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Palladium-Catalyzed Suzuki–Miyaura Reaction Involving a Secondary sp^3 Carbon: Studies of Stereochemistry and Scope of the Reaction

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Abstract: Palladium-catalyzed C–C bond formation involving secondary sp^3-hybridized carbon is described. These reactions occur with secondary 1-bromoethyl arylsulfoxides and different arylboronic acids, to produce the corresponding arylated sulfoxides in moderate to high yields and with complete stereospecificity. Despite the presence of β hydrogens in the substrate, the competitive β-hydride elimination is not a significant side reaction when coordinating solvents are used. The reported cross-coupling involves secondary C_{sp^3}–C_{sp^2} bond formation: this is the first time that a mechanistic study has been carried out with such substrates. The reaction proceeds with inversion of configuration at the stereogenic C_{sp^3} carbon. The high stereospecificity of the coupling and the mildness of the reaction conditions allow for the preservation of the optical purities of reagents and products and the preparation of useful chiral targets.

Keywords: bromo sulfoxide · cross-coupling · palladium · stereochemistry · sulfur

Introduction

Palladium-catalyzed cross-coupling between organic electrophiles and organometallic compounds has developed to become a useful methodology for the formation of C–C bonds.[1,2,3] Combinations of aryl halides or pseudohalides with different organometallic compounds to provide new C_{sp^2}–C_{sp^2} bonds have been extensively reported.[4] In contrast, reactions between alkyl halides and organometallics to form C_{sp^3}–C_{sp^2} or C_{sp^3}–C_{sp^3} bonds are much less usual[5] and remain a challenging problem in organic synthesis. In general, oxidative addition to C_{sp^3}–X bonds is slow[6] and the β-elimination process becomes an important competitive side reaction. Functionalized primary halo alkyl compounds lacking β hydrogens are therefore suitable substrates for cross-coupling reactions involving sp^3-hybridized carbons since the undesired β-hydride elimination cannot take place, while the presence of functional groups allows for synthetic applications, and in this context a few examples of Suzuki–Miyaura cross-coupling reaction using functionalized halo compounds are known. Reactions involving primary α-halo carbonyls have been reported by Suzuki and Miyaura,[7] Gooßen et al.,[8] and Deng et al.[9] In this context, we recently reported[10] the first example of this type of reaction with primary α-halo sulfoxides. A complementary approach consists of the cross-coupling of an aryl halide (electrophile) and a palladium enolate (nucleophile bearing the function) generated in situ with base. This procedure has been developed by Buchwald et al.[11] and Hartwig et al.,[12] while nitriles[13] and activated sulfones[14] have also been reported as suitable substrates for this kind of reaction. Despite ongoing work in the development of suitable methodologies in the field of palladium-catalyzed cross-coupling reactions with functionalized alkyls and the potential synthetic utility of the described procedures, cross-coupling reactions involving functionalized secondary halides—and also the stereochemical course of the cross-coupling when a reaction involve a stereogenic center—remain unexplored. Although secondary halides are uncommon substrates[5a,15] in transition-metal cross-coupling reactions, several examples of reactions of unfunctionalized secondary alkyls have been reported recently.[5a,15] Metals other than palladium (Ni, Fe, Co) have been used with these substrates, and radical mechanisms seem to be involved.[5a,15] With regard to studies of the stereochemical courses of palladium-catalyzed reactions at stereogenic carbons, examples are scarce, being practically reduced to the pioneering reports by Stille et al.[16] on the

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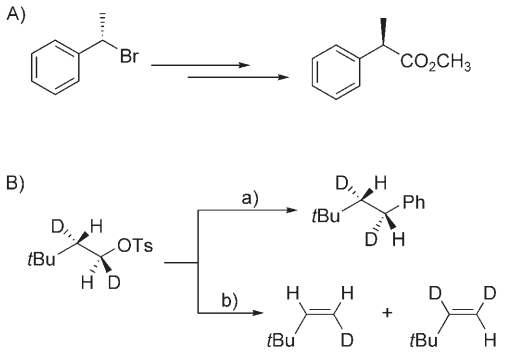
mechanism of the oxidative addition of alkyl halides to zero-valent palladium compounds (Scheme 1A), together with the recent report by Fu and Netherton[17] on the cou-



Scheme 1. Palladium-catalyzed reactions at stereogenic carbon centers. A) 1) $[Pd(PPh_3)_4]/CO$; 2) Br_2; 3) CH_3OH; B) $Pd/PtBu_2Me$ and a) 9-BBN-Ph (BBN = 9-borabicyclo[3.3.1]nonane) or b) dioxane, 70 °C.

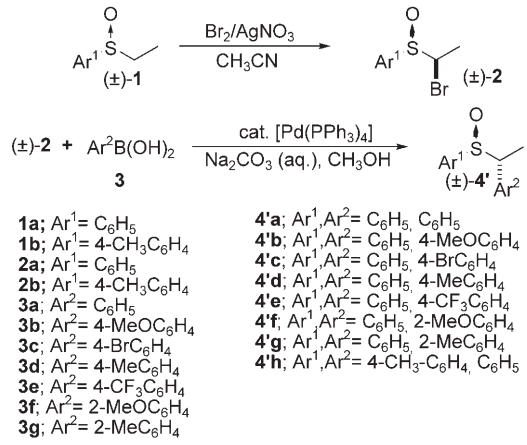
pling of chiral unfunctionalized deuterated primary tosylates (Scheme 1B). Stille et al.[16] used the insertion of carbon monoxide in a mechanistic study targeted towards suppression of the β-elimination process in the oxidative addition intermediate complex. In the process they found indirect evidence of inversion of configuration at the carbon atom in the oxidative addition step, on the assumption that the insertion of carbon monoxide into the palladium-carbon σ bond occurs with retention of configuration (Scheme 1). On the other hand, Fu et al.[17] deduced the stereochemistry of the oxidative addition reaction of palladium(0) to deuterated primary alkyl tosylates from the stereochemistry of the deuterated coupling product and the stereochemistry of the olefins obtained by β elimination of hydride from the oxidative addition complex (Scheme 1).

Against this background, we felt it would be interesting to determine the synthetic scope of palladium-catalyzed Suzuki reactions of secondary α-bromo sulfoxides and the stereochemical course of the cross-coupling reaction itself.

Results and Discussion

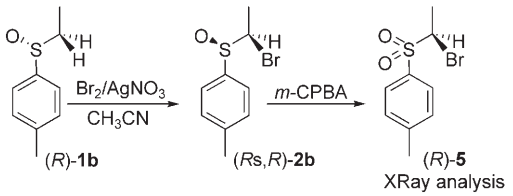
Secondary bromo sulfoxides **2**, obtained by bromination of sulfoxides **1**, react with boronic acids **3** with complete stereospecificity and inversion of configuration at the stereogenic carbon to give the corresponding arylated product **4′** (we have used **X′** to denote that the relative configuration in the product has changed with respect to the starting material) (Scheme 2). Surprisingly we found very remarkable diastereoselectivity in the coupling reaction. While (±)-**2a** reacted readily to give the arylated products (±)-**4′a–g**, the epimer with inverse relative configuration—(±)-**2′a**—was found to be unreactive under similar reaction conditions.

For an attempt to determine the stereochemical course of the reaction, the target chiral bromo sulfoxide **2b** was ob-



Scheme 2. Palladium-catalyzed Suzuki–Miyaura coupling of secondary bromo sulfoxides **2** with boronic acids **3**.

tained in high yield in two steps. First, the homochiral ethyl-*p*-tolyl sulfoxide (*R*)-**1b**[18] (Scheme 3) was synthesized from commercially available (*S*)-(−)-menthyl-*p*-toluenesulfinate.



Scheme 3. Determination of the absolute configuration of (*Rs,R*)-**2b**.

Bromination of the chiral sulfoxide was carried out with $Br_2/AgNO_3/CH_3CN$/pyridine by a described procedure[19] to afford the bromo derivative **2b** in high diastereomeric purity. Although it is known from this work that the configuration at the sulfur atom is inverted in the bromination reaction, the configuration of the new chiral center remained unknown. The bromo sulfoxide **2b** was isolated as an oil and was then converted by oxidation into sulfone **5**, which afforded a crystalline solid (Scheme 3), and the absolute configuration of sulfone **5** was determined by single-crystal X-ray diffraction studies (Figure 1). In the crystal structure the stereocenter shows an *R* configuration with the *p*-tolyl group *gauche* to both the bromine and the methyl group in relation to the S1−C1 bond. Intermolecular C(Br)−H···O−S hydrogen bonds form infinite molecular chains. In short, the reaction between sulfoxide (*R*)-**1b** and $Br_2/AgNO_3/CH_3CN$/pyridine affords enantiomerically pure bromo sulfoxide (R_S,*R*)-**2b**.[20]

With the configuration of (R_S,*R*)-**2b** unequivocally established, we examined the palladium-catalyzed reaction between the bromo sulfoxide (R_S,*R*)-**2b** and phenylboronic acid (**3a**) under standard Suzuki–Miyaura conditions. The reaction occurred in a stereospecific fashion, with enantiomerically pure (S_S,*R*)-**4′h** (Figure 1) being obtained and char-

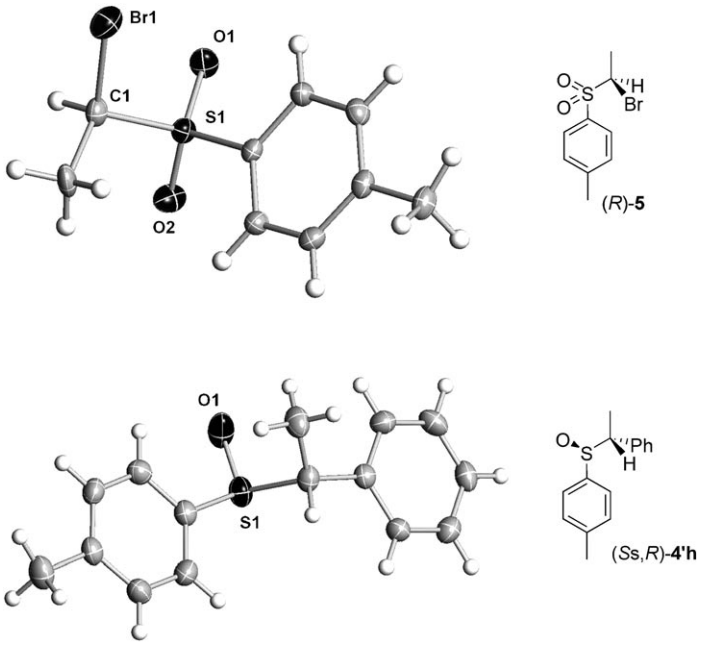


Figure 1. X-ray ellipsoid plot of compounds (*R*)-**5** and (*Ss,R*)-**4′h** (50% probability level).

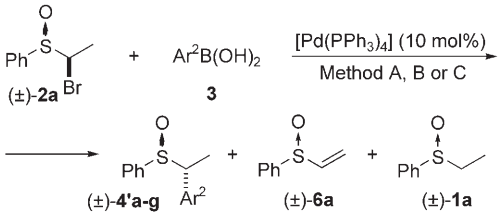
acterized by X-ray analysis.[20] The absolute structure of a single crystal, obtained by slow evaporation of a dichloromethane/*n*-hexane solution of (S_S,*R*)-**4′h**, shows the new stereocenter with an *R* configuration with both aromatic groups *anti* in relation to the S1–C1 bond. The ^{1}H NMR data were consistent with those reported in the literature for racemic **4′h**,[21] so the arylation process takes place with an inversion of configuration, as (R_S,*R*)-**2b** gave (S_S,*R*)-**4′h**. It is noteworthy that no epimerization either of the starting material (R_S,*R*)-**2b** or of the reaction product (S_S,*R*)-**4′h** occurred under our mild reaction conditions, despite the acidic character of the C–H$_\alpha$ hydrogen in both compounds.

This result is in good agreement with reports by Stille[16] and Fu[17] relating to the carbonylation of chiral secondary benzyl bromides and the oxidative addition process in deuterated primary alkyl tosylates, respectively. Inversion of configuration can in principle occur in the catalytic cycle either in the additive oxidation or in the reductive elimination step. All attempts to isolate a crystallized pure sample of the corresponding oxidative addition complex resulting from the reaction between (R_S,*R*)-**2b** and [Pd(PPh$_3$)$_4$]—to provide direct evidence of the stereochemical course of the process—failed because of the lack of complex stability. However, decomposition products were identified as vinyl sulfoxide **6b** (as **6a** but with 4-CH$_3$C$_6$H$_4$ group instead of Ph) and dibromobis(triphenylphosphine)palladium(II) [Pd(PPh$_3$)$_2$Br$_2$], the latter being characterized by X-ray diffraction analysis.[22] The lack of stability of the oxidative addition complex has precluded its isolation, and consequently the direct determination of its stereochemistry by X-ray analysis.

In this study, the exclusive formation of the cross-coupling product (S_S,*R*)-**4′h** from (R_S,*R*)-**2b** strongly suggests that the oxidative addition step proceeds with an inversion of configuration, as it is well documented that reductive elimination always occurs with a retention[23] of configuration. It is thus likely that the inversion of configuration observed though the cross-coupling reaction occurs during the oxidative addition step. The conclusions reached in our study regarding the stereochemical outcome of the process should not be generalized, as the situation might be different for other classes of organohalides. The reaction between (R_S,*R*)-**2b** and a palladium(0) complex reported by us in this work represents the second example of an oxidative palladium addition to a secondary sp^3 hybridized carbon, after Stille's pioneering report[16] in the seventies. In addition, as far as we are aware, there are no literature precedents for palladium-catalyzed cross-coupling reactions involving secondary halides, so the reactions between secondary α-bromo sulfoxides and boronic acids constitute the first examples in this area. Moreover, the high stereoselectivity observed in the reaction of the chiral bromo sulfoxide (R_S,*R*)-**2b** seems to exclude a radical mechanism, in sharp contrast with the results reported for reactions with unfunctionalized secondary halides performed with other metals such as nickel and iron, in which a radical mechanism has been invoked to explain the stereochemical outcome of the reactions.[15]

Owing to the novelty of the reaction of the secondary bromo sulfoxide, we decided to study the scope of such cross-coupling reactions with a series of representative boronic acids (Table 1). The racemic bromo sulfoxide (±)-**2a** was selected as the benchmark substrate in order to determine the best conditions and the reaction scope (Table 1). The required starting material was obtained from racemic ethyl phenyl sulfoxide (**1a**) by treatment with Br$_2$/CH$_3$CN/pyridine, and the reaction behavior of (±)-**2a** under stan-

Table 1. Palladium-catalyzed Suzuki–Miyaura reactions between secondary bromo sulfoxide (±)-**2a** and boronic acids **3a–g**.

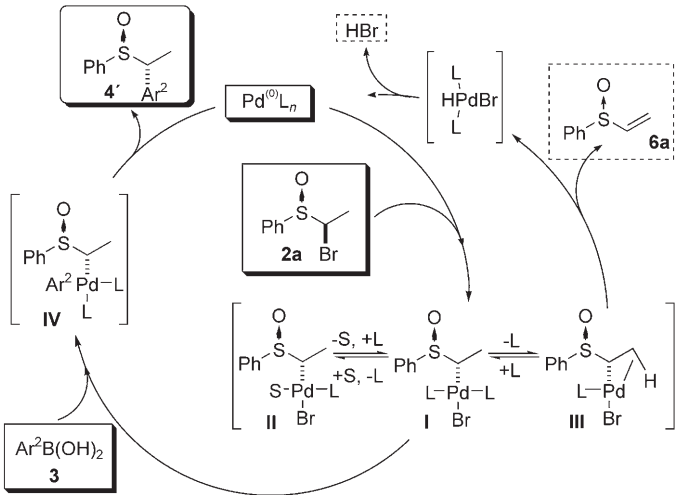


Run	3	Ar^2	Method[a]	4′	Yield [%] 4′	6a	1a
1	**a**	C_6H_5	A	**a**	43	19	23
2	**b**	4-MeOC$_6$H$_4$	A	**b**	48	17	
3	**c**	4-BrC$_6$H$_4$	A	**c**	46	18	29
4	**b**	4-MeOC$_6$H$_4$	B	**b**	18	52	
5	**a**	C_6H_5	C	**a**	66	33	
6	**b**	4-MeOC$_6$H$_4$	C	**b**	87	13	
7	**d**	4-MeC$_6$H$_4$	C	**d**	82	15	
8	**c**	4-BrC$_6$H$_4$	C	**c**	62	31	
9	**e**	4-CF$_3$C$_6$H$_4$	C	**e**	10[b]	35	
10	**f**	2-MeOC$_6$H$_4$	C	–		20	
11	**g**	2-MeC$_6$H$_4$	C	–		20	

[a] Reaction conditions: A) Na_2CO_3 (aq)/MeOH, B) CsF/THF, C) CsF/*tert*-amyl alcohol. [b] Determined by NMR analysis.

dard Suzuki–Miyaura conditions (aqueous base and methanol as a solvent) was assayed with representative boronic acids **3a–c**, possessing substituents of different electronic character (Table 1, entries 1–3). Under these conditions, the corresponding cross-coupled derivative was in each case the major reaction product, although the conversion was in all cases only moderate.

Dehalogenation product **1a** and β-elimination product **6a** were also isolated as minor side products. To optimize the yield for the cross-coupling product, we assayed the reactions under the best conditions previously found by us for Suzuki–Miyaura reactions with unsubstituted sulfoxides as substrates.[10] Accordingly, CsF was used as an non-aqueous base in anhydrous THF as a solvent. We reasoned that the conversion of the oxidative addition intermediate, an intermediate common to the cross-coupling and β-elimination processes (Scheme 4) should give rise to the transmetallated

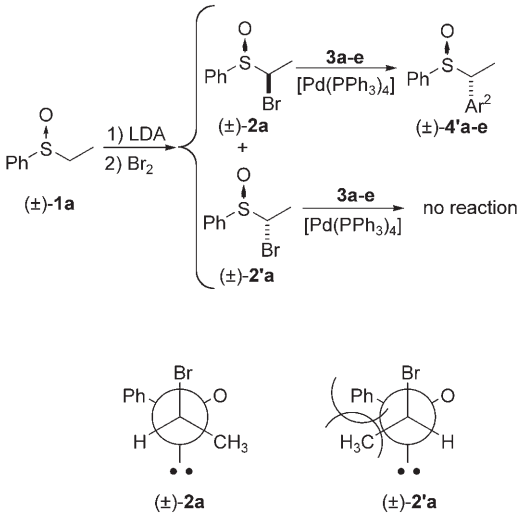


Scheme 4. Catalytic cycle of the palladium-catalyzed reaction of (±)-**2a** with boronic acids.

intermediate precursor of the cross-coupled product more efficiently with use of a fluoride ion as base, while on the other hand, substitution of methanol for THF as a solvent should minimize the dehalogenation pathway.[10] Under these conditions, however, the reaction between (±)-**2a** and **3b** indeed took place without dehalogenation, but the formation of vinyl sulfoxide **6a** by β elimination became an important side reaction, probably because of the low coordinating ability of the solvent (Table 1, entry 4). The THF was therefore substituted by *tert*-amyl alcohol, which is a non-oxidizable solvent capable of occupying vacant sites in the palladium coordination sphere, favoring the conversion of complex **I**, the common intermediate for the cross-coupling and β-elimination reactions, to complex **II**. Similarly, the rate of formation of complex **III** decreases because of the presence of the coordinating solvent in the coordination sphere of palladium, which disfavors the occurrence of the agostic palladium C–H bond interaction[24] and consequently hampers the β-hydrogen elimination (Scheme 4). The use of *tert*-amyl alcohol, of a non-aqueous base such as CsF, and of degassed solvents thus allowed the best selectivities towards the formation of the cross-coupling product to be achieved in the reactions between (±)-**2a** and the parent boronic acid **3a** (Table 1, entry 5), the electron-rich arylboronic acids **3b** (Table 1, entry 6) and **3d** (Table 1, entry 7), and the slightly electron-deficient boronic acid **3c** (Table 1, entry 8). In the case of **3e**, in which the aryl group is strongly electron-deficient because of the presence of the *p*-CF_3 substituent, only a poor yield of the cross-coupling product (±)-**4′e** was obtained (Table 1, entry 9).

The reaction was also sensitive to steric effects. Arylboronic acids **3f** (Table 1, entry 10) and **3g** (Table 1, entry 11), bearing *o*-substituents, failed in the cross-coupling reaction and consequently vinyl sulfoxide **6a**, resulting from the β-hydride elimination, was the only product in these cases. The high selectivity for the cross-coupling process achieved in the reactions between (±)-**2a** and the parent boronic acid **3a** and the nonhindered substituted boronic acids **3b**, **3c**, and **3d** might be related to the presence of the bulky sulfinyl moiety. Conformational restrictions could disfavor attainment of the required disposition to allow the β-hydrogen elimination reaction,[25] and this effect might act together with the solvent effect, which could minimize the β-hydride elimination side reaction. If we compare these results with those previously obtained for the unsubstituted bromomethyl phenyl sulfoxide,[10] we can see that the efficiency of the cross-coupling reaction decreases with the steric hindrance. This is a general trend in the Suzuki–Miyaura reaction.[2]

We next extended our study to test the reactivity of the bromo sulfoxide (±)-**2′a** in cross-coupling reactions (Scheme 5). For this purpose we prepared this bromo sulfoxide as a mixture of racemic diastereomers (±)-**2′a** and (±)-**2a** by treating the racemic sulfinyl anion (±)-**1a**-Li with Br_2. The mixture of diastereomers was separated by column



Scheme 5. Palladium-catalyzed cross-coupling reaction of (±)-**2′a** and (±)-**2a**.

chromatography. Surprisingly though, bromo sulfoxide (±)-**2′a** was recovered unchanged when it was subjected to treatment with boronic acids under the same reaction conditions as previously described for the (±)-**2a** diastereomer. Moreover, when the reaction was carried out with a mixture of (±)-**2′a** and (±)-**2a**, only (±)-**4′a**, derived from (±)-**2a**, was formed, while the (±)-**2′a** remained unchanged.

As far as we are aware, such remarkable differences in the reactivities of diastereomers have not been reported previously in cross-coupling reactions with achiral palladium catalysts. A possible explanation for this unusual behavior might be that the additive oxidation step takes place in a complex of Pd^0 with the sulfinyl moiety. In such a case, repulsive steric interactions between the *gauche* methyl and phenyl groups should disfavor the conformation of bromosulfoxide (±)-**2′a** with the lone electron pair *anti* to the bromine (Scheme 5). This arrangement is necessary to account for the inversion of configuration at carbon observed in the coupling reaction. In the diastereoisomer (±)-**2a**, in contrast, the conformation with the lone electron pair *anti* to the bromine also has the methyl and phenyl groups in an *anti* relationship and should predominate. The difference in reactivity found for pairs of diastereoisomers opens up the possibility to explore the potential of the cross-coupling reaction for kinetic resolution of a diastereomeric racemic mixture with a chiral catalyst.

With regard to synthetic applications, the described procedure constitutes a convenient method for the synthesis of the chiral sulfoxide (S_S,*R*)-**4′h** in enantiomerically pure form. The chiral sulfoxide (S_S,*R*)-**4′h** itself, or a direct derivative such as the corresponding chiral sulfide, might find applications as, say, chiral ligands. Chiral sulfoxides have been used, for example, as chiral ligands in the asymmetric allylation of aldehydes[26] or in the asymmetric Trost reaction.[27] Sulfides similar to those expected from simple reduction of (S_S,*R*)-**4′h** are known to form palladacycles and might find applications in asymmetric Heck reactions.[28] From the perspective of sulfoxide chemistry, our route to (S_S,*R*)-**4′h** offers better results than alternative methods such as methylation of chiral benzyl *p*-tolyl sulfoxide, which always affords a mixture of diastereomers that are difficult to separate.[21]

Conclusion

In summary, we have described for the first time the stereochemical course of a palladium-catalyzed Suzuki–Miyaura cross-coupling reaction involving a stereogenic sp^3-carbon atom in a secondary functionalized alkyl halide. The secondary halide used in the stereochemical study is a bromo sulfoxide. Secondary halides are uncommon electrophilic partners in transition-metal-catalyzed cross-coupling reactions and only a few examples with metals other than palladium have been reported in the literature. The reaction described here takes place with complete inversion of configuration at the stereogenic carbon atom. Evidence strongly suggests that the inversion of configuration occurs in the oxidative addition step, if it is assumed that the usual reductive elimination proceeds with retention of configuration. Our results are in sound agreement with the course of palladium(0)-catalyzed carbonylations of benzyl halides or β eliminations in unfunctionalized primary tosylates. The complete substrate selectivity encountered in the palladium cross-coupling reaction with the diastereomeric (±)-**2′a** and (±)-**2a** bromo sulfoxides is noteworthy; while the (±)-**2′a** diastereomer does not react, the (±)-**2a** isomer affords the cross-coupling product with high stereospecificity in moderate to good yields. Despite the presence of β hydrogens in the substrate, the expected β-hydride elimination process can be minimized by using a coordinating solvent. The reaction can be conducted with chiral substrates without loss of optical purity, so the palladium-catalyzed Suzuki–Miyaura reaction with the easily accessible chiral bromo sulfoxide (R_S,*R*)-**2b** affords the chiral sulfoxide (S_S,*R*)-**4′h** in an enantiomerically pure form.

Experimental Section

General: ^{1}H and ^{13}C spectra were recorded with a Bruker AC 300. Chemical shifts are reported in δ (ppm) relative to the $CHCl_3$ peak at $\delta = 7.27$ ppm (^{1}H) or $\delta = 77.0$ ppm (^{13}C). High-resolution mass spectra were recorded on a Fisons VG Autospec instrument. Optical rotations were determined on a Perkin–Elmer 241 polarimeter at room temperature. The *ee* values were determined by HPLC (Chiralcel OD-H). Reactions were monitored by analytical thin-layer chromatography on commercial aluminium sheets pre-coated (0.2-mm layer thickness) with silica gel 60 F_{254} (E. Merck). Product purification by flash chromatography was performed on silica gel (E. Merck 230–400 mesh). All experiments were carried out under dry argon. For reactions in degassed solvents, three freeze-pump-thaw cycles were performed before the reagents were mixed, in order to exclude atmospheric oxygen from the reaction media.

Preparation of (±)-(1-bromoethylsulfinyl)benzene [(±)-2a]: This compound was prepared by bromination of ethyl phenyl sulfoxide (**1a**)[29] with Br_2/pyridine/CH_3CN by a described procedure.[19] Yield: 90%; *de*: 95%; colorless oil; ^{1}H NMR: $\delta = 7.63$–7.61 (m, 2H), 7.47–7.46 (m, 3H), 4.68 (q, $J = 6.8$ Hz, 1H), 1.74 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR: $\delta = 139.8$ (s), 132.4 (d), 129.2 (d), 126.2 (d), 62.8 (d), 18.7 ppm (q); HRMS (EI$^+$): *m*/*z* calcd for C_8H_9OBrS: 232.9636 $[M]^+$; found: 232.9631.

Synthesis of (R_S,*R*)-1-(1-bromoethylsulfinyl)-4-methylbenzene [(−)2b]: This compound was prepared by bromination of (*R*)-ethyl *p*-tolyl sulfoxide ((*R*)-**1b**)[18] with Br_2/pyridine/CH_3CN by a described procedure.[19] Yield: 86%; *ee*: 99%; colorless oil; $[\alpha]_D^{lit.:[19]} = -115°$ ($c = 1$, acetone), $[\alpha]_D = -113.8°$ ($c = 1$, acetone); ^{1}H NMR: $\delta = 7.50$ (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 8.1$ Hz, 2H), 4.66 (q, $J = 6.8$ Hz, 1H), 2.34 ppm (s, 3H), 1.72 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR: $\delta = 142.4$ (s), 135.9 (s), 129.4 (d), 125.7 (d), 62.4 (d), 21.4(q), 18.0 ppm (q); HRMS (EI$^+$): *m*/*z* calcd for $C_9H_{11}OSBr$: 245.9714 $[M]^+$; found: 245.9701; HPLC analysis (Chiralcel OD-H, 10% propan-2-ol/hexane, 0.8 mL min^{-1}).

Synthesis of the diastereomeric mixture of (R_S,*R*)- and (S_S,*S*)-(1-bromoethylsulfinyl)benzene ((±)-2a) and (R_S,*S*)- and (S_S,*R*)-(1-bromoethylsulfinyl)benzene ((±)-2′a): Ethyl phenyl sulfoxide (5 mmol) in THF (20 mL) was added dropwise at −78 °C under argon to a solution of LDA (5.75 mmol) in THF (12 mL), and the solution was stirred for 1 h at the same temperature. The mixture was then allowed to warm gradually to 0 °C. The solution was again cooled to −78 °C and added dropwise at the same temperature to precooled neat Br_2 (3 mmol). The resulting solution was stirred at −78 °C for 5 min and the mixture was treated with a solution of $Na_2S_2O_3$ (2 N, 10 mL), extracted with dichloromethane, dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude material was purified by flash column chromatography to yield a mixture of bromo

sulfoxides (±)-**2b** and (±)-**2′b** (60:40, 82%); colorless oil; ^{1}H NMR: δ = 7.74–7.71 (m, 2H), 7.55–7.52 (m, 3H), 4.61 (q, J = 6.8 Hz, 1H), 1.90 ppm (d, J = 6.8 Hz, 3H); HRMS (EI$^+$): m/z calcd for C_8H_9OBrS: 232.9636 $[M]^+$; found: 232.9633.

Cross-coupling between bromo sulfoxides 2 and boronic acids 3a–g—general procedure: The boronic acid **3** (0.8 mmol), $[Pd(PPh_3)_4]$ (0.04 mmol) and CsF (1.6 mmol) were added to a solution of the appropriate α-bromo sulfoxide (±)-**2a** or (−)-**2b** (0.4 mmol) in degassed *tert*-amyl alcohol (8 mL). After having been heated at reflux for an appropriate duration (see Table 1), the reaction mixture was allowed to cool to room temperature, quenched with water (10 mL) and extracted with diethyl ether (2×15 mL) and dichloromethane (2×15 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure to yield products **1**, **4′** and **6**.[30]

(±)-(1-Phenylethylsulfinyl)benzene ((±)-4′a): Yield: 66%; m.p. 67–68°C; ^{1}H NMR: δ = 7.34–6.91 (m, 10H) 3.73 (q, J = 7.1 Hz, 1H), 1.63 ppm (d, J = 7.1 Hz, 3H); ^{13}C NMR: δ = 142.9 (s), 135.9 (s), 131.4 (d), 128.9 (d), 125.3 (d), 67.5 (d), 14.6 ppm (q); HRMS(FAB$^+$): m/z calcd for $C_{14}H_{14}OS$ $[M+1]^+$: 231.0844; found: 231.0842.

(±)-1-Methoxy-4-[1-(phenylsulfinyl)ethyl]benzene ((±)-4′b): Yield: 87%; m.p. 77–80° C; ^{1}H NMR: δ = 7.35–7.16 (m, 5H), 6.84 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 3.72 (s, 3H) 3.75–3.69 (m, 1H), 1.59 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR: δ = 159.9 (s), 142.4 (s), 131.3 (d), 130.2 (d), 128.8 (d), 127.7 (s), 125.4 (d), 114.2 (d), 66.7 (d), 55.8 (q), 14.7 ppm (q); HRMS(FAB$^+$): m/z calcd for $C_{15}H_{17}O_2S$ $[M+1]^+$: 261.0949; found: 261.0959.

(±)-1-Bromo-4-[1-(phenylsulfinyl)ethyl]benzene ((±)-4′c): Yield: 62%; m.p. 137–138° C; ^{1}H NMR: δ = 7.39–7.28 (m, 5H), 7.25 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 3.80 (q, J = 7.1 Hz, 1H), 1.63 ppm (d, J = 7.1 Hz, 3H); ^{13}C NMR: δ = 141.5 (s), 134.4 (s), 131.5 (d), 131.2 (d), 130.2 (d), 128.6 (d), 124.9 (d), 122.4 (s), 66.1 (d), 13.7 ppm (q); HRMS(EI$^+$): m/z calcd for $C_{14}H_{13}OBrS$: 307.9867 $[M]^+$; found: 307.9873.

(±)-1-Methyl-4-[1-(phenylsulfinyl)ethyl]benzene ((±)-4′d): Yield: 82%; m.p. 77–80° C; ^{1}H NMR: δ = 7.34–7.17 (m, 5H), 6.98 (d, J = 7.9 Hz, 2H), 6.81 (d, J = 7.9 Hz, 2H), 3.69 (q, J = 7.1 Hz, 1H), 2.25 (s, 3H), 1.59 ppm (d, J = 7.1 Hz, 3H); ^{13}C NMR: δ = 142.1 (s), 138.1 (s), 132.4 (s), 130.9 (d), 129.1 (d), 128.5 (d), 128.4 (d), 124.9 (d), 66.7 (d), 21.1 (q), 13.9 ppm (q); HRMS(EI$^+$): m/z calcd for $C_{15}H_{16}OS$: 244.0918 $[M]^+$; found: 244.0921.

(S_S,*R*)-1-Methyl-4-(1-phenylethylsulfinyl)benzene ((S_S,*R*)-4′h): Yield: 65%; m.p. 83–86° C; ^{1}H NMR: δ = 7.19–6.92 (m, 9H), 3.71 (q, J = 7.1 Hz, 1H), 2.29 (s, 3H), 1.63 ppm (d, J = 7.1 Hz, 3H); ^{13}C NMR: δ = 141.4 (s), 138.7 (s), 135.6 (s), 129.2 (d), 128.7 (d), 128.4 (d), 128.2 (d), 124.9 (d), 67.0 (d), 21.4(q), 14.6 ppm (q); HRMS (EI$^+$): m/z calcd for $C_{15}H_{16}OS$: 244.0918 $[M]^+$; found: 244.0921. HPLC analysis (Chiralcel OD-H, 10% propan-2-ol/hexane, 0.8 mL min^{-1}).

(*R*)-1-(1-Bromoethylsulfonyl)-4-methylbenzene ((−)-5): This compound was prepared by oxidation of (R_S,*R*)-**2a** with *m*-CPBA by a described procedure.[19] Yield: 80%; *ee*: 80% ; m.p. 93–96°C; $[\alpha]_D^{lit.:[31]}$: −11.9° (c = 1, acetone); $[\alpha]_D$: −14.9° (c = 1, acetone); ^{1}H NMR: δ = 7.78 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 4.77 (q, J = 6.9 Hz, 1H), 2.41 (s, 3H), 1.90 ppm (d, J = 6.9 Hz, 3H); ^{13}C NMR: δ = 146.2 (s), 132.0 (s), 130.5 (d), 130.1 (d), 59.6 (d), 22.1 (q), 19.9 ppm (q); HRMS(EI$^+$): m/z calcd for $C_9H_{11}O_2SBr$: 261.9663 $[M]^+$; found: 261.9623; HPLC analysis (Chiralcel OD-H, 5% propan-2-ol/hexane, 0.8 mL min^{-1}).

Single-crystal X-ray diffraction

X-ray data for compound (S_S,*R*)-4′h: Colorless needle, 0.48×0.10×0.08 mm size, orthorhombic, $P2_12_12_1$, a = 5.8007(12), b = 7.4505(15), c = 29.585(6) Å, V = 1278.6(5) Å^3, Z = 4, ρ_{calcd} = 1.269 g cm^{-3}, θ_{max} = 27.88, $Mo_{K\alpha}$, λ = 0.71073 Å, ω-scan, diffractometer Nonius Kappa CCD, T = 150(2) K, 9384 reflections collected, of which 3027 were independent (R_{int} = 0.050), 2473 observed reflections ($I > 2\sigma I$), direct primary solution and refinement on F^2,[32] 156 refined parameters, methyl hydrogen atoms refined as *rigid*, others as *riding*, the absolute structure was determined from anomalous dispersion effects (Flack parameter 0.10(8),[33]), R_1-[$I > 2\sigma(I)$] = 0.0391, wR_2(all data) = 0.0870.

X-ray data for compound (−)-5: Colorless prism, 0.38×0.36×0.28 mm size, orthorhombic, $P2_12_12_1$, a = 6.9382(14), b = 10.725(2), c = 13.532(3) Å, V = 1007.0(4) Å^3, Z = 4, ρ_{calcd} = 1.736 g cm^{-3}, θ_{max} = 30.00, $Mo_{K\alpha}$, λ = 0.71073 Å, ω-scan, diffractometer Nonius Kappa CCD, T = 150(2) K, 18033 reflections collected, of which 2897 were independent (R_{int} = 0.069), 2566 observed reflections ($I > 2\sigma I$), absorption correction based on multi-scans, μ = 4.253, T_{min} 0.205, T_{max} 0.304, direct primary solution and refinement on F^2,[32] 120 refined parameters, methyl hydrogen atoms refined as *rigid*, others as *riding*, the absolute structure was determined by anomalous dispersion effects (Flack parameter 0.001(8),[33]), R_1-[$I > 2\sigma(I)$] = 0.0323, wR_2(all data) = 0.0753.

CCDC-616336 and CCDC-616335 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.

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