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Enantioselective Synthesis of N-C Axially Chiral Compounds by Cu-Catalyzed Atroposelective Aryl Amination.

Johanna Frey,^[a] Alaleh Malekafzali,^[a] Isabel Delso,^[a] Sabine Choppin,^[a] Françoise Colobert,^[a] and Joanna Wencel-Delord^{*,[a]}

Abstract: N-C axially chiral compounds have emerged recently as appealing motifs for drug design. However, enantioselective synthesis of such molecules is still poorly developed and surprisingly no metal-catalyzed atroposelective N-arylation have been described. Herein we disclose an unprecedented Cu-catalyzed atroposelective N-C coupling, occurring at room temperature. Such mild reaction conditions, crucial parameter to warrant atropostability of the newly generated products may be reached thank to the use of hypervalent iodines as highly reactive coupling partner. A large panel of the N-C axially chiral compounds is hence afforded in very high enantioselectivities (up to > 99% ee) and good yields (up to 76%). Post-modifications of thus accessed atropisomeric compounds allows further expanding the diversity of these appealing compounds.

Axial chirality is an intriguing feature of an array of natural products, biologically active molecules, privileged chiral ligands and sophisticated materials.^[1] This field of asymmetric organic chemistry has been dominated, for decades, by the axial chirality existing between two aromatic or aromatic-heteroaromatic units. However, since several years, atropisomerism arising from a restricted rotation of a N-C bond has been attracting a growing attention,^[2] with appealing applications in drug design.^[3] Besides, the applications of N-C axially chiral compounds encompass also fields of agrochemistry (Metolachlore),^[4] asymmetric catalysis via development of new chiral ligands^[5] and material science (Figure 1).^[6] The enantioselective synthesis of N-C axially chiral molecules remains however strongly underdeveloped (Figure 2). The state-of-the-art approaches are mainly based on stereoselective transformations of scaffold bearing already existing N-C motif, including desymmetrization reactions,^[7] N-functionalization of anilide derivatives,^[8] construction of aromatic ring on amine precursors via cycloaddition reactions^[9] and C-H functionalization of N-Ar unit.^[10] In contrast, enantioselective synthesis of N-C axially chiral molecules via stereoselective metal-catalyzed aryl amination,^[11] although retrosynthetically the most attractive route, remains unprecedented and presents a tremendous challenge.^[12] Indeed, both Buchwald-Hartwig and Ullmann couplings for example are sensitive to the steric encumbrance of the coupling partners and therefore high

reaction temperatures are generally needed to promote the bond formation between a secondary amine and an *ortho*-substituted aryl. Thus, a clear antagonism between steric requirements to warrant atropostability of a molecule and reaction conditions necessary to promote N-C coupling exists, rendering atroposelective Buchwald-Hartwig or Ullmann couplings still the unmet challenge. Herein we disclose a unique synthetic solution allowing overcoming this difficulty and unlocking the door towards atroposelective Ullmann-type N-arylation.

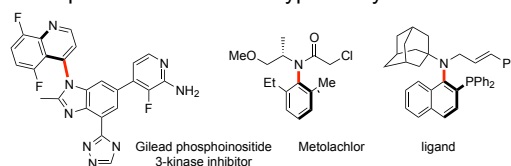


Figure 1. Important compounds featuring N-C axially chiral compounds.

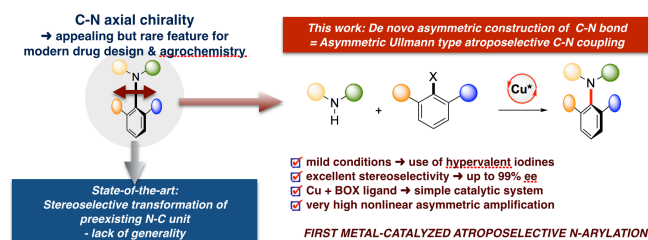
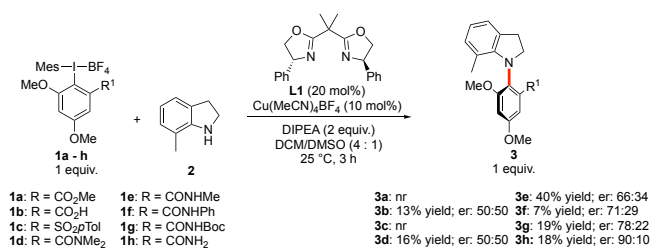


Figure 2. New approach for the synthesis of N-C axially chiral compounds.

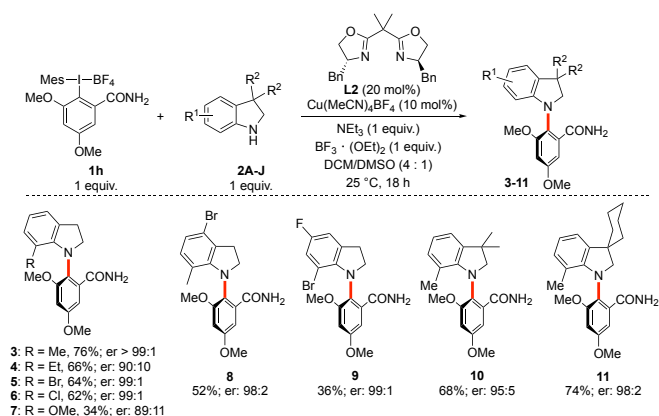
Following our recently designed diastereoselective transformation^[13] and Suna's work on the iodane-enabled couplings,^[14] we hypothesized that a Cu-catalyzed Ullmann-type reaction should be possible under mild reaction conditions when using a highly active arylating agent, such as hypervalent iodine,^[15] in combination with a well selected chiral ligand. Following this analysis, we embarked on exploring a coupling between dissymmetrical mesityl-aryl iodanes^[16] bearing a coordinating motifs **1** and indoline **2**, using Cu(I)-catalyst in combination with a BOX ligand.^[17] No reactivity was observed when ester and sulfone-derived hypervalent iodines **1a** and **1c** were used and in presence of carboxylic-acid derived iodane **1b** only a small amount of the desired product **3** was afforded as a racemic mixture. Dimethylamide-substituted **1d** delivered racemic **3d** in 16% yield. Secondary amides **1e-g** furnished the required N-C axially chiral compounds with promising enantiomeric excesses (32 – 56%). The major improvement was observed when using an unsubstituted primary amide **1h**, delivering the desired product in 80% ee and 18% yield. **3h** was thus selected for the further fine optimization.

[a] J. Frey, Dr. A. Malekafzali, I. Delso, Dr. S. Choppin, Prof. F. Colobert, Dr. J. Wencel-Delord
Laboratoire d'Innovation Moléculaire et Applications (UMR CNRS 7042), Université de Strasbourg/Université de Haute Alsace, ECPM
25 rue Becquerel, 67087, Strasbourg (France)
E-mail: wenceldelord@unistra.fr



Scheme 1. Determination of effective hypervalent iodine reagent (DIPEA: diisopropylamine).

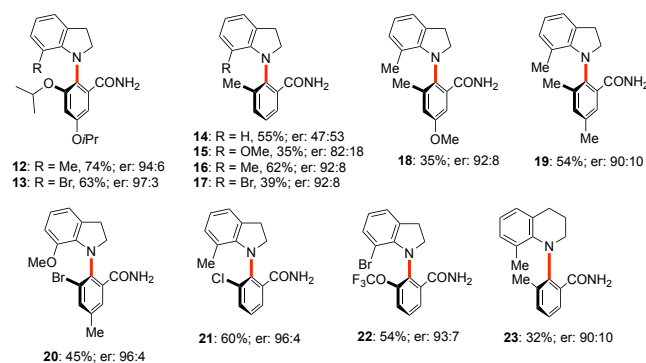
Further optimization study (for details see SI) revealed that Et₃N is the optimal base, Bn-substituted BOX in combination with Cu(MeCN)₄BF₄ generates the most selective catalysts and addition of a Lewis acid additive, such as BF₃·(OEt)₂, helps reaching high conversions. Under the optimized conditions the asymmetric Ullmann coupling occurs smoothly at room temperature, delivering atropisomerically pure **3** in 76% yield and 99:1 er. Notably, the herein described coupling failed under metal-free achiral N-arylation protocol disclosed by Olofsson.^[18] Subsequently, the scope of this unique atroposelective Cu-coupling was explored regarding N-coupling partner. Et-substituted N-C axially chiral compound **4** was isolated in 90:10 er. Indolines substituted by strategic Br- and Cl-atoms at C7-position reacted smoothly, furnishing the expected products in good yields (64 and 62% yield) and excellent enantiopurity. Drop of stereoinduction was observed when OMe- substituted indoline was used, delivering **7** in 89:11 er. In contrast, high enantioselectivity was restored, when using polysubstituted indolines and thus **8-9** were afforded with excellent ees. Of note is that the reaction tolerated well both, Br-substituent at different positions that opens a door towards further post-functionalizations and F-atom of key importance for biological applications. Besides, 3-disubstituted indolines are also effective coupling partners delivering **10** and **11** in high yields and ees.



Scheme 2. Scope of the reaction with respect to indolines **2A-J**.

Subsequently, various hypervalent iodines were tested. As expected, the substitution pattern of the newly generated N-C axially chiral products has a major impact on the enantioselectivity of the reaction. When O*i*Pr substituent is present in *ortho*-position to the chiral axis, a slight decrease in

the stereoselectivity was detected for the coupling with 7-methyl indoline, furnishing **12** in 94:6 er. However, using more encumbered Br-substituted indoline excellent chiral induction was restored, as **13** was isolated in 97:3 er. In the case of Me-substituted iodane, the coupling with non-substituted indoline delivers the almost racemic product **14**, clearly showing that the steric hindrance around the N-C linkage is insufficient to restrict the rotation. However, the introduction of OMe-, Me- and Br-substituents at the strategic C7-position of the indoline results in the increased atropostability of the products and thus **15**, **16** and **17** were furnished in respectively 82:18, 92:8 and 92:8 er. These observations are consistent with the determination of rotational barriers (see Figure 4). Of note is that the presence of OMe substituent at *para*-position of the iodane has a unfavorable impact on the reactivity of the iodane, as **18** was isolated in only 35% yield, compared to 62% yield observed in case of **16**. In contrast, as expected, the enantioselectivity of the reaction is not affected by this *para*-substituent. Remarkably, Br-substituted iodane is also a suitable coupling partner; the highly atropoenriched product **20** was prepared in excellent er of 96:4 thus giving access to strongly modular atropisomeric scaffold. Coupling with Cl-substituted iodane delivers **21** with identical enantioselectivity and increased efficiency. Finally, biologically relevant OCF₃ motif may also be introduced with success on the hypervalent iodine moiety as illustrated by the synthesis of **22** in good yield of 54% and high enantioselectivity of 93:7. Finally, tetrahydroquinoline is also an effective coupling partner; the corresponding product **23** was isolated in promising 90:10 er albeit in lower 32% yield.



Scheme 3. Scope of the reaction with respect to iodanes

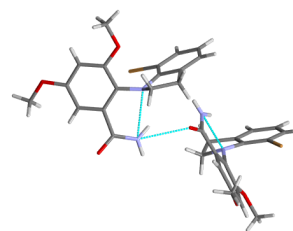


Figure 3. X-Ray structure of (aR)-**3**.

The absolute *aR* configuration of **3** was determined based on X-Ray structure.^[19] Notably, the crystal structure shows hydrogen bonding between N-atom of indoline and N-atom of the amide what is coherent with a particular importance of this DG for the efficiency of the reaction. Besides, two chiral molecules are present in a chiral unit and intermolecular hydrogen bonding between NH₂- and O-atom is hence evidenced.

In order to further characterize the newly generated N-C axis, the rotational barriers for the few selected examples were measured (see SI). The data (Figure 4) clearly show that the increased bulk at C7-position of indoline allows improving the atropostability of the compounds; modification of the Me-substituent by a more congesting Br-atom results in significantly higher ΔG^\ddagger , rising from approx. 27.5 kcal/mol for **3** to 29.7 kcal/mol for **5**. A comparable atropostability is observed for **3** and **15** suggesting that the relative positions of Me- and OMe-substituents have a minor impact. However, decreased enantioselectivity observed in case of **15** might suggest that undesirable weak interactions between OMe substituent on the indoline destabilize the stereo-determining intermediate during the catalytic cycle. A very high rotational barrier of 31 kcal/mol was measured for **16**, indicating that this molecule should be atropostable over prolonged time even at higher temperature.

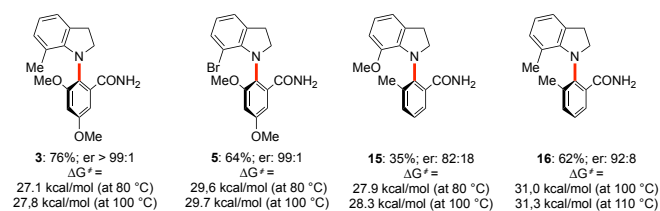
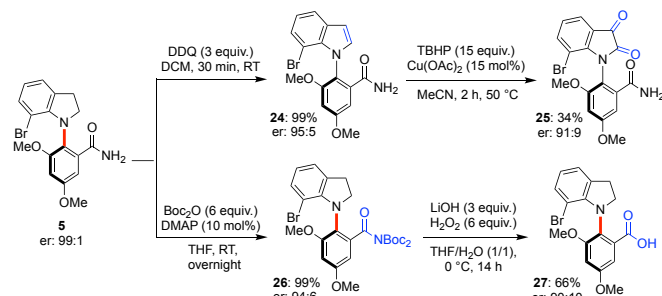


Figure 4. Determination of the rotational barriers for the selected products.

The synthetic importance of this new methodology to access new N-C axially chiral compounds was further highlighted by possible post-functionalizations (Scheme 4). Large-scale (1.95 mmol) synthesis of **5** was performed under standard protocol, delivering 470 mg of the product in unchanged, 64% yield and total enantioselectivity. Subsequently, **5** was oxidized into the corresponding axially chiral indole **24** or indoline-2,3-dione **25**, *N*-arylisatin analogue, which is a privileged synthetic intermediate of oxindole scaffolds.^[20] The modular character of the amide directing group was also illustrated as a two-step protocol allows converting the CONH₂ group into the carboxylic acid **27**, isolated in 66% yield and slightly decreased optical purity (er of 90:10).



Scheme 4. Post-modifications of **5**. (DDQ : 2,3-Dichloro-5,6-dicyano-p-benzoquinone; Boc₂O: Boc₂O: Di-tert-butyl dicarbonate, DMAP: 4-Dimethylaminopyridine; TBHP: tert-Butyl hydroperoxide

Subsequently, we embarked on the mechanistic studies. First, the non-linear effects (NLE) were investigated^[21] and we were pleased to discover that this Cu-catalyzed transformation features very strong amplification (Figure 5a) Indeed, the axially chiral **3** is obtained with high 46% ee using the ligand with very low 6% ee and to access the almost enantiopure product (ee of 92%), the ligand of only 20% ee is needed. This important amplification clearly indicates formation of complex (Cu-L₂)_n metallic species, with homochiral species exhibiting highly increased reactivity. Remarkably, this nonlinear amplification is among the strongest effects reported in the literature, in particular considering the Cu-catalyzed transformations.^[22]

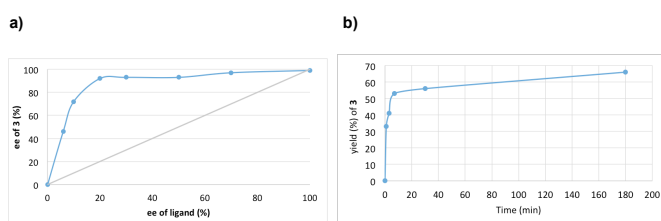


Figure 5. a) Non-linear effects study observed for the asymmetric synthesis of **3**; b) Kinetic study of the synthesis of **3**

In addition, kinetic studies of this reaction revealed extremely fast initial reaction rate (Figure 5b). Indeed, within only 1 min, **3** was afforded in 33% isolated yield and the reaction time of only 7 min is necessary to furnish **3** in 50% yield. However, after reaching 50% conversion the rate decreases drastically. Reaction time of 3h is needed to increase the yield up to 66% and the optimal result of 76% yield necessities 18h reaction time. To complement this study, a stoichiometric reaction was followed by HRMS ESI analysis. As expected based on NLE observed, the initial formation of Cu(BOX)₂ complex was evidenced and the structure of this catalyst was further conformed by X-ray analysis (see SI). Subsequently, addition of iodane **1** to the solution of the complex results in instantaneous decoordination of one BOX ligand and oxidative addition of iodane, resulting in formation of CuBOX-Ar species (ESI analysis). This extremely fast oxidative addition clearly illustrates the superiority of iodanes over Ar-I coupling partner, for which OA step is frequently sluggish and rate determining. Unfortunately, other intermediates resulting from coordination of the amine to the catalyst were not detected but formation of the expected product was finally evidenced by ESI analysis. Based on these results and the literature data,^[23] a catalytic cycle can be proposed implying (Figure 6): 1) generation of Cu(BOX)₂ complex; 2) fast OA of iodane **1**, enhanced by the Cu-amide coordination, and subsequent decoordination of one BOX ligand, 3) coordination of the amine coupling partner and 4) final reductive elimination delivering the expected axially chiral compound. Alternatively, initial coordination of amine to CuBOX complex followed by oxidative addition may also be envisioned.

In depth further mechanistic studies are needed to elucidate this catalytic cycle as well as the stereoselectivity.

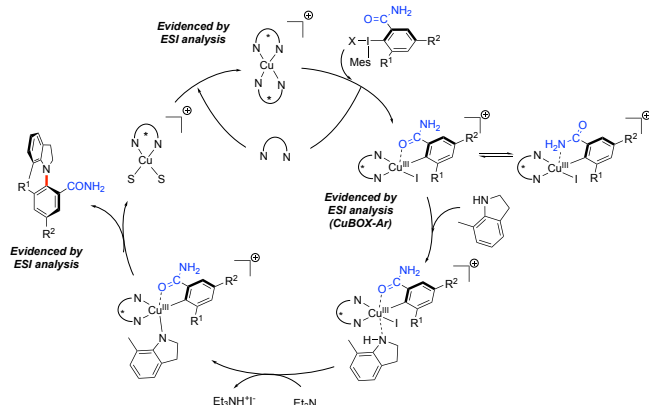


Figure 6. Proposed catalytic cycle.

In conclusion, we report herein the first example of atroposelective metal catalyzed N-arylation delivering N-C axially chiral compounds. Use of various hypervalent iodine coupling partners allows this Cu-catalyzed hindered coupling to occur at room temperature, thus warranting excellent stereoselectivity. This protocol delivers efficiently original N-C atropisomeric compounds, molecules of interest for pharmaceutical industry. In addition, preliminary mechanistic studies show exceptional non-linear amplification and very fast initial rate of the reaction, thus further illustrating the uncommon features of this original transformation.

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Keywords: N-C axial chirality • atropisomerism • asymmetric C-N coupling • hypervalent iodine

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