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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1628–1634

The first stereoselective Pd-catalyzed addition of boronic acids onto aldehydes

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Received 19 June 2007; accepted 25 June 2007

Abstract—The coupling reaction between 2-*p*-tolylsulfinyl benzaldehyde and substituted boronic acids catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ proceeds in a stereoselective manner, demonstrating the efficiency of the sulfinyl group as a chiral inductor. Enantiopure secondary diaryl alcohols become easily accessible by subsequent sulfoxide–lithium exchange.

1. Introduction

The addition of a metal–carbon bond to the carbon–heteroatom double bond is a very popular reaction in main group metal reagents of lithium and magnesium, but less attention has been paid to the corresponding reaction of transition-metal compounds.[1] Recent results have described the addition of arylboronic acids to aldehydes in the presence of catalytic amounts of rhodium and phosphine additives[2] or *N*-heterocyclic carbenes.[3] In spite of the rare activity of Pd-catalysts for the 1,2-addition of arylboronic acids to aromatic aldehydes, two examples[4] have been reported but no application to asymmetric synthesis has been developed in order to obtain pure chiral carbinols. We previously demonstrated the efficient atropo-diastereoselective Suzuki–Miyaura coupling reaction by means of a stereogenic benzylic carbinol bearing a chiral sulfoxide at the β-position.[5]

Chiral diaryl methanols are important intermediates for the synthesis of biologically active compounds.[6] Two general approaches exist for their catalytic enantioselective synthesis. They can be obtained either by reduction of the corresponding unsymmetrical diaryl ketones[7] or are accessible by enantioselective aryl transfer reactions to aldehydes.[8] However, both methods have severe limitations and only work well for a limited range of substrates. For example, the reduction methodology requires the presence of an *ortho*-substituent on one of the aryls or electronically very different aryl groups. In the catalyzed additions to aldehydes, only phenyl transfer reactions have been developed to a satisfying level to afford arylphenylmethanols with high enantioselectivities. Other protocols employing arylboronic acids,[2,3] arylstannanes,[9] or arylsilanes[10] are either non-asymmetric or lead to products with low enantiomeric excess.[11]

Herein, we report a new approach toward optically active diaryl methanols, which employs readily accessible, commercially available arylboronic acids as aryl source. Recently, Ito and Ohta reported on the palladium-catalyzed reaction of arylboronic acids with aldehydes[4] and observed that general palladium complexes have no catalytic activity without chloroform meaning chloroform is essential for this reaction.

Therefore we planned to apply this procedure to a diastereoselective coupling. Using an inexpensive metal instead of rhodium, catalysis with $Pd_2(dba)_3{\cdot}CHCl_3$[12] is easy to perform and yields a broad range of products by the diastereoselective 1,2-addition of aromatic aldehydes with arylboronic acids in the presence of an enantiopure 2-*p*-tolylsulfinyl group as a traceless chiral auxiliary.[13] Sulfoxides as chiral auxiliaries have several features which make them highly useful for this purpose: firstly, they can be constructed in enantiomerically pure form by any of a number of methods, the most important for our purposes being the Andersen substitution of (2)-menthyl sulfinate.[14] Secondly,

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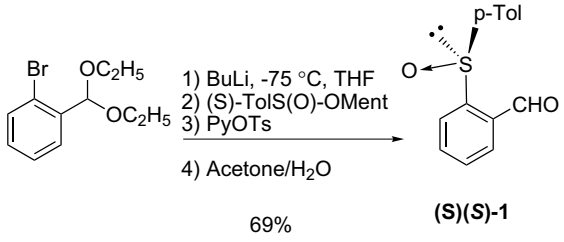
doi:10.1016/j.tetasy.2007.06.031

they have electronic properties, which exaggerate the contrast between the physical properties of the two stereoisomers, mainly because of dipole orientation.[15] And thirdly, they are very useful as traceless resolving agents, as they can undergo sulfoxide–lithium exchange[16] to afford new organometallic intermediates, which can subsequently be trapped by various electrophiles.[17]

2. Results and discussion

Enantiomerically pure (*S*)-2-*p*-tolylsulfinylbenzaldehyde **1** was prepared in high overall yield over a two-step sequence starting from commercially available 2-bromobenzaldehyde diethyl acetal. Sulfinylation and subsequent hydrolysis of the acetal function afforded our target molecule (Scheme 1).[18]

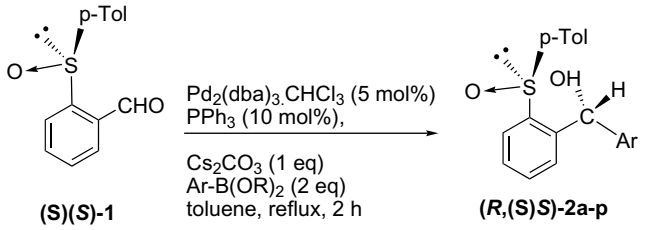


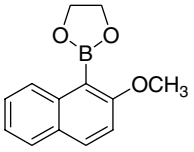
Scheme 1.

The palladium-catalyzed addition of phenylboronic acid and different substituted derivatives thereof are presented in Table 1.

As can be seen in entries 1–14, a remarkably high influence of electronic effects in the arylboronic acids can be observed. The yields vary only in a small range between 50% and 89% with electron-rich arylboronic acids. In the coupling reaction with 2-methoxyphenyl boronic acid, changing the solvent from toluene to either THF, CH_3CN, or dioxane decreased the diastereomeric excess but increased the yield in the case of dioxane (entries 2–5). However, electron-deficient arylboronic acids showed no reaction at all (entries 12–14). Ito and Ohta have reported similar results. In their case, arylation with electron-deficient arylboronic acids in the presence of Pd–$CHCl_3$ proceeded only very sluggishly.[4] Changing from an arylboronic acid to an arylester does not significantly influence the yields (entry 15). Although in our case the aldehyde is bearing the highly sterically demanding 2-*p*-tolylsulfinyl group as a chiral inductor, our yields are only slightly inferior to those of Ito and Ohta. However in terms of selectivity, Table 1 clearly shows the need for a coordinating substituent in the *ortho*-position. The selectivity increases from phenylboronic acid (62:38, entry 1) over 2-methoxyphenylboronic acid (86:14, entry 2) to 2,6-dimethoxyphenylboronic acid (100:0, entry 8). Unfortunately, 2-dimethylaminophenylboronic acid did not react under these conditions (entry 11). In all cases, the diastereoisomers could easily be separated either by column chromatography or by crystallization.

Table 1. $Pd_2(dba)_3{\cdot}CHCl_3$-catalyzed diastereoselective 1,2-addition of aromatic aldehydes with arylboronic acids[a]



Entry	$ArB(OR)_2$	Selectivity [*R*,(S)*S*]:[*S*,(S)*S*]	Yield[b] [%]
1	$C_6H_5B(OH)_2$	62:38	67 (**2a**)
2	$2\text{-}H_3COC_6H_4B(OH)_2$	86:14	51 (**2b**)
3	$2\text{-}H_3COC_6H_4B(OH)_2$	74:26	65 (**2b**)[c]
4	$2\text{-}H_3COC_6H_4B(OH)_2$	71:29	43 (**2b**)[d]
5	$2\text{-}H_3COC_6H_4B(OH)_2$	75:25	89 (**2b**)[e]
6	$3\text{-}H_3COC_6H_4B(OH)_2$	61:39	56 (**2c**)
7	$4\text{-}H_3COC_6H_4B(OH)_2$	61:39	62 (**2d**)
8	$2,6\text{-}(H_3CO)_2C_6H_3B(OH)_2$	100:0	61 (**2e**)
9	$2\text{-}H_3CC_6H_4B(OH)_2$	57:43	59 (**2f**)
10	$2\text{-}H_3CO\text{-}5\text{-}H_3C\text{-}C_6H_3$	80:20	50 (**2g**)
11	$2\text{-}(H_3C)_2NC_6H_4B(OH)_2$	nr[d]	<1 (**2h**)
12	$3\text{-}O_2NC_6H_4B(OH)_2$	nr	<1 (**2k**)
13	$2\text{-}NCC_6H_4B(OH)_2$	nr	<1 (**2l**)
14	$4\text{-}F_3CC_6H_4B(OH)_2$	nr	<1 (**2m**)
15		96:4	55 (**2p**)

[a] The reaction was carried out using 2-*p*-tolylsulfinylbenzaldehyde (1.0 mmol), the corresponding aryl boronic acid (2.0 equiv), Cs_2CO_3 (1.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), and PPh_3 (10 mol %) in 2.0 mL of toluene at 120 °C. The reaction was followed by TLC analysis.
[b] Yield of product isolated by silica gel column chromatography.
[c] Reaction conducted in THF.
[d] Reaction conducted in CH_3CN.
[e] Reaction conducted in dioxane.

The (*R*)-absolute configuration of the stereogenic center formed in the major diastereomer was determined by analysis of the carbinol **2b** by X-ray crystallography (Fig. 1).[19,20]

In order to investigate the scope and limitations of this coupling procedure, we decided to modify as well the substituent pattern of the aldehyde. Several groups observed an increased regioselectivity of the addition of aluminum and magnesium reagents onto aldehydes,[21] as well as the hydrocyanation of δ-ketosulfoxides[22] and benzaldehydes[23] in the presence of a remote 2-*p*-tolylsulfinyl group and coordinating methoxy substituents. Therefore we decided, to introduce a methoxy substituent next to the aldehyde (compound **3**, Scheme 2).

The coupling between derivative **3** and phenylboronic acid was conducted as described above. However, probably due to steric reasons, we were unable to observe any coupling reaction. Increasing the amount of palladium (15 mol %) did not change the situation.

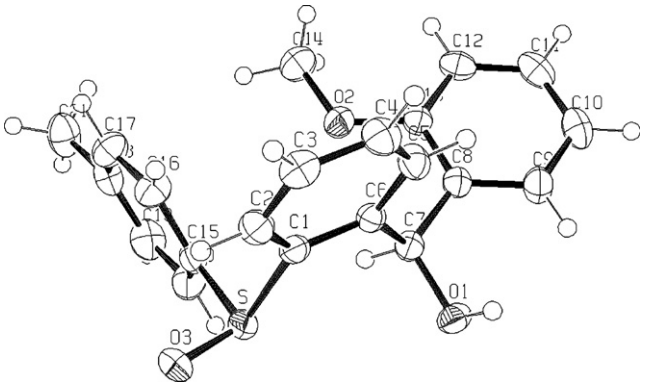
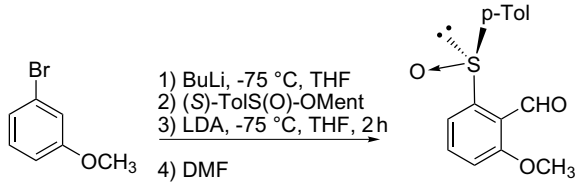


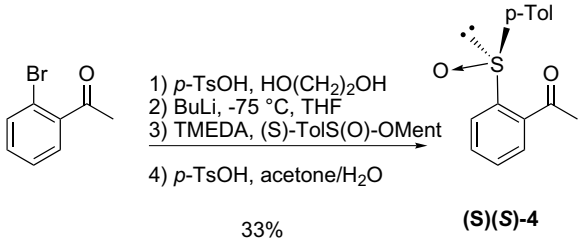
Figure 1. X-ray crystal structure of **2b**.



56% **(S)(*S*)-3**

Scheme 2.

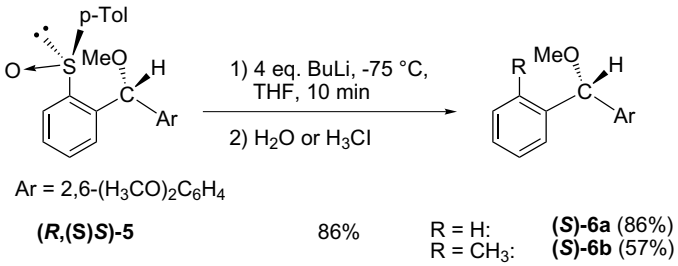
Next, we wanted to investigate, whether this addition is restricted to just aldehydes or if ketones are also suitable substrates giving rise to substituted benzyl alcohols. Thus, we prepared the 2-*p*-tolylsulfinyl substituted ketone **4** depicted in Scheme 3. However again, the substrate underwent no coupling reaction with phenylboronic acid.



33% **(S)(*S*)-4**

Scheme 3.

As enantiopure diaryl carbinols are important starting materials for the total synthesis of natural products,[5] we were interested to see, if the 2-*p*-tolylsulfinyl group could be removed without any loss of chirality by sulfoxide–lithium exchange. As a model compound we took the methyl ether **5** generated from **2e** by treatment with NaH/MeI with the 2,6-dimethoxyphenyl unit. Its precursor, alcohol **2e** was obtained diastereomerically pure. The sulfoxide–lithium exchange proceeded smoothly with butyllithium without any loss of chirality at −78 °C giving rise to the corresponding diaryl compound **6a** in high yield. Analogously, alkylation of the intermediate aryllithium species with iodomethane afforded derivative **6b** in a yield of 57% (Scheme 4).



Scheme 4.

The ^{1}H NMR spectrum of (*S*)-**6a** using the chiral shift reagent Eu(hfc)$_3$ showed that no racemization took place during the sulfoxide–lithium exchange. Only one signal assignable to the protons of the non-aromatic methoxy group appeared in the ^{1}H NMR spectrum, while two signals of the methoxy protons were separately observed in a similar NMR experiment of the corresponding racemic mixture (obtained by addition of 2,6-dimethoxyphenyllithium to benzaldehyde followed by conversion of the benzyl alcohol into the methyl ether).

3. Conclusion

In conclusion, arylboronic acids having electron-donor functions react with 2-*p*-tolylsulfinyl benzaldehyde in the presence of base and a catalytic amount of $Pd_2(dba)_3 \cdot CHCl_3$, to afford the corresponding secondary alcohols in good yields and high diastereoselectivity when donor-substituents are present at the *ortho*-position. The chiral sulfoxide auxiliary can be easily removed by means of sulfoxide–lithium exchange affording the enantiopure secondary alcohols in high yields.

4. Experimental

4.1. General

Starting materials, if commercial, were purchased and used as such, provided that adequate checks (melting ranges, refractive indices, and gas chromatography) had confirmed the claimed purity. When known compounds had to be prepared according to literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in Schlenk tubes or Schlenk buret. They were protected by and handled under an atmosphere of argon, using appropriate glassware. Diethyl ether and tetrahydrofuran were dried by distillation from sodium after the characteristic blue color of sodium diphenyl ketyl (benzophenone–sodium 'radical–anion') had been found to persist. Ether or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. If no reduced pressure is specified, boiling ranges (bp) refer to ordinary atmospheric conditions (725 ± 25 Torr). Melting ranges (mp) given were found to be reproducible after resolidification, unless stated otherwise ('decomp.'), and were corrected using a calibration curve established with authentic standards. The temperature of dry ice/acetone baths is

consistently indicated as −75 °C and 'room temperature' (22–26 °C) as 25 °C. Silica gel (Merck Silica Gel Si60, 40–63 μm) particle size was used for column chromatography. The solid support was suspended in cyclohexane and, when all air bubbles had escaped, was washed into the column. When the level of the liquid was still 3–5 cm above the support layer, the dry powder, obtained by adsorption of the crude mixture to some 25 mL of silica and subsequent evaporation of the solvent, was poured on top of the column. ^{1}H and (^{1}H decoupled) ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported in δ units, parts per million (ppm) and were measured relative to the signals for residual chloroform (7.27 ppm). Coupling constants J are given in Hz. Coupling patterns are abbreviated as, for example, s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), td (triplet of doublets), and m (multiplet).

4.2. Starting materials

4.2.1. (*S*)-2-(*p*-Tolylsulfinyl)benzaldehyde 1

4.2.1.1. 2-(*S*)-(*p*-Tolylsulfinyl)benzaldehyde diethyl acetal. At −78 °C, butyllithium (25 mmol) in hexanes (15.6 mL) was added dropwise to a solution of 2-bromobenzaldehyde acetal (5.00 mL, 6.48 g, 25 mmol) in tetrahydrofuran (125 mL). After 40 min *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (3.73 mL, 25 mmol) and (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate (6.47 g, 22 mmol) was added. After 3 h, saturated aqueous NH_4Cl (100 mL) was added, followed by extraction with diethylether (3 × 100 mL). The combined organic layers were dried, filtered, and evaporated. The yellow oil was purified by chromatography on silica gel (DEE/cHex 1:1) to afford 2-(*S*)-(*p*-tolylsulfinyl)benzaldehyde diethyl acetal; 6.68 g (84%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.95$ (dd, $J = 6.9$, 2.1 Hz, 1H), 7.64 (dd, $J = 7.0$, 2.1 Hz, 1H), 7.55 (d, $J = 8.3$ Hz, 2H), 7.50–7.43 (m, 2H), 7.22 (d, $J = 7.9$ Hz, 2H), 5.74 (s, 1H), 3.71–3.45 (m, 4H), 2.35 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.10 (t, $J = 7.2$ Hz, 3H).

4.2.1.2. (*S*)-2-(*p*-Tolylsulfinyl)benzaldehyde 1. A mixture of pyridinium *p*-toluensulfonate (3.00 g, 11.94 mmol) and 2-(*S*)-(*p*-tolylsulfinyl)benzaldehyde diethyl acetal from Section 4.2.1.1 (5.00 g, 15.72 mmol) was dissolved in a mixture of water (30 mL) and acetone (450 mL). The solution was heated under reflux. After 4 h, the solution was evaporated and more water (100 mL) was added, followed by extraction with EtOAc (3 × 200 mL). The combined organic layers were dried and evaporated. The yellow solid was purified by crystallization from hexanes, which afforded **1**; 3.15 g (82%) as yellow solid. Mp 87–91 °C, $[\alpha]_D = -278$ (*c* 1, acetone). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 10.00$ (s, 1H), 8.52 (d, $J = 8.3$ Hz, 1H), 7.92–7.86 (m, 2H), 7.68 (ddd, $J = 7.5$, 7.4, 1.1 Hz, 1H), 7.59 (d, $J = 8.3$ Hz, 2H), 7.17 (d, $J = 7.9$ Hz, 2H), 2.31 (s, 3H).

4.2.2. (*S*)-2-Methoxy-6-(*p*-tolylsulfinyl)benzaldehyde 3

4.2.2.1. (*S*)-1-Methoxy-3-(*p*-tolylsulfinyl)benzene. At −75 °C, butyllithium (25 mmol) in hexanes (15.6 mL) was added to a solution of 3-bromoanisole (3.17 mL, 4.68 g, 25 mmol) in diethyl ether (50 mL). After 30 min, the mixture was canulated into a 0 °C cold solution of (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate (7.35 g, 25 mmol) in diethyl ether (50 mL). After stirring for 3 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried, and evaporated. The residue was purified by column chromatography on silica gel (EtOAC/cHex = 1:4) to afford (*S*)-1-methoxy-3-(*p*-tolylsulfinyl)benzene, which crystallizes from EtOAC/hexanes as colorless cubes; 5.35 g (87%). $[\alpha]_D = +49.8$ (*c* 1, acetone). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.55$ (d, $J = 8.21$ Hz, 2H), 7.35 (t, $J = 7.94$, 7.94 Hz, 1H), 7.30–7.23 (m, 3H), 7.15 (ddd, $J = 7.65$, 1.49, 0.98 Hz, 1H), 6.96 (ddd, $J = 8.22$, 2.57, 0.92 Hz, 1H), 3.83 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 160.3$, 147.1, 142.4, 141.6, 130.1, 130.0, 125.0, 117.2, 116.8, 109.0, 55.5, 21.4. Anal. Calcd for $C_{14}H_{14}O_2S$ (246.32): C, 68.26; H, 5.73. Found: C, 68.13; H, 5.76.

4.2.2.2. (*S*)-2-Methoxy-6-(*p*-tolylsulfinyl)benzaldehyde 3. Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and (*S*)-1-methoxy-3-(*p*-tolylsulfinyl)benzene (5.67 g, 23 mmol) from Section 4.2.2.1 were consecutively added to a solution of butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (15.6 mL) at −75 °C. After 2 h at −75 °C, *N*-formylmorpholine (3.02 mL, 3.45 g, 30 mmol) was added. The reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried, and evaporated. The residue was purified by column chromatography on silica gel (EtOAC/cHex = 1:4) to afford **3**, which crystallizes from EtOAC/hexanes as colorless cubes; 4.04 g (64%); $[\alpha]_D = -368$ (*c* 1, acetone). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 10.31$ (s, 1H), 8.05 (d, $J = 7.88$ Hz, 1H), 7.75 (t, $J = 8.14$, 8.14 Hz, 1H), 7.54 (d, $J = 8.25$ Hz, 2H), 7.07 (t, $J = 8.79$, 3H), 3.87 (s, 3H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 188.8$, 162.9, 150.3, 143.3, 141.2, 136.0, 129.5, 126.8, 121.1, 116.3, 113.5, 56.3, 21.4. Anal. Calcd for $C_{15}H_{14}O_3S$ (274.33): C, 65.67; H, 5.14. Found: C, 65.81; H, 5.23.

4.2.3. (*S*)-1-(2-(*p*-Tolylsulfinyl)phenyl)ethanone 4

4.2.3.1. 2-(2-Bromophenyl)-2-methyl-1,3-dioxolane. A mixture of 1-(2-bromophenyl)ethanone (16.97 mL, 25.05 g, 125.80 mmol), *p*-TSOH (1.20 g, 6.29 mmol) and ethane-1,2-diol (10.52 mL, 11.72 g, 188.76 mmol) was dissolved in benzene (300 mL). The solution was heated at reflux for 2 h. Water (200 mL) was added followed by extraction with EtOAc (3 × 200 mL). The combined organic layers were dried and evaporated to afford 2-(2-bromophenyl)-2-methyl-1,3-dioxolane; 28.48 g (93%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.53$ (d, $J = 7.9$ Hz, 1H), 7.44 (d, $J = 7.7$ Hz, 1H), 7.14 (t, $J = 6.4$ Hz, 1H), 6.99 (t, $J = 7.2$ Hz, 1H), 3.90 (s, 2H), 3.60 (s, 2H), 1.67 (s, 3H).

4.2.3.2. (*S*)-2-Methyl-2-(2-(*p*-tolylsulfinyl)phenyl)-1,3-dioxolane. At −78 °C, butyllithium (25 mmol) in hexanes (15.6 mL) was added dropwise to a solution of 2-(2-bromophenyl)-2-methyl-1,3-dioxolane from Section 4.2.3.1 (6.08 g, 25 mmol) in tetrahydrofuran (125 mL). After

40 min *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (3.73 mL, 25 mmol) and (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate (6.47 g, 22 mmol) was added. After 3 h, saturated aqueous solution of ammonium chloride (100 mL) was added, followed by extraction with diethylether (3 × 100 mL). The combined organic layers were dried and evaporated. The oily residue was purified by chromatography on silica gel (DEE/cHex 1:1) to afford (*S*)-2-methyl-2-(2-(*p*-tolylsulfinyl)phenyl)-1,3-dioxolane; 4.47 g (59%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 9.33$ (dd, $J = 7.9$, 1.1 Hz, 1H), 7.58–7.41 (m, 5H), 7.18 (d, $J = 7.9$ Hz, 2H), 4.02–3.93 (m, 1H), 3.73 (symm. m, 2H), 3.16–3.02 (m, 1H), 2.32 (s, 3H), 1.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 143.5$, 142.4, 141.1, 130.6, 129.5, 129.2, 127.0, 126.6, 125.1, 108.9, 64.2, 63.9, 27.3, 21.3. Anal. Calcd for $C_{17}H_{18}O_3S$ (302.39): C, 67.52; H, 6.00. Found: C, 67.70; H, 6.08.

4.2.3.3. (*S*)-1-(2-(*p*-Tolylsulfinyl)phenyl)ethanone 4. (*S*)-2-Methyl-2-(2-(*p*-tolylsulfinyl)phenyl)-1,3-dioxolane (6.94 g, 23 mmol) from Section 4.2.3.2 and PTSA (2.62 g, 13.77 mmol) was dissolved in a mixture of acetone (0.5 L) and water (33 mL). After 3 h, more PTSA was added and the solution was heated at reflux for 4 h. Water (200 mL) was added followed by extraction with EtOAc (3 × 200 mL). The combined organic layers were dried and evaporated. The solid was washed with ethyl acetate to afford **4** as a colorless solid; 3.47 g (57%); mp 136–140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.59$ (dd, $J = 7.9$, 0.9 Hz, 1H), 7.91 (dd, $J = 7.7$, 1.1 Hz, 1H), 7.86 (td, $J = 7.5$, 1.3 Hz, 1H), 7.62 (d, $J = 7.9$ Hz, 2H), 7.59 (s, 1H), 7.18 (d, $J = 7.9$ Hz, 2H), 2.56 (s, 3H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 197.5$, 148.6, 143.7, 140.9, 133.9, 133.8, 130.6, 130.2, 129.5, 126.7, 125.2, 21.3. Anal. Calcd for $C_{15}H_{14}O_2S$ (258.07): C, 69.74; H, 5.46. Found: C, 69.76; H, 5.65.

4.3. General procedure for the coupling

A mixture of 2-*p*-(tolylsulfinyl)benzaldehyde **1** (0.244 g, 1.00 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.052 g, 5 mol %), triphenylphosphine (0.026 g, 10 mol %), boronic acid (2.00 mmol, 2 equiv) and cesium carbonate (0.326 g, 1.00 mmol) was dissolved in toluene (2 mL) and stirred under argon. 15 min later, the mixture was heated at 120 °C. After 2 h, water (5 mL) was added, followed by extraction with ethyl acetate (3 × 10 mL). The combined organic layers were dried and evaporated. The compound was purified by chromatography on silica gel (EtOAc/cHex = 3:2) and crystallized from hexanes.

4.3.1. (*R*)-Phenyl(2-((*S*)-*p*-tolylsulfinyl)phenyl)methanol 2a. 0.22 g, (67%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 7.76 (dd, $J = 7.50$, 1.68 Hz, 1H), 7.60–7.04 (m, 13H), 6.43 (s, 1H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 142.5$, 142.2, 141.3, 131.4, 129.7, 128.9, 128.5, 127.9, 127.7, 127.3, 125.5, 71.7, 21.3. Anal. Calcd for $C_{20}H_{18}O_2S$ (322.10): C, 74.50; H, 5.63. Found: C, 74.71; H, 5.46.

4.3.2. (*R*)-(2-Methoxyphenyl)(2-((*S*)-*p*-tolylsulfinyl)phenyl)-methanol 2b. 0.18 g, (51%); mp 173–176 °C; $[\alpha]_D^{20} = -127.6$ (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.93$–7.80 (m, 1H), 7.51–7.39 (m, 3H), 7.28–7.19 (m, 3H), 7.04 (d, $J = 7.9$ Hz, 2H), 6.86 (d, $J = 8.1$ Hz, 1H), 6.78–6.72 (m, 2H), 6.52 (d, $J = 4.2$ Hz, 1H), 3.81 (s, 3H), 3.30 (d, $J = 4.2$ Hz, 1H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 156.7$, 143.7, 141.5, 141.1, 140.8, 130.9, 130.1, 129.5, 129.0, 128.9, 128.5, 127.8, 125.8, 125.2, 120.6, 110.5, 68.2, 55.4, 21.3. Anal. Calcd for $C_{21}H_{20}O_3S$ (352.45): C, 71.56; H, 5.72. Found: C, 71.13; H, 5.64.

4.3.3. (*R*)-(4-Methoxyphenyl)(2-((*S*)-*p*-tolylsulfinyl)phenyl)-methanol 2d. 0.22 g (62%); mp 127–131 °C, $[\alpha]_D^{20} = -108$ (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.79$ (dd, $J = 7.4$, 1.7 Hz, 1H), 7.60 (dd, $J = 7.4$, 1.5 Hz, 1H), 7.51–7.40 (m, 2H), 7.14–7.06 (m, 6H), 6.76 (d, $J =$ 8.7 Hz, 2H), 6.38 (s, 1H), 3.77 (s, 3H), 2.68 (br s, 1H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 159.3$, 143.0, 142.6, 141.2, 134.5, 131.5, 129.7, 128.9, 128.7, 127.6, 126.0, 125.6, 113.9, 71.7, 55.3, 21.3. Anal. Calcd for $C_{21}H_{20}O_3S$ (382.12): C, 71.56; H, 5.72. Found: C, 71.34; H, 5.66.

4.3.4. (*R*)-(2,6-Dimethoxyphenyl)(2-((*S*)-*p*-tolylsulfinyl)phenyl)methanol 2e. 0.23 g (61%); mp 163–166 °C, $[\alpha]_D^{20} =$ −128 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.15$ (dd, $J = 7.9$, 1.3 Hz, 1H), 7.53 (d, $J = 8.1$ Hz, 2H), 7.42 (ddd, $J = 8.1$, 0.8 Hz, 1H), 7.28–7.19 (m, 4H), 6.91 (d, $J = 7.7$ Hz, 1H), 6.57 (d, $J = 8.3$ Hz, 2H), 6.23 (d, $J = 11.5$ Hz, 1H), 4.34 (d, $J = 11.5$ Hz, 1H), 3.70 (s, 6H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 157.8$, 144.5, 142.6, 141.6, 140.8, 130.0, 129.6, 128.0, 126.6, 126.3, 124.9, 117.6, 104.5, 67.2, 55.8, 21.3. Anal. Calcd for $C_{22}H_{22}O_4S$ (382.47): C, 69.09; H, 5.80. Found: C, 69.29; H, 5.81.

4.3.5. (*R*)-*o*-Tolyl(2-((*S*)-*p*-tolylsulfinyl)phenyl)methanol 2f. 0.20 g (59%); mp 165–170 °C, $[\alpha]_D^{20} = -216$ (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.72$–7.69 (m, 1H), 7.46–7.39 (m, 3H), 7.32–7.06 (m, 7H), 6.58 (d, $J = 4.3$ Hz, 1H), 2.75 (d, $J = 4.5$ Hz, 1H), 2.32 (s, 3H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 143.3$, 142.0, 141.6, 140.3, 139.7, 135.9, 131.3, 130.7, 129.8, 128.8, 128.0, 127.7 (d, $J = 2.2$), 126.2, 125.9, 125.7, 69.1, 21.3, 19.0. Anal. Calcd for $C_{21}H_{20}O_2S$ (336.45): C, 74.97; H, 5.99. Found: C, 74.62; H, 5.99.

4.3.6. (*R*)-(2-Methoxy-5-methylphenyl)(2-((*S*)-*p*-tolylsulfinyl)phenyl)methanol 2g. 0.18 g (50%); mp 154–158 °C, $[\alpha]_D^{20} = -59.6$ (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.97$ (d, $J = 6.4$ Hz, 1H), 7.53–7.43 (m, 3H), 7.24 (d, $J = 8.3$ Hz, 2H), 7.01 (d, $J = 7.9$ Hz, 2H), 6.98 (d, $J = 1.9$ Hz, 1H), 6.74 (d, $J = 8.3$ Hz, 1H), 6.46 (d, $J = 4.1$ Hz, 1H), 6.38 (d, $J = 1.7$ Hz, 1H), 3.80 (s, 3H), 3.37 (br s, 1H), 2.27 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 154.7$, 143.5, 141.1, 140.6, 130.9, 129.7, 129.4, 129.2, 129.1, 128.8, 127.8, 125.9, 124.9, 110.4, 68.2, 55.5, 30.9, 21.2, 20.3. Anal. Calcd for $C_{22}H_{22}O_3S$ (366.13): C, 72.10; H, 6.05. Found: C, 71.52; H, 6.42.

4.3.7. (*R*)-(2-Methoxynaphthalen-1-yl)(2-((*S*)-*p*-tolylsulfinyl)phenyl)methanol 2p. 0.22 g (55%); mp 178–182 °C, $[\alpha]_D^{20} = +5.2$ (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz):

$\delta = 8.26$ (dd, $J = 7.9$, 1.3 Hz, 1H), 7.86 (d, $J = 9.1$ Hz, 1H), 7.78 (d, $J = 7.9$ Hz, 1H), 7.43 (d, $J = 7.4$ Hz, 2H), 7.39 (d, $J = 8.5$ Hz, 1H), 7.34–7.20 (m, 7H), 6.82 (d, $J = 7.7$ Hz, 1H), 6.40 (s, 1H), 4.41 (br s, 1H), 3.87 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 155.2$, 144.1, 141.7, 141.6, 141.1, 131.9, 130.6, 130.2, 129.8, 129.3, 128.6, 128.2, 127.3, 127.1, 127.0, 125.2, 123.8, 122.7, 121.8, 113.4. Anal. Calcd for $C_{25}H_{22}O_3S$ (402.13): C, 74.60; H, 5.51. Found: C, 74.95; H, 5.71.

4.4. Sulfoxide–lithium exchange

4.4.1. Preparation of 1,3-dimethoxy-2-((*R*)-methoxy(2-((*S*)-*p*-tolylsulfinyl)phenyl)methyl)benzene 5. Sodium hydride (0.11 g, 2.87 mmol) was added to the carbinol **2e** (0.91 g, 2.39 mmol) in tetrahydrofuran (6.41 mL) at 0 °C. After 10 min, methyl iodide (0.3 mL, 0.68 g, 4.78 mmol) was added and the reaction mixture then allowed to reach 25 °C. After 1 h, the same amount of sodium hydride and methyl iodide was added and the reaction stirred for another 1 h. Water (5 mL) was carefully added, followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried and evaporated. The residue was purified by chromatography on silica gel (EtOAc/cHex = 1:1) and crystallization from hexanes afforded **5** as colorless needles; 0.61 g (64%); mp 148–151 °C, $[\alpha]_D = -316$ (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.76$ (dd, $J = 7.54$, 1.32 Hz, 1H), 7.68 (d, $J = 7.54$ Hz, 1H), 7.42–7.30 (m, 2H), 7.20 (t, $J = 7.98$ Hz, 1H), 7.03 (d, $J = 8.1$ Hz, 2H), 6.86 (d, $J = 8.28$ Hz, 2H), 6.45 (d, $J = 8.28$ Hz, 2H), 6.38 (s, 1H), 3.62 (s, 6H), 3.37 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 159.0$, 142.6, 142.4, 141.4, 140.2, 130.2, 129.8, 129.3, 127.7, 125.4, 125.0, 117.1, 104.6, 73.5, 57.0, 55.7, 21.1. Anal. Calcd for $C_{23}H_{24}O_4S$ (396.14): C, 69.67; H, 6.10. Found: C, 69.83; H, 6.22.

4.4.2. (*S*)-1,3-Dimethoxy-2-(methoxy(phenyl)methyl)benzene 6a. Butyllithium (1.40 mmol) in hexanes (0.875 mL) was added at −75 °C to a solution of **5** (119 mg, 0.30 mol) in tetrahydrofuran (4.00 mL). After 10 min, excess methanol (2 mL) was added. At 25 °C, water (10 mL) was added followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried and evaporated. Pure carbinol **6a** was obtained after chromatography on silica gel (EtOAc/cHex = 1:4). Colorless oil. 66.3 mg (86%); $[\alpha]_D = -107.5$ (*c* 1, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.45$–7.36 (m, 2H), 7.32–7.13 (m, 4H), 6.59 (d, $J = 8.35$ Hz, 2H), 6.09 (s, 1H), 3.74 (s, 6H), 3.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 159.1$, 142.8, 129.3, 127.6, 127.5, 126.0, 117.9, 104.8, 75.8, 57.2, 56.0. Anal. Calcd for $C_{16}H_{18}O_3$ (258.31): C, 74.39; H, 7.02. Found: C, 74.51; H, 7.11.

4.4.3. (*S*)-1,3-Dimethoxy-2-(methoxy(phenyl)methyl)benzene 6b. Butyllithium (1.40 mmol) in hexanes (0.875 mL) was added at −75 °C to a solution of **5** (119 mg, 0.30 mol) in tetrahydrofuran (4.00 mL). After 10 min, iodomethane (0.09 mL, 0.212 g, 1.50 mmol) was added. At 25 °C, water (10 mL) was added followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried and evaporated. The pure carbinol **6b** was obtained after chromatography on silica gel (EtOAc/cHex = 1:4) followed by crystallization from EtOAc/hexanes. Colorless needles. 46.5 mg (57%); mp 89–91 °C; $[\alpha]_D = -116.7$ (*c* 0.8, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.75$ (d, $J = 7.6$ Hz, 1H), 7.43–7.39 (m, 2H), 7.26–7.21 (m, 2H), 6.56 (d, $J = 7.1$ Hz, 2H), 6.03 (s, 1H), 3.71 (s, 6H), 3.44 (s, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 159.2$, 142.8, 139.9, 135.1, 129.7, 129.4, 127.5, 126.1, 125.9, 124.6, 116.5, 104.8, 74.2, 57.1, 55.9, 19.0. Anal. Calcd for $C_{17}H_{20}O_3$ (272.34): C, 74.97; H, 7.40. Found: C, 75.11; H, 7.51.

Acknowledgments

We are grateful to the CNRS and Ministère de la Recherche. A.N. and M.D. are grateful for a SOCRATES/ERASMUS fellowship.

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19. We thank Dr André DeCian for his assistance with the analysis of the crystal structure (Service commun Rayons X, 4 rue Blaise Pascal 67070 Strasbourg cedex e-mail: sercomrx@chimie.u-strasbg.fr).
20. Crystallographic data (excluding structure factors) for structure **2b** in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 650915. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 lEZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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