chiral ligand, in
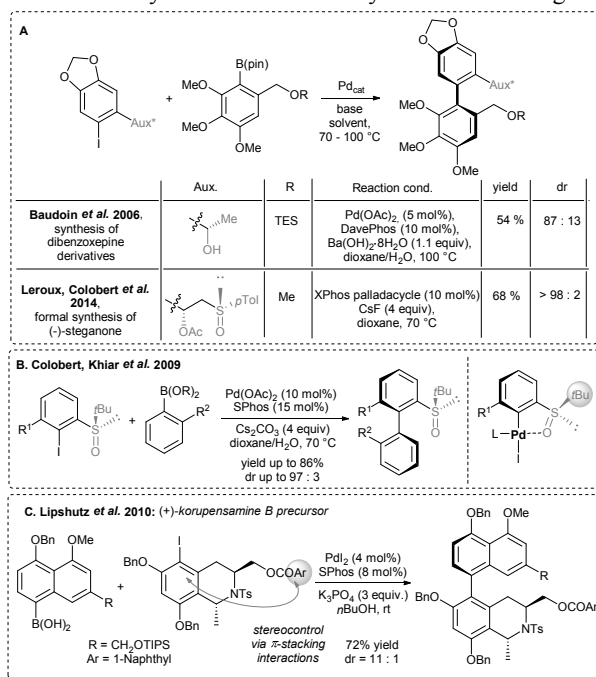
Scheme 4 Diastereoselective Suzuki-Miyaura coupling.

combination with Pd(OAc)₂ and tetrabutylammonium fluoride, mediates the Suzuki-arylation yielding challenging tetrasubstituted atropisomeric cores with ee's up to 94%. This transformation occurs in water and an efficient catalyst recycling is feasible.[25]

Thanks to these latest achievements in enantioselective Suzuki-Miyaura reactions, this transformation is now recognized as a valuable synthetic tool for the construction of axially-chiral natural products, as exemplified in 2014 by the total synthesis of korupensamine and its analogues.[26]
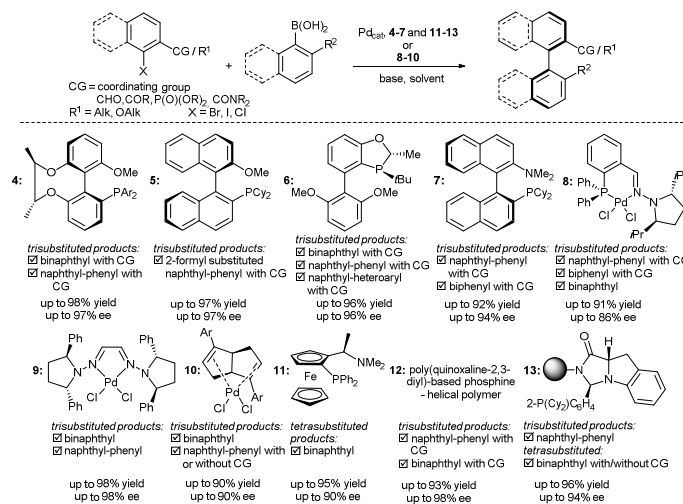
Scheme 5 Enantioselective Suzuki-Miyaura coupling.

I.A.3 ATROPOSELECTIVE C-H ARYLATION.

Since the beginning of this century, the C-H activation field has been imposing as a truly valuable alternative to standard cross-couplings. Accordingly, several approaches targeting the construction of Ar-Ar bonds, either *via* direct arylation (reaction of one prefunctionalized substrate with a simple aromatic) or *via* dehydrogenative couplings (reaction between two non-prefunctionalized arenes) have been designed. A first example of such atroposelective transformation between substituted thiophenes and hindered naphthylboronic acids was reported in 2012 by Yamaguchi and Itami.[27] Moderate levels of
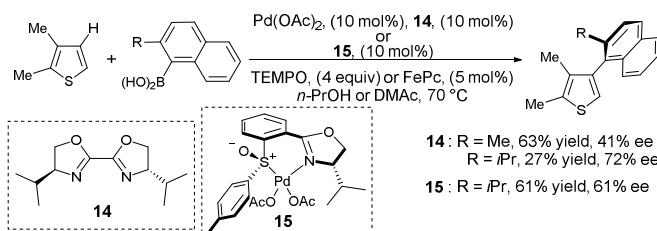

Scheme 6 Atroposelective direct arylation.

enantioselectivity were obtained using the C₂-symmetric biox ligand **14**, in combination with a Pd-precatalyst and TEMPO as oxidant. Not surprisingly, a clear activity-selectivity dilemma was observed; an important steric congestion boosts the

chirality transfer but has a detrimental impact on the reaction yield. Subsequently, a second-generation catalytic system employing a chiral Pd-sulfoxide-oxazoline complex **15** and a catalytic amount of iron-phthalocyanine (FePC) as co-oxidant was disclosed.[28] Although these results remain to be improved in terms of stereoselectivity and efficiency, they clearly highlight the potential and challenge of C-H arylations to access atropisomeric backbones.

I. B Organocatalyzed Ar-Ar couplings.

Pioneering works concerning application of organocatalysis to access atropisomeric scaffolds were reported independently in 2013 by Kürti[29] and List[30]. Both research groups employed benzidine rearrangements to construct the BINAM (1,1'-binaphthalene-2,2'-diamine) backbone (**Scheme 7**). In the presence of an axially chiral phosphoric acid catalyst (**16**), *N,N'*-dinaphthylhydrazines undergo a stereoselective [3+3]-rearrangement hence delivering BINAM derivatives in good yields and high atroposelectivity. Concerning the mechanistic scenario, density functional calculations support 1) a full proton transfer from the catalyst to one of the substrate's N-atoms and 2) atropo-determining C-C bond formation step induced by the stereogenic counter-anion.[29] A significant negative non-linear effect for this transformation was observed by List, suggesting a dicationic mechanism.[30]
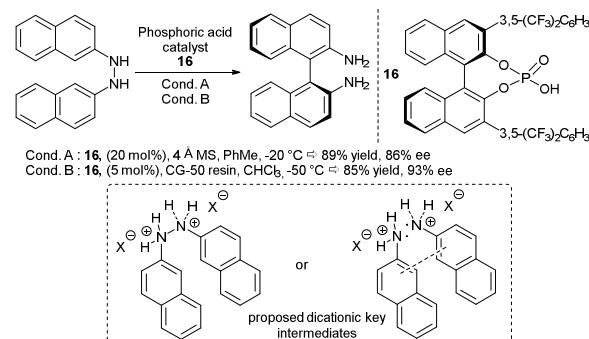

Scheme 7 BINAM synthesis *via* an atroposelective [3+3]-rearrangement.

II. Atropisomerism *via* construction of aromatic ring(s).

A conceptually different pathway toward axially chiral biaryls consists in the construction of either one or two aromatic rings. Stereoselective [2+2+2] cycloadditions of alkynes enabling formation of a new (hetero)aromatic ring with concomitant stereoinduction perfectly exemplify this approach. Because of their high atom economy and convergent nature, these transformations have received much attention since the beginning of this century. A panel of cobalt-, iridium- and rhodium-based catalysts have been used to promote inter- and intramolecular transformations. The pioneering work and recent achievements concerning stereoselective [2+2+2]

cycloadditions were reviewed recently[31] and thus will not be discussed in this article.

In 2014 Sparr *et al.* adopted a distinct, biosynthetically inspired route toward atroposelective biaryls implying a (2-pyrrolidinyl)tetrazole-catalyzed aldol condensation cascade (**Scheme 8**).[32] The authors envisioned that ζ–ketoaldehydes, in the presence of a chiral secondary amine catalyst **17**, should undergo α-activation *via* dienamine formation. Subsequent rotation around the *Z*-alkene-aryl bond places perfectly the dienamine moiety thus facilitating the expected aldolization with an efficient transfer of stereochemical information during the dehydration step. The targeted transformation, affording *ortho*-formyl substituted binaphthyls, was achieved under extremely mild reaction conditions, with excellent atroposelectivity and in synthetically useful yields.
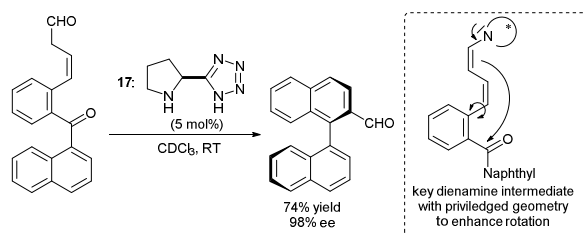
Scheme 8 Atroposelective aldol condensation.

## III Stereoselective functionalization of racemic or prochiral biaryls

III. A Desymmetrization of prochiral substrates.

III.A.1 DESYMMETRIZATION VIA FUNCTIONALIZATION OF ENANTIOTOPIC *ORTHO*, *ORTHO*'-SUBSTITUENTS. Given the multitude and the efficiency of synthetic routes yielding prochiral biaryls (bearing two identical substituents in *ortho,ortho'*-positions of one aromatic ring), desymmetrizing reactions occurring with absolute stereochemical outcome, thus yielding atropisomeric compounds, are highly tempting. Because enzymatic transformations are amongst the most powerful desymmetrization strategies, quite naturally such an approach has been investigated in the context of the preparation of axially chiral scaffolds. In 2014 Turner and Clayden performed enzymatic redox reactions converting prochiral dialdehydes and diols into enantioenriched monoaldehydes (**Scheme 9A**).[33] The model product, 3-(hydroxymethyl)-2-(naphthalene-1-yl) benzaldehyde, was obtained in good yield and excellent enantiomeric excess either by the monooxidation of a diol with galactose oxidase or by the monoreduction of a dialdehyde with ketoreductase. Intriguingly, the optical purity of the products was further improved *via in situ* partial kinetic resolution occurring during the second oxidation of the monoaldehyde product. As the rate of this second diastereotopic enzymatic transformation is unequal for each atropisomer of the chiral monoaldehyde, the undesired enantiomer is converted preferentially, hence enhancing the

optical purity of the monoaldehyde with a concomitant slight sacrifice of the chemical yield.

A related tandem desymmetrization/kinetic resolution (KR) mechanism implying asymmetric nucleophilic aromatic substitution was disclosed by Smith (**Scheme 9B**).[34] Axially chiral 5-aryl-4-chloro-6-(phenylthio)pyrimidines were accessed *via* selective functionalization of a sterically encumbered dichloropyrimidine electrophile with thiophenol. *N*-Benzylcinchonidinium chloride **18** was selected as the optimal catalyst. As previously, when a slight excess of a nucleophilic coupling partner was used, the stereoselective outcome of this transformation was improved by the kinetic resolution occurring during the second nucleophilic substitution (i.e. rapid thiolation of a minor isomer of the 5-aryl-4-chloro-6-(phenylthio)pyrimidine).

Transition metal-catalyzed conversion of one of the two enantiotopic substituents is an additional solution toward desymmetrization of the C_S-symmetric achiral biaryls. Such an approach is exemplified by a recent enantioposition-selective Cu-catalyzed azide-alkyne cycloaddition (CuAAC) (**Scheme 9C**).[35] When a Cu(I) catalyst was used in combination with L-serine-derived PyBox ligand **19**, a targeted cycloaddition on the
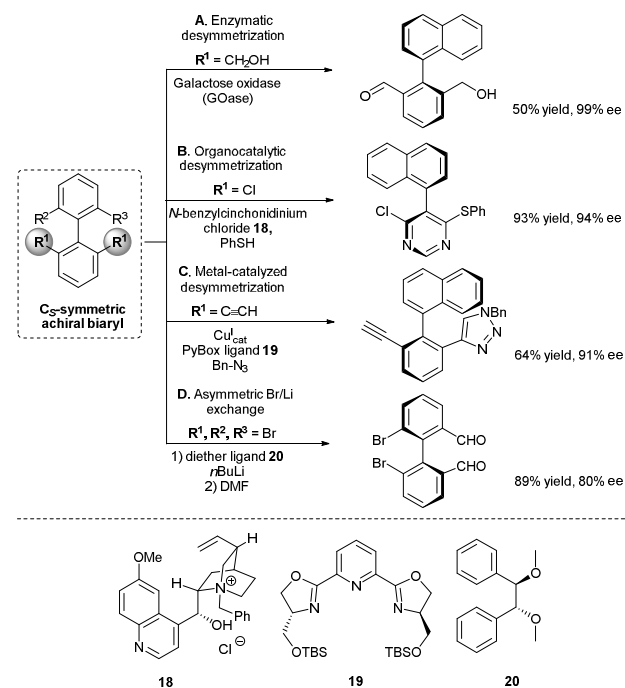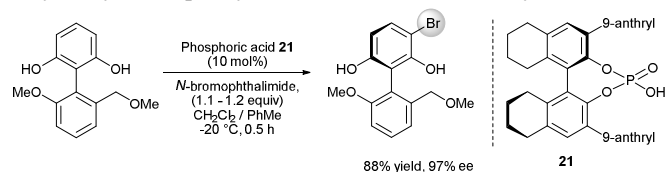

Scheme 9 Desymmetrization of prochiral substrates.

ortho-alkyne substituent was promoted with an excellent atropocontrol (ee up to 99%) and in a synthetically useful yield. Another innovative desymmetrization, based on a stereoselective halogen/lithium exchange strategy was investigated by Alexakis (**Scheme 9D**).[36] The author hypothesized that atropisomeric aryl lithium species may be generated by performing a Br/Li exchange in the presence of a catalytic amount of chiral bicoordinating ligands, such as diamines or diethers. Subsequently, electrophilic quenching of

the diasteroisomeric intermediate should afford an axially stereoenriched biaryl. After extended ligand screening, a hydrobenzoin-derived diether was selected as an optimal chiral auxiliary, delivering targeted scaffolds with 80% ee. Although the stereocontrol of this transformation is not yet optimal, its versatility is a strong advantage. Not only the electrophilic trapping enables to introduce a variety of functionalities but also, as enantioenriched di-halogenated tetrasubstituted biaryls are generated, further post-modifications are feasible.

III.A.2 DESYMMETRIZATION VIA INTRODUCTION OF AN ADDITIONAL SUBSTITUENT. An original desymmetrization strategy relaying on the introduction of an additional *meta*-substituent on the symmetrically 2,6-disubstituted aromatic ring of a prochiral biaryl substrate was reported in 2013 by Akiyama (**Scheme 10**).[37] A stereo- and regioselective phosphoric acid-catalyzed bromination of tetrasubstituted prochiral 2,6-dihydroxy-1,1'biphenyls enabled to efficiently access the

Scheme 10 Desymmetrization via introduction of an additional *meta*-substituent

corresponding axially chiral scaffolds. Similarly to previous examples, the optimal chiral induction is achieved in a stepwise fashion. Firstly, a hydrogen bond network between phenolic hydroxyl groups of the substrate, the phosphoric acid catalyst and *N*-bromosuccinimide favours atroposelection during the first C-Br bond formation. As the following second bromination occurs under kinetic resolution conditions (preferentially on the minor atropisomer), a further increase of the enantiomeric enrichment of the monobrominated biaryl product may be obtained.

III.A.3 DESYMMETRIZATION FOLLOWED BY RESOLUTION OF ATROPODIASTEREOMERIC MIXTURE. In 2012 Leroux, Colobert *et al.* reported a transition metal-free 3-step approach toward atropisomerically enriched compounds (**Scheme 11**)[38] consisting in 1) generation of achiral polyhalogenated biaryls *via* a transition metal-free ARYNE coupling, followed by 2) non-asymmetric introduction of a chiral sulfoxide auxiliary and
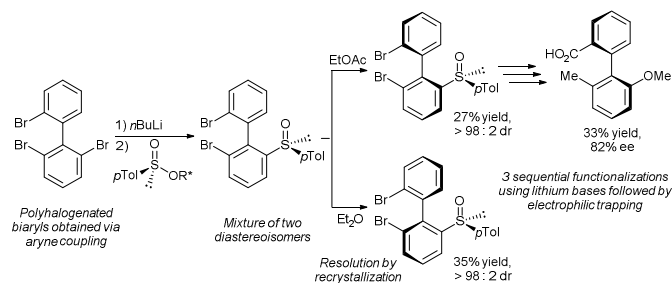

Scheme 11: Resolution *via* separation of diastereoisomeric mixture

3) subsequent separation of the newly formed diastereomers by a simple recrystallization. Such "stepwise" synthesis and resolution of diastereoisomeric mixtures afforded optically pure biaryls in synthetically useful yields. Notably, as further chemoselective functionalization of the chiral products at each of the three *ortho*-positions with slight loss of atropoenrichment is possible, this concept may be applied to access structurally diversified trisubstituted biphenyls.

III. B Functionalization of configurationally unstable "lactone bridged" biaryls.

A remarkable step forward in the construction of axially chiral biaryls was achieved in the 1990s when Bringmann discovered the "lactone" strategy based on a stereoselective cleavage of configurationally unstable biaryl lactones in the presence of chiral nucleophiles (**Scheme 12A**).[1a,f] Such an approach relying on a dynamic kinetic resolution (DKR) (*via* rapid interconversion of two lactone-bridged atropisomeric moieties) enables highly enantio- and diastereoselective construction of sterically congested biaryls. Although this route has been successfully employed for the synthesis of several natural products, the need for a stoichiometric amount of chiral nucleophiles strongly hampers its widespread applicability. Recently, an interesting example of a catalytic atropo-enantioselective reduction of axially prostereogenic lactones was disclosed by Yamade (**Scheme 12B**).[39] A chiral cobalt(II) complex **22** proved to be an efficient and stereoselective catalyst for a reductive opening of the biaryl lactone in the presence of an excess of modified NaBH$_4$ species, yet affording configurationally stable, tetrasubstituted biaryls with high to excellent enantioselectivity. Temperature is a key parameter of this transformation; as the reaction operates under dynamic kinetic resolution a sufficiently high temperature is compulsory to enhance the *in situ* racemisation of the lactones, whereas a too high temperature might be detrimental for chiral induction.
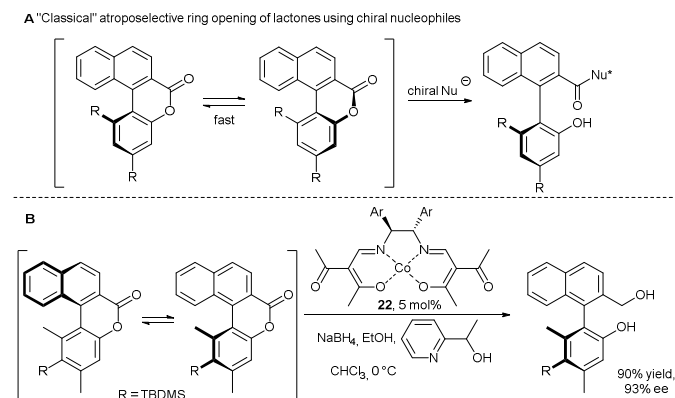

Scheme 12 Catalytic atropo-enantioselective biaryl lactone cleavage.

III. C Transformations of racemic axially chiral biaryls.

III. C. 1. KINETIC RESOLUTION OF RACEMIC MIXTURES OF BIARYLS. The kinetic resolution of racemic starting materials was considered for decades as one of the most reliable strategies for the synthesis of optically enriched compounds. In contrast, its application to the enantioselective synthesis of axially chiral backbones was somewhat limited (we draw, however, the readers' attention to the resolution of diastereomeric salts of axially chiral compounds, which are not covered in this review). The potential of enantioselective kinetic resolution to prepare atropisomeric molecules was initially proven by designing enzymatic kinetic resolution, as illustrated by an elegant work of Aoyagi *et al.*[40] Lipase (*Candida antarctica*)-catalyzed hydrolysis of BINOL monoester-derivatives (**Scheme 13A**) was performed at 80 °C delivering (*R*)-BINOL in 51% yield and good optical enrichment (93%) along with the unreacted substrate in 49% yield and 92% ee.
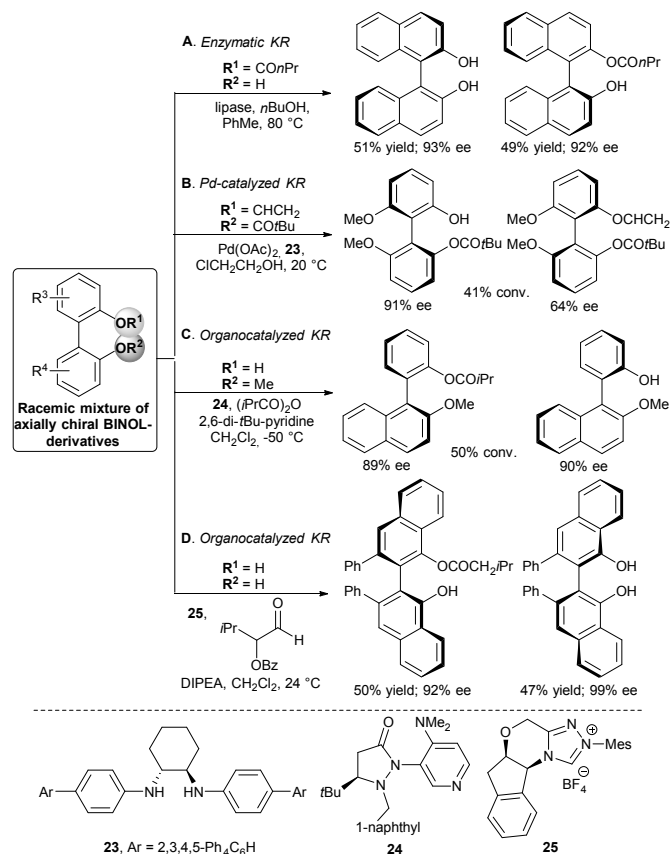

Scheme 13 Kinetic resolution of biphenol-derivatives.

Regarding the key importance of BINOL-derived scaffolds as privileged chiral ligands, their atroposelective preparation has focused considerable attention and hence complementary synthetic approaches based on kinetic resolution have been investigated. In 2005 Tokunaga and Tsuji reported palladium-catalyzed hydrolysis of vinyl ether monoester derivatives of BINOL and biphenols (**Scheme 13B**).[41] A combination of Pd(OAc)$_2$ with the chiral diamine ligand **23** was efficiently

used for atroposelective alcoholysis affording the expected product with high enantiomeric excess (91%) and 41% conversion (selectivity of 39.8; (selectivity factor: $s = k_{fast}/k_{slow}$)). Such excellent results rendered this transformation the first truly valuable catalytic system promoting construction of optically enriched axially chiral 1,1'-bi-2-phenols.

A further example of the kinetic resolution of axially chiral biaryls was accomplished by means of organocatalysis. The group of Sibi designed fluxionally chiral DMAP catalyst **24** as a chiral inductor for kinetic resolution of racemic secondary alcohols *via* stereoselective acylation.[42] This reaction was further extended to axially chiral BINOL scaffolds (**Scheme 13C**). The targeted resolution was achieved with moderate to high selectivity ranging from 10 to 51; its stereochemical outcome being strongly influenced by the steric demand of the β–OR-substituent. Atroposelective acylative kinetic resolution may also be mediated using oxidative *N*-heterocyclic carbene catalysis (**Scheme 13D**).[43] Zhao discovered that chiral acyl azolium species, generated from a stereogenic azolium **25** and judiciously chosen α-aroyloxy aldehydes, react selectively with one atropisomer of axially chiral diols thus promoting efficient and mild kinetic resolution of the racemic substrate. In addition, this catalytic system is compatible with 2-amino-2'-hydroxybiaryls thus permitting the synthesis of NOBIN (2-amino-2'-hydroxy-1,1'-binaphthyl) derivatives.
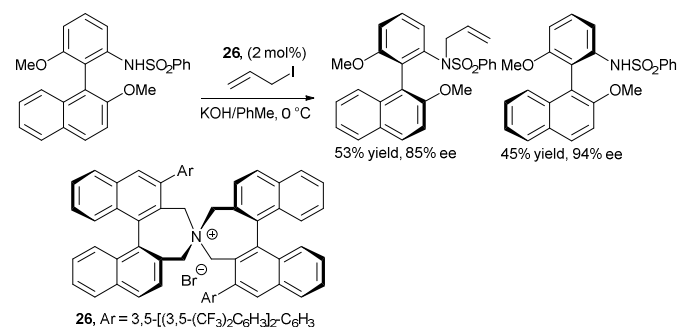

Scheme 14 Kinetic resolution of 2-amino-1,1'-biaryls.

A complementary route toward NOBIN precursors was developed by Maruoka (**Scheme 14**).[44] The authors speculated that an efficient chiral recognition of the optically active 2-amino-1,1'-biaryls could be attained *via* formation of an atropomeric ion pair between the substrate and a phase-transfer catalyst. This hypothesis was successfully validated by the discovery of an atroposelective *N*-allylation reaction catalyzed by chiral quaternary ammonium salt **26**. In the presence of only 2 mol% of the axially chiral **26** and using a biphasic reaction medium (50% aqueous KOH / toluene), the selective allylation was performed with selectivity up to 43, delivering allylated NOBIN in 53% yield and 85% ee. The remaining starting material was recovered in optically enriched form (94% ee) and in 45% yield.

To further highlight the synthetic potential of kinetic resolution to access axially chiral precursors of privileged chiral ligands, Tian, Liu and Tan focused on the synthesis of BINAM (**Scheme 15**).[45] The strategy adopted by this group involves

sequential 1) chiral Brønsted acid-catalyzed imine formation followed by 2) transfer hydrogenation using the Hantzsch ester. During this transformation the NH_2-substituent reacted initially with an aromatic aldehyde. The chiral information was probably induced *via* cooperative action of the Hantzsch ester and a phosphoric acid catalyst in the reduction step. The resulting kinetic resolution occurred with an impressive level of selectivity (even superior to 300); the atropisomerically pure BINAM derivatives were isolated in 98 and 93% ee and 47 and 46% yields respectively.
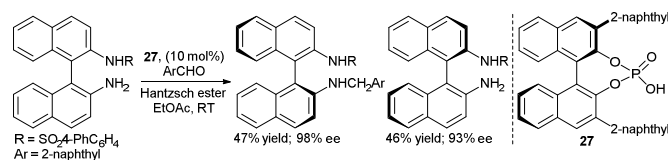
**Scheme 15** Kinetic resolution of BINAM derivatives.

III. C. 2. DYNAMIC KINETIC RESOLUTION OF RACEMIC MIXTURES OF BIARYLS.

Despite the undeniable importance of kinetic resolutions, their synthetic utility is strongly hampered by a maximal 50% yield expected for such transformations. This limitation is obviated if a starting material undergoes *in situ* epimerization thus allowing formation of targeted optically pure products in, theoretically, quantitative yield. To the best of our knowledge a very first example of dynamic kinetic resolution in the context of atroposelective synthesis of biaryls was reported in 2009 by Urbano and Carreño.[46] The authors investigated an asymmetric synthesis of [5]helicane quinones by an asymmetric Diels-Alder reaction using chiral (*S,S*)-5-methyl-2-(p-tolylsulfinyl)-1,4-benzoquinone (stereogenic dienophile) together with a racemic, axially chiral diene (**Scheme 16**). In the initial study a high steric demand around the biaryl axis of the diene led to the formation of an atropisomeric 1:1 mixture of quinones bearing both axial and helical chiral elements. However, when a diene with a decreased steric hindrance around the chiral axis was submitted to the otherwise identical reaction conditions, the desired

moderate steric hindrance around biaryl axis
⇨ rotation around biaryl axis under reaction conditions
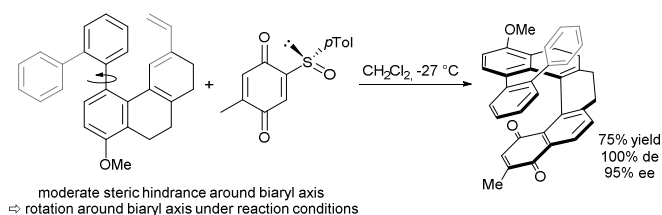
Scheme 16 DKR in the synthesis of axially chiral helicane quinone.

product could be isolated in high yield and in enantiomerically pure form. As both atropisomers of the substrate were converted into a same product, a dynamic kinetic resolution occurs. The interconversion between both diene atropisomers is believed to arise readily before the cycloaddition step in which both axial and helical chiralities are efficiently controlled.

The potential of dynamic kinetic resolution to prepare atropisomeric biaryls was further recognized by Miller.[47] In his working premise the author hypothesized that if a biaryl substrate, with a configurationally labile chiral axis, undergoes transformation resulting in a significant increase of the rotational barrier around the Ar-Ar bond, nonracemizing products could be accessed. Moreover, a finely selected chiral catalyst should have a substantial capacity to mediate an atroposelective outcome of such a transformation. Following these considerations, atroposelective electrophilic bromination of 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid was successfully undertaken in the presence of a peptide catalyst (**Scheme 17**). The targeted, tribrominated biaryl with a significant configurational stability was obtained in 80% yield and with an excellent atropoenrichment (94% ee) clearly indicating that this transformation operates *via* a dynamic kinetic resolution pathway.
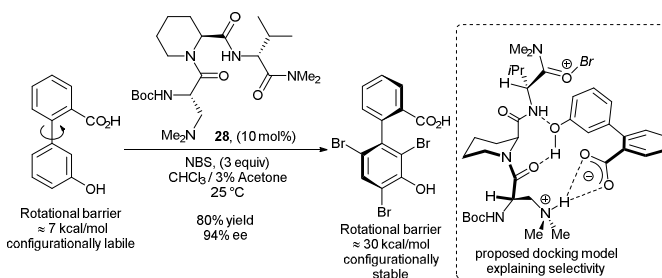
Scheme 17 DKR by atroposelective electrophilic aromatic substitution.

Further advances were reported three years later in the concomitant but independent reports by Fernández and Lassaletta,[48] and Stoltz and Virgil.[49] Both research groups focused on Pd-catalyzed cross-coupling reactions using *ortho*-functionalized racemic QUINAP derivatives as starting materials (**Scheme 18**). The initial hypothesis of Fernández and Lassaletta was that the cationic palladacycle intermediate generated after oxidative addition of the Pd(0) catalyst, might be configurationally unstable at the biaryl bond due to coordination of the isoquinoline nitrogen, thus enabling dynamic kinetic asymmetric transformation (DYKAT). In contrast, and to begin with, Stoltz and Virgil considered that chiral Pd-complexes are purportedly able to differentiate two atropisomers of the racemic substrate and hence selective cross-coupling resulting in kinetic resolution is possible. Moreover, even if the substrate is atropo-stable, insertion of palladium into the activated carbon-heteroatom bond would lead to a Ar-Pd intermediate whose both atropisomers could interconvert, thus allowing for dynamic kinetic resolution. Following such assumptions, two catalytic systems employing either Duphos or Taddol-derived stereogenic ligands (**29 and 30**) were designed. The expected dynamic kinetic cross-coupling was achieved; under finely optimized reaction conditions the racemic mixture of the substrate was converted into desired strongly optically enriched biaryls in high yield (> 50%) and excellent chiral induction. As the starting materials are configurationally stable under the reaction conditions, different hypotheses were put

forward to explain the racemization step. Following their initial premise, Fernández and Lassaletta suggested that rotation around the Ar-Ar bond is due to the widened angle between two benzo rings of palladacyclic intermediate which decreases the rotation barrier of this species. Stoltz and Virgil observed a clear ion-accelerated effect on the transformation which might indicate a favourable isomerisation occurring when the Pd^+ intermediate is formed, probably caused by an agnostic interaction between the C8-H bond of the isoquinoline and the cationic palladium center. Apart from the innovative and fundamental research aspect of these works, its propensity to generate highly valuable optically enriched QUINAP derivatives is a strong asset of this methodology.
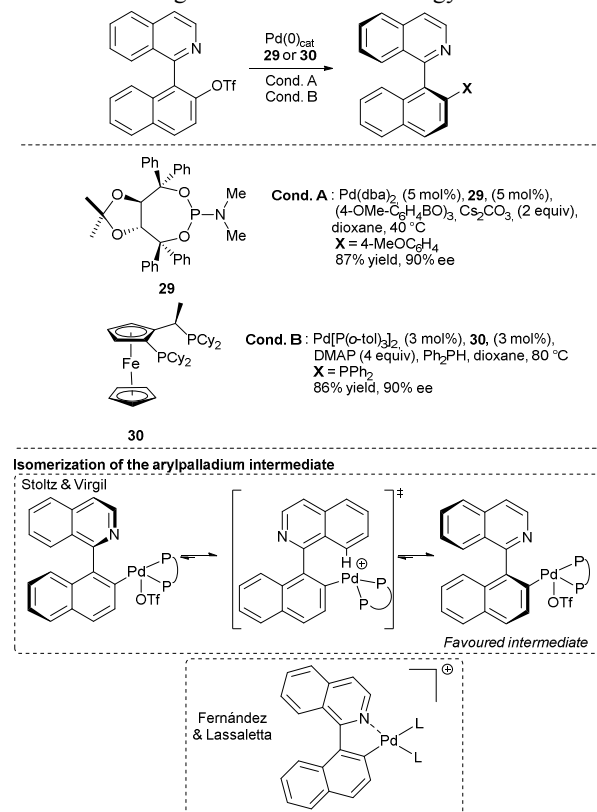
Scheme 18 DKR in Pd-catalyzed cross-couplings.

Inspired by these elegant reports other research groups have focused on the design of even more challenging and synthetically appealing C-H activation-based transformations. Regarding to the similarity between metallacyclic intermediates generated either *via* oxidative addition (in the case of classical cross-couplings) or direct insertion of the metal into a C-H bond (C-H activation reactions), it can be reasonably speculated that a closely related DKR transformation could be performed using non-prefunctionalized substrates and an appropriate catalyst.

Targeting this ambitious goal, Wencel-Delord and Colobert have endeavoured exploring the diastereoselective functionalization of biaryl substrates (**Scheme 19**).[50] They presumed that diastereomeric or axially pro-chiral biaryls bearing a judiciously chosen stereogenic coordinating group in 2-position could undergo an atroposelective direct metalation in 2'-position. Moreover, if either the substrate or the metallacyclic intermediate were exhibiting low rotational barriers, an epimerization could be expected leading to dynamic kinetic resolution. Following these considerations a S-stereogenic sulfoxide was selected as the chiral auxiliary/directing group thanks to its good coordinating properties, straightforward, large scale and enantioselective preparation, considerable configurational stability and a truly traceless character. The efforts toward atropo-diastereoselective C-H functionalization/DKR transformations were rewarded by the discovery of a highly efficient direct acetoxylation (**Scheme 19**). A panel of *ortho,ortho'*-di and tri-substituted biarylsulfoxide substrates, used as a mixture of two axially-chiral isomers, were readily functionalized in the presence of $Pd(OAc)_2$ as precatalyst with almost total atropocontrol and excellent yields. Importantly, this reaction occurs readily at room temperature suggesting that the rotation around the biaryl linkage takes place preferentially when the assumed S-coordinated palladacyclic intermediate is formed. In addition, it was observed that a closely related C-I coupling occurs under only slightly modified reaction conditions.
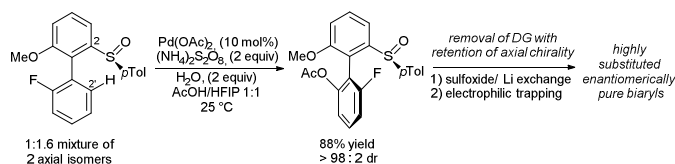
Scheme 19 DKR in Pd-catalyzed diastereoselective C-H activation.

A related research project, aiming at an atropo-enantioselective C-H activation/DKR reaction was conducted simultaneously by You.[51] The authors selected 1-(naphthalen-1-yl)isoquinoline derivatives as a racemic biaryl substrate to perform an oxidative Heck reaction (Fujiwara-Moritani coupling) (**Scheme 20**). The desired transformation was mediated by a Rh^{III} catalyst **31** bearing an axially chiral, C_2-symmetric Cp ligand, and yielded atropisomeric scaffolds with good enantioselectivity (ee up to 86%). Notably, the dynamic

outcome of this transformation was ensured at rather elevated temperatures (80 – 120 °C).
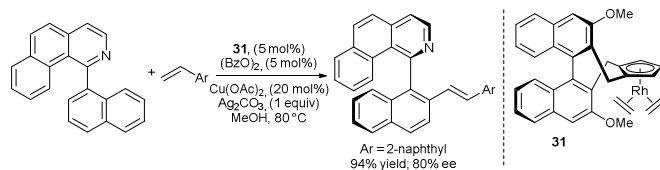
Scheme 20 DKR in Rh-catalyzed enantioselective direct olefination.

III. C. 3. DYNAMIC THERMODYNAMIC RESOLUTION OF RACEMIC BIARYLS.

Stereogenic auxiliary-induced formation of axially chiral compounds *via* thermodynamic controlled dynamic kinetic resolution was investigated by Clayden *et al.*[52] In this study, a dynamic behaviour of 2-arylpyridines and 1–arylisoquinolines bearing a chiral sulfoxide group adjacent to the Ar-Ar bond was followed. The intramolecular interactions between the N-atom and the chiral sulfoxide were expected to stimulate the substrates to preferentially adopt one of two possible axial conformations. This hypothesis was validated by discovering that a 1:1 diastereomeric mixture of 1-(2-sulfinylnaphthalen-1-yl)isoquinoline, when heated at 120 °C (a temperature high enough to overcome the rotational barrier), is converted spontaneously into a thermodynamically favoured 4:1 mixture
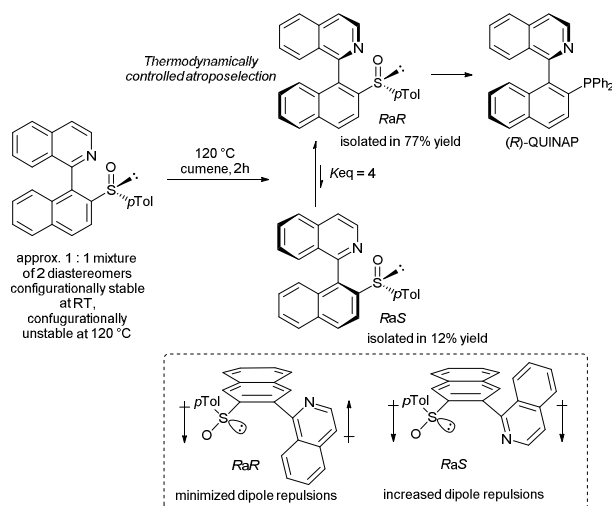

Scheme 21 Dynamic thermodynamic resolution.

of the atropomeric conformers (**Scheme 21**). Such thermodynamic preferences for one diastereomer result from dipole repulsions between the aryl C-N bond and the sulfoxide S-O bond and hence the privileged conformation decreasing the later interactions is adopted in solution. The synthetic utility of this concept was illustrated by its application to the preparation of the chiral QUINAP ligand.

IV Stereoselective rearomatization: "central-to-axial chirality exchange"

The panel of strategies toward axially chiral biaryls is further complemented by the transformations permitting conversion of chiral non-aromatic bicyclic precursors into closely related atropisomeric biaryls. During such a reaction the stereogenic
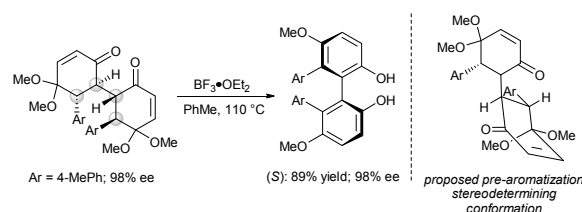
Scheme 22 Synthesis of biphenols by traceless central-to-axial chirality exchange.

centres present on the substrate should promote an efficient central-to-axial chirality transfer thus delivering atropisomerically enriched moieties. An interesting example of this concept was disclosed in 2011 by Thomson and collaborators (**Scheme 22**).[53] This research group assumed that under aromatization conditions, highly sterically congested bicyclic diones bearing four stereogenic carbons might be converted into an axially chiral biphenol. The validity of this concept was established by performing the expected aromatization of β-alkyl or aryl-substituted symmetric diones in the presence of BF$_3$•OEt$_2$. Importantly, as the newly generated biphenols do not contain stereogenic atoms, this transformation can be considered as "traceless stereochemical exchange". The aromatization occurs without rotation around the central carbon-carbon bond and thus the configuration of the axial chirality can be reliably predicted.

Conclusions

Over the past decade the scientific community has been witnessing major advances in asymmetric synthesis and several astute strategies to access optically pure compounds have been disclosed. An important part of these transformations takes profit from atropisomeric ligands as privileged chiral inductors. Such prevalence of axially chiral motifs has stimulated not only the significant improvements in already existing strategies but also the development of new synthetic routes to access axially chiral biaryls (**Scheme 23**). Importantly, many distinct approaches steaming from enzymatic chemistry, organocatalysis and transition metal promotion have hence been disclosed, enabling the formation of a large panel of high

value-added and previously difficult-to-access asymmetric backbones. Arguably the most remarkable progress in this field comes from the employment of previously underestimated (dynamic) kinetic resolution of racemic biaryls. Accordingly, many axially chiral compounds and particularly, the precursors of atropisomeric ligands, may now be obtained in a straightforward manner and in excellent optical purity. Nevertheless, the real synthetic usefulness of such modern routes is frequently limited by the substrate scopes. A vast majority of transformations relies on the finely tuned reactivity of designed substrates hence remaining highly specific to a rather narrow class of functionalized products.

Consequently, the design of truly versatile, atroposelective syntheses still remains an ambitious goal. Innovative solutions are required, especially in the context of the total synthesis of complex and/or tetrasubstituted axially chiral molecules. By summarizing and discussing the recent concepts in this rapidly developing field, we hope that this review article will inspire further progress and breakthroughs.

Type of atropisomeric biaryl	Synthetic methods	Ref.
	⇨ heterogenous Suzuki-Miyaura coupling	25
	⇨ desymmetrization of prochiral biaryls	
	- *via* lithium/bromine exchange	36
	- non-asymmetric functionalization	38
	followed by resolution of diastereomeric mixtures *via* recrystallization	
	⇨ C-H activation / dynamic kinetic resolution and subsequent post-modification	50
	if R⁴ = coordinating group	
	⇨ enantioselective Suzuki-Miyaura coupling	19
	⇨ oxidative homocoupling of naphthols	3-5
	⇨ kinetic resolution of binaphthol derivatives (enzymatic, TM catalysis, organocatalysis)	40-43
	⇨ kinetic resolution of NOBIN derivatives (phase transfer)	44
	⇨ benzidine rearrangement	29,30
	⇨ kinetic resolution of BINAM derivatives (organocatalysis)	45
	⇨ Pd-catalyzed dynamic kinetic resolution	48,49
	⇨ dynamic thermodynamic resolution followed by post-functionalization	52

Scheme 23 Principal approaches to access different classes of axially chiral scaffolds (2005-2014).
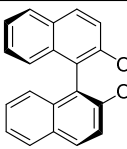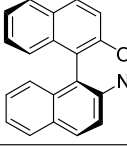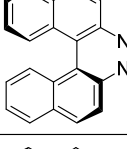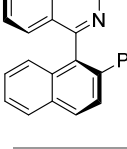
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