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Asymmetric Synthesis

1,1,1,3,3,3-Hexafluoroisopropanol as a Remarkable Medium for Atroposelective Sulfoxide-Directed Fujiwara–Moritani Reaction with Acrylates and Styrenes

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Abstract: Axially chiral biaryls are ubiquitous structural motifs of biologically active molecules and privileged ligands for asymmetric catalysis. Their properties are due to their configurationally stable axis, and therefore, the control of their absolute configuration is essential. Efficient access to atropo-enantioenriched biaryl moieties through asymmetric direct C–H activation, by using enantiopure sulfoxide as both the directing group (DG) and chiral auxiliary, is reported. The stereoselective oxidative Heck reactions are performed in high yields and with excellent atropo-stereoselectivities. The pivotal role of 1,1,1,3,3,3-hexafluoropropanol (HFIP) solvent, which enables a drastic increase in yield and stereoselectivity of this transformation, is evidenced and investigated. Finally, the synthetic usefulness of the herein disclosed transformation is showcased because the traceless character of the sulfoxide DG allows straightforward conversions of the newly accessed, atropopure sulfoxide-biaryls into several differently substituted axially chiral scaffolds.

Introduction

Sterically hindered biaryls with at least two bulky substituents in *ortho* positions of the biaryl axis are intriguing chiral skeletons. During the past two decades, increasing interest has been given to such atropisomeric compounds because of their prominent biological properties,[1] but also their unique aptitude to induce stereoselectivity in asymmetric homogenous catalysis.[2] Accordingly, multiple synthetic routes towards these important skeletons have been devised,[3] among which the asymmetric transition metal-catalyzed cross-coupling reaction between two aryl units is arguably the most general one.[4] Although the potential of the stereoselective Suzuki–Miyaura coupling is undeniable, this approach generally fails if the construction of highly sterically congested biaryls containing four substituents around the biaryl linkage is targeted.[5]

Over the last decade organic synthetic chemistry has been witnessing an incredible expansion of the transition-metal-catalyzed C–H activation field[6] and a variety of catalytic systems based on metals, such as Pd, Rh, Ru, Cu, Ni, and Co have been discovered. Consequently, not only more step- and waste-economic versions of classical cross-coupling reactions can now be performed with simple starting materials, but also unprecedented retrosynthetic disconnections that allow the rapid construction of complex molecular scaffolds can be envisioned.[7] In contrast, asymmetric C–H activation reactions remain rather rare and are mainly limited to the synthesis of compounds with central chirality.[8] Indeed, the application of direct functionalization to access axially chiral skeletons has remained, until recently, a barely explored field. An early example was disclosed by Murai in 2000 and concerned a rhodium-catalyzed atroposelective C–H activation/alkylation of 2-(1-naphthyl)-3-methylpyridine (Figure 1 A). Disappointingly, only moderate enantioselectivity (49%) and efficiency (37% yield) were achieved with a chiral ferrocenyl phosphine ligand.[9] A further major advance in this field was reported by You and concerned an oxidative Heck reaction between 1-(naphthalen-1-yl)benzo(*h*)isoquinoline derivatives and styrenes (Figure 1 B).[10] In parallel, a stereoselective construction of the Ar–Ar axis by means of a direct arylation was disclosed, but only a rather moderate level of chiral induction (72% *ee*) could be achieved when coupling a thiophene with a hindered boronic acid (Figure 1 C).[11,12]

Although the development of enantioselective transformations is particularly appealing because only a catalytic amount of a chiral source is required, the design of a chiral ligand compatible with C–H activation reactions is far from trivial. Indeed, in the key metallacyclic intermediates, at least two coordination sites are occupied by the C–H activation substrate (one M–C bond and at least one DG–M bond), and thus, coordination with an additional chiral inductor may be disfavored. An alternative solution to perform stereoselective C–H activation is to introduce the chiral information onto a DG.[13] To guaran-

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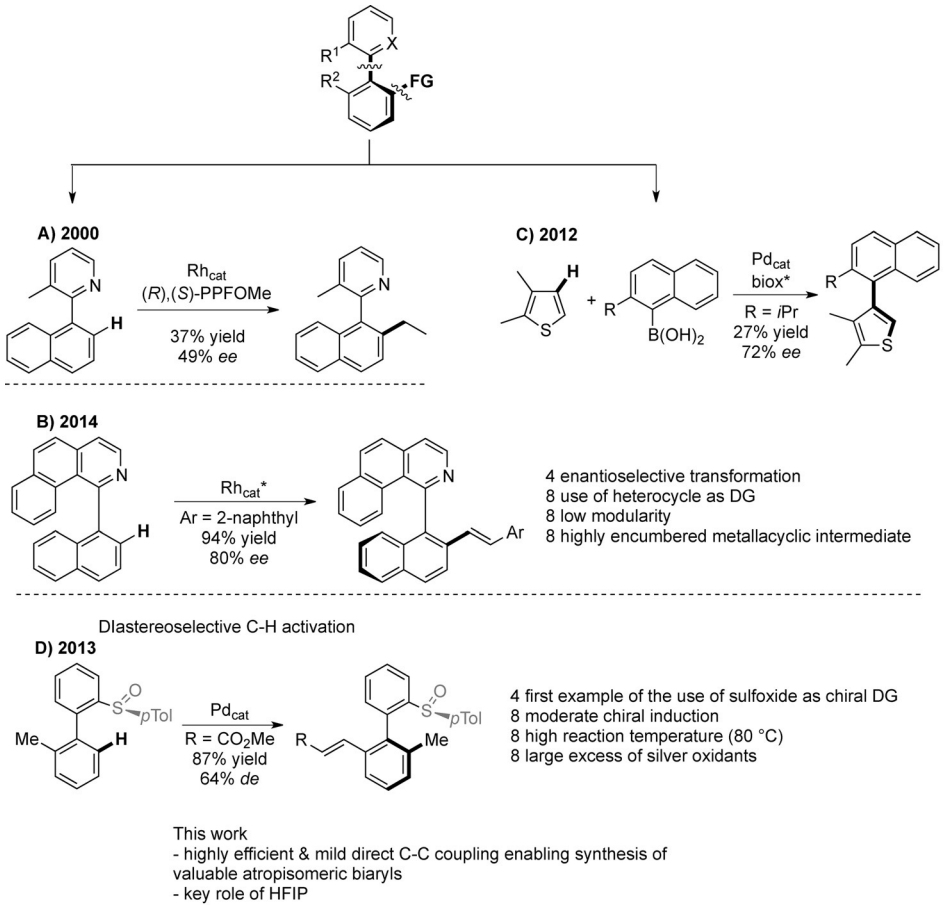


Figure 1. C–H activation based strategies towards the synthesis of axially chiral compounds. DG = directing group, *ee* = enantiomeric excess, biox* = 2,2′-bis(2-oxazoline, *de* = diastereomeric excess, Tol = tolyl.

tee the synthetic utility of such an approach, a chiral DG needs to be straightforwardly accessible from cheap precursors and easily removable after the C–H functionalization step. Because these requirements are fulfilled by enantiomerically pure sulfoxide moieties, previously employed in the palladium-catalyzed asymmetric Suzuki–Miyaura reaction,[14] we have recently endeavored to develop diastereoselective sulfoxide-directed C–H activation reactions.[15] In our pioneering work concerning a palladium-catalyzed direct olefination of a biaryl–sulfoxide, we demonstrated that this moiety could be efficiently used as the stereogenic DG to enable the formation of the axially chiral skeletons (Figure 1 D). Deceivingly, rather modest results in terms of stereodiscrimination and efficiency were obtained.[16] Moreover, quite a high reaction temperature (80 °C), a large excess of silver-based oxidant (6 equiv of AgOAc), and strongly activated coupling partners were crucial. A major advance was achieved a few months later, when we discovered that the same substrates might undergo direct C–O and C–X bond formations.[17] Intriguingly, these new couplings could be performed with excellent atroposelection and almost quantitative yields, which showcased the underestimated potential of chiral sulfoxides in the C–H activation field. Notably, related direct acetoxylation and iodination reactions, which delivered axially chiral compounds, by using a stereogenic phosphate as the DG*, were recently reported by Yang et al.[18]

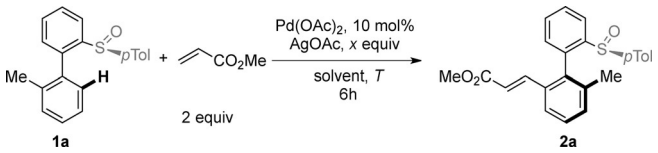
Encouraged by our results concerning carbon–heteroatom bond formation, we decided to revisit our pioneering work on oxidative olefination. Herein, we report our discoveries on the unique and intriguing role of 1,1,1,3,3,3-hexafluoropropanol (HFIP) solvent in atropo-diastereoselective, sulfoxide-directed C–C coupling. Notably, this polyfluorinated alcohol stood out recently as an optimal solvent for several challenging C–H activation reactions,[19] but its particular role has remained ambiguous. The mechanistic studies presented above indicate that the key feature of our catalytic system was the formation of hydrogen-bonded complex between the substrate and solvent facilitating the C–H activation step and improving the stereochemical outcome of this transformation. Importantly, such hydrogen-bonding-induced substrate activation could also account for the reactivity enhancement of other C–H activation reactions conducted in HFIP medium.

Results and Discussion

Fluorinated alcohols have attracted increasing attention from organic chemists as unusual media within which to perform

various transformations, including both transition-metal and organocatalyzed reactions.[20] It has been observed that due to their unique properties,[20a] such as extreme polarity (1.068 E^N_T), high acidity ($pK_a = 9.3$), excellent hydrogen-bond-donor abilities ($\alpha = 1.96$), and low nucleophilicity ($N = -4.23$), these solvents may exert an unexpected effect on an reaction outcome, modifying not only the reactivity of a catalytic system, but also its regio- and stereoselectivity. Accordingly, commercially available HFIP has recently been employed in several C–H activation reactions and clearly outcompeted other organic solvents.[19] Intrigued by the unique features of HFIP, we performed our previously developed sulfoxide-directed oxidative olefination in this polyfluorinated alcohol. Gratifyingly, the use of HFIP instead of 1,2-dichloroethane (DCE), when keeping other reaction parameters constant, enabled smooth functionalization of our standard substrate **1a** to deliver **2a** in 82% yield and, remarkably, as a single atropisomer (Table 1, entry 2).

Table 1. Optimization of the oxidative olefination of **1a**.



1a **2a**

Entry	Solvent	AgOAc [equiv]	T [°C]	Yield [%][a]	d.r. [%][b]
1	DCE	6	80	87	82:18
2	HFIP	6	80	82	>98:2
3	HFIP	4	80	88	>98:2
4	HFIP	2	80	93	>98:2
5	HFIP	1	80	60	>98:2
6	HFIP	–	80	8	>98:2
7[c]	HFIP	2	80	77	>98:2
8[d]	HFIP	2	RT	98	>98:2

[a] Yield of product isolated. [b] The diastereomeric ratio (d.r.) of the crude mixture was determined by ^{1}H NMR spectroscopy analysis. [c] 5 mol% of $Pd(OAc)_2$. [d] 30 h.

Encouraged by this solvent-improved chiral induction, we pursued optimization of the reaction conditions. Surprisingly, reduction of excess of silver oxidant allowed further enhancement of the efficiency of this transformation, while conserving the total diastereoselectivity. An optimal yield of 93% of **2a** was obtained with only 2 equivalents of AgOAc (Table 1, entry 4); merely a trace amount of **2a** was generated in absence of this terminal oxidant (Table 1, entry 6). Additionally, a lower catalyst loading (5 mol% of $Pd(OAc)_2$) resulted in a slightly decreased reaction yield (77%; Table 1, entry 7). Importantly, this modified catalytic system turned out to be efficient under significantly milder reaction conditions; the coupling could be performed at room temperature, but a longer reaction time was needed to complete this transformation. Finally, product **2a** was obtained in almost quantitative yield with total atroposelection when using HFIP as the solvent and 10 mol% of the $Pd(OAc)_2$ catalyst, in combination with 2 equivalents of AgOAc, at room temperature and after 30 h of reaction (Table 1, entry 8).

With the reoptimized reaction conditions in hand, we explored the scope of this transformation (Scheme 1). We were pleased to observe that the beneficial effect of HFIP in this stereoselective C–C coupling was general because now the reaction proceeded in quantitative yield with excellent atropo-diastereoselectivity for an array of 2′-substituted biaryl sulfoxides (Scheme 1; Cond A: previously reported conditions, Cond B: the newly reoptimized catalytic system). Substrates containing both electron-donating (Scheme 1, **1a–b**) and -withdrawing (Scheme 1, **1d–g**) substituents could be functionalized smoothly to deliver the desired atropopure scaffolds. Notably, under the newly optimized reaction conditions, the CF_3-substituted **1d** substrate could be efficiently functionalized to deliver atropopure **2d** in 80% yield, whereas the reaction conducted in DCE was extremely sluggish (30% yield and 74:26 d.r.). When **1g**, which contained two possible coordinating groups, namely, sulfoxide and ester, was submitted to the reaction conditions, the sulfoxide-directed C–H activation occurred selectively at the anticipated 6′-position. Furthermore, the reaction outcome for a proaxially chiral 6-substituted biaryl was investigated; the expected **2h** product was obtained as a single atropisomer in quantitative yield; this highlighted that double alkenylation was strongly disfavored. Finally, our attention turned towards *ortho*-trisubstituted substrates **1i–n**. Substrates **1i–j**, which bear small F-substituent at 2′-position, afforded **2i–j** in excellent yield and good diastereoselectivity. These results are of particular importance because the asymmetric synthesis of tetrasubstituted axially chiral scaffolds is a great synthetic challenge.[3a] Unfortunately, increased steric demand around the biaryl linkage has a detrimental effect on atroposelectivity; a modest diastereoselectivity was observed in the case of more hindered products **2k–n**. An increase in the reaction temperature to 80 °C generally does not enable improved chiral induction as products **2l** and **2n** were obtained with the same d.r. values. Only in the case of **2i** was the stereocontrol slightly enhanced to reach 95:5 d.r. when performing the reaction under refluxing conditions.

The structure of **2c** was confirmed by XRD analysis and the absolute (*SaR*) configuration was assigned (Figure 2).[21] This configuration of **2c** is coherent with the presumed favored pal-

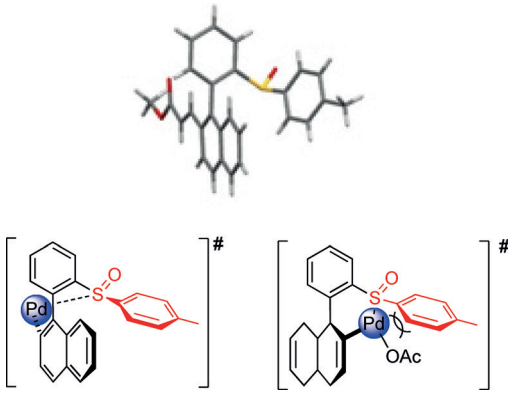
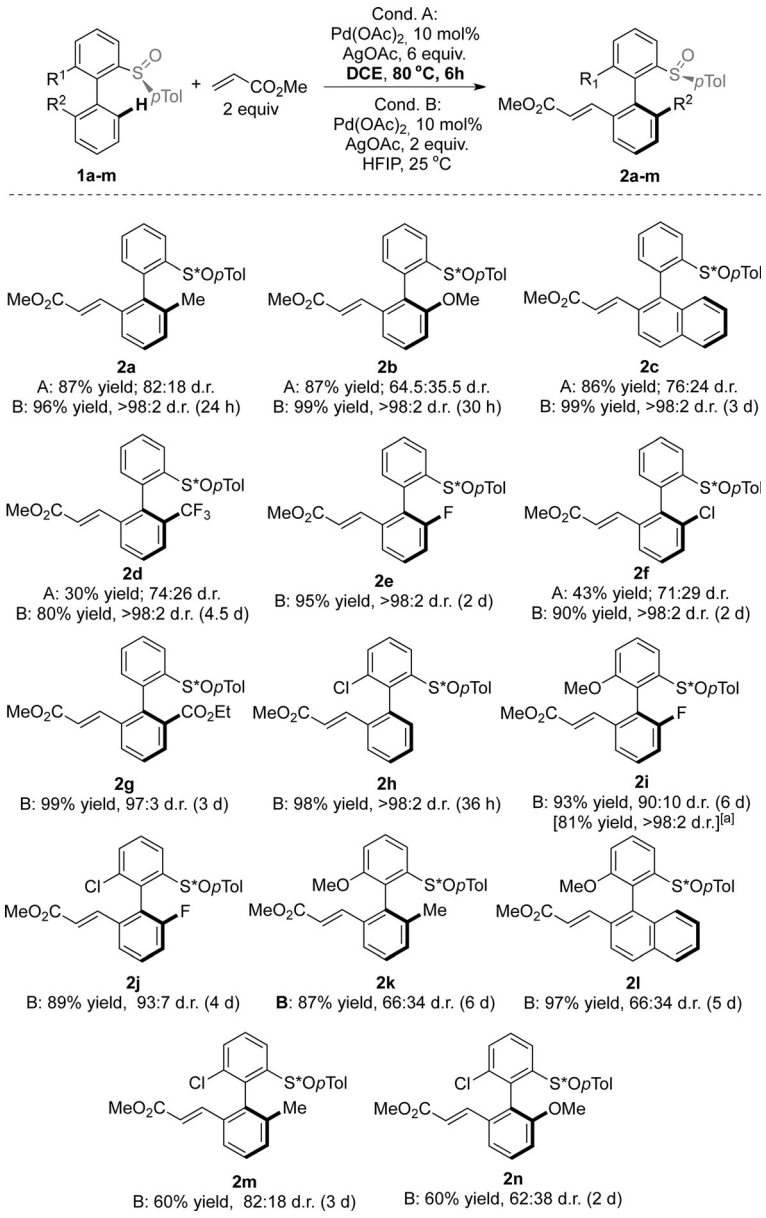


Figure 2. X-ray structure of (*SaR*)-**2c** and the proposed favored and unfavored metallacyclic intermediates.



Scheme 1. Scope of biphenylsulfoxide partners with acrylate derivatives.; Yield of isolated product; d.r. determined by ^{1}H NMR spectroscopy. [a] After recrystallization.

ladacylic intermediate, in which steric hindrance generated by the *p*Tol substituent of the sulfoxide and the Pd atom is minimized.

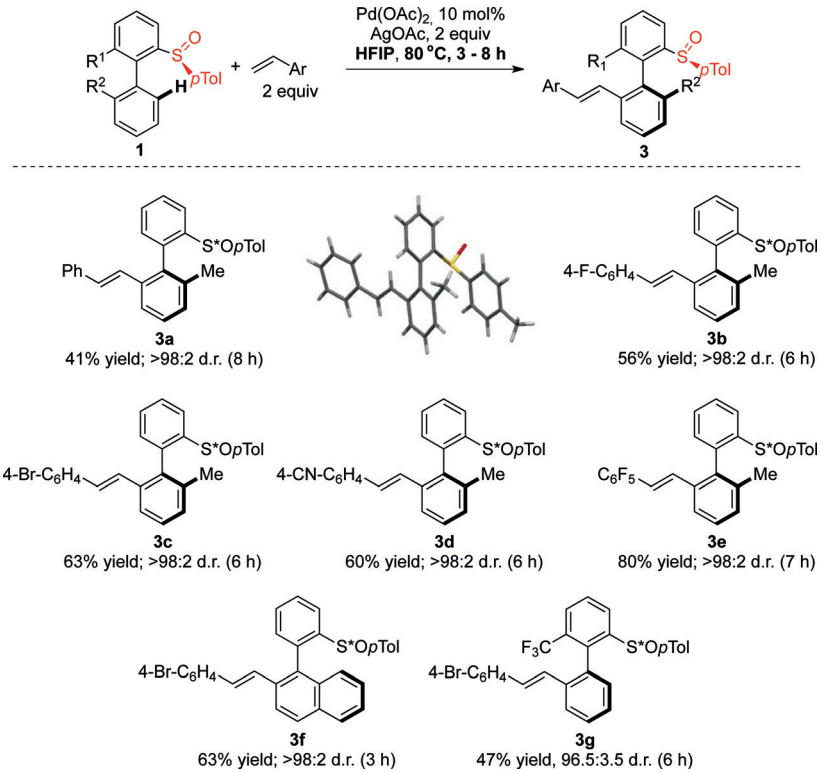
Encouraged by excellent results in term of both yield and atroposelectivity when using our reoptimized reaction conditions, obtained with methyl acrylate, we then focused on applying other, less activated coupling partners (Scheme 2). We were pleased to find that **1a**, when reacted with styrene at 80 °C, afforded desired **3a** as a single atropisomer, but in significantly decreased yield (41%). The structure of **3a** was confirmed by XRD analysis and its *SaR* configuration was evidenced. Subsequently, the scope of this transformation with regard to the styrene coupling partner was examined. The introduction of an electron-withdrawing substituent on the *para* position of the aromatic ring boosted the reactivity and the corresponding products **3b–d** were afforded in a completely atroposelective manner. The best yield of 80% and d.r. superior to 98:2 were obtained with 2,3,4,5,6-pentafluorostyrene (**3e**). Unfortunately, the reactivity was completely shut down when using electron-rich styrene derivatives, such as 4-methoxystyrene. Notably, this reaction tolerated different substitution patterns of the biaryl substrate well, since **3f** and proaxially chiral **3g** were isolated in comparable yields with excellent diastereoselectivity.

Moreover, we were pleased to find that an atropopure biaryl product containing a 1,1-disubstituted olefin moiety could also be synthesized (Scheme 3). Indeed, when diethyl 2-(ethoxymethyl)malonate was used as a precursor of diethyl 2-methylenemalonate, the reaction proceeded smoothly and the desired product **4a** was generated in 89% yield and d.r. of 97:3.

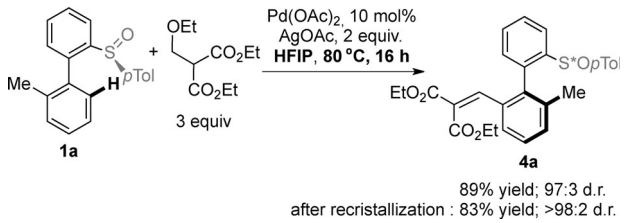
The results obtained for this oxidative Heck reaction clearly show the intriguing superiority of the catalytic system with the HFIP medium. Indeed, not only reactivity, but even more surprisingly, atroposelectivity could be drastically improved by using this extremely polar, fluorinated solvent. We therefore engaged experimental efforts to shed some light on this particular feature of our catalytic system.

First, to prove the unique reactivity of HFIP solvent, the standard olefination reaction of **1a** with methyl acrylate was conducted in several other media (Table 2). Small-scale solvent screening revealed that any coupling occurred when the non-fluorinated HFIP-congener, that is, *i*PrOH, was used as a solvent, which suggested that higher polarity and/or stronger acidity induced by the presence of the fluorine atom in HFIP were crucial (Table 2, entry 1). AcOH, DCE, and $CHCl_3$ were also totally inefficient in this reaction (Table 2, entries 2–4). Solvent mixtures were also tested. No desired product was obtained when HFIP was added as a cosolvent to *i*PrOH (9:1 v/v mixture) or in a mixture of DCE/AcOH (Table 2, entries 5 and 7, respectively). Finally, reactivity could be restored in a 9:1 mixture of DCE/HFIP, although a longer reaction time was required to complete this transformation (Table 2, entry 6). A comparable reactivity between a mixture of DCE/HFIP and HFIP alone was observed when using at least 20 equivalents of HFIP relative to **1a** (approximately 1.4:1 v/v mixture of DCE/HFIP). This study clearly highlights the unique properties of HFIP solvent that cannot be attributed directly to its acidic character or strong polarity.

Having demonstrated that HFIP was an exceptional solvent for our catalytic system, we focused on the origin of the remarkable stereoselectivity improvement. First, the influence of temperature was studied. Indeed, because the olefination with acrylate occurs smoothly in HFIP at room temperature, this decrease in the reaction temperature, compared with 80 °C in DCE, could account for the superior chiral induction. We there-

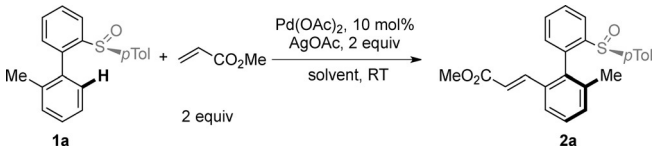


Scheme 2. Scope of biphenylsulfoxide partners with styrenes; yield of product isolated; d.r. determined by ^{1}H NMR spectroscopy.



Scheme 3. Synthesis of an atropopure biaryl containing a 1,1-disubstituted olefin moiety.

Table 2. Screening of solvents for the oxidative olefination of **1a**.



Entry	Solvent	Time [days]	Conversion [%][a]
1	*i*PrOH	3	0
2	AcOH	3	0
3	DCE	2	0
4	$CHCl_3$	3	<5
5	*i*PrOH/HFIP (9:1 v/v)	3	0
6	DCE/HFIP (9:1 v/v)	5	98
7	DCE/AcOH (9:1 v/v)	2	0

[a] Conversion determined by ^{1}H NMR spectroscopy.

fore performed the coupling of biaryls **1a–d** with methyl acrylate in HFIP at 80 °C (Figure 3). The corresponding products **2a–d** were isolated after only 6 h in 93, 98, 85, and 96% yield, respectively. Importantly, this direct functionalization at 80 °C occurred with no significant erosion of the atroposelection; thus proving that the reaction temperature had only a minor impact on chiral induction.

Subsequently, because HFIP is an excellent hydrogen-bond donor,[22] we surmised that this acidic fluorinated molecule might be involved in hydrogen bonding with the sulfoxide moiety. Indeed, it is well known in the literature that the sulfoxide group promptly undergoes hydrogen bonding with various solvents, such as alcohols, water, acetonitrile, and carboxylic acids.[23] Such weak bonding results in lengthening of the S=O bond, and hence, it can be reasonably expected that the coordinating properties of our DG would be altered, which would directly impact on the reactivity of the substrate towards the C–H activation step. Consequently, ^{1}H NMR spectroscopy studies were undertaken (for details, see the Supporting Information). A very strong downfield shift ($\Delta\delta = 2.473$ ppm) of the alcoholic proton was observed when a substoichiometric amount of HFIP (0.4 equiv) was added to a solution of **1a** in $CDCl_3$. In parallel, when HFIP was present in excess relative to **1a**, a significant upfield shift of the signal of the proton *ortho* to the sulfoxide by $\Delta\delta = 0.975$ ppm (2 signals corresponding to each atropisomers of **1a**) was evidenced, which suggested that the electron-withdrawing character of the sulfoxide moiety decreased upon hydrogen bonding.

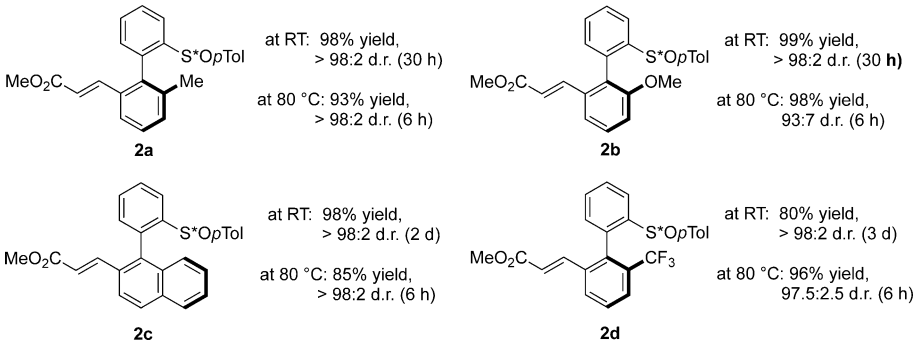


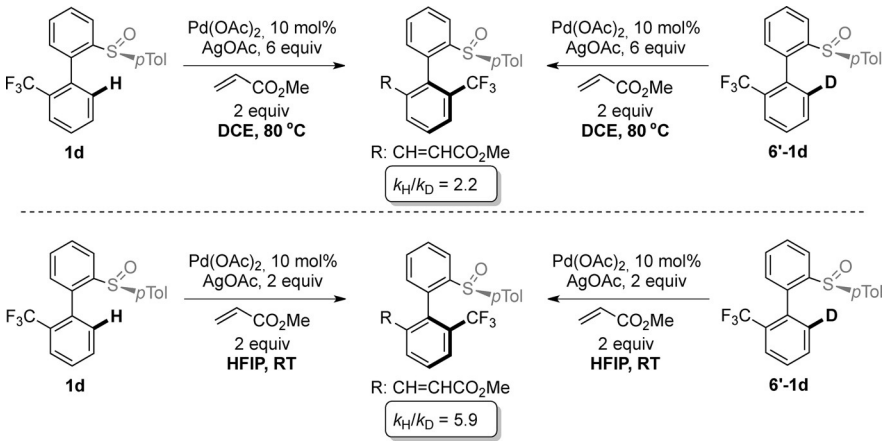
Figure 3. Influence of the reaction temperature on the diastereoselectivity of the olefination reaction with HFIP as a solvent.

Furthermore, the equilibrium constant for the formation of the hydrogen-bonded adduct between **1a** and HFIP was calculated by processing the NMR spectroscopy data.[24,25] Equilibrium constants, K_{eq}, of (18.5 ± 4.7) and $(23.5 \pm 9.8)\ M^{-1}$ for the major and minor atropodiastereomers of **1a** were determined, which clearly indicated a strong interaction between hydrogen-bond-donating HFIP and the hydrogen-bond-accepting sulfoxide. These values are of the same order of magnitude as those reported in related studies on hydrogen-bond complexes of various sulfoxides with alcohols.[26,27]

In addition, the expected complexation between HFIP and the sulfoxide moiety was investigated by IR spectroscopy analysis (for details, see the Supporting Information).[27] Initially, the hydrogenic stretching of the free OH group of HFIP absorbs IR radiation sharply at $\tilde{\nu} = 3542.8\ cm^{-1}$, whereas, upon addition of **2c**, the absorption is shifted to lower wavenumbers and flattened to give a broad bond, which is characteristic for an OH group involved in hydrogen bonding. Additionally, the SO moiety of **2c**, characterized by a stretching bond at $\tilde{\nu} = 1038.6\ cm^{-1}$, when complexed with HFIP, shows two absorption maxima at $\tilde{\nu} = 1022.7$ and $1011.1\ cm^{-1}$. The multiplicity of the S–O stretching frequency could be attributed either to the presence of two possible conformers (rotational isomerism about the S–C bond) or to Fermi resonance (an overtone of some other vibration that occurs near one-half of the S–O vibration frequency).[28]

Accordingly, both ^1H NMR and IR spectroscopy studies corroborate the formation of a hydrogen bond between our chiral DG and HFIP. Hence, it can be reasonably surmised that such substrate–solvent complexation has two major impacts on the outcome of the studied transformation. First, because this hydrogen bond results in a weakening of the S–O bond, the electronic properties of this coordinating group are modified and can directly influence the rate of the C–H activation step. Moreover, if the metalation step is rate determining, the kinetics of the overall transformation are therefore altered. In parallel, the involvement of the sulfoxide group in the hydrogen bond can reasonably influence the geometry of the pre-transition state and/or the key palladacyclic intermediate; hence enhancing efficient stereoinduction.

To examine the influence of HFIP on the rate of this oxidative olefination, kinetic isotope effect (KIE) studies were undertaken (Scheme 4).[29] Two sets of experiments were conducted. In the first one, a KIE of 2.2 from the two parallel reactions with **1d** and 6′-**1d** under our original reaction conditions (10 mol% of $Pd(OAc)_2$, 6 equiv of AgOAc, DCE, 80 °C) was determined. In the second one, with HFIP as a solvent, 2 equivalents of AgOAc, and conducting the reaction at room temperature, a much stronger KIE of 5.9 was measured. These results indicate that in both cases the rate-determining step involves breaking of a C–H bond. Moreover, the much stronger KIE in HFIP could suggest that the precise mechanism of this metala-



Scheme 4. KIE studies in DCE and HFIP.

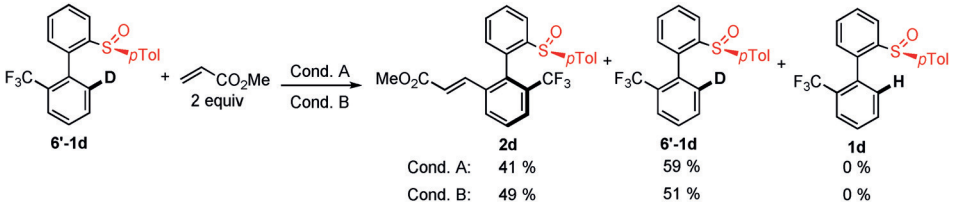
tion is different in both solvents and distinct transition states in both cases could be expected.[30] The modified value of the KIE effect could also result from the geometry change of **1d** and the corresponding intermediates upon hydrogen bonding by HFIP. In addition, the reversibility of this oxidative Heck reaction was investigated (Scheme 5). Under both reaction conditions, no H/D scrambling was observed on 6′-**1d**, which indicated the nonreversible character of C–H cleavage, and hence, supported its involvement in the rate-determining step.

An additional advantage of the reoptimized catalytic system involving HFIP as a solvent is that a decreased amount of silver salt oxidant, two equivalents versus six equivalents previously used, are sufficient to ensure optimal regeneration of the catalyst. The fluorinated solvents are prompt to reduce the oxidation potential of some organic species,[31] and hence, it could be possible that the reoxidation of the Pd^0 species in HFIP is facilitated.[32] Additionally, the distinct solubility of AgOAc in both solvents could also have an impact on this step.

On the basis of the above-presented mechanistic studies and literature data, the catalytic cycle presented in Figure 4 is proposed. Initially, a biarylsulfoxide substrate interacts through hydrogen bonding with HFIP to generate an "activated substrate". This substrate–solvent interaction is assumed to modify both the coordination properties and steric features of the chiral DG. Subsequently, precoordination of $Pd(OAc)_2$, followed by irreversible, rate-determining C–H bond cleavage occurs, to afford atropisomeric palladacyclic intermediates. The stereogenic environment of the sulfoxide, further increased by the involvement of the oxygen atom of the sulfoxide in a hydrogen bond with HFIP, results in the favorable generation of the intermediate Int A_{HFIP} with decreased steric hindrance. Insertion of the olefin coupling partner into the C–Pd bond, followed by β-H elimination, delivers functionalized product **2** as a single atropisomer. The catalytic cycle is completed by the reoxidation of palladium(0) into palladium(II) by the silver salt.

Finally, to illustrate the key advantage of the sulfoxide DG, that is, its traceless character, postmodifications of **2** were undertaken. Rewardingly, the sulfoxide DG could be efficiently transformed into several functional groups to give access to highly substituted atropopure biaryls.

As an example, optically pure atropisomeric **2a** (prepared in 98% yield and >98:2 d.r.) was first reduced with diisobutylaluminium hydride (DIBAL-H) followed by protection of the corresponding alcohol as a *tert*-butyldimethylsilyl ether (TBDMS) to afford **5** in 75% yield (Scheme 6). Subsequently, exchange with *tert*-butyllithium at −78 °C in THF afforded the atropo-enantio-



Scheme 5. Study of the reversibility of the oxidative Heck reaction.

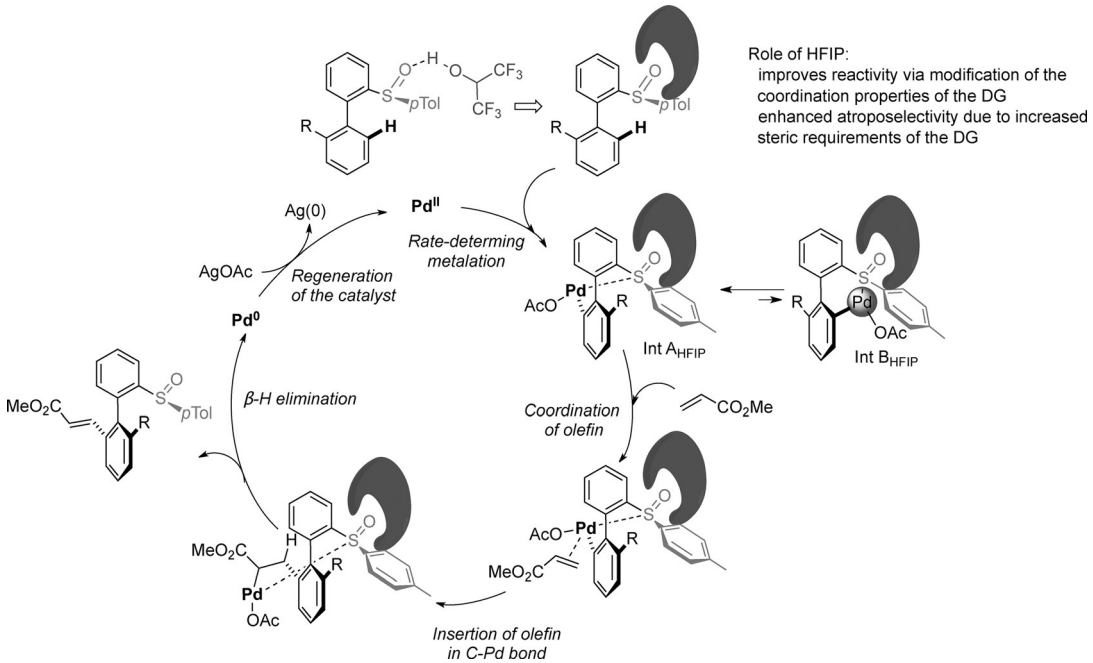
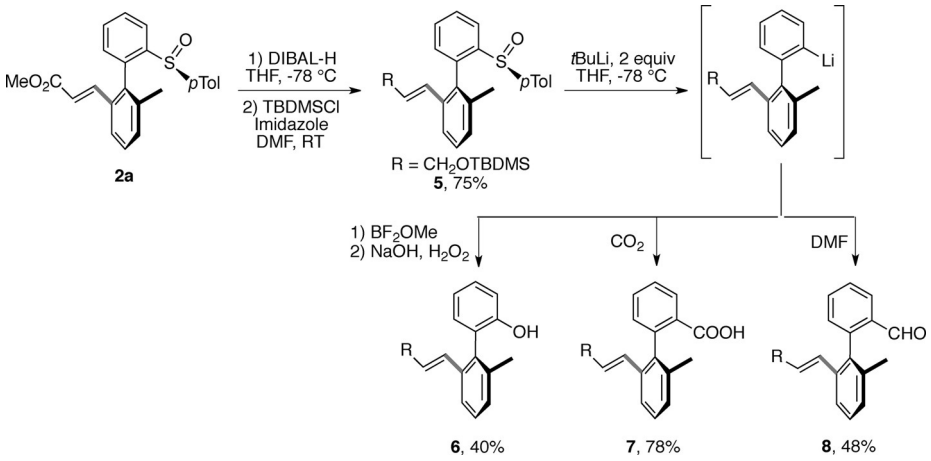


Figure 4. Proposed catalytic cycle.



Scheme 6. Examples of transformations of the sulfoxide DG.

pure biaryllithium species, which was trapped with various electrophiles to afford the corresponding enantiopure[33] biphenyl alcohol **6** (40% yield), biphenyl carboxylic acid **7**[34] (78% yield), and biphenyl aldehyde **8**[33] (48% yield).

Conclusion

We discovered that a very efficient atropo-diastereoselective oxidative olefination could now be performed by direct functionalization of biaryls containing a chiral sulfoxide as the DG. The reaction outcome in terms of both efficiency and stereoselectivity was drastically improved with HFIP as the reaction solvent, which enabled the accomplishment of this asymmetric C–H activation/C–C coupling at room temperature. Under these modified reaction conditions, not only could acrylate be used as a coupling partner, but also styrenes and 1,1-disubstituted activated olefin were applied efficiently. Mechanistic studies were undertaken to elucidate the particular role of HFIP in this reaction. The hydrogen bond between this solvent and the oxygen atom of the sulfoxide DG could be evidenced. The involvement of the sulfoxide in hydrogen bonding was expected to modify both the coordinating properties of this DG and its steric requirements; hence allowing an evidently superior transformation. Finally, the traceless character of this stereogenic DG was evidenced by performing postmodifications of the atropopure scaffolds. Three parent axially chiral compounds could thus be obtained without loss of optical purity.

Experimental Section

General procedure for the atroposelective oxidative Heck reaction

An oven-dried reactor was charged with substrate **1** (0.3 mmol, 1 equiv), AgOAc (0.6 mmol, 2 equiv), and $Pd(OAc)_2$ (10 mol%, 0.03 mmol). HFIP (1.5 mL, 0.2 M) and methyl acrylate (0.6 mmol, 2 equiv) were added, the reactor was sealed, and the reaction mixture was stirred at 25 °C. The reaction was monitored by TLC until total consumption of the starting material. The crude mixture was diluted with Et_2O, filtered through a plug of Celite, and the volatile compounds were removed under reduced pressure. The mixture was analyzed by ^1H NMR spectroscopy to determine the d.r. value and the product was purified by column chromatography on silica gel.

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[1] a) G. Bringmann, D. Menche, *Acc. Chem. Res.* **2001**, *34*, 615; b) P. Lloyd-Williams, E. Giralt, *Chem. Soc. Rev.* **2001**, *30*, 145; c) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563.

[2] a) In *Asymmetric Catalysis in Organic Synthesis* (Ed.: R. Noyori), Wiley Europe, Weinheim, **1994**; b) In *Chiral Auxiliaries and Ligands in Asymmetric Synthesis* (Ed.: J. Seyden-Penne), Wiley, New York, **1995**; in *New Frontiers in Asymmetric Catalysis* (Ed.: K. Mikami, M. Lautens), Wiley, **2007**.

[3] a) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* **2015**, *44*, 3418; b) G. Ma, M. P. Sibi, *Chem. Eur. J.* **2015**, *21*, 11644; 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) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193; e) G. Bringmann, J. Hinrichs, T. Pabst, P. Henschel, K. Peters, E.-M. Peters, *Synthesis* **2001**, *1*, 0155.

[4] a) O. Baudoin, *Eur. J. Org. Chem.* **2005**, 4223; b) D. Zhang, Q. Wang, *Coord. Chem. Rev.* **2015**, *286*, 1.

[5] For rare examples of atroposelective synthesis of tetrasubstituted biaryls through Suzuki coupling, see: a) M. Genov, A. Almorín, P. Espinet, *Chem. Eur. J.* **2006**, *12*, 9346; b) Y. Uozumi, Y. Matsuura, T. Arakawa, Y. M. A. Yamada, *Angew. Chem. Int. Ed.* **2009**, *48*, 2708; *Angew. Chem.* **2009**, *121*, 2746.

[6] For selected reviews, see: a) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107; b) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443; c) K. M. Engle, J.-Q. Yu, *J. Org.*

Chem. **2013**, *78*, 8927; d) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; e) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; f) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; *Angew. Chem.* **2012**, *124*, 10382; g) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; h) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; i) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; j) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.

[7] For selected reviews, see: a) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362; *Angew. Chem.* **2011**, *123*, 3422; b) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; c) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; d) D. Y.-K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452; e) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369.

[8] 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.

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

[10] J. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2014**, *53*, 13244; *Angew. Chem.* **2014**, *126*, 13460.

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

[12] K. Yamaguchi, H. Kondo, J. Yamaguchi, K. Itami, *Chem. Sci.* **2013**, *4*, 3753.

[13] For examples of diastereoselective C–H activation, see: a) R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112; *Angew. Chem.* **2005**, *117*, 2150; b) R. Giri, X. Chen, X.-S. Hao, J.-J. Li, J. Liang, Z.-P. Fan, J.-Q. Yu, *Tetrahedron: Asymmetry* **2005**, *16*, 3502; c) 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; for a recent review, see: d) J. Wencel-Delord, F. Colobert, *Synlett* **2015**, *26*, 2644.

[14] 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; d) F. Colobert, V. Valdivia, S. Choppin, F. R. Leroux, I. Fernández, E. Álvarez, N. Khiar, *Org. Lett.* **2009**, *11*, 5130; e) T. Leermann, P.-E. Broutin, F. R. Leroux, F. Colobert, *Org. Biomol. Chem.* **2012**, *10*, 4095.

[15] For examples of sulfoxide-directed non-asymmetric C–H activation, see: 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; e) K. Padala, M. Jeganmohan, *Chem. Commun.* **2014**, *50*, 14573.

[16] T. Wesch, F. R. Leroux, F. Colobert, *Adv. Synth. Catal.* **2013**, *355*, 2139.

[17] C. K. Hazra, Q. Dherbassy, J. Wencel-Delord, F. Colobert, *Angew. Chem. Int. Ed.* **2014**, *53*, 13871; *Angew. Chem.* **2014**, *126*, 14091.

[18] Y.-N. Ma, H.-Y. Zhang, S.-D. Yang, *Org. Lett.* **2015**, *17*, 2034.

[19] For selected examples, see: a) C. Zhang, Y. Rao, *Org. Lett.* **2015**, *17*, 4456; b) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518; c) G. Li, D. Leow, L. Wan, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2013**, *52*, 1245; *Angew. Chem.* **2013**, *125*, 1283; d) L. Wan, N. Dastbaravardeh, G. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18056; e) W. Gong, G. Zhang, T. Liu, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 16940; f) G. Chen, T. Shigenari, P. Jain, Z. Zhang, Z. Jin, J. He, S. Li, C. Mapelli, M. M. Miller, M. A. Poss, P. M. Scola, K.-S. Yeung, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 3338.

[20] For selected reviews, see: a) J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, *1*, 0018; b) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, *19*, 2925; c) T. Sugiishi, M. Matsugi, H. Hamamoto, H. Amii, *RSC Adv.* **2015**, *5*, 17269.

[21] CCDC-1423467 (**2c**) and 1423468 (**3a**). These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[22] a) A. Berkessel, J. A. Adrio, D. Hüttenhain, J. M. Neudörfl, *J. Am. Chem. Soc.* **2006**, *128*, 8421; b) K. S. Ravikumar, F. Barbier, J.-P. Bégué, D. Bonnet-Delpon, *J. Fluorine Chem.* **1999**, *95*, 123; c) D. Vuluga, J. Legros, B. Crousse, A. M. Z. Slawin, C. Laurence, P. Nicolet, D. Bonnet-Delpon, *J. Org. Chem.* **2011**, *76*, 1126.

[23] For examples of hydrogen bonding involving sulfoxides, see: a) J. Kiefer, K. Noack, B. Kirchner, *Curr. Phys. Chem.* **2011**, *1*, 340; b) M. K. D. L. Belarmino, V. F. Cruz, N. B. D. Lima, *J. Mol. Model.* **2014**, *20*, 2477.

[24] For details, see the Supporting Information.

[25] For related examples, see: a) K. F. Wong, S. Ng, *Spectrochimica Acta Part A* **1976**, *32*, 455; b) F. L. Slejko, R. S. Drago, D. G. Brown, *J. Am. Chem. Soc.* **1972**, *94*, 9210.

[26] a) P. Ruostesuo, P. Pirilä-Honkanen, S. Kaartinen, *Spectrochimica Acta Part A* **1988**, *44*, 359; b) P. Ruostesuo, J. Karjalainen, *Acta Chem. Scand.* **1982**, *36*, 273.

[27] L. S. Gabrielyan, L. G. Melik-Ohanjanyan, S. A. Markarian, *J. Appl. Spectrosc.* **2013**, *80*, 135.

[28] a) J. C. Tai, *J. Comput. Chem.* **1981**, *2*, 161, and references cited therein; b) L. Cazaux, J. D. Bastide, G. Chassaing, P. Maroni, *Spectrochimica Acta Part A* **1979**, *35*, 15.

[29] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066; *Angew. Chem.* **2012**, *124*, 3120.

[30] M. Gómez-Gallego, M. A. Sierra, *Chem. Rev.* **2011**, *111*, 4857.

[31] a) E. Gaster, Y. Vainer, A. Regev, S. Narute, K. Sudheendran, A. Werbeloff, H. Shalit, D. Pappo, *Angew. Chem. Int. Ed.* **2015**, *54*, 4198; *Angew. Chem.* **2015**, *127*, 4272; b) B. Elsler, A. Wiebe, D. Schollmeyer, K. M. Dyballa, R. Franke, S. R. Waldvogel, *Chem. Eur. J.* **2015**, *21*, 12321.

[32] For an example of the solvent-dependent potential for the oxidation of Pd^0 species, see: C. Amatore, A. Jutand, M. J. Medeiros, L. Mottier, *J. Electroanal. Chem.* **1997**, *422*, 125.

[33] During all postmodification transformations of the sulfoxide DG presented herein, a common axially chiral biphenyllithium intermediate was generated. The synthesis of **7** with 99% *ee* clearly shows that this common intermediate is configurationally stable, and therefore, it may be assumed that compounds **6** and **8** are also generated without epimerization.

[34] Determined by chiral HPLC by using an AD-H column; for details, see the Supporting Information.

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