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Synthetic Studies on the Preparation of Alanyl Epoxysulfones as Cathepsin Cysteine Protease Electrophilic Traps

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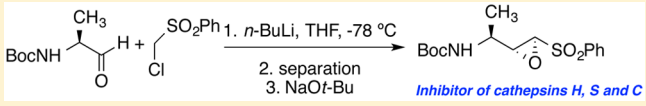
Supporting Information

ABSTRACT: A Darzens reaction between *tert*-butoxycarbonyl alaninal and chloromethyl phenyl sulfone afforded chlorohydrins, which were converted into epoxysulfones by reaction with sodium *tert*-butoxide. Epoxysulfone **10** and chloroketone **14** derived from chlorohydrins by oxidation proved to be inhibitors of cathepsins H, S, and C as determined by competitive activity-based protein profiling.



Lysosomal cysteine proteases (cathepsins) have been identified as therapeutic targets in the search for new drugs against a number of human pathologies, including cancer,[1] Alzheimer's disease,[2] and osteoporosis.[3] The design of new cathepsin inhibitors is intimately based on the discovery of new chemical moieties that react effectively and selectively with the cysteine thiol nucleophile present in the enzyme active site. Thiol-reactive groups present in cathepsin inhibitors include Michael acceptors, such as the vinyl sulfone K1777,[4] nitriles,[5] and azanitriles,[6] as well as electrophiles reactive toward S_N2 substitution. The most representative examples of the latter group are the epoxysuccinates,[7] as present for instance in the natural product E-64 and its derivatives,[8,9] halomethyl ketones[10] and acyloxymethyl ketones[11−13] (Figure 1). The here-studied epoxysulfone moiety is designed to combine structural features of two cysteine protease-reactive electrophiles: vinyl sulfones and epoxysuccinates.

In the context of our investigations of the preparation of new epoxide-based cathepsin inhibitors,[14] we became interested in the synthesis of epoxysulfones. The preparation of epoxysulfones derived from amino acids as new warheads of cysteine proteases was previously attempted through nucleophilic epoxidation of vinyl sulfones,[15] but it was reported that when vinyl sulfones were treated with lithium *tert*-butyl peroxide, allyl sulfones were formed instead of the desired epoxysulfones. We report herein the synthesis of epoxysulfones derived from amino acids through a Darzens reaction using amino aldehydes derived from the corresponding amino acids and chloromethyl phenyl sulfone.

In a first attempt, the Darzens reaction between *tert*-butoxycarbonyl alaninal (1 equiv) and chloromethyl phenyl sulfone (1 equiv) using 1 equiv of *n*-butyllithium in tetrahydrofuran as a solvent at low temperature (−78 °C) proved abortive in that the starting materials were recovered. After carrying out a set of experiments using increasing amounts of sulfone and base, we found that optimal results were obtained when 2.5 equiv of chloromethyl phenyl sulfone and 2.5 equiv of *n*-butyllithium were employed (Table 1, entry 1). In this case, a mixture of all four possible isomeric chlorohydrins **1**−**4** were obtained in good chemical yield. No significant changes were observed upon increasing the reaction time (entry 2) or performing the reaction at lower temperature (entry 3). This also held true when lithium diisopropylamide or lithium bis(trimethylsilyl)amide was used as the base instead of *n*-butyllithium (entries 4 and 5). In contrast, when dimethylformamide was added to the reaction mixture as a cosolvent, the *syn* isomer **3** was formed as the main reaction product (entry 6). On the other hand, when potassium *tert*-butoxide was used as the base under the same conditions as above, the *syn* isomers **3** and **4** were the main products isolated (entry 7). When the same reaction was performed at room temperature, a complex mixture of nonidentifiable products resulted, as observed by NMR spectroscopy of the crude reaction mixture.

Similar $J_{3,4}$ coupling constants were observed for *anti* chlorohydrins **1** and **2** and also for *syn* chlorohydrins **3** and **4**. For *anti* chlorohydrins **1** and **2**, $J_{3,4}$ was equal to 9.0 and 9.6 Hz respectively, while for *syn* chlorohydrins **3** and **4**, $J_{3,4}$ was equal to 0 Hz.

The mixture of four chlorohydrins **1**−**4** derived from the Darzens reaction was separated by silica gel chromatography. In order to establish the stereochemistries of the obtained chlorohydrins, they were transformed into oxazolidinones **6**−**9**. This transformation was attempted by initial deprotection the *tert*-butoxycarbonyl group followed by treatment with triphosgene (Scheme 1). When compound **1** was reacted with trifluoroacetic acid and the resulting ammonium salt was directly treated with triphosgene in the presence of triethylamine, unexpectedly chlorovinyl sulfone **5** was isolated as the single reaction product. Compound **5** results from N-deprotection and trifluoroacetamide formation followed by

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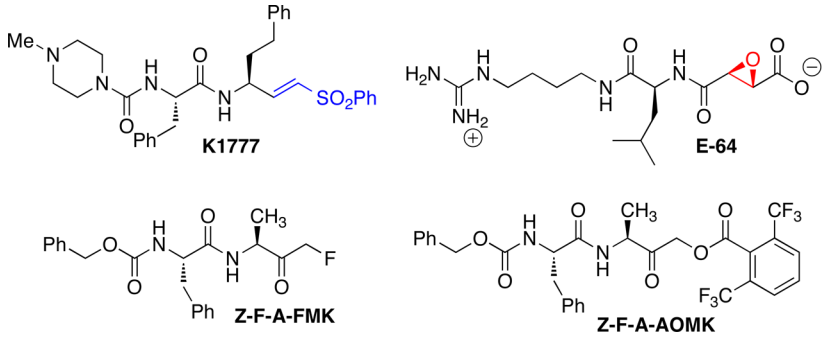
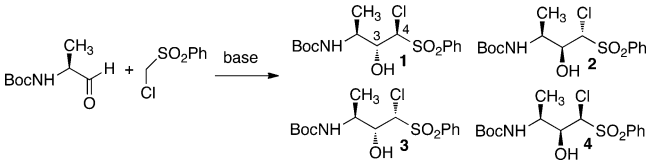


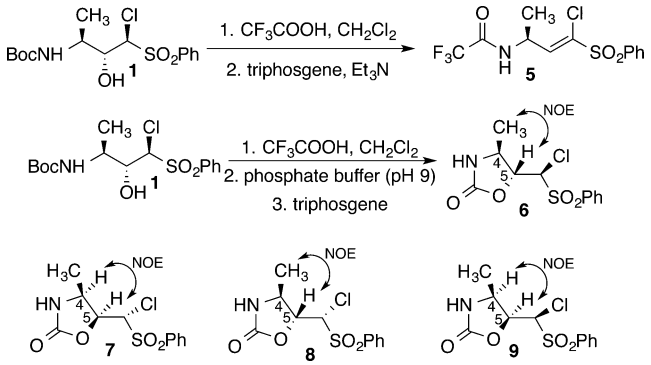
Figure 1. Known cysteine protease inhibitors.

Table 1. Darzens Reactions



entry	base	conditions	1:2:3:4	yield (%)
1	*n*-BuLi	THF, −78 °C, 30 min	33:27:24:16	75
2	*n*-BuLi	THF, −78 °C, 5 h	35:26:25:14	77
3	*n*-BuLi	THF, −90 °C, 2 h	33:24:24:19	71
4	LDA	THF, −78 °C, 30 min	36:29:21:13	70
5	LiHMDS	THF, −78 °C, 30 min	35:25:25:15	67
6	*n*-BuLi	THF/DMF, −78 °C, 30 min	27:15:46:12	66
7	*t*-BuOK	THF, −78 °C, 30 min	17:8:42:33	55

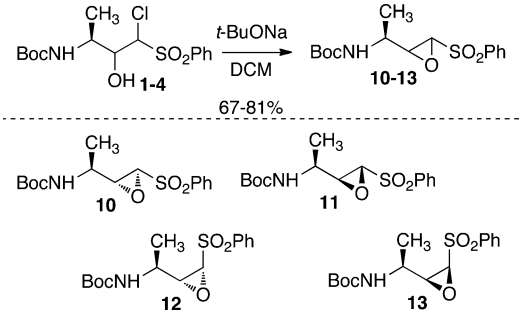
Scheme 1. Transformation of Chlorohydrins into Oxazolidinones



elimination of water. In order to avoid the formation of such undesired compounds, the ammonium salt resulting from deprotection was transformed into the free amine with a phosphate buffer (pH 9.0), and then the free amine was converted into oxazolidinone **6** by reaction with triphosgene (Scheme 1). The same synthetic sequence was followed to prepare oxazolidinones **7**, **8**, and **9** starting from chlorohydrins **2**, **3**, and **4**, respectively. The configurations of the asymmetric carbon atoms in oxazolidinones **6**–**9** were established by NMR experiments (Scheme 1). Both oxazolidinones **6** and **8** exhibited NOEs between H-5 and the methyl protons, while oxazolidinones **7** and **9** exhibited NOEs between H-5 and H-4.

An extensive experimental investigation was then carried out to convert chlorohydrins into epoxysulfones by base treatment. First, chlorohydrin **1** was treated with sodium hydride, but NMR spectra of the crude mixture showed starting material, isomer **3** resulting from epimerization, and, as major products, alaninal and chloromethyl sulfone resulting from a retro-Darzens reaction. When chlorohydrin **2** was treated with sodium hydride, conversion into the isomeric compound **4** and retro-Darzens products was also observed. Triethylamine did not afford the desired compounds. Potassium carbonate in different solvents was next attempted. When methanol was used, the epoxide was detected as a minor product, and mainly starting material was recovered. When tetrahydrofuran was used as the solvent, traces of epoxide were detected, but epimerization to give compound **3** was also observed. Potassium carbonate in dimethylformamide gave the desired epoxide, but the retro-Darzens reaction also took place. Potassium *tert*-butoxide was then tried. When it was used in tetrahydrofuran as the solvent, the retro-Darzens reaction took place. Finally, sodium *tert*-butoxide gave *trans*-epoxysulfone **10** as the only reaction product when dichloromethane was applied as the solvent. In the case of *cis*-epoxysulfones, a mixture of dichloromethane and *tert*-butanol was used as a solvent. Under these reaction conditions, *trans*-epoxide **11** and *cis*-epoxides **12** and **13** were obtained from compounds **2**, **3**, and **4** respectively (Scheme 2).

Scheme 2. Transformation of Chlorohydrins into Epoxysulfones



Chlorohydrin **1** was transformed into chloroketone **14** through oxidation. Compound **14** was also prepared by addition of chloromethyl phenyl sulfone to N-protected methyl L-alaninate (Scheme 3). Chloroketone **14** was obtained in both cases as an equimolar mixture of epimers.

Compounds **10** and **14** were investigated for their ability to inhibit cathepsins by using a competitive activity-based protein profiling (ABPP) assay against the known cysteine protease cathepsin activity-based probe DCG04-BodipyFL.[16] Proteins from mouse liver lysates at pH 5.0 were treated with compounds **10** and **14** for 1 h at 37 °C, and the residual

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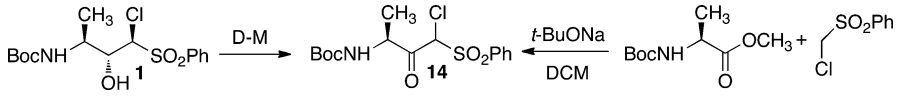
Scheme 3. Preparation of Chloroketone 14



cathepsin activity was captured by the DCG04-BodipyFL probe. After SDS-PAGE separation and in-gel fluorescence imaging, a typical band pattern was seen, which was compared with reported activity-based cathepsin profiling gels.[17] By comparison of the molecular weights of the individual bands seen, we have assigned the nature of the individual cathepsins labeled by DCG04-BodipyFL as indicated in Figure 2.

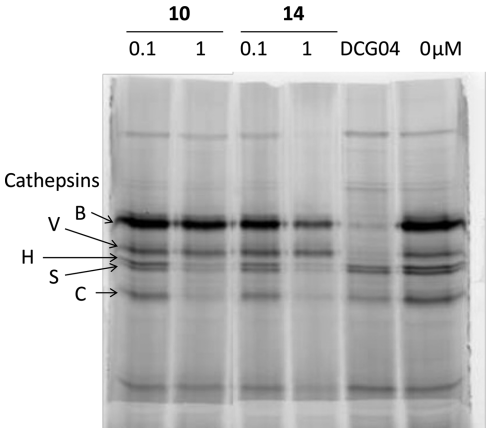


Figure 2. Competitive activity-based protein profiling (ABPP) assay of compounds **10** and **14** against the DCG04-Bodipy-FL probe in mouse liver lysate at pH 5.0. The inhibitors were used at 0.1 and 1 μM concentration, and the cathepsin probe was used at 0.5 μM. DMSO (1 μL) was used as negative control (0).

Competition for most of the bands was observed upon cotreatment with DCG04-BodipyFL, a result that underscores the annotation of the bands as being DCG04-BodipyFL-sensitive cathepsins. Compound **10** is a more selective inhibitor than DCG04-BodipyFL, as it inhibits one to three cathepsins, while compound **14** inhibits four cathepsins at the 1 μM concentration used in this assay. Compounds **10** and **14** are able to outcompete the DCG04-BodipyFL inhibitor, and we can conclude that they bind in a covalent and irreversible fashion to the cathepsins, inhibiting their activity.

In summary, the Darzens reaction between *tert*-butoxycarbonyl alaninal and chloromethyl phenyl sulfone afforded chlorohydrins, which were converted into epoxysulfones by reaction with sodium *tert*-butoxide. Epoxysulfone **10** and chloroketone **14** derived from chlorohydrins by oxidation proved to be inhibitors of cathepsins H, S, and C, as determined by competitive activity-based protein profiling. The introduction of epoxysulfone warheads, including those obtained from further amino acid-derived amino aldehydes, into more elaborate peptidic sequences may result in more specific and/or more active cysteine protease inhibitors, whereas introduction of a reporter molecule (as in DCG-04) may yield a new class of activity-based cysteine protease probes.

EXPERIMENTAL SECTION

Competitive Activity-Based Profiling of Cathepsins in Mouse Liver Lysates. Mouse liver was obtained from a Balb/c mouse (in conformity with the Leiden University animal experimentation protocol 13191u), cut into ca. 100 mg pieces, and frozen in liquid N_2. For lysate production, the liver segment was taken up in 3× volumes of ice-cold lysis buffer (50 mM MES, pH 5.0, 250 mM sucrose, 0.025% digitonin) for 30 min on ice and disrupted 10 times with 15 s sonication pulses interrupted by 5 s breaks on ice. The insoluble fraction was pelleted by centrifugation at 14 000 rpm in a cooled Eppendorf centrifuge, the supernatant was collected, and the protein concentration was determined with the Bradford (BioRad) colorimetric method using a BSA calibration curve. For competitive activity-based profiling, some 20 μg of total protein in 8 μL of lysis buffer at pH 5.0 was first incubated by addition of 1 μL of 10× solution of the indicated inhibitor concentration for 30 min at 37 °C, followed by addition of 1 μL of a 5 μM solution of the broad-spectrum cathepsin activity-based probe (ABP) DCG04-BodipyFL to label the residual cathepsin activity for 30 min at 37 °C. Nonfluorescent DCG04 cathepsin inhibitor at a final concentration of 1 μM was used as a positive control. To assess the total labeling pattern of the DCG04-BodipyFL ABP, the lysate was first incubated with 1 μL of DMSO, and then samples were boiled with 6 μL of 4× Laemmli's sample buffer under reducing conditions and resolved for 2 h on a 12.5% SDS-PAGE gel. After rinsing with water, gel slabs were imaged with a Typhoon 2000 imager (GE Healthcare) using the fluorescein setting (λ_{ex} = 490 nm, λ_{em} = 510 nm). Gel images were acquired with ImageQuant and colored with ImageJ.

General Experimental Methods. All of the solvents used in reactions were freshly distilled from appropriate drying agents before use. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ (^{1}H, 7.24 ppm; ^{13}C, 77.0 ppm) at 30 °C on a 300 or 500 MHz NMR spectrometer. IR spectra were recorded on oil films, KBr discs, or NaCl pellets on an FT-IR spectrometer. Mass spectra were measured in a QTOF I (quadrupole−hexapole TOF) mass spectrometer with an orthogonal *Z*-spray-electrospray interface. EM Science silica gel 60 was used for column chromatography, while TLC was performed with precoated plates (Kieselgel 60, F_{254}, 0.25 mm). Unless otherwise specified, all of the reactions were carried out under an argon atmosphere with magnetic stirring.

General Experimental Procedure for the Preparation of Amino Aldehydes. To a cold (−78 °C) solution of *tert*-butoxycarbonyl alanine methyl ester (406 mg, 2 mmol) in DCM (20 mL) was added dropwise diisobutylaluminum hydride (1 M in hexane, 4 mL, 4 mmol). The resulting mixture was stirred for 30 min. Then Rochelle salt saturated aqueous solution (50 mL) was added, and the resulting mixture was stirred at room temperature until two phases were separated. After extraction with DCM (3 × 15 mL), the organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography (silica gel, hexanes/ethyl acetate (7:3)) to afford the desired compound (288 mg, 83%).

General Experimental Procedure for the Preparation of Chlorohydrins. To a stirred solution of chloromethyl phenyl sulfone (2.5 mmol) in THF (5 mL) at −78 °C was added slowly *n*-BuLi (1.6 M in hexanes, 1.56 mL, 2.5 mmol). The mixture was stirred for 15 min, and then a solution of aldehyde (173 mg, 1 mmol) in THF (5 mL) was added slowly. The mixture was stirred for 1.5 h, and the reaction was monitorized by TLC. The reaction was quenched with ammonium chloride saturated aqueous solution (25 mL), and the reaction mixture was allowed to warm to room temperature and then extracted with ethyl ether (3 × 15 mL). The organic layers were washed with 1 M hydrochloric acid (15 mL), sodium bicarbonate saturated aqueous solution (15 mL), and brine, dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography (silica gel, hexanes/ethyl acetate (9:1 to 7:3)) to afford the desired compound.

Spectroscopic Data for tert-Butyl ((2S,3R,4R)-4-Chloro-3-hydroxy-4-(phenylsulfonyl)butan-2-yl)carbamate (1). White solid, mp

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84−87 °C. Yield 91 mg, 25%. $[\alpha]_D^{20}$ +18.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 7.5 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 5.01 (d, J = 9.8 Hz, 1H), 4.68 (d, J = 9.0 Hz, 1H), 4.12 (m, 1H), 3.97 (d, J = 9.3 Hz, 1H), 1.36 (s, 9H), 1.20 (d, J = 6.8 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 135.3, 134.6, 129.6, 129.2, 79.6, 73.5, 73.4, 47.2, 28.2, 18.4 ppm. HRMS (ESI) calcd for $C_{15}H_{22}ClNNaO_5S$ ($[M + Na]^+$) 386.0805, found 386.0800. IR (NaCl) ν 3390, 3020, 2980, 2930, 1711, 1498, 1449, 1393, 1368, 1345, 1322, 1311, 1152, 1100, 1081, 1060, 1018, 998, 822, 699, 686, 578, 553, 543, 456, 432, 418 cm^{-1}.

*Spectroscopic Data for tert-Butyl ((2S,3S,4S)-4-Chloro-3-hydroxy-4-(phenylsulfonyl)butan-2-yl)carbamate (**2**).* White solid, mp 87−91 °C. Yield 73 mg, 20%. $[\alpha]_D^{20}$ −10.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 7.3 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 5.04 (s, 1H), 4.52 (d, J = 9.6 Hz, 1H), 4.24 (d, J = 9.5 Hz, 1H), 4.16 (m, 1H), 4.05 (s, 1H), 1.45 (s, 9H), 1.14 (d, J = 6.6 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 135.0, 134.6, 130.2, 129.3, 79.6, 73.3, 71.4, 47.6, 28.2, 13.0 ppm. HRMS (ESI) calcd for $C_{15}H_{22}ClNNaO_5S$ ($[M + Na]^+$) 386.0805, found 386.0805. IR (NaCl) ν 3444, 3019, 2980, 2360, 2342, 1707, 1500, 1449, 1393, 1368, 1348, 1312, 1220, 1153, 1136, 1099, 1058, 1024, 997, 818, 686, 577, 558, 532, 487, 461, 430, 418 cm^{-1}.

*Spectroscopic Data for tert-Butyl ((2S,3R,4S)-4-Chloro-3-hydroxy-4-(phenylsulfonyl)butan-2-yl)carbamate (**3**).* White solid, mp 85−90 °C. Yield 65 mg, 18%. $[\alpha]_D^{20}$ −14.0 (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.0 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 4.85 (s, 1H), 4.79 (d, J = 8.4 Hz, 1H), 4.51 (s, 1H), 3.92 (m, 1H), 3.34 (m, 1H), 1.40 (s, 9H), 1.25 (d, J = 6.8 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 136.0, 135.2, 130.7, 129.5, 80.7, 76.9, 71.3, 50.8, 28.9, 18.5 ppm. HRMS (ESI) calcd for $C_{15}H_{22}ClNNaO_5S$ ($[M + Na]^+$) 386.0805, found 386.0811. IR (NaCl) ν 3444, 3019, 2980, 2934, 1703, 1504, 1449, 1393, 1368, 1345, 1322, 1311, 1156, 1101, 1083, 1055, 1026, 998, 686, 576, 559, 540, 503, 472, 429, 418 cm^{-1}.

*Spectroscopic Data for tert-Butyl ((2S,3S,4R)-4-Chloro-3-hydroxy-4-(phenylsulfonyl)butan-2-yl)carbamate (**4**).* White solid, mp 85−89 °C. Yield 44 mg, 12%. $[\alpha]_D^{20}$ +20.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 4.95 (s, 1H), 4.58 (d, J = 7.7 Hz, 1H), 4.45 (d, J = 7.6 Hz, 1H), 3.84 (s, 1H), 3.16 (s, 1H), 1.42 (s, 9H), 1.30 (d, J = 6.7 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 135.5, 134.8, 130.0, 129.2, 80.1, 74.7, 71.5, 49.0, 28.3, 17.5 ppm. HRMS (ESI) calcd for $C_{15}H_{22}ClNNaO_5S$ ($[M + Na]^+$) 386.0805, found 386.0804. IR (NaCl) ν 3378, 3019, 2980, 1707, 1504, 1449, 1393, 1368, 1324, 1312, 1154, 1083, 1049, 1028, 686, 587, 576, 540 cm^{-1}.

General Experimental Procedure for the Preparation of Epoxysulfones from Chlorohydrins. To an ice-bath-cold solution of chlorohydrin (1 mmol) in DCM/*tert*-butanol (1:1) (3 mL) was added slowly sodium *tert*-butoxide (0.95 mmol) in one portion. The mixture was stirred for 30 min, and then the reaction was quenched with ammonium chloride saturated aqueous solution (25 mL). The resulting mixture was extracted with DCM (3 × 15 mL), and then the organic layers were washed with 1 M hydrochloric acid (15 mL), sodium bicarbonate saturated aqueous solution (15 mL), and brine, dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography (silica gel, hexanes/ethyl acetate (7:3)) to afford the desired compound.

*Spectroscopic Data for tert-Butyl ((S)-1-((2R,3R)-3-(Phenylsulfonyl)oxiran-2-yl)ethyl)carbamate (**10**).* Colorless oil. Yield 275 mg, 84%. $[\alpha]_D^{20}$ +2.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 1H), 7.71 (t, J = 6.9 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 4.37 (br s, 1H), 4.17−4.08 (m, 1H), 4.00 (t, J = 1.4 Hz, 1H), 3.69 (d, J = 1.3 Hz, 1H), 1.42 (s, 9H), 1.26 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 136.0, 134.5, 129.4, 128.8, 80.1, 66.3, 59.9, 44.3, 28.3, 18.4 ppm. HRMS (ESI) calcd for $C_{15}H_{21}NNaO_5S$ ($[M + Na]^+$) 350.1038, found 350.1032. IR (NaCl) ν 3020, 2981, 1712, 1498, 1449, 1393, 1368, 1327, 1265, 1083, 1058, 686, 580, 555 cm^{-1}.

*Spectroscopic Data for tert-Butyl ((S)-1-((2S,3S)-3-(Phenylsulfonyl)oxiran-2-yl)ethyl)carbamate (**11**).* Colorless oil. Yield 258 mg, 79%. $[\alpha]_D^{20}$ +6.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 7.9 Hz, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.60 (t, J = 7.9 Hz, 1H), 4.54 (m, 1H), 4.23 (m, 1H), 3.68 (m, 1H), 3.57 (dd, J = 6.1, 1.0 Hz, 1H), 1.44 (s, 9H), 1.23 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 137.1, 134.5, 129.4, 128.8, 80.2, 67.6, 59.5, 46.4, 28.2, 17.0 ppm. HRMS (ESI) calcd for $C_{15}H_{21}NNaO_5S$ ($[M + Na]^+$) 350.1038, found 350.1039. IR (NaCl) ν 3019, 2980, 1748, 1733, 1699, 1684, 1498, 1473, 1457, 1329, 1157, 1087, 686, 418 cm^{-1}.

*Spectroscopic Data for tert-Butyl ((S)-1-((2R,3S)-3-(Phenylsulfonyl)oxiran-2-yl)ethyl)carbamate (**12**).* Colorless oil. Yield 229 mg, 70%. $[\alpha]_D^{20}$ −2.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 7.3 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 4.55 (s, 1H), 4.15 (m, 1H), 3.87 (m, 1H), 3.70 (m, 1H), 1.43 (s, 9H), 1.28 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 136.9, 134.5, 129.5, 128.8, 80.1, 67.5, 59.9, 44.4, 28.3, 18.2 ppm. HRMS (ESI) calcd for $C_{15}H_{21}NNaO_5S$ ($[M + Na]^+$) 350.1038, found 350.1034. IR (NaCl) ν 3020, 2981, 1710, 1499, 1456, 1449, 1369, 1329, 1311, 1233, 1017, 583 cm^{-1}.

*Spectroscopic Data for tert-Butyl ((S)-1-((2S,3R)-3-(Phenylsulfonyl)oxiran-2-yl)ethyl)carbamate (**13**).* Colorless oil. Yield 209 mg, 64%. $[\alpha]_D^{20}$ −4.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 7.3 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 4.55 (s, 1H), 4.25 (m, 1H), 3.68 (m, 1H), 3.57 (dd, J = 6.1, 1.5 Hz, 1H), 1.44 (s, 9H), 1.23 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 137.1, 134.4, 129.4, 128.8, 80.2, 67.5, 59.5, 46.4, 28.3, 17.0 ppm. HRMS (ESI) calcd for $C_{15}H_{21}NNaO_5S$ ($[M + Na]^+$) 350.1038, found 350.1044. IR (NaCl) ν 3019, 1714, 1497, 1456, 1448, 1369, 1330, 1312, 1157, 1087, 687, 584 cm^{-1}.

General Experimental Procedure for the Preparation of Chloroketone 14 from Chlorohydrin 1. To an ice-bath-cold solution of chlorohydrin **1** (363.5 mg, 1 mmol) in DCM (5 mL) was added slowly Dess−Martin periodinane (424.1 mg, 1 mmol) in one portion. The reaction mixture was stirred for 2 h, and then the reaction was quenched with sodium thiosulfate (10%)/sodium carbonate saturated aqueous solution (1:1) (25 mL). The mixture was stirred for 30 min and then extracted with DCM (3 × 15 mL), and the organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography (silica gel, hexanes/ethyl acetate (7:3)) to afford the desired compound (yield 321 mg, 89%).

General Experimental Procedure for the Preparation of Chloroketones from Esters. To a stirred solution of chloromethyl phenyl sulfone (3 mmol) in THF (10 mL) at −78 °C was added slowly *n*-BuLi (1.6 M in hexanes, 3 mmol), and the mixture was stirred for 30 min. The amino ester (1 mmol) in THF (5 mL) was added, and the resulting mixture was gradually warmed to rt and stirred overnight. The reaction was quenched with NH_4Cl saturated solution (25 mL). The resulting mixture was extracted with ethyl ether (3 × 15 mL), and then the organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography (silica gel, hexanes/ethyl acetate (7:3)) to afford the desired compound (yield 217 mg, 60%).

*Spectroscopic Data for tert-Butyl ((2S)-4-Chloro-3-oxo-4-(phenylsulfonyl)butan-2-yl)carbamate (**14**).* White solid, mp 103−106 °C. $[\alpha]_D^{20}$ −8.0 (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 7.7 Hz, 4H), 7.74 (t, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 4H), 5.87 (s, 1H), 5.75 (s, 1H), 5.29 (s, 1H), 4.99 (s, 1H), 4.71 (s, 2H), 1.48 (s, 9H), 1.43 (s, 15H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 155.0, 135.3, 135.2, 134.3, 130.6, 130.4, 129.1, 81.0, 80.7, 73.3, 71.9, 55.5, 54.7, 28.3, 28.2, 17.2, 16.1 ppm. HRMS (ESI) calcd for $C_{15}H_{20}ClNNaO_5S$ ($[M + Na]^+$) 384.0648, found 384.0642. IR (NaCl) ν 3019, 2981, 2930, 1771, 1540, 1498, 1449, 1394, 1369, 1331, 1313, 1158, 1082, 1072, 1032, 1007, 686, 570, 553, 533, 525, 514, 418 cm^{-1}.

General Experimental Procedure for the Preparation of Oxazolidinones. To an ice-bath-cold solution of chlorohydrin (1 mmol) in DCM (3 mL) was added slowly trifluoroacetic acid/DCM (1:1) (3 mL). The mixture was stirred for 30 min and directly concentrated. DCM (5 mL) and then phosphate buffer (pH 9) were

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added, and the mixture was stirred for 15 min and then extracted with DCM. If the aqueous phase still contained free amine as determined by TLC, it was treated with phosphate buffer and 1 M potassium hydroxide. Then the organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude mixture was dissolved in DCM (6 mL) and cooled with an ice bath. Then a solution of triphosgene (1.2 mmol) in DCM (5 mL) was added dropwise. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with ammonium chloride saturated aqueous solution (25 mL). The resulting mixture was extracted with DCM (3 × 15 mL), and then the organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography (silica gel, hexanes/ethyl acetate (1:1)) to afford the desired compound.

*Spectroscopic Data for (4S,5R)-5-((R)-Chloro(phenylsulfonyl)-methyl)-4-methyloxazolidin-2-one (**6**).* White solid, mp 129−132 °C. Yield 194 mg, 67%. $[\alpha]_D^{20}$ +8.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.65 (t, J = 7.9 Hz, 2H), 5.90 (br s, 1H), 5.05 (d, J = 3.1 Hz, 1H), 5.01 (d, J = 2.4 Hz, 1H), 4.35−4.27 (m, 1H), 1.49 (d, J = 6.1 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 135.6, 135.3, 129.7, 129.5, 79.1, 73.9, 49.4, 21.6 ppm. HRMS (ESI) calcd for $C_{11}H_{12}ClNNaO_4S$ ($[M + Na]^+$) 312.0073, found 312.0074. IR (NaCl) ν 3019, 2965, 2929, 1698, 1685, 1519, 1508, 1448, 1367, 1328, 1311, 1156, 1085, 686, 590, 571, 418 cm^{-1}.

*Spectroscopic Data for (4S,5S)-5-((S)-Chloro(phenylsulfonyl)-methyl)-4-methyloxazolidin-2-one (**7**).* White solid, mp 127−129 °C. Yield 188 mg, 65%. $[\alpha]_D^{20}$ +4.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.5 Hz, 2H), 7.76 (t, J = 6.6 Hz, 1H), 7.64 (t, J = 7.9 Hz, 2H), 5.43 (br s, 1H), 4.85 (d, J = 9.9 Hz, 1H), 4.76 (dd, J = 6.6, 9.95 Hz, 1H), 4.01 (m, 1H), 1.32 (d, J = 6.4 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 135.4, 135.3, 130.4, 129.5, 79.6, 70.2, 51.3, 15.8 ppm. HRMS (ESI) calcd for $C_{11}H_{12}ClNNaO_4S$ ($[M + Na]^+$) 312.0073, found 312.0068. IR (NaCl) ν 3019, 2960, 2928, 2855, 1698, 1684, 1520, 1448, 1386, 1367, 1328, 1311, 1260, 1156, 1127, 1085, 1051, 1035, 1017, 686, 612, 591, 571, 418 cm^{-1}.

*Spectroscopic Data for (4S,5R)-5-((S)-Chloro(phenylsulfonyl)-methyl)-4-methyloxazolidin-2-one (**8**).* White solid, mp 127−131 °C. Yield 199 mg, 69%. $[\alpha]_D^{20}$ +4.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.7 Hz, 2H), 7.76 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 5.45 (br s, 1H), 4.95 (t, J = 3.4 Hz 1H), 4.77 (d, J = 2.9 Hz, 1H), 4.04 (m, 1H), 1.44 (d, J = 6.2 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 140.9, 135.2, 135.0, 130.6, 129.1, 79.6, 74.7, 51.2, 21.3 ppm. HRMS (ESI) calcd for $C_{11}H_{12}ClNNaO_4S$ ($[M + Na]^+$) 312.0073, found 312.0077. IR (NaCl) ν 3019, 2963, 2927, 2871, 1715, 1698, 1540, 1508, 1448, 1386, 1366, 1328, 1311, 1156, 1127, 1085, 1017, 686, 612, 590, 571, 418 cm^{-1}.

*Spectroscopic Data for (4S,5S)-5-((R)-Chloro(phenylsulfonyl)-methyl)-4-methyloxazolidin-2-one (**9**).* White solid, mp 126−129 °C. Yield 211 mg, 73%. $[\alpha]_D^{20}$ +4.0 (c = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 6.9 Hz, 3.1, 1.5 Hz, 2H), 7.77 (tt, J = 7.6, 0.4 Hz, 1H), 7.63 (t, J = 8.3 Hz, 2H), 5.43 (dd, J = 8.3, 3.2 Hz, 1H), 5.27 (br s, 1H), 4.82 (d, J = 3.2 Hz, 1H), 4.33 (dq, J = 13.4, 6.8 Hz, 1H), 1.43 (d, J = 6.6 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 135.3, 134.5, 130.6, 129.2, 74.6, 72.9, 50.9, 15.3 ppm. HRMS (ESI) calcd for $C_{11}H_{12}ClNNaO_4S$ ($[M + Na]^+$) 312.0073, found 312.0074. IR (NaCl) ν 3020, 2956, 2927, 1734, 1457, 1448, 1396, 1378, 1328, 1322, 1312, 1156, 1082, 1056, 1035, 699, 686, 585, 573, 552, 459, 435, 418 cm^{-1}.

*Spectroscopic Data for (S,Z)- and (S,E)-N-(4-Chloro-4-(phenylsulfonyl)but-3-en-2-yl)-2,2,2-trifluoroacetamide (**5**).* Yellow oil. Yield 153 mg, 45%. $[\alpha]_D^{20}$ −46.0 (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 7.3 Hz, 2H), 7.91 (d, J = 7.5 Hz, 2H), 7.69 (m, 3H), 7.59 (m, 3H), 7.18 (d, J = 8.1 Hz, 1H), 6.92 (br s, 1H), 6.78 (br s, 1H), 6.32 (d, J = 9.2 Hz, 1H), 5.82 (dq, J = 9.2, 7.2 Hz, 1H), 4.85 (dq, J = 8.1, 6.9 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H), 1.42 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0 (q, J = 37.7 Hz), 142.0, 138.1, 136.3, 134.7, 134.6, 132.4, 129.5, 129.4, 129.0, 115.6 (d, J = 289.6 Hz), 45.4, 45.0, 20.5, 18.8 ppm. HRMS (ESI) calcd for $C_{12}H_{11}ClF_3NNaO_3S$ ($[M + Na]^+$) 363.9998, found 363.9994. IR (NaCl) ν 3428, 3020, 1728, 1540, 1508, 1448, 1331, 1312, 1288, 1124, 1087, 922, 882, 856, 684, 586, 570, 553, 524, 517, 503, 489, 473, 418 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Graphical NMR spectra of all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01013.

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Notes

The authors declare no competing financial interest.

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