Asymmetric Synthesis of Chiral Organosulfur Compounds Using *N*-Sulfinyloxazolidinones

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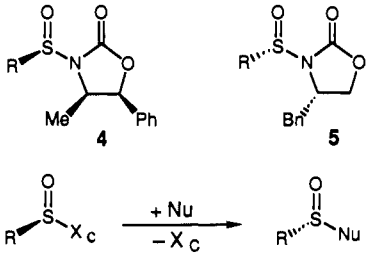
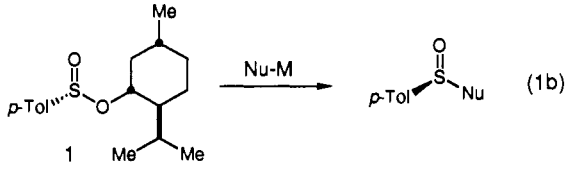
Abstract: This paper describes a new class of chiral sulfinyl transfer reagents, **4** and **5** (R = aryl, alkyl), which are readily prepared from the oxazolidinones derived from (4*R*,5*S*)-norephedrine (HX_N) and (4*S*)-phenylalanine (HX_P), respectively.



(1a)

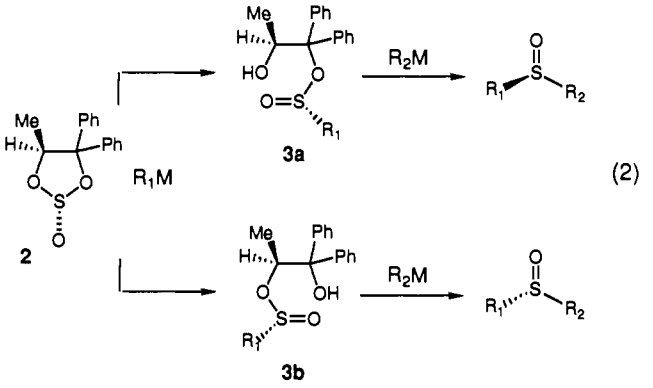
These *N*-sulfinyloxazolidinone reagents can be synthesized either by sulfinylation of the metalated oxazolidinones or by oxidation of the derived *N*-sulfenimides to afford the diastereomeric *N*-sulfinyloxazolidinones which may be readily purified by chromatography. These sulfinylating agents react with a wide range of nucleophiles such as Grignard reagents, enolates, lithium alkoxides, or metalated amides, with inversion of configuration at the sulfur center to afford the derived chiral sulfoxides, sulfinate esters, and sulfinamides in high yields and enantioselectivities. Competition experiments have established that this family of chiral sulfinylating agents is at least 100 times as reactive as the corresponding menthyl sulfinate esters toward Grignard reagents.

Chiral sulfoxides are routinely employed in organic synthesis as chiral controllers for asymmetric C–C bond formation.[1] The traditional method of choice for the preparation of enantiomerically pure sulfoxides has been the Andersen synthesis[2] which utilizes (*S*)-menthyl *p*-toluenesulfinate (**1**) in the transfer of a chiral sulfinyl moiety to a variety of nucleophiles with excellent enantioselection (eq 1b). In spite of the recent improvements in the synthesis of the menthyl sulfinate reagents[3] generally recognized liabilities are associated with their use. One of the principal drawbacks in the preparation of **1** is that multiple recrystallizations must be employed to achieve high diastereomeric purity, since chromatographic diastereomer resolution is not possible due to the similarities in the R_fs of the individual diastereomers. Moreover, this method is restricted to the synthesis of diaryl or aryl–alkyl sulfoxides. For the synthesis of dialkyl sulfoxides, the required menthyl alkanesulfinate esters cannot be prepared enantiomerically pure at sulfur.[4]



(1b)

More recent methodology developed by Kagan[5] utilizes the chiral sulfite **2**, which can be readily obtained in two steps from (*S*)-ethyl lactate. This compound reacts with a variety of organometallics (R_1M) to provide the intermediate sulfinate esters **3a** and **3b** the ratios of which are dependent on the structure of the organometallic reagent employed (eq 2). After diastereomer purification, the addition of a second organometallic reagent (R_2M) to **3** results in the transformation of the purified sulfinate to the chiral sulfoxide in good yield and excellent enantioselectivity.



(2)

The asymmetric oxidation of prochiral sulfides with optically active oxidizing reagents is also a viable alternative. The first

† Harvard University.
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(1) For excellent reviews on the synthesis and application of chiral sulfoxides, see: (a) Posner, G. N. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons, Ltd.: 1988; Chapter 16, pp 823–849. (b) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Eds.; Academic Press: 1983; Vol. 2, Chapter 8, pp 225–241. (c) Barbachyn, M. R.; Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: 1984; Vol. 4, Chapter 2, pp 227–261. (d) Solladié, G. *Synthesis* **1981**, 185–196. (e) Mikołajczyk, M.; Drabowicz, J. *Top. Stereochem.* **1982**, *13*, 333–468. (f) Andersen, K. K. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons, Ltd.: 1988; Chapter 3, pp 55–94. (g) Kresze, G. In *Methoden der Organischen Chemie (Houben-Weyl)*; Klamann, D., Ed.; Georg Thieme Verlag, Stuttgart: 1985; Vol. E11; pp 669–886.

(2) (a) Andersen, K. K. *Tetrahedron Lett.* **1962**, 93–95. (b) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am Chem. Soc.* **1964**, *86*, 5637–5646. (c) Andersen, K. K. *Int. J. Sulfur. Chem.* **1971**, *6*, 69–76.

(3) The yield of desired (−)-(*S*)-menthyl *p*-toluenesulfinate can be improved to 90% by making use of the epimerization of sulfinate esters in acidic medium to equilibrate the two diastereomers: (a) Mioskowski, C.; Solladié, G. *Tetrahedron* **1980**, *36*, 227–236. (b) Ref 1d. (c) Estep, R. E.; Tavares, D. F. *Int. J. Sulfur Chem.* **1973**, *8*, 279–280. (d) Klunder, J. M.; Sharpless, K. B. *J. Org. Chem.* **1987**, *52*, 2598–2602.

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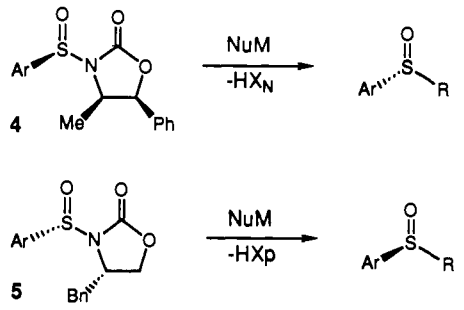
Table I. Synthesis and Chromatographic Characterization of *N*-Sulfinyloxazolidinones (Eqs 4, 5, and 7)

N-sulfinyl-oxazolidinone	method of synthesis	selectivity[a] S_S:R_S	isolated yield, % R_S isomer[b]	mp, °C R_S	isolated yield, % S_S isomer[b]	mp, °C S_S	separation factor[c] (α)
4a	acylation (eq 4)	34:66	69, **4a**(*R*)	131	1, **4a**(*S*)	74	3.9
4b	acylation (eq 4)	23:77	61, **4b**(*R*)	154	4, **4b**(*S*)	121	1.1
5a	acylation (eq 5)	68:22	9, **5a**(*R*)	70	61, **5a**(*S*)	102	1.3
5b	acylation (eq 5)	67:23	20, **5b**(*R*)	74	50, **5b**(*S*)	114	1.4
5b	oxidation (eq 6)[d]	29:71	68, **5b**(*R*)	74	28, **5b**(*S*)	114	1.4
5c	oxidation (eq 6)[d]	42:58	*e*		33, **5c**(*S*)	85	4.8
5d	oxidation (eq 6)[d]	42:58	35, **5d**(*R*)	136	49, **5d**(*S*)	88	5.4

[a] Diastereoselection at the sulfur center; ratios determined by HPLC analysis. [b] The configuration of the major diastereomer was determined either by X-ray crystallography or by nucleophilic displacement. [c] Defined as $\alpha = \Delta Z/W$, where ΔZ = the difference in retention times of the two diastereomers by analytical HPLC and W = average width of the two peaks. [d] MCPBA, −20 °C. [e] **5c**(*R*) was unstable to chromatographic purification.

approach reported by Kagan[6a-e] relies on a modified Sharpless diethyl tartrate/alkyl hydroperoxide/Ti(IV) oxidation which exhibits good levels of asymmetric induction for aryl–alkyl sulfoxides (70–90% ee). Although this procedure has been employed for the synthesis of dialkyl sulfoxides the enantioselectivities are lower (42–71% ee) in these cases. A second stoichiometric asymmetric oxidation method recently reported by Davis[6f] exploits a chiral oxaziridine reagent and affords good enantioselectivities (84–95% ee) for a variety of dialkyl and aryl–alkyl sulfoxides.

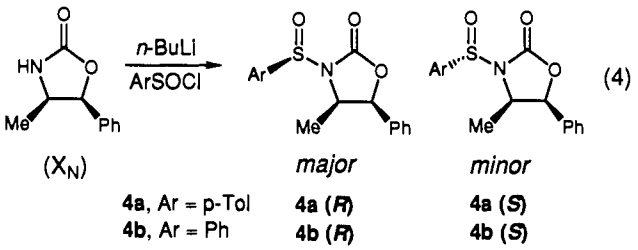
In the present study we report the new class of chiral sulfinyl transfer reagents (eq 3) which is complementary to the chiral sulfur methodology described above. Reagents **4** and **5** may be readily prepared from the (4*R*,5*S*)-norephedrine (HX_N) and (4*S*)-phenylalanine-derived oxazolidinones (HX_P), respectively,[7] either by sulfinylation of the lithiated chiral auxiliary or by oxidation of the derived *N*-(arylthio)oxazolidinones. These crystalline reagents are readily purified to high diastereomeric purity by chromatography and their reactivity toward nucleophiles which is at least 100 times that of the popular menthyl sulfinate ester **1**. In the following discussion, the synthesis of **4** and **5** and their reactions with representative carbon and heteroatom nucleophiles (eq 3) is discussed.



(3)

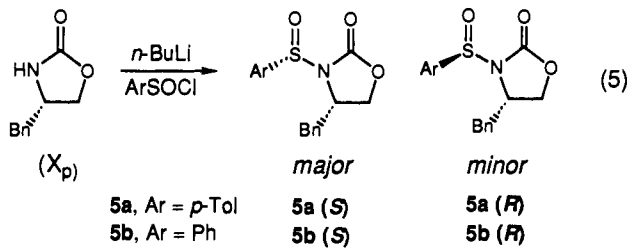
Results and Discussion

Synthesis of *N*-(Arylsulfinyl)oxazolidinones 4 and 5. The reaction of the lithiated oxazolidinone derived from either (4*R*,5*S*)-norephedrine (HX_N) or (4*S*)-phenylalanine (HX_P) with phenyl- or *p*-toluenesulfinyl chloride[8] (1.2–1.5 equiv, THF, −78 °C) affords the crystalline *N*-sulfinyloxazolidinones in good overall yield (65–70%) (eqs 4 and 5). The products are obtained as a mixture of diastereomers from which the major diastereomer (>99% ee) can be directly isolated after a single recrystallization. In the arylsulfinylation of the norephedrine-derived auxiliary (eq 4) the unpurified product ratios were 4.6:1 for **4a**(*R*):**4a**(*S*) and



(4)

(X_N)	major	minor
4a, Ar = p-Tol	**4a** (*R*)	**4a** (*S*)
4b, Ar = Ph	**4b** (*R*)	**4b** (*S*)



(5)

(X_P)	major	minor
5a, Ar = *p*-Tol	**5a** (*S*)	**5a** (*R*)
5b, Ar = Ph	**5b** (*S*)	**5b** (*R*)

4:1 for **4b**(*R*):**4b**(*S*). In the analogous sulfinylation of the phenylalanine-derived oxazolidinone (eq 5), the unpurified product ratios were 2:1 for both **5a**(*S*):**5a**(*R*) and **5b**(*S*):**5b**(*R*). In contrast to the menthyl sulfinate esters, the *N*-(arylsulfinyl)oxazolidinones are readily separable by flash or medium-pressure chromatography with separation factors (α)[9] ranging from 1.1 to 3.9 (Table I).[10] In all four sets of *N*-arylsulfinyl diastereomer pairs, the minor diastereomers were found to possess the shorter chromatographic retention times on both HPLC and silica gel.

The *N*-sulfinyloxazolidinones can alternatively be prepared by oxidation of the *N*-(arylthio)- and *N*-(alkylthio)oxazolidinone derivatives **6**. These crystalline derivatives may be prepared in good yield (77–86%) by treatment of the lithiated chiral auxiliary with the corresponding alkyl- and arylthiosulfonate esters (eq 6).

On the basis of the considerable precedent[11] that conformationally biased sulfides may be oxidized to their derived sulfoxides with good diastereoselectivity,[12] we examined a range of oxidants in the transformation of **6** → **5**; however, in no instance was the **5**(*R*)–**5**(*S*) diastereoselection greater than 2.5:1. In our preliminary investigations, we observed that the sense of asymmetric

(4) Andersen, K. K.; Bujnicki, B.; Drabowicz, J.; Mikołajczyk, M.; O'Brien, J. B. *J. Org. Chem.* **1984**, *49*, 4070–4072.

(5) (a) Rebiere, F.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 3659–3662. (b) Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991–5999.

(6) (a) Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193. (b) Duñach, E.; Kagan, H. B. *Nouv. J. Chim.* **1985**, *9*, 1–3. (c) Kagan, H. B.; Duñach, E.; Nemecek, C.; Pitchen, P.; Samuel, O.; Zhao, S.-H. *Pure Appl. Chem.* **1985**, *57*, 1911–1916. (d) Kagan, H. B. *Phosphorous and Sulfur* **1986**, *27*, 127–132. (e) Zhao, S.-H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135–5144. (f) Davis, F. A.; Thimma Reddy, R.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428–1437.

(7) For the experimental procedures for the synthesis of (4*R*,5*S*)-norephedrine-derived oxazolidinone, see: Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830–1835. For (4*S*)-phenylalanine-derived oxazolidinones (HX_P), see: Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 77–82.

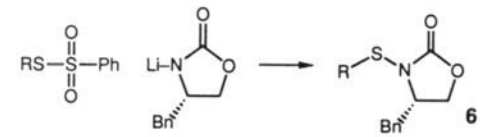
(8) Kurzer, F. *Organic Synthesis*; Wiley: New York, 1963; Collect. Vol. IV, pp 937–939.

(9) For the chromatographic resolution of other *N*-acyloxazolidinones, see: (a) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520–2527. (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525–5540.

(10) The product diastereomers obtained from reaction of (4*R*,5*S*)-norephedrine oxazolidinone with *p*-toluenesulfinyl chloride are unstable and have proven difficult to isolate. All *N*-sulfinyloxazolidinones should be stored in the freezer at −20 °C.

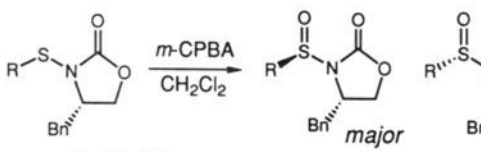
(11) For a recent review on the oxidation of sulfides, see: Madesclaire, M. *Tetrahedron* **1986**, *42*, 5459–5495.

(12) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1109–1114.



(6)

6b, R = Ph	86%	mp 79-79.3 ° C
6c, R = Me	77%	mp 54.9-55.7 °C
6d, R = *t*-Bu	83%	mp 121.4-122.9 °C



(7)

6b, R = Ph	**5b** (*R*)	**5b** (*S*)
6c, R = Me	**5c** (R)	**5c** (*S*)
6d, R = *t*-Bu	**5d** (*R*)	**5d** (*S*)

induction in the oxidation process could be inverted with *tert*-butyl hypochlorite.[13,14] In the present study, *m*-chloroperoxybenzoic acid proved to be the most expedient oxidant yielding the *N*-sulfinyloxazolidinones **5b–d** in good yields (72–96%) as 1.4–2.5:1.0 mixtures of diastereomers which were readily purified by chromatography ($\alpha > 1$) (eq 7, Table I). With one exception, the products were quite stable to chromatography. In the attempted chromatographic purification of the (methylsulfinyl)oxazolidinone **5c**(***R***) some decomposition was observed. It is noteworthy that the stereochemistry of the major diastereomer obtained in the oxidation of (phenylthio)oxazolidinone **6b** has the (*R*) configuration at sulfur and consequently has the opposite stereochemistry to the major diastereomer isolated in the sulfinylation reaction with the same chiral auxiliary.[15]

Stereochemical Assignments. The absolute configurations of the *N*-sulfinyloxazolidinones prepared during the course of this study (Table I) were determined by a combination of X-ray crystallography and chemical correlation of the derived sulfoxides obtained by displacement by Grignard reagents.

The stereochemical assignment of the major diastereomer **5a**(***S***) isolated from the reaction of the (4*S*)-phenylalanine-derived oxazolidinone with *p*-toluenesulfinyl chloride (eq 5a) was determined by X-ray crystallography (Figure 1).[16] The results establish that the configuration at the sulfur center in this product is (*S*).[17] The X-ray structure of the analogous phenylsulfinyl derivative **5b**(***S***) also confirmed that the sulfur configuration in this compound was also (*S*).

In order to unequivocally establish the stereochemical course of the substitution process with Grignard reagents, **5a**(***S***) was

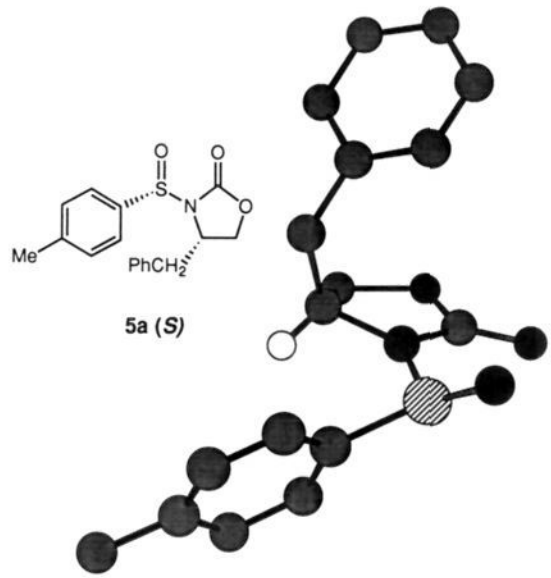
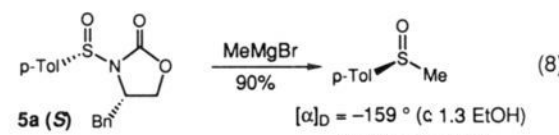


Figure 1. X-ray strucvture of **5a**(*S*).

transformed into (*S*)-methyl *p*-tolyl sulfoxide, $[\alpha]_D$ −159° (EtOH), with methylmagnesium bromide (THF, −78 °C, 30 min, 90%) (eq 8). On the basis of the reported rotation for the (*R*) enantiomer, $[\alpha]_D$ +156° (EtOH),[18] the resulting methyl *p*-tolyl sulfoxide obtained from this reaction possessed the (*S*) configuration. HPLC analysis of **5a**(***S***)[19] confirmed the presence of only one enantiomer in the sample.



(8)

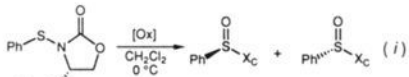
This result confirms that this sulfur substitution process with methylmagnesium bromide proceeds with complete inversion of configuration at sulfur.

The stereochemical assignments of the other *N*-(arylsulfinyl)oxazolidinones were then deduced in an analogous manner. In all instances, conservation of enantiopurity was observed in the Grignard reactions of each of the diastereomer pairs of **4a**, **4b**, and **5a**, **5b**. From this body of data we conclude that the sulfinylation process (eqs 4 and 5) is stereoregular in nature.

Origin of Sulfinylation Diastereoselection. In the early phases of the study it was presumed that sulfinylation diastereoselection was controlled by kinetic factors; however, the following observation led us to conclude that this was not the case. In surveying other organometallic reagents for the transformation of **5a**(***S***) to the derived (*S*)-methyl *p*-tolyl sulfoxide (eq 8), we were surprised to find that the reaction **5a**(***S***) with methyllithium resulted in the formation of the derived sulfoxide with substantially reduced enantiomeric purity. Accordingly, the control experiment was conducted where the configurational stabilities of the diastereomeric sulfinimides **5a**(***S***) and **5a**(***R***) were evaluated in the presence of the lithiated chiral auxiliary (eq 9). For experiments in which either 1.0 or 0.1 equiv of lithiated oxazolidinone was treated with an equiv of **5a**(***S***), equilibrium at the sulfur center was observed in less than 1 min at −78 °C to yield at 71:29 mixture of diastereomers. This same equilibrium ratio was also obtained from the analogous experiment employing diastereomer **5a**(***R***). On

(13) For example, see: Johnson, C. R.; Rigau, J. J. *J. Am. Chem. Soc.* **1969**, *91*, 5398–5399, and references cited therein.

(14) In the early phases of this study, the *N*-(phenylthio)oxazolidinone **A** was subjected to the illustrated range of oxidants under comparable conditions, CH_2Cl_2, 0 °C (eq i).



Oxidant	Ratio, R_S:S_S
MCPBA	62 : 28
O_3	58 : 42
TFA, H_2O_2	67 : 33
t-BuOCl; MeOH	30 : 70

(15) This oxidation procedure for the synthesis of the *N*-sulfinyloxazolidinones is also successful using (4*S*)-valinol and (4*R*,5*S*)-norephedrine as chiral auxiliaries.

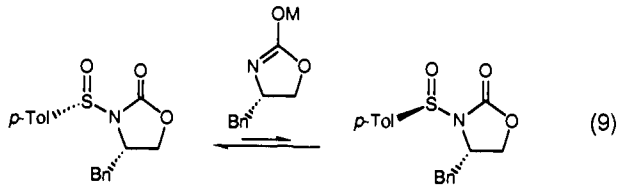
(16) X-ray crystallography has also been carried out on the major diastereomer isolated from reaction of the lithiated oxazolidinone derived from (4*S*)-phenylalanine with phenyl sulfinyl chloride. These results show that the major diastereomer is (4*S*)-4-benzyl-3-[(*S*)-phenylsulfinyl]oxazolidinone (**5b**(***S***)).

(17) On the basis of results previously reported by Posner for (*S*)-(+)-2-(*p*-tolylsulfinyl)-2-cyclopentenone, it was expected that the carbon–oxygen and sulfur–oxygen bonds would orient themselves in an antiperiplanar fashion. In contrast, for **5a**(***S***), it was found that the dihedral angle between the two dipoles was only 58°: Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Asirvatham, E.; Cun-Heng, H.; Clardy, J. *Tetrahedron* **1986**, *42*, 2919–2929.

(18) Mislow, K.; Axelrod, M.; Rayner, D. R.; Gotthardt, H.; Coyne, L. M.; Hammond, G. S. *J. Am. Chem. Soc.* **1965**, *87*, 4958–4959.

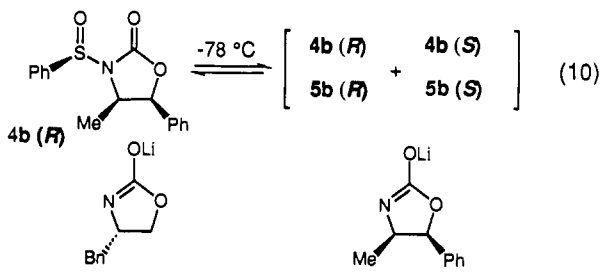
(19) The enantiomeric purities of the chiral sulfoxides prepared during the course of this study were determined by optical rotation and by analytical HPLC using a chiral Pirkle column [type 1A, 4.6 mm × 25 cm, hexane/isopropyl alcohol (98.0:2.0), flow rate 3 mL/min].

the other hand, the magnesium conjugate of the oxazolidinone auxiliary only slowly effects epimerization over an extended time period at low temperature.



(9)

M = Li: Equilibration reached within 1 min at -78 °C
M = MgX: Equilibration incomplete after 2 days at -78 °C
M = MgX: Equilibration reached after 3 hr at 0 °C



(10)

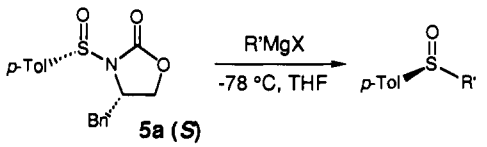
Additional experiments demonstrated that bimolecular sulfinyl transfer is occurring with concomitant epimerization at sulfur. For example, when the diastereomerically pure sulfinyl imide **4b(*R*)** is treated with 1 equiv of Li–Xp (–78 °C, 10 min), the fully randomized product set is obtained (eq 10).

These studies thus establish two important points. First, we now have direct evidence that product equilibration is occurring in conjunction with the oxazolidinone sulfinylation experiments (eqs 4 and 5). Second, since the stereochemical integrity of the sulfinyl imide is strongly dependent on the specific metal counterion associated with the chiral auxiliary ($M–X_c$) generated during an organometallic sulfur substitution process, well-defined limits must be placed on the nature of the metal counterion in the nucleophilic substitution process if high levels of chirality transfer are to be achieved. The following section surveys the reactions of these sulfinyl imides with Grignard reagents.

Synthesis of Chiral Sulfoxides. The *N*-sulfinyloxazolidinones are efficient sulfinyl transfer reagents which react rapidly with a variety of Grignard reagents to give the corresponding aryl–alkyl (eq 11, Table II, entry 1, Table III) and dialkyl sulfoxides (eq 12, entries 2–6, Table III) in high yields (78–92%) and enantioselectivities (>90%).

The homologous series of transformations of *N*-*p*-toluenesulfinyloxazolidinone **5a(*S*)** with Grignard reagents of increasing steric hindrance (entries 1–4, Table II) could be carried out at –78 °C within a reaction time of 30 min. In each of these cases, the enantioselection was found to be ≥97% as judged by HPLC analysis on a chiral Pirkle type 1A column. Dialkyl sulfoxides can be readily prepared by reaction of the *N*-(alkylsulfinyl)oxazolidinones **5c**(*S*) (R = Me) and **5d**(*S*) (R = *t*-Bu) with a variety of alkyl Grignard reagents. The reactions can be carried out at –78 °C and are complete within 10 min for the more reactive methylsulfinyl derivative **5c**(*S*). On the other hand, the analogous reactions of the *N*-*tert*-butyl sulfinyl imide **5d**(*S*) require longer reaction times. For example, the synthesis of (*S*)-*tert*-butyl methyl sulfoxide from **5d**(*S*) required 24 h at –78 °C for complete conversion (entry 5, Table III). Alternatively, (*S*)-*n*-butyl *tert*-butyl sulfoxide could be obtained in 91% yield from **5d**(*S*) after 3 h at –78 °C (entry 6, Table III). The dialkyl sulfoxides are obtained in high enantiomeric purity (≥93%) as determined by optical rotation and comparison to the maximum specific rotation given in the literature. In all cases, the absolute configuration of the sulfoxide obtained is in agreement with the fact that nucleophilic displacement occurs with inversion of configuration at the sulfur center in the starting *N*-sulfinyloxazolidinone.[1d,20]

Table II. Synthesis of Aryl–Alkyl Sulfoxides (eq 11)

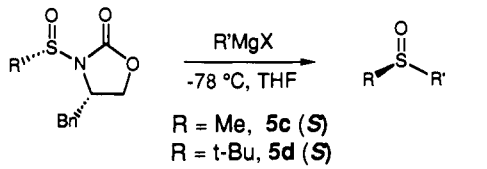


(11)

entry	R′	yield,[a] %	ee[b], %	$[\alpha]_D$[c]	config at sulfur
1	Me	90	99	–132 (*c* 1.3)[d]	*S*
2	Et	90	98	–204 (*c* 2.0)	*S*
3	*i*-Pr	91	97	–181 (*c* 2.6)	*S*
4	*t*-Bu	88	97	–185 (*c* 0.77)[d]	*S*
5	Bn	86	99[e]	–213 (*c* 1.0)	*S*

[a] Reactions were performed in THF with 2 equiv of RMgX at –78 °C for 30 min. [b] Measured by HPLC using a chiral Pirkle column, type 1A, 4.6 mm × 25 cm, hexane/isopropyl alcohol (98:2), flow rate 3 mL/min. [c] Optical rotation in acetone unless stated. [d] Optical rotation recorded in EtOH. [e] Obtained after a single recrystallization from ethanol, initial enantioselectivity 94%.

Table III. Synthesis of Dialkyl and Aryl–Alkyl Sulfoxides (eq 12)

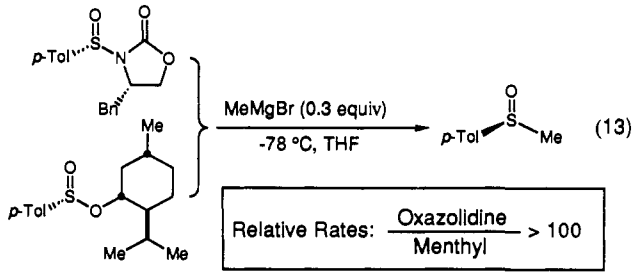


(12)

entry	R	R′	yield,[a] %	ee,[b] %	$[\alpha]_D$	config at sulfur
1	Me	Ph	87	90[c]	+120 (*c* 1.54)[e]	*R*
2	Me	*t*-Bu	78	93[d]	–7.3 (*c* 1.0)[f]	*R*
3	Me	Bn	82	91	+50 (*c* 0.9)[f]	*R*
4	Me	octyl	78	100	–79.7 (*c* 0.5)[e]	*R*
5	*t*-Bu	Me	92	100[d]	+7.8 (*c* 1.0)[f]	*S*
6	*t*-Bu	*n*-Bu	91	100	–129 (*c* 1.02)[e]	*S*

[a] Reactions were performed in THF with 1.5 equiv of RMgX at –78 °C. [b] Determined by comparison of the optical rotation to the maximum rotation in the literature. [c] Enantioselectivity determined by chiral shift studies with (*R*)-(*N*)-(trifluoroacetyl)(1-naphthylethyl)-amine.[37] [d] Enantioselectivity determined by chiral shift studies with (*R*)-(–)-*N*-(3,5-dinitrobenzoyl)(1-phenylethyl)amine.[37] [e] Optical rotation recorded in acetone. [f] Optical rotation recorded in $CHCl_3$.

In an effort to compare the reactivity of the chiral *N*-sulfinyloxazolidinones and Andersen's menthyl sulfinate esters, a competition experiment was carried out between the two chiral sulfinyl derivatives in the presence of 0.3 equiv of methylmagnesium bromide (eq 13). The reaction was analyzed by analytical HPLC. The ratio of the sulfinylating agents relative to an internal standard was determined at the start of the reaction and after 1 h when the reaction was complete. Within the detection limits of the experiment, none of the menthyl sulfinate had been transformed. These results demonstrate that the *N*-sulfinyloxazolidinones are at least two orders of magnitude more reactive than the corresponding menthyl sulfinate esters.

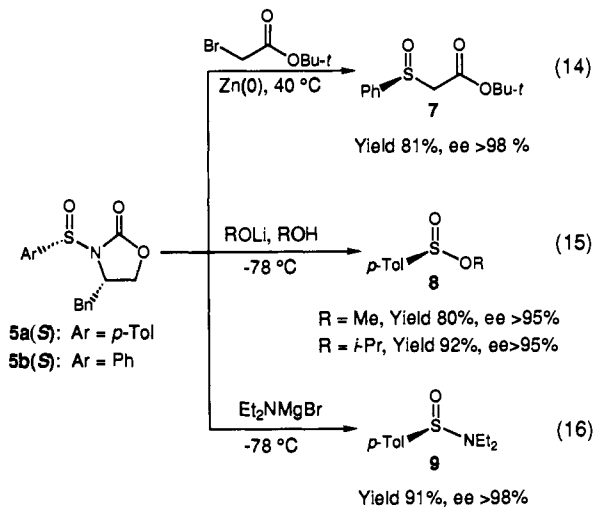


(13)

(20) Jacobus, J.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 5228–5234.

Synthesis of Other Chiral Organosulfur Compounds. The *N*-sulfinyloxazolidinones are also efficient reagents for the synthesis of other classes of chiral organosulfur compounds (eqs 14–16). Solladié has shown that magnesium enolates derived from chiral α-sulfinyl acetates are effective auxiliaries in the aldol reactions of aldehydes and ketones.[21] In the one enolate-based bond construction we have examined, the Reformatsky reagent derived from *tert*-butyl bromoacetate and activated zinc proved to be effective in the reaction with **5b**(*S*) to afford (*S*)-*tert*-butyl α-(phenylsulfinyl)acetate (**7**)[22] in high yield (81%) and enantioselectivity (>98%).[23]

Sulfinate esters have received considerable attention as starting materials in the synthesis of sulfoxides[1d] and as model compounds in the studies of nucleophilic substitution at sulfur;[24] however, few methods for the asymmetric synthesis of these compounds have been reported.[25] We have found that methyl and isopropyl *p*-toluenesulfinates[26] (**8**) can be obtained by reaction of the corresponding lithium alkoxide with the *N*-sulfinyloxazolidinone **5a**(*S*) in the presence of excess alcohol (eq 15) in 80 and 92% yields, respectively, with enantiomeric purities >95%.[27] It is noteworthy that racemization under these conditions is not observed. This method should be applicable to the synthesis of a wide range of sulfinate esters.



Finally, sulfinamides have been used as precursors in the synthesis of optically active sulfinates,[25b] sulfoxides,[28] and more recently in the synthesis of β- and γ-amino acids.[29] The *N*-sulfinyloxazolidinones are also efficient agents for the synthesis of this family of chiral sulfur derivatives (eq 16). Reaction of bromomagnesium diethylamide with **5a**(*S*) afforded (*S*)-*N*,*N*-diethyl *p*-toluenesulfinamide (**9**) in excellent yield (91%) and enantioselectivity (>98%).[30]

Selection of Sulfinylating Agent. Although any member of the set of *N*-sulfinyloxazolidinones derivatives **4a**,**b**, **5a–d** can be readily prepared and utilized in the substitution reactions described in the preceding study, we have found that the *N*-*p*-toluenesulfinyloxazolidinones **4a**(*R*) and **4a**(*S*) derived from norephedrine are less stable to storage than the corresponding phenylsulfinyl analogs **4b**(*R*) and **4b**(*S*). These well-behaved reagents have exhibited a shelf life of at least 3 years at −20 °C with no sign of decomposition. The decision to employ the (4*S*)-phenylalanine-derived oxazolidinone derivatives, **5a–d**, for the principal reactions reported in this study was made for the sake of internal consistency; however, the other sulfinylation reagents described have been found to perform equally well in similar transformations.

Experimental Section

General Methods. Infrared spectra were recorded on a Perkin Elmer 781 spectrometer. ^{1}H NMR spectra were recorded on Brucker AM-500 (500 MHz), AM-400 (400 MHz), AM-300 (300 MHz), and AM-250 (250 MHz) spectrometers at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, and m = multiplet), integration, coupling constant (Hz), and assignment. ^{13}C NMR were recorded on a Bucker AM-500 (126 MHz), AM-400 (101 MHz), AM-300 (75 MHz), and AM-250 (62.5 MHz) spectrometers at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). Combustion analyses were performed by Spang Microanalytical Laboratory (Eagle Harbor, MI). High resolution mass spectra were obtained on Joel AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory. Optical rotations were measured on a Jasco DIP-181 digital polarimeter.

Analytical thin-layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Purification of reaction products was carried out either by liquid chromatography using a forced flow (flash chromatography) of the indicated solvent system on EM Reagents silica gel 60 (230–400 mesh) or by medium pressure liquid chromatography using Michel–Miller columns (Ace Glass, Inc.) dry-packed with 230–400 mesh silica gel.

All reactions were carried out under an atmosphere of nitrogen in glassware that had been flame dried under a stream of nitrogen. When necessary solvents and reagents were distilled under nitrogen prior to use. Dichloromethane and chlorotrimethylsilane were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone ketyl. Sodium benzenesulfinate and sodium *p*-toluenesulfinate were dried in a vacuum oven at 140 °C overnight prior to use. Grignard reagents were purchased from the Aldrich Chemical Company and used as received.

General Procedure for the Preparation of *p*-Toluenesulfinyl Chloride.[8] To a well-stirred suspension of sodium *p*-toluenesulfinate (1.0 equiv) in toluene (4.5 mL/mmol) at 0 °C was added dropwise via syringe oxalyl chloride (1.0 equiv) over a 15-min period. The resultant pale yellow suspension was stirred at 0 °C for 30 min and at room temperature for 1 h. The mixture was diluted with THF (0.5 mL/mmol) prior to addition to the imide enolate.

General Procedure for the Preparation of Benzenesulfinyl Chloride. To a well-stirred suspension of sodium benzenesulfinate (1.0 equiv) in toluene (0.25 mL/mmol) under nitrogen at 0 °C was added dropwise via syringe oxalyl chloride (0.96 equiv) over a 15-min period. The suspension was stirred at 0 °C for 30 min and at room temperature for 1 h. The mixture was diluted with THF (0.5 mL/mmol) prior to addition to the imide enolate.

***p*-Toluenesulfinylation of the (4*R*,5*S*)-Norephedrine-Derived Oxazolidin-2-one (HX_N). Synthesis of 4a.** To a solution of 6.75 g (38.1 mmol) of the (4*R*,5*S*)-norephedrine-derived oxazolidin-2-one (HX_N) in 50 mL of THF under nitrogen at 0 °C was added dropwise 18.1 mL (2.0 M in hexane, 36.2 mmol) of *n*-butyllithium over a 15-min period. The resultant suspension was stirred at 0 °C for 10 min and then cooled to −78

(21) For a review on the addition of various nucleophiles to aldehydes and ketones, see: Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Eds.; Academic Press: 1983; Vol. 2, Chapter 6, pp 157–199.

(22) (a) Mioskowski, C.; Solladié, G. *J. Chem. Soc., Chem. Commun.* **1977**, 162–163. (b) Mioskowski, C.; Solladié, G. *Tetrahedron* **1980**, *36*, 227–236. (c) Solladié, G.; Matloubi-Moghadam, F. *J. Org. Chem.* **1982**, *47*, 91–94.

(23) The enantiomeric excess of (*S*)-*tert*-butyl α-(phenylsulfinyl)acetate was determined by the use of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).

(24) Mikołajczyk, M. In *Perspectives in the Organic Chemistry of Sulfur*; Zwanenburg, B., Klunder, A. H. J., Eds.; Elsevier: 1987; p 23.

(25) (a) Mikołajczyk, M.; Drabowicz, J.; Bujnicki, B. J. *J. Chem. Soc., Chem. Commun.* **1976**, 568–569. (b) Hiroi, K.; Kitayama, R.; Sato, S. *Synthesis* **1983**, 1040–1041.

(26) (*R*)-Isopropyl *p*-toluenesulfinate was prepared using (4*R*,5*S*)-4-methyl-5-phenyl-3-[(*R*)-*p*-toluenylsulfinyl]-2-isoxazolidinone **4a**(*R*).

(27) ^{1}H NMR chiral shift studies with (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated the product methyl sulfinate ester was generated in enantiomeric excess (>95%): Pirkle, W. H.; Hoekstra, M. S. *J. Am. Chem. Soc.* **1976**, *89*, 1832–1839.

(28) (a) Colonna, S.; Giovini, R.; Montanari, F. *J. Chem. Soc., Chem. Commun.* **1968**, 865–866. (b) Jacobus, J.; Mislow, K. *J. Chem. Soc., Chem. Commun.* **1968**, 253–254.

(29) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4–6.

(30) The enantiomeric excess of (*S*)-*N*,*N*-diethyl *p*-toluenesulfinamide was determined by both optical rotation and by analytical HPLC using a chiral Pirkle column [type 1A, 4.6 mm × 25 cm, hexane/isopropyl alcohol (98.0:2.0), flow rate 3 mL/min]. The optimum conditions for the separation of the enantiomers was determined on a racemic sample of the material preparation by reaction of *p*-toluene sulfinyl chloride with dialkylaminomagnesium halide.

°C. A suspension of 53.4 mmol (1.4 equiv) of *p*-toluenesulfinyl chloride solution freshly prepared according to the General Procedure was added over a 2-min period (as a slurry with NaCl) to the enolate suspension by a dropping funnel. The reaction was stirred at −78 °C for 10 min, quenched by the addition of 80 mL of saturated aqueous sodium bicarbonate, and diluted with 120 mL of ethyl acetate. The aqueous layer was extracted with 50 mL of ethyl acetate, and the combined organic layers were washed sequentially with 100 mL of saturated aqueous ammonium chloride and 100 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$), and the solvent removed in vacuo to leave 12.74 g of a white solid. Analysis of HPLC (4.6 mm × 25 cm DuPont Zorbax, 5 mm silica gel, isooctane/isopropyl alcohol (97:3), 2.0 mL/min) afforded a 4.6:1 ratio of **4a(*R*)** (R_t = 4.4 min) to **4a(*S*)** (R_t = 4.3 min). The reaction mixture was triturated with 300 mL of diethyl ether, and the solid material collected proved to be 98% diastereomerically pure **4a(*R*)**. It was recrystallized from hexane/ethyl acetate to give pure **4a(*R*)** (7.44 g, 65%). The residues derived from filtration and recrystallization were collected and purified by flash chromatography (7 × 15 cm, hexane/isopropyl alcohol (95:5), 125-mL fraction): a 83:17 mixture of **4a(*R*)** and **4a(*S*)** was first eluted (2.06 g). This mixture was chromatographed (gradient MPLC, from hexane (100%) to hexane/isopropyl alcohol (9:1), linear gradient, 4.7 × 45 cm column, flash silica gel, 50-mL fractions) to give only one pure fraction of **4a(*S*)** as a colorless oil which solidified upon standing (162 mg). A mixture enriched in the diastereomer **4a(*R*)** eluted second, affording after recrystallization from hexane/ethyl acetate 767 mg of pure crystalline **4a(*R*)**. The overall yield of **4a(*R*)** was 69%.

(4*R*,5*S*)-4-Methyl-5-phenyl-3-[(*R*)-*p*-tolylsulfinyl]-2-isoxazolidinone (4a(*R*)): mp 130–133 °C (dec); IR ($CHCl_3$) 3030, 1770, 1332, 1195, 1150, 1121, 1080, 1020, 973, 812, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.66 (d, 2 H, aromatic, J = 8.2 Hz), 7.44 (d, 2 H, aromatic, J = 8.2 Hz), 7.19–7.39 (m, 5 H, aromatic), 5.46 (d, 1 H, C_5-*H*, J = 7.4 Hz), 3.80 (qn, 1 H, C_4-*H*), 2.49 (s, 3 H, ArCH_3), 0.92 (d, 3 H, CH_3, J = 6.7 Hz); $[\alpha]_{589}$ −260.6° (*c* 0.77, CH_2Cl_2).

(4*R*,5*S*)-4-Methyl-5-phenyl-3-[(*S*)-*p*-tolylsulfinyl]-2-isoxazolidinone (4a(*S*)): mp 73.5–74.5 °C; IR ($CHCl_3$) 3030, 2930, 1768, 1600, 1500, 1458, 1372, 1195, 1138, 1117, 1101, 1080, 1020, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.66 (d, 2 H, aromatic, J = 8.3 Hz), 7.20–7.40 (m, 7 H, aromatic), 5.68 (d, 1 H, C_5-*H*, J = 7.9 Hz), 4.59 (qn, 1 H, C_4-*H*), 2.41 (s, 3 H, ArCH_3), 0.21 (d, 3 H, CH_3, J = 6.8 Hz); $[\alpha]_{589}$ +38.8° (*c* 1.08, CH_2Cl_2).

Phenylsulfinylation of the (4*R*,5*S*)-Norephedrine-Derived Oxazolidin-2-one (HX_N). Synthesis of 4b. To a solution of 10 g (56.4 mmol) of the (4*R*,5*S*)-norephedrine-derived oxazolidin-2-one (HX_N) in 60 mL of THF under nitrogen at 0 °C was added dropwise 33.5 mL (1.60 M in hexane, 53.6 mmol) of *n*-butyllithium over a 15-min period. The resultant suspension was stirred at 0 °C for 5 min and then cooled to −78 °C. A suspension of 79.0 mmol (1.4 equiv) of benzenesulfinyl chloride solution freshly prepared according to the General Procedure was added over a 2-min period (as a slurry with NaCl) to the enolate suspension by a dropping funnel. The reaction was stirred at −78 °C for 10 min, quenched by the addition of 150 mL of saturated aqueous ammonium chloride, and diluted with 600 mL of ethyl acetate. The organic layer was washed successively with 200 mL of saturated aqueous sodium bicarbonate and 250 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to afford 17.8 g of a white solid. Analysis of HPLC (8 mm × 10 cm Radial Pak, 10 mm silica gel, isooctane/ethyl acetate (85:15), 2.0 mL/min) afforded a 4.0:1.0 ratio of **4b(*R*)** (R_t = 5.7 min) to **4b(*S*)** (R_t = 4.3 min). Recrystallization from hexane/ethyl acetate yielded 8.5 g of **4b(*R*)** as short fine needles. The mother liquors were purified by flash chromatography (7.0 × 20 cm, 125 mL fractions); sequential elution with 2 L of hexane/ethyl acetate (7:3), 2.25 L of hexane/ethyl acetate (2:1), and 0.7 L of hexane/ethyl acetate (6:4) gave 1.76 g of pure **4b(*S*)** and 2.45 g of a mixture of both diastereomers. This mixture was recrystallized from hexane/ethyl acetate to afford 1.42 g of pure **4b(*R*)**. Fractions containing **4b(*S*)** were recrystallized from hexane/ethyl acetate to give 685 mg of white plates. The overall yield of recrystallized **4b(*R*)** and **4b(*S*)** was 61 and 4%, respectively.

(4*R*,5*S*)-4-Methyl-5-phenyl-3-[(*R*)-phenylsulfinyl]-2-isoxazolidinone (4b(*R*)): mp 152–156 °C (dec); IR ($CHCl_3$) 3080, 3020, 1768, 1447, 1332, 1195, 1121, 1069, 1022, 973, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.77–7.81 (m, 2 H, aromatic), 7.63–7.69 (m, 3 H, aromatic), 7.32–7.40 (m, 3 H, aromatic), 7.19–7.27 (m, 2 H, aromatic), 5.48 (d, 1 H, C_5-*H*, J = 7.4 Hz), 3.80 (qn, 1 H, C_4-*H*), 0.93 (d, 3 H, CH_3, J = 6.7 Hz); $[\alpha]_{589}$ −234.7° (*c* 1.3, CH_2Cl_2). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02. Found: C, 63.52; H, 5.19.

(4*R*,5*S*)-4-Methyl-5-phenyl-3-[(*S*)-phenylsulfinyl]-2-isoxazolidinone (4b(*S*)): mp 121–122 °C; IR ($CHCl_3$) 3070, 3020, 1768, 1448, 1370, 1342, 1197, 1110, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.76–7.80 (m, 2 H, aromatic), 7.52–7.57 (m, 3 H, aromatic), 7.27–7.40 (m, 3 H, aromatic), 7.20–7.24 (m, 2 H, aromatic), 5.69 (d, 1 H, C_5-*H*, J = 7.9 Hz), 4.59 (qn, 1 H, C_4-*H*), 0.18 (d, 3 H, CH_3, J = 6.8 Hz); $[\alpha]_{589}$ +29.0° (*c* 1.2, CH_2Cl_2). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02. Found: C, 63.57; H, 5.15.

***p*-Toluenesulfinylation of the (4*S*)-Phenylalanine-Derived Oxazolidin-2-one (HX_P). Synthesis of 5a.** To a solution of 5.0 g (28.2 mmol) of the (4*S*)-phenylalanine-derived oxazolidin-2-one (HX_P) in 60 mL of THF under nitrogen at 0 °C was added dropwise 20.1 mL (1.51 M in hexane, 30.5 mmol) of *n*-butyllithium over a 15-min period. The resultant suspension was stirred at 0 °C for 5 min and then cooled to −78 °C. A suspension of 42.0 mmol (1.5 equiv) of *p*-toluenesulfinyl chloride solution freshly prepared according to the General Procedure was added over a 2-min period (as a slurry with NaCl) to the enolate suspension by a dropping funnel. The reaction mixture was stirred at −78 °C for 15 min, quenched by the addition of 80 mL of saturated aqueous sodium bicarbonate, and diluted with 80 mL of ethyl acetate. The aqueous layer was extracted with a further 50 mL of ethyl acetate, and the combined organic layers were washed sequentially with 100 mL of saturated aqueous ammonium chloride followed by 100 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to afford 8.32 g of a white solid. Analysis by HPLC (4.6 mm × 25 cm DuPont Zorbax, 5 mm silica gel, hexane/ethyl acetate (4:1), 2.0 mL/min) showed a 2.1:1.0 ratio of **5a(*S*)** (R_t = 12.4 min) to **5a(*R*)** (R_t = 9.2 min). Separation of the diastereomers was achieved using the Waters Prep-500 HPLC, solvent system hexane/ethyl acetate (85:15) to yield 5.4 g (61%) of **5a(*S*)** and 0.78 g (9%) of **5a(*R*)**.

(4*S*)-4-Benzyl-3-[(*S*)-*p*-tolylsulfinyl]-2-isoxazolidinone (5a(*S*)): mp 101.3–102.9 °C; IR ($CHCl_3$) 3010, 1770, 1195, 1135, 1105, 1075, 1015, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.69–7.72 (d, 2 H, aromatic), 7.46–7.49 (d, 2 H, aromatic), 7.19–7.28 (m, 3 H, aromatic), 6.93–6.95 (m, 2 H, aromatic), 4.07 (dd, 1 H, C_5-*H*, J = 3.8 Hz), 3.96 (t, 1 H, C_5-*H*), 3.71 (m, 1 H, C_4-*H*), 3.37 (dd, 1 H, CH_2Ph, J_{vic} = 3.6 Hz, J_{gem} = 10.0 Hz), 2.90 (dd, 1 H, CH_2Ph, J_{vic} = 3.6 Hz, J_{gem} = 10.2 Hz), 2.51 (s, 3 H, ArCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 155.8, 143.2, 137.8, 135.0, 130.4, 129.0, 128.8, 127.2, 125.0, 67.4, 56.1, 40.4, 21.4; $[\alpha]_{589}$ +169.4° (*c* 1.97, acetone). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.76; H, 5.39. Found: C, 64.75; H, 5.34.

(4*S*)-4-Benzyl-3-[(*R*)-*p*-tolylsulfinyl]-2-isoxazolidinone (5a(*R*)): mp 69.1–70.8 °C; IR ($CHCl_3$) 3015, 1770, 1495, 1385, 1340, 1195, 1100, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.75–7.78 (d, 2 H, aromatic), 7.39–7.46 (d, 2 H, aromatic), 7.19–7.26 (m, 3 H, aromatic), 6.90–6.94 (m, 2 H, aromatic), 4.54 (m, 1 H, C_4-*H*), 4.16 (t, 1 H, C_5-*H*), 4.08 (dd, 1 H, C_5-*H*, J = 4.8 Hz), 2.41 (s, 3 H, ArCH_3), 2.14–2.18 (d, 2 H, CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.5, 143.3, 139.1, 135.0, 130.1, 128.8, 127.2, 125.0, 69.0, 50.4, 39.4, 21.5. $[\alpha]_{589}$ −106.7° (*c* 1.3, acetone). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.76; H, 5.39. Found: C, 64.68; H, 5.43.

Phenylsulfinylation of the (4*S*)-Phenylalanine-Derived Oxazolidin-2-one (HX_P). Synthesis of 5b. To a solution of 5.0 g (28.2 mmol) of the (4*S*)-phenylalanine-derived oxazolidin-2-one (HX_P) in 60 mL of THF under nitrogen at 0 °C was added dropwise 20.2 mL (1.51 M in hexane, 30.5 mmol) of *n*-butyllithium over a 10-min period. The resultant suspension was stirred at 0 °C for 5 min and then cooled to −78 °C. A suspension of 33.8 mmol (1.2 equiv) of benzenesulfinyl chloride solution freshly prepared according to the General Procedure was added over a 2-min period (as a slurry with NaCl) to the enolate suspension by a dropping funnel. The reaction was stirred at −78 °C for 15 min, quenched by addition of 80 mL of saturated aqueous ammonium chloride, and diluted with 150 mL of ethyl acetate. The organic layer was washed successively with 100 mL of saturated aqueous sodium bicarbonate and 130 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to leave 9.77 g of a pale yellow oil. Analysis of HPLC (4.6 mm × 25 cm DuPont Zorbax, 5 mm silica gel, hexane/ethyl acetate (7:3), 2.0 mL/min) afforded a 2.0:1.0 ratio of **5b(*S*)** (R_t = 4.7 min) to **5b(*R*)** (R_t = 3.9 min). Separation of the diastereomers was achieved using a Waters Prep-500 HPLC, solvent system eluant hexane/ethyl acetate (85:15) to yield 4.24 g (50%) of **5b(*R*)** and 1.67 g (20%) of **5b(*S*)**.

(4*S*)-4-Benzyl-3-[(*S*)-phenylsulfinyl]-2-isoxazolidinone (5b(*S*)): mp 113–115 °C; IR ($CHCl_3$) 3020, 1768, 1385, 1233, 1195, 1132, 1110, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.81–7.85 (m, 2 H, aromatic), 7.67–7.71 (m, 3 H, aromatic), 7.21–7.27 (m, 3 H, aromatic), 6.89–6.92 (m, 2 H, aromatic), 4.08 (dd, 1 H, C_5-*H*, J_{vic} = 3.8 Hz, J_{gem} = 8.9 Hz), 3.99 (t, 1 H, C_5-*H*), 3.70 (m, 1 H, C_4-*H*), 3.36 (dd, 1 H, CH_2Ph, J_{vic} = 3.5 Hz, J_{gem} = 13.9 Hz), 2.90 (dd, 1 H, CH_2Ph, J_{vic} = 10.5 Hz, J_{gem} = 13.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 155.8, 140.9, 134.9, 132.4, 129.7, 129.0, 128.8, 127.2, 125.0, 67.4, 56.3, 40.3; $[\alpha]_{589}$ +163.3° (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02. Found: C, 63.86; H, 5.07.

(4*S*)-4-Benzyl-3-[(*R*)-phenylsulfinyl]-2-isoxazolidinone (5b(*R*)): mp 74–75 °C; IR ($CHCl_3$) 3020, 1768, 1385, 1232, 1130, 1100, 1062 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ ppm 7.78–7.91 (m, 2 H, aromatic), 7.59–7.66 (m, 3 H, aromatic); 7.17–7.27 (m, 3 H, aromatic), 6.89–6.92 (m, 2 H, aromatic), 4.53 (m, 1 H, C_4-*H*), 4.18 (t, 1 H, C_5-*H*), 4.10 (dd, 1 H, C_5-*H*, J_{viv} = 4.8 Hz, J_{gem} = 8.9 Hz), 2.16 (dd, 1 H, CH_2Ph, J_{vic} = 10 Hz, J_{gem} = 13.4 Hz), 2.10 (dd, 1 H, CH_2Ph, J_{vic} = 4.6 Hz, J_{gem} = 13.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm 157.1, 142.6, 134.9, 132.4, 129.4, 128.9, 128.8, 127.3, 125.0, 69.1, 50.6, 39.6; $[\alpha]_{589}$ −103.7° (*c* 1.13 CH_2Cl_2). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02. Found: C, 63.83; H, 5.18.

(4*S*)-4-Benzyl-3-(phenylthio)-2-isoxazolidinone (6b). To a solution of 6.0 g (33.9 mmol) of the (4*S*)-phenylalanine-derived oxazolidin-2-one (HX_P) in 60 mL of THF under nitrogen at 0 °C was added dropwise 13.5 mL (2.5 M in hexane, 33.8 mmol) of *n*-butyllithium. The resulting suspension was stirred at 0 °C for 5 min and then cooled to −78 °C. A solution of 10.17 g (40.7 mmol) of phenyl benzenethiolsulfonate[31] in 20 mL of THF was added over a 2-min period to the enolate suspension, and the reaction was stirred at −78 °C for 5 min and 0 °C for 2 h. The reaction was quenched by the addition of 100 mL of saturated aqueous ammonium chloride and diluted with 200 mL of diethyl ether. The organic layer was removed, and the aqueous layer was extracted with 100 mL of diethyl ether. The combined organic layers were washed with 150 mL of saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo to give 11.14 g of a pale yellow oil which was purified by MPLC (Michel–Miller column, 51 mm × 450 mm) gradient elution hexane/ethyl acetate (5:1) to hexane/ethyl acetate (3:1) to give 8.26 g (86%) of **6b** as a white crystalline solid: mp 79.0–79.3 °C; IR ($CHCl_3$) 3010, 1765, 1585, 1481, 1390, 1200, 1131, 1055, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.10–7.48 (m, 10 H, aromatic), 4.2 (t, 1 H, C_5-*H*), 4.1 (t, 1 H, C_5-*H*), 4.06 (m, 1 H, C_4-*H*), 3.32 (dd, 1 H, CH_2Ph, J_{gem} = 13.7 Hz, J_{vic} = 3.7 Hz), 2.7 (dd, 1 H, CH_2Ph, J_{gem} = 13.7 Hz, J_{vic} = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 159.0, 135.8, 134.9, 129.3, 129.1, 128.8, 128.5, 128.4, 127.2, 67.3, 59.3, 38.5; $[\alpha]_{589}$ +51.5° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.36; H, 5.26. Found: C, 67.45; H, 5.19.

***m*-Chloroperoxybenzoic Acid Oxidation of 6b. Synthesis of 5b.** To a solution of 1.0 g (3.5 mmol) of **6b** in 20 mL of CH_2Cl_2 at −20 °C was added a solution of 0.85 g (4.9 mmol) of *m*-chloroperoxybenzoic acid in 20 mL of CH_2Cl_2. The reaction was stirred at −20 °C for 36 h, then quenched with 100 mL of saturated aqueous sodium bicarbonate, and diluted with 100 mL of CH_2Cl_2. The organic layer was removed, and the aqueous layer was extracted with 50 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo to give 1.18 g of a colorless oil. Analysis by HPLC (4.6 mm × 25 cm DuPont Zorbax, 5 mm silica gel, hexane/ethyl acetate (7:3), 2.0 mL/min) afforded a ratio of 2.5:1.0 of **5b(*R*)** (R_t = 5.3 min) to **5b(*S*)** (R_t = 6.3 min). Separation of the diastereomers was achieved by MPLC (Michel–Miller column, 40 mm × 350 mm) hexane/ethyl acetate (4:1) as eluant to give 0.71 g (68%) of **5b(*R*)** and 0.3 g (28%) **5b(*S*)**.

(4*S*)-4-Benzyl-3-(methylthio)-2-isoxazolidinone (6c). To a solution of 1.3 g (7.5 mmol) of the (4*S*)-phenylalanine-derived oxazolidin-2-one (HX_P) in 20 mL of THF under nitrogen at 0 °C was added 3.0 mL (2.5 M in hexane, 7.5 mmol) of *n*-butyllithium. The resulting suspension was stirred at 0 °C for 30 min. A solution of 1.0 g (7.9 mmol) of methyl methanethiolsulfonate[32] in 10 mL of THF was added over a 2-min period to the enolate suspension, the reaction was stirred at 0 °C for 10 min and room temperature for 90 min, and the product was isolated as described for the synthesis of **6b**. The resultant oil was purified by MPLC (Michel–Miller column, 40 mm × 350 mm) hexane/ethyl acetate (1:1) as eluant to give 1.3 g (77%) of **6c** which was recrystallized from hexane/diethyl ether as white needles: mp 54.9–55.7 °C; IR (CCl_4) 1775, 1387, 1354, 1265, 1210, 1100, 1141, 1050, 960, 731, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.37–7.16 (m, 5 H, aromatic), 4.2 (t, 1 H, C_5-*H*), 4.1 (t, 1 H, C_5-*H*), 4.05 (m, 1 H, C_4-*H*), 3.36 (dd, 1 H, CH_2Ph, J_{gem} = 13.7 Hz, J_{vic} = 3.7 Hz), 2.72 (dd, 1 H, CH_2Ph, J_{gem} = 13.7 Hz, J_{vic} = 9.3 Hz), 2.5 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 158.4, 134.9, 129.0, 128.7, 127.0, 66.9, 59.2, 38.6, 21.0; $[\alpha]_{589}$ +85° (*c* 1.0, acetone). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.19; H, 5.83. Found: C, 59.01; H, 5.94.

***m*-Chloroperoxybenzoic Acid Oxidation of 6c. Synthesis of 5c.** To a solution of 8.0 g (35.7 mmol) of **6c** in 50 mL of CH_2Cl_2 at −20 °C was added a clear solution of 9.3 g (53.8 mmol) of *m*-chloroperoxybenzoic acid in 150 mL of CH_2Cl_2. The reaction was stirred at −20 °C for 2 h, and the desired product was isolated as described in the oxidation of **6b** to give 8.1 g of a colorless oil. Analysis by HPLC (4.6 mm × 25 cm DuPont Zorbax, 5 mm silica gel, hexane/ethyl acetate (1:1), 20 mL/min) afforded a 1.4:1.0 ratio of **5c(*R*)** (R_t = 7.8 min) to **5c(*S*)** (R_t = 12.6 min). Separation of the diastereomers was achieved by MPLC (Michel–Miller column, 40 mm × 350 mm) hexane/ethyl acetate (1:1) as eluant to give 2.8 g (33%) **5b(*S*)**. The major diastereomer **5c(*R*)** was unstable to chromatography and proved difficult to obtain in pure form. The configuration at the sulfur center in the product diastereomers was determined by reaction with 1.5 equiv of phenylmagnesium chloride, which yielded (*R*)-methyl phenyl sulfoxide (vide infra). Assuming that inversion of configuration occurs at the sulfur center during the displacement, the absolute configuration of the isolated compound **5c** was assigned as (*S*).

(4*S*)-4-Benzyl-3-[(*R*)-methylsulfinyl]-2-isoxazolidinone (5c(*R*)): mp 96.3–97.7 °C; IR (CH_2Cl_2) 1770, 1608, 1385, 1182, 1124, 1100, 948 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.36–7.19 (m, 5 H, aromatic), 4.54 (m, 1 H, C_5-*H*), 4.20 (m, 2 H, C_5-*H*, C_4-*H*), 3.35 (dd, 1 H, CH_2Ph), 2.91 (m, 4 H, CH_3 and CH_2Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 155.9, 134.8, 129.0, 128.9, 127.5, 68.8, 52.8, 42.5, 40.8; $[\alpha]_{589}$ +25.94° (*c* 1.6, acetone). Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.23; H, 5.44. Found: C, 55.23; H, 5.63.

(4*S*)-4-Benzyl-3-[(*S*)-methylsulfinyl]-2-isoxazolidinone (5c(*S*)): mp 85–86 °C; IR (CH_2Cl_2) 1770, 1608, 1501, 1480, 1455, 1412, 1385, 1352, 1346, 1200, 1100, 1040, 990 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.19–7.35 (m, 5 H, aromatic), 4.55 (m, 1 H, C_5-*H*), 4.27 (t, 1 H, C_5-*H*), 4.15 (m, 1 H, C_4-*H*), 3.34 (dd, 1 H, CH_2Ph, J_{vic} = 4.9, J_{gem} = 13.9), 3.08 (s, 1 H, CH_3), 2.96 (dd, 1 H, CH_2Ph, J_{vic} = 9.0, J_{gem} = 13.9); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 154.7, 134.7, 129.2, 128.9, 127.5, 67.7, 56.6, 40.2, 40.0; $[\alpha]_{589}$ +131.7° (*c* 1.0, acetone); HRMS exact mass calcd for $C_{11}H_{13}NO_3S$ (M + Na) 262.0514, found 262.0497.

(4*S*)-4-Benzyl-3-(*tert*-butylthio)-2-isoxazolidinone (6d). To a solution of 1.9 g (10.9 mmol) of the (4*S*)-phenylalanine-derived oxazolidin-2-one (HX_P) in 20 mL of THF under nitrogen at 0 °C was added dropwise 4.4 mL (2.5 M in hexane, 7.5 mmol) of *n*-butyllithium. The resulting suspension was stirred at 0 °C for 20 min. A solution of 2.4 g (11.4 mmol) of *tert*-butyl 2-methyl-2-propanethiolsulfonate[33] in 10 mL of THF was added over a 2-min period to the enolate suspension, the reaction was stirred at 0 °C for 10 min and 75 °C for 46 h, and the product was isolated as described for the synthesis of **6b** to give 4.3 g of a pale yellow oil that was purified by MPLC (Michel–Miller column, 40 mm × 350 mm) hexane/ethyl acetate (3:1) to give 2.4 g (83%) of **6d** as a pale yellow solid which was recrystallized from hexane/ethyl acetate: mp 121.4–122.9 °C; IR (CCl_4) 1782, 1455, 1380, 1262, 1190, 1130 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ ppm 7.35–7.14 (m, 5 H, aromatic), 4.24 (t, 1 H, C_5-*H*), 4.07 (m, 2 H, C_5-*H* and C_4-*H*), 3.31 (dd, 1 H, CH_2Ph, J_{vic} = 2.8 Hz, J_{gem} = 14.0 Hz), 2.70 (dd, 1 H, CH_2Ph, J_{vic} = 9.8 Hz, J_{gem} = 13.4 Hz), 1.39 (s, 9 H, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.6, 135.2, 129.2, 128.9, 127.2, 66.4, 61.4, 50.4, 38.2, 29.2; $[\alpha]_{589}$ +58° (*c* 0.5, acetone). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.39; H, 7.17. Found: C, 63.33; H, 7.12.

***m*-Chloroperoxybenzoic Acid Oxidation of 6d. Synthesis of 5d.** To a solution of 1.2 g (4.5 mmol) of **6d** in 40 mL of CH_2Cl_2 at −20 °C was added a solution of 1.1 g (6.3 mmol) of *m*-chloroperoxybenzoic acid in 10 mL of CH_2Cl_2. The reaction was stirred at −20 °C for 75 min, and the desired product was isolated as described for the oxidation of **6b** to give 1.2 g of a colorless oil. Analysis by HPLC (4.6 mm × 25 cm DuPont Zorbax, 5 mm silica gel, hexane/ethyl acetate (4:1), 2.0 mL/min) afforded a 1.4:1.0 ratio of **5d(*R*)** (R_t = 6.9 min) to **5d(*S*)** (R_t = 14.5 min). Separation of the diastereomers was achieved by MPLC (Michel–Miller 51 mm × 450 mm) hexane/ethyl acetate (4:1) as eluant to give 0.447 g (35%) of **5d(*R*)** and 0.624 g (49%) of **5d(*S*)**. The configuration at the sulfur center in the product diastereomers was determined by nucleophilic displacement reactions with Grignard reagents assuming inversion of configuration occurs at the sulfur center during displacement (vida infra).

(4*S*)-4-Benzyl-3-[(*R*)-*tert*-butylsulfinyl]-2-isoxazolidinone (5d(*R*)): mp 135.6–136.3 °C; IR (CCl_4) 3117, 2970, 1770, 1550, 1454, 1390, 1251, 1195, 1121, 1090, 1006, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.36–7.19 (m, 5 H, aromatic), 4.43 (m, 1 H, C_5-*H*), 4.20 (m, 2 H, C_5-*H* and C_4-*H*), 3.43 (dd, 1 H, CH_2Ph, J_{vic} = 3.9 Hz, J_{gem} = 12.9 Hz), 2.67 (dd, 1 H, CH_2Ph, J_{vic} = 11.2 Hz, J_{gem} = 12.9 Hz), 1.4 (s, 9 H, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 158.4, 135.3, 129.0, 128.9, 127.4, 69.6, 59.4, 52.7, 41.6, 22.6; $[\alpha]_{365}$ +28.6° (*c* 1.1, acetone). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.78; H, 6.76. Found: C, 59.91; H, 6.74.

(4*S*)-4-Benzyl-3-[(*S*)-*tert*-butylsulfinyl]-2-isoxazolidinone (5d(*S*)): mp 88.5–89.9 °C; IR (CCl_4) 3117, 2971, 2928, 2909, 1775, 1548, 1372, 1338, 1250, 1231, 1220, 1130, 1092, 1002, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.36–7.20 (m, 5 H, aromatic), 4.45 (m, 1 H, C_5-*H*), 4.19 (m, 2 H, C_5-*H* and C_4-*H*), 3.58 (dd, 1 H, CH_2Ph, J_{vic} = 3.2 Hz, J_{gem} = 13.6 Hz), 2.88 (dd, 1 H, CH_2Ph, J_{vic} = 10.2 Hz, J_{gem} = 13.6 Hz), 1.38

(31) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405–4412.
(32) Methyl methanethiolsulfonate was purchased from the Aldrich Chemical Company.

(s, 9 H, $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 155.5, 135.6, 129.3, 128.9, 127.3, 67.7, 60.8, 57.7, 39.4, 22.8; $[\alpha]_{589}$ +63.7° (*c* 1.3, acetone). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.78; H, 6.76. Found: C, 59.44; H, 6.58.

General Procedure for the Preparation of Aryl–Alkyl Sulfoxides. To a solution of 1.0 g (3.17 mmol) of **5a**(*S*) in 20 mL of THF under nitrogen at −78 °C was added 6.34 mmol of alkylmagnesium halide over a 0.5-min period. The reaction mixture was stirred at −78 °C for 30 min, then quenched by the addition of 50 mL of saturated aqueous ammonium chloride, and diluted with 100 mL of ethyl acetate. The organic layer was removed, and the aqueous phase was extracted with 50 mL of ethyl acetate. The combined organic layers were washed with 100 mL of saturated aqueous sodium chloride and dried ($MgSO_4$), and the solvent was removed in vacuo. The resultant oil was purified by MPLC (Michel–Miller column, 30 mm × 350 mm). HPLC analysis was carried out using a chiral column (Pirkle Type 1A, 4.6 mm × 25 cm, hexane/isopropyl alcohol (98:2), 3 mL/min).

(*S*)-Methyl *p*-Tolyl Sulfoxide. MPLC purification was carried out by elution with hexane/ethyl acetate (1:4) to yield 0.44 g (90%) of (*S*)-methyl *p*-tolyl sulfoxide as a white crystallite solid and 0.52 g (92%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one. HPLC analysis indicated >99% enantiomeric excess: (*S*)-methyl *p*-tolyl sulfoxide (R_t = 22.2 min). (*R*)-Methyl *p*-tolyl sulfoxide (R_t = 23.6 min): mp 72.9–73.8 °C; ^1H NMR (250 MHz, $CDCl_3$) δ ppm 7.5 (d, 2 H, aromatic, *J* = 8.2 Hz), 7.3 (d, 2 H, aromatic, *J* = 7.9 Hz), 2.70 (s, 3 H, $ArCH_3$), 2.42 (s, 3 H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm 142.5, 141.2, 129.8, 123.4, 44.0, 21.4; $[\alpha]_{589}$ −159° (*c* 1.3, EtOH); lit.[18] $[\alpha]_{589}$ +156° (EtOH) for (*R*)-methyl *p*-tolyl sulfoxide.

(*S*)-Ethyl *p*-Tolyl Sulfoxide. MPLC purification was carried out by elution with hexane/ethyl acetate (1:9) to give 0.48 g (90%) of (*S*)-ethyl *p*-tolyl sulfoxide as a colorless oil and 0.56 g (91%) of (4*S*)-phenylalanine-derived oxazolidin-2-one. HPLC analysis indicated 98% enantiomeric excess: (*S*)-ethyl *p*-tolyl sulfoxide (R_t = 16.4 min). (*R*)-Ethyl *p*-tolyl sulfoxide (R_t = 17.9 min): ^1H NMR (250 MHz, $CDCl_3$) δ ppm 7.5 (d, 2 H, aromatic, *J* = 8.2 Hz), 7.3 (d, 2 H, aromatic, *J* = 7.9 Hz), 2.80 (m, 2 H, CH_2), 2.40 (s, 3 H, $ArCH_3$), 1.17 (t, 3 H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm 140.9, 139.9, 129.0, 123.8, 50.0, 21.1, 5.7; $[\alpha]_{589}$ −204° (*c* 2.0, acetone); lit.[2a] $[\alpha]_{589}$ −186° (*c* 2.0, acetone).

(*S*)-Isopropyl *p*-Tolyl Sulfoxide. MPLC purification was carried out by elution with hexane/ethyl acetate (1:1) to give 0.53 g (91%) of (*S*)-isopropyl *p*-tolyl sulfoxide as a colorless oil and 0.47 g (85%) of (4*S*)-phenylalanine-derived oxazolidin-2-one. HPLC analysis indicated 97% enantiomeric excess: (*S*)-isopropyl *p*-tolyl sulfoxide (R_t = 11.9 min). (*R*)-Isopropyl *p*-tolyl sulfoxide (R_t = 13.1 min): ^1H NMR (250 MHz, $CDCl_3$) δ ppm 7.5 (d, 2 H, aromatic, *J* = 8.2 Hz), 7.3 (d, 2 H, aromatic, *J* = 7.9 Hz), 2.8 (m, 1 H, C*H*), 2.4 (s, 3 H, $ArCH_3$), 1.17 (dd, 6 H, $(CH_3)_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm 141.0, 138.4, 129.3, 124.8, 54.4, 21.3, 15.7, 13.9; $[\alpha]_{589}$ −181° (*c* 2.6, acetone); lit.[6a] $[\alpha]_{589}$ +176° (*c* 2.6, acetone) for (*R*)-isopropyl *p*-tolyl sulfoxide.

(*S*)-*tert*-Butyl *p*-Tolyl Sulfoxide. MPLC purification was carried out by elution with hexane/ethyl acetate (2:3) to give 0.55 g (88%) of (*S*)-*tert*-butyl *p*-tolyl sulfoxide as a white solid and 0.47 g (83%) of (4*S*)-phenylalanine-derived oxazolidin-2-one. HPLC analysis indicated 97% enantiomeric excess: (*S*)-*tert*-butyl *p*-tolyl sulfoxide (R_t = 11.1 min). (*R*)-*tert*-Butyl *p*-tolyl sulfoxide (R_t = 12.5 min): mp 88.2–88.8 °C; ^1H NMR (250 MHz, $CDCl_3$) δ ppm 7.5 (d, 2 H, aromatic, *J* = 8.2 Hz), 7.3 (d, 2 H, aromatic, *J* = 7.9 Hz), 2.40 (s, 3 H, $ArCH_3$), 1.12 (s, 9 H's, $(CH_3)_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm 141.3, 136.8, 128.9, 126.1, 55.6, 22.8, 21.4; $[\alpha]_{589}$ −184.8° (*c* 0.77 EtOH); lit.[34] $[\alpha]_{589}$ −190° (*c* 0.77, EtOH).

(*S*)-Benzyl *p*-Tolyl Sulfoxide. The General Procedure was followed as described except 0.5 g (1.58 mmol) of **5a**(*S*) was employed and reacted with 1.58 mL (2.0 M in THF, 3.17 mmol) of benzylmagnesium chloride. MPLC purification was carried out by elution with hexane/ethyl acetate (2:3) to give 0.305 g (89%) of (*S*)-benzyl *p*-tolyl sulfoxide as a white crystalline solid and 0.23 g (80%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one. HPLC analysis indicated a 94% enantiomeric excess: (*S*)-benzyl *p*-tolyl sulfoxide (R_t = 19.5 min). (*R*)-Benzyl *p*-tolyl sulfoxide (R_t = 23.0 min). Recrystallization from ethanol followed by repeated HPLC analysis showed an enantiomeric excess >99% for (*S*)-benzyl *p*-tolyl sulfoxide: mp 168.8–169.3 °C; lit.[35] 169–169.5 °C; ^1H NMR (250 MHz, $CDCl_3$) δ ppm 7.31–7.2 (m, 7 H, aromatic), 7.0–6.97 (m, 2 H, aromatic), 4.02 (m, 2 H, CH_2), 2.38 (s, 3 H, $ArCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm 141.4, 139.5, 130.2, 129.4, 128.3, 128.0, 124.4, 63.8, 21.5; $[\alpha]_{589}$ −213.2° (*c* 1.0, acetone); lit.[6a] $[\alpha]_{589}$ +252° (*c* 1.0, acetone).

(*R*)-Methyl Phenyl Sulfoxide. The General Procedure was followed as described except 0.4 g (1.67 mmol) of **5c**(*S*) was employed as the sulfinyl transfer reagent which was treated with 1.25 mL (2.0 M in THF, 2.5 mmol) of phenylmagnesium chloride. MPLC purification was carried out by elution with hexane/ethyl acetate (1:4) to give 0.256 g (87%) of (*R*)-methyl phenyl sulfoxide as a colorless oil and 0.315 g (85%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.48–7.65 (m, 5 H, aromatic), 2.71 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 145.3, 130.7, 129.0, 123.1, 43.6; $[\alpha]_{589}$ +121° (*c* 1.5, acetone); lit.[36] $[\alpha]_{589}$ +149° (*c* 1.5, acetone). Chiral shift studies using (*R*)-(trifluoroacetyl)(1-naphthylethyl)amine[37] indicated that the product (*R*)-methyl phenyl sulfoxide had an enantiomeric excess >90%.

General Procedure of the Preparation of Dialkyl Sulfoxides. The quantities of reagents and the reaction time required are given in the individual experimentals. When complete the reactions were quenched by the addition of 50 mL of saturated aqueous ammonium chloride and diluted with 100 mL of ethyl acetate. The organic layer was removed, and the aqueous phase layer was extracted with 50 mL of ethyl acetate. The combined organic layers were washed with 100 mL of saturated aqueous sodium chloride and dried ($MgSO_4$), and the solvent was removed in vacuo. The resultant oil was purified by MPLC (Michel–Miller column, 30 mm × 350 mm).

(*R*)-*tert*-Butyl Methyl Sulfoxide. To a solution of 0.4 g (1.67 mmol) **5c**(*S*) in 5 mL of THF under nitrogen at −78 °C was added 1.25 mL (2.0 M in THF, 2.51 mmol) of *tert*-butyl magnesium chloride. The reaction was stirred at −78 °C for 10 min. MPLC purification was carried out by elution with ethyl acetate/methanol (98:2) to give 0.155 g (78%) of (*R*)-*tert*-butyl methyl sulfoxide as a colorless oil and 0.290 g (98%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.38 (s, 3 H, CH_3), 1.95 (s, 9 H, $(CH_3)_3$; ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 31.4, 22.3; $[\alpha]_{589}$ −7.3° (*c* 1.0, $CHCl_3$); lit.[38] $[\alpha]_{589}$ +7.55° (*c* 1.0, $CHCl_3$). Chiral shift studies using (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)(1-phenylethyl)amine indicated that the product had an enantiomeric excess >98%.[37]

(*S*)-*tert*-Butyl Methyl Sulfoxide. To a solution of 1.0 g (3.56 mmol) of **5d**(*S*) in 10 mL of THF under nitrogen at −78 °C was added 1.78 mL (3.0 M in Et_2O, 5.34 mmol) of methyl magnesium bromide. The reaction was stirred at −78 °C for 24 h. MPLC purification was carried out by elution with ethyl acetate/methanol (98:2) to give 0.392 g (92%) of (*S*)-*tert*-butyl methyl sulfoxide as a colorless oil and 0.601 g (95%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: $[\alpha]_{589}$ +7.8° (*c* 1.0, $CHCl_3$). Chiral shift studies using (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)(1-phenylethyl)amine indicated that the product had an enantiomeric excess >98%.[37]

(*R*)-Benzyl Methyl Sulfoxide. To a solution of 0.3 g (1.25 mmol) of **5c**(*S*) in 5 mL of THF under nitrogen at −78 °C was added 0.94 mL (2.0 M in THF, 1.88 mmol) of benzyl magnesium chloride. The reaction was stirred at −78 °C for 30 min. MPLC purification was carried out by gradient elution with hexane/ethyl acetate (1:2)–ethyl acetate (100%) to give 0.158 g (82%) of (*R*)-benzyl methyl sulfoxide as a white solid and 0.215 g (98%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: mp 53–55 °C; lit.[39] 53–54 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.37–7.26 (m, 5 H, ArH), 3.96 (dd, 2 H, CH_2Ph), 2.42 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 129.6, 129.3, 128.4, 127.9, 59.6, 36.8; $[\alpha]_{589}$ +50° (*c* 0.9, $CHCl_3$); lit.[40] $[\alpha]_{589}$ −55° (*c* 0.9, $CHCl_3$) for (*S*)-benzyl methyl sulfoxide.

(*R*)-Methyl Octyl Sulfoxide. To a solution of 0.5 g (2.09 mmol) of **5c**(*S*) in 5 mL of THF under nitrogen at −78 °C was added 3.14 mmol of freshly prepared octyl magnesium bromide in 10 mL of THF. The reaction was stirred at −78 °C for 10 min. MPLC purification was carried out by elution with ethyl acetate/methanol (98:2) to give 0.286 g (78%) of (*R*)-methyl octyl sulfoxide as a crystalline solid and 0.336 g (91%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.76–2.62 (m, 2 H, CH_2), 2.56 (s, 3 H, CH_3), 1.78–1.71 (m, 2 H, CH_2), 1.48–1.25 (m, 10 H, $((CH_2)_5)$,

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0.9–0.86 (t, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 54.1, 38.0, 31.2, 28.8, 28.6, 28.5, 28.2, 22.0, 13.5; $[\alpha]_{589}$ −79.7° (*c* 0.5, acetone); lit.[6a] $[\alpha]_{589}$ −62° (*c* 0.5, acetone).

(*S*)-*n*-Butyl *tert*-Butyl Sulfoxide. To a solution of 0.5 g (1.78 mmol) of **5d(*S*)** in 5 mL of THF under nitrogen at −78 °C was added 1.33 mL (2.0 M in Et_2O, 2.67 mmol) of *n*-butyl magnesium chloride. The reaction was stirred at −78 °C for 3 h. MPLC purification was carried out with ethyl acetate/CH_2Cl_2 (1:1) to give 0.262 g (91%) (*S*)-*n*-butyl *tert*-butyl sulfoxide as a colorless oil and 0.285 g (91%) recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.53–2.41 (m, 2 H, CH_2), 1.90–1.71 (m, 2 H, CH_2), 1.59–1.41 (m, 2 H, CH_2), 1.25 (s, 9 H, $((CH_3)_3)$, 0.99–0.97 (t, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 52.2, 44.9, 25.3, 22.4, 21.8, 13.1; $[\alpha]_{589}$ −129° (*c* 1.02, acetone); lit.[5b] $[\alpha]_{589}$ +125° (*c* 1.0, acetone) for (*R*)-*n*-butyl *tert*-butyl sulfoxide.

(*S*)-*tert*-Butyl (Phenylsulfinyl)acetate (7). A three-necked 100-mL flask equipped with a condenser and a dropping funnel was charged with 1.57 g (24.0 mmol) of activated zinc and 20 mL of THF. After the addition of a small crystal of iodine, a portion of the 4.5 g (23 mmol) of *tert*-butyl bromoacetate in 20 mL of THF was added from the dropping funnel, and the reaction mixture was brought to reflux with vigorous stirring. The remaining *tert*-butyl bromoacetate solution was added at a rate that maintained a gentle reflux (10 min) without heating. The reaction mixture was heated at reflux for a 30-min period. The resultant greenish solution was cooled to 50 °C, and solid **5b(*S*)** (2.7 g, 0.9 mmol) was rapidly added. The clear solution was cooled to 40 °C and stirred for 1 h. The reaction was quenched by addition of 70 mL of saturated aqueous ammonium chloride and diluted with 80 mL of diethyl ether. The aqueous layer was extracted with 30 mL of CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to leave 4.51 g of a pale yellow oil. Flash chromatography on silica gel [3.5 × 15 cm + 2 cm of alumina on the top of the silica (alumina decomposes the small amount of starting material present in the reaction mixture), hexane/ethyl acetate (2:1) as eluant] gave 1.75 g (81%) of **7(*S*)** as a white solid, which can be recrystallized from hexane as white needles and 1.57 g (98%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: mp 69.5–70.0 °C; IR ($CHCl_3$) 3005, 2990, 1723, 1448, 1397, 1371, 1300, 1157, 1090, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.70–7.75 (m, 2 H, aromatic H), 7.52–7.60 (m, 3 H, aromatic), 3.81 (d, 1 H, S(O)C*H*, *J* = 13.7 Hz), 3.60 (d, 1 H, S(O)C*H*, *J* = 13.7 Hz), 1.40 (s, 9 H, C-CH_3); $[\alpha]_{589}$ −146° (*c* 2.25, EtOH).

The enantiomeric purity was determined on a sample of (*R*)-*tert*-butyl (*p*-toluenesulfinyl)acetate, $[\alpha]_{589}$ +166.6° (*c* 1.0, EtOH), obtained by a similar procedure from **4a(*R*)**. Chiral shift studies with tris[3-(heptafluoropropylhydroxymethylene)-*d*-camporato]europium(III) indicated that the product (*R*)-*tert*-butyl (*p*-toluenesulfinyl)acetate had an enantiomeric excess >98%.

(*S*)-Methyl *p*-Toluenesulfinate (8, R = Me). To a solution of 5.1 mL (126 mmol) of methanol in 40 mL of THF under nitrogen at 0 °C was added dropwise 5.04 mL (2.5 M in hexane, 12.6 mmol) of *n*-butyllithium over a 5-min period. The solution was stirred at 0 °C for 20 min, cooled to −78 °C, stirred for 10 min, and treated with 1.0 g (3.17 mmol) of **5a(*S*)**. The reaction mixture was stirred at −78 °C for 90 s, then quenched by the addition of 50 mL of saturated aqueous ammonium chloride, and diluted with 50 mL of diethyl ether. The organic layer was removed, and the aqueous layer was extracted with 50 mL of diethyl ether. The combined organic layers were washed with 50 mL of saturated aqueous sodium chloride and dried ($MgSO_4$), and the solvent was removed in vacuo to give an oil that was purified by MPLC (Michel-Miller column, 30 mm × 350 mm) gradient elution hexane/ethyl acetate (4:1) to hexane/ethyl acetate (1:1) to yield 0.43 g (80%) of **8(*S*)** (R = Me) and 0.46 g (81%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: IR ($CHCl_3$) 3510–3310, 1600, 1494, 1130, 965, 883, 818, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ ppm (7.5 (d, 2 H, aromatic, *J* = 8.2 Hz), 7.3 (d, 2 H, aromatic, *J* = 8.0 Hz), 3.44 (s, 3 H, CH_3O), 2.42 (s, 3 H, ArCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm 142.3, 140.6, 129.3, 124.9, 48.9, 21.1; $[\alpha]_{589}$ −201.3° (*c* 4.5, EtOH); lit.[41] $[\alpha]_{589}$ +218.8° (*c* 4.5, EtOH) for (*R*)-methyl *p*-toluenesulfinate. Use of the chiral shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated that the product methyl *p*-toluenesulfinate had an enantiomeric excess of >95%.

(*R*)-Isopropyl *p*-Toluenesulfinate (8, R = *i*-Pr). To a solution of 0.53 mL (0.42 g, 6.92 mmol) of isopropyl alcohol in 5 mL of THF under nitrogen at 0 °C was added 1.44 mL (2.0 M in hexane, 2.88 mmol) of *n*-butyllithium over 1 min. The solution of lithium isopropoxide was then cooled to −78 °C and treated with 0.17 g (0.56 mmol) of **4a(*R*)** in 4 mL of THF. The reaction mixture was stirred at −78 °C for 1 min and then quenched by addition of 1.5 mL of acetic acid in 3 mL of THF. After dilution with 30 mL of diethyl ether, the mixture was washed with 4 × 20 mL of saturated aqueous ammonium bicarbonate, 20 mL saturated aqueous ammonium chloride, and 20 mL saturated aqueous sodium chloride. The organic phase was dried ($MgSO_4$), and the solvent was removed in vacuo to leave 0.255 g of a colorless oil. Purification by flash chromatography on silica gel (2 × 15 cm, hexane/ethyl acetate (4:1)) yielded 0.102 g (92%) of **8(*R*)** (R = *i*-Pr) as a colorless oil: IR (liquid film) 2980, 2930, 2870, 1600, 1495, 1465, 1450, 1385, 1375, 1180, 1140, 1135, 1102, 1080, 1015, 915, 905, 840, 810, 740, 710, 700, 635, 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 7.60 (d, 2 H, aromatic, *J* = 8.2 Hz), 7.32 (d, 2 H, aromatic, *J* = 8.2 Hz), 4.6 (s, 1 H, S(O)C*H*, *J* = 6.2 Hz), 2.41 (s, 3 H, ArCH_3), 1.38 (d, 3 H, CH_3, *J* = 6.2 Hz), 1.24 (d, 3 H, CH_3, *J* = 6.2 Hz); $[\alpha]_{589}$ +199.7° (*c* 2.2, EtOH); lit.[25] $[\alpha]_{589}$ +199.9°.

(*S*)-(*N*,*N*)-Diethyl *p*-Toluenesulfinamide (9). To a solution of 1.63 mL (15.8 mmol) of diethylamine (dried over 4 Å molecular sieves) in 15 mL of THF under nitrogen at 0 °C was added dropwise 3.17 mL (3.0 M in diethyl ether, 9.5 mmol) of methylmagnesium bromide, and the resultant solution was stirred at 0 °C for 10 min and then at room temperature for 2 h. The pale yellow solution was cooled to −78 °C and stirred for 5 min, and 1.0 g (3.17 mmol) of **5a(*S*)** in 10 mL of THF added. After stirring at −78 °C for 25 min, the reaction was quenched by the addition of 25 mL of saturated aqueous ammonium chloride and diluted with 25 mL of diethyl ether. The organic layer was removed, and the aqueous layer was extracted with 25 mL of diethyl ether. The combined organic layers were washed with 25 mL of saturated aqueous sodium chloride and dried ($MgSO_4$), and the solvent was removed in vacuo to give a pale yellow oil that was purified by MPLC (Michel-Miller column, 30 mm × 350 mm) hexane/ethyl acetate (1:1) as eluant to give 0.61 g (91%) of **9(*S*)** and 0.52 g (93%) of recovered (4*S*)-phenylalanine-derived oxazolidin-2-one: IR (liquid film) 2982, 2942, 2880, 1600, 1495, 1468, 1458, 1385, 1190, 1180, 1090, 1070, 1015, 900, 820, 785, 710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ ppm 7.54 (d, 2 H, aromatic, *J* = 8.2 Hz), 7.24 (d, 2 H, aromatic, *J* = 8.0 Hz), 3.13 (qn, 4 H, N-CH_2), 2.41 (s, 3 H, ArCH_3), 1.12 (t, 6 H, 2(CH_3), *J* = 7.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm 141.1, 140.5, 129.2, 126.0, 41.8, 21.2, 14.4; $[\alpha]_{589}$ −106° (*c* 2.6, acetone); lit.[42] $[\alpha]_{589}$ +110° (acetone) for (*R*)-*N*,*N*-diethyl *p*-toluenesulfinamide; HPLC analysis using a chiral column (Pirkle type 1A, 4.6 mm × 25 cm, hexane/isopropyl alcohol (99:1), 0.8 mL/min) indicated a 98% enantiomerically pure compound; **9(*S*)** (R_t = 25.7 min); **9(*R*)** (R_t = 26.8 min).

Competition Experiment between (*S*)-(−)-Menthyl *p*-Toluenesulfinate and (4*S*)-4-Benzyl-3-[(*S*)-*p*-tolylsulfinyl]-2-isoxazolidinone (5a(*S*)). A solution of methyl magnesium bromide (0.3 mL, 0.47 mmol) was added slowly to a solution of (*S*)-(−)-menthyl *p*-toluenesulfinate (0.46 g, 1.58 mmol) and **5a(*S*)** (0.5 g, 1.58 mmol) and 1,2-dimethoxyethane (0.08 g, 6.32 mmol), which was used as an internal standard, in anhydrous benzene (10 mL) under nitrogen at 0 °C. The reaction mixture was then stirred at 0 °C for 1 h and quenched by the addition of 20 mL of saturated aqueous ammonium chloride and diluted with diethyl ether. The organic layer was then washed with saturated sodium chloride solution and dried ($MgSO_4$). The solvent was concentrated in vacuo to give an oil which was examined by analytical HPLC (4.6 mm × 25 cm DuPont Zorbax, 5 mm silica gel, hexane/ethyl acetate (85:15), 2 mL/min). The results indicate that **5a(*S*)** is at least two orders of magnitude more reactive than (*S*)-(−)-menthyl *p*-toluenesulfinate.

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