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Asymmetric intramolecular C-H insertion of sulfonyldiazoacetates catalyzed by Rh(II)

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Abstract

The asymmetric C-H insertion of alkyldiazosulfones has been studied. High selectivity was achieved using a combination of a chiral catalyst and a chiral auxiliary ($\text{Rh}_2(\text{S-pttl})_4$ and menthyl ester).

1. Introduction

Carbene C-H insertion has become an important synthetic method over the past few decades.^{1,2} The great advantage of this reaction is its ability to create a carbon-carbon bond at an unfunctionalized C-H reaction site. However, the necessity for precise selectivity among multiple C-H bonds in the substrate, still remains the key issue in this reaction and its application in synthesis. As has been previously demonstrated,^{3,4} rhodium catalyzed C-H insertion on diazosulfonates and diazosulfones exhibits an unusual selectivity, producing six membered cyclic products rather than the usually observed five membered compounds, as shown by the examples in Scheme 1.^{5,6}

After initial studies of this transformation we became in performing this reaction enantioselectively. Recently, an enantioselective version of this reaction was reported using chiral copper catalysts with excellent enantioselectivity and generally good yields.⁷ However, there have been no reports on using chiral rhodium catalysts to perform this transformation. Only a single report on the use of a chiral rhodium(II) catalyst to effect asymmetric C-H insertion involving α -sulfonyl substituted diazo carbonyl compounds appears to exist,⁸ citing low yields (several other reports of this transformation using the same copper chiral catalyst system are also found⁹). Rhodium(II) catalysts are usually the catalysts of choice for C-H insertion reactions, often favoring C-H insertion over other reactions of carbenes. Thus, the development of an asymmetric Rh(II) catalytic system for this transformation is desirable. Herein we report our initial findings on using chiral Rh(II) catalysts for enantioselective C-H insertions on diazosulfones.

2. Results and discussion

We started our studies by screening common chiral rhodium catalysts (Table 1). The use of $\text{Rh}_2(\text{S-MEPY})_4$ and $\text{Rh}_2(\text{S-DOSP})_4$ resulted in no selectivity. The use of a non-polar solvent (2,2-dimethylbutane) with $\text{Rh}_2(\text{S-DOSP})_4$ catalyst¹⁰ provided the first glimpse of selectivity,

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although complications arose due to the poor solubility of the diazocompound in this solvent. Next, we explored the class of catalyst derived from a phthalimide protected aminoacid,¹¹ starting with $\text{Rh}_2(\text{S-pttl})_4$, derived from *tert*-leucine. This provided the first encouraging results, with the additional bonus of an increased yield of the product. Following this, we attempted to optimize the catalyst structure by increasing and decreasing the size of the substituents at the aminoacid stereogenic center (using $\text{Rh}_2(\text{S-ptad})_4$,¹² $\text{Rh}_2(\text{S-nttl})_4$, $\text{Rh}_2(\text{S-ptpa})_4$, $\text{Rh}_2(\text{S-nta})_4$). All modifications failed to increase the enantioselectivity when compared to $\text{Rh}_2(\text{S-pttl})_4$. Lowering the reaction temperature to 0°C provided a small increase in selectivity, at the expense of the yield, while a further decrease of temperature (to -20°C) had no effect. The reason appears to be due to a lack of decomposition of the diazocompound at temperatures significantly below 0°C. Changing the solvent to toluene also had no effect.

We proceeded by exploring the influence of the ester alkyl group on the selectivity of the reaction. For this purpose esters were prepared by hydrolysis of the ethyl ester and coupling of the resulting acid with the appropriate alcohols (Scheme 2).

Changing the alkyl from ethyl to methyl, isopropyl and *t*-butyl, or even bulkier 2,4-dimethyl pentan-2-yl did not have a significant effect (Table 2).

As a result, we resorted to using a chiral auxiliary on the ester. The very first attempt using (-)-menthol as an auxiliary resulted in a sharp increase in selectivity. This is notably different from the cyclization of a similar diazoacetoacetate substrate to cyclopentanone,¹³ where the effect of menthyl was not as significant, and the switch to 2,4-dimethyl pentan-2-yl ester did improve the selectivity. To determine whether menthyl acts as a directing chiral auxiliary or just as a sterically bulky group, we performed the reaction with the enantiomer of menthol. This resulted in a reversal of the selectivity towards the other enantiomer, suggesting the auxiliary influence to be the main one. However, in combination with an achiral catalyst (rhodium acetate), the menthol auxiliary gave no selectivity. Therefore, the selectivity is a synergetic cooperative effect. It also appears that outer sphere interactions are important for the selectivity.

To determine the absolute configuration of the C-H insertion product, we prepared enantiopure **2** using an independent method (Scheme 3). Enantiopure (*R*)-pentane-1,4-diol **7** was obtained as described from L-glutamic acid,¹⁴ and converted into ditosylate **8**. Selective substitution of the primary tosylate with ethyl thioglycolate, followed by oxidation, yielded sulfone **9**. Its treatment with base in DMSO gave **2** via intramolecular $\text{S}_{\text{N}}2$ substitution, along with a *cis*-isomer (*R,S*)-**2**. The configuration of the product was assigned as (*2S,3S*), assuming an inversion over the course of the substitution. The specific rotation of the alcohol, obtained upon reduction of this product, along with NMR analysis its acetyl mandelate indicated that it is the enantiomer of the material obtained by reduction of **6e**.

3. Conclusion

We have studied the influence of the structure of the ester and the catalyst on the stereoselectivity of the C-H insertion of pentylsulfonyldiazoacetates. High stereoselectivity was observed from the synergetic cooperative influence of the chiral catalyst and the chiral auxiliary, thus providing a synthetically useful method for performing this reaction. These findings are also valuable for the design of a more effective asymmetric Rh(II) catalysts for this reaction. Further studies will be reported in due course.

4. Experimental

4.1. General experimental details

All reactions were carried out under an inert atmosphere of dry nitrogen. Proton magnetic resonance spectra were recorded at 500 MHz on an Avance 500 Bruker spectrometer. Carbon magnetic resonance spectra were recorded at 125 MHz on an Avance 500 Bruker spectrometer. All chemical shifts are reported in δ units relative to tetramethylsilane. High resolution mass spectra were obtained on an Agilent 61969A TOF high resolution mass spectrometer using electrospray ionization, direct infusion, 10 ml/min in 50% MeOH 5mM ammonium formate. Melting points were determined on a MEL-TEMP melting point apparatus. Flash column chromatography was performed using 40–63 μ m silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Tetrahydrofuran (THF) and ether were distilled over lithium aluminum hydride prior to use.

4.2. Preparation of 2-(pentylsulfonyl)acetic acid **3**

To a solution of ethyl 2-(pentylsulfonyl)acetate (720 mg, 3.24 mmol), dissolved in MeOH (8 mL), was added KOH (85%, 250 mg, 3.8 mmol) dissolved in MeOH (8 mL) at room temperature. The resulting solution was then stirred for 3 hours after which time the reaction was complete as indicated by TLC analysis. The reaction mixture was concentrated under reduced pressure, diluted with water (20 mL), washed with dichloromethane (3x10 mL), diluted with 20 mL of 1M HCl, and extracted with ethyl acetate (3x20 mL). The ethyl acetate extract was washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to afford **3** (570 mg, 91%) as a white crystalline powder that was used without further purification. m.p. 78–79°C. ¹H NMR (CDCl₃, 500 MHz): δ 9.20 (br s, 1H), 4.04 (s, 2H), 3.26–3.31 (m, 2H), 1.85–1.93 (m, 2H), 1.35–1.50 (m, 4H), 0.94 (t, J = 7.3 Hz, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 170.0(C), 57.3(CH₂), 54.0(CH₂), 30.6(CH₂), 22.3(CH₂), 21.7(CH₂), 13.9(CH₃). HRMS (ESI) calcd for C₇H₁₈O₄NS [M+NH₄]⁺ 212.0956, found 212.0983.

4.3. General procedure for the preparation of sulfonylacetates **4a–4e**

2-(Pentylsulfonyl)acetic acid **3** (1 equiv), benzoyl chloride (1 equiv) and THF (2.5 mL/mmol) were added to a round bottom flask equipped with a magnetic stirrer. To the resulting solution Et₃N (2 equiv) was slowly added, followed by the corresponding alcohol (1 equiv), and DMAP (0.25 equiv). The mixture obtained was stirred at room temperature for 6 hours (TLC analysis revealed that the reaction was complete). The reaction mixture was diluted with EtOAc (40 mL) and washed with water (3x30 mL). The organic phase was further washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to afford the crude product which was purified by flash chromatography on a silica gel column using EtOAc-Hexanes (0:1 to 1:9).

Methyl 2-(pentylsulfonyl)acetate 4a—¹H NMR (CDCl₃, 500 MHz): δ 3.96 (s, 2H), 3.83 (s, 3H), 3.22–3.27 (m, 2H), 1.83–1.91 (m, 2H), 1.34–1.48 (m, 4H), 0.93 (t, J = 7 Hz, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 163.8(C), 57.4(CH₂), 53.7(CH₂), 53.5(CH₃), 30.6(CH₂), 22.3 (CH₂), 21.7(CH₂), 13.9(CH₃). HRMS (ESI) calcd for C₈H₁₇O₄S [M+H]⁺ 209.0842, found 209.0848.

Isopropyl 2-(pentylsulfonyl)acetate 4b—¹H NMR (CDCl₃, 500 MHz): δ 5.11 (septet, J = 6.5 Hz, 1H), 3.91 (s, 2H), 3.22–3.27 (m, 2H), 1.84–1.92 (m, 2H), 1.34–1.48 (m, 4H), 1.31 (d, J = 6.5 Hz, 6H), 0.93 (t, J = 7 Hz, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 162.8(C), 70.9(CH), 57.8(CH₂), 53.7(CH₂), 30.6(CH₂), 22.3(CH₂), 21.7(CH₂), 21.8(CH₃), 13.9(CH₃). HRMS (ESI) calcd for C₁₀H₂₁O₄S [M+H]⁺ 237.1160, found 237.1158.

tert-Butyl 2-(pentylsulfonyl)acetate 4c— ^1H NMR (CDCl_3 , 500 MHz): δ 3.86 (s, 2H), 3.21–3.25 (m, 2H), 1.83–1.90 (m, 2H), 1.51 (s, 9H), 1.33–1.48 (m, 4H), 0.92 (t, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 162.3(C), 84.3(C), 58.6(CH_2), 53.6(CH_2), 30.6(CH_2), 28.0(CH_3), 22.3(CH_2), 21.8(CH_2), 13.9(CH_3). HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{26}\text{O}_4\text{NS} [\text{M} + \text{NH}_4]^+$ 268.1582, found 268.1588.

2,4-Dimethylpentan-3-yl 2-(pentylsulfonyl)acetate 4d— ^1H NMR (CDCl_3 , 500 MHz): δ 4.69 (t, $J = 6$ Hz, 1H), 3.97 (s, 2H), 3.24–3.28 (m, 2H), 1.84–2.00 (m, 4H), 1.33–1.48 (m, 4H), 0.92 (t, $J = 7.5$ Hz, 3H), 0.91 (t, $J = 6$ Hz, 12H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 163.4(C), 86.2(CH), 57.5(CH_2), 53.7(CH_2), 30.6(CH_2), 29.6(CH), 22.3(CH_2), 21.9(CH_2), 19.6(CH_3), 17.3(CH_3), 13.9(CH_3). HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{32}\text{NO}_4\text{S} [\text{M} + \text{NH}_4]^+$ 310.2052, found 310.2054.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(pentylsulfonyl)acetate 4e— $[\alpha]_{\text{D}}^{20} = -45.9$ (c 0.035, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ 4.79 (td, $J = 11, 4.5$ Hz, 1H), 3.93 (s, 2H), 3.20–3.29 (m, 2H), 2.01–2.07 (m, 1H), 1.84–1.96 (m, 3H), 1.68–1.74 (m, 2H), 1.34–1.55 (m, 6H), 1.02–1.12 (m, 2H), 0.85–0.96 (m, 10H), 0.77 (d, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 163.0(C), 77.4(CH), 57.9(CH_2), 53.8(CH_2), 47.0(CH), 40.7(CH_2), 34.3(CH_2), 31.7(CH), 30.7(CH_2), 26.3(CH), 23.4(CH_2), 22.3(CH_3), 22.1(CH_2), 21.8(CH_3), 20.9(CH_3), 16.2(CH_3), 13.9(CH_3). HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{36}\text{NO}_4\text{S} [\text{M} + \text{NH}_4]^+$ 350.2365, found 350.2350.

4.4. General procedure for the preparation of sulfonyldiazoacetates 5a–5e

The corresponding alkyl 2-(pentylsulfonyl)acetate (1 equiv) was dissolved in THF (2.5 mL/mmol) and cooled to -45°C . Mesityl azide (2.5 equiv) was then added, followed by the dropwise addition of 1.5 equiv of DBU. The reaction mixture was stirred for 1 hour, while maintaining the temperature at -45°C , after which it was warmed up to room temperature over a 15–20 minute interval. The mixture obtained was poured over 20 mL of a half-saturated $(\text{NH}_4)_2\text{SO}_4$ solution, extracted with CH_2Cl_2 (3x20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product which was purified by flash chromatography on a silica gel column using EtOAc-Hexanes (0:1 to 1:9).

Note: The diazo carbon does not appear in the ^{13}C NMR spectra of all diazocompounds. IR shows a strong diazo stretch at $\sim 2130\text{ cm}^{-1}$.

Methyl 2-(pentylsulfonyl)diazoacetate 5a— ^1H NMR (CDCl_3 , 500 MHz): δ 3.87 (s, 3H), 3.35–3.40 (m, 2H), 1.80–1.87 (m, 2H), 1.32–1.46 (m, 4H), 0.92 (t, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 160.7(C), 56.8(CH_2), 53.3(CH_3), 30.3(CH_2), 22.5(CH_2), 22.3(CH_2), 13.9(CH_3). IR (CH_2Cl_2 , cm^{-1}): 2132, 1719, 1338, 1147.

Isopropyl 2-(pentylsulfonyl) diazoacetate 5b— ^1H NMR (CDCl_3 , 500 MHz): δ 5.18 (septet, $J = 6.5$ Hz, 1H), 3.35–3.41 (m, 2H), 1.80–1.87 (m, 2H), 1.32–1.46 (m, 4H), 1.32 (d, $J = 6.5$ Hz, 6H), 0.91 (t, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 159.9(C), 71.0(CH), 56.7(CH_2), 30.3(CH_2), 22.5(CH_2), 22.3(CH_2), 22.0(CH_3), 13.9(CH_3). IR (CH_2Cl_2 , cm^{-1}): 2131, 1710, 1341, 1147.

tert-Butyl 2-(pentylsulfonyl) diazoacetate 5c— ^1H NMR (CDCl_3 , 500 MHz): δ 3.34–3.39 (m, 2H), 1.80–1.87 (m, 2H), 1.54 (s, 9H), 1.33–1.47 (m, 4H), 0.93 (t, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 159.4(C), 85.1(C), 56.6(CH_2), 30.3(CH_2), 28.5(CH_3), 22.6(CH_2), 22.3(CH_2), 13.9(CH_3). IR (CH_2Cl_2 , cm^{-1}): 2128, 1708, 1338, 1146.

2,4-Dimethylpentan-3-yl 2-(pentylsulfonyl) diazoacetate 5d— ^1H NMR (CDCl_3 , 500 MHz): δ 4.75 (t, $J = 6$ Hz, 1H), 3.35–3.40 (m, 2H), 1.93–2.01 (m, 2H), 1.79–1.87 (m, 2H), 1.32–1.46 (m, 4H), 0.89–0.94 (m, 15H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 160.6(C), 86.2(CH), 56.7(CH_2), 30.3(CH_2), 29.7 (CH), 22.8(CH_2), 22.3(CH_2), 19.7(CH_3), 17.4(CH_3), 13.9(CH_3). IR (CH_2Cl_2 , cm^{-1}): 2130, 1709, 1338, 1147.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(pentylsulfonyl)diazoacetate 5e— $[\alpha]_{\text{D}}^{20} = -56.5$ (c 0.021, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ 4.86 (td, $J = 11, 4.5$ Hz, 1H), 3.31–3.42 (m, 2H), 2.02–2.08 (m, 1H), 1.78–1.89 (m, 3H), 1.66–1.74 (m, 2H), 1.31–1.56 (m, 6H), 1.02–1.12 (m, 2H), 0.83–0.94 (m, 10H), 0.78 (d, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 160.0(C), 77.3(CH), 56.7(CH_2), 47.2(CH), 41.1(CH_2), 34.2(CH_2), 31.6(CH), 30.3(CH_2), 26.6(CH), 23.6(CH_2), 22.6(CH_2), 22.3(CH_2), 22.1(CH_3), 20.9(CH_3), 16.5(CH_3), 13.9(CH_3). IR (CH_2Cl_2 , cm^{-1}): 2131, 1705, 1336, 1146.

(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl 2-(pentylsulfonyl)diazoacetate [enantiomer of 5e, from (+)menthol]—Spectroscopic data identical to 5e. $[\alpha]_{\text{D}}^{20} = +54.7$ (c 0.035, CHCl_3).

4.5. General procedure for C-H insertion

To a solution of Rh(II) catalyst (1 mol%) in CH_2Cl_2 (2.5 mL/mmol) was added the corresponding diazo alkyl 2-(pentylsulfonyl)acetate (1 equiv) dissolved in CH_2Cl_2 (2.5 mL/mmol) over 2 hours *via* syringe pump. The resulting mixture was stirred at room temperature for 12 hours after which time the reaction was complete as indicated by TLC analysis. The reaction mixture was then evaporated under reduced pressure to afford the crude product which was purified by flash chromatography using EtOAc-Hexanes.

trans-Ethyl tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate 2—The data matched that previously reported.³

trans-Methyl tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate 6a— ^1H NMR (CDCl_3 , 500 MHz): δ 3.86 (s, 3H), 3.58 (d, $J = 11$ Hz, 1H), 3.18 (dt, $J = 14, 4$ Hz, 1H), 2.88–2.96 (m, 1H), 2.52–2.62 (m, 1H), 2.09–2.23 (m, 2H), 1.94–2.01 (m, 1H), 1.23–1.33 (m, 1H), 1.07 (d, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 164.5(C), 72.7(CH), 53.4(CH_3), 52.0(CH_2), 34.5(CH), 32.0(CH_2), 22.9(CH_2), 20.0(CH_3). HRMS (ESI) calcd for $\text{C}_8\text{H}_{15}\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 207.0691, found 207.0668.

trans-Isopropyl tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate 6b— ^1H NMR (CDCl_3 , 500 MHz): δ 5.18 (septet, $J = 6.5$ Hz, 1H), 3.52 (d, $J = 11$ Hz, 1H), 3.16 (dt, $J = 14, 4$ Hz, 1H), 2.86–2.94 (m, 1H), 2.51–2.61 (m, 1H), 2.08–2.23 (m, 2H), 1.93–1.99 (m, 1H), 1.33 (d, $J = 6.5$ Hz, 3H), 1.32 (d, $J = 6.5$ Hz, 3H), 1.23–1.30 (m, 1H), 1.08 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 163.5(C), 72.9(CH), 70.6(CH), 52.0(CH_2), 34.5(CH), 32.0(CH_2), 22.8(CH_2), 21.9(CH_3), 21.8(CH_3), 19.8(CH_3). HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{22}\text{O}_4\text{NS}$ $[\text{M}+\text{NH}_4]^+$ 252.1269, found 252.1390.

trans-tert-Butyl tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate 6c— ^1H NMR (CDCl_3 , 500 MHz): δ 3.44 (d, $J = 11$ Hz, 1H), 3.14 (dt, $J = 14, 4$ Hz, 1H), 2.84–2.92 (m, 1H), 2.46–2.56 (m, 1H), 2.06–2.21 (m, 2H), 1.90–1.97 (m, 1H), 1.53 (s, 9H), 1.20–1.30 (m, 1H), 1.08 (d, $J = 6$ Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 163.0(C), 83.9(C), 73.4(CH), 52.0(CH_2), 34.5(CH), 32.0(CH_2), 28.1(CH_3), 22.9(CH_2), 19.8(CH_3). HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{24}\text{O}_4\text{NS}$ $[\text{M}+\text{NH}_4]^+$ 266.1426, found 266.1383.

trans-2,4-Dimethylpentan-3-yl tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate 6d—¹H NMR (CDCl₃, 500 MHz): δ 4.75 (t, *J* = 6 Hz, 1H), 3.60 (d, *J* = 11 Hz, 1H), 3.16 (dt, *J* = 14, 4 Hz, 1H), 2.92 (td, *J* = 13, 4 Hz, 1H), 2.51–2.61 (m, 1H), 2.07–2.23 (m, 2H), 1.91–2.01 (m, 3H), 1.23–1.33 (m, 1H), 1.10 (d, *J* = 6 Hz, 3H), 0.96 (d, *J* = 7 Hz, 3H), 0.96 (d, *J* = 7 Hz, 3H), 0.91 (t, *J* = 7 Hz, 6H). ¹³C NMR (CDCl₃, 125 MHz): δ 164.1(C), 86.1(CH), 72.9(CH), 52.1(CH₂), 34.3(CH), 32.1(CH₂), 29.7(CH), 29.5(CH), 22.8(CH₂), 20.3(CH₃), 19.8(CH₃), 17.7(CH₃), 17.2(CH₃). HRMS (ESI) calcd for C₁₄H₃₀NO₄S [M+NH₄]⁺ 308.1895, found 308.1877. Note: accidental equivalence of two methyls at 19.8.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*R*)-tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate 6e—[α]_D²⁰ = –28.7 (*c* 0.013, CHCl₃). ¹H NMR (CDCl₃, 500 MHz): δ 4.84 (td, *J* = 11, 4.5 Hz, 1H), 3.54 (d, *J* = 11 Hz, 1H), 3.15 (dt, *J* = 14, 4 Hz, 1H), 2.90 (td, *J* = 14, 4 Hz, 1H), 2.50–2.60 (m, 1H), 2.08–2.23 (m, 3H), 1.92–2.01 (m, 2H), 1.66–1.74 (m, 2H), 1.44–1.54 (m, 2H), 1.21–1.31 (m, 1H), 1.02–1.14 (m, 5H), 1.07 (d, *J* = 6.5 Hz), 0.84–0.95 (m, 7H), 0.92 (d, *J* = 6.5 Hz), 0.91 (d, *J* = 6.5 Hz), 0.77 (d, *J* = 7 Hz, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 163.5(C), 77.4(CH), 73.1(CH), 52.1(CH₂), 46.9(CH), 40.6(CH₂), 34.4(CH), 34.4(CH₂), 32.1(CH₂), 31.7(CH), 26.2(CH), 23.3(CH₂), 22.9(CH₂), 22.1(CH₃), 21.0(CH₃), 19.8(CH₃), 16.1(CH₃). HRMS (ESI) calcd for C₁₇H₃₄NO₄S [M+NH₄]⁺ 348.2208, found 348.2206.

For entries 6 and 7 in Table 2, inseparable mixtures of **6e** and its diastereomer were obtained. They were directly reduced to alcohol **10** for determination of the ratio.

4.6. Reduction of esters 6a–6e, and 2

To the corresponding thiopyran-1,1-dioxide carboxylate (1 equiv) in CH₂Cl₂ (2.5 mL/mmol) was added DIBALH (2.2 equiv) and the resulting mixture stirred at room temperature for 12 hours. The reaction was then quenched with MeOH (0.7 mL). Next, a 10% solution of Rochelle salt (5 mL) was added and stirred vigorously for several hours, until the solids disappeared. The water layer was extracted with CH₂Cl₂ (3x5mL) and then EtOAc (5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to afford a crude product, which was purified by flash chromatography using EtOAc-Hexanes (1:4 to 1:1).

trans-(Tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-yl)methanol 10—M.p. 94–95°C. ¹H NMR (CDCl₃, 500 MHz): δ 4.45 (dd, *J* = 13, 3.5 Hz, 1H), 4.00 (ddd, *J* = 5.5, 9, 14 Hz, 1H), 3.11 (dt, *J* = 14, 3.5 Hz, 1H), 2.90–2.98 (m, 1H), 2.60 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.50 (dd, *J* = 9, 4.5, 1H), 2.34–2.44 (m, 1H), 2.06–2.19 (m, 2H), 1.92 (dd, *J* = 14.5, 3 Hz, 1H), 1.28–1.37 (m, 1H), 1.14 (d, *J* = 6.5 Hz, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 68.4(CH), 56.2(CH₂), 52.2(CH₂), 33.3(CH₂), 31.8(CH), 23.1(CH₂), 19.1(CH₃). HRMS (ESI) calcd for C₇H₁₅O₃S [M+H]⁺ 179.0741, found 179.0746.

((2*R*,3*R*)-Tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-yl)methanol (*R,R*)-10—Obtained by reduction of **6e**: [α]_D²⁰ = –16.7 (*c* 0.005, CHCl₃)

((2*S*,3*S*)-Tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-yl)methanol (*S,S*)-10—Obtained by reduction of (*S,S*)-**2**: [α]_D²⁰ = +14.1 (*c* 0.004, CHCl₃)

4.7. Determination of the enantiomeric ratio

An oven-dried round bottom flask, equipped with a magnetic stirrer, was charged with DCC (1.5 equiv), (*S*)-acetylmandelic acid (1.5 equiv), and CH₂Cl₂ (2.5 mL/mmol). The resulting solution was stirred at room temperature for 30 minutes, after which alcohol **10** (1 equiv)

dissolved in CH_2Cl_2 (2.5 mL/mmol) was added, followed by DMAP (0.5 equiv). The reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was taken up in EtOAc (50 mL), washed with 1M HCl (2x10 mL) and then with saturated NaHCO_3 . The organic phase was further washed with brine, dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure to afford the crude product which was used for ^1H NMR analysis without further purification to determine the diastereomeric ratio. The enantioselectivity or diastereoselectivity was measured by integration of the diastereomeric signals ($\text{CH}-\text{CH}_2-\text{O}-\text{CO}$, CH_3-CH , $\text{Ph}-\text{CH}(\text{OAc})-\text{CO}$) in the ^1H NMR spectrum. It was shown that chromatographic purification of the product could be performed without affecting the measured ratio.

4.8. Preparation of (*R*)-1,4-bis(4-toluenesulfonyloxy)pentane 8

To the solution of (*R*)-pentane-1,4-diol **7** (75 mg, 0.72 mmol), prepared as described from L-glutamic acid,¹⁴ in pyridine (1.8 mL) at 0°C was added *p*-toluenesulfonyl chloride (345 mg, 1.8 mmol) and DMAP (8 mg, 0.07 mmol). The mixture was kept at 0°C for 24 h, then warmed up to rt and allowed to stand at this temperature for 1 h. The mixture was then diluted with ethyl acetate, washed with 1M HCl, saturated NaHCO_3 , brine, dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified using flash chromatography to provide the pure ditosylate **8** (223 mg, 75%). $[\alpha]_{\text{D}}^{20} = +15.1$ (*c* 0.023, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ 7.76 (d, *J* = 8.5 Hz, 2H), 7.755 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 4.57 (sextet, *J* = 6 Hz, 1H), 3.90–4.00 (m, 2H), 2.45 (s, 3H), 2.44 (s, 3H), 1.55–1.71 (m, 4H), 1.19 (d, *J* = 6 Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 145.1(C), 144.9(C), 134.4(C), 133.1(C), 130.1(CH), 130.0(CH), 128.0(CH), 127.8(CH), 79.3(CH), 69.3(CH_2), 32.6(CH_2), 24.6(CH_2), 21.8(CH_3), 20.9(CH_3). HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_6\text{S}_2$ $[\text{M}+\text{NH}_4]^+$ 430.1352, found 430.1301. Note: accidental equivalence of two methyls at 21.8.

4.9. Preparation of ethyl 2-((*R*)-4-(4-toluenesulfonyloxy)pentylsulfonyl)acetate 9

Ditosylate **8** (18 mg, 0.04 mmol) and ethylthioglycolate (8 mg, 0.07 mmol) under nitrogen were dissolved in acetone (0.1 mL), and K_2CO_3 (10 mg, 0.07 mmol) was added. The reaction mixture was then stirred at rt for 18h, after which the solvent was removed under reduced pressure, and the residue was treated with water (5 mL) and ethyl acetate (10 mL). The layers were separated, and the organic layer washed with brine, dried and concentrated. The crude was dissolved in CH_2Cl_2 (0.2 mL) and treated with *m*-CPBA (70%, 27 mg, 0.22 mmol), and left at rt for 20 h. The mixture was then diluted with ethyl acetate, washed with NaHSO_3 , saturated NaHCO_3 , brine, dried and concentrated. Chromatography provided **9** as a yellow oil (14 mg, 82%). $[\alpha]_{\text{D}}^{20} = +14.1$ (*c* 0.017, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 4.62–4.70 (m, 1H), 4.27 (q, *J* = 7 Hz, 2H), 3.92 (s, 2H), 3.19–3.26 (m, 2H), 2.45 (s, 3H), 1.70–1.96 (m, 4H), 1.33 (t, *J* = 7 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 163.2(C), 145.1(C), 134.3(C), 130.1(CH), 127.9(CH), 79.0(CH), 63.0(CH_2), 57.7(CH_2), 53.0(CH_2), 35.1(CH_2), 21.9(CH_3), 20.9(CH_3), 17.9(CH_2), 14.2(CH_3). HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{28}\text{NO}_7\text{S}_2$ $[\text{M}+\text{NH}_4]^+$ 410.1301, found 410.1315.

4.10. Preparation of ethyl (2*S*,3*S*)-tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate (*S*,*S*)-2

Sulfone **9** (35 mg, 0.089 mmol) was dissolved in DMSO (0.5 mL) under a nitrogen atmosphere, and K_2CO_3 (18.5 mg, 0.134 mmol) was added. The mixture was stirred vigorously at rt for 24 h, then diluted with water (10 mL), and extracted with ethyl acetate (2x10 mL). The organic layer was washed with brine, dried over MgSO_4 and concentrated.

Chromatography provided (*S,S*)-**2** (12.7 g, 65%), along with the *cis*-isomer (*R,S*)-**2** (5 mg, 25%). The spectroscopic data for the compounds were in agreement with the literature.^{3,5}

Ethyl (2*S*,3*S*)-tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate (*S,S*)-2****— $[\alpha]_{\text{D}}^{20} = +32.5$ (*c* 0.005, CHCl₃).

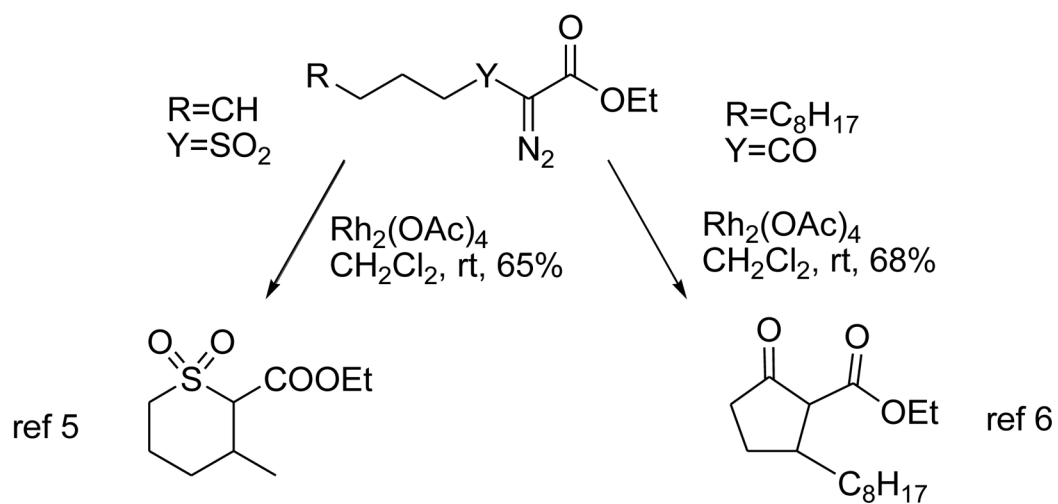
Ethyl (2*R*,3*S*)-tetrahydro-3-methyl-2H-thiopyran-1,1-dioxide-2-carboxylate (*R,S*)-2****— $[\alpha]_{\text{D}}^{20} = -36.8$ (*c* 0.003, CHCl₃).

Acknowledgments

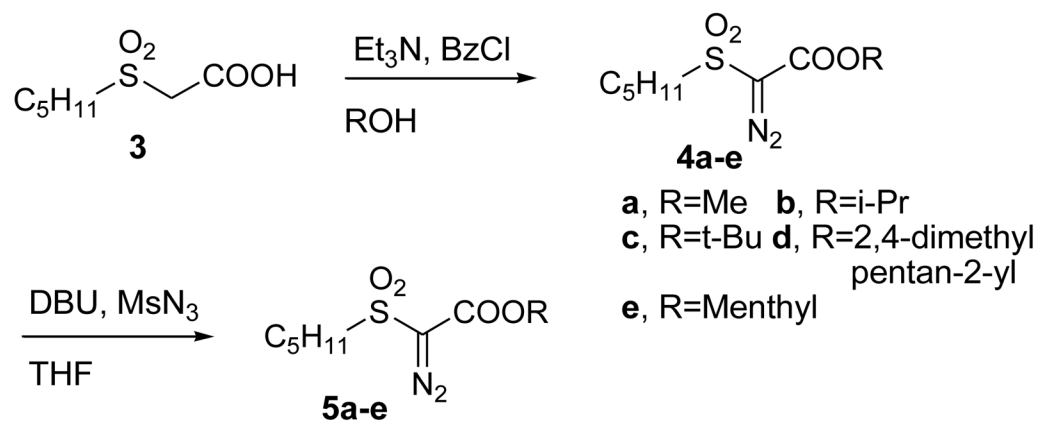
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References and notes

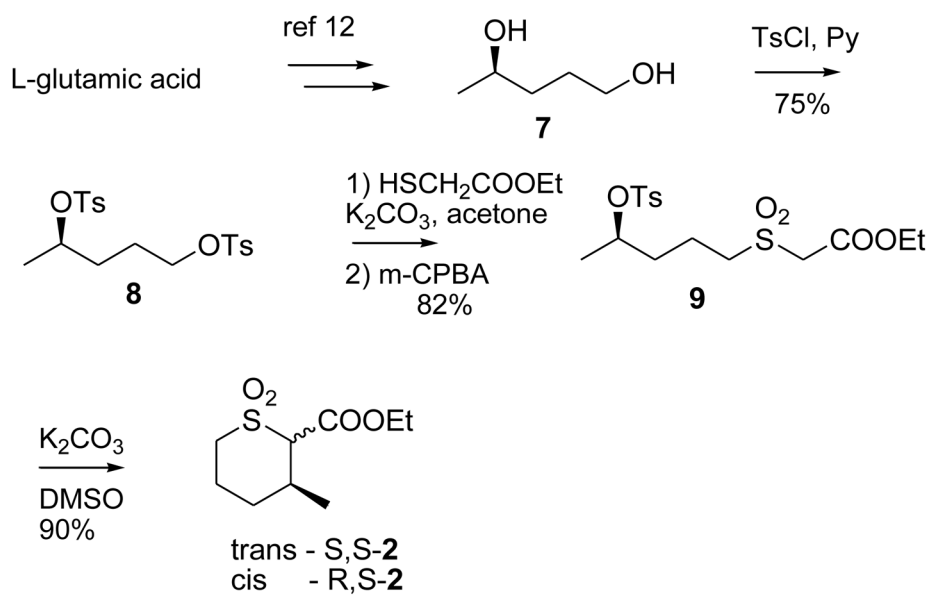
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Scheme 1.
C-H insertion on diazosulfones



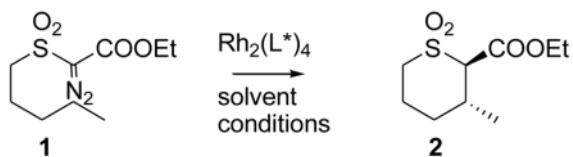
Scheme 2.
Preparation of esters



Scheme 3.
Synthesis of enantiopure **2**

Table 1

Screening of rhodium catalysts



Entry	Catalyst, conditions	Yield	ee
1	$\text{Rh}_2(\text{S-MEPY})_4$, 80°C, $(\text{CH}_2\text{Cl})_2$	55%	0%
	$\text{Rh}_2(\text{S-DOSP})_4$, rt, CH_2Cl_2	50%	0%
3	$\text{Rh}_2(\text{S-DOSP})_4$, rt, 2,2-dimethylbutane	45%	13%
4	$\text{Rh}_2(\text{S-pttl})_4$, rt, CH_2Cl_2	85%	45%
5	$\text{Rh}_2(\text{S-ptad})_4$, rt, CH_2Cl_2	90%	45%
6	$\text{Rh}_2(\text{S-ptpa})_4$, rt, CH_2Cl_2	70%	33%
7	$\text{Rh}_2(\text{S-nttl})_4$, rt, CH_2Cl_2	88%	33%
8	$\text{Rh}_2(\text{S-ntpa})_4$, rt, CH_2Cl_2	86%	33%
9	$\text{Rh}_2(\text{S-nta})_4$, rt, CH_2Cl_2	87%	30%
10	$\text{Rh}_2(\text{S-pttl})_4$, 0°C, CH_2Cl_2	65%	50%
11	$\text{Rh}_2(\text{S-pttl})_4$, -20°C, CH_2Cl_2	61%	50%
12	$\text{Rh}_2(\text{S-pttl})_4$, rt, toluene	78%	45%

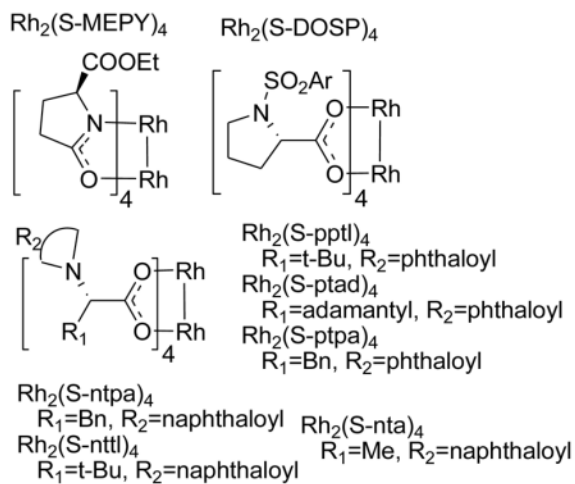
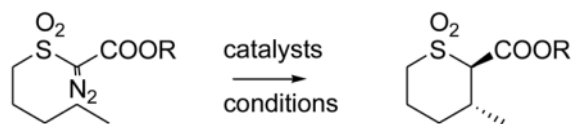


Table 2

Screening of rhodium catalysts



Entry	R	Catalyst and conditions	Yield %	ee or de
1	Me	Rh ₂ (S-pttl) ₄ , rt, CH ₂ Cl ₂	85%	43%
2	<i>i</i> -Pr	Rh ₂ (S-pttl) ₄ , rt, CH ₂ Cl ₂	81%	40%
3	<i>t</i> -Bu	Rh ₂ (S-pttl) ₄ , rt, CH ₂ Cl ₂	32% ^a	45%
5	2,4-dimethylpentyl	Rh ₂ (S-pttl) ₄ , rt, CH ₂ Cl ₂	83%	40%
4	(-)-Menthyl	Rh ₂ (S-pttl) ₄ , rt, CH ₂ Cl ₂	94%	90%
6	(+)-Menthyl	Rh ₂ (S-pttl) ₄ , rt, CH ₂ Cl ₂	82%	-40%
7	(-)-Menthyl	Rh ₂ (OAc) ₄ , rt, CH ₂ Cl ₂	60%	0%