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Sulfoxide-Directed or 3d-Metal Catalyzed C–H Activation and Hypervalent Iodines as Tools for Atroposelective Synthesis

Sabine Choppin and Joanna Wencel-Delord*

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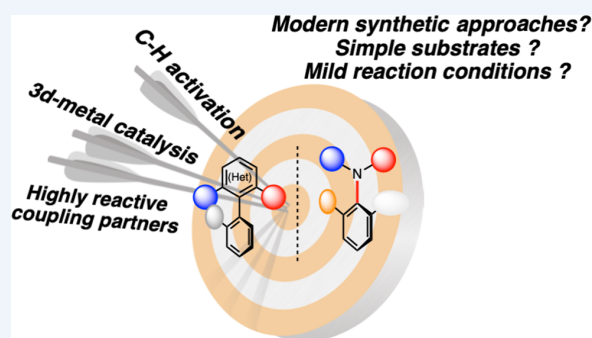
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CONSPECTUS: The expanding applications of atropisomeric compounds combined with the growing diversity of such chiral molecules translate into an urgent need for innovative synthetic strategies allowing their rapid, efficient, and sustainable synthesis. Recently, the C–H activation approach has provided new opportunities for synthesizing axially chiral compounds. The two complementary approaches allowing implementation of the C–H activation methodology toward the synthesis of the chiral molecules imply either ortho-functionalization of the preexisting prochiral or atropo-unstable biaryl substrates or direct C–H arylation of sterically encumbered aromatics. The first approach required the preinstallation of a directing group on a biaryl precursor, which drastically limits the diversity of thus generated products. To tackle

this important synthetic limitation, we have envisioned using a chiral sulfoxide as both directing group and chiral auxiliary. Indeed, in addition to efficiently coordinating the Pd-catalyst thus allowing chiral induction, the sulfoxide moiety can be easily removed, via the sulfoxide/lithium exchange, after the C–H activation step, thus guaranteeing an almost unlimited postdiversification of the atropisomeric products. The efficiency and generality of this concept could be illustrated by developing atropo-diastereoselective oxidative Heck reaction, direct acetoxylation, and iodination, as well as direct arylation. Besides, the synthetic utility of this methodology was demonstrated by designing an expedient synthesis of a direct steganone precursor. This unique transformation also allowed us to build up unprecedented triaryl scaffolds with two perfectly controlled chiral axes, original chiral skeletons for new ligand design. While considering the atroposelective direct arylations, the clear antagonism between the harsh reaction conditions frequently required for the coupling of two sterically hindered compounds and the atropo-stability of the new product, resulted in the scarcity of such transformations. To solve this fundamental challenge, we have focused on the application of a low-valent cobalt catalyst, prompted to catalyze C–H activation of indoles at the C2 position under extremely mild reaction conditions (room temperature). Accordingly, atroposelective C2-arylation of indoles could be achieved using an original carbene ligand and delivering the uncommon atropoisomerically pure indoles in excellent yields and enantioselectivities. Detailed combined experimental and theoretical mechanistic studies shed light on the mechanism of this transformation, providing strong evidence regarding the origin of the enantioselectivity. Finally, the antagonism between steric hindrance required to guarantee the atropo-stability of a molecule and harsh reaction conditions required to couple two partners is a strong limitation not only for the development of atroposelective C–H arylation reaction but also for the development of direct synthesis of the C–N axially chiral compounds. Despite the long history and incredible advances achieved in Ullmann–Goldberg and Buchwald–Hartwig couplings, atroposelective versions of such transformations have remained unprecedented until recently. Our idea to tackle this challenging issue consisted in using hypervalent iodines as highly reactive coupling partners, thus allowing the desired N-arylations to occur at room temperature. This hypothesis could be validated by reporting first atropo-diastereoselective Cu-catalyzed N-arylation, using sulfoxide λ^3 -iodanes as the coupling

continued...



partners. Subsequently, the enantioselective version of this atroposelective N-arylation was successfully established by using a chiral Cu-complex bearing a BOX ligand. In conclusion, we report herein designing tailored-made solutions to provide new synthetic strategies to construct the atropisomeric molecules, including biaryls and C–N axially chiral molecules.

KEY REFERENCES

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- Dherbassy, Q.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. Two Stereoinduction Events in One C–H Activation Step: A Route towards Terphenyl Ligands with Two Atropisomeric Axes. *Angew. Chem., Int. Ed.* **2018**, *57*, 4668–4672.² This work demonstrates that the concept of the sulfoxide-directed atroposelective C–H activation can be efficiently used to perform a stereoselective direct arylation while controlling simultaneously two chiral axes. Thanks to this reactivity, original chiral triphenyl scaffolds could be efficiently prepared.
- Jacob, N.; Zaid, Y.; Oliveira, J. C. A.; Ackermann, L.; Wencel-Delord, J. Cobalt-Catalyzed Enantioselective C–H Arylation of Indoles. *J. Am. Chem. Soc.* **2022**, *144*, 798–806.³ This article discloses the first example of direct atroposelective arylation using a 3d-metal catalyst. This unique reactivity could be reached using an original low valent Co-NHC complex.
- Frey, J.; Malekafzali, A.; Delso, I.; Chopin, S.; Colobert, F.; Wencel-Delord, J. Enantioselective Synthesis of N–C Axially Chiral Compounds by Cu-Catalyzed Atroposelective Aryl Amination. *Angew. Chem., Int. Ed.* **2020**, *59*, 8844–8848.⁴ Atroposelective Ullmann-type arylation is reported herein, allowing the synthesis of C–N axially chiral compounds. This challenging transformation could be achieved at room temperature thanks to the use of hypervalent iodine as a highly reactive coupling partner.

INTRODUCTION

Atropisomerism arising from a restricted rotation around a single bond is a unique feature of various natural products and pharmaceutical candidates with antibiotic, antiviral, and anticancer properties.⁵ However, over the years, this type of chirality has remained rather a scientific curiosity than an appealing and broadly applied tool to introduce chiral information within molecules of interest. Nevertheless, the past decade is clearly marked by a rapid expansion of this field.⁶ On the one hand, various synthetic approaches have been designed to prepare efficiently atropisomeric compounds, including organocatalytic approaches, metal-catalyzed reactions, axial-to-chiral chirality transfer, and others. On the other hand, the field of asymmetric synthesis has been marked by rapidly increasing applications of atropisomeric compounds in the pharmaceutical industry, agrochemistry, and material science.⁷ Notably, the diversity of atropisomeric compounds has also expanded considerably.⁸ While initially atropisomeric molecules were almost exclusively limited to biaryl compounds, C–N axially chiral molecules⁹ and atropisomeric styrenes have emerged over recent years as rapidly evolving research fields.

The increasing importance of the atropisomeric products combined with the expanding diversity of such compounds stimulates the rapid development of modern, straightforward, efficient, and sustainable synthetic routes to prepare such molecules. Accordingly, the C–H activation field has opened new perspectives to afford original atropisomeric compounds.¹⁰ On the other hand, construction of atropisomeric molecules featuring a restricted rotation around an N–Ar bond via metal-catalyzed direct N-arylation has remained unprecedented until recently.¹¹ Herein, we report our contributions to the field of atropisomeric synthesis. First, the synthesis of axially chiral biaryls via the C–H activation approach is presented. Subsequently, the development of the first metal-catalyzed asymmetric Ullman coupling affording C–N axially chiral molecules is described.

SYNTHESIS OF ATROPIOMERIC BIARYLS VIA C–H FUNCTIONALIZATION OF ATROPO-UNSTABLE BIARYLS

C–H activation has emerged over the past decade as one of the privileged modern and sustainable tools to reach molecular complexity.¹² Indeed, the C–H activation strategy allows converting simple, non-prefunctionalized substrates into functionalized products and offers new possibilities for conceiving innovative retrosynthetic disconnections. Accordingly, implementation of the C–H activation mindset into the synthesis of chiral compounds seems particularly appealing.¹³

While considering the synthesis of atropisomeric compounds via C–H activation, three alternative solutions have been proposed (Figure 1). The most obvious retrosynthetic

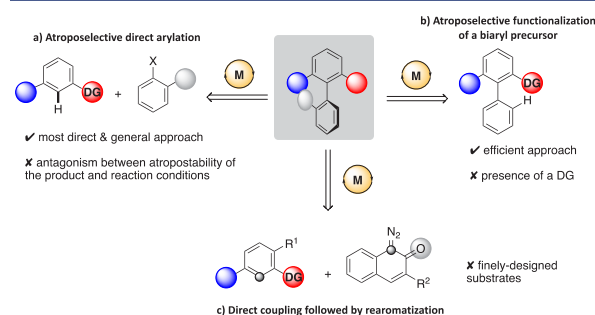


Figure 1. C–H activation-based approaches for the synthesis of atropisomeric biaryls.

disconnection relates to the direct stereoselective arylation reaction (Figure 1a). This reaction presents however a fundamental difficulty.^{10b} While important steric hindrance around the Ar–Ar' bond is generally required to guarantee atropo-stability of a newly generated compound, a high reaction temperature might be required to promote efficient coupling. The atropo-stability of the new compound under the reaction conditions might thus be compromised. In contrast, the C–H activation approach seems to be particularly appealing for direct functionalization of already existing prochiral or atropo-unstable biaryls (Figure 1b). Indeed, the introduction of an additional substituent at the *ortho*-position to the atropisomeric axis

translates into a generation of the atropisomerically stable compounds. Finally, the synthesis of atropisomeric compounds via metal-catalyzed coupling with diazo coupling partners followed by a rearomatization step may be considered as a complementary solution (Figure 1c).¹⁴

Although the field of C–H activation has witnessed a real expansion in the second decade of the 21st century, the pioneering example of C–H activation-based atroposelective synthesis was reported already in 2000 by Murai (Figure 2a).¹⁵

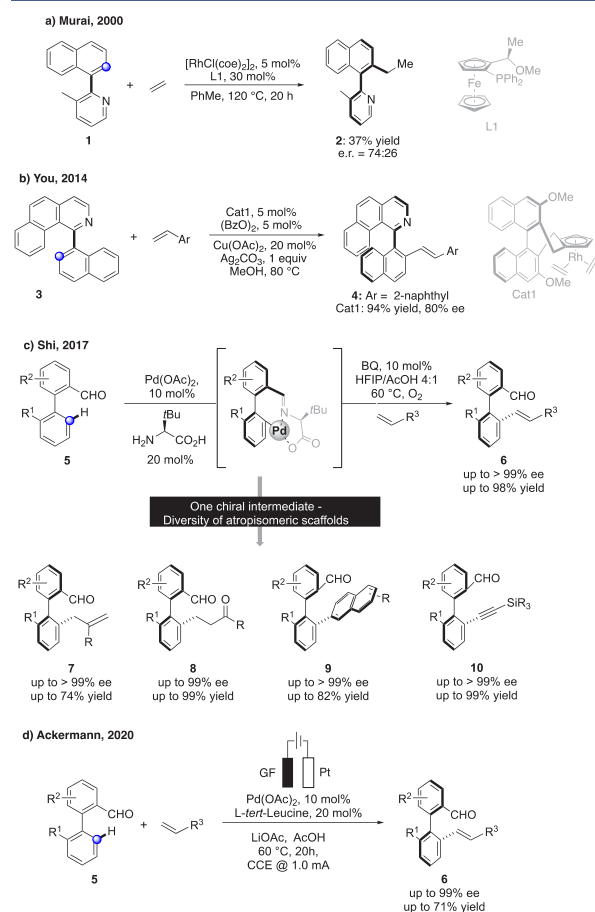


Figure 2. Pioneering examples of atropisomeric C–H activation via direct functionalization of biaryl precursors.

The authors astutely designed naphthyl-pyridine substrate **1** as a precursor of an axially chiral compound. Capitalizing on the coordinating properties of the pyridine motif, metalation using a chiral Rh-catalyst occurred selectively in the *ortho*-position to the biaryl axis, thus furnishing, after the functionalization step, atropisomerically enriched compound **2**. Despite moderate yield and enantiomeric excess of **2**, this pioneering contribution demonstrated the great potential of the C–H activation mindset for the synthesis of atropisomeric compounds. More than a decade later, conceptually similar direct atroposelective functionalization of 1-(naphthalene-1-yl) benzo[*h*]isoquinoline **3** was explored by You.¹⁶ The use of the pyridine core as the DG in combination with the chiral Cp-derived Rh(III) complex afforded the desired chiral biaryls **4** with up to 80% ee (Figure 2b).

Despite the appealing features of such couplings, the substrate design implying the presence of the pyridine core to facilitate and direct the metalation step inherently limits the synthetic utility and generality of such an approach. Drawing inspiration from the “transient directing group approach” spread by Yu, Shi has beautifully implemented the idea of using biaryl aldehydes **5** in combination with a monoprotected amino acids (chiral auxiliary) to elaborate a more general C–H activation strategy (Figure 2c).^{17,18} Indeed, Pd-catalyst is perfectly suited to promote, after the coordination to the in situ generated chiral imine core, the atropo-stereoselective *ortho*-functionalization, thus furnishing a diversity of axially chiral biaryl aldehydes **6**. After the pioneering example of the oxidative atroposelective C–H transformations including direct olefination, this reactivity could be extended to various C–C couplings, including allylation,¹⁹ alkylation,²⁰ naphthylation,²¹ and alkylation.²² Remarkably, seeking even more sustainable reaction conditions, Ackermann has explored an electro-atroposelective version of this coupling, by replacing the requested oxidant with the cheapest and the greenest energy source, electric power (Figure 2d).²³ This work can clearly be considered as a cornerstone for the development of extremely rare asymmetric electrocatalysis by obviating challenges such as (a) cathodic catalyst reduction, (b) electrochemical degradation of chiral ligands, and (c) unfavorable interactions of the electrolyte within the enantio-determining transition state. The overall stereoselectivity and efficiency of such transformation have not been impacted by the electrochemical reoxidation of Pd, thus furnishing the desired products **7–10** in excellent yields and optical purity up to 99% ee.

These elegant strategies for the atroposelective direct functionalization of biaryls are certainly very tempting. However, the presence of the DG on the substrate, even the modular aldehyde, may considerably limit the general applicability of this strategy to a rather narrow panel of (Het) Ar–Ar atropisomeric compounds. The key to more wide-ranging applications of such an approach lays therefore in the selection of a directing group that, ideally, should be easily modifiable after the C–H activation step. Following this idea, the use of the sulfoxide moiety²⁴ as an enantiopure and traceless DG emerged.²⁵ Indeed, the sulfoxide/Pd coordination has already been explored in the Suzuki coupling,²⁶ for example, while the sulfoxide/lithium exchange process followed by electrophilic trapping has been relatively well investigated (Figure 3).²⁷

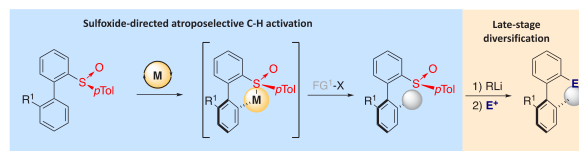


Figure 3. Concept of the atropo-diastereoselective sulfoxide-directed C–H activation.

The feasibility of such an atropo-diastereoselective sulfoxide-directed functionalization of biaryls has been rapidly illustrated by an oxidative Heck reaction (Figure 4a).²⁸ The direct olefination of substrate **11** occurred fully regioselectively at the *ortho*-position to the Ar–Ar’ linkage, furnishing the expected atropo-stable product **12**. However, the potential of this system was rather limited in terms of both stereoselectivity and

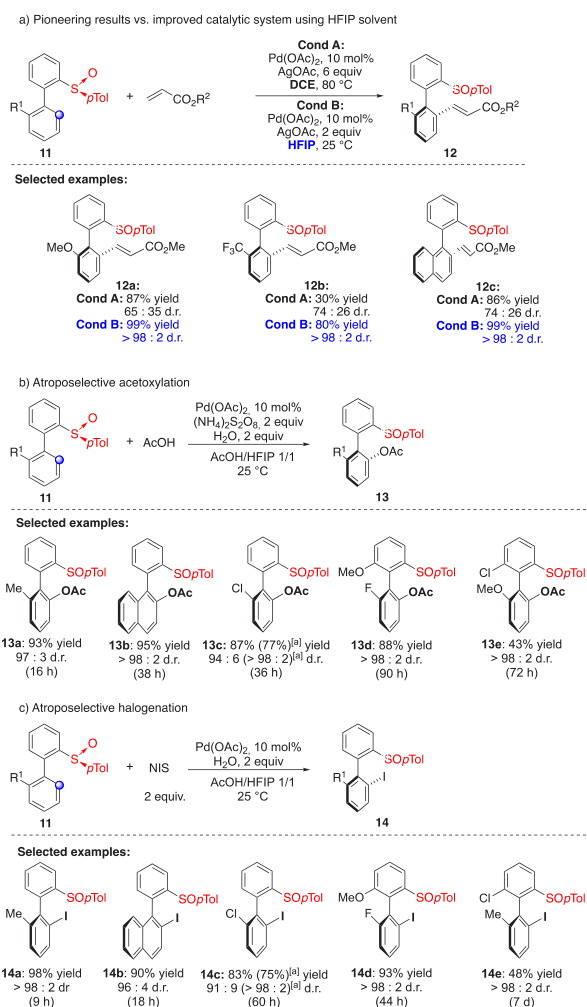


Figure 4. Sulfoxide-directed atroposelective C–H activation. [a] After recrystallization.

efficiency. While good yields could be reached using electron-rich substrates, the C–H activation process was sluggish in the case of substrates bearing electron-withdrawing substituents. The chirality of the sulfur atom induced also a rather moderate diastereoselectivity (Conditions A). A breakthrough in the sulfoxide-directed atropo-diastereoselective C–H activation was however realized while discovering a unique combination between the 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) solvent and the sulfoxide moiety (Conditions B).²⁹ Indeed, we were surprised to realize that the Fujiwara–Moritani reaction using **11** occurred smoothly in HFIP delivering the desired compound **12** as a single atropisomer. Importantly, in this fluorinated solvent the direct functionalization of **11** proceeds efficiently regardless of the electronic properties of the substrate, delivering the expected products in generally >98:2 dr. Thanks to the drastically amplified catalytic reactivity of this system, the silver salt loading could be considerably reduced from an excessive 6 equiv to 2 equiv, while decreasing simultaneously the reaction temperature from 80 °C to room temperature. Less reactive styrenes also now became potent coupling partners, in the presence of electron-withdrawing substituents on the aromatic ring (lower reactivity of electron-rich styrenes could be

attributed to a polymerization side reaction occurring in HFIP). Accordingly, under the optimized and operationally very simple protocol (no air or water sensitive), a diversity of biaryl olefins could be obtained with excellent optical purity. Various experiments were subsequently conducted to shed light on the unique role of HFIP in our catalytic system. First, the particular activating mode of HFIP was clearly illustrated by a detailed solvent screening. While no reaction occurred in *i*PrOH, AcOH, DCE, CH₃Cl, and *i*PrOH/HFIP (9:1 v/v) mixture, good reactivity albeit over drastically increased reaction time (5 days compared to several hours in HFIP) could be achieved in DCE/HFIP 9:1 v/v mixture. Besides, an interesting correlation with the amount of HFIP added to DCE was established. The addition of 1 equiv of HFIP to DCE translates into the generation of the desired product in only a trace amount, while adding 5 equiv of HFIP with respect to the biaryl substrate, the amount of the desired product was doubled, and the best reactivity was reached using 20 equiv of HFIP (1:4 mixture of DCM and HFIP).

Subsequently, based on NMR and IR studies, strong complexation between the sulfoxide and HFIP was evidenced, which radically modifies the coordinating properties of the sulfoxide group rendering it a weak DG. Indeed, H-bond formation between HFIP and O atom translates into weakening of the S=O bond, which can (1) directly influence the rate of the C–H activation step and (2) significantly impact the stereoenvironment around the metallic center (H-bonding network). In addition, modification of the redox potential of the palladium catalyst may also result from the coordination of Pd(II) by HFIP.³⁰

While further exploring the reactivity of **11**, we were rapidly able to extend this reactivity toward stereoselective acetoxylation occurring smoothly in HFIP (Figure 4b).¹ The catalytic system including (NH₄)₂S₂O₈ as the oxidant in combination with AcOH used as the OAc-source and cosolvent allowed the first atroposelective direct C–O coupling. Interestingly, the acetoxylation is also effective in water, clearly highlighting important stability and robustness of this catalytic system, but the functionalized product was obtained in slightly lower diastereoselectivity (dr of 83:17). Mild reaction conditions, operational simplicity together with high yields, and excellent atroposelectivities are additional salient features of this reaction. Interestingly, during the optimization study, complementary reactivity was evidenced while using NIS as an oxidant (Figure 4c). In this case, fully selective iodination took place, furnishing rare and chiral biaryls bearing iodine substituent in excellent yields and stereoselectivities. This strategy may also be used to perform direct bromination although longer reaction times were necessary to complete the reaction. Unfortunately, the chlorination turned out to be ineffective.

Regarding the mechanism of this transformation, first, the kinetic isotope effects of both olefination and acetoxylation were investigated (Figure 5a). Interestingly, while in the case of the C–O bond formation a KIE value of 1.09 was measured, the direct Fujiwara–Moritani reaction is characterized by a KIE of 5.9. In addition, H/D scrambling was observed in the first case while H/D exchange does not occur in the second case. These results clearly show an interesting feature: In the case of the directed acetoxylation occurring via the Pd^{II}/Pd^{IV} catalytic cycle, the C–H activation is reversible and is not the rate-determining step. In contrast, the metalation becomes irreversible and rate-determining in the case of the oxidative Heck reaction. This interesting mechanistic switch is coherent with the experimental

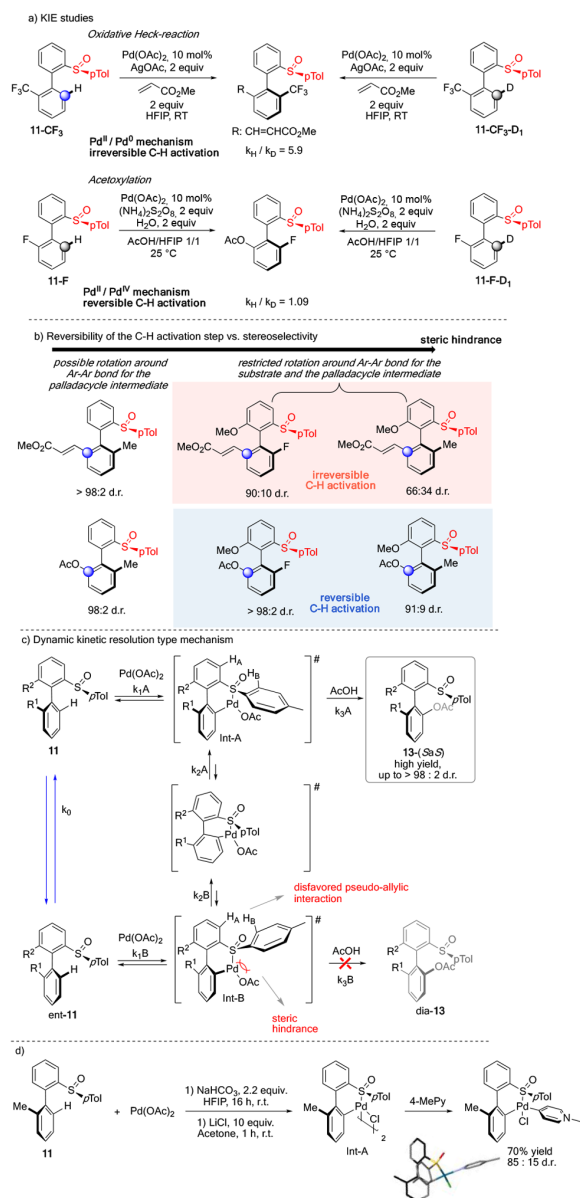


Figure 5. Dynamic kinetic resolution type mechanism.

results. Indeed, the reversibility vs irreversibility of the C–H activation step directly impacts the stereoselectivity of the reaction in the case of the more sterically hindered compounds (Ar–Ar bond rotation does not occur for the substrate nor once the metallacyclic intermediate is formed) (Figure 5b). For the sterically encumbered substrates, the reversibility of the C–H activation promotes highly stereoselective C–O bond formation as the disfavored atropisomeric metallacycle may be converted into the most favored one via a reversible C–H metalation/decoordination sequence. In contrast, the direct olefination affords the desired product in significantly reduced optical purity because the irreversibility of the C–H activation does not allow “correction” of the initial ratio between the two atropisomers of the metallacyclic intermediate (Figure 5b).

Likewise, the substrate scope study revealed that for a majority of atropo-unstable substrates **11**, a dynamic kinetic

resolution type process takes place (Figure 5c). The increased steric hindrance around the Ar–Ar bond, as in the case of **13e** and **14e**, may translate into simple kinetic resolution-type transformation furnishing the expected optically pure acetoxy-lated or iodinated products in approximately 50% yield together with the remaining 50% of the unreacted but now atropisomerically pure substrate. In the case of the dynamic kinetic resolution type reaction, the racemization occurring through the rotation around the biaryl axis is expected to be facilitated via the generation of the metallacyclic intermediate. As an example, the rotational barrier of the substrate **11** (OMe/F) of 30 kcal/mol renders the epimerization at room temperature unlikely. In clear contrast, the calculated rotational barriers of the corresponding diastereomeric palladacycle intermediates are significantly lower, (20 and 25 kcal/mol), compared to the substrate. Besides, a related metallacyclic intermediate could indeed be synthesized, isolated, and fully characterized. The X-ray structure clearly confirms the expected Pd–S coordination (generation of the 6-member metallacyclic intermediate), and its dynamic behavior could be demonstrated. Interestingly, the phenomenon of the rotation around the Ar–Ar bond in such biaryl sulfoxide-palladacycles was brilliantly used by Feringa to construct molecular machines.³¹

Of note is that the concept of atropo-diastereoselective biaryl functionalization is not limited to the use of the sulfoxide directing group. Alternative chiral auxiliaries, such as enantio-pure phosphine oxide motifs can also be employed in this context delivering via C–H activation of atropisomerically pure biaryl phosphate type compounds.³² The scope of this transformation is, however, more limited, and the stereoselectivity was strongly dependent on the electronic and steric properties of the substrate. Use of the phosphine-type directing group imposed however higher reaction temperature, thus particular attention needs to be put on the atropo-stability of newly generated molecules (Figure 6).

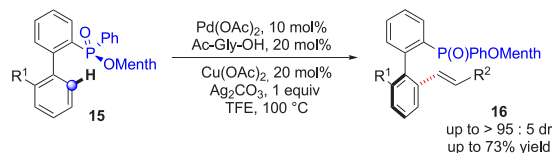


Figure 6. Atroposelective synthesis via C–H activation using phosphine-oxide substituted precursors.

To demonstrate the synthetic utility of our methodology, we have embarked on the synthesis of steganone, an interesting natural product exhibiting axial chirality.³³ We hypothesized that the key advanced intermediate, the atropisomerically pure aldehyde **20**, should be available via stereoselective C–H activation followed by the sulfoxide/lithium exchange step (Figure 7). Following this idea, the biaryl-sulfoxide substrate **17** was synthesized in quantitative yield. The key stereoselective C–C coupling occurred efficiently even at gram-scale, furnishing the atropo-pure **18** in 92% yield. Indeed, although an initial stereoselectivity of 95:5 was measured for this reaction, straightforward purification of the diastereomeric product via silica gel column allows a further increase of the optical purity of the desired product, thus illustrating another appealing feature of this catalytic system. The initial efforts to convert the acrylate motif into a CH₂OH-group turned out to be challenging. Ozonolysis of the double bond failed, and while using OsO₄-

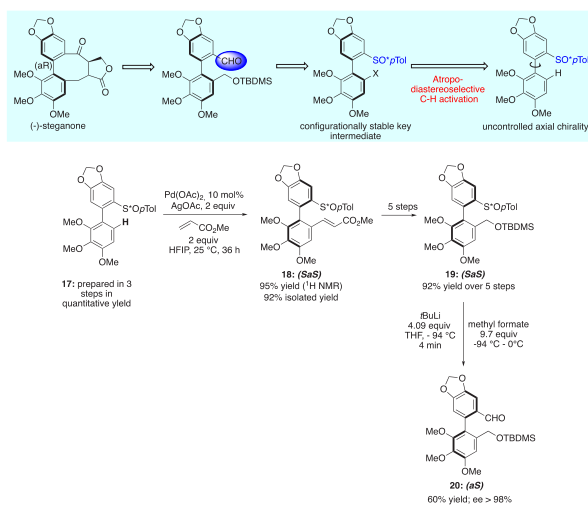


Figure 7. Application of the methodology for the synthesis of the direct precursor of steganone.

catalyzed oxidative conditions, only complex reaction mixtures were obtained. Rewardingly, an expedient five step/one purification sequence combining ester reduction, followed by olefin dihydroxylation, $\text{Pb}(\text{OAc})_4$ mediated C–C cleavage, aldehyde reduction, and benzylic alcohol protection was used to convert the acrylate unit into the protected alcohol, delivering the desired **19** in 92% yield. Remarkably, the sulfoxide/lithium exchange took place with no loss of the optical purity, and the following trapping with DMF furnished **20** in 60% yield and >98% ee. Importantly, in this specific case and due to the relatively small steric hindrance around the Ar–Ar bond, a temperature as low as $-94\text{ }^\circ\text{C}$ was essential for the sulfoxide/lithium exchange to perfectly conserve the atropo-purity of lithiated intermediate, while at a higher temperature ($-78\text{ }^\circ\text{C}$) partial racemization was observed. The overall synthesis of the advanced precursor was thus accomplished in only 10 steps, with 42% overall yield and full stereoselectivity, thus illustrating the unparalleled potential of the C–H activation approach for the total synthesis of a known compound.

The synthetic potential of this methodology was further elegantly demonstrated within the synthesis of isoriccardin C. In this case, sulfoxide-directed atroposelective intramolecular Heck reaction was used to close the macrocyclic structure and induce the chirality of the final natural product.³⁴

An additional important advantage of the C–H activation mindset is the possibility of designing new and original molecular structures, difficult to access via standard protocols. With this in mind, we were wondering if our sulfoxide-directed atroposelective approach could be used to construct unique triaryl scaffolds bearing two chiral axes. Indeed, the synthesis of optically pure molecules bearing two chirality elements, perfectly controlled in a single step, is very attractive but also rare. Another key difficulty in such a transformation concerns the direct Ar–H/Ar–X coupling occurring in a highly stereoselective manner. Indeed, due to the antagonism between the steric requirements essential to generate atropisomerically stable compounds and the common sensitivity of the C–H arylation reaction to the steric hindrance combined with the elevated temperatures often required to promote the direct functionalization of the encumbered compounds, atroposelective direct arylations remain extremely challenging and poorly

developed.^{10b} The pioneering example of atroposelective coupling between hindered thiophene and sterically encumbered boronic acid was reported in 2012 by Itami.³⁵ The first-generation catalytic system combining Pd-catalyst and BOX type ligand (L2) allowed coupling of the hindered thiophene **21** with 2-Me and 2-*i*Pr naphthyl boronic acids. Interestingly, it was clearly demonstrated that while an interesting level of reactivity was reached with the less sterically hindered boronic acid, the coupling product was isolated with a rather moderate diastereoselectivity. In contrast, increased steric hindrance of the boronic acid resulted in improved atropo-purity of product **22** but significantly decreased yield (Figure 8a). The second

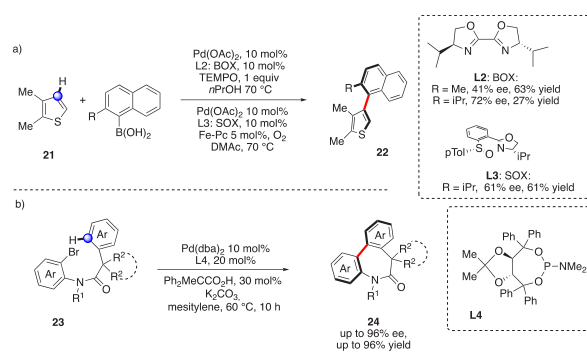


Figure 8. Pioneering examples of atroposelective direct arylation.

generation of the catalyst, i.e., Pd-metal complexed with a mixed oxazoline-sulfoxide SOX ligand (L3) did not allow a significant improvement of the chirality transfer, but thanks to the use of Fe-Pc as a catalytic co-oxidant, an aerobic reaction took place. A few years later, the group of Cramer designed an intramolecular direct arylation, occurring via Pd(0)/Pd(II) catalytic cycle. Taddol-derived phosphoramidite ligand (L4) was able to perfectly control the stereochemical outcome of this transformation, thus delivering axially chiral dibenzazepinone-type scaffolds **24** with ee up to 96% (Figure 8b).³⁶

Aiming for sulfoxide-directed atroposelective arylation, we hypothesized that unique bis-atropisomeric compounds could be accessed via direct arylation of our biaryl-precursor using *ortho*-substituted aryl iodanes (Figure 9a).² The preliminary studies first allowed us to determine the optimal reaction conditions for the direct arylation of the benchmark biaryl sulfonamide **11** (Figure 9b).³⁷ Surprisingly, under the standard reaction conditions employed in the Fujiwara–Moritani reaction, coupling with *p*-iodoanisole failed. An extensive optimization study showed that the addition of an external ligand is required to promote this reaction. While some success was encountered using sterically encumbered pyridine ligands, *N*-heterocyclic carbenes turned out to be the most efficient ligands. Finally, the desired arylation could be achieved with full conversion using Pd(OAc)₂ catalyst together with IPrHCl carbene and TFA additive. However, the initial catalytic system turned out to be poorly general and robust, as several electron-rich (iodotoluene) or electron-neutral (iodobenzene) aryl iodides reacted sluggishly under such conditions. The hint to improve the efficiency of this catalytic system consisted in adding a stoichiometric amount of ethyl iodoacetate. This additive is expected to play the role of an organic oxidant, preventing the deactivation of the Pd catalyst via formation of the Pd(0)-species. Under such reoptimized reaction conditions,

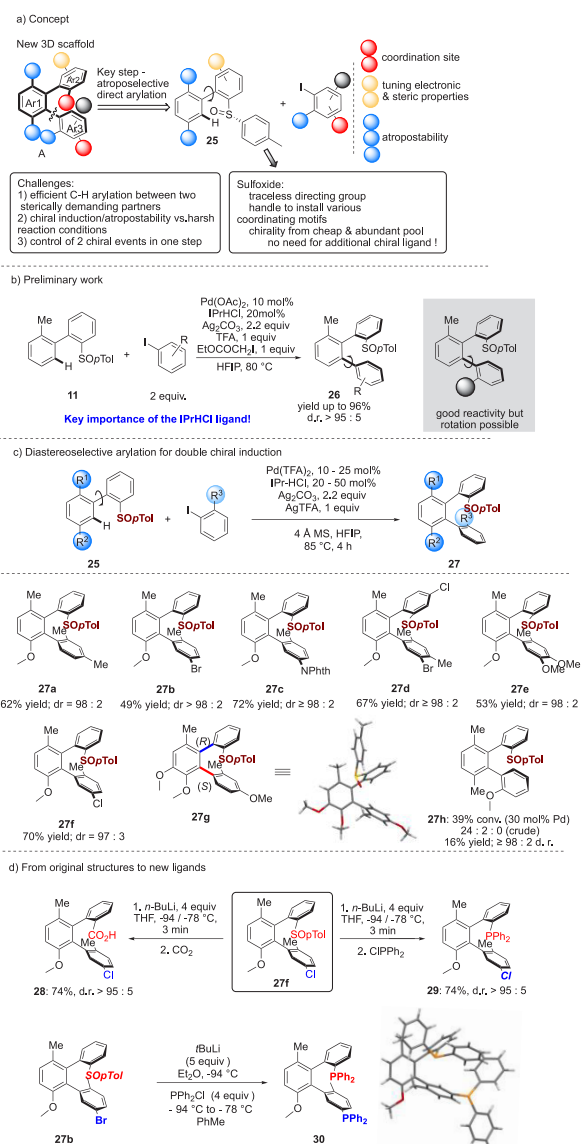


Figure 9. Double atroposelectivity via sulfoxide-directed C–H activation.

the desired triphenyl **26** was thus afforded in 96% yield and >95:5 dr albeit increased reaction temperature (80 °C) was necessary. The reaction showed good functional group tolerance regarding the substitution pattern of the aryl-iodide coupling partner. Importantly, the *ortho*-substituted coupling partners performed well under the standard reaction conditions while increasing the reaction time to 24 h. However, due to the low atropo-stability of the second chiral axis of **26**, this chiral element cannot be controlled under the reaction conditions, i.e., temperature of 80 °C and long reaction time.

This preliminary work clearly suggested that the desired bis-atropo-chiral compounds require increased steric hindrance. Accordingly, the *meta*-substituted biaryl sulfoxide **25** was designed as a new substrate.² Direct arylation of **25** with the *ortho*-substituted aryl iodide was though clearly more challenging and only trace amounts of the desired product could be detected under the previously optimized reaction conditions

(Figure 9c).³⁵ Interestingly, the use of Pd(OAc)₂ or Pd(OPiv)₂ resulted in the formation of unexpected C–OAc and C–OPiv coupling products. The formation of such side products could be hampered by adding well-soluble silver salts, such as AgTFA, AgOTf, or AgBF₄. Finally, the synthetically useful protocol could be established using Pd(TFA)₂ catalyst and replacing the TFA additive with the corresponding silver salt. The reaction is also highly water-sensitive and therefore the addition of the molecular sieve guaranteed higher efficiency. The optimized protocol allowed coupling of **25** with the *ortho*-substituted iodoarenes, delivering the expected triaryl scaffold **27** as a single diastereomer. Remarkably, the presence of the optically pure sulfoxide directing group allowed perfect control of both chiral elements, and therefore one out of 4 possible diastereomers is formed despite the relatively high reaction temperatures. The rotational barriers of both chiral axes are sufficiently high ($\Delta G = 37$ kcal/mol for Ar¹–Ar² and $\Delta G = 32.5$ kcal/mol for Ar²–Ar³) to prevent the racemization even at 80 °C over the prolonged reaction time. The reaction scope investigations showed that various *ortho*-substituted partners are compatible with this reaction protocol, furnishing, among others, the halogen-substituted **27b**, **27d**, and **27f**. Various substituents may also be introduced on the aromatic ring bearing the sulfoxide DG. In contrast but not surprisingly, the reaction is sensitive to the steric hindrance induced by the *meta*-substituent as in case of **27h**.

The unique stereoselectivity observed during this transformation can be attributed to two distinct events. While the Ar¹–Ar² axis is controlled via a dynamic kinetic resolution type process comparable to the previously observed direct acetoxylation, the second Ar²–Ar³ axis is expected to result from a stereoselective oxidative addition of the aryl-iodide coupling partner to the chiral palladacyclic intermediate.

Among the newly generated triphenyl compounds, products **27b**, **27d**, and **27f** caught our particular attention. Indeed, previously demonstrated stereoretentive sulfoxide–lithium exchange/electrophilic trapping should allow us to further diversify these unique chiral scaffolds. Moreover, the presence of Br or Cl atoms on the other aromatic ring opens additional perspectives for the synthesis of unprecedented mono- or bicoordinating ligands exhibiting original architecture. As expected, selective monolithiation of **27f** furnished the enantiomerically pure triaryl carboxylic acid **28** and monophosphine **29** (Figure 9d). Besides, double sulfoxide/lithium and Br/lithium exchange could be astutely exploited to prepare in one step the new BiaxPhos type ligand **30** featuring high potential in asymmetric hydrogenation type reactions (Figure 9d).

NEW CHALLENGE: 3d-METAL-CATALYZED ATROPOSELECTIVE DIRECT ARYLATION

Although the sulfoxide-directed atroposelective functionalization of the biaryl precursors could be established as a powerful tool to reach a large panel of axially chiral compounds, the design of an enantioselective direct arylation reaction would provide a complementary tool to diversify the panel of chiral biaryls. Recently, major advances in organocatalytic direct arylations have been achieved.³⁸ However, metal-catalyzed atroposelective direct arylation appears as a complementary and attractive methodology to access heteroaromatic atropisomeric scaffolds.^{10b} However, as mentioned before, from a conceptual viewpoint such a transformation presents a key difficulty: how to perform Ar–H/Ar–X coupling between two sterically demanding partners under sufficiently low temperatures to guarantee the

atropo-stability of the newly generated compounds under the reaction conditions. Following the pioneering example by Yamaguchi and Itami,³⁵ Cramer and Baudoin developed in collaboration the first highly selective Pd-catalyzed arylation of triazoles **31**, furnishing the desired products **32** in high yields and enantioselectivities up to 94% ee (Figure 10a).³⁹ In this case, the selection of *N*-heterocyclic substrates guarantees relatively easy and regioselective metalation, using a finely designed axially chiral phosphine/phosphine oxide type ligand. The impressive atropo-stability of the newly generated atropisomeric compounds guarantees the perfect chiral induction and conservation of the optical integrity of the products despite relatively high reaction temperature. Very recently, a panel of atroposelective direct arylations was complemented with Ir-catalyzed coupling between tetralone derivatives **33** bearing an imine directing group and *ortho*-substituted aryl boronic acid derivatives. In this case excellent enantioselectivity could be reached using a chiral version of CpIr(III)-complex, while a stoichiometric amount of a Cu-catalyst is required to guarantee an efficient transmetalation step. Under the optimized reaction conditions and mild reaction temperature (45 °C), atropisomeric aryl-tetralones **34** were delivered with excellent enantiomeric ratios (Figure 10a).⁴⁰ However, not only the scarcity of atroposelective direct arylation reactions but also the need for a noble metal catalyst to promote such reactions clearly illustrate the infancy of this research field.

Recent major developments in the field of 3d-metal-catalyzed C–H activation open new perspectives for the rapid construction of more complex molecules from simple precursors.^{12c} Induction of chiral information using 3d-metal-based catalysts is still particularly challenging, and only recently several key contributions have been reported.⁴¹ While considering applications of 3d-metals in C–H activation, the particular reactivity of low valent cobalt catalyst rapidly caught our attention. Indeed, the pioneering examples by Yoshikai⁴² and Ackermann⁴³ clearly illustrated the high reactivity of the *in situ* generated low valent cobalt species to promote the C–H activation step at temperatures as low as room temperature. Such a high reactivity under mild reaction conditions seemed particularly appealing for the development of direct enantioselective arylation reaction. However, design of a chiral catalytic system based on Co(I)-species is far from trivial as illustrated by a single example in the literature corresponding to the direct alkylation of the indole core reported by Yoshikai in 2015 (Figure 10b).⁴⁴

To initiate this project on enantioselective Co(I)-catalyzed direct arylation, conducted in collaboration with the group of Ackermann, indole **35** bearing an imine directing group at the C3 position was designed as substrate. Indeed, based on the literature precedent, insertion of Co into C2–H was expected to be facile and achievable at the room temperature (Figure 10c). In addition, the synthesis of atropisomeric C2-aryl indoles is extremely rare and limited to organocatalytic approaches.⁴⁵

Initially, direct coupling of the indole **35** with *ortho*-iodotoluene was explored using various phosphine and carbene type ligands (Figure 10d).³ Unfortunately, relatively poor reactivity and enantioselectivity were observed. The optimal results were obtained using an unusual *meta*-substituted NHC ligand (L6), previously designed by Ackermann for Fe-catalyzed enantioselective C–H activation,⁴⁶ but the ee of product still did not exceed 35%, regardless of the intensive optimization study. Remarkably, chloronaphthalene **36** turned out to be a more suitable substrate, and the desired direct arylation occurred with

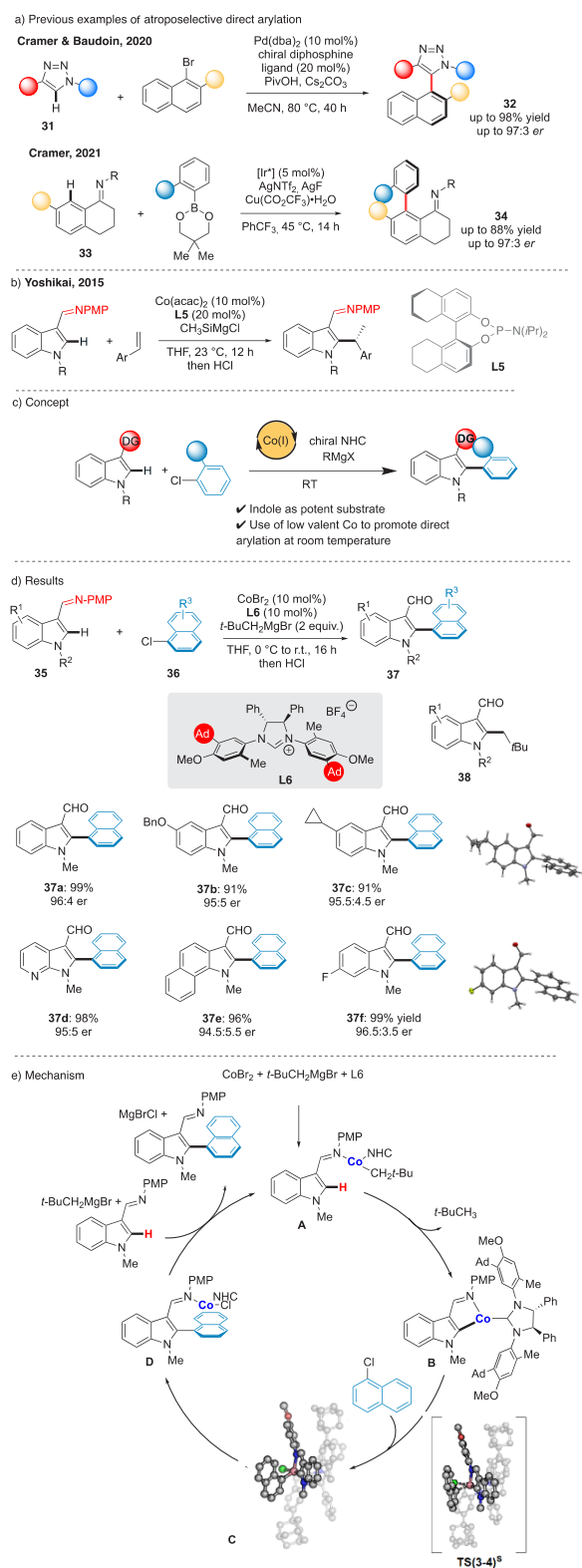


Figure 10. Atropo-enantioselective Co-catalyzed C–H activation.

a very high 86% ee and 70% yield. Following fine-tuning of the ligand's structure and optimization of the reaction conditions

resulted in the generation of **37** in exceptional 92% ee and quantitative yield. Regarding the ligand design, the precise substitution of the aromatic rings is absolutely crucial for the reactivity and the stereoselectivity of the reaction. Indeed, with increasing (*i*Pr) or decreasing (OMe) steric hindrance at the *ortho*-position, significantly lower atroposelectivity was reached. An adamantyl-substituent at the *meta*-position is essential for dispersive interaction controlling the key transition state while the introduction of an additional electron-donating substituent at the *para*-position increases the reactivity of the catalytic cycle guaranteeing full conversion of the substrate. In addition, fine design of the ligand is also important to prevent the formation of the side product **38** resulting from the C2-alkylation of the substrate (transfer of the alkyl group from the Grignard reagent). Notably, while the reaction is not sensitive to the Co-precursor, the desired reactivity is reached exclusively in the presence of (CH₃)₃CCH₂MgBr Grignard reagent. The quality of the Grignard reagent and its concentration were also primary parameters to be perfectly controlled to ensure reproducibility. Substrate scope investigation revealed good functional group tolerance as various indoles performed well, including aza-indole or indoles bearing biorelevant fluorinated motifs. In-depth experimental mechanistic studies suggest that the C–H activation is not rate-determining (KIE of approx. 1), but oxidative addition of the chloronaphthalene is expected to be the limiting step (1st order reaction with respect to chloronaphthalene). Besides, the reaction is extremely fast, as >50% conversion is reached within only 10 min. DFT calculations conducted in parallel allowed us to propose the catalytic cycle (Figure 10e). After the initial generation of the active Co(I)-catalyst via reduction of the Co-precursor in the presence of RMgBr, C–H activation takes place at the C2 position, arguably via a ligand-to-ligand hydrogen transfer (LLHT)-type mechanism.⁴⁷ Subsequent oxidative addition of the Ar–Cl is a rate- and stereodetermining step. Importantly, the excellent chiral induction can be attributed to the agostic interaction between the ligand and the indole substrate.

The synthetic utility of this transformation was further exemplified by various postfunctionalizations, thus affording a large panel of C2-atropisomeric indoles.

This work clearly showed that due to the complementary reactivity of 3d-metals alternative mechanistic scenarios may be enhanced, thus allowing mild metalation and opening therefore new opportunities for the atroposelective synthesis.

■ C–N ATROPISOMERISM: INTRIGUING CHIRALITY ELEMENT

Over the years, atropisomerism has been mainly reduced to the axial chirality of biaryl and heterobiaryl compounds. However, restricted rotation around a single bond is not limited to the Ar–Ar motif and may concern C–N or C–olefin motifs as well. C–N atropisomeric compounds have been attracting increasing attention as appealing candidates in the pharmaceutical industry.⁴⁸ However, despite the expanding importance of C–N atropisomeric molecules, their asymmetric synthesis has remained, over the years, a niche topic, and only recently extensive efforts have been developed to solve this important synthetic challenge.⁵ The initially reported strategies, including desymmetrization type reactions, *N*-functionalization of benzamides, and construction of an aromatic ring, have been recently complemented with the C–H activation approach used to selectively decorate the prochiral *N*-Ar motifs. Surprisingly, the generation of C–N atropisomeric compounds via stereo-

selective *N*-arylation has remained poorly explored. The organocatalytic approach was used to functionalize 2-naphtholes,⁴⁹ while aromatic substitution type reactivity could be used to prepare atropisomeric indoles in the presence of a planar chiral Cr-containing coupling partner.⁵⁰ In clear contrast, metal-catalyzed transformations have remained unprecedented despite the extraordinary potential of the Buchwald–Hartwig, Ullmann, or Cham–Lam couplings.^{9,12b,51} The lack of such asymmetric methodology can be attributed to the inconsistency between the reaction conditions, frequently requiring high reaction temperatures, and the atropo-stability of the newly generated products.

To address this challenge, we surmised that metal-catalyzed *N*–Ar coupling of sterically hindered partners should be facilitated by increasing the reactivity of the arylating agent (Figure 11a). Accordingly, hypervalent aryl iodines appeared as

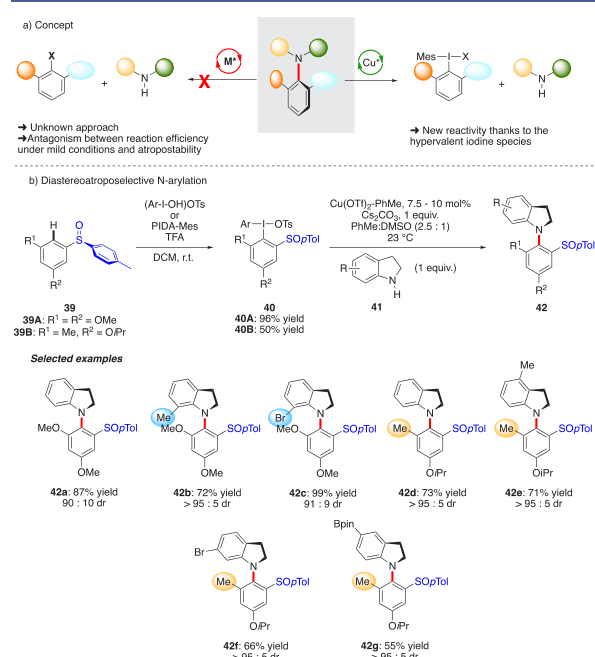


Figure 11. Atropo-diastereoselective Ullmann coupling.

promising candidates, as their reactivity in oxidative addition is significantly higher compared to the corresponding aryl iodides.⁵² Targeting a sustainable catalytic system, we have thus endeavored to develop asymmetric Ullmann coupling using hypervalent aryl iodines as coupling partners.⁵³ To maximize the chances of efficient stereoinduction, a diastereoselective reaction was first envisioned, using enantiopure hypervalent iodine **40** bearing the sulfoxide motif as the chiral auxiliary.⁵⁴

At the outset, **40** could be prepared from the corresponding 3,5-dimethoxybenzylsulfoxide, using Koser or Mes-PIDA reagents. Subsequent coupling of **40A** with indoline, using Cu(II)-catalyst and a base delivered the desired product in satisfying diastereoselectivity (90:10), albeit low yield. Extensive optimization of the reaction conditions revealed that the choice of the base and the use of DMSO/DCE solvent mixture are crucial for reaching synthetically useful yields. Notably, the rotational barrier of the coupling product **42a** of 24.8 kcal/mol is insufficient to guarantee the atropo-stability of this molecule over prolonged reaction time even at room temperature. Consequently, steric hindrance of the C–N axially chiral

indolines was amplified either by introducing an additional substituent at the C7 position of the indoline or by using more sterically encumbering hypervalent aryl iodine **40B**. Accordingly, excellent diastereoselectivity up to >95:5 was reached. Good functional-group tolerance of this catalytic system allows interesting postfunctionalization of the newly generated atropisomeric compounds, including Pd-catalyzed cross-couplings. The indoline core can also be efficiently oxidized into the indole motif, while efficient sulfoxide/lithium exchange further illustrates the traceless character of this chiral auxiliary.

The generality of this first atroposelective Ullmann N-arylation (Figure 11b) is however limited by the accessibility of the hypervalent aryl iodines bearing the sulfoxide auxiliary. Indeed, their preparation via ligand exchange-type reactions is possible only for highly electron-rich aryl-sulfoxides, while the use of dissymmetrical precursors raises regioselectivity problems. On the other hand, the general methodology to access hypervalent iodines via oxidation of the corresponding Ar–I precursors is not relevant in this case as concomitant I(I)/I(III) and sulfoxide/sulfone oxidations. To overcome this difficulty and to further expand the panel of compounds accessible via this methodology, the development of an enantioselective version using simplified, achiral hypervalent iodines appeared as a solution of choice.⁴ While considering the choice of the catalytic system, a combination of the Cu-precatalyst with BOX-type ligand **L7** was rapidly selected as the promising candidate.⁵⁵ Accordingly, a large screening of the hypervalent iodine coupling partners bearing various coordinating groups in the *ortho*-position has been undertaken. The choice of the coordinating group is expected to have a key role in (1) the catalytic cycle via precoordination of the Cu-catalyst prior to the oxidative addition step and (2) the stabilization of the metallacyclic intermediate. In addition, (3) the steric hindrance induced by this coordinating group will also impact the atropo-stability of the desired product. Accordingly, while this N-arylation failed using acid or ester coordinating groups, the introduction of the amide motif was beneficial, and the optimal chiral induction was attained using the CONH₂ motif. With **43** selected as the benchmark substrate, reaction optimization was conducted indicating that optimal chiral induction is observed using Bn-substituted BOX ligand **L7** and Cu(MeCN)₄BF₄ is the most efficient catalyst source. Although the efficiency of this transformation was initially limited to approximately 40–50%, due to the probable catalyst poisoning by the coordinating product, significantly higher yields could be reached by adding Lewis acid, such as BF₃–OEt₂ in the reaction mixture to liberate Cu for additional catalytic cycles. Under such optimized reaction conditions, various indolines reacted smoothly, furnishing functionalized atropisomeric compounds **44** in generally high yields. Besides, a panel of hypervalent iodines is compatible with this reaction, thus translating into a diversity of Ar-motifs on the final product. Remarkably the reaction is characterized by extremely fast initial rate; even at room temperature 50% conversion could be reached in only a few minutes. In addition, it features extremely strong nonlinear amplification (Figure 12b). Indeed, the ligand exhibiting only 20% ee is able to promote already highly enantioselective transformation, furnishing the expected product in 90% ee. The origin of the exceptional nonlinear amplification could be attributed to the initial synthesis of a Cu₂ type complex, i.e., coordination of the metal with two BOX ligands. In such a case, the heteroleptic CuL₂ complex is inactive in the catalytic cycle, allowing scavenging of the minor enantiomer of the ligand. In the first

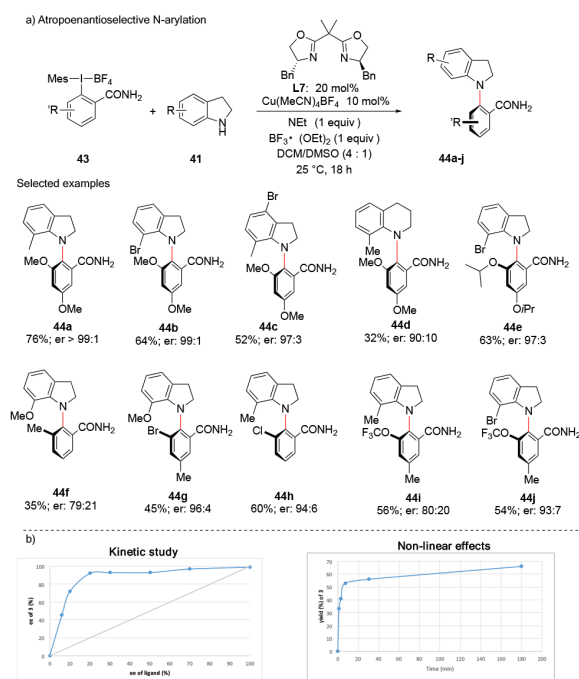


Figure 12. Hypervalent iodine as new reactants allowing atroposelective Ullmann–Goldberg coupling.

step of the catalytic cycle such CuL₂ complex undergoes decoordination of one BOX ligand, thus delivering the catalytically active complex. This hypothesis could be confirmed by the generation of the Cu(L7)₂ complex and its characterization via X-ray structure. Further intermediates of the catalytic cycles have been detected via in situ HRMS-ESI analysis. The final diversification of these C–N atropisomeric compounds via coordinating group transformation and oxidation of the indole motif further illustrated the more general synthetic utility of this new methodology.

Interestingly, the potential of the Cu/Box-catalytic system in combination with hypervalent iodine is not limited to the synthesis of the C–N atropisomeric compounds. Recently, a closely related protocol was used to promote atroposelective C3-arylation of indoles, thus furnishing C–C atropisomeric compounds.⁵⁶

Even though atroposelective metal-catalyzed N-arylation still remains a niche topic, several intramolecular transformations have been recently reported. In 2019 Gu and co-workers reported a new Cu/*N,N'*-(cyclohexane-1,2-diyl) dipicolinamide catalyst for an intramolecular Ullmann-type C–N coupling occurring with concomitant control of the stereochemistry of the N–Ar bond. Accordingly, a diversity of phenanthridin-6(*5H*)-one structures could be prepared in excellent enantiopurities.⁵⁷ While considering an atroposelective version of the Buchwald reaction, a pioneering example of an intramolecular Pd-catalyzed coupling was reported already in 2016 by Kitagawa. Using Pd/R-DTBM-Segphos ligand, the C–N coupling was promoted, delivering phenanthridin-6(*5H*)-one-type products, albeit only a moderate level of enantioselectivity could be reached (68% ee).⁵⁸

CONCLUSIONS

The growing importance of atropisomeric compounds and their expanding application call for the development of innovative and sustainable strategies to access rapidly, efficiently, and highly stereoselectively such compounds. In this context, the C–H activation field has recently opened new avenues for the straightforward preparation of various atropisomeric compounds, including biaryls and C–N axially chiral compounds from relatively simple precursors. Where the strategy involving C–H activation of the preexisting biaryl unit is concerned, recent major achievements in this field (transient directing group approach and Rh-catalyzed enantioselective reactions) together with our own contributions on sulfoxide-directed atropo-diastereoselective reactions certainly provide synthetically useful and easy to apply methodologies. Significant postmodularity of the atropisomeric biaryl aldehydes and biaryl sulfoxides render these approaches highly appealing for total synthesis and preparation of more complex atropisomeric molecules. Currently, these strategies are mainly limited to C–C bond formations, while direct acetoxylation and iodinations remain rare, and therefore the development of new protocols allowing direct installation of alternative functionalities would further improve the synthetic value of this approach. Unfortunately, the use of a Pd-catalyst in relatively high catalyst loading (typically 5–10 mol %) might be a significant limitation when considering large-scale implementation of such reactions.

Regarding direct arylation-type reactions, the compatibility of such transformations with heterocyclic substrates seems particularly appealing and complementary to the direct functionalization of biaryls. Accordingly, original atropisomeric compounds can be rapidly afforded. Within the next years, this type of transformation will certainly catch increasing attention, and original catalytic cycles based on the use of nontoxic and abundant 3d metals are expected to provide highly appealing solutions.

In addition, the design of innovative, highly reactive coupling partners, such as hypervalent iodine, provides also new opportunities for previously inaccessible atropisomeric syntheses. We have discovered that metal-catalyzed atroposelective N-arylation can indeed be possible thanks to the use of hypervalent iodines as superior coupling partners. However, the generality of atroposelective N-arylation remains to be achieved to access an unlimited panel of C–N atropisomeric compounds for future applications in pharmaceutical and agrochemical industries. In parallel to the metal-catalyzed methodologies, alternative strategies including organocatalytic reactions have been attracting growing attention to building up atropisomeric compounds.

The new methodologies developed for atropisomeric synthesis open various new possibilities. Certainly, over the next years, new types of axially chiral compounds will be synthesized, targeting original applications in not only the pharmaceutical industry but also fragrances, agrochemistry, and material science.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Sabine Choppin** conceptualization (supporting), data curation (supporting), writing-review & editing (supporting); **Joanna Wencel-Delord** conceptualization (lead), data curation (lead), funding acquisition (lead), writing-original draft (lead), writing-review & editing (lead).

Notes

The authors declare no competing financial interest.

Biographies

Sabine Choppin studied chemistry at the University Henri Poincaré in Nancy. From 1998 to 2001, she undertook her Ph.D. studies under the supervision of Prof. Yves Fort and Dr. P. Gros. Then she moved to Louvain La Neuve, Belgium, in the group of Prof. Olivier Riant. In 2002, she became assistant professor at the engineering school, Ecole Européenne de Chimie, Polymères et Matériaux ECPM, University of Strasbourg, and 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.

Joanna Wencel-Delord was educated in chemistry at the Ecole Nationale Supérieure de Chimie de Rennes, France, and she received her Ph.D. 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 temporary assistant professor position (ATER) at the University of Strasbourg (Prof. P. Compain), she joined the French National Center for Scientific Research (CNRS) in 2013 as an associate researcher in the group of Prof. F. Colobert (University of Strasbourg, France). In 2021 she was promoted to Research Director. Her recent research interests mainly focus on the development of new methodologies for the asymmetric C–H activation. In parallel, she is working on the synthesis of the C–N axially chiral compounds via metal-catalyzed atroposelective N-arylations and the chemistry of rare hypervalent compounds.

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■ DEDICATION

Dedicated to Prof. Françoise Colobert for her pioneering contributions in the field of atroposelective synthesis.

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