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Palladium-catalyzed allylic nucleophilic substitution reactions of (*E*)-γ-acetoxy-α,β-unsaturated *p*-tolylsulfoxides

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Abstract—Regio- and diastereoselective nucleophilic allylic substitutions of optically pure (*E*)-γ-acetoxy-α,β-unsaturated *p*-tolylsulfoxides **2** and **3** with sodium dimethyl malonate have been carried out. The reactivity of these substrates is controlled by both the chiral sulfinyl group and the size of the alkyl group attached at the γ-terminus of the allylic system. This process constitutes an example of palladium-mediated resolution of a 1:1 mixture of acetates **2** and **3**. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

During the last 20 years, the palladium-catalyzed nucleophilic substitution reaction of allylic oxygenated compounds (esters, carbonates and epoxides) has emerged as a powerful methodology for the formation of carbon–carbon and carbon–heteroatom bonds.[1] Both the regio- and stereoselectivity of the process, as well as the nature of the nucleophile have been widely studied. Stereoselective variants of the reaction have focused primarily on enantioselective processes, which employ chiral ligands and achiral substrates.[2] When chiral substrates and soft nucleophiles are used the configuration of the allylic carbon atom bearing the oxygenated leaving group always controls the configuration of the product through a double inversion mechanism (retention of the configuration). In contrast, little attention has been paid to diastereoselectivity in the nucleophilic addition to π-allyl palladium complexes with an adjacent stereocenter.[3] Usually, allylic alcohols substituted at the double bond with alkyl, aryl or electron-donating substitutents have been used in this reaction, while those allylic systems bearing an electron-withdrawing ester,[4] carbonyl,[5] cyano,[6] or sulfonyl[7] groups at the double bond have been studied much less. This is due to the lower reactivity of these compounds toward the palladium catalysts, their high tendency to undergo conjugate addition of the nucleophile, and the easier deprotonation of the π-allylpalladium intermediate to give 1,3-dienes by β-elimination. In all of these substrates, it is well known that substitution takes place at the most electron deficient position of the allylic system (the γ-carbon atom with respect to the electron-withdrawing group).[4–7]

We are interested in developing methods for the asymmetric synthesis of optically active sulfoxides with a second stereogenic center in a 1,4-relationship tethered by a carbon–carbon double bond, since they are attractive building blocks for preparing optically active natural products and bioactive molecules.[8,9] We report herein our results on the regio- and diastereoselective palladium-catalyzed allylic nucleophilic substitution reactions with soft carbon nucleophiles to give new γ-carbon-substituted vinyl sulfoxides, which could be used in further stereoselective transformations. To the best of our knowledge this process constitutes the first example of palladium-mediated allylic substitutions on enantiomerically pure γ-oxygenated-α,β-unsaturated sulfoxides.

2. Results and discussion

2.1. Preparation of allylic acetates 2 and 3

The starting materials for palladium-catalyzed allylic substitution (chiral non-racemic allylic acetates **2** and **3**) were readily prepared using the SPAC (sulfoxide pipe-

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ridine aldehyde condensation) protocol developed previously by us,[8] followed by enzymatic resolution[9] and acetylation (Scheme 1). First, (*E*)-γ-hydroxy-α,β-unsaturated *p*-tolylsulfoxides **1** were prepared as inseparable 1:1 mixtures of diastereomers (epimers at the hydroxylic carbon atom) through Knoevenagel condensation of methylene active (*S*,*S*)-bis-*p*-tolylsulfinylmethane with enolizable aldehydes, followed by in situ olefin migration and sulfoxide–sulfonate [2,3]sigmatropic rearrangement.

Efficient kinetic resolution of (*E*)-γ-hydroxy-α,β-unsaturated *p*-tolylsulfoxides **1** via irreversible enzymatic acylation with lipase PS (*Pseudonomas cepacia*) and vinyl acetate, yielded the acetate (R_S,R_C)-**2** and unreacted alcohol (R_S,S_C)-**1** with very high diastereoselectivity.[9] (*E*)-γ-Acetyl-α,β-unsaturated sulfoxides (R_S,S_C)-**3** were conveniently prepared (in 87–93% yield) by standard acylation of alcohols (R_S,S_C)-**1** with acetic anhydride, DMAP and *N*,*N*-di-*iso*-propylethylamine in dichloromethane.

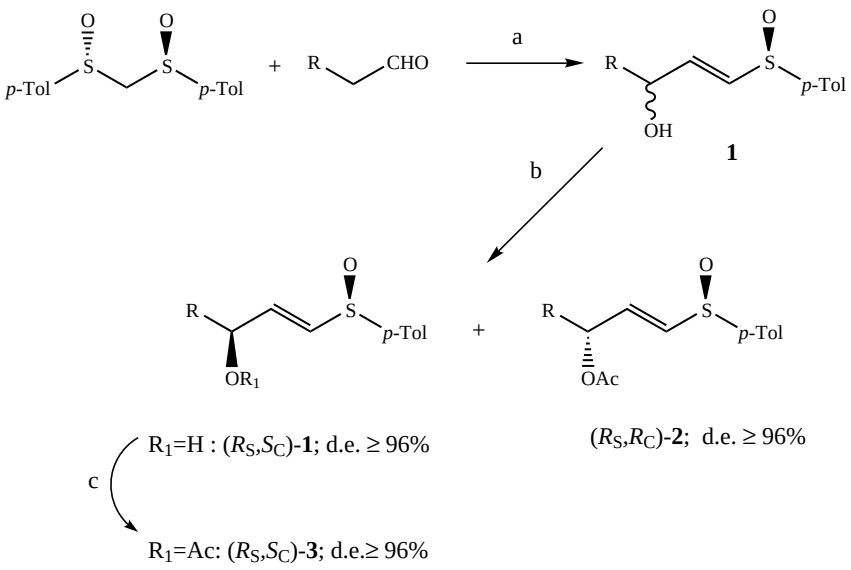
2.2. Palladium-catalyzed allylic substitution

With (*E*)-γ-acetoxy-α,β-unsaturated sulfoxides (R_S,R_C)-**2** and (R_S,S_C)-**3** in hand, the standard palladium-catalyzed allylic alkylation with dimethyl malonate was investigated. Two common catalysts, $Pd(Ph_3P)_4$ and $[Pd_2(dba)_3]CHCl_3/PPh_3$ were used in order to carry out the nucleophilic displacement using the pre-formed soft nucleophile sodium dimethyl malonate (NaH/CH_2CO_2Me/THF). Results are collected in Table 1.

For allylic acetates (R_S,R_C)-**2**, both catalysts were similarly effective affording exclusively the γ-substituted product **4** regardless of the steric size of the R alkyl group. The regioselectivity found in the reaction is in complete agreement with the precedents[4–7] and can be explained taking into account that the terminus of the allylic unit not bearing the electron withdrawing sulfinyl group is the most electron deficient position of the system. Results for sulfoxide **2a** (R = Me; entry 1), as compared with those obtained for the rest of the series, show that both chemical yield of the process and reactivity of the acetate decrease with the steric bulk of the R alkyl group. Despite the large steric requirement of the *iso*-Pr group, γ-acetoxy sulfoxide **2e** (entry 5) was reactive enough to give the substitution product in good chemical yield, although the reaction rate was about three times slower than that of γ-acetoxy sulfoxide **2a** (entry 1). In all instances the d.e.s of the final substitution products were similar to those of the starting acetates, as determined by ^{1}H NMR at 500 MHz and HPLC.

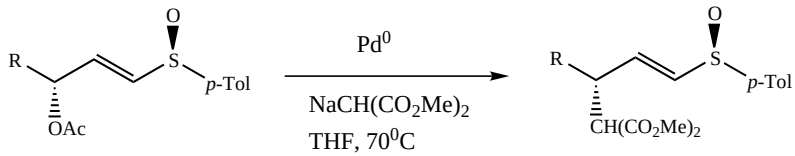
Next, we tried to extend the reaction conditions used for the palladium(0)-catalyzed allylic substitutions on acetates (R_S,R_C)-**2** to (*E*)-γ-acetoxy-α,β-unsaturated sulfoxides (R_S,S_C)-**3** (Table 2). Surprisingly, after 24 h, only the γ-acetoxy sulfoxide **3a** reacted using $Pd(Ph_3P)_4$ as catalyst.

Results collected in Tables 1 and 2 show that palladium(0)-catalyzed allylic substitution reactions on acetates (R_S,R_C)-**2b** and (R_S,S_C)-**3b** are controlled by the chiral sulfinyl group and the size of the R (alkyl) group attached to the allylic system. Both the yield and rate of the process were similar for diastereomers **2a** and **3a** (R = Me), however, the starting allylic acetates **3b**–**3e** were recovered unaffected using the same reaction conditions under which their diastereomers **2b**–**2e** gave the substitution products **4**.



Scheme 1. (a) Piperidine, CH_3CN; (b) Lipase PS, *iso*-Pr_2O, vinyl acetate, molecular sieve; (c) Ac_2O, *iso*-Pr_2NEt, DMPA, CH_2Cl_2.

Table 1. Palladium-catalyzed reactions of acetates (R_S,R_C)-**2** with sodium dimethyl malonate

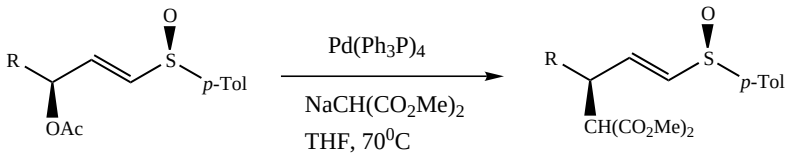


(R_S,R_C)-**2**; d.e. ≥ 96% (R_S,S_C)-**4**; d.e. ≥ 96%

Entry	R	Pd^0	Time (h)	Yield (%)
1	Me, **2a**	$[Pd_2(dba)_3]CHCl_3/PPh_3$	4	93 (92)[a]
2	Et, **2b**	$[Pd_2(dba)_3]CHCl_3/PPh_3$	8	89 (87)[a]
3	*n*-Pr, **2c**	$[Pd_2(dba)_3]CHCl_3/PPh_3$	10	86 (83)[a]
4	*n*-Pen, **2d**	$[Pd_2(dba)_3]CHCl_3/PPh_3$	12	78 (76)[a]
5	*iso*-Pr, **2e**	$[Pd_2(dba)_3]CHCl_3/PPh_3$	12	71 (64)[a]

[a] Using $Pd(PPh_3)_4$ as catalyst.

Table 2. Palladium-catalyzed reactions of acetates (R_S,S_C)-**3** with sodium dimethyl malonate



(R_S,S_C)-**3**; d.e. ≥ 96% (R_S,R_C)-**5**; d.e. ≥ 96%

Entry	R	Time (h)	Yield (%)
1	Me, **3a**	4	87
2	Et, **3b**	24	–
3	*n*-Pr, **3c**	24	–
4	*n*-Pen, **3d**	24	–
5	*iso*-Pr, **3e**	24	–

Taking into account that, as stated above, allylic alcohols **1** were obtained as an inseparable 1:1 mixture of epimers at the carbinol center,[8] enzyme mediated resolution[9] was carried out to effect their separation (see Scheme 1), it occurred to us that the higher reactivity of **2b**–**2d** towards $Pd(0)/NaCH(CO_2Me)_2$ with respect to that of their epimers **3b**–**3d**, could be used for the resolution of the mixture, directly available by acetylation from (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1**.

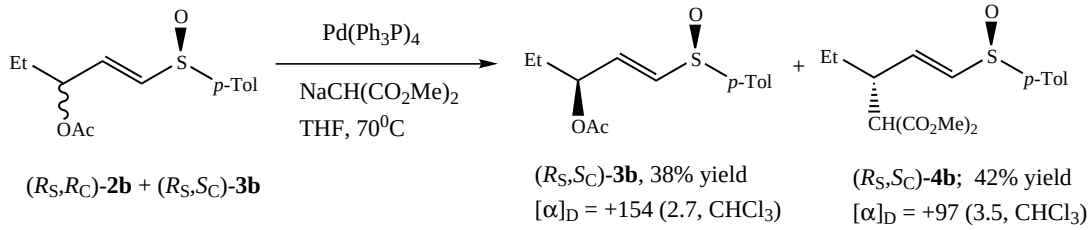
In order to evaluate the palladium-mediated resolution of (*E*)-γ-acetoxy-α,β-unsaturated sulfoxides we studied the most reactive substrates (apart from **2a** and **3a**, R = Me) derivatives **2b** and **3b** (R = Et). A (1:1) diastereomeric mixture of acetates (R_S,R_C)-**2b** and (R_S,S_C)-**3b** was prepared from alcohols **1b** by standard acylation, and treated with 10 mol% of $Pd(PPh_3)_4$ and sodium dimethyl malonate in THF at 70°C for 8 h. Column chromatography of the reaction mixture yielded (R_S,R_C)-**4b** and unreacted acetate (R_S,S_C)-**3b** with very high diastereoselectivity, as confirmed by ^1H NMR at 500 MHz and comparison with the optical rotation of previously prepared samples of **3b** and **4b** (Scheme 2).

3. Conclusion

In conclusion, the presence of an (R_S)-configured chiral sulfinyl group attached to the double bond of an allylic system allows the discrimination between (S_C)- or (R_C)-allylic acetates in the palladium-catalyzed nucleophilic reaction, provided that an alkyl group bulkier than Me is present at the γ-terminus of the allylic system. In this way, allylic acetates with (R_C)-configuration at carbon are reactive enough towards soft nucleophiles, although the reaction rates and chemical yields decrease slightly with the steric bulk of the alkyl substituent. In contrast, the allylic esters with (S_C)-configuration at carbon remained unaffected under these experimental conditions. The palladium-catalyzed substitution reaction on (*E*)-γ-acetoxy-α,β-unsaturated sulfoxides constitutes an example of palladium-mediated resolution of this type of substrate.

4. Experimental

Melting points were determined in open capillary tubes on a Gallenkamp apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AC-200 (200 MHz) or AMX-500 (500 MHz) and ^{13}C NMR on



(R_S,R_C)-**2b** + (R_S,S_C)-**3b**

(R_S,S_C)-**3b**, 38% yield
$[\alpha]_D$ = +154 (2.7, $CHCl_3$)

(R_S,S_C)-**4b**; 42% yield
$[\alpha]_D$ = +97 (3.5, $CHCl_3$)

Scheme 2.

AC-200 (50.3 MHz) or AMX-500 (125.72 MHz). All spectra were obtained using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in ppm and coupling constants in Hz. Optical rotations were measured on a Perkin–Elmer 241-MC polarimeter in a 1 dm tube; concentrations are given in g/100 mL. High resolution mass measurements were performed on a Kratos MS-80-RFA spectrometer. HPLC analysis was carried out on a Waters, Millipore 600A model using a Chiral OD (Diacel) column or reverse phase column Lichrocart C-18. Routine monitoring of reactions was performed using Merck 60 F 254 silica gel, aluminum supported TLC plates. For the flash chromatography,[10] silica gel 60 (230–400 mesh ASTM, Merck) was used.

Flasks, stirrings bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120°C and allowed to cool in a dessicator over anhydrous calcium sulphate. Anhydrous ethers were obtained by distillation from benzophenone ketyl.[11]

4.1. (*E*)-γ-Hydroxy-α,β-unsaturated sulfoxides (R_S,S_C)-1a–1e and (*E*)-γ-acetoxy-α,β-unsaturated sulfoxides (R_S,R_C)-2a–2e

The procedure described by Llera et al. was followed.[9]

4.2. General procedure for acylation of compounds (R_S,S_C)-1a–1e

To a cold (0°C) solution of (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides (R_S,S_C)-**1a**–**1e** (1 equiv.) and catalytic DMAP in CH_2Cl_2 was added *iso*-Pr_2EtN (5 equiv.) and Ac_2O (5 equiv.). The reaction mixture was allowed to warm at room temperature and hydrolyzed with water, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with a saturated NaCl solution, dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

4.2.1. (R_S,S_C)-(*E*)-3-Acetoxy-1-(*p*-tolylsulfinyl)-1-butene (R_S,S_C)-3a. The general procedure was followed for the acylation of (R_S,S_C)-**1a** (76 mg, 0.362 mmol). Purification of the reaction mixture by flash chromatography (AcOEt:hexane, 2:1) afforded (R_S,S_C)-**3a** as a viscous oil (86 mg, 89%). $[\alpha]_D$ = +172.5 (c = 1.5, $CDCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, J = 6.6 Hz, 3H, CH_3), 1.89 (s, 3H, CH_3CO), 2.25 (s, 3H, CH_3Ar), 5.35 (m, 1H, CHOAc), 6.27 (dd, J = 15.1 Hz, J = 0.9 Hz, 1H, =CH-S(O)), 6.41 (dd, J = 15.1 Hz, J = 4.7 Hz, 1H, CH=), 7.16–7.36 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (50.29 MHz, $CDCl_3$) δ 19.5, 20.7, 21.0, 68.5, 124.5, 129.8, 135.1, 136.1, 139.7, 141.5, 169.4. HRMS calcd m/z for $C_{13}H_{16}O_3S$: 252.0832. Found: 252.0851.

4.2.2. (R_S,S_C)-(*E*)-3-Acetoxy-1-(*p*-tolylsulfinyl)-1-pentene (R_S,S_C)-3b. The general procedure was followed for the acylation of (R_S,S_C)-**1b** (80 mg, 0.357 mmol). Purification of the reaction mixture by flash chromatography (AcOEt:hexane, 2:1) afforded (R_S, S_C)-**3b** as a viscous oil (92 mg, 92%). $[\alpha]_D$ = +155 (c = 2.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (t, J = 7.4 Hz, 3H, CH_3), 1.62 (m, 2H, CH_2), 1.96 (s, 3H, CH_3CO), 2.30 (s, 3H, CH_3Ar), 5.28 (m, 1H, CHOAc), 6.27 (dd, J = 15.0 Hz, J = 0.8 Hz, 1H, =CH-S(O)), 6.44 (dd, J = 15.0 Hz, J = 4.9 Hz, 1H, CH=), 7.21–7.41 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (50.29 MHz, $CDCl_3$) δ 8.9, 20.7, 21.2, 26.8, 73.2, 124.9, 130.0, 135.3, 135.4, 139.6, 141.8, 169.9. HRMS calcd m/z for $C_{14}H_{18}O_3S$: 266.0990. Found: 266.0968.

4.2.3. (R_S,S_C)-(*E*)-3-Acetoxy-1-(*p*-tolylsulfinyl)-1-hexene (R_S,S_C)-3c. The general procedure was followed for the acylation of (R_S,S_C)-**1c** (100 mg, 0.336 mmol). Purification of the reaction mixture by flash chromatography (AcOEt:hexane, 2:1) afforded (R_S,S_C)-**3c** as a viscous oil (111 mg, 89%). $[\alpha]_D$ = +163.5 (c = 2.7, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81 (t, J = 7.4 Hz, 3H, CH_3), 1.25 (m, 2H, CH_2), 1.56 (m, 2H, CH_2), 1.94 (s, 3H, CH_3CO), 2.29 (s, 3H, CH_3Ar), 5.34 (m, 1H, CHOAc), 6.26 (d, J = 15.1 Hz, 1H, =CH-S(O)), 6.44 (dd, J = 15.1 Hz, J = 5.0 Hz, 1H, CH=), 7.20–7.39 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (50.29 MHz, $CDCl_3$) δ 13.5, 17.9, 20.7, 21.1, 35.7, 71.8, 124.8, 129.9, 135.1, 135.7, 139.6, 141.7, 169.7. HRMS calcd m/z for $C_{15}H_{20}O_3S$: 280.1148. Found: 280.1131. Anal. calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 64.56; H, 7.23%.

4.2.4. (R_S,S_C)-(*E*)-3-Acetoxy-1-(*p*-tolylsulfinyl)-1-octene (R_S,S_C)-3d. The general procedure was followed for the acylation of (R_S,S_C)-**1d** (90 mg, 0.338 mmol). Purification of the reaction mixture by flash chromatography (AcOEt:hexane, 2:1) afforded (R_S,S_C)-**3d** as a viscous oil (102 mg, 93%). $[\alpha]_D$ = +120.5 (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75 (t, J = 5.9 Hz, 3H, CH_3), 1.15 (m, 6H, $(CH_2)_3$), 1.71 (m, 2H, CH_2), 1.92 (s, 3H, CH_3CO), 2.28 (s, 3H, CH_3Ar), 5.27 (m, 1H, CHOAc), 6.23 (dd, J = 15.1 Hz, J = 1.1 Hz, 1H, =CH-S(O)), 6.42 (dd, J = 15.1 Hz, J = 5.1 Hz, 1H, CH=), 7.18–7.38 (AA′BB′ system, 4H, aromatics). ^{13}C NMR

(50.29 MHz, $CDCl_3$) δ 13.9, 21.0, 21.4, 22.4, 24.5, 31.4, 33.9, 72.3, 125.0, 130.1, 135.6, 135.7, 140.1, 141.9, 170.0. HRMS calcd m/z for $C_{17}H_{24}O_3S$: 308.1464. Found: 308.1470.

4.2.5. (R_S,S_C)-(*E*)-3-Acetoxy-4-methyl-1-(*p*-tolylsulfinyl)-1-pentene (R_S,S_C)-3e. The general procedure was followed for the acylation of (R_S,S_C)-**1e** (50 mg, 0.210 mmol). Purification of the reaction mixture by flash chromatography (AcOEt:hexane, 2:1) afforded (R_S,S_C)-**3e** as a viscous oil (54 mg, 87%). $[\alpha]_D = +173$ ($c = 2.4$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (d, $J = 6.8$ Hz, 6H, $(CH_3)_2$), 1.77 (m, 1H, CH), 1.97 (s, 3H, CH_3CO), 2.32 (s, 3H, CH_3Ar), 5.19 (m, 1H, CHOAc), 6.26 (dd, $J = 15.1$ Hz, $J = 1.2$ Hz, 1H, =CH-S(O)), 6.45 (dd, $J = 15.1$ Hz, $J = 5.3$ Hz, 1H, CH=), 7.22–7.42 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 17.6, 17.8, 20.7, 21.2, 31.9, 76.5, 124.9, 130.0, 133.9, 136.3, 140.0, 141.8, 169.8. HRMS calcd m/z for $C_{15}H_{20}O_3S$: 280.1148. Found: 280.1143. Anal. calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 63.77; H, 6.97%.

4.3. General procedure for the palladium-catalyzed allylic substitution

To a solution of (*E*)-γ-acetoxy-α,β-unsaturated sulfoxides (R_s,R_c)-**2a**–**2e** (1 equiv.) in dry THF (5 mL) was added $[Pd_2(dba)_3]CHCl_3$ (0.01 equiv.) and Ph_3P (0.1 equiv.) (method A) or $(Ph_3P)_4Pd$ (0.01 equiv.) (method B). The resulting solution was vigorously shaken and heated at 70°C and a suspension of dimethyl malonate (1.5 equiv.) and NaH (1.6 equiv.) in anhydrous THF (2 mL) was added. The reaction mixture was stirred at this temperature until the conversion was complete (TLC). The solvent was evaporated and the crude product was purified by column chromatography.

4.3.1. Methyl (R_S,S_C)-(*E*)-2-methoxycarbonyl-3-methyl-5-(*p*-tolylsulfinyl)-4-pentenoate (R_S,S_C)-4a. The general procedure (method A) was followed for the allylic substitution of (R_S,R_C)-**2a** (50 mg, 0.198 mmol). The reaction time was 4 h. Purification of the reaction mixture by flash chromatography (Et_2O:hexane, 2:3) afforded (R_S,S_C)-**4a** as a white solid (56 mg, 93%) (92% yield, method B). Mp = 77–79°C, $[\alpha]_D = +119$ ($c = 4.7$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, $J = 6.8$ Hz, 3H, CH_3), 2.35 (s, 3H, CH_3Ar), 3.10 (m, 1H, CH), 3.35 (d, $J = 8.5$ Hz, 1H, $CH(CO_2Me)_2$), 3.59 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 6.22 (dd, $J = 15.1$ Hz, $J = 0.5$ Hz, 1H, =CH-S(O)), 6.48 (dd, $J = 15.1$ Hz, $J = 8.0$ Hz, 1H, CH=), 7.25–7.43 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 17.4, 21.3, 36.3, 52.4, 52.5, 56.6, 124.6, 130.0, 136.4, 139.7, 140.5, 141.5, 167.9, 168.0. HRMS calcd m/z for $C_{16}H_{20}O_5S$: 340.1046. Found: 324.1029. Anal. calcd for $C_{16}H_{20}O_5S$: C, 59.20; H, 6.21. Found: C, 59.26; H, 6.17%.

4.3.2. Methyl (R_S,S_C)-(*E*)-2-methoxycarbonyl-3-ethyl-5-(*p*-tolylsulfinyl)-4-pentenoate (R_S,S_C)-4b. The general procedure (method A) was followed for the allylic substitution of (R_S,R_C)-**2b** (50 mg, 0.188 mmol). The reaction time was 8 h. Purification of the reaction mixture by flash chromatography (Et_2O:hexane, 3:2) afforded (R_S,S_C)-**4b** as a white solid (52 mg, 89% yield) (87% yield, method B). Mp = 53.5–55.5°C, $[\alpha]_D = +95.7$ ($c = 2.8$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, $J = 6.8$ Hz, 3H, CH_3), 2.35 (s, 3H, CH_3Ar), 3.10 (m, 1H, CH), 3.35 (d, $J = 8.5$ Hz, 1H, $CH(CO_2Me)_2$), 3.59 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 6.22 (dd, $J = 15.1$ Hz, $J = 0.5$ Hz, 1H, =CH-S(O)), 6.48 (dd, $J = 15.1$ Hz, $J = 8.0$ Hz, 1H, CH=), 7.25–7.43 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 17.4, 21.3, 36.3, 52.4, 52.5, 56.6, 124.6, 130.0, 136.4, 139.7, 140.5, 141.5, 167.9, 168.0. HRMS calcd m/z for $C_{17}H_{22}O_5S$: 338.1204. Found: 338.1201. Anal. calcd for $C_{17}H_{22}O_5S$: C, 60.35; H, 6.51. Found: C, 60.34; H, 6.36%.

4.3.3. Methyl (R_S,S_C)-(*E*)-2-methoxycarbonyl-3-propyl-5-(*p*-tolylsulfinyl)-4-pentenoate (R_S,S_C)-4c. The general procedure (method A) was followed for the allylic substitution of (R_S,R_C)-**2c** (60 mg, 0.214 mmol). The reaction time was 10 h. Purification of the reaction mixture by flash chromatography (Et_2O:hexane, 7:3) afforded (R_S,S_C)-**4c** as a white solid (59 mg, 86%) (83% yield, method B). Mp = 51–53°C, $[\alpha]_D = +90$ ($c = 2.0$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, $J = 7.3$ Hz, 3H, CH_3), 1.22 (m, 1H, CH_2), 1.34 (m, 1H, CH_2), 1.43 (m, 2H, CH_2), 2.39 (s, 3H, CH_3Ar), 2.86 (m, 1H, CH), 3.44 (d, $J = 8.4$ Hz, 1H, $CH(CO_2Me)_2$), 3.61 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 6.28 (dd, $J = 15.1$ Hz, $J = 0.5$ Hz, 1H, =CH-S(O)), 6.43 (dd, $J = 15.1$ Hz, $J = 9.6$ Hz, 1H, CH=), 7.29–7.47 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.6, 20.1, 21.2, 34.0, 41.8, 52.2, 52.4, 55.7, 124.5, 129.9, 137.9, 138.3, 140.5, 141.4, 167.8, 168.0. HRMS calcd m/z for $C_{18}H_{24}O_5S$: 352.1362. Found: 352.1365. Anal. calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86. Found: C, 61.08; H, 6.56%.

4.3.4. Methyl (R_S,S_C)-(*E*)-2-methoxycarbonyl-3-pentyl-5-(*p*-tolylsulfinyl)-4-pentenoate (R_S,S_C)-4d. The general procedure (method A) was followed for the allylic substitution of (R_S,R_C)-**2d** (40 mg, 0.130 mmol). The reaction time was 12 h. Purification of the reaction mixture by flash chromatography (Et_2O:hexane, 7:3) afforded (R_S,S_C)-**4d** as a viscous oil (35 mg, 78%) (76% yield, method B). $[\alpha]_D = +120.4$ ($c = 3.3$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, $J = 6.8$ Hz, 3H, CH_3), 1.23 (m, 6H, $(CH_2)_3$), 1.45 (m, 2H, CH_2), 2.39 (s, 3H, CH_3Ar), 2.94 (m, 1H, CH), 3.44 (d, $J = 8.4$ Hz, 1H, $CH(CO_2Me)_2$), 3.61 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 6.27 (d, $J = 15.1$ Hz, 1H, =CH-S(O)), 6.43 (dd, $J = 15.1$ Hz, $J = 3.4$ Hz, 1H, CH=), 7.29–7.47 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CHCl_3$) δ 13.8, 21.3, 22.3, 26.6, 31.3, 32.0, 42.0, 52.3, 52.5, 55.8, 124.5, 129.7, 137.4, 138.1, 140.6, 141.5, 167.9, 168.1. HRMS calcd m/z for $C_{20}H_{28}O_5S$: 380.1678. Found: 360.1659. Anal. calcd for $C_{20}H_{28}O_5S$: C, 63.13; H, 7.42. Found: C, 63.09; H, 7.13%.

4.3.5. Methyl (R_S,S_C)-(*E*)-2-methoxycarbonyl-3-*iso*-propyl-5-(*p*-tolylsulfinyl)-4-pentenoate (R_S,S_C)-4e. The general procedure (method A) was followed for the allylic

substitution of (R_S,R_C)-**2e** (40 mg, 0.143 mmol). The reaction time was 12 h. Purification of the reaction mixture by flash chromatography (Et_2O:hexane, 7:3) afforded (R_S,S_C)-**4d** as a viscous oil (36 mg, 71% yield) (64% yield, method B). $[\alpha]_D = +173$ ($c = 5.5$, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, $J = 7.0$ Hz, 6H, $(CH_3)_2$), 1.81 (m, 1H, CH), 2.38 (s, 3H, CH_3Ar), 2.82 (m, 1H, CH), 3.61 (s, 6H, CH_3O), 3.63 (d, $J = 8.8$ Hz, 1H, $CH(CO_2Me)_2$), 6.26 (d, $J = 15.1$ Hz, 1H, =CH-S(O)), 6.51 (d, $J = 15.1$ Hz, $J = 10.2$ Hz, 1H, CH=), 7.29–7.47 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 18.1, 21.3, 29.4, 48.3, 52.4, 52.5, 54.0, 124.7, 130.0, 136.0, 138.9, 140.6, 141.5, 168.0, 168.3. HRMS calcd m/z for $C_{18}H_{24}O_5S$: 352.1362. Found: 352.1355. Anal. calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86. Found: C, 61.13; H, 6.60%.

4.3.6. Methyl (R_S,R_C)-(*E*)-2-methoxycarbonyl-3-methyl-5-(*p*-tolylsulfinyl)-4-pentenoate (R_S,R_C)-5a. The general procedure (method B) was followed for the allylic substitution of (R_S,S_C)-**3a** (30 mg, 0.119 mmol). The reaction time was 4 h. Purification of the reaction mixture by flash chromatography (Et_2O:hexane, 2:3) afforded (R_S,R_C)-**5a** as a white solid (32 mg, 87%). Mp = 83–85°C, $[\alpha]_D = +204$ ($c = 1.8$, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, $J = 6.8$ Hz, 3H, CH_3), 2.39 (s, 3H, CH_3Ar), 3.17 (m, 1H, CH), 3.39 (d, $J = 8.5$ Hz, 1H, $CH(CO_2Me)_2$), 3.60 (s, 3H, CH_3O), 3.72 (s, 3H, CH_3O), 6.26 (dd, $J = 15.1$ Hz, $J = 1.0$ Hz, 1H, =CH-S(O)), 6.54 (dd, $J = 15.1$ Hz, $J = 7.9$ Hz, 1H, CH=), 7.29–7.48 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 17.4, 21.3, 36.3, 52.4, 52.5, 56.6, 124.6, 130.0, 136.4, 139.7, 140.5, 141.5, 167.9, 168.0. HRMS calcd m/z for $C_{16}H_{20}O_5S$: 340.1046. Found: 324.1029. Anal. calcd for $C_{16}H_{20}O_5S$: C, 59.20; H, 6.21. Found: C, 59.17; H, 6.22%.

4.4. Palladium-mediated resolution of (*E*)-γ-acetoxy-α,β-unsaturated sulfoxides 2b and 3b

To a solution of the mixture of acetates (R_S,R_C)-**2b** and (R_S,S_C)-**3b** (1:1 mixture, 70 mg, 0.248 mmol) in dry THF (5 mL) was added $(Ph_3P)_4Pd$ (12.8 mg, 0.012 mmol). The resulting solution was vigorously shaken and heated at 70°C and a suspension of dimethyl malonate (34.7 mg, 0.26 mmol) and NaH (15 mg, 0.63 mmol) in anhydrous THF (2 mL) was added. The reaction mixture was stirred at this temperature for 4 h. The solvent was evaporated and the crude product was purified by flash chromatography (Et_2O:hexane, 7:3) affording (R_S,S_C)-**4b** as a white solid (35 mg, 42%), mp = 53.5–55.5°C, $[\alpha]_D = +97$ ($c = 3.5$, $CHCl_3$), and (R_S,S_C)-**3b** as a viscous oil (27 mg, 38%), $[\alpha]_D = +154$ ($c = 2.7$, $CHCl_3$).

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References

1. For recent reviews, see: (a) Tsuji, J. *Palladium Reagents and Catalysis*; Wiley: New York, 1995; (b) Hegedns, L. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994; pp. 385–459. (c) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Semmelhock, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, p. 585.
2. For reviews on asymmetric palladium-catalyzed allylic substitutions, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395; (b) Williams, J. M. J. *Synlett* **1996**, 705; (c) Reiser, O. *Angew. Chem*. **1993**, *105*, 576; (d) Reiser, O. *Angew. Chem., Int. Ed*. **1993**, *32*, 547; (d) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089; (f) Consiglio, G.; Waymouth, R. M. *Chem. Rev*. **1989**, *89*, 257; (g) *Organopalladium Chemistry*, recent advances; Yamamoto, Y.; Negishi, E. (Guest Editors) *J. Organomet. Chem*. **1999**, 576 (1–2) (16 reviews).
3. (a) Pyne, S. G.; Dong, Z. *Tetrahedron Lett*. **2000**, *41*, 5387; (b) Pyne, S. G.; Dong, Z. *Tetrahedron Lett*. **1999**, *40*, 6131; (c) Cook, G. R.; Shanker, P. S.; Pararajosingham, K. *Angew. Chem., Int. Ed*. **1999**, *38*, 110; (d) Atlan, V.; Racouchot, S.; Rubin, M.; Bremer, C.; Olliver, J.; De Meijere, A.; Salaün, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1131; (e) Cook, G.; Shanker, P. S. *Tetrahedron Lett*. **1998**, *39*, 3405; (f) Cook, G.; Shanker, P. S. *Tetrahedron Lett*. **1998**, *39*, 4991; (g) Michelet, V.; Besnier, I.; Genêt, J. P. *Synlett* **1996**, 215; (h) Michelet, V.; Genêt, J. P. *Bull. Soc. Chim. Fr*. **1996**, *133*, 881.
4. (a) Suzuki, T.; Sato, T.; Hirama, M. *Tetrahedron Lett*. **1990**, *31*, 4747; (b) Tanikaga, R.; Jun, T. X.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1185; (c) Tsuda, T.; Horii, Y.; Nakagawa, Y.; Ishida, T.; Saegusa, T. *J. Org. Chem*. **1989**, *54*, 977; (d) Tanikaga, R.; Takeuchi, J.; Takyu, M.; Kaji, A. *J. Chem. Soc., Chem. Commun*. **1987**, 386; (e) Tsuji, J.; Ueno, H.; Kobayashi, Y.; Okumoto, H. *Tetrahedron Lett*. **1981**, *22*, 2573.
5. Sugiura, M.; Yagi, Y.; Wei, S.-Y.; Nukai, T. *Tetrahedron Lett*. **1998**, *39*, 4351.
6. (a) Hunt, D. A.; Quante, J. M.; Tyson, R. L.; Dasher, L. W. *J. Org. Chem*. **1984**, *49*, 5262; (b) Tsuji, J.; Ueno, H.; Kobayashi, Y.; Okumoto, H. *Tetrahedron Lett*. **1981**, *22*, 2573; (c) Jackson, W. R.; Staruss, J. U. *Aust. J. Chem*. **1977**, *30*, 553.
7. (a) Garrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem*. **1998**, *63*, 9406; (b) Alonso, I.; Carretero, J. C.; Garrido, J. L.; Magro, V.; Pedregal, C. *J. Org. Chem*. **1997**, *62*, 5682.
8. Guerrero de la Rosa, V.; Ordóñez, M.; Alcudia, F.; Llera, J. M. *Tetrahedron Lett*. **1995**, *36*, 4889.
9. Guerrero de la Rosa, V.; Ordóñez, M.; Llera, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2991.
10. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
11. Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975; p. 256.