Tetrahedron: *Asymmetry* 24 (2013) 151–155

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

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

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ARTICLE INFO

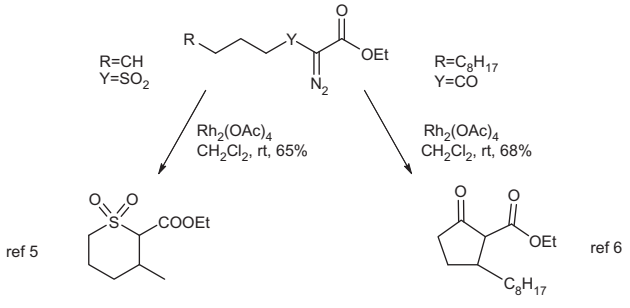
Article history:
Received 26 November 2012
Accepted 11 December 2012

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 (Rh_2(S-pttl)$_4$ and menthyl ester).
Published by Elsevier Ltd.

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]



Scheme 1. C–H insertion on diazosulfones.

After initial studies of this transformation we became interested 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 ees (several other reports of this transformation using the same copper chiral catalyst system are also found[9]). 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 Rh_2(S-MEPY)$_4$ and Rh_2(S-DOSP)$_4$ resulted in no selectivity. The use of a non-polar solvent (2,2-dimethylbutane) with Rh_2(S-DOSP)$_4$ catalyst[10] provided the first glimpse of selectivity, 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 Rh_2(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 Rh_2(S-ptad)$_4$,[12] Rh_2(S-nttl)$_4$), Rh_2(S-ptpa)$_4$, and Rh_2(S-nta)$_4$). All modifications failed to increase the enantioselectivity when compared to Rh_2(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.

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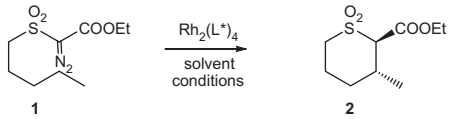
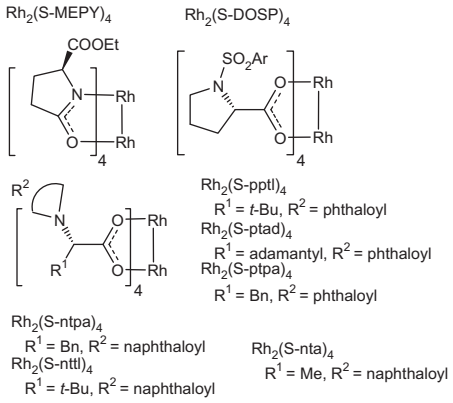
0957-4166/$ - see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetasy.2012.12.002

Table 1
Screening of rhodium catalysts



1 2

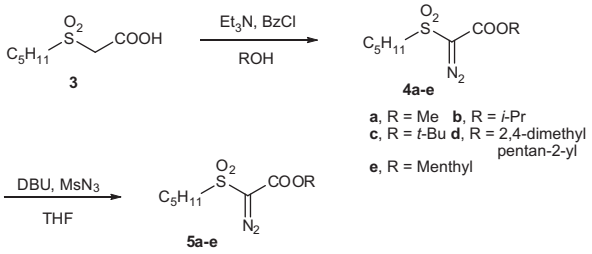
Entry	Catalyst, conditions	Yield (%)	ee (%)
1	Rh_2(S-MEPY)$_4$, 80 °C, $(CH_2Cl)_2$	55	0
2	Rh_2(S-DOSP)$_4$, rt, CH_2Cl_2	50	0
3	Rh_2(S-DOSP)$_4$, rt, 2,2-dimethylbutane	45	13
4	Rh_2(S-pttl)$_4$, rt, CH_2Cl_2	85	45
5	Rh_2(S-ptad)$_4$, rt, CH_2Cl_2	90	45
6	Rh_2(S-ptpa)$_4$, rt, CH_2Cl_2	70	33
7	Rh_2(S-nttl)$_4$, rt, CH_2Cl_2	88	33
8	Rh_2(S-ntpa)$_4$, rt, CH_2Cl_2	86	33
9	Rh_2(S-nta)$_4$, rt, CH_2Cl_2	87	30
10	Rh_2(S-pttl)$_4$, 0 °C, CH_2Cl_2	65	50
11	Rh_2(S-pttl)$_4$, −20 °C, CH_2Cl_2	61	50
12	Rh_2(S-pttl)$_4$, rt, toluene	78	45



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).

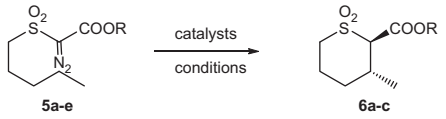
As a result, we resorted to using a chiral auxiliary on the ester. The very first attempt using (−)-menthol as an auxiliary resulted in a sharp increase in selectivity. This is notably different from the cyclization of a similar diazoacetoacetate substrate to cyclopentanone,[13] where the effect of menthyl 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 toward the other enantiomer, suggesting the auxiliary



3 4a-e 5a-e

Scheme 2. Preparation of esters.

Table 2
Screening of rhodium catalysts

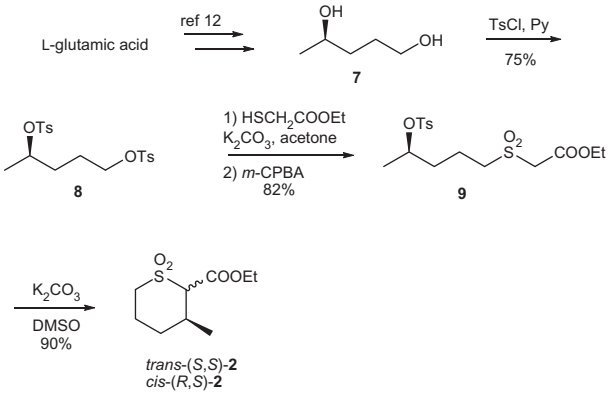


5a-e 6a-c

Entry	R	Catalyst and conditions	Yield (%)	ee or de (%)
1	Me	Rh_2(S-pttl)$_4$, rt, CH_2Cl_2	85	43
2	*i*-Pr	Rh_2(S-pttl)$_4$, rt, CH_2Cl_2	81	40
3	*t*-Bu	Rh_2(S-pttl)$_4$, rt, CH_2Cl_2	32	45
5	2,4-dimethylpentyl	Rh_2(S-pttl)$_4$, rt, CH_2Cl_2	83	40
4	(−)-Menthyl	Rh_2(S-pttl)$_4$, rt, CH_2Cl_2	94	90
6	(+)-Menthyl	Rh_2(S-pttl)$_4$, rt, CH_2Cl_2	82	−40
7	(−)-Menthyl	$Rh_2(OAc)_4$, rt, CH_2Cl_2	60	0

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



7 8 9

Scheme 3. Synthesis of enantiopure **2**.

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 S_N2 substitution, along with a *cis*-isomer (*R*,*S*)-**2**. The configuration of the product was assigned as (2*S*,3*S*), 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 of 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 5 mM ammonium formate. Melting points were determined on a MEL-TEMP melting point apparatus. Flash column chromatography was performed using 40–63 μm 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 h 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 (3×10 mL), diluted with 20 mL of 1 M HCl, and extracted with ethyl acetate (3×20 mL). The ethyl acetate extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **3** (570 mg, 91%) as a white crystalline powder that was used without further purification. Mp 78–79 °C. ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0(C), 57.3(CH_2), 54.0(CH_2), 30.6(CH_2), 22.3(CH_2), 21.7(CH_2), 13.9(CH_3). HRMS (ESI) calcd for $C_7H_{18}O_4NS$ $[M+NH_4]^+$ 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 Et_3N (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 h (TLC analysis revealed that the reaction was complete). The reaction mixture was diluted with EtOAc (40 mL) and washed with water (3×30 mL). 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 purified by flash chromatography on a silica gel column using EtOAC–Hexanes (0:1–1:9).

4.3.1. Methyl 2-(pentylsulfonyl)acetate 4a

^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.8(C), 57.4(CH_2), 53.7(CH_2), 53.5(CH_3), 30.6(CH_2), 22.3 (CH_2), 21.7(CH_2), 13.9(CH_3). HRMS (ESI) calcd for $C_8H_{17}O_4S$ $[M+H]^+$ 209.0842, found 209.0848.

4.3.2. Isopropyl 2-(pentylsulfonyl)acetate 4b

^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.8(C), 70.9(CH), 57.8(CH_2), 53.7(CH_2), 30.6(CH_2), 22.3(CH_2), 21.7(CH_2), 21.8(CH_3), 13.9(CH_3). HRMS (ESI) calcd for $C_{10}H_{21}O_4S$ $[M+H]^+$ 237.1160, found 237.1158.

4.3.3. *tert*-Butyl 2-(pentylsulfonyl)acetate 4c

^{1}H 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 $C_{11}H_{26}O_4NS$ $[M+NH_4]^+$ 268.1582, found 268.1588.

4.3.4. 2,4-Dimethylpentan-3-yl 2-(pentylsulfonyl)acetate 4d

^{1}H 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 $C_{14}H_{32}NO_4S$ $[M+NH4]^+$ 310.2052, found 310.2054.

4.3.5. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(pentylsulfonyl)acetate 4e

$[\alpha]_D^{20} = -45.9$ (c 0.035, $CHCl_3$). ^{1}H 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 $C_{17}H_{36}NO_4S$ $[M+NH_4]^+$ 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. Mesyl 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 h, while maintaining the temperature at −45 °C, after which it was warmed up to room temperature over a 15–20 min interval. The mixture obtained was poured over 20 mL of a half-saturated $(NH_4)_2SO_4$ solution, extracted with CH_2Cl_2 (3×20 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 (0:1–1:9).

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

4.4.1. Methyl 2-(pentylsulfonyl)diazoacetate 5a

^{1}H 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.

4.4.2. Isopropyl 2-(pentylsulfonyl) diazoacetate 5b

^{1}H 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.

4.4.3. *tert*-Butyl 2-(pentylsulfonyl) diazoacetate 5c

^{1}H 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.

4.4.4. 2,4-Dimethylpentan-3-yl 2-(pentylsulfonyl)diazoacetate 5d

^{1}H 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.

4.4.5. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(pentylsulfonyl)diazoacetate 5e

$[\alpha]_D^{20} = -56.5$ (c 0.021, $CHCl_3$). ^{1}H 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.

4.4.6. (1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl 2-(pentylsulfonyl)diazoacetate [enantiomer of 5e, from (+)-menthol]

Spectroscopic data identical to **5e**. $[\alpha]_D^{20} = +54.7$ (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 h via syringe pump. The resulting mixture was stirred at room temperature for 12 h 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.

4.5.1. *trans*-Ethyl tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-carboxylate 2

The data matched that previously reported.[3]

4.5.2. *trans*-Methyl tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-carboxylate 6a

^{1}H 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(CH3), 52.0(CH_2), 34.5(CH), 32.0(CH2), 22.9(CH_2), 20.0(CH_3). HRMS (ESI) calcd for $C_8H_{15}O_4S$ $[M+H]^+$ 207.0691, found 207.0668.

4.5.3. *trans*-Isopropyl tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-carboxylate 6b

^{1}H 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 $C_{10}H_{22}O_4NS$ $[M+NH_4]^+$ 252.1269, found 252.1390.

4.5.4. *trans-tert*-Butyl tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-carboxylate 6c

^{1}H 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 $C_{11}H_{24}O_4NS$ $[M+NH_4]^+$ 266.1426, found 266.1383.

4.5.5. *trans*-2,4-Dimethylpentan-3-yl tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-carboxylate 6d

^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.1(C), 86.1(CH), 72.9(CH), 52.1(CH_2), 34.3(CH), 32.1(CH_2), 29.7(CH), 29.5(CH), 22.8(CH_2), 20.3(CH_3), 19.8(CH_3), 17.7(CH_3), 17.2(CH_3). HRMS (ESI) calcd for $C_{14}H_{30}NO_4S$ $[M+NH_4]^+$ 308.1895, found 308.1877. Note: accidental equivalence of two methyls at 19.8.

4.5.6. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*R*)-tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-carboxylate 6e

$[\alpha]_D^{20} = -28.7$ (c 0.013, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.5(C), 77.4(CH), 73.1(CH), 52.1(CH_2), 46.9(CH), 40.6(CH_2), 34.4(CH), 34.4(CH_2), 32.1(CH_2), 31.7(CH), 26.2(CH), 23.3(CH_2), 22.9(CH_2), 22.1(CH_3), 21.0(CH_3), 19.8(CH_3), 16.1(CH_3). HRMS (ESI) calcd for $C_{17}H_{34}NO_4S$ $[M+NH_4]^+$ 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 CH_2Cl_2 (2.5 mL/mmol) was added DIBALH (2.2 equiv) and the resulting mixture stirred at room temperature for 12 h. 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 CH_2Cl_2 (3 × 5 mL) and then EtOAc (5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford a crude product, which was purified by flash chromatography using EtOAC–Hexanes (1:4–1:1).

4.6.1. *trans*-(Tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-yl)methanol 10

Mp 94–95 °C. ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 68.4(CH), 56.2(CH_2), 52.2(CH_2),

33.3(CH_2), 31.8(CH), 23.1(CH_2), 19.1(CH_3). HRMS (ESI) calcd for $C_7H_{15}O_3S$ $[M+H]^+$ 179.0741, found 179.0746.

4.6.2. ((2*R*,3*R*)-Tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-yl)methanol (*R*,*R*)-10

Obtained by reduction of **6e**: $[\alpha]_D^{20} = -16.7$ (*c* 0.005, $CHCl_3$).

4.6.3. ((2*S*,3*S*)-Tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-yl)methanol (*S*,*S*)-10

Obtained by reduction of (*S*,*S*)-**2**: $[\alpha]_D^{20} = +14.1$ (*c* 0.004, $CHCl_3$).

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 CH_2Cl_2 (2.5 mL/mmol). The resulting solution was stirred at room temperature for 30 min, 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 h. The reaction mixture was taken up in EtOAc (50 mL), washed with 1 M HCl (2 × 10 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 ^{1}H NMR analysis without further purification to determine the diastereomeric ratio. The enantioselectivity or diastereoselectivity was measured by integration of the diastereomeric signals (CH-C*H*$_2$-O-CO, C*H*$_3$-CH, Ph-C*H*(OAc)-CO) in the ^{1}H 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 1 M 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%). $[\alpha]_D^{20} = +15.1$ (*c* 0.023, $CHCl_3$). ^{1}H 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 $C_{19}H_{28}NO_6S_2$ $[M+NH_4]^+$ 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 18 h, 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%). $[\alpha]_D^{20} = +14.1$ (*c* 0.017, $CHCl_3$). ^{1}H 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 $C_{16}H_{28}NO_7S_2$ $[M+NH_4]^+$ 410.1301, found 410.1315.

4.10. Preparation of ethyl (2*S*,3*S*)-tetrahydro-3-methyl-2*H*-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 (2 × 10 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]

4.10.1. Ethyl (2*S*,3*S*)-tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-carboxylate (*S*,*S*)-2

$[\alpha]_D^{20} = +32.5$ (*c* 0.005, $CHCl_3$).

4.10.2. Ethyl (2*R*,3*S*)-tetrahydro-3-methyl-2*H*-thiopyran-1,1-dioxide-2-carboxylate (*R*,*S*)-2

$[\alpha]_D^{20} = -36.8$ (*c* 0.003, $CHCl_3$).

Acknowledgments

This work was supported by the National Institutes of Health under Grant No. GM085645. We thank Alena Kubatova for HRMS analyses. The work on TOF MS was supported by the National Foundation under Grant No. CHE-0216038.

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