Pergamon

Tetrahedron 58 (2002) 207–213

TETRAHEDRON

Asymmetric conjugate additions to chiral α,β-unsaturated oxazolines with sulfonyl carbanions

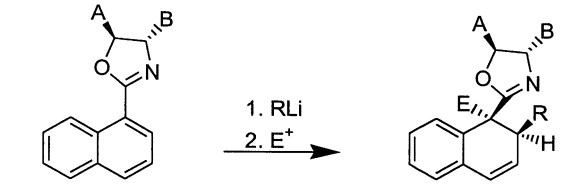
Laura F. Basil,[a] A. I. Meyers[a,*] and A. Hassner[b]

[a]*Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA*
[b]*Department of Chemistry, Bar Ilan University, Ramat-Gan 52990, Israel*

Received 30 August 2001; revised 30 October 2001; accepted 15 November 2001

Abstract—Addition of sulfonyl carbanions with or without an electrophilic tether has been shown, under certain conditions, to add to α,β-unsaturated oxazolines in good yields and high de's. When 4-bromobutylsulfonyl carbanions are added to unsaturated oxazolines, three contiguous stereocenters are formed and good yields of 1,2,3-substituted cyclohexanes are obtained as a 5:1 mixture of only two diastereomers. The sulfonyl substituent may be reductively cleaved to form selectively 1,2-disubstituted cyclohexanes. © 2002 Published by Elsevier Science Ltd.

Over the years, chiral α,β-unsaturated oxazolines have been utilized as Michael acceptors with the oxazoline moiety exerting high stereocontrol over the newly formed stereocenters. Examples have been reported using naphthyl, cinnamyl, and alkyl conjugated systems.[1] For instance, when a variety of organolithiums were added to 1-naphthyl oxazolines (**1** and **1a**) followed by addition of an external electrophile, the resulting tandem addition products were obtained in good yield with high de's[1a,b] (Scheme 1).

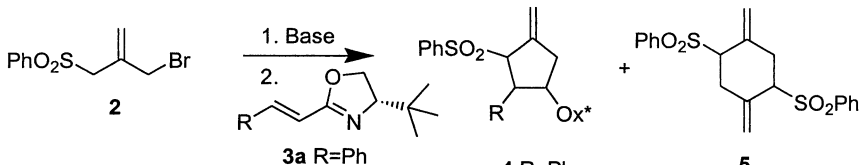


1 A=Ph, B=MeOCH$_2$
1a A=H, B= *t*-Bu

Scheme 1.

Recently, one of us[2] has observed interesting conjugate additions with allylic sulfonyl carbanions to achiral cyclic and acyclic enones. Products were obtained in good chemical yields with excellent relative stereoselectivity. While conjugate additions with highly reactive organolithiums to chiral oxazolines are well precedented,[1a,c] addition with more stabilized carbanions (e.g. sulfonyl carbanions), have, to date, not been studied. In light of earlier results, we decided to explore sulfonyl carbanion additions using chiral α,β-unsaturated oxazolines with the intention of obtaining control of absolute stereochemistry.

Initial results using the allylic sulfonyl carbanion **2**[2a] were interesting though not synthetically useful. After much experimental manipulation, the yield of **4** using the styryl oxazoline **3a**[1c] was never greater than 25%. The best conditions involved forming the sulfonyl carbanion (1.4 equiv. in THF) with LDA (1.2 equiv.) at −95°C followed by addition of the oxazoline (1.0 equiv. in THF) then HMPA (4.3 equiv.). The reaction was allowed to proceed at −95°C for 1 h, then warmed to −78°C and quenched with saturated



2

3a R=Ph
3b R=CH$_3$

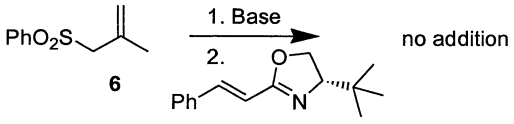
4 R=Ph
~25% yield
6:1 d.r.

5

Scheme 2.

Keywords: Michael additions; pK_a of sulfonylmethylenes and unsaturated oxazolines; chiral β-substituted carboxylic acids.
* Corresponding author. Tel.: +1-970-491-6897; fax: +1-970-491-2114; e-mail: aimeyers@lamar.colostate.edu

0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(01)01151-6



Scheme 3.

aqueous NH_4Cl solution. Interestingly, only two of the possible eight diastereomers were observed, consistent with previous results,[2] with the major being favored by 6:1 (determined by GC/MS). No addition was seen with the 2-propenyl oxazoline **3b**.[3] Not surprisingly, due to the reactivity of the allylic bromide, sulfone self-cyclization to **5** was found to be a competing process (Scheme 2).

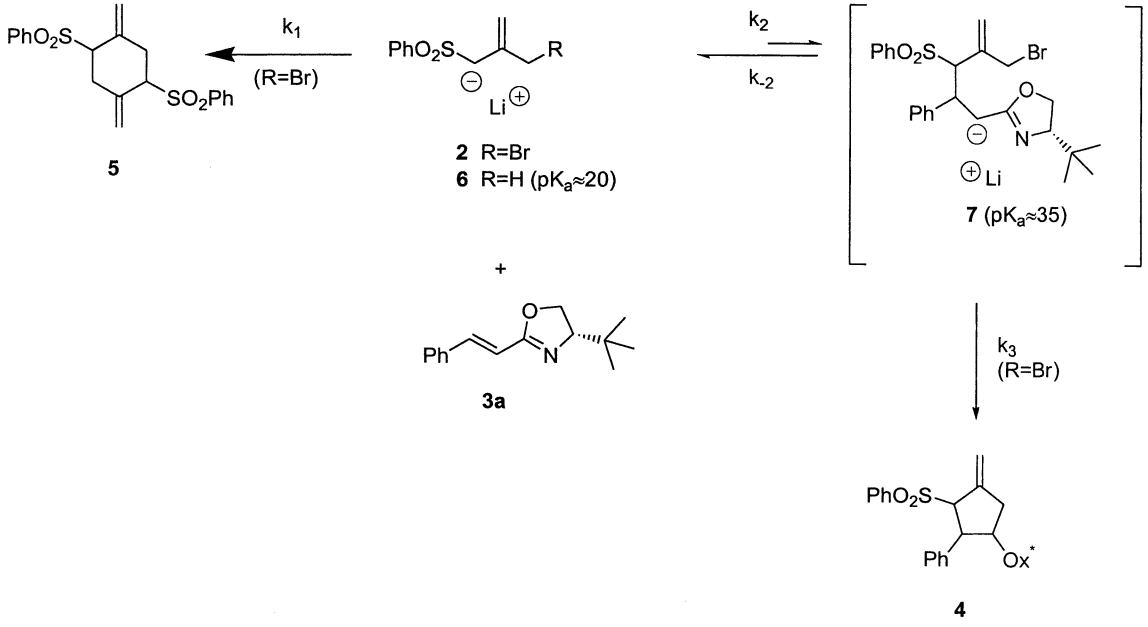
In order to circumvent the formation of **5**, the debromo-allylic sulfone **6**[2a] was employed, but no addition to the oxazoline **3a** was observed (Scheme 3).

This unexpected lack of addition led us to reexamine the reaction partners. The pK_a of a C–H that is both allylic and adjacent to a sulfone is in the low 20s,[4] while the pK_a of a C–H next to an oxazoline is generally assumed to be in the mid-30s. From these relative acidities it is reasonable to assume that addition should not be a favored process. When intramolecular self-cyclization becomes an option (cf. **2**), the small amount of addition product formed can be funneled on to oxazoline adduct **4**. However, when self-cyclization is not an option, as with the sulfone **6**, the reversal of the intermediate **7** is highly favored to return to **3a** and **b** and no addition process can occur. In this case where **2** is employed, most of the sulfonyl anion will be shunted off to dimerization to give **5** (Scheme 4).

To increase the efficiency of addition, the less acidic alkyl sulfone **8** was utilized. Since the pK_a of a C–H α to a sulfone[4] is ca. 30 and closer to that of the oxazoline anion, it should be reasonable to expect to force the equilibrium toward product. When an excess of the sulfone **8** was added to the oxazoline **3a**, a respectable yield of addition product was observed, and only one diastereomer was detected, indicating that the addition took place with high stereoselectivity (Table 1, entry 1). The synthesis of the α,β-unsaturated oxazolines (**3a–f**) were readily achieved with high *trans* selectivity by previously described procedures.[1c] Interestingly, if the reaction mixture was quenched at −78°C, only the adduct **9** was seen, yet if the reaction solution was allowed to warm (−50°C) before quenching, only starting materials were observed, further supporting the reversibility of the process. Other α,β-unsaturated oxazolines were examined and the mixed results obtained are summarized in Table 1. It seems that electron donating groups (at the vinylic position of the α,β-unsaturated oxazolines) on the oxazolines lead to poor yields of product (entries 3, 4) whereas electron withdrawing groups are much more efficient (entries 1, 2, 5), accompanied by excellent diastereoselectivities (>20:1).

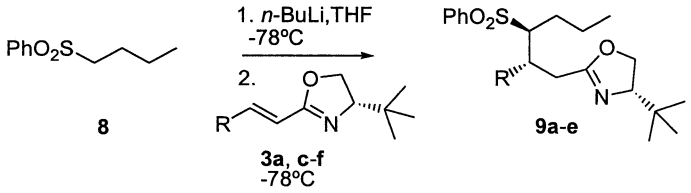
From earlier work,[2] the sulfonyl anion additions to electrophilic olefins occur with high *anti* selectivity (as drawn in adduct **9**). The structures were determined by nOe NMR studies on both cyclic and acyclic addition products. NOESY data on adduct **9a** supported *anti* addition with the oxazoline systems (Fig. 1). There was a strong nOe correlation between the H_a methylene protons (2.7 and 3.5 ppm, benzene-d_6, 500 MHz) and the H_b methylene protons (1.6 and 2.0 ppm, benzene-d_6, 500 MHz) which should not be observable with the *syn* isomer.

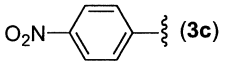
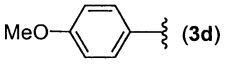
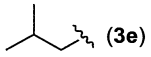
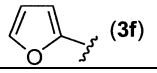
Additions were also carried out with the 4-bromobutyl sulfone **10** to form the cyclohexyl oxazolines, **11** and **12**. As observed with the previously described cyclopentyl oxazoline **4**, only two of the eight possible diastereomers were formed with the major one favored by at least 5:1. Also, in this instance, the chemical yield of the cyclohexyl derivatives was higher. After many experimental variations were examined, the optimum conditions appeared to be the formation of the sulfone anion in THF at −78°C with



Scheme 4.

Table 1. Addition of alkyl sulfonyl carbanions to chiral α,β-unsaturated oxazolines



Entry	R	Product	Conditions[a]	Yield (%)	d.r.[b]
1	Ph (**3a**)	**9a**	A	72[c]	>96:4
2	 (**3c**)	**9b**	B	78[c]	96:4
3	 (**3d**)	**9c**	A	20[d]	–
4	 (**3e**)	**9d**	A	10[d]	–
5	 (**3f**)	**9e**	A	70[d]	>96:4

[a] (A) To a solution of **8** (5 equiv.), containing *n*-BuLi (4.5 equiv.) in THF was added **3**. The reaction stirred at −78°C for 30 min, then quenched with 2-propanol. (B) To a solution of **8** (1.2 equiv.), containing *n*-BuLi (1.0 equiv.) in THF was added **3**. Upon addition of **3**, the reaction was quenched immediately with 2-propanol.
[b] Based on NMR and GC/MS data.
[c] Isolated yield.
[d] GC yield.

5 equiv. of sulfone **10** and 4.5 equiv. LTMP as the base, followed by addition of the oxazoline **3a**. After stirring the reaction for 16 h at −78°C, the cyclized products **11** and **12** were isolated in 67% combined yield. The separation of **11** and **12** was readily accomplished, and the structure of the major adduct **11** was determined by X-ray crystallography. The major diastereomer possessed, as expected, all its substituents *trans* to each other and equatorially disposed. As was observed with **9a**, the initial addition yielded the *anti* adduct. Desulfonylation[5] of **11** and **12** produced distinctly different diastereomers. Along with the X-ray structures, this further supported the notion that the sulfonyl carbon stereocenters were identical in **11** and **12** and that cyclization with bromide displacement had occurred from different faces. Moreover, comparison of the ^{1}H NMR (300 MHz) spectra of the desulfonylated compounds showed that the phenyl ring and the oxazoline moiety were *cis* to each other in the minor adduct **12** (Scheme 5).

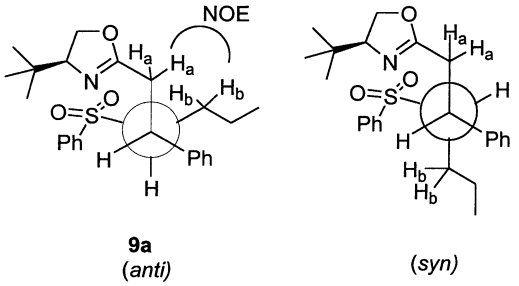
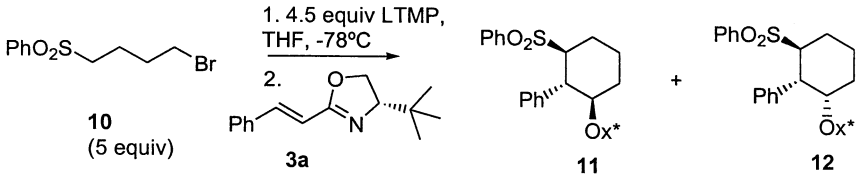


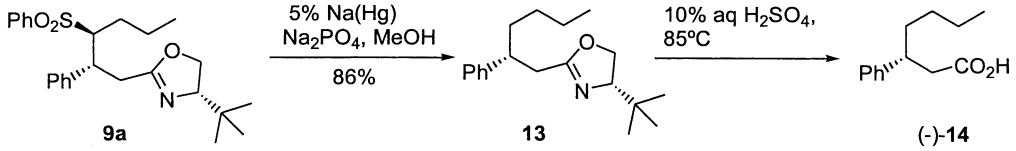
Figure 1.

When adducts **11** and **12** were separately resubjected to either sulfone anion **10** or to NaOMe, no change in diastereomeric composition of **11** and **12** occurred. This indicated that the observed diastereomeric ratio found is not due to equilibration during the reaction conditions, and that the products are kinetically formed.

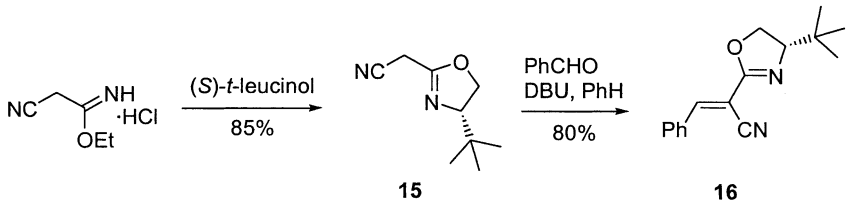
As the cyclization step was responsible for the loss of stereoselectivity, it was felt that by slowing the rate of ring closure, the diastereoselectivity might be increased. To this end, the less reactive 4-chloro analog of the halo sulfone **10** was investigated. Unfortunately, not only was the ring closure not improved, but also the initial addition step by the sulfonyl anion was no longer selective. It is conceivable that the solution structure of the sulfonyl anion had dramatically changed in the presence of the chloride, which may be complexed with Li ion.[2d]



Scheme 5.



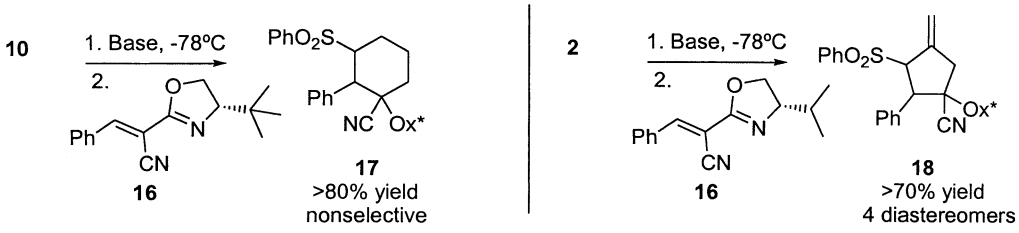
Scheme 6.



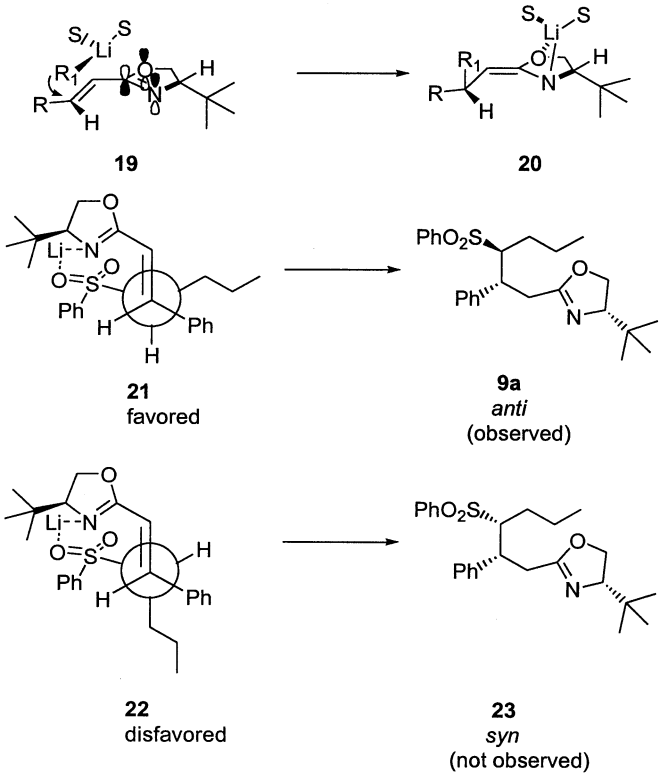
Scheme 7.

Reductive desulfonylation of the addition products **9a**, **11**, and **12** proceeded well using 5% Na(Hg).[5] Once desulfonylated, the oxazoline moiety of **13** was hydrolyzed to the known carboxylic acid, **14**.[6] Comparison of optical rotation of **14** with the literature value supported the absolute stereochemistry shown ([α]=21 (*c* 1, $CHCl_3$); lit.[6]: [α]=23, neat) (Scheme 6).

Further studies were initiated in an attempt to enhance the reactivity of the Michael acceptor. To this end, oxazoline **16**



Scheme 8.



Scheme 9.

was prepared containing a cyano group adjacent to the oxazoline. The synthesis of **16** was achieved by first condensing (*S*)-*t*-leucinol with the ethyl imidate of malononitrile, and followed with a base-catalyzed condensation with benzaldehyde. This sequence furnished a single olefin isomer **16** in an overall yield of 68% (Scheme 7).

The anion, which should develop α to the cyano-oxazoline during Michael addition, is now a much weaker base than the previously mentioned alkyl sulfone **6**. When the addition reaction was undertaken, the starting oxazoline **16** was consumed very quickly both by the 4-bromobutyl sulfone anion of **10** and by the allylic sulfone anion **2**. Not surprisingly, the reactions leading to **17** and **18** were found to be non-stereoselective. Due to the poor selectivity observed for **17** and **18**, no experimental details are included in this report. Thus, another example has been presented where comparing the relative pK_a's of the nucleophile and the addition product predicted feasibility of the reaction. Therefore, adjusting the reversibility to maximize the rate of product formation (via pK_a values) can lead to a process which is: 'too successful' where the delicate balance of stereochemistry will suffer (Scheme 8).

The high stereoselectivity observed by these successful conjugate additions (**9a**, **9b**, **9e**, **11**) are consistent with the previously described rationale.[1c] Thus, complexation of the solvated lithium cation with the π-cloud of the Michael acceptor **19** may occur on the face *anti* to the bulky *t*-butyl group, leading to **20** by addition to the β face. In addition, since more than one stereocenter is being created in this process the selectivity of the newly formed center adjacent to the sulfone appears to be quite high. This is in agreement with the model proposed for kinetically-controlled Michael additions by Seebach and Golinski.[7] In this model, the donor–acceptor π-systems prefer a *gauche* relationship to each other, with the H-atom of the donor in an antiperiplanar orientation to the π-system of the acceptor (as shown in **21**). The former (**21**) is more stereoelectronically favored than the alternative approach model **22**. The stereochemistry of the products we obtained are in agreement with the Seebach model, as seen by the NOE of the α-methylene of the propyl group and the α-methylene in the 2-position of the oxazoline in **9a**. Thus, the proximity of propyl group to the 2-methylene protons, as seen in **21**, supports the stereochemistry (Scheme 9).

In conclusion the conjugate addition of sulfonyl carbanions to chiral α,β-unsaturated oxazolines can occur with very high diastereoselectivity when the appropriate substituents are present. In the examples where cyclization followed the addition step, this produced three contiguous stereocenters formed selectively in one reaction. When the pK_a of both partners are matched appropriately, the addition is not only very stereochemically efficient but also synthetically practical.

1. Experimental

Alkyl sulfones **8** and **10** were synthesized according to procedures set forth by Crandall and Pradat.[8]

1.1. Synthesis of *trans* α,β-unsaturated oxazolines

New compounds **3c–f** were synthesized by the procedure outlined by Shipman and Meyers[1c] and physical data are described later.

1.1.1. (4*S*)-*tert*-Butyl-2-((*E*)-2-(4-nitrophenyl)ethenyl)-oxazoline, 3c. From *para*-nitrobenzaldehyde, 52% as a yellow solid mp=97–99°C; $[\alpha]^{25}_D=-81.6$ (*c* 1.5; $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 9H), 4.01 (dd, *J*=10.2, 8.1 Hz, 1H), 4.15 (app t, *J*=8.4 Hz, 1H), 4.3 (dd, *J*=9.9, 8.4 Hz, 1H), 6.79 (d, *J*=16.2 Hz, 1H), 7.34 (d, *J*=16.2 Hz, 1H), 7.6 (d, *J*=8.7 Hz, 1H), 8.22 (d, *J*=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8, 33.8, 68.5, 76.3, 119.6, 124.1, 127.8, 136.8, 141.5, 147.8, 162.2; IR (neat) 1652, 1610, 1530, 1346 cm^{-1}; HRMS (FAB+) for $C_{15}H_{19}N_2O_3$ $(M+H)^+$: Calcd 275.1397 Found 275.1394.

1.1.2. (4*S*)-*tert*-Butyl-2-((*E*)-2-(4-methoxyphenyl)ethenyl)-oxazoline, 3d. From *para*-anisaldehyde, 51% yield as a light yellow powder mp=82–84°C; $[\alpha]^{25}_D=-74.8$ (*c*1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 9H), 3.82 (s, 3H), 3.97 (dd, *J*=9.9, 7.8 Hz, 1H), 4.12 (app t, *J*=8.4 Hz, 1H), 4.26 (dd, *J*=10.2, 8.4 Hz, 1H), 6.54 (d, *J*=16.2 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=16.2 Hz, 1H), 7.42 (d, *J*=8.4 Hz, 2H); *m/z* 259 $(M)^+$, 202 $(M-57\ (t\text{-Bu}))^+$.

1.1.3. (4*S*)-*tert*-Butyl-2-((*E*)-(4-methylpentenyl)-oxazoline, 3e. From isovaleraldehyde, 62% yield as an opaque oil $[\alpha]^{25}_D=-16.5$ (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (br s, 12H), 0.92 (s, 3H), 1.72 (sept., *J*=6.6 Hz, 1H), 2.06 (t, *J*=7.5 Hz, 2H), 3.89 (dd, *J*=9.9, 8.1 Hz, 1H), 4.04 (dd, *J*=8.4, 8.4 Hz, 1H), 4.19 (dd, *J*=9.9, 8.6 Hz, 1H), 5.99 (d, *J*=15.9 Hz, 1H), 6.51 (ddd, *J*=15.2, 7.2, 7.2 Hz, 1H); HRMS (FAB+) for $C_{13}H_{24}NO$ $(M+H)^+$: Calcd 210.1858 Found 218.1863.

1.1.4. (4*S*)-*tert*-Butyl-2-((*E*)-2-(2-furanyl)ethenyl)-oxazoline, 3f. From 2-furaldehyde, 44% yield as a yellow solid which darkens over time mp=74–76°C; $[\alpha]^{25}_D=-83$ (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (s, 9H), 3.97 (dd, *J*=10.2, 7.8 Hz, 1H), 4.1 (app t, *J*=8.1 Hz, 1H), 4.24 (dd, *J*=9.9, 8.4 Hz, 1H), 4.24 (dd, *J*=9.9, 8.4 Hz, 1H), 6.41–6.48 (m, 1H), 6.55 (d, *J*=16.2 Hz, 1H), 7.08 (d, *J*=16.2 Hz, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.9, 33.9, 68.2, 76.3, 111.8, 112.3, 113.2, 126.4, 143.8, 151.4, 162.8; IR (film) 1652, 1624, 981, 967 cm^{-1}; HRMS (FAB+) for $C_{13}H_{18}NO_2$ $(M+H)^+$: Calcd 220.1338 Found 220.1328.

1.2. General procedure for addition of sulfone 8 to α,β-unsaturated oxazolines

Method A: To a solution of **8** (2 mmol) in 5 ml dry THF at −78°C was added *n*-butyllithium (2 M in hexanes, 1.8 mmol). The bright yellow solution was stirred for 15 min at −78°C and the oxazoline (0.4 mmol, dried azeotropically with toluene) was added in 2 ml THF. A dark red color soon followed and, after stirring for 20 min at −78°C, the reaction was quenched with 2-propanol. The solution was allowed to warm to room temperature, and then was diluted with H_2O (15 ml). The mixture was extracted with

EtOAc (3×30 ml), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (5% EtOAC/hexanes–20% EtOAC/hexanes).

Method B: To a solution of **8** (0.48 mmol) in 5 ml dry THF at −78°C was added *n*-butyllithium (2 M in hexanes, 0.4 mmol). The bright yellow solution was stirred for 15 min at −78°C and the oxazoline (0.4 mmol, dried azeotropically from toluene) was added in 2 ml THF. A dark red color soon followed and the reaction was quenched with 2-propanol within 5 min. The remainder of the procedure was identical to method A.

1.2.1. (4*S*)-*tert*-Butyl-2-((2*R*,3*S*)-2-phenyl-3-phenylsulfonylhexyl)-oxazoline, 9a. From oxazoline **3a**,[1c] method A, 72% isolated yield as a viscous, colorless oil $[\alpha]^{25}_D$=−13.8 (*c* 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.5–2.0 (m, 16H), 2.88 (dd, *J*=15, 11 Hz, 1H), 3.16 (dd, *J*=15, 4.5 Hz, 1H), 3.25 (ddd, *J*=4.5, 4.5, 3 Hz, 1H), 3.65 (ddd, *J*=10.5, 9, 1.5 Hz, 1H), 3.83–3.96 (m, 3H), 7.15–7.25 (m, 5H), 7.6 (dd, *J*=7.8, 7.8 Hz, 2H), 7.65 (d, *J*=7.2 Hz, 1H), 7.9 (d, *J*=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 21.4, 25.6, 26.3, 27.1, 33.4, 40.2, 68.9, 75.5, 126.9, 128.4, 128.6, 129.1, 133.5, 139, 140, 164.8; IR (neat) 1668 cm^{-1}; HRMS (FAB+) for $C_{25}H_{34}NO_3S$ $(M+H)^+$: Calcd 428.2259 Found 428.2266.

1.2.2. (4*S*)-*tert*-Butyl-2-((2*R*,3*S*)-2-(4-nitrophenyl)-3-phenylsulfonylhexyl)-oxazoline, 9b. From oxazoline **3c**, method B, 78% isolated yield as a colorless oil $[\alpha]^{25}_D$=−15 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.6–0.7 (m, 12H), 1.15–1.28 (m, 2H), 1.85–2.10 (m, 2H), 3.19 (dd, *J*=13.5, 11.4 Hz, 1H), 3.38–3.49 (m, 3H), 3.7 (app t, *J*=8.4 Hz, 1H), 3.82 (app t, *J*=8.7 Hz, 1H), 4.03 (dd, *J*=10.2, 8.7 Hz, 1H), 7.47 (d, *J*=9 Hz, 2H), 7.59 (app t, *J*=7.5 Hz, 2H), 7.66–7.71 (m, 1H), 7.95 (d, *J*=8 Hz, 2H), 8.10 (d, *J*=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 21.6, 25.8, 26.9, 32.2, 33.3, 39.8, 65.2, 68.7, 75.8, 123.2, 128.3, 129.3, 130.3, 133.9, 138.9, 146.5, 147.8, 164.6; IR (neat) 1667, 1520 cm^{-1}; HRMS (FAB+) for $C_{25}H_{32}N_2O_5S$ $(M+H)^+$: Calcd 473.2112 Found 473.2095.

1.2.3. (4*S*)-*tert*-Butyl-2-((2*R*,3*S*)-2-(2-furyl)-3-phenylsulfonylhexyl)-oxazoline, 9e. From oxazoline **3f**, method A, 70% isolated yield as a light yellow oil $[\alpha]^{25}_D$=−16.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67 (t, *J*=7.2 Hz, 3H), 0.78 (s, 9H), 1.11–1.25 (m, 2H), 1.62–1.99 (m, 2H), 2.76 (dd, *J*=15.3, 11.1 Hz, 1H), 3.16 (d, *J*=14.1 Hz, 1H), 3.47 (ddd, *J*=10, 3.3, 3.3 Hz, 1H), 3.74 (app t, *J*=8.4 Hz, 1H), 3.93–4.07 (m, 3H), 6.15 (d, *J*=3.3 Hz, 1H), 6.21 (br s, 1H), 7.21 (s, 1H), 7.53–7.67 (m, 3H), 7.93 (d, *J*=6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 21.1, 25.8, 26.6, 26.7, 33.7, 35.0, 65.9, 68.7, 75.7, 107.4, 110.5, 128.9, 129.3, 133.8, 138.8, 141.6, 153.4, 164.9; HRMS (FAB+) for $C_{23}H_{31}NO_4S$ $(M+H)^+$: Calcd 418.2052 Found 418.2056.

1.3. Cyclohexyl oxazolines 11 and 12

The sulfone **10** and the oxazoline **3a** were dried azeotropically prior to use. To a solution of tetramethylpiperidine (0.86 mmol, 150 μl) in 2.5 ml dry THF at −78°C was added *n*-butyllithium (2 M in hexane, 0.4 ml, 0.77 mmol) and the solution was stirred for 20 min. Sulfone **10** (242 mg, 0.86 mmol) in 1.5 ml dry THF was added and the mixture was stirred for 10 min while the reaction turned yellow in color. The oxazoline **3a** (40 mg, 0.17 mmol) in 1 ml THF was added. The reaction was stirred at −78°C and after 16 h, 1 ml MeOH was added. The solvent was removed, and the residue was dissolved in EtOAc (30 ml) and H_2O (15 ml). The EtOAc layer was washed with a phosphate buffer (pH=4) and brine (15 ml each). The EtOAc layer was then dried over Na_2SO_4, filtered, and concentrated. The residue mixture was purified by flash chromatography (10% EtOAc/hexanes and 25% EtOAc/hexanes) yielding 40 mg of **11** (56%) and 18 mg of **12** (11%).

1.3.1. (1*R*,2*R*,3*S*)-1-((4*S*)-4-*tert*-Butyl-2-oxazolinyl)-2-phenyl-3-phenylsulfonylcyclohexane, 11. Colorless needles (recrystallized from EtOH); mp=183–185°C; $[\alpha]^{25}_D$=−102 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.66 (s, 9H), 1.44–1.82 (m, 3H), 1.94–2.16 (m, 2H), 2.46–2.54 (m, 1H), 2.61 (ddd, *J*=11.4, 11.4, 3.3 Hz, 1H), 3.3 (dd, *J*=11.4, 11.4 Hz, 1H), 3.38 (ddd, *J*=7.5, 7.5, 7.5 Hz, 1H), 3.47 (ddd, *J*=11.4, 11.4, 3.3 Hz, 1H), 3.76 (dd, *J*=8.7, 8.7 Hz, 1H), 3.81 (dd, *J*=7.2, 7.2 Hz, 1H), 6.94 (br s, 5H), 7.17 (dd, *J*=9, 6 Hz, 2H), 7.32 (d, *J*=8.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8, 26.4, 26.5, 31.4, 323.4, 46.7, 47.8, 68, 69.1, 76.1, 128, 128.8, 128.9, 129.5, 130, 133.3, 139.5, 141, 168. This sample was subjected to single crystal X-ray determination, and the data deposited with the Cambridge Crystallographic Data Center.

1.3.2. (1*S*,2*R*,3*S*)-1-((4*S*)-4-*tert*-Butyl-2-oxazolinyl)-2-phenyl-3-phenylsulfonylcyclohexane, 12. Colorless solid; mp=164–167°C; $[\alpha]^{25}_D$=+33 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.38 (s, 9H), 1.42–1.84 (m, 3H), 1.95–2.0 (m, 1H), 2.07–2.14 (m, 1H), 2.5–2.55 (m, 1H), 2.69 (ddd, *J*=11.7, 11.7, 3.3 Hz, 1H), 3.3 (dd, *J*=11.4, 11.4 Hz, 1H), 3.47 (ddd, *J*=12, 12, 3.6 Hz, 1H), 3.54–3.64 (m, 2H), 3.92–4.02 (m, 1H), 6.93 (br s, 5H), 7.18 (dd, *J*=7.8, 7.8 Hz, 2H), 7.3–7.37 (m, 3H); Anal. Calcd for $C_{25}H_{31}NO_3S\cdot 1/2H_2O$: C, 69.09; H, 7.42. Found: C, 69.24; H, 7.30.

1.4. Desulfonylation of 11 and 12

Following the procedure of Trost et al.,[5] the sulfonyl oxazoline **11** or **12** (20 mg), powdered Na_2HPO_4 (400 mg), and 5% Na(Hg) beads (~600 mg) were added to 2 ml dry MeOH at 0°C. The mixture was allowed to warm to room temperature and was stirred 12 h. The mercury was removed by filtration, and the solvent was removed in vacuo. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$. After drying over Na_2SO_4 and concentrating, the residue was purified by flash chromatography (5% EtOAc/hexane).

1.4.1. *trans*-2-Phenylcyclohexyl oxazoline. From oxazoline **11**, 11 mg as a colorless oil, 85% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.65 (s, 9H), 1.4–1.6 (m, 4H), 1.7–1.9 (m, 3H), 2.1–2.2 (m, 2H), 2.6–2.7 (m, 1H), 2.7–2.9 (m, 1H), 3.5–3.6 (m, 1H), 3.8–3.9 (m, 2H), 7.1–7.2 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.4, 26.8, 27.4, 32.7, 36.3, 44.4, 47.8, 69.5, 127.8, 128.5, 129.2, 146.4, 170; *m/z* 285 $(M)^+$, 228 $(M-t\text{-Bu})^+$.

1.4.2. *cis*-2-Phenylcyclohexyl oxazoline. From oxazoline **12**, 8 mg as a colorless oil. 62% yield; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.58 (s, 9H), 1.2–1.9 (m, 9H), 2.6–2.7 (m, 2H), 3.5–3.6 (m, 2H), 3.9 (dd, J=6.9, 6 Hz, 1H), 7.0–7.2 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.5, 26.7, 31.9, 33.4, 35.8, 45.3, 48.2, 69.3, 76.4, 127.3, 128.6, 129.3, 145.7, 160.8; *m*/*z* 285 $(M)^+$, 228 $(M-t\text{-}Bu)^+$.

1.4.3. (4*S*)-4-*tert*-Butyl-2-((*E*)-1-cyano-2-phenylethenyl)-oxazoline, 16. To 30 ml Et_2O was added malononitrile (21 mmol) and ethanol (0.8 ml, 21 mmol). While maintaining vigorous stirring, the solution was aerated with dry HCl gas for 30 min. The mixture was allowed to stir for 6 h at room temperature, and then cooled to 0°C. The resultant precipitate (the desired imidate) was collected, washed with Et_2O_m and used without further purification. The imidate was dissolved in dry CH_2Cl_2 (30 ml), (*S*)-*t*-leucinol was added, and the mixture was stirred for 12 h at room temperature. The solution was diluted with saturated aqueous $NaHCO_3$ (50 ml) and extracted with EtOAc (2×50 ml). The layers were separated and the organic phase was washed with saturated aqueous NH_4Cl (2×50 ml). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (10% EtOAc/hexanes) to yield 1.3 g of oxazoline **15** as a dark yellow film (85% yield from the imidate). To a round-bottomed flask equipped with a Dean–Stark condenser was combined oxazoline **15** (1.4 g, 8.43 mmol), benzaldehyde (0.78 ml, 7.67 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.34 ml, 2.3 mmol) in benzene (40 ml). The solution was heated at reflux for 12 h, then cooled and the solution was washed with brine (30 ml) and the organic layer drawn off. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (2% EtOAc/hexanes and 5% EtOAc/hexanes) to give the desired compound **16** (1.56 g, 80% yield) as off-white needles. Mp=81–83°C; $[\alpha]^{25}_D$=−89.7 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (s, 9H), 4.06 (dd, J=9.9, 7.8 Hz, 1H), 4.23 (dd, J=8.4, 8.3 Hz, 1H), 4.35 (dd, J=10.2, 8.6 Hz, 1H), 7.41–7.51 (m, 3H), 7.88 (s, 1H), 7.9–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6, 149.8, 132.2, 132.1, 130.3, 129.1, 115.5, 100.3, 76.4, 69.6, 34.0, 25.7; HRMS (FAB+) for $C_{16}H_{19}N_{2O}$ $(M+H)^+$: Calcd 255.14974 Found 255.14973.

2. Supporting information

^{1}H and most ^{13}C NMR spectra for **3c**, **3d**, **3e**, **3f**, **9a**, **9b**, **9e**, **11**, **12**, **16**, **17**, and **18**. X-Ray crystallographic data for compound **11**. NOESY and TOCSY data for adduct **9a**.

Acknowledgements

Authors (L. B., A. I. M.) are grateful to the National Science Foundation for partial financial support. A. I. M. and A. H. are also grateful to the US–Israel Binational Science Foundation for financial support. Dr Chris Rithner and Susie Miller are gratefully acknowledged for obtaining NOESY, TOCSY NMR and X-ray crystal data, respectively.

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