

Towards Atropoenantiopure N–C Axially Chiral Compounds *via* Stereoselective C–N Bond Formation

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Abstract: N–C axial chirality, although disregarded for decades, is an interesting type of chirality with appealing applications in medicinal chemistry and agrochemistry. However, atroposelective synthesis of optically pure compounds is extremely challenging and only a limited number of synthetic routes have been designed. In particular, asymmetric *N*-arylation reactions allowing atroposelective N–C bond forming events remain scarce, although great advances have been achieved recently. In this minireview we summarize the synthetic approaches towards synthesis of N–C axially chiral compounds *via* stereocontrolled N–C bond forming events. Both organo-catalyzed and metal-catalyzed transformations are described, thus illustrating the diversity and specificity of both strategies.

Keywords: Asymmetric synthesis · Axial chirality · Hypervalent iodine · C–N axial chirality · N–C atropisomerism · N–C axial chirality



In 2016, **Johanna Frey** received her engineering degree from the Ecole Nationale Supérieure de Chimie de Paris and her master degree from the University Pierre et Marie Curie in Paris. She then started her PhD at the University of Strasbourg, working on copper-catalyzed atroposelective C–N coupling using hypervalent iodine, under the direction of Prof. Françoise Colobert and the supervision of Dr. Joanna Wencel-Delord and Dr. Sabine Choppin, which she defended in 2020. She is currently doing a post-doctoral degree in Prof. Ackermann's group at the University of Göttingen.



Sabine Choppin studied chemistry at the University Henri Poincaré in Nancy. From 1998 to 2001, she undertook her PhD studies under the supervision of Pr. Yves Fort and Dr. P. Gros, focusing on the development of new metallated superbases applied to the metallation of chloropyridines and different sulfur derivatives. Then she moved to Louvain La Neuve, Belgium in the group of Prof. Olivier Riant, and was initiated to the field of asymmetric copper catalysis and in particular the enantioselective hydrosilylation of aromatic ketones. In 2002, she became assistant professor at the engineering school, Ecole Européenne de Chimie, Polymères et Matériaux ECPM, a component of the University of Strasbourg. For her research activities, she joined the group of Prof. Françoise Colobert. Her main research interests include the development of new asymmetric methodologies for the control of axial C–C or N–C chirality, but also central chirality with the preparation of quaternary centers. These methodologies are applied to the synthesis of biologically active compounds such as strained cyclophanes or sesquiterpenes.



Françoise Colobert received a PhD in organic chemistry in 1985 from the University Pierre et Marie Curie (Paris) working with Prof. Jean-Pierre Genêt in the field of asymmetric catalysis. After a post-doctoral stay in the group of Prof. Jules Hoffman (Nobel Prize, Strasbourg) in molecular biology, she became an assistant professor in the group of Prof. Guy Solladié and was appointed full professor of organic chemistry in 2001 at the University of Strasbourg. Her current research interests are oriented towards transition metal-catalyzed asymmetric C–H functionalization, the access of axially chiral molecules, the use of chiral hypervalent iodine in copper catalysis and the synthesis of biologically active molecules.



Joanna Wencel-Delord was educated in chemistry at the Ecole Nationale Supérieure de Chimie de Rennes, France and she received her PhD in 2010 from the University of Rennes 1, France (Dr. C. Crévisy and Dr. M. Mauduit). After postdoctoral studies with Prof. F. Glorius at the Westfälische Wilhelms-Universität Münster (Germany) and a temporary assistant professor position (ATER) at the University of Strasbourg (Prof. P. Compain), she joined CNRS (The French National Centre for Scientific Research) in 2013 as an associate researcher in the group of Prof. F. Colobert (University of Strasbourg, France). Her research focuses on the transition metal-catalyzed asymmetric C–H activation and synthesis of axially chiral compounds, including N–C atropisomeric molecules. Her recent awards and distinctions include an Emerging Investigator Prize of the Organic Chemistry Division, French Chemical Society (2018), Bronze Medal of CNRS (2020), and ERC SG (2020).

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1. Introduction

Chirality is an intriguing feature of nature and many natural, biologically active compounds are chiral. Indeed, the unique three-dimensional structure of chiral compounds frequently accounts for specific interactions with active sites of enzymes, allowing highly selective therapeutic actions.^[1] Such three-dimensionality may arise from the presence not only of chiral stereocenters but also of atropisomerism, corresponding to restricted rotation about an axis.^[2] Indeed, an analysis of 1900 small-molecule drugs in the USD FDA Drug Bank (FDA: Food and Drug Administration) reveals that approximately 15% of FDA-approved scaffolds contain one or more atropisomeric axis and an additional 10% of molecules are 'proatropisomeric'. Even more markedly, the prevalence of atropisomeric compounds has been expanding drastically since 2011 and over the last years almost one in three FDA approved small molecules contains an atropisomeric element and an additional 16% are proatropisomeric.

Currently, atropisomerism generally concerns the C–C bond and is the most frequently present in the case of biaryl and heterobiaryl compounds.^[3] In contrast, the atropisomerism arising from a restricted rotation around an N–C bond is clearly underdeveloped.^[4–6] This type of chirality has been disregarded for decades, arguably due to the low atropostability of such compounds. However, recently this field has been witnessing a real resurgence and over the last few years, N–C atropisomeric compounds have emerged as a privileged class of biologically active compounds (Fig. 1), featuring unique kinase inhibitor activity and uricemic acid regulation potency, as illustrated by the synthesis of compounds such as (*S*_a)-**1**: PI4KIII inhibitor, PH-797804 (**2**): p38 kinase inhibitor or GlyT1 inhibitor **3**.^[7]

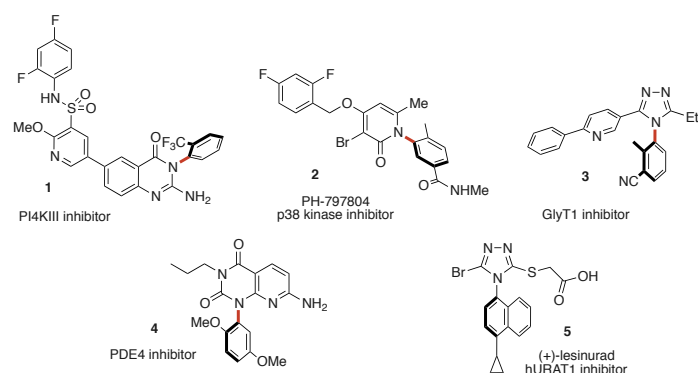


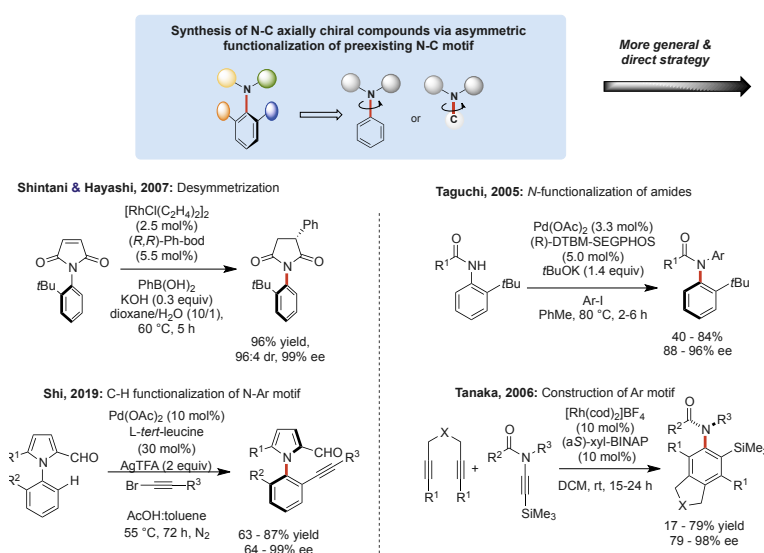
Fig. 1. Examples of N–C axially chiral compounds.

While the synthesis of biaryls has been attracting considerable attention in the scientific community for more than two decades, resulting in the development of a multitude of synthetic routes to construct such compounds, the synthesis of N–C axially chiral molecules has remained for a long time a niche topic (Scheme 1). Several strategies have been imagined, mainly involving stereoselective transformations and functionalizations of molecular scaffolds already containing a N–C motif, including a) desymmetrization reactions,^[8] b) *N*-functionalization of anilide derivatives,^[9] c) C–H functionalization of *N*-arylated pyrrole derivatives^[10] and d) construction of aromatic rings from amine precursors *via* cycloaddition reactions.^[11] In spite of the innovative character of these transformations, they are rather limited to one type of product and frequently imply functionalization of proatropisomeric compounds. In clear contrast, the construction of such original chiral molecules *via* direct arylation of *N*-precursors, although the most direct and potentially general strategy, remains extremely challenging and has attracted growing attention very recently. This mini-review summarizes the different synthetic approaches towards atroposelective N–C bond formation delivering the N–Ar atropisomeric compounds.^[12]

2. Metal-free Atroposelective N–C Coupling

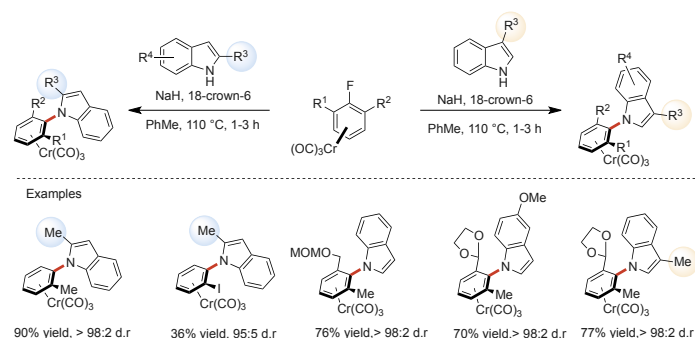
2.1 Diastereoselective Couplings

Although the early reports on N–C atropisomeric compounds and their asymmetric synthesis were published at the beginning of this century, late 2005 was clearly marked by designing two pioneering strategies delivering such molecules *via* asymmetric N–C bond formation. Kamikawa and Uemura reported for the first time the synthesis of N–C atropisomeric indoles, constructed *via* stereoselective nucleophilic aromatic substitution.^[13] The authors hypothesized that, using planar chiral arene chromium complexes as optically active activated arenes, aromatic nucleophilic substitution with *N*-unprotected indoles should be possible and chiral induction might be expected, thus delivering diastereomeric N–C chiral compounds (Scheme 2). Rewardingly, *ortho*-substituted fluorinated tricarbonyl arene chromium complexes reacted smoothly with indolyl anions (generated *in situ* from indole and NaH), delivering the expected coupling product as a single diastereomer. Remarkably, the atropostability of the newly prepared compounds was not compromised even under a high reaction temperature of 110 °C. The reaction tolerates different substituents on both coupling partners, including ether, iodo, alkyl, aryl and TES groups, delivering the expected products in high yields and excellent diastereoselectivities. Interestingly, the stereochemistry



Scheme 1. Various approaches towards synthesis of the N–C axially chiral compounds.

of the products is clearly controlled by the substitution pattern of the indoles; the coupling of C2-unsubstituted indoles delivers anti-product with respect to the benzene ring of the indole and the chromium tricarbonyl group. In clear contrast, the presence of substituents such as Me, TES and Ph group in C2 position of indole results in the construction of the inverse product, wherein the benzene ring of the indole is directed towards the chromium tricarbonyl group. Importantly, the oxidative demetalation of the newly accessed axially chiral compounds is feasible, delivering the optically active compound in high yield. Further derivatisation of the products *via* tricarbonylchromium migration and post-functionalization using lithium bases followed by electrophilic trapping were also achieved.



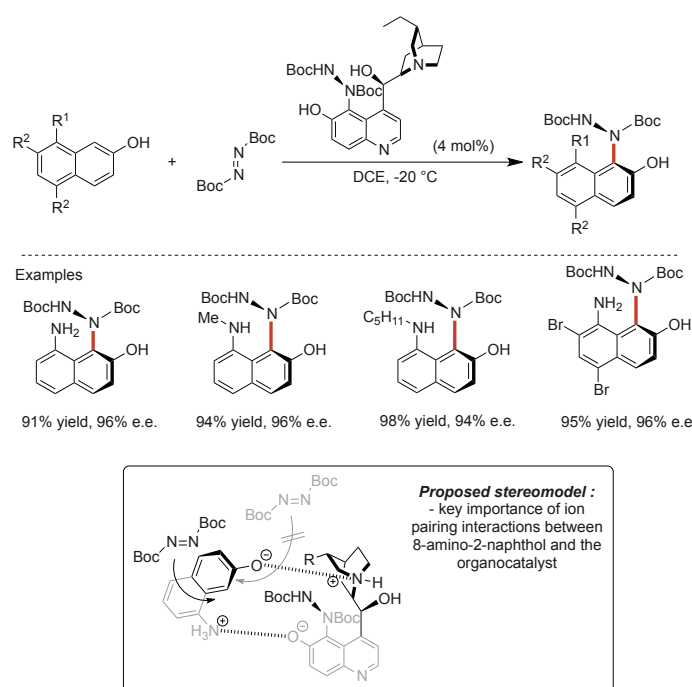
Scheme 2. Diastereoselective aromatic nucleophilic substitution.

2.2 Enantioselective Couplings

Simultaneously, Bella and Jørgensen reported a very different strategy employing an enantioselective organocatalyzed Friedel-Crafts amination.^[14] Inspired by early work from Diels and Back,^[15] they hypothesized that upon deprotonation, hydroxynaphthalene should be sufficiently active to react with azodicarboxylates, thus allowing the generation of Ar–N bonds. The use of chiral tertiary amine as a catalyst offers, therefore, a unique opportunity to induce chiral information during such a reaction, furnishing the atropisomerically enriched 2-naphtholes. As expected, cinchonine-type molecules turned out to be promising chiral organocatalysts for such a reaction. The initial studies showed that despite the high reactivity of the 2-naphthol substrate, a configurationally unstable product was generated (Scheme 3). The introduction of an additional NH₂-substituent at the 8-position was the solution of choice to ensure the atropostability of the products, hence permitting highly enantioselective transformation. Interestingly, it was found that the cinchonine scaffold is also a suitable substrate for this electrophilic aromatic substitution and is thus functionalized *in situ*.^[16] Accordingly, the aminated cinchonine catalyst turned out to be the optimal promoter of the overall transformation, fostering generation of the desired N–C axially chiral amino-naphthols in excellent yields (generally above 90%) and up to 98% ee. Several different chemical transformations, including orthogonal deprotections and conversion of the product into novel axially chiral ureas, further illustrate the potential of this transformation.

From a mechanistic viewpoint, both organocatalyst and 8-amino-2-naphthol are expected to exist as zwitterionic species in solution, thus generating a two-point-contact ion pair. Such ion pairing results in the shielding of one face of 8-amino-2-naphthol, hence guiding the approach of azodicarboxylate from the other face. The crucial importance of the NH₂-motif in the 8-position supports the key role of ionic interactions in this organocatalytic transformation.

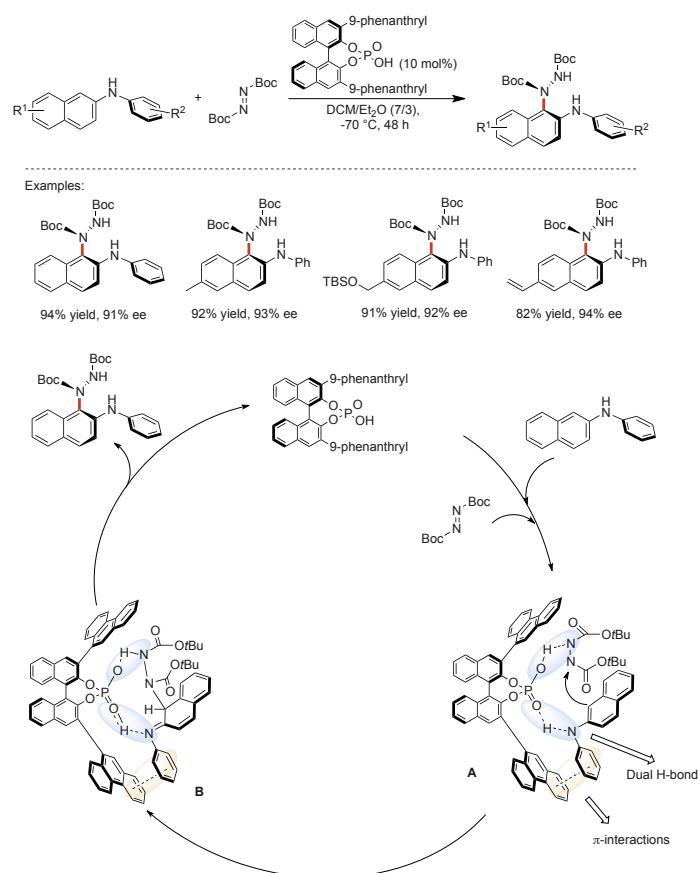
This seminal work has recently inspired new developments in the field of N–C atropisomers. In 2019 Zhang astutely obviated the limitation of this strategy, *i.e.* the presence of an NH₂



Scheme 3. Enantioselective organocatalytic Friedel-Crafts-type amination

group at C8-position (Scheme 4).^[17] The authors surmised that a well-organized intermediate may be achieved while using a finely designed chiral phosphoric acid (CPA) catalyst, able not only to generate hydrogen bonding but also to induce concerted control *via* π -interactions. Both azodicarboxylate and *N*-aryl substituted 2-naphthylamine substrates should be activated by CPA *via* hydrogen bonding while a secondary π -interaction between an aryl substituent of the naphthylamine and a side substituent of the CPA should stabilize the key intermediate, thus avoiding rotation (favored due to the lack of a substituent at the C8 position). Confirming this working hypothesis, the amination of 2-naphthylamine with azodicarboxylate occurred smoothly and in a highly selective manner while using a 9-phenanthryl-substituted CPA acid. A diverse variety of N–C axially chiral compounds was afforded in very high yields and generally excellent enantioselectivities. The reaction tolerated well various substituents on the naphthyl ring. Not surprisingly, decreased steric hindrance of the azodicarboxylate coupling partner resulted in a significant drop in the optical purity and atropostability of the products. The chiral induction is also strongly impacted by the substitution pattern of the aromatic *N*-substituent, due to the modification of the π -interactions. From a mechanistic viewpoint, simultaneous activation of both coupling partners by CPA allows the generation of intermediate A. Subsequent stabilization of A *via* π -interactions allows concerted stereocontrol during the nucleophilic addition of the *N*-phenyl-2-naphthylamine to the azodicarboxylate, delivering intermediate B. Final rearomatization with central-to-axial chirality transfer provides the expected product.

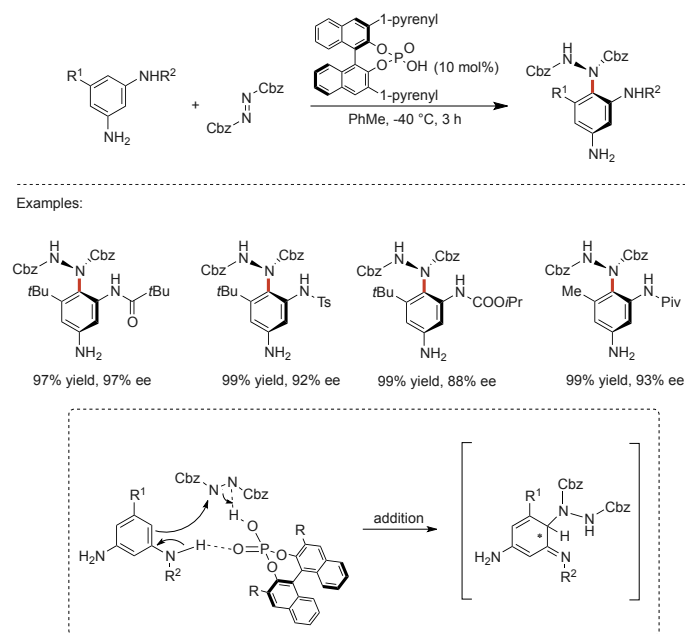
A few months later, the group of Yang further expanded this reactivity by developing an organocatalyzed atroposelective amination of 1,3-benzenediamines (Scheme 5).^[18] When using benzenediamine substrates, together with azodicarboxylate partner and CPA catalyst, dual H-bonding activation was operating, thus promoting highly enantioselective Friedel-Craft amination. This reaction tolerates well a variety of aromatic substrates, bearing either *N*-acyl, *N*-alkoxycarbonyl, *N*-Ts or *N*-Ph substituents at C1 position. The presence of an additional NH₂-substituent at the C3 position is required to increase the electron-richness of the substrate and ensure sufficient nucleophilicity at the *para*-position, while an alkyl substituent at C5 position is necessary



Scheme 4. Atropoenantioselective amination of naphthylamines.

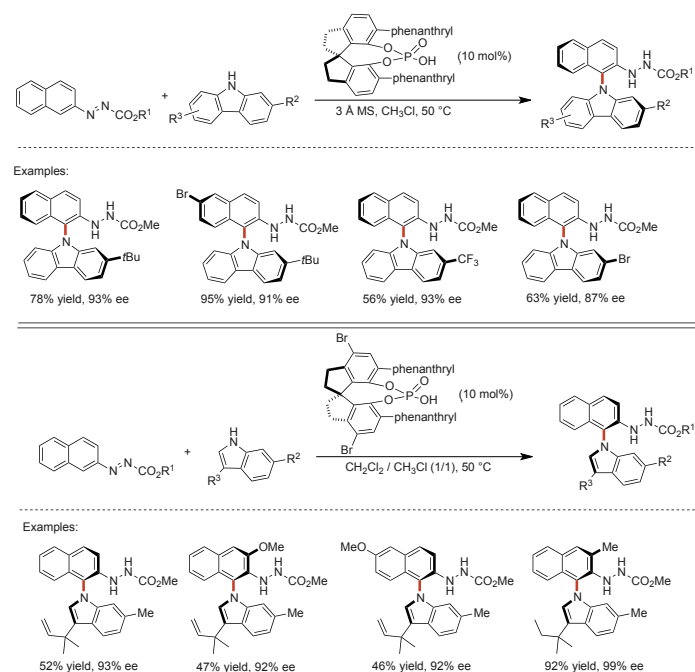
to guarantee the atropostability of the newly generated products. The products are isolated in good to excellent optical purity and are generally atropostable, even at higher temperatures over several days.

Very recently, the portfolio of organocatalyzed reactions furnishing N–C axially chiral compounds has been complemented with an elegant synthesis of atropisomeric *N*-arylcabazoles *via* direct dehydrogenative coupling between azonaphthalenes and unsymmetrical cabazoles (Scheme 6).^[19] The successful out-



Scheme 5. Atropoenantioselective amination of 1,3-benzenediamines.

come of this transformation is based on the observation that azo groups serve for aryl ring activation,^[20] thus rendering the reaction with an amino-coupling partner feasible. To validate this hypothesis, a catalytic system using a CPA as the organocatalyst has been designed to promote the formation of unique atropisomeric *N*-arylcabazoles. Optimal results were obtained using a spirocyclic CPA catalyst, thus delivering the axially chiral products in remarkably high enantiopurities. Various functional groups are tolerated, including alkyl, halogen and aromatic units, delivering the desired chiral *N*-arylcabazoles. While using 2,6-diazonaphthalene substrate, double C–H amination takes place, furnishing original chiral 1,5-dicabazole naphthalene derivatives, appealing scaffolds for potential OLED materials. Of note is that this reactivity could be further extended towards indoles. As in the previous studies, the CPA plays the role of the double H-bonding catalyst, activating both the aromatic substrates and the diazo-carboxylate coupling partner. A plausible stereochemical model features H-bonding-controlled generation of well-organized intermediates, followed by a rearomatization step inducing central-to-axial chirality transfer.

Scheme 6. Atropoenantioselective synthesis of *N*-arylcabazoles and *N*-arylindoles.

3. Metal-catalyzed Atroposelective N–C Coupling

Metal-catalyzed protocols, such as Buchwald-Hartwig or Ullmann couplings, are amongst the most powerful and widely applied strategies to construct N–C linkages.^[21] However, despite general applications of such reactions in both academia and industry, asymmetric versions of these cross-coupling reactions delivering N–C atropisomeric compounds have remained unprecedented until recently. The challenging character of these reactions relies on the clear conflict between the reaction conditions required to promote coupling between two highly sterically congested partners and the atropostability of the newly generated compounds. Indeed very high reaction temperatures are generally needed to render effective Pd- or Cu-catalyzed *N*-arylations of hindered substrates, while the rotational barrier of the newly generated compound might be not high enough to prevent *in situ* racemization. Accordingly, innovative solutions are needed to overcome this fundamental issue and establish a general method for the metal-catalyzed N–C coupling.

3.1 Atropo-diastereoselective C–H Activation

In order to propose an innovative approach to solve the above-mentioned conflict and to promote the coupling between sterically demanding coupling partners under mild reaction conditions, we hypothesize that increased reactivity in the metal-catalyzed cross-coupling might be expected using a hypervalent iodine species as the arylating agent,^[22] instead of the commonly used aryl iodides. Indeed, when considering the strong electrophilicity of such iodanes, the insertion of the Cu-catalyst into the C–I bond is thermodynamically favored, thus opening the door to mild transformations. Following this analysis, we surmised that the first Cu-catalyzed atroposelective N–C coupling might be possible using a hypervalent iodine species as the arylating agent.^[23] In addition, the introduction of a chiral auxiliary on the hypervalent iodine, in proximity to the reactive site, should induce coordination of the metal catalyst, thus imposing stereoselectivity in this N–C bond-forming reaction.

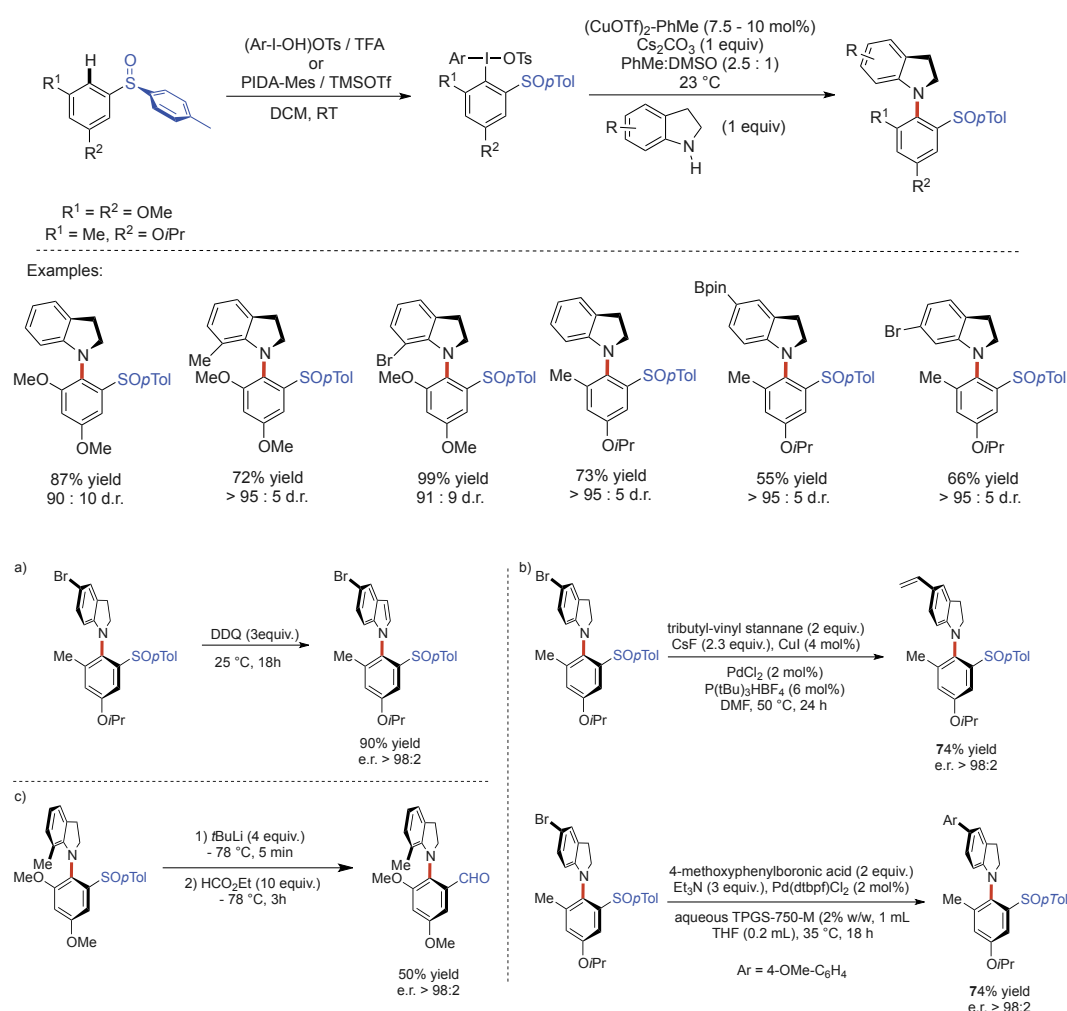
Following this hypothesis, and based on our interest in the use of the sulfoxide motif in asymmetric reactions,^[24] we have designed enantiopure hypervalent iodine reagents bearing an enantiopure sulfoxide motif, as the test substrate. Rewardingly, coupling with indolines occurred smoothly using Cs₂CO₃ base, and the desired product was isolated in 90:10 diastereomeric ratio (Scheme 7).^[25] However, due to the limited atropostability of this compound (rotational barrier of 24.8 kcal/mol), the optical purity of the product decreases slowly even at room temperature. Introduction of a Me-substituent at 7-position of the indolines allowed a significant increase of the rotational barrier (up to 27.4 kcal/mol) and thus atropoenriched product was obtained in >95:5 dr. This first metal-catalyzed atroposelective N–C coupling is efficient using various indolines, bearing valuable substituents such

as Br, Cl, and Bpin for example, delivering highly optically enriched compounds. When considering the iodane coupling partners, the reaction is limited by their accessibility, as only iodanes bearing electron-rich substituents were successfully synthesized. The synthetic value of this reaction was further illustrated by the post-modifications of the newly accessed scaffolds (Scheme 8). Remarkably, the chiral sulfoxide auxiliary may be readily removed in the presence of lithium bases, and subsequent electrophilic trapping allows the introduction of various motifs with no loss of optical purity.

From a mechanistic viewpoint, this asymmetric Ullmann-type reaction is believed to occur *via* initial coordination of Cu with indolines, followed by rapid oxidative addition, clearly facilitated by the hypervalent character of the iodine (Scheme 9). In this key step, π -interactions between the aromatic ring of the indolines and the *p*-Tol substituent of the sulfoxide are expected to control the spatial arrangement around the Cu-catalyst, thus enhancing the highly stereoselective N–C bond formation event.

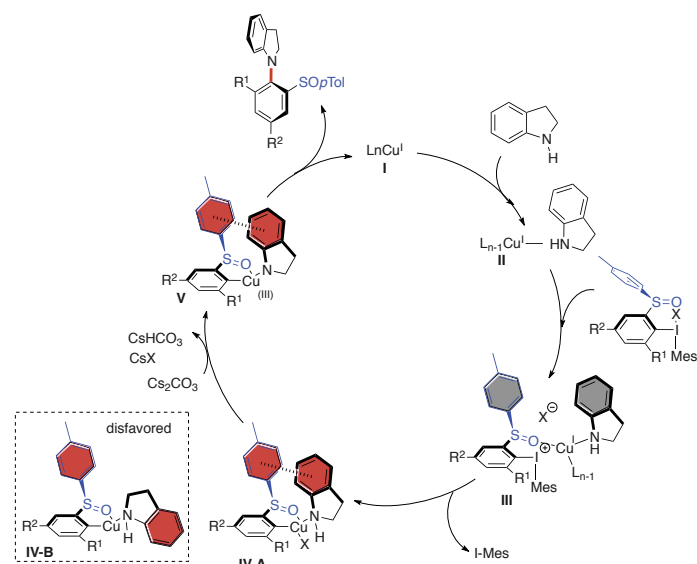
3.2 Atropo-enantioselective C–H Activation

Despite the potential of this Cu-catalyzed diastereoselective Ullman-type N–C coupling, challenging and poorly general synthesis of hypervalent iodines bearing the enantiopure sulfoxide motif has hampered its general application. Accordingly, our efforts have focused on designing an enantioselective version of this reaction. We hypothesized that simple diaryliodanes could be used as potent coupling partners in combination with a chiral Cu-catalyst (Scheme 10).^[26] Drawing inspiration from the recent examples of asymmetric Cu-catalyzed reactions using iodanes as the coupling partners, enantiopure bisoxazoline ligands emerged as ligands of choice. In parallel, the sulfoxide motif on the hyper-



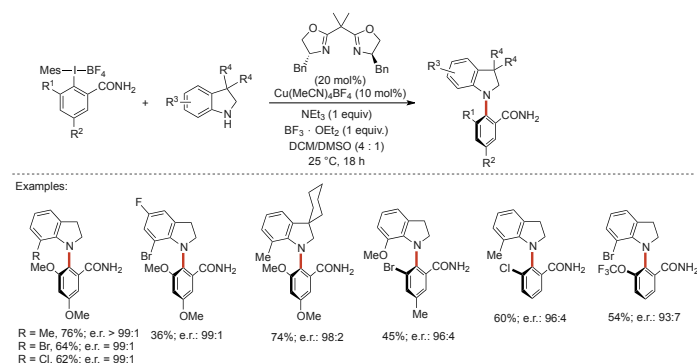
Scheme 7. Atropodiastereoselective N–C coupling with chiral iodanes.

Scheme 8. Post-modifications of the sulfoxide-substituted N–C axially chiral compounds.



Scheme 9. Proposed mechanism.

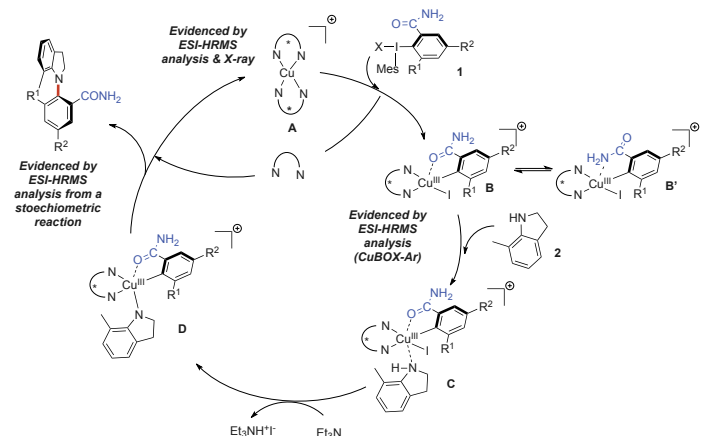
valent iodine should be replaced by an alternative, achiral coordinating motif, thus ensuring coordination with the Cu catalyst and facilitating the selective arylation process. Several different unsymmetrical diaryl iodanes, bearing various coordinating groups *ortho*- to the I-atom have been synthesized and evaluated in this reaction. While iodanes bearing carboxylic acid, ester, or sulfonyl groups failed to undergo this N–C coupling, promising preliminary results were obtained using CONH₂-substituted iodane.^[27] Extensive optimization encompassing ligand, solvent, base, Cu-source selection, and temperature screening revealed that this challenging transformation may be conducted with excellent enantioselectivity (up to 98%) but the desired product was generally isolated in moderate yield not exceeding 50%. Significant improvement was thus accomplished while adding a Lewis acidic additive and the optimal yield of 74% was reached in the presence of BF₃·OEt₂. Such additives are believed to facilitate the release of the N–C coupling product from the Cu catalyst, thus ensuring more efficient catalytic turnover and limiting catalyst poisoning by the product.



Scheme 10. Atropoenantioselective N–C coupling between iodanes and indolines.

Under the optimized reaction conditions, the desired reaction shows great generality regarding both the indoline coupling partner and the arylating agent (Scheme 10). As the synthesis of iodanes is now clearly simplified, various motifs are tolerated on the aromatic ring, including electron-donating and electron-withdrawing groups. Besides, a large panel of indolines, substituted at different positions by Br, Cl, F, OMe, alkyl groups *etc.* react smoothly, delivering the N–C axially chiral compounds in good to excellent

enantiopurities. Interestingly, this transformation is characterized by very strong non-linear amplification as the desired product may be accessed in 90% ee using poorly enantioenriched chiral ligands. The kinetics of this reaction shows an extremely rapid initial rate (yield of >50% achieved within the first 5 min). When considering the mechanism of this reaction, it might be suggested that the overall reaction is promoted at room temperature due to the facile oxidative addition step between the hypervalent iodine and the Cu catalyst (Scheme 11). After the initial generation of the catalytically active Cu species, oxidative addition and subsequent amine coordination result in the formation of the key intermediate species. Base-assisted amine deprotonation and final reductive elimination release the N–C atropisomeric compound together with the Cu(I) species, thus completing the catalytic cycle.



Scheme 11. Mechanism of atropoenantioselective N-arylation.

4. Conclusions

N–C atropisomeric compounds are clearly an emerging class of chiral molecules, with appealing applications in medicinal chemistry and agrochemistry. However, this field suffers from limited synthetic tools providing access to such compounds. In particular, the generation of N–C atropisomeric compounds *via* the atroposelective N-arylation has been neglected over the last decade. Very recently, great advances have been achieved in this field, employing both organo- and metallocatalytic approaches. Chiral phosphoric acids have established themselves as organocatalysts of choice, promoting highly stereoselective coupling between activated arenes and diazo-derivatives, due to the double H-bonding activation. In parallel, while regarding metal-catalyzed transformation, the key difficulty in developing atroposelective Buchwald-Hartwig or Ullmann reaction corresponds to the low reactivity of highly congested coupling partners and thus the need for a high reaction temperature to conduct such reactions. The atropostability of the newly generated N–C atropisomeric compounds might be compromised under such harsh reaction conditions. Remarkably, the use of hypervalent iodines as extremely reactive coupling partners turned out to be the solution of choice, allowing yet unprecedented Ullmann-couplings at room temperature. Both diastereo- and enantioselective N-arylations are now feasible, delivering a variety of axially chiral compounds in excellent optical purity.

The following years will certainly be marked by the growing interest of the scientific community in this research field. We are strongly convinced that alternative protocols to access N–C axially chiral compounds will flourish, thus providing progressively a comprehensive toolbox to construct such scaffolds. The progress in synthetic chemistry will certainly also inspire medicinal chemists, and the design of innovative drug candidates featuring N–C atropoisomerism might be expected.

Acknowledgements

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