DOI: 10.1002/adsc.201300446

Atropodiastereoselective C–H Olefination of Biphenyl *p*-Tolyl Sulfoxides with Acrylates

Thomas Wesch,[a] Frédéric R. Leroux,[a] and Françoise Colobert[a,*]

[a] Laboratoire de Chimie Moléculaire (UMR CNRS 7509), Université de Strasbourg, ECPM, 25 Rue Becquerel, 67087 Strasbourg, France
Fax: (+33)-3-6885-2742; phone: (+33)-3-6885-2744; e-mail: francoise.colobert@unistra.fr

Received: May 22, 2013; Published online: August 9, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300446.

Abstract: A stereoselective method for the synthesis of axially chiral biaryl scaffolds by C–H bond functionalization was accomplished using chiral sulfoxide both as the directing group enabling the regioselective activation of a C–H bond and as the chiral auxiliary generating an asymmetric environment in the coordination sphere of the metal complex. We have demonstrated the directing ability of the *p*-tolylsulfinyl group in promoting the Pd(II)-catalyzed C–H olefination of biphenyls.

Keywords: axial chirality; biaryls; C–H functionalization; olefination; sulfoxides

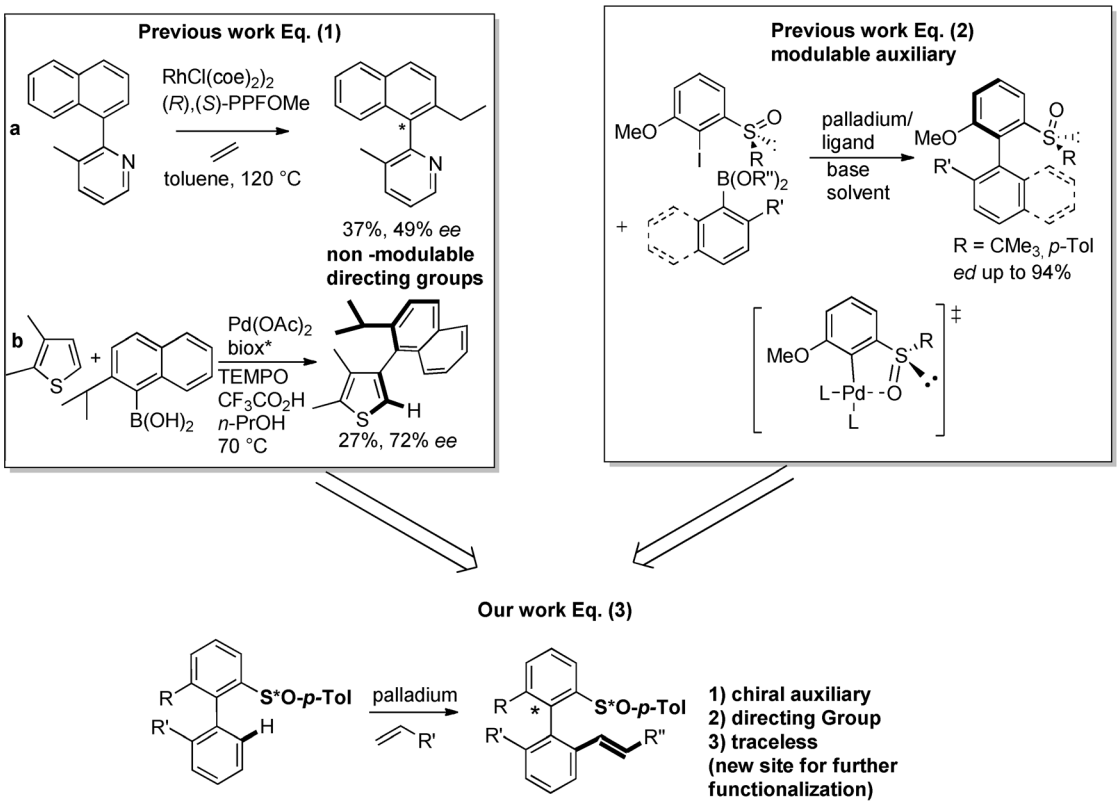
Over the past decade, the use of C–H bonds as functional groups similar to carbon-halogen bonds has represented a powerful, valuable and straightforward strategy for C–C bond formation. Thus, activation of C–H bonds to form C–C bonds in a single step has been efficiently developed and the direct functionalization of these bonds constitutes a fast and atom-economical synthetic approach.[1] However asymmetric C–H bond transformations involving an enantiomerically pure [C–M]* intermediate are still very rare and limited to fairly specific substrates or transformations.[2] Moreover, the synthesis of axially chiral scaffolds by C–H bond activation was the subject of only two works. In 2000 S. Murai[3] reported the Rh-catalyzed atroposelective C–H activation/alkenylation of 2-(1-naphthyl)-3-methylpyridine. The best enantiomeric excess (49%) was obtained by the use of a chiral ferrocenyl phosphine ligand giving the coupling product in 37% yield [Scheme 1, Eq. (1a)]. More recently, J. Yamaguchi and K. Itami[4] described the Pd-catalyzed atroposelective C–H arylation of thiophenes with arylboronic acids in 2012. Chiral bisoxazolines allowed the synthesis of the arylthiophenes in 27% yield and 72% *ee* as best enantioselectivity [{Scheme 1, Eq. (1b)]. Both reports showed the difficulty to control axial chirality in high yield in this C–H activation process. Moreover in both examples pyridine and thiophene moieties, part of the biaryl scaffold, play the role of non-modulable directing groups.

On the other hand, various different approaches have been developed to construct axially chiral biaryl scaffolds.[5] Among them our group has recently reported a highly diastereoselective biaryl Suzuki–Miyaura cross-coupling reaction mediated by sulfoxides between *ortho,ortho'*-disubstituted aryl iodides bearing in *ortho* position a *tert*-butyl or *p*-tolylsulfinyl group and *ortho*-substituted phenylboronic acids or esters.[6] We could show that the diastereoselectivity is facilitated by the formation of a five-membered palladacycle in which the oxygen atom of the sulfoxide coordinates to palladium [Scheme 1, Eq. (2)]. This methodology shows the efficiency of sulfinyl groups as chiral controllers in asymmetric biaryl coupling reactions.[7]

Inspired by this previous work, we hypothesized that in view of the coordinating ability of the sulfoxide moiety, it could be astutely applied in C–H activation to act as both directing group and chiral auxiliary.

Herein we describe the first examples where an easily available enantiopure *p*-tolyl sulfoxide[8] acts as directing group for C–H activation and we evidence its ability as chiral controller in the atroposelective construction of highly functionalized axially chiral biaryls [Scheme 1, Eq. (3)]. Sulfoxide moieties are known to be easily transformed into myriads of synthetically valuable functional groups by sulfoxide/metal interconversion followed by trapping with a range of electrophiles and consequently represent a new site for further functionalization.[9]

Quite surprisingly, the potential of sulfoxides in the context of C–H bond activation had remained underestimated until 2011, when the first reports concern-



Scheme 1. Control of axial chirality by C–H functionalization using a chiral sulfinyl group.

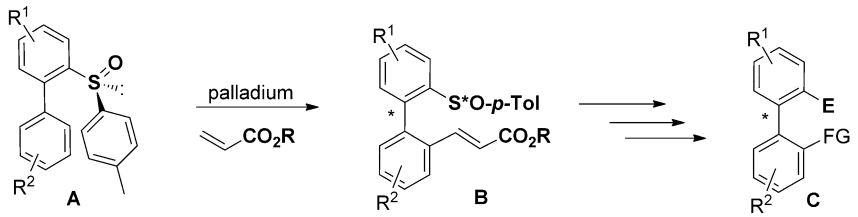
ing the application of 2-pyridyl sulfoxide as directing group were independently published by several groups. These early reports concern palladium-catalyzed directed C–H functionalization of arenes such as acetoxylations,[10] alkenylations and arylations[11] and olefination and coupling reactions with boron reagents.[12] However, the key point in all these reactions is the use of pyridyl-substituted sulfoxides. Indeed, it is rather the pyridyl moiety, known and extensively used in the field of C–H bond activation, that plays the role of the directing group. The sulfoxide is therefore simply used as an "easily removable linker" prone to temporarily install the chelating group.

Very recently, the first example concerning the use of the chelating properties of sulfoxides to direct the C–H bond activation event was reported by Antonchick et al.[13] The key step of this transformation is the sulfoxide-directed cyclometallation of the aromatic ring, followed by the second, intramolecular C–H bond activation and Pummerer rearrangement, giving access to dibenzothiophene scaffolds. Simultaneously and independently our group developed a sulfoxide-mediated intermolecular C–H bond activation and cyclization towards dibenzothiophene sulfoxides.[14]

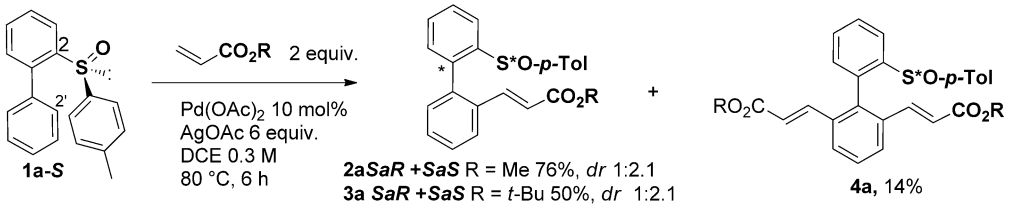
However, the use of sulfoxides as both directing group and chiral auxiliary in C–H functionalization processes has no precedent in the literature.

Our preliminary effort focused on a palladium-catalyzed alkenylation of biaryl moieties **A** with acrylates *via* C–H activation employing an enantiopure sulfoxide as traceless directing group. In this way, configurationally stable biaryls **B**, powerful intermediates towards a family of atropoenantiopure biaryl moieties **C**, become accessible (Scheme 2).

Biaryl sulfoxides **A** were synthesized by means of a palladium-catalyzed Suzuki–Miyaura coupling reaction between aryl iodides bearing in the *ortho* posi-



Scheme 2. C–H activation/alkenylation reaction of biphenyl *p*-tolyl sulfoxide with acrylates.



Scheme 3. Direct C–H activation/alkenylation reaction of biphenyl *p*-tolyl sulfoxide **1a-*S*** with methyl and *tert*-butyl acrylate.

tion the widely used *p*-tolylsulfinyl group and various commercially available arylboronic acids.[15]

Our study commenced by selection of 2-*p*-tolylsulfinylbiphenyl **1a-*S*** as test substrate to explore the role of sulfoxide as directing group in the C–H alkenylation with methyl acrylate. A direct C–H activation/olefination reaction was readily accomplished with AgOAc as oxidant in the presence of palladium(II) acetate as catalyst precursor, and selective product formation was observed. Dichloroethane was identified as the best solvent affording **2a** in 76% yield after 6 h at 80 °C (Scheme 3). We also noticed the formation of di-*ortho*-alkenylated products (through a sequential double C–H alkenylation) with 14% yield. No product was obtained in the absence of palladium catalyst or AgOAc.

The general structure of the new product **2a** was unambiguously determined by ^{1}H and ^{13}C NMR studies showing the presence of two diastereoisomers in a 1:2.1 ratio. The coalescence temperature of **2a** has been determined by variable temperature ^{1}H NMR studies [$\Delta G^{\#}$(363 K) = 17.0 kcal mol^{-1}]. This result indicates that biaryl **2a** is configurationally stable at the reaction temperature and that the enantiopure sulfinyl moiety is not only acting as a directing group for C–H activation in position 2′ but also induces atropodiastereoselectivity during the alkenylation process. The coupling reaction with *tert*-butyl acrylate gave the corresponding biaryl in a lower yield (50%) and the same atropodiastereoselectivity.

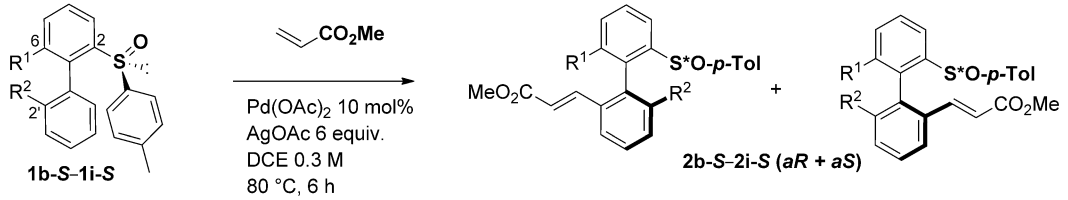
With these optimized reaction conditions in hand, the C–H alkenylation of 2-*p*-tolylsulfinylbiphenyls bearing substituents either in position 6 or 2′ as R^1 and/or R^2 was investigated (Table 1). A wide array of 2-*p*-tolylsulfinylbiphenyls **1b-*S*–1i-*S*** was subjected to the C–H alkenylation with methyl acrylate and the corresponding coupling products **2b–i** were isolated in good to excellent yields showing moderate to excellent atropodiastereoselectivity.

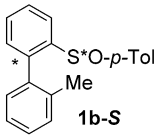
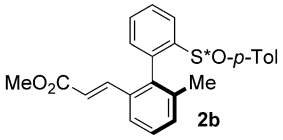
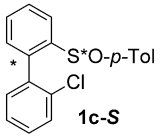
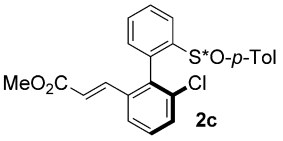
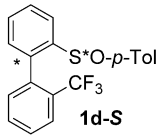
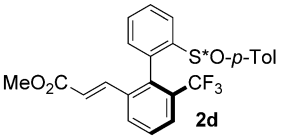
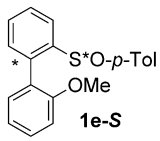
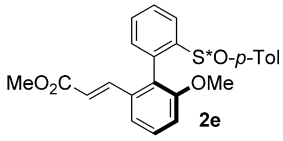
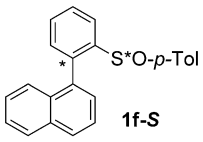
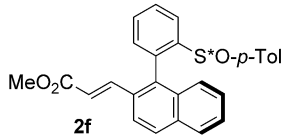
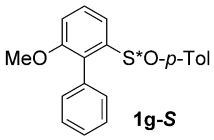
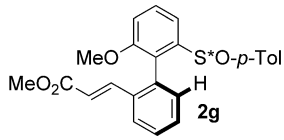
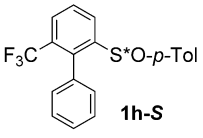
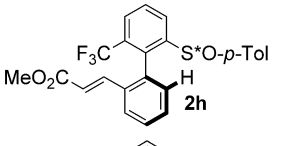
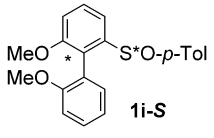
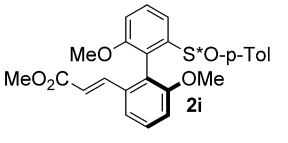
In order to increase the atropodiastereoselectivity during the C–H alkenylation process, compared to our first reaction (Scheme 3), 2′-methyl-2-*p*-tolylsulfinylbiphenyl **1b-*S*** was prepared.[15] Starting from biaryl sulfoxide **1b-*S***, we performed the C–H alkenylation with methyl acrylate and the coupling product **2b** was obtained in an excellent yield of 87% and, as expected, with a better atropodiastereoselectivity (**2b-*SaR*/2b-*SaS*** = 4.6:1)[16] than for **2a** (Table 1, entry 1). Biaryl **1c-*S*** with a chlorine atom and **1d-*S*** with a trifluoromethyl group in position 2′ gave the alkenylation products **2c** and **2d** in 43% and 30% yield and lower atroposelectivity (**2c-*SaS*/2c-*SaR*** = 2.5:1 and **2d-*SaS*/2d-*SaR*** = 2.8:1) (Table 1, entries 2 and 3). With a methoxy group in position 2′, an excellent yield for the C–H alkenylation was observed (87%) but lower control of the chiral axis (**2e-*SaS*/2e-*SaR*** = 1.8:1) (Table 1, entry 4). Starting from biaryl **1f-*S*** with a naphthyl moiety, **2f** was obtained in excellent 86% yield and 3.1:1 atropodiastereomeric ratio (Table 1, entry 5).

To our delight, the atropodiastereoselectivity could be further improved with a substituent at position 6 of biaryl substrates **1g** and **1h**. For example, with a methoxy group at position 6 (**1g-*S***), the C-H alkenylation coupling product **2g** was obtained in 56% yield showing both atropodiastereomers in a 5:1 ratio (Table 1, entry 6). Moreover, with a trifluoromethyl group at position 6 (**1h-*S***), an excellent atropodiastereoselectivity was observed giving the alkenylation product **2h** in 36% yield and 10:1 diastereomeric ratio (Table 1, entry 7). Finally 2′,6-dimethoxy-2-*p*-tolylsulfinylbiphenyl **1i-*S*** gave in the C–H alkenylation process the corresponding tetra-*ortho*-substituted biaryl as a single atropodiastereomer **2i-*SaS*** in 40% yield. The absolute configuration of **2i-*SaS*** was determined by single crystal X-ray diffraction analysis[17] (Figure 1) and we deduced the absolute configuration of all major atropoisomers **2a–h** by comparison of ^{1}H NMR spectra.

We noticed that 2-*p*-tolylsulfinylbiphenyls bearing electron-withdrawing groups at the aryl ring are less active under the reaction conditions (Table 1, entries 2, 3 and 7). Consequently, an electrophilic metallation mechanism is probably favored. Moreover, a total regioselectivity was observed during the olefination reaction, which reasonably suggests that only one specific C–H bond is activated. This selectivity suggests the formation of a 6-membered palladacycle intermediate **D** resulting from the coordination of palladium to the lone pair of the sulfur atom and a subsequent stereoselective insertion of the metal into the appropriately positioned C–H bond (Scheme 4). Subsequently the insertion of the olefin partner into the Pd–C bond leads to the formation of

Table 1. Direct C–H activation/alkenylation reaction of biphenyl *p*-tolyl sulfoxides **1b-*S*–1i-*S*** with methyl acrylate.[a]



Entry	Substrate[d]	Coupling Product	Yield[c] [%]	*dr*[b] *SaR*:*SaS*
1	 **1b-*S***	 **2b**	87	4.6:1
2	 **1c-*S***	 **2c**	43	1:2.5
3	 **1d-*S***	 **2d**	30	1:2.8
4	 **1e-*S***	 **2e**	87	1:1.8
5	 **1f-*S***	 **2f**	86	3.1:1
6	 **1g-*S***	 **2g**	56	5:1
7	 **1h-*S***	 **2h**	36	10:1
8	 **1i-*S***	 **2i**	40	1:50

[a] Biaryl sulfoxides were synthesized by a palladium-catalyzed Suzuki–Miyaura coupling reaction.[15]
[b] Determined by ^{1}H NMR.
[c] Isolated yield.
[d] Atropoenriched starting products racemized at the coupling temperature (see the Supporting Information).

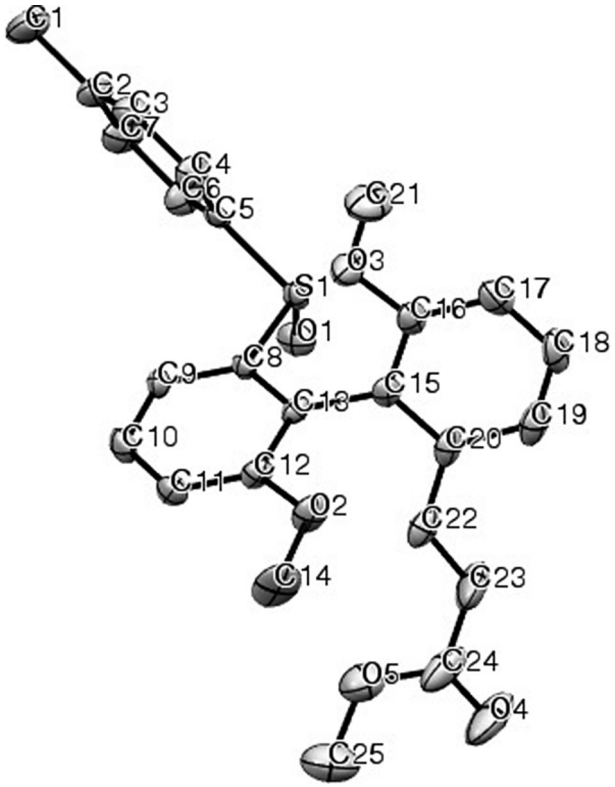
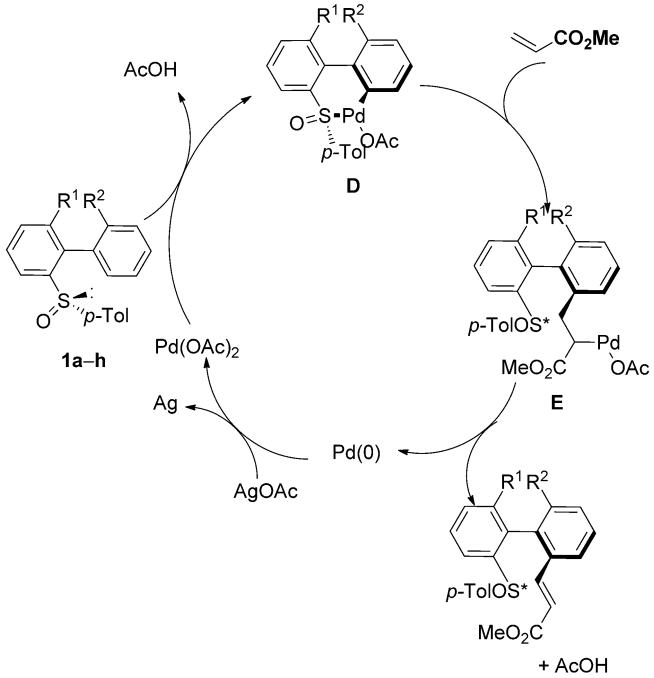


Figure 1. X-ray crystal structure of **2i-*SaS***.



Scheme 4. Plausible mechanism for the direct C–H activation/alkenylation reaction of biphenyl *p*-tolyl sulfoxides **1a-*S*–1i-*S*** with acrylate.

E. The atroposelectivity observed during this reaction results probably from diastereomeric discrimination during the formation of **D**. Coordination between palladium and sulfur favors the cyclometallation step from the sterically less hindered side, opposite to the bulky *p*-tolyl group, affording atropoenriched intermediate **D**. Subsequent β-hydride elimination leads then to the atropodiastereomer and liberation of Pd(0). Pd(II) is regenerated by oxidation of Pd(0) with silver(I).[18]

In summary, we have demonstrated the directing ability of an enantiopure *p*-tolylsulfinyl group in the Pd(II)-catalyzed C–H olefination of biphenyls. Electron-deficient acrylates serve as efficient coupling partners, giving access to *ortho*-alkenylated products in good yields and atropodiastereoselectivities. The significance of this strategy can be further highlighted by the fact that, in contrast to the majority of other asymmetric C–H bond activations where the asymmetric discrimination operates posterior to the insertion of the metal into the C–H bond, here the activation of the C–H bond is the asymmetrically discriminating step. This manuscript represents a proof of concept for the use of sulfoxides as both directing group and chiral auxiliary and opens new perspectives in the field of C–H bond activation reaction using a chiral sulfoxide, a very special motif which presents a unique opportunity for the development of technologies for asymmetric transformation *via* C–H bond activation.

Further investigations are ongoing to extend the scope of the reaction and to apply the process in the synthesis of more complex biaryls.

Experimental Section

General Procedure for the C–H Alkenylation with Methyl Acrylate

2-(*p*-Tolylsulfinyl)biphenyl **1a–i** (0.8 mmol) was dissolved in 1,2-dichloroethane (2.6 mL, 3.25 M). After addition of AgOAc (4.8 mmol, 6 equiv.), $Pd(OAc)_2$ (0.08 mmol, 10 mol%) and methyl acrylate (1.6 mmol, 2 equiv.), the reaction mixture was put in a preheated oil bath at 80 °C and stirred for 6 h. Then the dark reaction mixture was cooled down to room temperature and filtered over Celite. After distillation of the solvent under reduced pressure, the coupling product was purified by silica gel column chromatography.

Supporting Information

Experimental protocols and characterization data for new compounds, copies of ^{1}H, ^{13}C NMR spectra are available in the Supporting Information.

Acknowledgements

We thank the CNRS (Centre National de la Recherche Scientifique) and the "Ministere de l'Education Nationale et de la

Recherche", France for financial support. T.W. is very grateful to the French Embassy in Germany for a postdoctoral grant.

References

[1] a) S. R. Neufeldt, M. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936; b) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; c) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; d) D. A. Dolby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; e) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177; f) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31; g) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; h) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; i) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; j) C.-L. Sun, B. J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; k) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; l) H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191; m) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; n) C. L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677; o) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; p) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890; q) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; r) J. Bouffard, K. Itami, *Top. Curr. Chem.* **2010**, *292*, 213; s) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; t) O. Daugulis, D.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; u) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; v) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.

[2] Recent reviews on asymmetric C−H activation: a) L. Yang, H. Huang, *Catal. Sci. Technol.* **2012**, *2*, 1099; b) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; c) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242.

[3] F. Kakiuchi, P. Le Gendre, A. Yamada, H. Ohtaki, S. Murai, *Tetrahedron: Asymmetry* **2000**, *11*, 2647.

[4] K. Yamaguchi, J. Yamaguchi, A. Studer, K. Itami, *Chem. Sci.* **2012**, *3*, 2165.

[5] Recent reviews on the synthesis of axially chiral biaryls: a) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; c) T. D. Nelson, R. D. Crouch, in: *Organic Reactions*, Vol. 63, Wiley, New Jersey, **2004**, pp 265; d) G. Bringmann, M. Breuning, R.-M. Pfeifer, W. A. Schenk, K. Kamikawa, M. Uemura, *J. Organomet. Chem.* **2002**, *661*, 31; e) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563; f) G. Bringmann, D. Menche, *Acc. Chem. Res.* **2001**, *34*, 615; g) G. Bringmann, M. Breuning, S. Tasler, *Synthesis* **1999**, 525; h) G. Bringmann, S. Tasler, in: *Current Trends in Organic Synthesis*, (Eds.: C. Scolastico, F. Nicotra), Plenum Publishing Corporation, New York, **1999**, pp 105; i) K. Khanbabaee, *Nachr. Chem.* **2003**, *51*, 163; j) K. Kamikawa, M. Uemura, *Synlett* **2000**, 938; k) P. Lloyd-Williams, E. Giralt, *Chem. Soc. Rev.* **2001**, *30*, 145; l) T. Hayashi, *J. Organomet. Chem.* **2002**, *653*, 41; m) Q. Perron, A. Alexakis, *Adv. Synth. Catal.* **2010**, *352*, 2611; n) Q. Perron, J. Praz, A. Alexakis, *Tetrahedron: Asymmetry* **2009**, *20*, 1004; o) C.-A. Fan, B. Ferber, H. B. Kagan, O. Lafon, P. Lesot, *Tetrahedron: Asymmetry* **2008**, *19*, 2666.

[6] F. Colobert, V. Valdivia, S. Choppin, F. R. Leroux, I. Fernández, E. Álvarez, N. Khiar, *Org. Lett.* **2009**, *11*, 5130.

[7] a) P.-E. Broutin, F. Colobert, *Org. Lett.* **2003**, *5*, 3281; b) P.-E. Broutin, F. Colobert, *Eur. J. Org. Chem.* **2005**, 1113; c) P.-E. Broutin, F. Colobert, *Org. Lett.* **2005**, *7*, 3737.

[8] (M->)-(*S*)-menthyl *p*-tolylsulfinate was obtained on a gram scale (50 g) starting from cheap and commercially available natural (−)-menthol. Condensation of the aryllithium species to (−)-(S_S)-menthyl *p*-tolylsulfinate gave the corresponding enantiopure aryl sulfoxides.

[9] F. R. Leroux, A. Berthelot, A. Panossian, F. Colobert, *Chem. Eur. J.* **2012**, *18*, 14232–14236.

[10] H. Richter, S. Beckendorf, O. G. Mancheňo, *Adv. Synth. Catal.* **2011**, *353*, 295.

[11] a) M. Yu, Z. Liang, Y. Wang, Y. Zhang, *J. Org. Chem.* **2011**, *76*, 4987; b) X. Zhang, M. Yu, J. Yao, Y. Zhang, *Synlett* **2012**, 463.

[12] a) A. Garcia-Rubia, M. A. Fernández-Ibáňez, R. Gómez Arráyas, J. C. Carretero, *Chem. Eur. J.* **2011**, *17*, 3567; b) J. A. Romero-Revilla, A. Garcia-Rubia, R. Gómez Arráyas, M. A. Fernández-Ibáňez, J. C. Carretero, *J. Org. Chem.* **2011**, *76*, 9525.

[13] R. Samanta, A. P. Antonchick, *Angew. Chem.* **2011**, *123*, 5323; *Angew. Chem. Int. Ed.* **2011**, *50*, 5217.

[14] T. Wesch, A. Berthelot-Bréhier, F. R. Leroux, F. Colobert, *Org. Lett.* **2013**, *15*, 2490.

[15] Syntheses of biaryl sulfoxides **1a–i** are detailed in the Supporting Information.

[16] In Table 1 the ratios ***SaR***/***SaS*** were attributed by comparison of ^{1}H NMR spectra with that of **2i-*SaS*** whose absolute configuration has been determined by X-ray crystal structure analysis.

[17] CCDC 928824 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[18] ^{1}H NMR experiments at high temprature showed that the coupling products **2b–i** are atropoconfigurationnaly stable up to at least 100 °C.

