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Two Chiral Events in One C-H Activation Step: a route towards terphenyl ligands with two atropisomeric axes.

Quentin Dherbassy,[a] Jean-Pierre Djukic,[b] Joanna Wencel-Delord,*[a] and Françoise Colobert*[a]

Abstract: Herein we disclose the synthesis of original chiral scaffolds - *ortho*-orientated terphenyls presenting two atropisomeric Ar-Ar axes. These unusual structures are built up using the C-H activation approach and remarkably both chiral axes are controlled with excellent stereoselectivities in a single transformation. During the reaction, not only atroposelective functionalization of a biaryl precursor occurs imposing one chiral axis, but also an unprecedented atropo-stereoselective C-H arylation takes place generating the second chiral element. These enantiopure *ortho*-terphenyls shows an original tridimensional structure and thus constitute a unique ground to build-up a library of enantiopure bicoordinating ligands such as new **S/N-Biax** and diphosphine **BiaxPhos**.

Axial chirality, arising from the hindered rotation about the Ar-Ar axis, is an important feature of a variety of molecular scaffolds[1] conferring unique properties to certain biologically active compounds[2] and advanced materials.[3] But arguably the most prominent application of the atropisomeric biaryls relates to their use as stereogenic ligands.[4] Quite surprisingly, polyaromatic structures presenting two *ortho*-orientated chiral Ar-Ar axes are extremely rare (Figure 1). In 2006, Shibata astutely used [2+2+2] cycloadditions to convert triynes into symmetrical *ortho*-terphenyls[5] while Sparr *et al.* reported the synthesis of oligo-1,2-naphthylenes bearing two atropocontrolled binaphthyl axes.[6] Besides, molecules exhibiting both C-C and C-N axial chiralities were also disclosed.[7] In contrast, doubly atropisomeric, *ortho*-orientated dissymmetrical terphenyls **A** (Figure 1), exhibiting important structural diversity, remain elusive although their unusual "open clam shell" geometry seems highly appealing for stereogenic ligands design. To address this synthetic challenge we embarked on designing a general, step-economic and stereoselective protocol, focusing on unprecedented atroposelective directed C-H arylation.[8],[9] Such a C-H coupling presents however major difficulties: 1) reacting together a metallacyclic intermediate resulting from a challenging metallation at a sterically congested position and an *ortho*-substituted iodoarene (recognized as difficult coupling partner); 2) an inherent antagonism between efficiency and atroposelectivity whereas such conditions are detrimental for atropostability. Furthermore, as we target terphenyls with two chiral axes, a perfect stereocontrol of both asymmetric events is necessary. Such a double stereocontrol can be achieved by means of: 1) atroposelective introduction of an aryl substituent on a configurationally unstable biaryl precursor (control of the Ar^1-Ar^2 bond)[10] and 2) direct stereoselective Ar^1-Ar^3 bond formation.

To access terphenyl precursors that can be used as a platform to build up few families of unprecedented ligands, biaryl **1** (Figure 1) bearing a stereogenic sulfoxide moiety, appears as a promising substrate. Few key parameters speak in favor of such a substrate design: 1) the sulfoxide moiety is both, an efficient directing group and a chiral auxiliary accessible in large scale[11] from menthol as chiral pool, 2) traceless character of the sulfoxide [12] should allow convenient installation of various coordinating motifs via post-modifications, 3) chiral ligand-free transformation may be expected as the chirality on the sulfur atom is expected to induce chiral information, 4) access to optically pure compounds is facilitated by a convenient purification of diastereomeric products.[13] Direct arylation of **1** with *ortho*-substituted iodoarenes bearing judiciously selected and located functionalities should thus deliver the terphenyl skeletons, the precursor of several various families of stereogenic ligands with one or two coordination sites (modification of red/orange sphere) and adjustable electronic and steric properties (grey/black sphere). In order to warrant atropostability of the desired terphenyls, important steric hindrance around both Ar-Ar bonds is required (blue spheres).

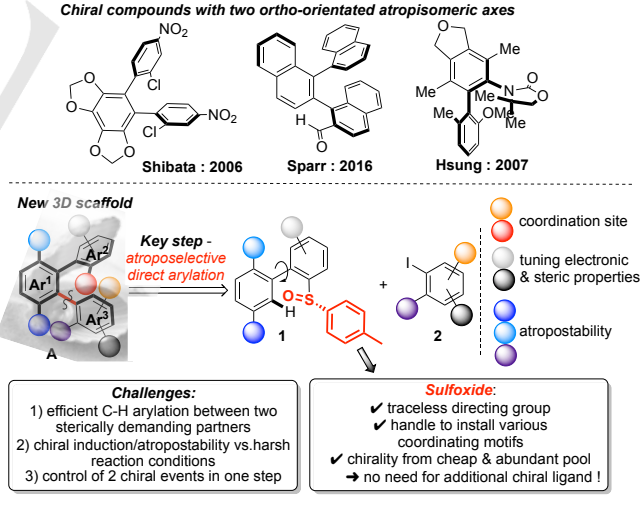

Figure 1. Concept of terphenyl scaffolds as precursor for original chiral ligands

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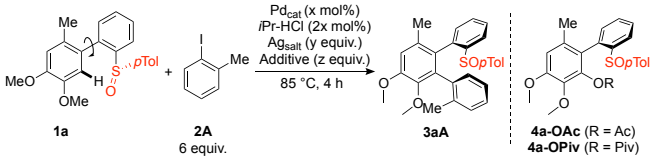
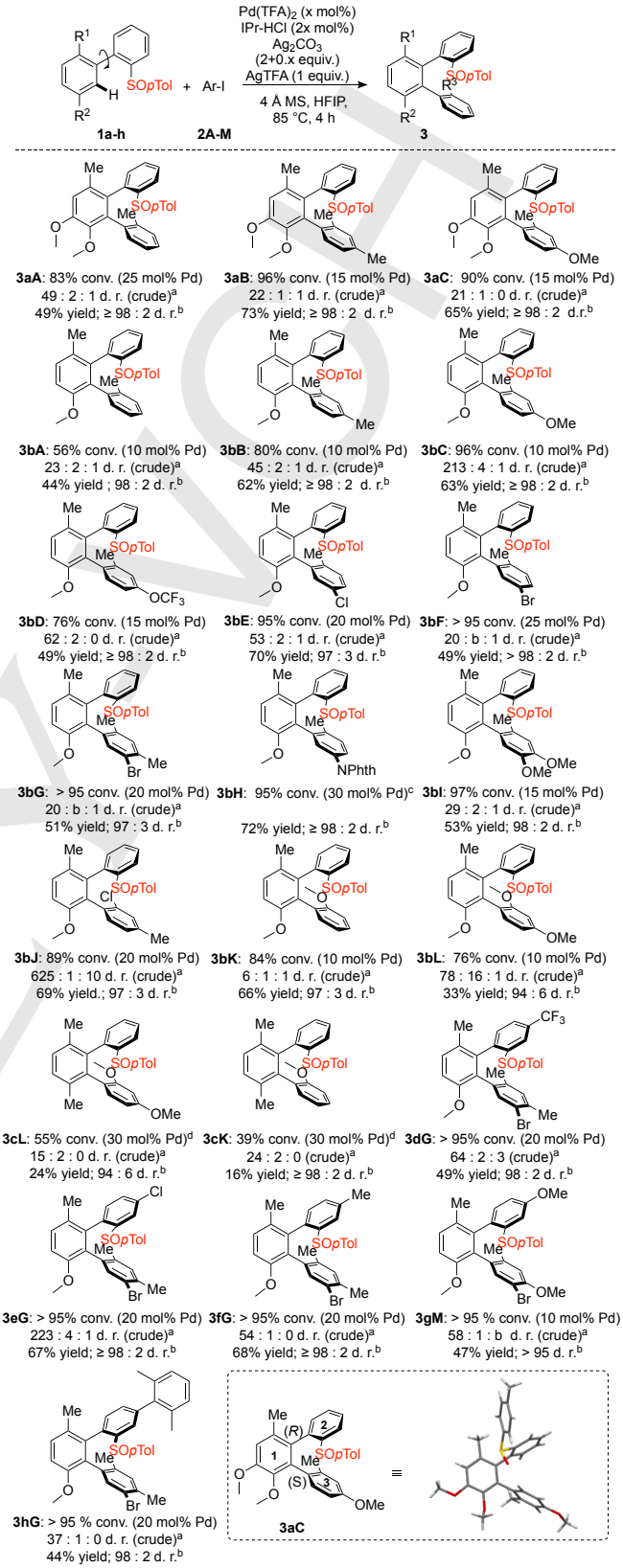
Accordingly, coupling between **1a** and *ortho*-iodotoluene **2A** was selected as a test reaction (Scheme 1). Although initial attempts using standard reaction conditions for direct arylation failed,[14] desired product **3aA** was formed in small amount when using a large catalyst loading of $Pd(OAc)_2$ in combination with N-heterocyclic carbene (NHC) ligand, Ag_2CO_3 salt and trifluoroacetic acid (TFA) as additive. Detailed optimization of the reaction conditions revealed that: 1) $Pd(TFA)_2$ is more effective catalyst than $Pd(OAc)_2$ as side reactions are limited (formation of **4a**); 2) replacement of TFA by AgTFA salt is essential for reactivity and 3) the coupling is highly water sensitive thus addition of an optimized amount of 4Å molecular sieve is crucial to prevent deactivation of the catalyst. Accordingly, under the optimal reaction conditions, *i.e.* $Pd(TFA)_2$ (25 mol%) and IPr-HCl ligand, Ag_2CO_3 (2.5 equiv.) together with AgTFA (1 equiv.) and 4Å MS, in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 85 °C, the desired product was isolated in 49% yield within 4h. Remarkably, ^{1}H NMR analysis of the crude reaction mixture shows formation of **3aA** with excellent diastereoselectivity (d.r. of 49 : 2 : 1) and the purified product is a single atropisomer.



Scheme 1. Test reaction for the synthesis of terphenyls via asymmetric direct arylation

Next, the coupling of **1a** with electron-rich 2-iodotoluene derivatives **2A-C** was completed delivering **3aA**, **3aB** and **3aC** in moderate to good yields, with no loss of the atroposelection (Scheme 2). An additional electron donating substituent on **2** increased the reactivity of this coupling partner and therefore catalytic loading for **3aB** and **3aC** could be decreased to 15 mol%. In contrast, less electron rich biaryl substrate **1b** was more effective than **1a** as the desired arylation was achieved with only 10 mol% of Pd (**3bA-C**). The reaction is compatible with different heteroatoms; not only Cl- and Br-atoms were tolerated but also coordinating motifs such as NPhth or OMe. Besides, *ortho*-position of the aryl-iodide may be substituted by Cl or OMe group (products **3bJ** and **3bK**, **3bL**). More sterically demanding Me substituent could also be introduced at the key, *meta* position of Ar^1 and **3cL** and **3cK** were isolated as atropoisomerically pure compounds albeit in low yield. Finally, electron donating and electron withdrawing substituents are well tolerated on Ar^2, delivering **3dG, 3eG, 3fG, 3gM** and **3hG** in 44-68 % yield. Noteworthy, crystal structure of **3aC** shows the expected spatial proximity of Ar^2 and Ar^3 and the "cavity-like" architecture of the molecule.[15]



Scheme 2. Scope of the terphenyls with two axial chiralities (a) 4 diastereomers could be potentially obtained and 3 of them were identified in "crude" ^{1}H NMR spectra, b) 2 diastereomers detected on the ^{1}H NMR spectra of the purified products, c) for details see SI; d) reaction performed at 115 °C).

In order to unambiguously prove the optical purity of the products, few fundamental tests were performed and the rotational barriers were determined (Figure 2). Firstly, the configurational stability of the sulfoxide was proved by chiral HPLC analysis. Subsequently, the rotational barrier for the Ar^1-

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Ar^2 axis of **3bN** of +37 kcal/mol in the gas phase was computed using Density Functional Theory studies (cf. SI) (calculated half-life of c.a. 112 years at 85 °C) suggesting that the stereoinduction is kinetically controlled. Next, atropodiastereomerically pure **3bB** was subjected to thermal treatment and partial racemization of the Ar^1-Ar^3 axis was evidenced; $\Delta G^{\ddagger}$ (32.4 ± 0.3) kcal/mol (413.15 K) for Ar^1-Ar^3 axis of **3bB** was determined (epimerization half-life of c.a. 73 days at 85 °C), in consistence with computed $\Delta G^{\ddagger}$ of 33 kcal/mol. Comparable stability of both atropo-diastereomers indicates that the Ar^1-Ar^3 coupling is under kinetic control.

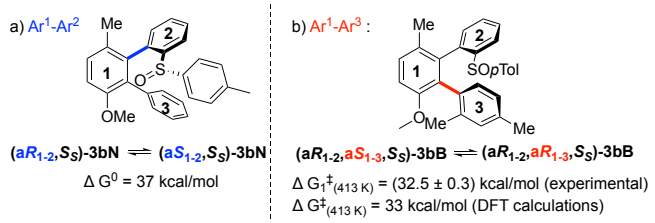
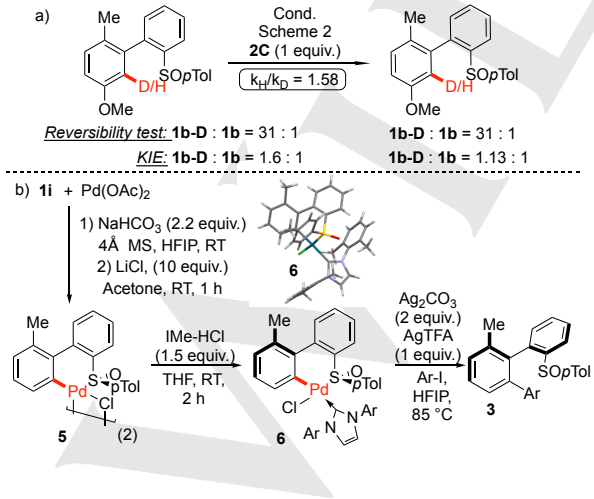


Figure 2. Determination of atropostability of terphenyl scaffolds.

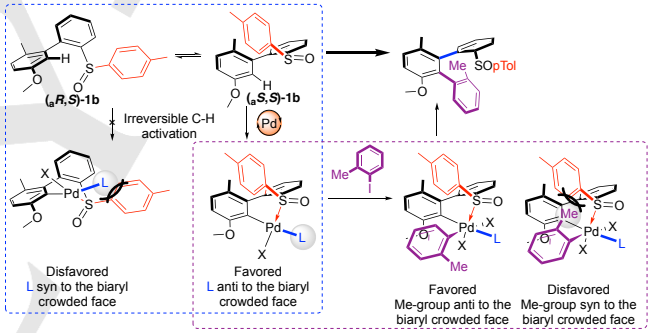
Further mechanistic studies (Scheme 3a) revealed the irreversibility of the C-H activation step (D/H scrambling test) and KIE of 1.58 suggesting that the turnover-limiting step occurs after the C-H cleavage.

Subsequently, in order to characterize the key intermediates, we strove on preparation of the metallacyclic species (Scheme 3b). Unfortunately all attempts of isolation of palladacycle intermediate using substrate **1b** failed but reaction between a simplified substrate **1i** and $Pd(OAc)_2$, followed by ligand exchange, delivered the complex **5**. In presence of the NHC, **5** was easily converted into the well-defined, atropisomeric Pd-NHC complex **6**. The X-Ray structure of **6** clearly shows coordination of Pd by the S-atom.[16] ^{1}H NMR analysis of **6** indicates that the Ar^1-Ar^2 axis is perfectly controlled (d.r. > 98 : 2) during formation of the organometallic intermediate.[17] Finally, while investigating reductive elimination from **6**, the importance of both Ag_2CO_3 and AgTFA salts to liberate the coupling product was confirmed.



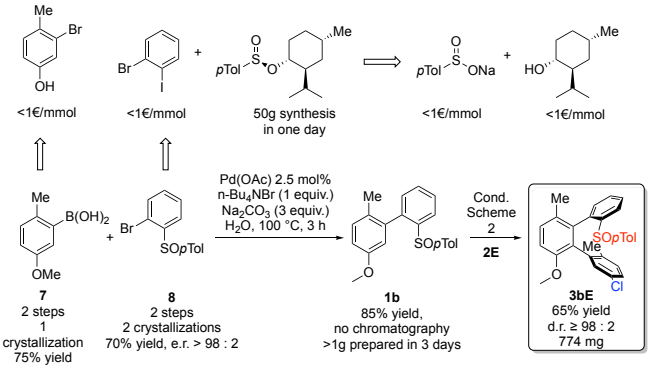
Scheme 3. Mechanistic studies.

The originality of this transformation comes from the unique possibility to control both axial chiralities in a single transformation (Scheme 4). Isolation of the atropisomerically pure palladacyclic intermediate **6** and rapid racemization of the substrate under the reaction conditions clearly suggest that the stereoselectivity of Ar^1-Ar^2 axis is induced during the C-H activation step. When diastereomer **($_a$*S,S*)-1b** reacts with NHC-Pd catalyst, the interactions between the chiral auxiliary and the NHC ligand are minimized (*p*Tol moiety above the plane vs. NHC ligand underneath the plane). In contrast, palladation of **($_a$*R,S*)-1b** would require accommodation of the bulky ligand and *p*Tol group in the same plane and is yet disfavored and the transformations implies Dynamic Kinetic Resolution. In contrast, chirality of the Ar^1-Ar^3 linkage arises from the favored oxidative addition of the Ar-I coupling partner from a sterically less congested face of the metallacyclic intermediate, *i.e.* minimizing a steric hindrance between the SO*p*Tol moiety and *ortho*-substituent of the Ar-I. In addition, reductive elimination from such a sterically less congested Pd(IV) intermediate seems also enhanced.



Scheme 4. Proposed stereoinduction model.

As our goal is to access ligand precursors, a large-scale synthesis of **3bE** was undertaken (Scheme 5). **1b** was prepared at gram scale, in 3 steps (53% total yield) from inexpensive starting materials, using only cheap reactants and catalysts and with no need for silica gel column purifications. The large scale direct atroposelective arylation with **2E** furnished optically pure **3bE** in 65% yield (774 mg).



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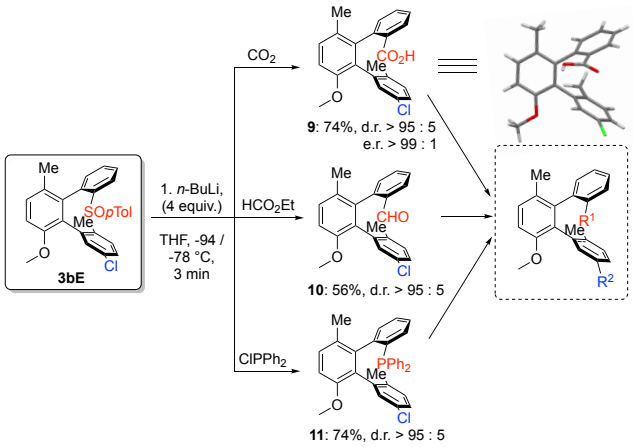
Scheme 5. Large-scale synthesis of **3bE**.

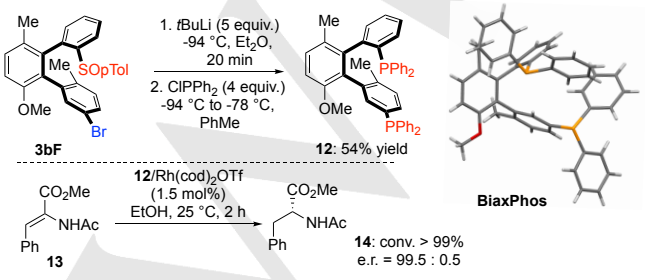
Next, in order to illustrate that the sulfoxide moiety is an useful handle to install a variety of coordinating motifs while conserving the optical purity of the scaffold, a sulfoxide/lithium exchange



Scheme 6. Post-functionalization of terphenyl scaffolds.

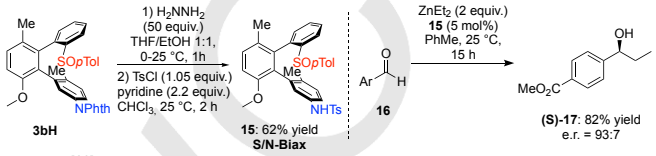
followed by trapping with CO_2, HCO_2Et or PPh_2Cl were performed, delivering the corresponding enantiomerically pure products **9**,[18] **10** and **11** (Scheme 6).

The key application of these terphenyls with two chiral axes concerns their use as chiral ligands. Based on the X-ray structure of **9**, it can be speculated that related ligands could show a "pseudo-planar chiral" geometry if one coordinating moiety is placed in *ortho*-position of Ar^2 and the second coordinating moiety in *meta*-position of Ar^3. Accordingly, brominated *ortho*-terphenyls **3bF**, **3bG**, **3(d-h)G**, **3gN**, all obtained in decent yields and excellent stereoinduction, are ligand precursors. As example, **3bF** was subjected to double lithium exchange followed by quenching with PPh_2Cl and delivered the diphosphine ligand **BiaxPhos 12**[19] in 54% yield (Scheme 7). **BiaxPhos**, the first ligand presenting such "open clam shell" tridimensional structure, revealed excellent reactivity in Rh-catalyzed benchmark hydrogenation of the trisubstituted methyl (Z)-α-acetamidocinnamate (MAC) **13** delivering the **14** with 99.5:0.5 e.r.



Scheme 7. BiaxPhos synthesis and its application in asymmetric hydrogenation.

Besides **S/N-Biax 15** ligand, synthesized in two steps from **3fR**, showed good activity in 1,2-addition of Et_2Zn to an aldehyde (Scheme 8). Under non-optimized reaction conditions the desired alcohol **17** was isolated in high yield and good e.r. of 93:7, comparable with a planar-chiral ferrocene-derived S/N ligand.[20]



Scheme 8. S/N-Biax and its application in asymmetric reaction.

We present herein a new family of enantiopure skeletons, terphenyls exhibiting two atropisomeric Ar-Ar axes. These original compounds are built up via a challenging asymmetric C-H activation route. This direct coupling is not only the first example of highly atroposelective Ar-Ar bond formation, but also two chiral elements are perfectly stereocontrolled during one synthetic event. Hence accessed terphenyls present a unique, tridimensional structure and by means of functional group modifications they can be easily converted into an array of unique bicoordinating ligands. Accordingly, diphosphine **BiaxPhos** and **S/N-Biax** ligands were prepared and both showed excellent stereoinduction in asymmetric hydrogenation and 1,2 addition of Et_2Zn respectively. These results clearly showcase the potential of these chiral ligands for various asymmetric transformations.

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Keywords: asymmetric C-H activation • axial chirality • terphenyl • chiral ligands • sulfoxide

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[14] For details see SI.

[15] CCDC 1557078 from the Cambridge Crystallographic Data contain the supplementary crystallographic data for **3aC**.

[16] CCDC 1557079 from the Cambridge Crystallographic Data contain the supplementary crystallographic data for **6**.

[17] The diastereopurity of **6** is also suggested by low temperature ^{1}H NMR study; for details see SI.

[18] CCDC 1557080 from the Cambridge Crystallographic Data contain the supplementary crystallographic data for **9**.

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