

Synthesis of Axially Chiral Biaryls through Sulfoxide-Directed Asymmetric Mild C–H Activation and Dynamic Kinetic Resolution**

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Abstract: A mild and robust direct C–H functionalization strategy has been applied to the synthesis of axially chiral biaryls. Such an efficient and stereoselective transformation occurs through an original dynamic kinetic resolution pathway enabling the conversion of diastereomeric mixtures of non-prefunctionalized substrates into atropisomerically pure, highly substituted biaryl scaffolds. The main feature of this transformation is the use of an enantiopure sulfoxide as both chiral auxiliary and traceless directing group. The potential of newly synthesized biaryls as valuable building blocks is further illustrated.

Axially chiral biaryls are intriguing molecular scaffolds with significant applications as biologically active compounds (vancomycin, korupensamin, steganacin, etc.), privileged ligands, and promising materials (e.g., liquid crystals).^[1] Despite their key importance, general, efficient, and stereoselective synthetic routes to access such atropisomeric moieties are still scarce. Recently, significant advances have been achieved in asymmetric Suzuki–Miyaura couplings.^[2,3] However, the difficulty of such transformations frequently lies in the antagonism between its efficiency and its selectivity, and thus the substrate scope remains limited.

In 2010, Miller developed an original approach toward axially chiral biaryls using the dynamic kinetic resolution (DKR) strategy occurring during the peptide-catalyzed bromination of racemic substrates.^[4] In 2013, the group of Fernández and Lassaletta^[5] and the group of Stoltz and Virgil^[6] discovered simultaneously but independently that racemic mixtures of prefunctionalized (naphthyl)quinoline derivatives underwent Pd⁰-catalyzed couplings and DKR affording atropisomerically pure scaffolds in synthetically useful yields (Scheme 1A). The key racemization step is believed to occur after the oxidative addition of the C–X bond to Pd⁰. Inspired by these seminal works we hypothesized that a related DKR-type transformation could be developed using a C–H activation^[7] strategy (Scheme 1B). Indeed,

a configurationally stable racemic biaryl substrate bearing a judiciously chosen coordinating group (directing group, DG) could undergo direct C–H cleavage, generating a metal-lacyclic intermediate. The formation of such a small-ring-size metal-bridged moiety should enable to lower the rotational barrier thus facilitating an isomerization step.^[8] A DKR could hence be feasible and the formation of desired functionalized Ar–Ar scaffolds in an atroposelective manner might be expected. Additionally, if a “traceless” DG^[9] is employed, the newly generated chiral biaryl could be further used as building block for the synthesis of high-value-added enantiopure scaffolds. The success of such an appealing transformation, however, depends on a few key points: 1) the selection of an efficient DG, 2) the choice of a chiral source prompt to efficiently induce axial stereocontrol, and 3) the use of mild reaction conditions under which the axial chirality of the biaryl substrate is uncontrolled and the isomerization will occur as the reaction proceeds.

Recently, our group focused on the use of chiral sulfoxides as DG in the context of diastereoselective C–H activation.^[10] We discovered that biarylsulfoxides undergo Pd-catalyzed asymmetric Fujiwara–Moritani (dehydrogenative Heck) reaction affording chiral biaryls with moderate diastereoselectivity. As such olefination requires rather harsh reaction conditions (80 °C; sealed tube), the biaryl substrates are configurationally unstable under the reaction conditions and the rotation around the biaryl axis is possibly enhancing the formation of functionalized products in an atropoenriched manner. However, this preliminary work made us confident about the potential of sulfoxides as stereogenic DGs.^[11]

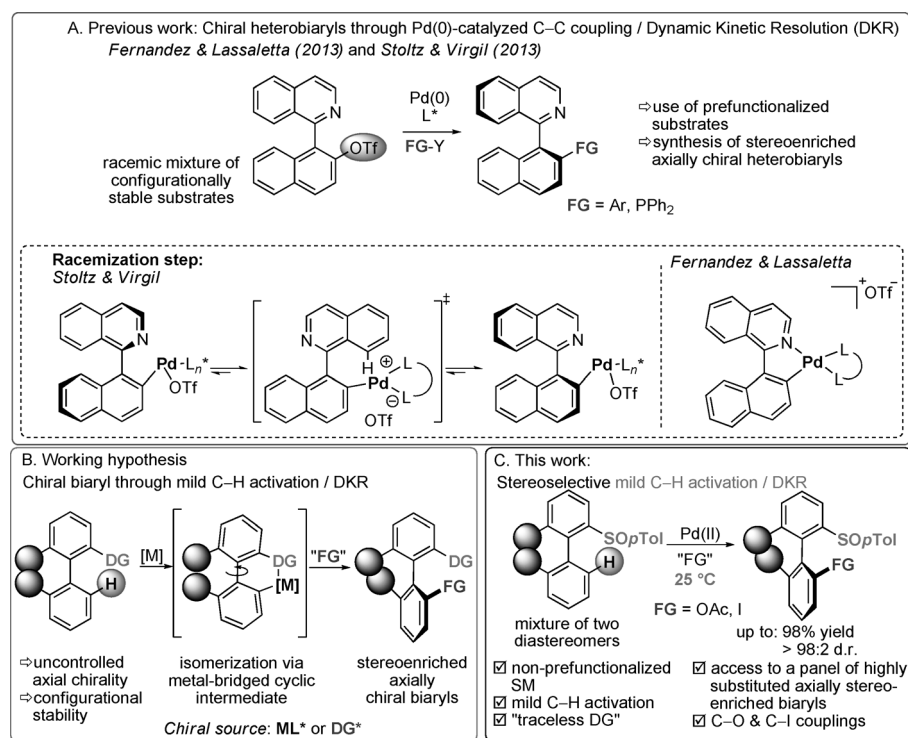
Herein, we report the stereoselective, sulfoxide-directed acetoxylation and iodination of biaryls occurring through a mild C–H activation/DKR sequence (Scheme 1C). Notably, this report is a rare example of the application of direct C–H functionalization to access atropisomeric scaffolds.^[12,13] Noteworthy, several elegant examples of diastereo-^[14] and enantioselective^[15] direct C–O and C–I couplings enabling the formation of carbon stereogenic centers have been reported.

Our endeavor toward a mild C–H activation/DKR reaction began by investigating the C–O coupling reaction (Table 1). Firstly, a standard substrate **1a**,^[16] used as a 1:1.1 mixture of two diastereomers, was reacted with Pd(OAc)₂ and PhI(OAc)₂ (used as both acetoxylation agent and oxidant). Although the desired product **2a** could be isolated in encouraging yield (up to 50 %) and excellent diastereoselectivity (> 98 %), a high reaction temperature was required (80 °C, Table 1, entry 1). Rewardingly, the replacement of PhI(OAc)₂ by acetic acid and persulfate oxidant drastically improved the efficiency of this C–O coupling (entry 2) and the reaction proceeded smoothly even at room temperature

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[**] We thank the CNRS (Centre National de la Recherche Scientifique) and the “Ministère de l'Éducation Nationale et de la Recherche” (France) for financial support. C.K.H. is very grateful to CiRFC of Strasbourg for a postdoctoral grant. We also thank Dr. Lydia Brelot for single-crystal X-ray diffraction analysis.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201407865>.



Scheme 1. Synthesis of chiral biaryls through DKR/transition metal-catalyzed cross couplings.

Table 1: Optimization of the acetoxylation reaction.

	"OAc" (x equiv), Oxidant	Solvent	T [°C]/t [h]	Yield [%] ^[a]	d.r. ^[b]
1	PhI(OAc) ₂ (2.4)	HFIP	80/16	41	> 98:2
2	AcOH (46), K ₂ S ₂ O ₈	HFIP	80/24	89	90:10
3	AcOH (46), (NH ₄) ₂ S ₂ O ₈	HFIP	25/14	88	96:4
4 ^[c]	AcOH (46), (NH ₄) ₂ S ₂ O ₈	HFIP	25/14	93	98:2
5	AcOH (46), (NH ₄) ₂ S ₂ O ₈	H ₂ O	25/16	86	83:17

[a] Yield of the isolated product. [b] Determined by crude ¹H NMR spectroscopy. [c] Reaction was conducted with 2 equiv of H₂O and under air.

(entry 3). The catalytic system was also robust as no precaution toward air and moisture were required. A small amount of water was even beneficial and **2a** was isolated in 93% yield and 98:2 d.r. (entry 4).^[17] The transformation was still efficient in aqueous medium (entry 5). Notable, no acetoxylation of **1a** occurred in the absence of the Pd-catalyst. The structure of **2a** was confirmed by X-ray diffraction analysis and the absolute (*SaR*) configuration was attributed.^[18]

With the optimized reaction conditions in hand, the scope of this reaction was explored using diastereomeric mixtures of differently substituted biphenyl substrates (Scheme 2).^[19]

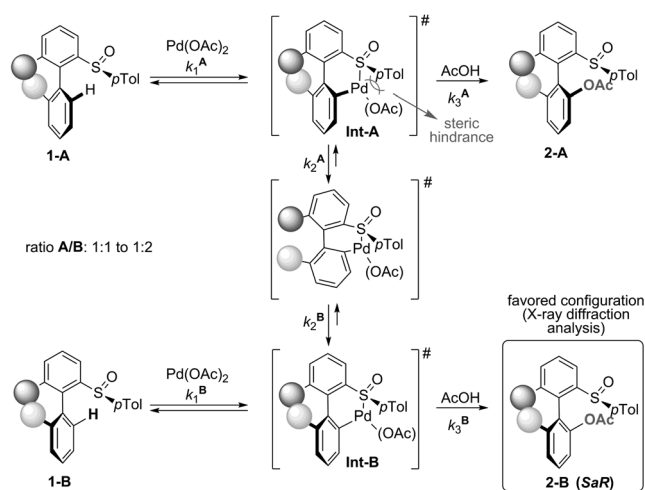
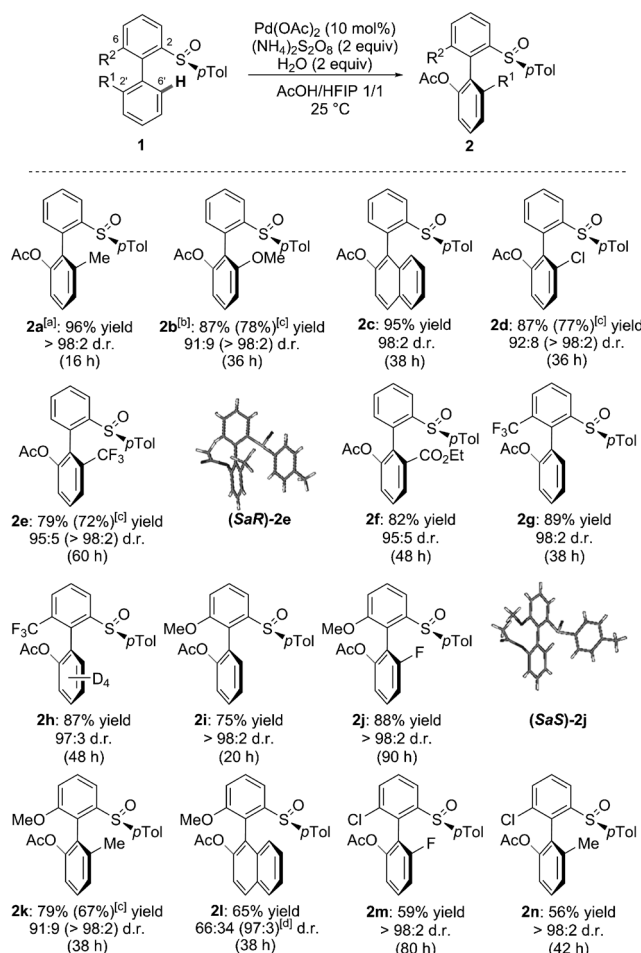
The reaction proceeded smoothly for an array of 2'-substituted biaryls (Scheme 2, **2a–f**). A slight decrease in the

diastereoselectivity for **2b** was probably due to the less sterically demanding OMe group. Recrystallization of **2b**, however, enabled to isolate the atropisomerically pure product in 78% yield. Our catalytic system is also compatible with electron-poor substrates (**1d–f**). When **1f**, bearing two possible coordinating groups, i.e., sulfoxide and ester, was submitted to the reaction conditions, the sulfoxide-directed C–H activation occurred selectively at the expected 6'-position. Subsequently, 6-substituted biaryls have been tested; such proaxially chiral **1g–1i** underwent highly diastereoselective C–O coupling and no diacetoxylation occurred. Finally, our attention turned towards *ortho*-trisubstituted substrates. **1j**, bearing less bulky OMe and F substituents afforded **2j** in excellent yield and stereoselectivity. In contrast, a decreased chiral induction was observed in the case of the more hindered **1k** and **1l**. Surprisingly, when trisubstituted biaryls bearing a rather bulky Cl

substituent at the 6-position and F or Me groups at the 2'-position (**1m,n**) were submitted to the reaction conditions, the corresponding acetoxylation products **2m** and **2n** were isolated in atropisomerically pure form but in lower yields. Notably, the remaining **1m,n** were recovered as sole diastereomers in 40 and 41% yields, respectively.

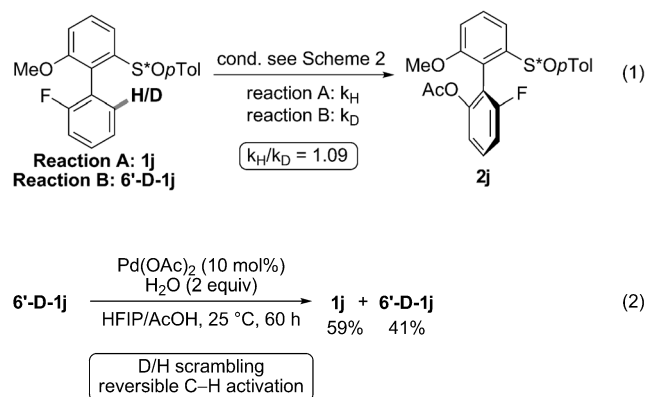
Regarding the scope of the reaction, two key trends emerge. Firstly, the diastereomeric mixture of substrates bearing substituents at either 6- or 2'-positions or weakly hindering substituents at both 6- and 2'-positions are converted into atropisomerically pure products (**2a–2j**) in excellent yields. These results clearly suggest an expected C–H activation/DKR pathway (Scheme 3). As the axial chirality of the substrates is uncontrolled at 25 °C, we assume that the rotation around the biaryl axis might occur when the Pd-bridged metallacycle is formed.^[5,20] The mechanistic scenario in which 1) both diastereomers of **1** undergo rapid C–H activation, followed by 2) a reductive elimination from **Int-B** and an isomerization of **Int-A** into a presumably more stable **Int-B** is proposed.^[21] The key feature of this transformation is that the reductive elimination from **Int-A** seems to be unfavored and sufficiently slow to enable isomerization. Such hypothesis is consistent with the literature as C–O and C–N bond forming reductive eliminations are reputed to be energetically difficult.^[22]

In contrast, the acetoxylation of the biaryls bearing sterically more demanding substituents (**1m,n**) leads to the formation of the atropisomerically pure product but full conversion is not achieved. The functionalized products are isolated in moderate yields and remaining starting materials are recovered as sole diastereomers. In such a case, a simple



kinetic resolution operates and we believe that the functionalization on one diastereomer of the substrate (**1-A**) is unfavored due to steric reasons.

To get insight on this original C–H activation/DKR transformation, several mechanistic studies were undertaken. First, an intermolecular kinetic isotope effect of 1.09 was measured when **1j** and **6'-D-1j**^[23] were submitted to the acetoxylation reaction conditions [Eq. (1)]. Moreover, the C–H activation step is reversible. When **6'-D-1j** was reacted with Pd(OAc)₂ in HFIP/AcOH mixture, significant D/H scrambling was observed [Eq. (2)]. These results indicate that direct metalation is rather rapid, not rate-determining, and coherent with the hypothesis that the overall outcome of this transformation is probably controlled by the kinetics of reductive elimination and isomerization.



Subsequently, to provide experimental evidence for the (dynamic) kinetic resolution pathway, the kinetics of the acetoxylation reactions of **1e**, **1j**, and **1m** (used as diastereomeric mixtures (approximately 1:1.5 d.r.)) were followed using ¹⁹F NMR (Figure 1).^[24] For each substrate, the change of

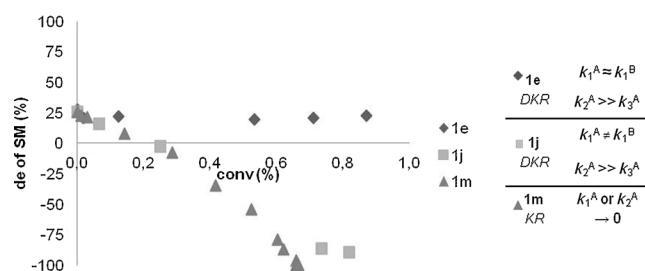


Figure 1. Variation of the diastereomeric excess of **1e**, **1j**, and **1m** as a function of conversion.

the diastereomeric excess was measured during the reaction and plotted as a function of conversion. When **1e** was submitted to the reaction conditions, its diastereomeric ratio remains constant which might suggest that both diastereomers of **1e** undergo rapid C–H activation. However, as (SaR)-**2e** is isolated in 79 % yield and 95.5 d.r., reductive elimination from **Int-A** seems to be significantly slower than the rotation around the Ar–Ar axis. In contrast, during the reaction of **1j**, the d.e. changes significantly indicating a faster conversion of

one diastereomer ($k_1^A \neq k_1^B$). However, the isolation of (*SaS*)-**2j** in atropomerically pure form and in 88 % yield clearly indicates a DKR mechanism and unfavored reductive elimination from **Int-A**. Finally, the acetoxylation of the mixture of two diastereomers of **1m** led to full conversion of (*SaR*)-**1m** (i.e., **1-B** Scheme 3)^[25] and the transformation literally stops when reaching 65 % conversion (total consumption of the major diastereomer). The increased steric hindrance around the biaryl axis of **1m** might prevent the DKR pathway and simple kinetic resolution (KR) occurs.

Encouraged by the efficiency of this diastereoselective acetoxylation reaction, we subsequently focused on proving a more general character of such an original asymmetric C–H activation reaction. Aiming at the construction of synthetically useful axially chiral scaffolds, we turned our attention toward an iodination reaction. Rapidly, we discovered that a simple replacement of the (NH₄)₂S₂O₈ oxidant by *N*-iodosuccinimide (NIS; 1.3 equiv) led to a complete switch in the reactivity of our catalytic system enabling smooth, mild, and highly diastereoselective C–I coupling (Scheme 4). The standard substrate **1a** could thus be converted to atropisomerically pure **3a** in excellent 98 % yield.^[26]

The study of the reaction scope showed that quite similar DKR occurs for this C–I coupling. However, slightly lowered diastereoselectivities were observed and longer reaction times were required to achieve full conversions (Scheme 4). Yet, disubstituted biaryls could be converted at room temperature and in good yields to iodinated products with diastereoselectivities ranging from 91:9 to >98:2 (**3a–3i**). The efficiency of this C–I coupling for *ortho*-trisubstituted molecules strongly depends on the steric hindrance generated by the 6- and 2'-substituents. Comparable to the acetoxylation reaction, an excellent atroposelectivity was achieved for **3j** bearing less bulky substituents. A progressive increase of the steric demand around the Ar–Ar axis, firstly, led to a lower level of diastereoselectivity (**3k**, **3l**). Finally, the highly congested substrate **3n** underwent iodination under a simple kinetic resolution scenario. Besides, in the presence of NBS, **1a** could also be converted into the expected brominated **4a**; however, a slight decrease in stereocontrol was found (d.r. of 93:7).

The additional key advantage of the herein presented strategy relies on the traceless character of the chiral sulfoxide DG, which paves the way toward a general application of our transformation. This DG can be readily removed from the chiral products with retention of axial stereocontrol by a sulfoxide/lithium exchange followed by electrophilic trapping (various electrophiles are compatible).^[27] As a representative example (Figure 2), chiral **2a** (prepared at 1.5 mmol scale in 96 % yield and d.r. >98:2) was first converted to the protected alcohol **6** (in 89 % yield). Subsequently, low-temperature exchange with lithium and electrophilic trapping using dry ice afforded chiral carboxylic acid **7** in non-optimized 57 % yield and *ee* higher than 98 %.

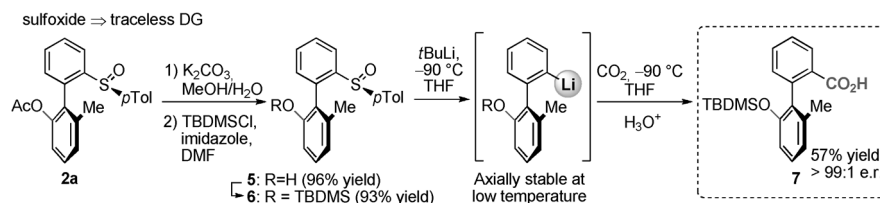
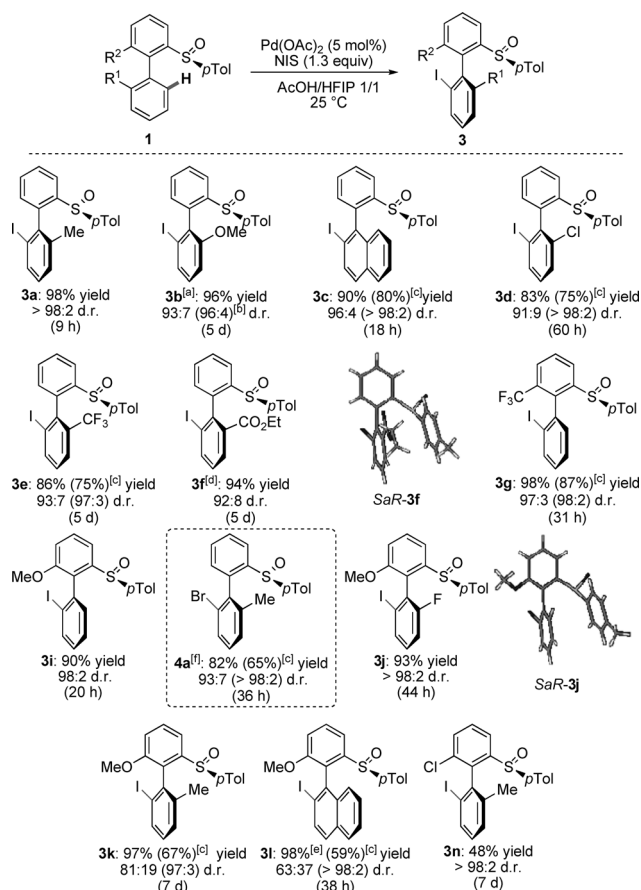


Figure 2. Representative example of the transformation of the sulfoxide DG.



Scheme 4. Substrate scope of the asymmetric direct iodination occurring through (dynamic) kinetic resolution. Standard reaction conditions: **1** (0.3–0.2 mmol); Pd(OAc)₂ (5 mol%); NIS (1.3 equiv), HFIP/AcOH 1/1 v/v, air, 25 °C; yields of isolated products; d.r. determined by ¹H NMR analysis of the crude mixture. [a] DCE as solvent at 40 °C, 10 mol % of Pd(OAc)₂. [b] d.r. after column chromatography. [c] Yield and d.r. after recrystallization. [d] 10 mol % of Pd(OAc)₂. [e] Conversion and d.r. measured on crude mixture. [f] NBS was used and the reaction was performed at 40 °C. DCE=dichloroethane; NBS = *N*-bromosuccinimide.

In conclusion, an original atroposelective mild C–H activation occurring through dynamic kinetic resolution is reported. The isomerization of the diastereomeric mixture of biaryl substrates is believed to occur when bridging palladacyclic intermediates with decreased configurational stability are generated. Such an original transformation paves the way toward the synthesis of acetoxyated and iodinated atropisomeric biaryls and is a rare example of C–H activation-based asymmetric strategy enabling axial stereocontrol.

Moreover, as sulfoxides are easily transformable into a myriad of functionalities, the herein presented strategy offers general access toward a plethora of highly valuable chiral biaryl building blocks.

Received: August 1, 2014

Revised: August 23, 2014

Published online: October 10, 2014

Keywords: asymmetric synthesis · atroposelectivity · C–H activation · dynamic kinetic resolution · sulfoxides

- [1] For recent reviews on the synthesis of axially chiral biaryls, see: a) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563; b) M. C. Kozłowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193; c) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; *Angew. Chem.* **2005**, *117*, 5518; d) O. Baudoin, *Eur. J. Org. Chem.* **2005**, 4223.
- [2] For selected recent enantioselective transformations, see: a) T. Yamamoto, Y. Akai, Y. Nagata, M. Sugimoto, *Angew. Chem. Int. Ed.* **2011**, *50*, 8844; *Angew. Chem.* **2011**, *123*, 9006; b) S. Wang, J. Li, T. Miao, W. Wu, Q. Li, Y. Zhuang, Z. Zhou, L. Qiu, *Org. Lett.* **2012**, *14*, 1966; c) Y. Zhou, S. Wang, W. Wu, Q. Li, Y. He, Y. Zhuang, L. Li, J. Pang, Z. Zhou, L. Qiu, *Org. Lett.* **2013**, *15*, 5508; d) G. Xu, W. Fu, G. Liu, C. H. Senanayake, W. Tang, *J. Am. Chem. Soc.* **2014**, *136*, 570.
- [3] For selected diastereoselective transformations, see: a) P.-E. Broutin, F. Colobert, *Org. Lett.* **2003**, *5*, 3281; b) O. Baudoin, A. Décor, M. Cesario, F. Guéritte, *Synlett* **2003**, 2009; c) P.-E. Broutin, F. Colobert, *Org. Lett.* **2005**, *7*, 3737; d) T. Leermann, P.-E. Broutin, F. R. Leroux, F. Colobert, *Org. Biomol. Chem.* **2012**, *10*, 4095.
- [4] J. L. Gustafson, D. Lim, S. J. Miller, *Science* **2010**, *328*, 1251.
- [5] A. Ros, B. Estepa, P. Ramírez-López, E. Álvarez, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2013**, *135*, 15730.
- [6] V. Bhat, S. Wang, B. M. Stoltz, S. C. Virgil, *J. Am. Chem. Soc.* **2013**, *135*, 16829.
- [7] Selected recent reviews: a) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443; b) A. Ros, R. Fernández, J. M. Lassaletta, *Chem. Soc. Rev.* **2014**, *43*, 3229; c) X.-S. Zhang, K. Chen, Z.-J. Shi, *Chem. Sci.* **2014**, *5*, 2146; d) M.-L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901; e) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; f) K. M. Engle, J.-Q. Yu, *J. Org. Chem.* **2013**, *78*, 8927; g) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; h) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31; i) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; *Angew. Chem.* **2012**, *124*, 10382; j) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; k) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; l) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; m) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; n) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315.
- [8] C. Wolf in *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications* (Ed.: C. Wolf), The Royal Society of Chemistry, London, **2008**, pp. 84–135.
- [9] F. Zhang, D. R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906.
- [10] T. Wesch, F. R. Leroux, F. Colobert, *Adv. Synth. Catal.* **2013**, *355*, 2139.
- [11] Use of racemic sulfoxides as DG: a) R. Samanta, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2011**, *50*, 5217; *Angew. Chem.* **2011**, *123*, 5323; b) T. Wesch, A. Berthelot-Bréhier, F. R. Leroux, F. Colobert, *Org. Lett.* **2013**, *15*, 2490; c) B. Wang, C. Shen, J. Yao, H. Yin, Y. Zhang, *Org. Lett.* **2014**, *16*, 46; d) K. Nobushige, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2014**, *16*, 1188.
- [12] a) F. Kakiuchi, P. Le Gendre, A. Yamada, H. Ohtaki, S. Murai, *Tetrahedron: Asymmetry* **2000**, *11*, 2647; b) K. Yamaguchi, J. Yamaguchi, A. Studer, K. Itami, *Chem. Sci.* **2012**, *3*, 2165; c) K. Yamaguchi, H. Kondo, J. Yamaguchi, K. Itami, *Chem. Sci.* **2013**, *4*, 3753; d) D.-W. Gao, Q. Gu, S.-L. You, *ACS Catal.* **2014**, *4*, 2741.
- [13] For recent reviews on asymmetric C–H activation, see: a) C. Zheng, S.-L. You, *RSC Adv.* **2014**, *4*, 6173; b) J. Wencel-Delord, F. Colobert, *Chem. Eur. J.* **2013**, *19*, 14010; c) N. Cramer, *Chimia* **2012**, *66*, 869; d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242.
- [14] a) R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112; *Angew. Chem.* **2005**, *117*, 2150; b) R. Giri, J. Liang, J.-G. Lei, J.-J. Li, D.-H. Wang, X. Chen, I. C. Naggar, C. Guo, B. M. Foxman, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 7420; *Angew. Chem.* **2005**, *117*, 7586.
- [15] a) L. Chu, X.-C. Wang, C. E. Moore, A. L. Rheingold, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 16344; b) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 1236.
- [16] Substrates were prepared by Suzuki coupling between (2-bromoaryl)-sulfoxides and boronic acids, for details see the Supporting Information.
- [17] We hypothesize that a small amount of water may improve the solubility of (NH₄)₂S₂O₈ in the reaction mixture.
- [18] CCDC-1015458 ((*SaR*)-**2a**), 1015459 ((*SaR*)-**2e**), 1015460 ((*SaS*)-**2j**), 1015461 ((*SaR*)-**3f**), and 1015462 ((*SaR*)-**3j**) contain 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.
- [19] Diastereomeric ratios of substrates range from 1:1 to 1:2; two diastereomers are clearly distinguishable by NMR at room temperature and a coalescence temperature superior to 100°C for **1e**, **1j**, and **1m** was determined by variable temperature ¹H NMR spectroscopy. In the case of **1b** the coalescence temperature is significantly lower (60°C).
- [20] Coordination of Pd with S atom is proposed based on the literature (for representative example see: **11a,c**) and the observed regioselectivity.
- [21] As the absolute *SaR* configuration of the products was determined by X-ray analysis, it is assumed that reductive elimination from **Int-B** is favored.
- [22] See for example: M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 8232; for review see: J. F. Hartwig, *Inorg. Chem.* **2007**, *46*, 1936.
- [23] **6'-D-1j** was prepared from **1j** via 6'-H/D exchange; for details see the Supporting Information.
- [24] For details and plots of the conversion of **1e,j,m** as function of time see the Supporting Information.
- [25] Confirmed by X-ray analysis of (*SaR*)-**1m**.
- [26] No iodinated product was detected in the absence of Pd-catalyst.
- [27] F. R. Leroux, A. Berthelot, L. Bonnafoux, A. Panossian, F. Colobert, *Chem. Eur. J.* **2012**, *18*, 14232, and references herein.