Enantioselective Synthesis of 1,4-Dihydrobenzoxathiins via Sulfoxide-Directed Borane Reduction

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Received 12 May 2006; revised 5 June 2006

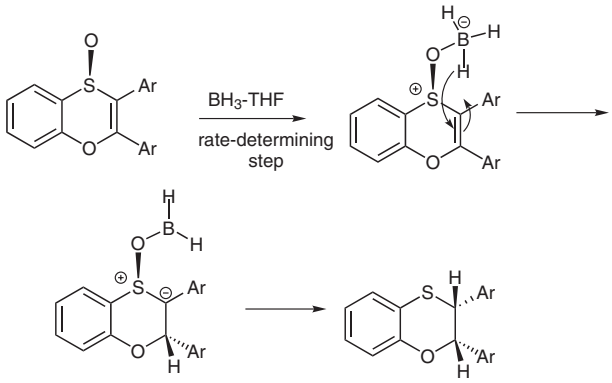
Abstract: A novel sulfoxide-directed borane reduction was shown to give a variety of 2-substituted 1,4-dihydrobenzoxathiins. For all substrates evaluated, the reaction is completely stereospecific. Application of this methodology to the chiral synthesis of an artificial sweetener was demonstrated.

Key words: asymmetric synthesis, sulfoxide, dihydrobenzoxathiin, reduction

The dihydrobenzoxathiin ring structure is present in a variety of compounds of biological interest, including antihypertensive agents, antioxidants, estrogen receptor modulators, adrenoreceptor antagonists and artificial sweeteners.[1] Previous methods for the preparation of the dihydrobenzoxathiin core structure include intramolecular alkoxide displacement,[1a] ring-closing Michael addition of a phenol to an α,β-unsaturated ester,[2] Diels–Alder reactions of *o*-thioquinones with substituted styrenes,[3] and acid-catalyzed reductive ring closure of phenol ketones.[4] Although extension of these methodologies would be expected to allow for absolute stereochemical control of the C-2 and C-3 dihydrobenzoxathiin centers, examples of such stereocontrol have been conspicuously absent from the literature.

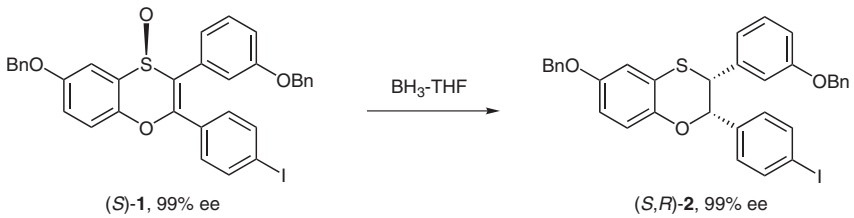
During the development of a practical synthesis of a selective estrogen receptor modulator (SERM),[5] we discovered a novel sulfoxide directed borane reduction of vinyl sulfoxide **1** which gave dihydrobenzoxathiin **2** with complete stereospecificity (Equation 1). This unusual and efficient reaction was unprecedented in the literature.[6]

In our initial study, we demonstrated through labeling experiments with BD_3 that the reduction of **1** occurs with both hydrogens originating from the borane species. We also observed that the stereoconfigurations of the newly generated centers are independently controlled by the chiral sulfoxide.[7] From these results and additional kinetic data, we proposed the mechanism shown in Scheme 1 in which the sulfoxide directs the borane to deliver the two hydrogens from the same face of the molecule as the oxygen.[8] In further studies, the reaction rates of **1** with BH_3-THF and BD_3-THF were measured and the isotope effect k_H/k_D was determined to be 1.4. This low value is consistent with hydride transfer not being the rate-determining step.[9] A plausible scenario is that transfer of the borane from THF to the sulfoxide is rate-determining.[9e]



Scheme 1 Proposed mechanism for borane reduction

The generality of this novel oxidation–reduction sequence for the enantioselective synthesis of dihydrobenzoxathiins has not previously been demonstrated. Herein we wish to report the enantioselective synthesis of a variety of 2-substituted-1,4-benzoxathiins. We further demonstrate the value of this novel methodology by completing the first enantioselective synthesis of isovanillin sweetener **14**.



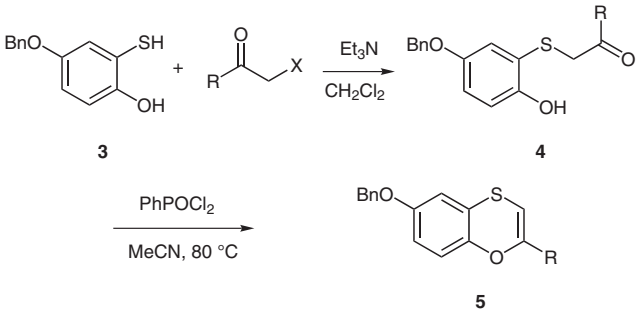
(*S*)-**1**, 99% ee (*S*,*R*)-**2**, 99% ee

Equation 1

SYNTHESIS 2006, No. 20, pp 3389–3396
Advanced online publication: 10.10.2006
DOI: 10.1055/s-2006-950243; Art ID: M03106SS

Previously the precursor 1,4-benzoxathiins have been prepared in modest yield by intramolecular ring closure of alkynylselenonium salts[10] and, more recently, via sodium hydride-induced ring opening and closing of 5-aryloxy-1,2,3-thiadiazoles.[11] Dehydrative cyclization of phenol ketones would provide a facile entry into the benzoxathiin core and we have found that phenylphosphonic dichloride is an effective dehydrating agent for this purpose.[5] Thus, a series of dihydroquinones **4** were prepared in good yield by alkylation of 2-mercapto-1,4-dihydroquinone **3** with commercially available α-haloketones. When the crude dihydroquinones **4** were treated with two equivalents of phenylphosphonic dichloride in acetonitrile, the desired benzoxathiins **5a–e** were isolated in 40–88% yield from **3** (Table 1).

Table 1 Preparation of 1,4-Benzoxathiins

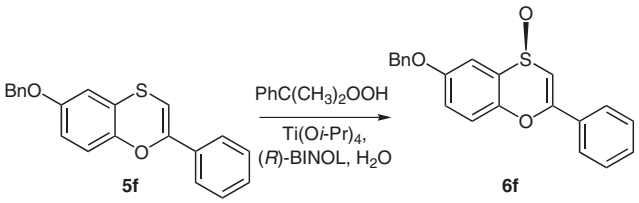


Entry	Product	R	Yield (%)
1	**5a**	4-$CH_3C_6H_4$	69
2	**5b**	4- $CH_3OC_6H_4$	40
3	**5c**	4-BrC_6H_4	88
4	**5d**	CH_3	55
5	**5e**	*t*-Bu	71

With the benzoxathiin substrates in hand, we turned our attention to the development of an efficient asymmetric oxidation of the sulfide.[12] The Kagan system which employs Ti(O*i*-Pr)$_4$/diethyl tartrate/water as the catalyst system has been shown to be particularly effective in achieving high selectivity for alkyl aryl sulfides.[13] Modifications of the original procedure have been reported allowing the use of catalytic amounts of the titanium reagent and using alternate ligands that provide enhanced selectivity for specific substrates.[14] Previously, we reported that the oxidation to give **1** in 90–91% ee was best performed using a modified Kagan-type oxidation.[15] When the 2-phenyl-1,4-benzoxathiin **5f** was subjected to the same oxidation conditions, the sulfoxide **6f** was obtained in only 7% ee.[16] Using the original Kagan system at room temperature,[17] the sulfoxide **6f** was obtained with only slightly better enantioselectivity (33% ee). A variety of alternate ligands was evaluated under the same conditions; none gave significantly improved enantioselectivity.

Uemura and co-workers have shown that BINOL is an effective ligand for catalytic titanium-mediated oxidation of alkyl aryl sulfides.[14a] In contrast to the tartrate system, the Uemura system requires at least a full equivalent of water relative to the sulfide, and nonpolar solvents to obtain high yields and enantioselectivities, CCl_4 being optimal. Oxidation of **5f** with cumene hydroperoxide using a stoichiometric amount of the catalyst mixture 2:1:20 Ti(O*i*-Pr)$_4$/(*R*)-BINOL/H_2O gave the sulfoxide **6f** in 54% ee (Table 2, entry 1). Several solvent systems were evaluated as an alternative to using CCl_4. Slightly reduced enantioselectivity was seen with toluene (entry 2) and using DME gave racemic product (entry 3). Interestingly, when the oxidation was run in ester solvents, good conversion was seen with enantioselectivity comparable to the CCl_4 system. Ethyl, isopropyl, and butyl acetate all gave reasonable enantioselectivity (entries 4–6) for the sulfoxide.

Table 2 Optimization of the Oxidation Sulfide **5f** to Sulfoxide **6f**

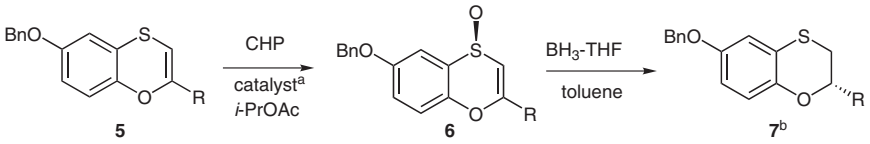


Entry	Solvent	ee (%)
1	CCl_4	54
2	toluene	38
3	dimethoxyethane	0
4	EtOAc	52
5	*i*-PrOAc	54
6	*n*-BuOAc	55

A variety of aryl and alkyl 1,4-benzoxathiins were oxidized with cumene hydroperoxide using a 15 mol% catalyst mixture of 2:1:20 (*R*)-BINOL/Ti(O*i*-Pr)$_4$/H_2O in isopropyl acetate at room temperature. The observed enantioselectivity varied greatly for the substrates. Aryl substrates bearing electron-donating and electron-neutral substituents gave modest selectivity (48 and 52%, Table 3, entries 1, 2). For aryl substrates with an electron-withdrawing substituent (Table 3, entry 3), significantly decreased enantioselectivity was obtained. For the alkyl substrates, the methyl compound gave only modest 52% ee (entry 4), while the more bulky *tert*-butyl substrate gave excellent selectivity (entry 5), giving the sulfoxide in 96% ee.

Upon completion of the oxidation reaction, the crude reaction mixtures were passed through silica gel, diluted with toluene and treated with 1.2 equivalents of borane-THF to effect olefin reduction. In every instance, the sulfoxide-directed reduction occurred with complete stereospecificity and generally good yields to provide the

Table 3 Enantioselective Preparation of 1,4-Dihydrobenzoxathiins

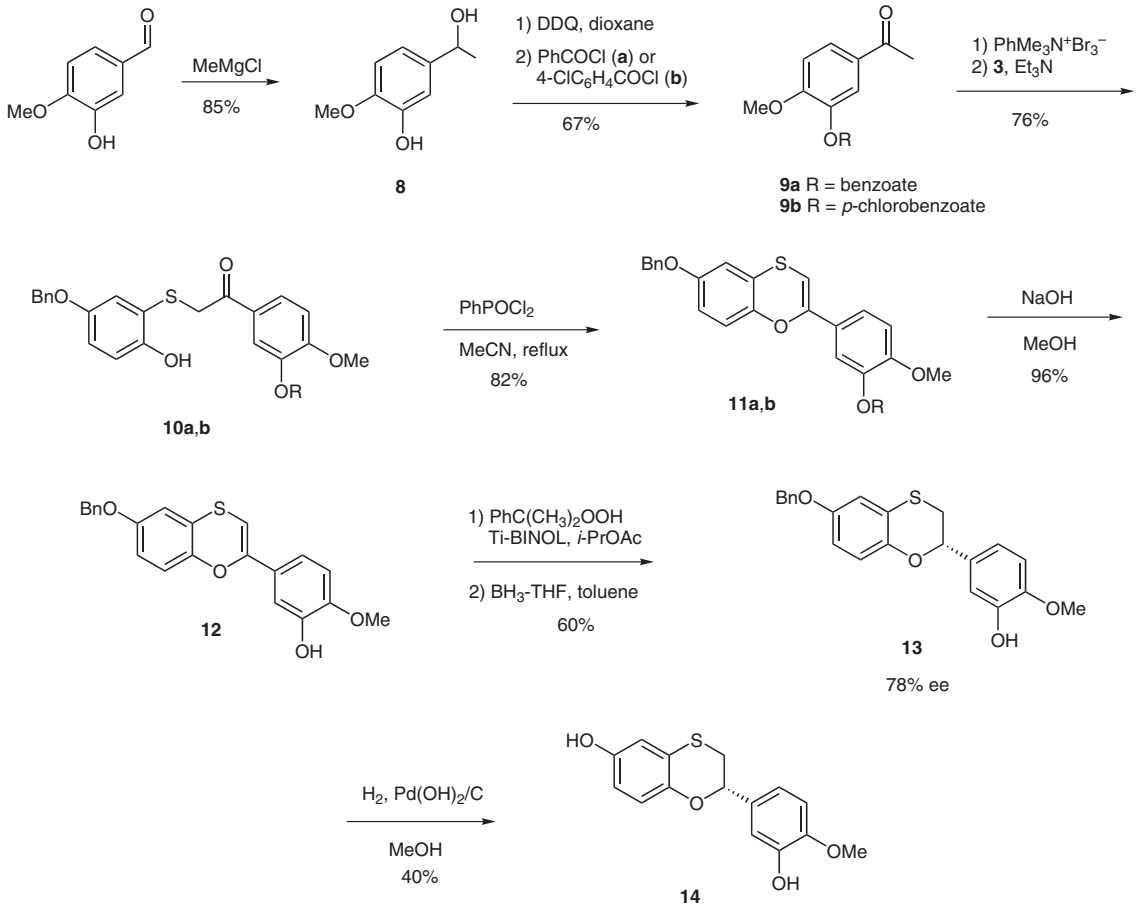


Entry	Product	R	**6** ee (%)	**7** ee (%)	Yield (%)
1	**7a**	*p*-Tol	59	60	64
2	**7b**	4-$MeOC_6H_4$	48	48	70
3	**7c**	4-BrC_6H_4	26	26	68
4	**7d**	Me	52	51	63
5	**7e**	*t*-Bu	96	97	86

[a] The catalyst was 15 mol% of 2:1:20 (*R*)-BINOL/Ti(O*i*-Pr)$_4$/H_2O.
[b] The *S*-configuration was assigned based on X-ray data of **7e** (see below).

enantiomerically enriched dihydrobenzoxathiin. The enantiomeric excess of the reduced products were identical to that of the sulfoxide intermediates. This is consistent with our previous observations and the proposed mechanism in Scheme 2.

The absolute configuration of product **7e** was unambiguously determined as the (*S*)-dihydrobenzoxathiin by X-ray crystallography on a single crystal (Figure 1).[18] Thus the corresponding chiral sulfoxide **6e** is believed to be the *S*-isomer based on the known correlation between the sulfoxide **1** and the dihydrobenzoxathiin **2**.[19]



Scheme 2

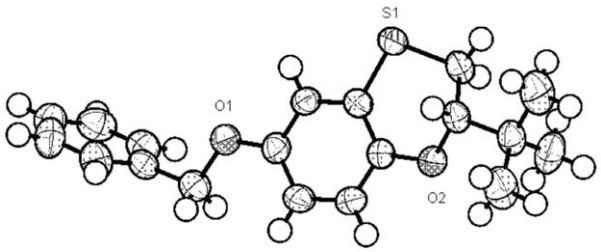


Figure 1 ORTEP diagram of **7e**

This oxidation-reduction sequence allows for the preparation of a class of compounds which were previously available only in racemic form. We applied this reduction methodology to the preparation of potential food additives such as **14**, a compound reported to be 500 times sweeter than sucrose.[1e] The synthesis starting from isovanillin is shown in Scheme 2. Grignard addition to the aldehyde[20] followed by oxidation with DDQ[21] furnished the ketone intermediate.[22] Since previous experiments have shown that the dehydrative cyclization is more effective when the aromatic ring contains electron-withdrawing substituents (Table 1, entries 1–3), the phenol was protected as an ester. Using the benzoate ester, the dehydrative cyclization gave the desired product **11a** in only 60% yield. To decrease the aromatic ring electron-density, the *p*-chlorobenzoate **9b** was prepared. After bromination and alkylation with **3** to give the hydroxyketone **10b**, the dehydrative cyclization cleanly furnished the desired benzoxathiin **11b** in 82% isolated yield.

Although electron-poor substrates are more effective in the cyclization, the resulting benzoxathiins give lower selectivity in the subsequent oxidation (Table 3, entries 1–3). Compound **11** was oxidized using the typical procedure, giving the sulfoxide in only 40% ee. When the ester group was hydrolyzed to give the free phenol, oxidation of compound **12** gave the corresponding sulfoxide in 78% ee. Borane reduction of the crude product furnished the desired dihydrobenzoxathiin **13** in 78% ee and 60% yield. Debenzylation via hydrogenolysis using Pearlman's catalyst provided the target compound **14** in 40% yield, completing the first asymmetric synthesis of this compound.

In summary, we have developed a practical and catalytic asymmetric synthesis of 1,4-dihydrobenzoxathiins, which was successfully applied to the asymmetric synthesis of a sweetener. This novel sulfoxide-directed reduction methodology should find its applications in the synthesis of similar compounds.

All solvents and reagents were obtained from commercial sources and used without further purification. BD_3-THF was purchased from Alfa Aesar. Reactions were run under N_2 and monitored by HPLC on an HP1100. Flash chromatography was performed on silica gel (230–400 mesh). NMR data were obtained on a Bruker 400 MHz instrument. Racemic sulfoxides were prepared by oxidation with MCPBA for use as reference compounds for ee determination. Melting points are uncorrected.

Determination of Kinetic Isotope Effect

A slurry of **1** in CH_2Cl_2 (59.5 mg/mL) was cooled and maintained at –12 °C. A solution of borane (10–30 mol%) was added and the reaction progress monitored by React-IR. Kinetic data was collected and analyzed from 5% to 90% completion to determine the rate constants. The reaction has previously been shown to be first order in both borane and substrate. The experimental rate constants from two separate runs are shown below in Table 4.

Table 4 Kinetics of Borane Reduction of **1**

Borane	Conversion (mol%)	k_{obs} (s^{-1})	k_{obs} Borane (average)
BH_3	28.9	5.1×10^{-4}	6.0×10^{-4}
BH_3	11.9	6.9×10^{-4}	
BD_3	13.8	3.9×10^{-4}	4.3×10^{-4}
BD_3	15.0	4.6×10^{-4}	

Benzoxathiins 5; General Procedure

Benzyloxythiophenol **3** (2.32 g, 10 mmol) and haloketone (10.2 mmol) were dissolved in CH_2Cl_2 (20 mL). Et_3N (1.5 mL, 10.5 mmol) was added and the mixture stirred for 30–60 min. The mixture was poured into aq 2 N HCl (20 mL) and the product extracted with CH_2Cl_2 (20 mL). The combined organics were washed with aq 2 N HCl (20 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The crude intermediate **4** was combined with MeCN (50 mL) and refluxed with a slight N_2 purge. $PhPOCl_2$ (20 mmol) was added dropwise over 1–2 min. After 1–4 h at reflux, the reaction was cooled to r.t. and poured into aq 0.5 M Na_2CO_3 (100 mL). The product was worked up individually as follows:

2-(4-Methylphenyl)-6-(phenylmethoxy)-1,4-benzoxathiin (5a)

The product was isolated directly by filtration. The product was further purified by stirring in MeOH (25 mL) at 60 °C for 15 min followed by cooling to r.t. Filtration gave a pale yellow solid (2.38 g) in 69% yield; mp 143–144 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.41 (m, 7 H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 1 H), 6.73 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.67 (d, *J* = 2.8 Hz, 1 H), 5.74 (s, 1 H), 5.02 (s, 2 H), 2.39 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 150.7, 146.0, 138.6, 136.8, 130.8, 129.2, 128.7, 128.1, 127.5, 124.3, 120.7, 118.1, 114.0, 112.8, 92.4, 70.7, 21.3.

Anal. Calcd for $C_{22}H_{18}O_2S$: C, 76.27; H, 5.24. Found: C, 75.51; H, 5.13.

2-(4-Methoxyphenyl)-6-(phenylmethoxy)-1,4-benzoxathiin (5b)

The product was isolated directly by filtration. The product was further purified by stirring in MeCN (25 mL) at 60 °C for 15 min followed by cooling to r.t. Filtration gave a pale yellow solid (1.43 g) in 40% yield; mp 159–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.9 Hz, 2 H), 7.46–7.31 (m, 5 H), 6.90 (d, *J* = 8.8 Hz, 1 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 6.72 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.66 (d, *J* = 2.9 Hz, 1 H), 5.64 (s, 1 H), 5.01 (s, 2 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 155.8, 150.6, 146.0, 136.8, 128.7, 128.1, 127.5, 126.3, 125.8, 120.9, 118.1, 114.0, 113.9, 112.8, 91.1, 70.7, 55.4.

Anal. Calcd for $C_{22}H_{18}O_3S$: C, 72.90; H, 5.01. Found: C, 71.64; H, 4.73.

2-(4-Bromophenyl)-6-(phenylmethoxy)-1,4-benzoxathiin (5c)
The product was isolated directly by filtration. The product was further purified by stirring in MeOH (25 mL) at 60 °C for 15 min followed by cooling to r.t. Filtration gave a bright yellow solid (3.60 g) in 88% yield; mp 134–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 9 H), 6.87 (d, 8.8 Hz, 1 H), 6.71 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.64 (d, *J* = 2.8 Hz, 1 H), 5.79 (s, 1 H), 5.01 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 149.2, 145.5, 136.6, 132.2, 131.6, 128.6, 128.1, 127.4, 125.7, 122.5, 120.0, 118.0, 114.0, 112.7, 94.1, 70.6.

Anal. Calcd for $C_{21}H_{15}BrO_2S$: C, 61.32; H, 3.68. Found: C, 61.15; H, 3.40.

2-Methyl-6-(phenylmethoxy)-1,4-benzoxathiin (5d)
The product was extracted with EtOAc (2 × 50 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated to an oil. The product was purified by silica gel chromatography (5% MTBE in hexanes) to give 1.48 g (55%) of a colorless oil that solidified on standing.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 5 H), 6.68 (d, *J* = 8.8 Hz, 1 H), 6.64 (dd, *J* = 8.8, 2.8 Hz, 1 H), 6.57 (d, *J* = 2.8 Hz, 1 H), 4.99 (s, 2 H), 4.90 (dd, *J* = 2.0, 1.0 Hz, 1 H), 1.89 (d, *J* = 1.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 149.4, 145.5, 136.8, 128.6, 128.1, 127.5, 119.7, 117.8, 113.8, 112.8, 89.8, 70.6, 20.0.

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 70.73; H, 5.03.

2-(1,1-Dimethylethyl)-6-(phenylmethoxy)-1,4-benzoxathiin (5e)
The product was extracted with EtOAc (2 × 50 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel chromatography (30 g, 5% MTBE in hexanes) to give 2.19 g (71%) of a white crystalline solid; mp 93–94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 5 H), 6.78 (d, *J* = 8.7 Hz, 1 H), 6.69 (dd, *J* = 8.8, 2.8 Hz, 1 H), 6.65 (d, *J* = 2.8 Hz, 1 H), 5.14 (s, 1 H), 5.00 (s, 2 H), 1.18 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 155.6, 146.9, 136.9, 128.6, 128.1, 127.5, 121.9, 117.6, 113.9, 112.6, 89.8, 70.7, 36.4, 27.6.

Anal. Calcd for $C_{19}H_{20}O_2S$: C, 73.04; H, 6.45. Found: C, 72.94; H, 6.32.

Ti-BINOL Catalyst Stock Solution
(*R*)-BINOL (2.15 g, 7.5 mmol) was dissolved in *i*-PrOAc (75 mL). The solution was degassed and Ti(O*i*-Pr)$_4$ (1.06 g, 3.8 mmol) was added on the subsurface giving a dark red solution. H_2O (1.35 mL, 75 mmol) was added to the mixture on the subsurface over 2 min giving an orange slurry. The catalyst solution should be used within one day.

Dihydrobenzoxathiins 7; General Procedure
The benzoxathiin **5** (3 mmol) was dissolved in the catalyst stock solution (9 mL). Cumene hydroperoxide (87%, 550 mg, 3.1 mmol) was added and the reaction was left aside overnight until complete by HPLC. The crude mixture was assayed for ee of the vinyl sulfoxide **6**. The mixture was concentrated onto silica gel (5 g) and purified by flash chromatography (25 g silica gel, 3 × 50 mL CH_2Cl_2, 3 × 50 mL EtOAc). The EtOAc eluents were combined, concentrated and slurried in toluene (9 mL). The mixture was cooled to 5–10 °C and 1 M BH_3-THF (3.6 mL) was added dropwise. The solution was allowed to warm to r.t. The mixture was washed with aq 10% tartaric acid solution (2 × 10 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (5 mL) The combined organic layers were concentrated in vacuo and purified by chromatography (5% MTBE in hexanes).

Vinyl Sulfoxide 6a
A 59% ee was determined by SFC with a (*S*,*S*)-Whelko column, 4% MeOH/CO_2 for 4 min to 40% MeOH/CO_2 over 18 min, then hold for 3 min, 1.5 mL/min, 200 bar, 35 °C, UV at 215 nm; t_R (major) 14.4 min, t_R (minor) 11.3 min.

Vinyl Sulfoxide 6b
A 48% ee was determined by SFC with a (*S*,*S*)-Whelko column, 4% MeOH/CO_2 for 4 min to 40% MeOH/CO_2 over 18 min, then hold for 3 min, 1.5 mL/min, 200 bar, 35 °C, UV at 215 nm; t_R (major) 15.2 min, t_R (minor) 12.1 min.

Vinyl Sulfoxide 6c
A 26% ee was determined by SFC with a (*S*,*S*)-Whelko column, 4% MeOH/CO_2 for 4 min to 40% MeOH/CO_2 over 18 min, then hold for 3 min, 1.5 mL/min, 200 bar, 35 °C, UV at 215 nm; t_R (major) 13.6 min, t_R (minor) 11.4 min.

Vinyl Sulfoxide 6d
A 52% ee was determined by SFC with a (*S*,*S*)-Whelko column, 4% MeOH/CO_2 for 4 min to 40% MeOH/CO_2 over 18 min, then hold for 3 min, 1.5 mL/min, 200 bar, 35 °C, UV at 215 nm; t_R (major) 9.6 min, t_R (minor) 9.0 min.

Vinyl Sulfoxide 6e
A 96% ee was determined by SFC with a Chiralpak AS column, 4% MeOH/CO_2 for 4 min to 40% MeOH/CO_2 over 18 min, then hold for 3 min, 1.5 mL/min, 200 bar, 35 °C, UV at 215 nm, t_R (major) 14.4 min, t_R (minor) 18.1 min.

2-(4-Methylphenyl)-6-(phenylmethoxy)-2,3-dihydro-1,4-benzoxathiin (7a)
The combined fractions were slurried in MeOH and the product was isolated by filtration; yield: 0.67 g (64%); white solid; mp 115–117 °C.

A 60% ee was determined by HPLC with Chiralcel OD-H column, 2% *i*-PrOH–hexanes to 15% *i*-PrOH–hexanes over 30 min, 0.8 mL/min, 25 °C, 220 nm, t_R (major) 12.3 min, t_R (minor) 14.2 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.24 (m, 9 H), 6.88 (d, *J* = 8.9 Hz, 1 H), 6.77 (d, *J* = 2.9 Hz, 1 H), 6.69 (dd, *J* = 2.9, 8.9 Hz, 1 H), 5.10 (dd, *J* = 1.5, 9.6 Hz, 1 H), 5.02 (s, 2 H), 3.30 (dd, *J* = 9.6, 13.0 Hz, 1 H), 3.07 (dd, *J* = 1.8, 13.0 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 147.0, 138.3, 137.5, 137.2, 129.5, 128.6, 128.0, 127.6, 126.1, 119.5, 118.0, 113.2, 112.6, 70.7, 32.0, 21.3.

Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.83; H, 5.79. Found: C, 75.85; H, 5.67.

2-(4-Methoxyphenyl)-6-(phenylmethoxy)-2,3-dihydro-1,4-benzoxathiin (7b)
The combined fractions were slurried in MeOH and the product was isolated by filtration; yield: 0.77 g (70%); white solid; mp 112–115 °C.

A 48% ee was determined by HPLC with Chiralcel OD-H column, 2% *i*-PrOH–hexanes to 15% *i*-PrOH–hexanes over 30 min, 0.8 mL/min, 25 °C, 220 nm, t_R (major) 16.5 min, t_R (minor) 18.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.34 (m, 9 H), 6.99–6.95 (m, 2 H), 6.87 (d, *J* = 8.9 Hz, 1 H), 6.77 (d, *J* = 2.9 Hz, 1 H), 6.69 (dd, *J* = 8.9, 3.0 Hz, 1 H), 5.08 (dd, *J* = 9.6, 1.7 Hz, 1 H), 5.02 (s, 2 H), 3.85 (s, 3 H), 3.31 (dd, *J* = 13.1, 9.7 Hz, 1 H), 3.05 (dd, *J* = 13.1, 1.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 153.4, 147.0, 137.2, 132.7, 128.6, 128.0, 127.6, 127.4, 119.5, 118.0, 114.2, 113.2, 112.6, 76.3, 70.7, 55.4, 32.0.

Anal. Calcd for $C_{22}H_{20}O_3S$: C, 72.50; H, 5.53. Found: C, 72.72; H, 5.65.

2-(4-Bromophenyl)-6-(phenylmethoxy)-2,3-dihydro-1,4-benzoxathiin (7c)

The combined fractions were slurried in MeOH and the product was isolated by filtration; yield: 0.84 g (68%); white solid; mp 123–124 °C.

A 26% ee was determined by treatment of a sample with excess Mg in THF followed by hydrolysis with H_2O to furnish **7f** which was analyzed by literature procedure.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.54 (m, 2 H), 7.45–7.27 (m, 7 H), 6.86 (d, *J* = 8.9 Hz, 1 H), 6.75 (d, *J* = 2.9 Hz, 1 H), 6.69 (dd, *J* = 8.9, 3.0 Hz, 1 H), 5.10 (dd, *J* = 9.4, 1.8 Hz, 1 H), 5.01 (s, 2 H), 3.23 (dd, *J* = 13.0, 9.4 Hz, 1 H), 3.06 (dd, *J* = 13.0, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 146.4, 139.3, 137.0, 131.9, 128.6, 128.0, 127.7, 127.5, 122.4, 119.4, 117.7, 113.2, 112.5, 75.8, 70.6, 31.9.

Anal. Calcd for $C_{21}H_{17}BrO_2S$: C, 61.02; H, 4.15. Found: C, 61.16; H, 4.00.

2-Methyl-6-(phenylmethoxy)-2,3-dihydro-1,4-benzoxathiin (7d)

Yield: 0.52 g (63%); white solid; mp 52–53 °C.

A 51% ee was determined by SFC with Chiralpak AD column, 4% MeOH/CO_2 for 4 min, then to 40% MeOH/CO_2 over 18 min, holding at 40% MeOH for 3 min, 1.5 mL/min, 200 bar, 35 °C, UV at 215 nm, t_R (major) 13.3 min, t_R (minor) 12.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.34 (m, 5 H), 6.77 (d, *J* = 8.9 Hz, 1 H), 6.71 (d, *J* = 2.9 Hz, 1 H), 6.66 (dd, *J* = 8.8, 2.9 Hz, 1 H), 5.00 (s, 2 H), 4.30–4.26 (m, 1 H), 2.99 (dd, *J* = 12.9, 7.8 Hz, 1 H), 2.94 (dd, *J* = 12.8, 2.8 Hz, 1 H), 1.47 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 146.2, 137.2, 128.6, 128.0, 127.5, 119.2, 117.9, 113.1, 112.6, 70.7, 70.6, 31.4, 21.2.

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92. Found: C, 70.57; H, 5.77.

2-(1,1-Dimethylethyl)-6-(phenylmethoxy)-2,3-dihydro-1,4-benzoxathiin (7e)

Yield: 0.82 g (86%); white solid; mp 95–98 °C.

A 97% ee was determined by SFC with Chiralpak AD column, 4% MeOH/CO_2 for 4 min, then to 40% MeOH/CO_2 over 18 min, holding at 40% MeOH for 3 min, 1.5 mL/min, 200 bar, 35 °C, UV at 215 nm, t_R (major) 9.9 min, t_R (minor) 11.2 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.32 (m, 5 H), 6.78 (d, *J* = 8.9 Hz, 1 H), 6.71 (d, *J* = 2.9 Hz, 1 H), 6.65 (dd, *J* = 8.9, 2.9 Hz, 1 H), 5.00 (s, 2 H), 3.72 (dd, *J* = 9.9, 1.7 Hz, 1 H), 3.05 (dd, *J* = 12.6, 9.9 Hz, 1 H), 2.95 (dd, *J* = 12.7, 1.8 Hz, 1 H), 1.06 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 147.3, 137.2, 128.5, 127.9, 127.5, 118.9, 118.3, 112.8, 112.3, 82.3, 70.6, 34.8, 26.0, 25.7.

Anal. Calcd. for $C_{19}H_{22}O_2S$: C, 72.57; H, 7.05. Found: C, 72.72; H, 7.05.

3-(α-Hydroxyethyl)-6-methoxyphenol (8)

A 3 M solution of MeMgCl in THF (80 mL, 240 mmol) was diluted with THF (400 mL) and cooled to 5 °C. Isovanillin (14.92 g, 98.1 mmol) was dissolved in THF (100 mL) and added via an addition funnel to the MeMgCl solution over 1 h. The reaction was warmed to r.t. and allowed to stand overnight. The slurry was quenched into 5% H_3PO_4 (420 mL) and the product was extracted with EtOAc (2 × 250 mL). The combined organics were washed with aq 10 wt% K_2HPO_4 (200 mL). The organic layer was dried ($MgSO_4$) and concentrated to a white solid. The product was recrystallized from 2:1 hexanes–MTBE to give 14.04 g (85%) of **8** as a white solid which was identified by comparison with literature data.[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96–6.81 (m, 3 H), 5.83 (br s, 1 H, OH), 4.80 (q, *J* = 6.4 Hz, 1 H), 3.88 (s, 3 H), 1.87 (br s, 1 H, OH), 1.46 (d, *J* = 6.4 Hz, 3 H).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.39; H, 7.27.

5-Acetyl-2-methoxyphenyl 4-Chlorobenzoate (9b)

Alcohol **8** (14.45 g, 85.9 mmol) was dissolved in 1,4-dioxane (100 mL). DDQ (19.62 g, 86.4 mmol) was added portionwise under cooling using a cold water bath. The reaction was allowed to stay for 1 h. The mixture was concentrated in vacuo, taken up in CH_2Cl_2 (100 mL) and filtered through Solkaflok to remove $DDQH_2$. To the filtrate, Et_3N (14.4 mL, 103.3 mmol) was added followed by 4-chlorobenzoyl chloride (11.0 mL, 86.7 mmol) and was allowed to sit overnight. The mixture was washed with aq 1 N HCl (2 × 100 mL). The organic layer was slurried with DARCO G-60 (25 g) and filtered through silica gel (100 g). The cake bed was washed with CH_2Cl_2 (300 mL). The combined filtrates were concentrated to give an orange solid. The product was recrystallized twice from EtOAc–hexanes (1:1) to give **9b** (19.88 g, 76%) as a white solid; mp 150–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.6 Hz, 2 H), 7.90 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.78 (d, *J* = 2.1 Hz, 1 H), 7.49 (d, *J* = 8.5 Hz, 2 H), 7.04 (d, *J* = 8.6 Hz, 1 H), 3.88 (s, 3 H), 2.56 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 163.6, 155.2, 140.1, 139.5, 131.6, 130.4, 128.9, 128.1, 127.4, 123.2, 111.6, 56.1, 26.2.

Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.06; H, 4.30. Found: C, 63.01; H, 4.21.

5-(2-{[2-Hydroxy-5-(benzyloxy)phenyl]thio}acetyl)-2-methoxyphenyl 4-Chlorobenzoate (10b)

Ketone **9b** (13.72 g, 45.0 mmol) was slurried in 1:1 dimethoxyethane–CH_2Cl_2 (100 mL) and heated to 40-45 °C to dissolve. Phenyltrimethylammonium tribromide (17.71 g, 47.1 mmol) was added and the mixture was kept for 1 hour at 40–45 °C. The reaction was partitioned between EtOAc (240 mL) and H_2O (160 mL). The layers were separated and the organic layer washed with brine (160 mL). The organic layer was dried ($MgSO_4$) and filtered. Directly to the crude solution, was added benzyloxythiophenol **3** (10.50 g, 45.2 mmol) followed by Et_3N (6.5 mL, 46.6 mmol). The reaction was kept for 1.5 h at r.t. The mixture was concentrated in vacuo and the solvent was changed to MeOH (200 mL). The slurry was cooled to 10 °C and the solid was isolated by filtration to give **10b** (18.43 g, 76%) as a white solid; mp 134–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.6 Hz, 2 H), 7.88–7.85 (m, 1 H), 7.75 (dd, *J* = 0.5, 2.0 Hz, 1 H), 7.51–7.32 (m, 7 H), 7.11 (d, *J* = 2.6 Hz, 1 H), 7.03 (d, *J* = 8.6 Hz, 1 H), 6.92 (m, 2 H), 4.97 (s, 2 H), 4.17 (s, 2 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8, 163.5, 156.0, 152.4, 152.2, 140.3, 139.6, 136.9, 131.6, 128.9, 128.5$_4$, 128.4$_6$, 128.2, 127.9, 127.4, 127.2, 123.5, 121.8, 119.4, 118.3, 116.6, 111.8, 70.8, 56.1, 44.1.

Anal. Calcd for $C_{29}H_{23}ClO_6S$: C, 65.10; H, 4.33. Found: C, 64.76; H, 4.10.

5-[6-(Benzyloxy)-1,4-benzoxathiin-2-yl]-2-methoxyphenyl 4-Chlorobenzoate (11b)

Phenol ketone **10b** (16.04 g, 30.0 mol) was slurried in MeCN (150 mL) and heated to reflux. With slight N_2 purge to a reflux condenser, $PhPOCl_2$ (8.5 mL, 60.0 mmol) was added. The reaction was kept for 2.5 h until complete by HPLC. The reaction was cooled to r.t. and the solid was isolated by filtration. The vinyl sulfide **11b** was obtained as a white solid (12.76 g, 82%); mp 193–196 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.6 Hz, 2 H), 7.51–7.37 (m, 9 H), 7.00 (d, *J* = 8.7 Hz, 1 H), 6.87 (d, *J* = 8.8 Hz, 1 H), 6.70 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.64 (d, *J* = 2.9 Hz, 1 H), 5.68 (s, 1 H), 5.00 (s, 2 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 155.6, 151.4, 149.3, 145.6, 140.0, 139.6, 136.6, 131.6, 128.8, 128.5, 128.0, 127.6, 127.3, 126.6, 123.0, 119.0, 117.9, 113.8, 112.6, 112.1, 92.1, 70.5, 56.0.

Anal. Calcd for $C_{29}H_{21}ClO_5S$: C, 67.37; H, 4.09. Found: C, 67.22; H, 3.92.

5-[6-(Benzyloxy)-1,4-benzoxathiin-2-yl]-2-methoxyphenol (12)

Vinyl sulfide **11b** (6.45 g, 12.5 mol) was slurried in EtOH (50 mL EtOH). Aq 10 N NaOH (4 mL, 40 mmol) was added and the mixture was heated to 65–70 °C for 2 h. The mixture was cooled to r.t. resulting in a thick slurry formation. H_2O (100 mL) was added. With vigorous stirring, AcOH (1.5 mL) was added to adjust the pH to ~9. The resulting solid was isolated by filtration and the cake washed with H_2O (50 mL), 5% AcOH (2 × 50 mL), and MeOH (50 mL). The product **12** was obtained as an off white solid (4.54 g, 96%); mp 144–147 °C. NOTE: The product decomposed upon chromatography on silica gel.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.43–7.31 (m, 5 H), 7.09–7.07 (m, 1 H), 6.98–6.95 (m, 1 H), 6.91 (d, *J* = 8.8 Hz, 1 H), 6.81–6.78 (m, 1 H), 6.07 (s, 1 H), 5.04 (s, 2 H), 3.77 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.7, 149.9, 148.8, 146.9, 145.4, 137.2, 128.8, 128.2, 128.0, 126.1, 121.0, 118.4, 115.7, 114.5, 112.8, 112.3, 111.8, 92.0, 70.1, 56.0.

Anal. Calcd for $C_{22}H_{18}O_4S$: C, 69.82; H, 4.79. Found: C, 69.52; H, 4.46.

5-[(2*S*)-6-(Benzyloxy)-2,3-dihydro-1,4-benzoxathiin-2-yl]-2-methoxyphenol (13)

Vinyl sulfide **12** (2.26 g, 6.0 mmol) was slurried in *i*-PrOAc (18 mL). The catalyst stock solution (see general procedures, 18 mL) was added followed by cumene hydroperoxide (87%, 1.1 mL, 6.3 mmol). The orange slurry was stirred at r.t. overnight giving a yellow slurry. SFC assay showed the intermediate sulfoxide with 78% ee. The resulting solid was isolated by filtration and washed with *i*-PrOAc (10 mL). The solid was hot slurried in toluene (50 mL), cooled to r.t. and isolated by filtration. The crude orange solid was slurried in toluene (18 mL) and cooled to 10 °C. A 1 M borane-THF solution (8 mL, 8.0 mmol) was added dropwise. The reaction was warmed to r.t. and kept for 1 h giving complete dissolution. SFC analysis of the crude reaction gave 78% ee of the product. Aq 10% tartaric acid solution (20 mL) was added and the mixture was filtered through Solkaflok to remove solids. The filtrates were separated and the organic layer washed with aq 10% tartaric acid (20 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (20 mL). The combined organics were dried ($MgSO_4$) and concentrated to dryness. The product was purified by column chromatography on silica gel using 50% MTBE–hexanes as eluent. The product was further purified by stirring in MeOH (20 mL) at 60 °C for 15 min followed by cooling to r.t., and isolation by filtration to give **13** as a white solid (1.36 g, 60%); mp 132–134 °C.

An 84% ee was determined by SFC with Chiralpak AD-H, 30% MeOH/CO_2 for 90 min, 1.5 mL/min, 200 bar, 35 °C, UV at 215 nm, t_R (major) 48.5 min, t_R (minor) 59.6 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.31 (m, 5 H), 7.00–6.66 (m, 6 H), 5.66 (br s, 1 H, OH), 5.03 (dd, *J* = 9.7, 1.5 Hz, 1 H), 5.01 (s, 2 H), 3.92 (s, 3 H), 3.27 (dd, *J* = 13.0, 9.7 Hz, 1 H), 3.04 (dd, *J* = 13.0, 1.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 146.7, 146.5, 145.8, 137.0, 133.6, 128.5, 127.9, 127.4, 119.3, 117.8, 113.0, 12.3, 110.6, 76.1, 70.5, 56.0, 31.8.

Anal. Calcd for $C_{22}H_{20}O_4S$: C, 69.45; H, 5.30. Found: C, 69.13; H, 5.12.

(2*S*)-2-(3-Hydroxy-4-methoxyphenyl)-2,3-dihydro-1,4-benzoxathiin-6-ol (14) Dihydrobenzoxathiin **13** (700 mg, 1.84 mmol) was dissolved in MeOH (5.5 mL) and AcOH (0.6 mL) and hydrogenated using 20% $Pd(OH)_2$/C (1.5 g) as catalyst at 100 psi and 35 °C for 8 h. The catalyst was removed by filtration through Solkaflok and the filtrate concentrated to a solid. The solid was purified by chromatography on silica gel using 25% MTBE–hexanes as the eluent. The isolated solid was recrystallized from 1:2 MTBE–hexanes giving the desired product **14** as a white solid (216 mg, 40%), which was identified by comparison with literature data;[1e] mp 144 °C (Lit.[1e] mp 136 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 1.8 Hz, 1 H), 6.93–6.87 (m, 2 H), 6.80 (d, *J* = 8.8 Hz, 1 H), 6.60 (d, *J* = 2.9 Hz, 1 H), 6.51 (dd, *J* = 8.7, 2.9 Hz, 1 H), 5.67 (br s, 1 H, OH), 5.01 (dd, *J* = 9.6, 1.7 Hz, 1 H)), 4.47 (br s, 1 H, OH), 3.92 (s, 3 H), 3.26 (dd, *J* = 13.0, 9.6 Hz, 1 H), 3.03 (dd, *J* = 13.1, 1.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 146.6, 146.5, 145.7, 133.6, 119.4, 118.1, 117.7, 112.9, 112.8, 112.3, 110.6, 76.0, 56.0, 31.7.

Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86. Found: C, 62.13; H, 4.58.

Acknowledgment

We are grateful to Mirlinda Biba for analytical support and Matthew Bio for helpful suggestions and discussions.

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(15) Ti(O*i*-Pr)$_4$ (0.15 mol%), diisopropylethylamine (0.3 mol%), diisopropyl tartrate (0.3 mol%), and H_2O (0.15 mol%) as the catalyst and cumene hydroperoxide (CHP, 1.2 equiv) as the oxidant. See ref 5.
(16) Compounds **5f** and **6f** were prepared previously, see reference 5 for experimental details.
(17) The catalyst was 2:1:1 molar ratio of Ti(O*i*-Pr)$_4$/D-diethyl tartrate/H_2O in CH_2Cl_2. The substrate was added to the catalyst solution followed by cumene hydroperoxide (CHP).
(18) Crystal data for compound **7e**: $C_{19}H_{22}O_2S$, M = 314.44, orthorhombic, $P2_12_12_1$, a = 9.5087(11) Å, b = 9.5799(11) Å, c = 18.842(2) Å, α = 90, β = 90, γ = 90, V = 1716.4(3) Å^3, T = 298(2) K, Z = 4, rcalcd = 1.217 Mg/m^3, μ = 0.193 mm^{-1}, F(000) 672, 3456 independent reflections (R_{int} = 0.0421), 18173 reflections collected; refinement method, full-matrix least squares refinement on F2; Goodness-of-fit on F2 = 1.024; Final R indices [I > 2σ(I)] $R1$ = 0.0412, $wR2$ = 0.0958.
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