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Synthetic Strategies to Control C–N Atropisomerism in Acyclic Amines and Amides

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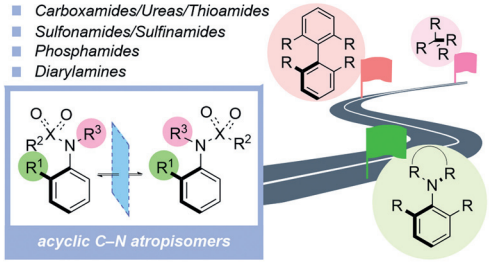

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Abstract Atropisomeric molecules are a privileged class of stereogenic material that have important applications in catalysis, materials science and medicines. To date, the majority of work has been focused upon biaryl and heterobiaryl scaffolds involving restricted rotation between a pair of cyclic fragments, but C–N atropisomeric molecules based upon amines and amides, where the nitrogen atom is not part of a ring system, are rapidly emerging as an important class of stereogenic molecules. This is the focus of this Short Review, which begins by discussing the factors which influence the configurational stability of such molecules and provides a historical background to their synthesis. This is followed by a detailed discussion of state-of-the-art catalytic asymmetric strategies that are now available to access C–$N_{acyclic}$ atropisomers including carboxamides, sulfonamides, sulfinamides, phosphamides and diarylamines. A variety of different synthetic approaches are discussed, including kinetic resolution/desymmetrization, amination, C–H functionalization, N-functionalization, and annulation.

Key words atropisomerism, axial chirality, amide, amine, asymmetric catalysis, anilide, stereoselectivity

Roly J. Armstrong (right) graduated with an MSci in Natural Sciences from Pembroke College, Cambridge (2011). He subsequently moved to Merton College, Oxford to carry out a DPhil under the supervision of Professor Martin Smith (2011–2015), followed by postdoctoral studies with Professor Varinder Aggarwal FRS at the University of Bristol (2015–2017) and Professor Timothy Donohoe at the University of Oxford (2017–2018). In 2018, he took up a Junior Research Fellowship at University College, Oxford, and in 2021 he joined Newcastle University as a lecturer in chemistry. His research interests include organic synthesis, asymmetric catalysis and medicinal chemistry.

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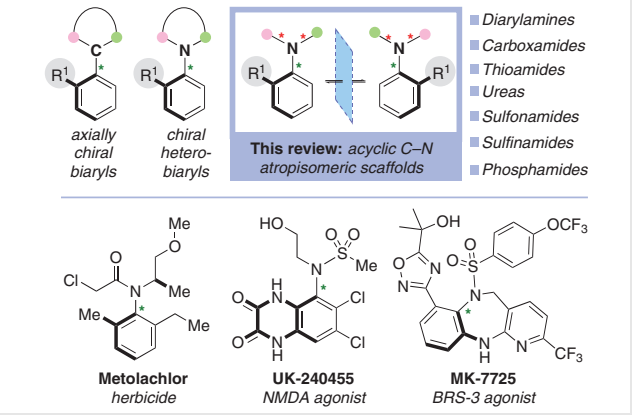
1 Introduction

Atropisomerism refers to the phenomenon by which slow rotation about a single bond allows the different conformers of a molecule to be isolated as distinct chemical entities.[1] The most widely studied examples are axially chiral biaryls and heterobiaryls, the stereoisomerism of which results from the non-planar arrangement of two ring systems connected by a single C–C or C–N bond (Scheme 1, top). Intensive research in this area has led to an extensive array of elegant synthetic methods for the stereoselective preparation of such materials, which have been shown to have powerful applications as chiral ligands and catalysts.[2] The high degree of conformational rigidity present within cyclic scaffolds leads to predictable and often very high levels of configurational stability, but atropisomerism is also possible with acyclic functional groups. Indeed, an increasing number of elegant reports have emerged involving C–N at-

ropisomerism in amines and amides where the nitrogen atom is not part of a ring system.[3] This is the focus of this Short Review.

The challenge in such systems is that the higher degree of conformational flexibility possible in acyclic functional groups can compromise the configurational stability of the key stereogenic C–N axis. Nevertheless, elegant work has shown that a wide variety of scaffolds can be prepared including diarylamines, carboxamides, thioamides, ureas, sulfonamides, sulfinamides, and phosphamides, which display remarkably robust configurational stability. The emerging potential of these scaffolds is highlighted by a number of reports of C–N atropisomeric molecules in drug discovery and agrochemistry, including the herbicide metolachlor as well as sulfonamide-based NMDA and BRS-3 agonists (Scheme 1, bottom).[4]



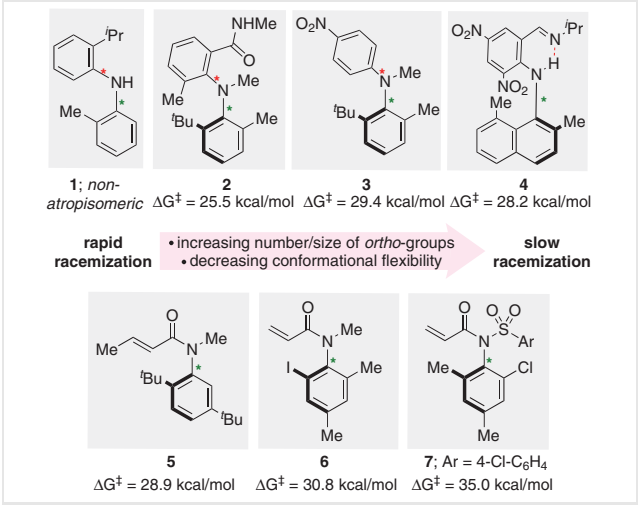
Scheme 1 Atropisomerism in cyclic and acyclic scaffolds along with important examples of medically relevant acyclic C–N atropisomeric molecules

This Short Review begins with a summary of the factors that influence configurational stability in C–$N_{acyclic}$ atropisomeric scaffolds, followed by a detailed synopsis of the methods available for their stereoselective synthesis. A wide variety of different synthetic strategies are included, from classical chiral-pool approaches to recent catalytic enantioselective methods, including desymmetrization, electrophilic amination, C–H functionalization, N–H functionalization and annulation.

2 Atropisomerism in Acyclic Amines and Amides

Conformational exchange and atropisomerism represent a continuum, with atropisomers arbitrarily defined as conformers that interconvert with a racemization half-life ($t_{1/2}^{rac}$) of more than 1000 s at a given temperature, corresponding to a Gibbs activation energy of enantiomerization ($\Delta G^{‡}$) > 22 kcal/mol at room temperature.[1] Clearly the rate of racemization of a potentially atropisomeric molecule is a crucial consideration when considering its possible applications and designing an asymmetric synthesis.

Aromatic *amines* typically do not display atropisomerism owing to the high degree of conformational flexibility arising from rotation about two C–N bonds. For example, Clayden and co-workers have reported that diarylamine **1**, possessing two *ortho*-substituents, is non-atropisomeric, with enantiomerization occurring too rapidly to be detected by ^{1}H NMR spectroscopy (Scheme 2, top).[5] In general, the rate of racemization in atropisomeric molecules can be slowed by introducing additional bulky *ortho*-substituents. For instance, Clayden and co-workers were able to resolve the enantiomers of tetra-*ortho*-substituted diarylamines (e.g., **2**), but even in this extremely hindered system, comparatively rapid racemization was observed ($\Delta G^{‡}$ = 25.5 kcal/mol; $t_{1/2}^{rac}$ = 84 min at 60 °C).[6] An exception is diarylamines with restricted conformational flexibility about the nitrogen atom. For example, Kitagawa and co-workers have also reported that tertiary diarylamines bearing an electron-withdrawing group at the *para* position display particularly high configurational stability (e.g., **3**, $\Delta G^{‡}$ = 29.4 kcal/mol), which was attributed to planarization of the electron-deficient ring with the nitrogen atom, which must be overcome during racemization.[7] A related effect has been reported by Kawabata and co-workers who reported that diarylamines such as **4** display high levels of configurational stability, which was attributed to an N–H–N intramolecular hydrogen bond that preorganizes one of the C–N axes into a planar conformation, leading to compounds which possess racemization barriers of up to 28.2 kcal/mol.[8] Several elegant asymmetric syntheses of hydrogen-bonded diarylamines featuring similar configurational stabilization have been reported. Although such systems could be considered



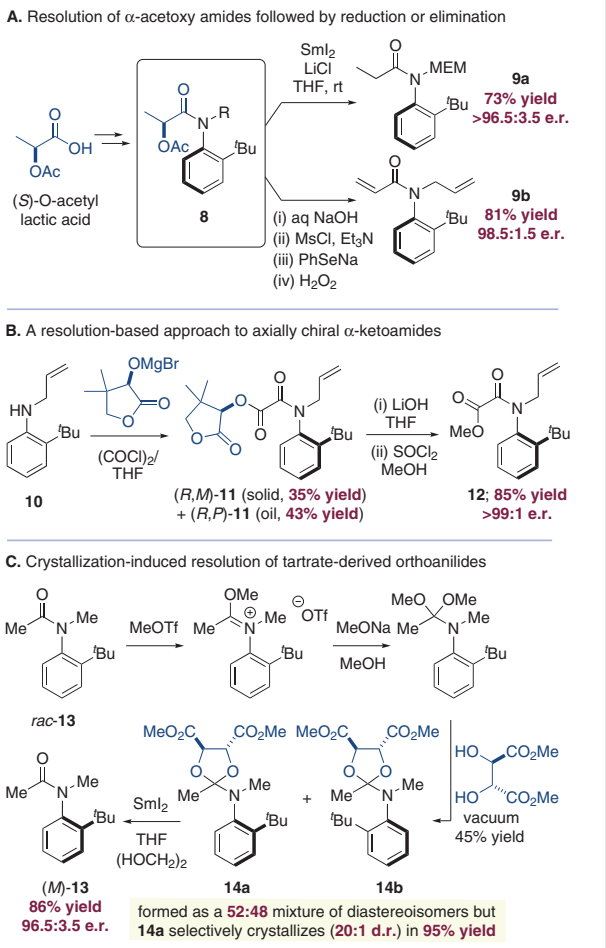
Scheme 2 Contrasting Gibbs activation energies of enantiomerization ($\Delta G^{‡}$) in a series of different amine (top) and amide (bottom) scaffolds

formally cyclic, given that their ring system relies upon a non-covalent interaction, they are included within the scope of this Short Review.

In contrast, aromatic *amides* often display robust configurational stability, which is a consequence of the planarity of the amide linkage due to conjugation between the carbonyl and amine groups (Scheme 2, bottom).[9] Even amides bearing a single bulky *ortho* substituent (e.g., **5**) display reasonable levels of configurational stability,[10] and this can be enhanced further by increasing the level of steric bulk at the *ortho* positions (e.g., **6**).[11] For similar reasons, atropisomerism is also possible for heteroatomic amide analogues (e.g., sulfonamides, sulfinamides and phosphamides), and combining these effects can produce scaffolds that display remarkably high configurational stability. For example, N-sulfonyl anilides (e.g., **7**) have been shown to possess racemization barriers of up to 35.0 kcal/mol, corresponding to a room-temperature racemization half-life in the order of $>10^4$ years.[12]

3 Synthesis Directed by a Chiral Auxiliary

Several elegant resolution-based methods have been reported for the synthesis of acyclic C–N atropisomeric molecules from chiral-pool starting materials. For example, Taguchi and Simpkins independently reported syntheses of enantio- and diastereomerically pure α-acetoxy amides **8** from (*S*)-O-acetyl lactic acid (Scheme 3A).[13,14] These proved to be versatile intermediates that could be straightforwardly reduced to the corresponding alkyl derivative **9a**,[14] or converted into unsaturated analogue **9b** via a four-step sequence consisting of ester hydrolysis, mesylation, substitution with PhSeNa and oxidative elimination.[13] In both cases, minimal erosion of the stereogenic axis was observed, enabling access to highly enantioenriched C–N atropisomeric building blocks, which have been employed in various downstream chemistry (e.g., enolate alkylation, cycloaddition and radical cyclization).[11,13,14] Taguchi and co-workers also reported a chiral-pool strategy for the synthesis of α-ketoamide atropisomers **11** from the magnesium alkoxide of (*R*)-pantolactone (Scheme 3B).[15] This reaction afforded a mixture of diastereomers (*R*,*M*)-**11** and (*R*,*P*)-**11**, which could be straightforwardly separated by recrystallization from Et_2O/hexane. Hydrolysis of the chiral auxiliary and esterification delivered the corresponding methyl ester **12** in 85% yield with no erosion of enantiomeric purity. Notably, the (*R*)-pantolactone auxiliary could be recovered from the hydrolysis reaction without racemization. Curran and Ates have reported an unusual method for the crystallographic resolution of racemic tertiary anilides *rac*-**13** with dimethyl tartrate (Scheme 3C).[16] The process involves O-alkylation with methyl trifluoromethanesulfonate followed by addition of sodium methoxide and transketalization with enantiopure dimethyl L-tartrate to afford a diastereomeric mixture of orthoamides **14a** and **14b**. Interestingly, crystallization of this mixture from hexane delivered near diastereomerically pure **14a** in 95% yield – presumably the two diastereoisomers undergo epimerization under these conditions, followed by selective crystallization of **14a**. Subsequent cleavage of the ketal with SmI_2 resulted in the formation of (*M*)-**13** in 86% yield with minimal loss of stereochemical integrity.



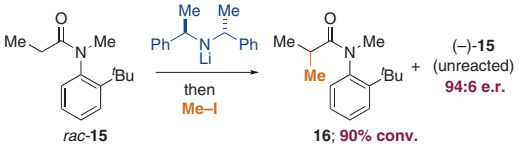
Scheme 3 Syntheses of acyclic axially chiral anilides from chiral-pool precursors

4 Atropselective Synthesis

Whilst chiral auxiliaries can provide simple and scalable methods to access enantioenriched axially chiral amides, the requirement to add and then remove the auxiliary reduces the overall efficiency and yield of the process. Direct atropselective synthesis can often provide a more efficient approach to enantiopure targets. In the context of achiral C–N atropisomeric scaffolds, several synthetic strategies have been explored, namely: (i) kinetic resolution/desymmetrization; (ii) electrophilic amination; (iii) C–H functionalization; (iv) N-functionalization; and (v) annulation.

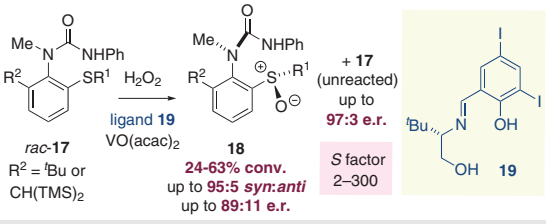
4.1 Kinetic Resolution and Desymmetrization

In 1996, Simpkins and co-workers reported a pioneering kinetic resolution reaction to obtain enantioenriched axially chiral anilides (Scheme 4).[17] In this process, the racemic anilide *rac*-**15** was deprotonated with a substoichiometric quantity of a chiral lithium amide base, and the resulting lithium enolate was alkylated with methyl iodide. The small quantity of recovered starting material (–)-**15** was shown to be highly enantioenriched (94:6 e.r.), establishing proof-of-concept for the direct atropselective synthesis of axially chiral anilides.



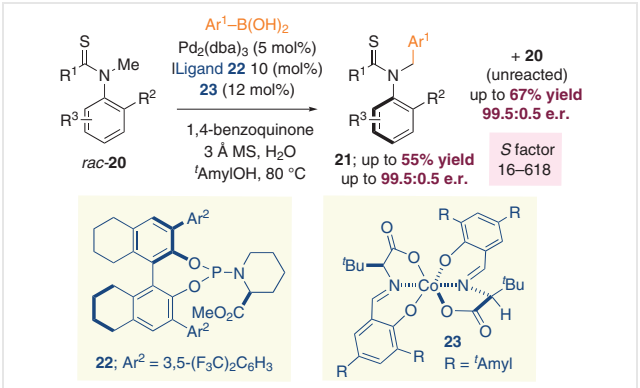
Scheme 4 Kinetic resolution of atropisomeric amides by deprotonation with a chiral base

Clayden and Turner have reported a kinetic resolution approach to access enantioenriched N,N′-diaryl ureas (Scheme 5).[18] Oxidation of racemic *ortho*-substituted thioether precursors *rac*-**17** in the presence of $VO(acac)_2$ modified with (*S*)-*tert*-leucinol-derived ligand **19** afforded sulfoxides **18** with high levels of enantio- and diastereoselectivity (up to 63% conversion). The unreacted starting materials displayed relatively high configurational stability and could be recovered with high enantiopurity (up to 97:3 e.r.), allowing calculation of selectivity (*S*) factors for the process, which ranged from 2 to 300 for different substrates. The method was most effective for oxidation of *ortho*-*tert*-butyl anilides bearing aliphatic thioethers.



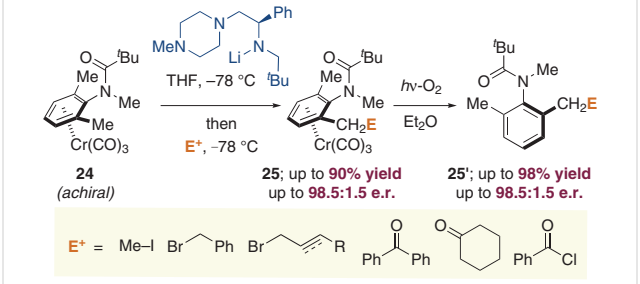
Scheme 5 Kinetic resolution of thioethers by asymmetric S-oxidation

Very recently, Gong and co-workers reported a kinetic resolution for the synthesis of atropisomeric thioanilides based upon Pd-catalyzed sp^3 C–H activation (Scheme 6).[19] This process employed $Pd_2(dba)_3$ in conjunction with phosphoramidite ligand **22** and chiral Co(III) complex **23**, allowing the isolation of C–H arylated products **21** in up to 95.5:0.5 e.r. Unreacted thioanilide **20** isolated from this reaction also proved to be highly enantioenriched, demonstrating the process to be an efficient kinetic resolution (*S* factor up to 618).



Scheme 6 Kinetic resolution of atropisomeric thioamides via Pd-catalyzed sp^3 C–H activation

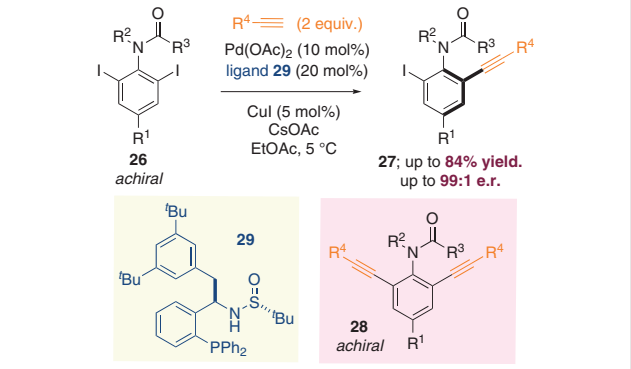
Uemura and co-workers have developed an elegant desymmetrization of prochiral anilide tricarbonyl chromium complexes **24** (Scheme 7).[20] Treatment of these starting materials with a chiral lithium amide base resulted in selective deprotonation of one of the enantiotopic methyl groups to afford a lithiated intermediate which could be quenched with a variety of electrophiles. The resulting axially chiral anilide chromium complexes **25** were obtained in good to excellent yields with high levels of enantioselectivity (up to 98.5:1.5 e.r.). Upon exposure to sunlight in Et_2O the decomplexed anilides **25′** could straightforwardly be accessed with almost no decrease in optical purity.



Scheme 7 Desymmetrization of prochiral arene chromium tricarbonyl complexes by asymmetric deprotonation with a chiral lithium amide base

Very recently, Yang and Zhang reported a desymmetrizing Sonogashira reaction for the synthesis of atropisomeric amides (Scheme 8).[21] In this reaction, prochiral diiodides **26** (possessing a plane of symmetry) were efficiently desymmetrized employing $Pd(OAc)_2$ modified by chiral Ming-Phos ligand **29**. Both diastereoisomers of the ligand were evaluated, and the (*R*,*R*)-epimer was found to be optimal, delivering desymmetrized products **27** in high yields with excellent levels of enantioselectivity (up to 99:1 e.r.). On the basis of control experiments, it was proposed that the enantioselectivity of the initial desymmetrization reaction is

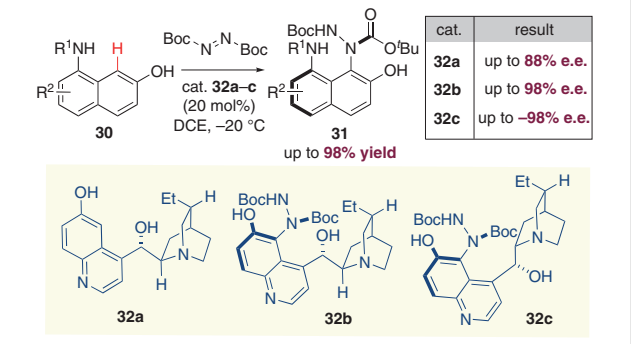
augmented by a subsequent kinetic resolution process, which removes small amounts of the minor enantiomer of **27** through conversion into doubly alkynylated anilide **28**.



Scheme 8 Desymmetrizing Sonogashira coupling for the synthesis of atropisomeric amides

4.2 Electrophilic Amination

Electrophilic amination is an attractive method for the formation of C–N atropisomers. This approach aims to achieve direct stereoselective formation of the key Ar–N bond, and several elegant examples have been developed. For example, Bella, Jørgensen and co-workers reported an efficient method to access axially chiral N,N-disubstituted 1-naphthamides, via a Friedel–Crafts amination (Scheme 9).[22] The reaction of 8-amino-2-naphthols **30** with di-*tert*-butyl azodicarboxylate in the presence of 20 mol% of chiral dihydroquinidine-derived catalyst **32a** afforded the corresponding aminated naphthols **31** in excellent yield and reasonable enantioselectivity (up to 88% e.e.). It was subsequently discovered that the catalyst itself can be aminated (employing more forcing reaction conditions), leading to new catalyst **32b**, which possesses an additional element of axial chirality. This modified catalyst proved even more effective for the atropselective amination of **30**, allowing isolation of products in up to 98% e.e. The other enantiomer of the products could be conveniently accessed with comparable levels of enantioselectivity by employing diastereomeric catalyst **32c**.



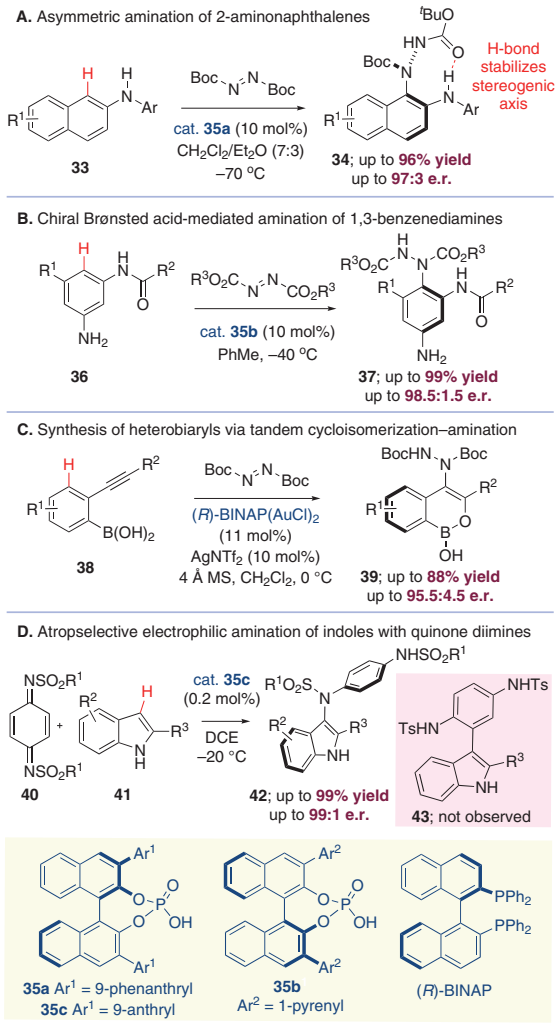
Scheme 9 Catalytic asymmetric amination of 8-amino-2-naphthols

Zhang and co-workers have developed a highly enantioselective C–H amination procedure for the synthesis of naphthylamine-1,2-diamine atropisomers **34** (Scheme 10A).[23] Employing chiral phosphoric acid catalyst **35a**, the aminated products were obtained with excellent yields and high levels of enantioselectivity. It was observed that an aromatic substituent at the 3,3′-positions of the catalyst (e.g., phenanthryl) was essential to achieve high enantioselectivity, and it was proposed that this group is able to form a key π–π interaction with the NAr group in the substrate. The relatively high configurational stability of the products ($t_{1/2}^{rac}$ >10 h) was attributed in part to an intramolecular hydrogen bond between the N–H of the diarylamine and the carbonyl of the terminal Boc group (supported by X-ray crystallographic analysis). Subsequently, Yang and co-workers reported a related chiral phosphoric acid catalyzed amination of 1,3-benzenediamines **36** that proceeded with excellent levels of enantioselectivity (Scheme 10B).[24] The configurational stability of the products depended strongly upon the nature of the *ortho* substituent (R^1), with products bearing a bulky *t*-Bu group at this position undergoing very slow racemization (more rapid racemization was observed with secondary or primary aliphatic groups). A series of control experiments revealed that the *para*-amino substituent is crucial to ensure reactivity in this process.

Zhu, Gong and co-workers have shown that it is also possible to access unique heteroaryl atropisomers **39** via a gold-catalyzed cycloisomerization–amination reaction of 2-alkynyl phenyl boronic acids with di-*tert*-butyl azodicarboxylate (Scheme 10C).[25] This reaction was promoted by a combination of (*R*)-BINAP(AuCl)$_2$ and AgNTf$_2$ and was proposed to occur via a mechanism involving Au-mediated cycloisomerization of **38** followed by amination of the resulting vinyl gold intermediate. The absolute configuration of the unusual heteroarylated products was tentatively assigned by vibrational circular dichroism analysis. Very recently, Liao, Zhong and co-workers reported an atropselective electrophilic amination of indoles **41** using quinone diimines **40** (Scheme 10D).[26] This process was promoted by a remarkably low loading (0.2 mol%) of chiral phosphoric acid **35c**, and afforded a broad scope of atropisomeric 3-aminoindoles **42** in excellent yields and enantioselectivities. Notably, very high regioselectivity was observed for 1,6-addition to the quinone diimines, with no evidence of competing 1,4-addition (e.g., products **43**) observed.

4.3 C–H Functionalization

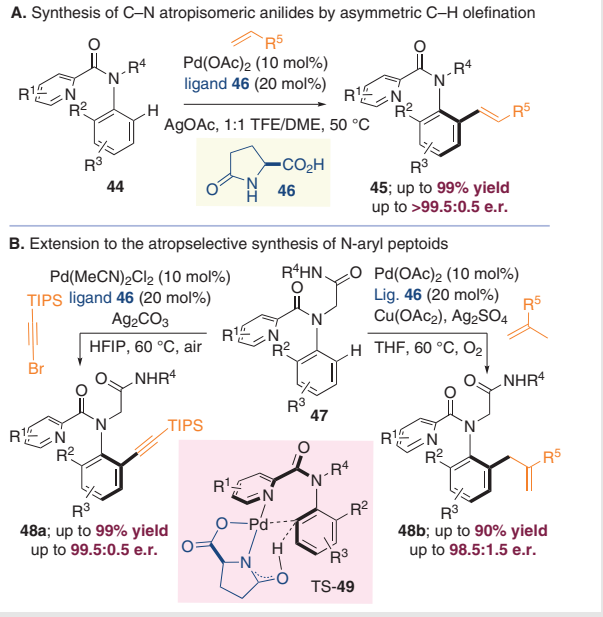
The functionalization of C–H bonds has proved to be a powerful strategy for the asymmetric synthesis of axially chiral amines and amides, and has been applied within both transition-metal catalyzed and organocatalytic reac-



Scheme 10 Formation of C–N atropisomers by asymmetric amination

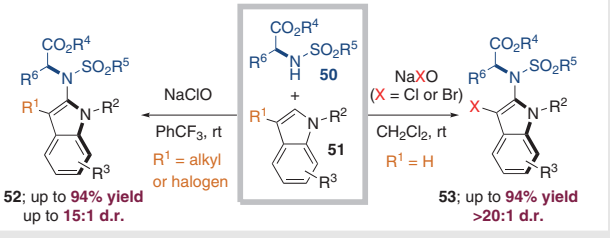
tion manifolds. For example, in 2020, Hong, Shi and co-workers reported an elegant approach in which configurationally unstable anilides **44** bearing a single *ortho*-substituent (R^2) could undergo highly enantioselective Pd-catalyzed C–H olefination to form products **45** displaying robust axial chirality ($\Delta G^{\ddagger}$ up to 33.5 kcal/mol) (Scheme 11A).[27] The optimal ligand for this process proved to be commercially available L-pyroglutamic acid (**46**), and on the basis of a detailed experimental and computational studies it was proposed that the enantiodetermining step involves concerted-metalation deprotonation directed by the picolinamide group via transition state TS-**49**. Subsequently, the Shi group were able to expand upon this approach to develop Pd-catalyzed C–H alkynylation and allylation reactions, targeting atropisomeric N-aryl peptoids **48a** and **48b**, respectively (Scheme 11B).[28]

Recently, Yu and co-workers reported a diastereoselective C2-amination of indoles with protected amino acids to



Scheme 11 Pd-catalyzed atropselective C–H functionalization of pro-atropisomeric picolinamides

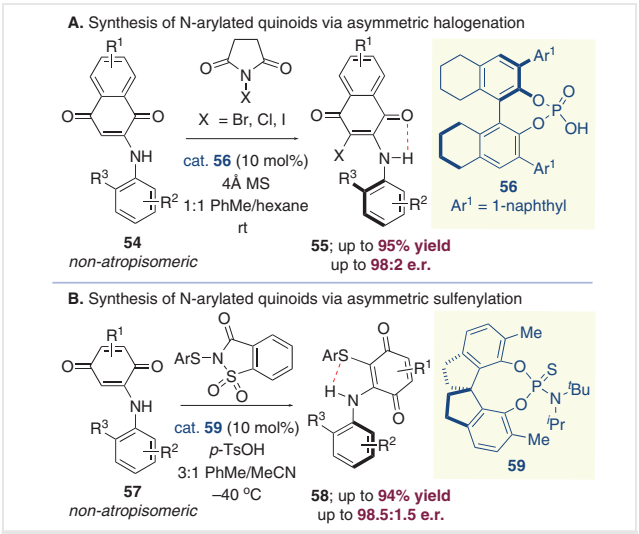
access unusual sulfonamide atropisomers (Scheme 12).[29a] Products **52**, bearing an alkyl or halogen group at the C3-position, were obtained in high yields with up to 15:1 d.r. This process was subsequently expanded to enable haloamidation to directly convert C3-unsubstituted indoles (R^1 = H) to chlorinated and brominated atropisomeric analogues **53**.[29b]



Scheme 12 Atropselective amidation and haloamidation reactions of indoles[29]

Gustafson and co-workers have developed an asymmetric halogenation reaction targeting N-aryl quinoid atropisomers (Scheme 13A).[30] Upon exposure to an electrophilic halogenating agent (NXS; X = Cl, Br or I) along with chiral phosphoric acid catalyst **56**, configurationally unstable precursors **54** could be efficiently converted into enantioenriched products **55** with up to 98:2 e.r. It was proposed that the surprisingly high configurational stability of these products is a result of a strong intramolecular hydrogen bond, which prevents rotation about the N–quinone bond, resulting in a high degree of structural rigidity. Subsequent-

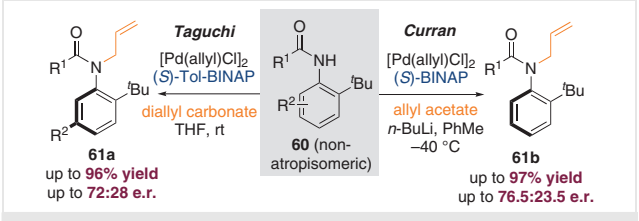
ly, Xue, Chen and co-workers reported that electrophilic sulfenylation can also be achieved in high yields and enantioselectivity employing a novel SPINOL-derived catalyst along with *p*-toluenesulfonic acid (Scheme 13B).[31]



Scheme 13 Asymmetric synthesis of atropisomeric N-aryl aminoquinones

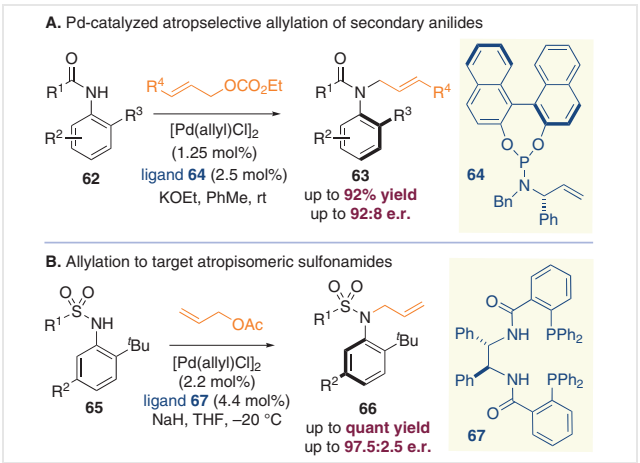
4.4 N-Functionalization

The most widely employed strategy for the synthesis of acyclic C–N atropisomers involves asymmetric N-functionalization of secondary anilides. Due to the small steric influence of the N–H group, these precursors are typically non-atropisomeric, but following N-functionalization configurationally stable products can be obtained. This concept was pioneered by Taguchi and Curran, who independently reported asymmetric syntheses of axially chiral anilides **61** via enantioselective Pd-catalyzed N-allylation (Scheme 14).[32,33] These reactions were mediated by $[Pd(allyl)Cl]_2$ modified by a chiral bisphosphine ligand. Despite relatively low enantioselectivities, this ground-breaking work paved the way for numerous future studies.



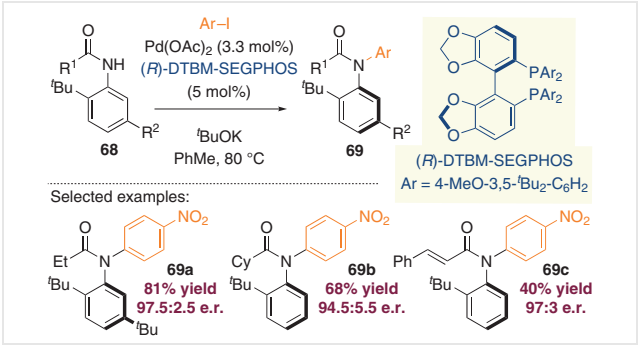
Scheme 14 Asymmetric Pd-catalyzed N-allylation of secondary anilides

Liu, Feng and Du subsequently reported that introducing a chiral P/olefin ligand **64** could overcome the issues of low enantiomeric excess that dominated the early methods for Pd-catalyzed allylation (Scheme 15A).[34] Under these conditions good levels of enantiomeric excess were observed for a variety of allylic carbonates and anilides (up to 92:8 e.r.). In 2019, Kitagawa and co-workers reported a related Pd-catalyzed reaction between secondary sulfonamides and allyl acetate to access atropisomeric products **66** (Scheme 15B).[35] The enantioselectivity of the process displayed a strong dependence upon the nature of the sulfonyl group (R^1), with high levels of enantioselectivity obtained for several examples (up to 97.5:2.5 e.r.). Analysis of the configurational stability of the C–N sulfonamide atropisomeric products was carried out, revealing them to undergo somewhat more facile racemization than the analogous carboxamides (values of $\Delta G^{\ddagger}$ 2–4 kcal/mol lower).



Scheme 15 Asymmetric synthesis of C–N atropisomers via Pd-catalyzed N-allylation

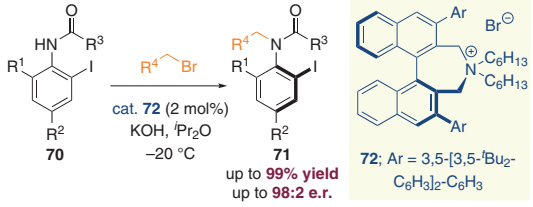
Kitagawa, Taguchi and co-workers have also reported a method for the enantioselective N-arylation of secondary anilides (Scheme 16).[36] After optimization, it was found that a combination of $Pd(OAc)_2$ and (*R*)-DTBM-SEGPHOS could effect Buchwald–Hartwig-type arylation in up to 98:2 e.r. The reaction displayed broad scope with respect to the anilide component, but a notable limitation was that a 4-NO_2 group was required on the aryl iodide to observe reactivity. Although outside the scope of this Short Review, sub-



Scheme 16 Pd-catalyzed asymmetric N-arylation of secondary anilides

sequent elegant work by Taguchi, Gu and others has shown that intramolecular variants of this transformation are possible with tethered aromatic partners.[36,37]

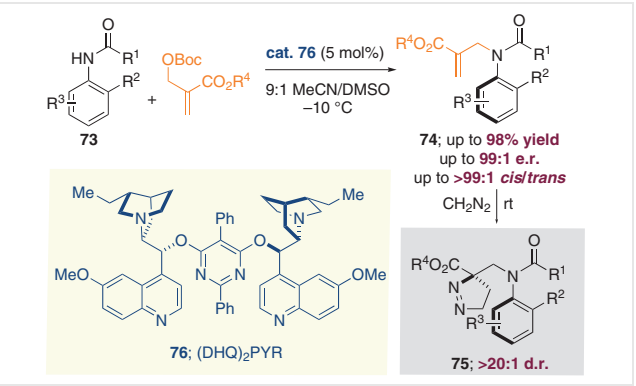
In 2012, Maruoka and co-workers reported an efficient synthesis of axially chiral anilides **71** via a phase-transfer-catalyzed alkylation reaction (Scheme 17).[38] The selectivity in this process was proposed to originate from the tight-ion pair formed between the deprotonated anilide and chiral ammonium cation in a non-polar organic solvent ($^{i}Pr_2O$). This approach produced products with very high levels of enantioselectivity, implying efficient recognition between the two *ortho*-substituents. This was rationalized on the basis of steric differentiation between the bulky iodide and smaller R^1 substituents (a clear trend was observed with the highest levels of enantioselectivity observed for examples with small R^1 substituents, e.g., R^1 = Me). A transition state model was proposed to account for the observed selectivity, with the *ortho*-iodo group of the anilide preferentially oriented away from the bulky C3/3′ aryl groups on the catalyst. In a subsequent publication, the authors were able to expand upon this approach to prepare enantioenriched anilides bearing a single bulky *ortho* substituent.[39]



Scheme 17 Atropselective phase-transfer-catalyzed alkylation of anilides

In 2018, Li and co-workers made use of achiral Morita–Baylis–Hillman (MBH) carbonates to develop an atropselective allylic alkylation reaction to synthesize axially chiral anilides (Scheme 18).[40] In the presence of $(DHQ)_2PYR$ (**76**) as the organocatalyst, a variety of atropisomeric anilides **74** were obtained in high yields, with high levels of enantioselectivity and with a strong preference for the *cis*-amide isomer. The mechanism and origins of selectivity in the reaction were probed by detailed DFT calculations and linear free-energy relationship analysis. Notably, treatment of the N-allylated products with diazomethane resulted in diastereoselective cycloaddition to afford products **75** with no erosion of enantiomeric purity.

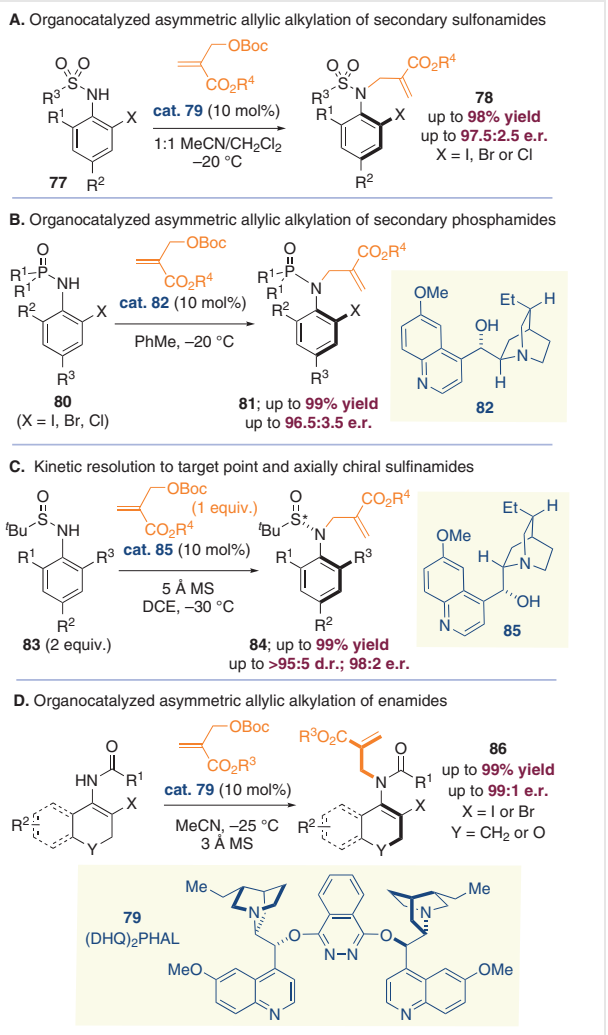
In 2019, Kürti, Zhao and co-workers reported that organocatalytic N-allylation can also be applied to the synthesis of atropisomeric sulfonamides **78** (Scheme 19A).[41] The configurational stability of these products proved to be slightly lower than the analogous carboxamides, with products **78** bearing a single bulky *ortho*-substituent (e.g., R^1 = R^2 = H; X = ^{t}Bu) undergoing relatively rapid racemization at room temperature. However, products possessing two *ortho*-substituents (e.g., R^1 = R^2 = Me; X = I) displayed robust



Scheme 18 Asymmetric allylic alkylation of anilides with Morita–Baylis–Hillman carbonates

configurational stability, and could be isolated with very high levels of enantioselectivity (up to 97.5:2.5 e.r.). Notably, the presence of an *ortho*-halogen substituent (X = I, Br, Cl) proved key in order to obtain efficient stereoinduction. Chen and co-workers subsequently developed a similar approach enabling reactions of allyl and allenyl electrophiles.[42] Li and co-workers have also shown that it is possible to target C–N axially chiral phosphamide products **81** (Scheme 19B).[43] In this case, commercially available hydroquinidine **82** was the optimal catalyst to promote N-allylation, enabling the synthesis of atropisomeric phosphamides **81** in good yields and with enantioselectivities of up to 96.5:3.5 e.r. The reaction could be executed on gram scale, and the utility of the *ortho*-iodinated atropisomeric phosphamide products was exemplified by applying them as chiral hypervalent iodine(III) catalysts for the oxidative spirolactonization of phenol derivatives. Li and co-workers have also employed a similar strategy to target atropisomeric sulfinamides (Scheme 19C).[44] In this case racemic starting materials **83** (point chiral at sulfur) underwent efficient kinetic resolution upon organocatalytic allylation to access atropisomeric sulfinamides **84** with excellent levels of diastereo- and enantioselectivity. Very recently, Li and Zhou reported that a similar strategy can be applied to target atropisomeric enamides **86** (Scheme 19D).[45] The partially saturated products of this reaction displayed comparatively low barriers to racemization ($\Delta G^{‡}$ = 25.9–28.4 kcal/mol), which is likely a reflection of their flexible skeletons leading to a higher degree of rotational freedom. However, ultimately the authors were able to overcome this challenge to access atropisomeric enamides with high yields and excellent levels of enantioselectivity (up to 99:1 e.r.).

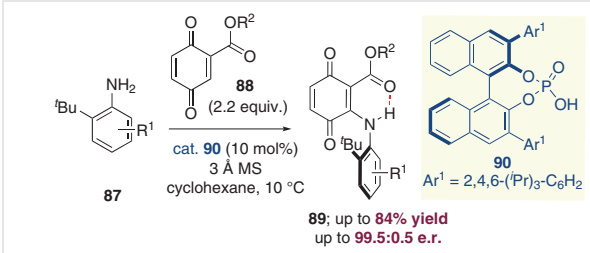
Liu and co-workers have reported an interesting N-functionalization reaction to access N-aryl quinone atropisomers (Scheme 20).[46] In the presence of the commercially available chiral phosphoric acid catalyst (*R*)-TRIP (**90**), primary anilines **87** reacted with quinone esters **88** to afford axially chiral products **89** in high yields and excellent enan-



Scheme 19 Asymmetric allylic alkylation reactions targeting novel atropisomeric scaffolds beyond aromatic carboxamides

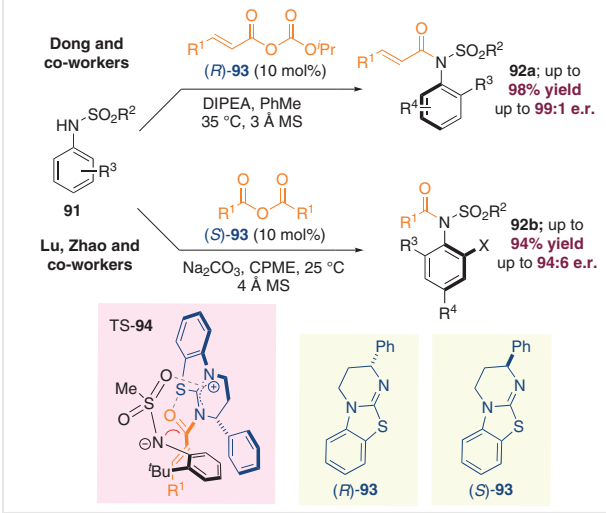
tioselectivities (up to 99.5:0.5 e.r.). The mechanism of this process is believed to proceed via an initial enantioselective conjugate addition reaction of the amine to form a hydroquinone intermediate, which is then oxidized by a second equivalent of quinone ester (present in excess) to generate the corresponding quinone product **89**. The configurational stability of the products was probed by DFT calculations and it was proposed that racemization is disfavored because of a planarizing H-bond between the N–H and the ester carbonyl.

In 2020, two independent reports emerged from Dong and co-workers and Lu, Zhao and co-workers describing the atropselective N-acylation of sulfonamides, catalyzed by a chiral isothiourea (Scheme 21).[47,48] The optimized conditions of these methods were similar, employing opposite enantiomers of the same isothiourea catalyst **93**, along with slightly different bases, solvents and temperatures. The substrate scopes of the two methods were broadly comple-



Scheme 20 Synthesis of N-arylated quinoids by asymmetric N-addition/oxidation

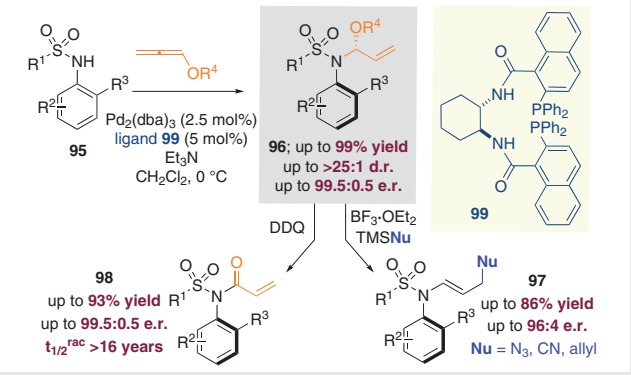
mentary, with Dong's method predominantly focused upon acylated sulfonamides bearing a single bulky *ortho* substituent (e.g., **92a**, where R^3 = ^{t}Bu), and the method developed by Lu, Zhao and co-workers exemplified with a series of doubly *ortho*-substituted targets (e.g., **92b**, where R^3 = Me; X = I/Br). A transition state TS-**94** was proposed by Dong whereby the deprotonated sulfonamide attacks the acylisothiouronium intermediate on the opposite face to the phenyl group, with the *ortho*-*tert*-butyl group oriented away from the catalyst to avoid an unfavorable interaction with the Ph group.[47] An interaction between the oxygen of the sulfonyl group and the positively charged thiouronium moiety was also suggested to play a key role in this transition state.



Scheme 21 Asymmetric isothiourea catalyzed N-acylation of sulfonamides

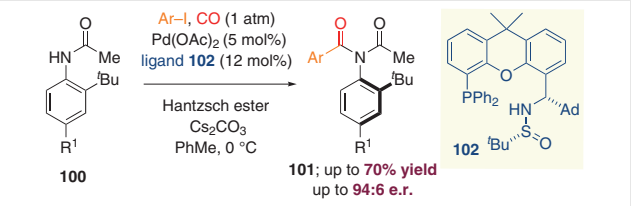
In 2021, Zhou, Zhang, Jiang and co-workers disclosed an efficient atropselective hydroamination of allenes for the synthesis of axially chiral sulfonamides (Scheme 22).[12] High enantioselectivity and diastereoselectivity were obtained using $Pd_2(dba)_3$ modified by C_2-symmetrical diaminocyclohexyl ligand **99**. Excellent selectivity for the branched isomer was observed, in preference over the linear isomer (B/L >25:1), and high enantioselectivities (up to 99.5:0.5 e.r.)

were obtained. The resulting N,O-acetals **96** could be oxidized with DDQ to yield atropisomeric N-sulfonyl anilides **98**, which were shown to exhibit remarkably high configurational stability ($\Delta G^{\ddagger}$ >35.0 kcal/mol). Treatment of the N,O-acetals with $BF_3{\cdot}OEt_2$ and silylated nucleophiles led to the formation of γ-addition products **97** with good to excellent levels of enantiospecificity.



Scheme 22 Atropselective Pd-catalyzed hydroamination of allenes

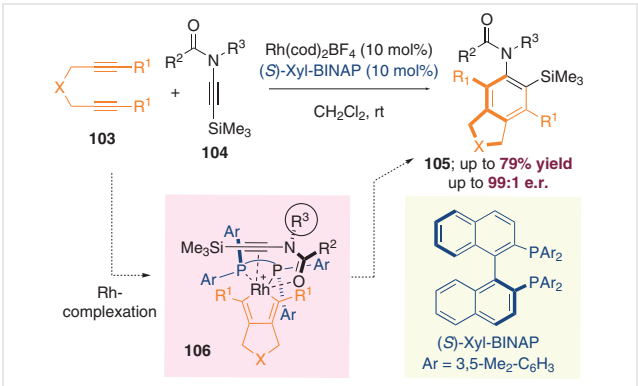
The palladium-catalyzed carbonylation of aryl iodides with amides has been reported by Teng, Sun, Li and co-workers (Scheme 23).[49] The predominant focus of this work was upon carbonylative cyclization to access heterocyclic atropisomers (outside the scope of this Short Review), but several intermolecular reactions between anilides, aryl iodides and CO were also reported. This enabled the synthesis of unusual doubly acylated anilide atropisomers **101** in good to excellent yields and with enantioselectivities of up to 94:6 e.r. Interestingly, the intermolecular process required the addition of Hantzsch ester, which may increase the yield by prolonging the lifetime of the catalyst.



Scheme 23 Asymmetric carbonylative coupling reactions to access doubly acylated anilide atropisomers

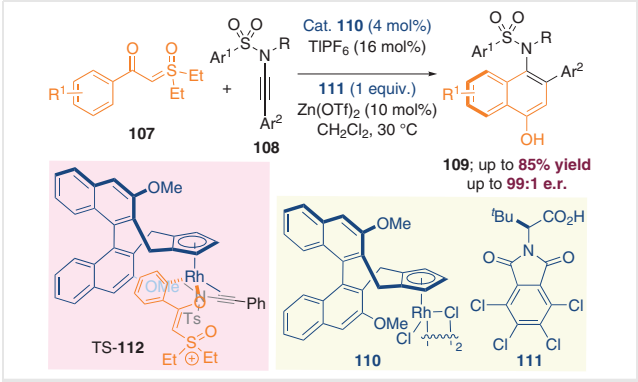
4.5 Annulation

Accessing axially chiral scaffolds by strategic formation of an aromatic ring is a powerful strategy that has been widely employed for the synthesis of biaryl and heterobiaryl atropisomers.[50] There have also been several elegant reports applying this strategy to the synthesis of atropisomeric amides. For example, in 2006, Tanaka and co-workers reported a pioneering Rh-catalyzed [2+2+2] cycloaddition reaction between 1,6-diynes **103** and ynamides **104** to afford bicyclic amides **105** (Scheme 24).[51] The reaction proceeded with moderate to good yields, and excellent levels of enantioselectivity were observed. It was proposed that the key step involved selective formation of Rh-complex **106**, in which the R^3 substituent is oriented away from the bulky PAr_2 groups of the ligand. A final reductive elimination then delivered atropisomeric products **105**.



Scheme 24 Rh-catalyzed atropselective [2+2+2] cycloaddition between 1,6-diynes and ynamides

Very recently, Wang, Li and co-workers reported that sulfoxonium salts **107** can also serve as efficient precursors for Rh-catalyzed annulation with ynamides **108** (Scheme 25).[52] The process was mediated by Cramer's second generation Rh(III)-Cp catalyst **110**, along with chiral acid **111**, catalytic $Zn(OTf)_2$ and $TlPF_6$ as a halide scavenger. Under these conditions, atropisomeric sulfonamides **109** were obtained in high yields and excellent levels of enantioselectivity. The transition state TS-**112** was proposed that accounts for the regio- and enantioselectivity observed within the process, which involves simultaneous activation of both the ynamide and sulfoxonium ylide.



Scheme 25 Synthesis of chiral anilides via atropselective annulation

5 Conclusions and Outlook

The asymmetric synthesis of atropisomers is currently an area that is undergoing a phase of rapid expansion. The synthesis of C–N atropisomeric amines and amides, where the nitrogen atom is not part of a ring system, is often particularly challenging because the increased conformational flexibility of such molecules can lead to reduced configurational stability. Nevertheless, recent years have seen huge advances in methods for the synthesis of C–$N_{acyclic}$ atropisomeric molecules, allowing access to a wide variety of scaffolds, including carboxamides, thioamides, ureas, sulfonamides, sulfinamides, phosphamides and diarylamines, displaying robust atropisomerism. The aim of this Short Review has been to summarize the synthetic methods that are currently available for the construction of such motifs. A wide variety of synthetic methods are covered, ranging from traditional chiral-pool approaches to modern catalytic asymmetric strategies. Given the increasing awareness of the importance of atropisomerism in pharmaceuticals and drug discovery, it is anticipated that future years will bring many further advances in the synthesis and applications of these materials.

Conflict of Interest

The authors declare no conflict of interest.

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