

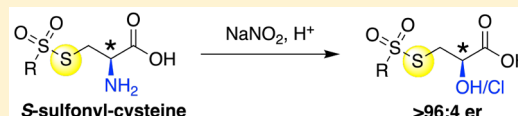
Diazotization of *S*-Sulfonyl-cysteines

Sarah Jane Mear and Timothy F. Jamison*[✉]

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: We report the preparation of enantiomerically enriched β -thio- α -hydroxy and α -chloro carboxylic acid and ester building blocks by diazotization of *S*-sulfonyl-cysteines. The thiosulfonate protecting group demonstrated resistance to oxidation and attenuation of sulfur's nucleophilicity by the anomeric effect. The key transformation was optimized by a 2^2 factorial design of experiment, highlighting the unique reactivity of cysteine derivatives in comparison with aliphatic amino acids.



Diazotization of naturally occurring α -amino acids yields enantiomerically enriched α -hydroxy or α -chloro acids, useful building blocks in medicinal chemistry,^{1–4} total synthesis of natural products,^{5–7} and polymer chemistry.^{8–11} Although α -hydroxy and α -chloro acids are commonly prepared by the diazotization of α -amino acids,^{7,12–15} cysteine remains an elusive substrate in this transformation because of the chemically sensitive sulfur atom. Cysteine derivatives offer many opportunities for synthesis and are prominently featured in the selective modification of polypeptides and in drug delivery.^{16–19} Herein we report that protection of the sulfur in cysteine as a thiosulfonate enables the preparation of enantiomerically enriched β -thio- α -hydroxy and α -chloro acids by diazotization (Figure 1a).

We were inspired to investigate the preparation of β -thio- α -hydroxy acids by diazotization of cysteine after the observation of Humber et al.'s use of α -hydroxy acid **1** as an intermediate in the synthesis of nucleoside reverse transcriptase inhibitor

lamivudine (**2**) (Figure 1b).² In this report, the enantiomerically enriched intermediate was prepared from racemic chlorohydrin, requiring chiral resolution with (–)-brucine.²⁰ A similar β -thio- α -hydroxy acid derivative **3** was used by Biel et al. in the synthesis of acyl protein thioesterase inhibitor **4**.³ We concluded from these examples that enabling the diazotization of cysteine could allow preparation of similar sulfur-containing enantiomerically enriched building blocks from the chiral pool.

In 2004, Deechongkit et al. demonstrated preparation of enantiomerically enriched α -hydroxy acids by diazotization of seven of the naturally occurring amino acids, describing cysteine as a limitation in the scope due to the acidic and oxidizing reaction conditions.¹⁵ Stuhr-Hansen et al.¹³ and Matthes et al.⁷ have reported diazotization of *S*-benzyl-cysteine derivatives with 8% and 57% yields; however, the enantiomeric ratio of the products was not reported in either case, and further elaboration of the side chain was not demonstrated. Given this precedent, we first investigated diazotization of cysteine using the common benzyl thioether protecting group, but we obtained less than 10% yield of the desired α -hydroxy product and observed a complex mixture of products, including debenzylated species (¹H NMR). Thioester protecting groups were also not viable because of known *S*-to-*N* acyl migration pathways.²¹ We learned in the course of these investigations that disulfides are oxidized by nitrogen oxides to thiosulfonates by an established mechanism.²² We therefore hypothesized that an *S*-sulfonyl protecting group may prevent undesired oxidation of the substrate. *S*-Sulfonyl-cysteines **5** and **6** were prepared on multigram scale by slight modification of reported procedures (Figure 2).^{23,24}

Our initial investigations into the diazotization of **5** with 2 equiv of nitrite, 4 equiv of sulfuric acid, and 24 h reaction time produced the targeted α -hydroxy acid **7** in 33% yield, according to ¹H NMR (Figure 2). This promising result demonstrated that the thiosulfonate was more stable to the acidic and oxidizing reaction conditions than the other thiol

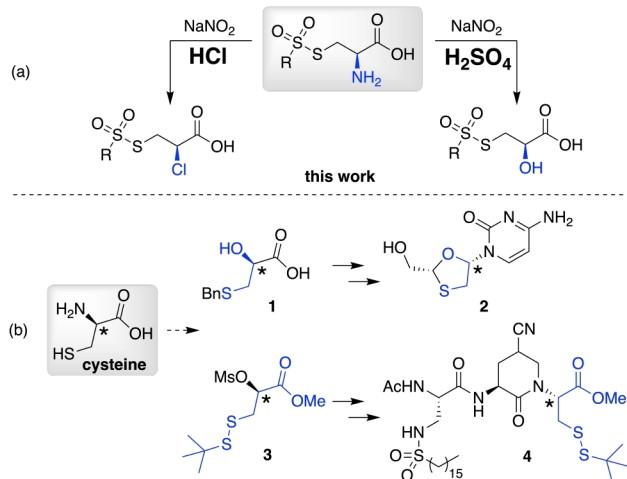
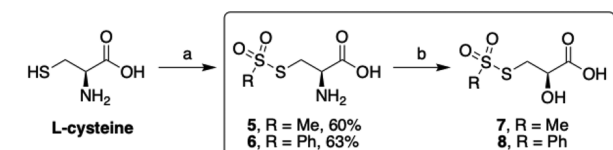


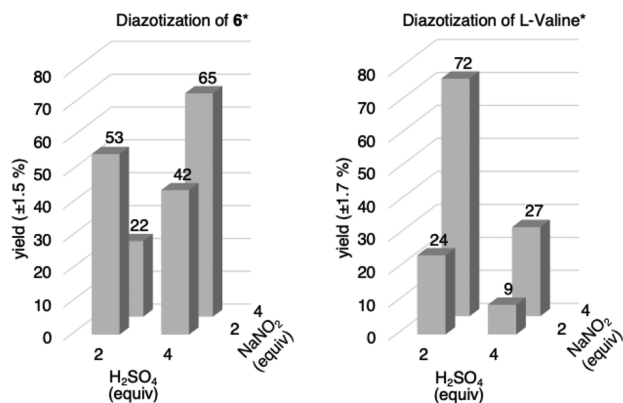
Figure 1. (a) General scheme for the diazotization of *S*-sulfonyl-cysteines and (b) applications in synthesis.^{2,3}

Received: September 27, 2019

Published: October 28, 2019



^a 3 equiv HCl, 1 equiv NaNO₂, then 2-2.5 equiv NaSO₂R, 0 °C
^b H₂SO₄, NaNO₂, H₂O, 0 °C to rt



*General screening procedure provided in the experimental section. Amino acid concentration 0.08 M post-reagent mixing. Acetone cosolvent (2:1 aq/organic post-reagent mixing). Yields determined by integration of α -proton in ¹H NMR using benzyl benzoate as internal standard. Yields are averages of triplicate runs.

Figure 2. Preparation of S-sulfonyl-cysteines and results for DoE optimization of diazotization of **6** (left) versus control substrate valine (right).

protecting groups tested. In the diazotization of **6**, benzenesulfonic acid was observed by ESI-MS as a side product, presumably by hydrolysis of the thiosulfonate. Derivatization of the products and separation of the enantiomers by HPLC using a column with a chiral stationary phase demonstrated that the reaction proceeds with >96:4 er (Figures S2–S4), despite the nucleophilic β -thio substituent. These results demonstrated that the sulfonyl protecting group

provides resistance to oxidation and also controls the undesired nucleophilicity of the β -substituent.

Initial reaction optimization with **5** and **6** by a one-factor-at-a-time (OFAT) approach led to yields ranging from 19 to 54%, as determined by ¹H NMR (see Tables S1 and S2). Reaction time of 4 h, higher dilution of starting material to 0.08 M, and use of acetone as cosolvent (with **6**) gave improved yields while minimizing formation of impurities. We hypothesized that the molar ratio of acid and nitrite employed would affect the yield based on the reported mechanism for diazonium formation, which proceeds via generation of the reactive nitrosyl cation from nitrite and two acidic protons. To investigate this possible variable interaction effect, we performed a two-level, two-factor design of experiment (2² DoE) investigating the stoichiometry of acid and nitrite in the diazotization reaction of **6**.²⁵ To compare the results of this study with an amino acid less prone to oxidation, we performed the same DoE on the aliphatic amino acid valine. The results are summarized in Figure 2 (see also Tables S3–S8).

The results of the DoE indicated that the stoichiometry of both reagents must be considered in combination to maximize the yield. For cysteine, the yield was maximized when equimolar amounts of the two reagents were employed, while lower yields were observed with an excess of either reagent (Figure 2). For valine, an inverse trend was observed and the yield was maximized when an excess of nitrite was used (Figure 2). This demonstrated that the optimal conditions for diazotization of cysteine derivatives are not obvious based on results for other amino acids. Further optimization confirmed that 4 equiv of nitrite and sulfuric acid produced the highest yield (Figure S1).

To demonstrate the utility of this method on preparative scale, the diazotization was performed on 1 mmol scale, and the resulting products were isolated and characterized (Figure 3).

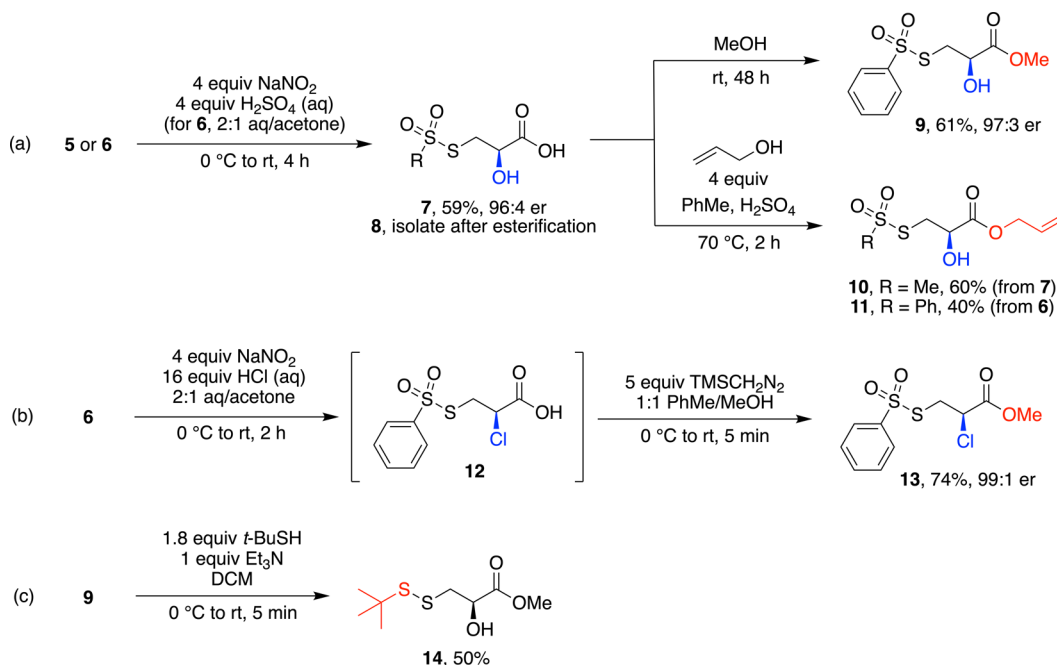


Figure 3. Isolated yields of cysteine diazotization products and derivatives on 1 mmol scale or greater.

We observed an approximate 10% improvement in mass balance when saturated sodium sulfate solution was added to the reaction mixture before workup to provide a salting-out effect.²⁶ The *S*-mesyl derivative **7** was sufficiently pure after aqueous workup, requiring no further purification. The *S*-phenylsulfonyl derivative **9** was prepared by a two-step procedure after esterification to form the methyl ester, which was purified by column chromatography. The allyl ester derivatives **10** and **11** were prepared by Fischer esterification; yields were limited by heat-sensitivity of **7** and **8**. By replacing sulfuric acid with hydrochloric acid in the diazotization of **6**, we found that α -chloro acid **12** is prepared; the methyl ester **13** was isolated by column chromatography after a two-step procedure involving methylation of **12** with trimethylsilyldiazomethane (see [Safety Considerations](#)). Furthermore, by reaction of the thiosulfonate **9** with a thiol and triethylamine, mixed disulfide product **14** is prepared in a single step. Preparation of **14** demonstrates a new synthetic route to medically relevant building block **3** from chiral pool precursor *L*-cysteine.

The stereochemical fidelity of this transformation is notable when compared with the diazotization of other β -substituted amino acids such as *O*-benzyl-*L*-serine, for which the hydroxy-acid derivative has been prepared previously with 80:20 *er*.¹² In the course of exploratory investigations with the disulfide cystine, we observed formation of thiirane carboxylic acid and acrylic acid in 51% and 19% yields after diazotization. We believe that the thiirane forms by nucleophilic displacement of the diazonium by sulfur. The observed thiirane product provides indirect evidence of the problematic nucleophilicity of the β -thio substituent. We propose that the successful diazotization of *S*-sulfonyl-cysteines results from minimization of this undesired substitution pathway.

We obtained a crystal structure of allyl ester derivative **11** and observed the thiosulfonate in a gauche conformation with a C–S–S–C dihedral angle of 64.33° (Figure 4). Existing

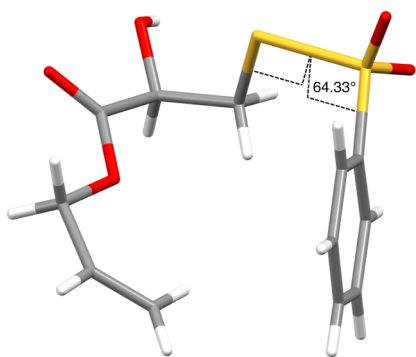
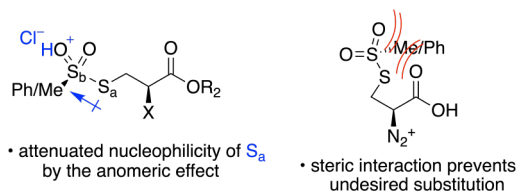


Figure 4. Crystal structure of **11** showing a gauche conformation about the thiosulfonate S–S bond.

theoretical and spectroscopic studies of dimethylthiosulfonate derivatives also demonstrate a preference for the gauche conformation.^{27,28} The anomeric effect explains this observation; the conformation is stabilized by delocalization of a sulfonyl lone pair into the antibonding orbital of the adjacent S–C bond.

Figure 5 illustrates how the anomeric effect in thiosulfonates could contribute to the stereochemical fidelity of this transformation by minimizing undesired substitution pathways. After diazotization, an episulfonium may form competitively

(a) Conformational analysis of the thiosulfonate protecting group



(b) Proposed mechanism for erosion in *er* by competing substitution pathways

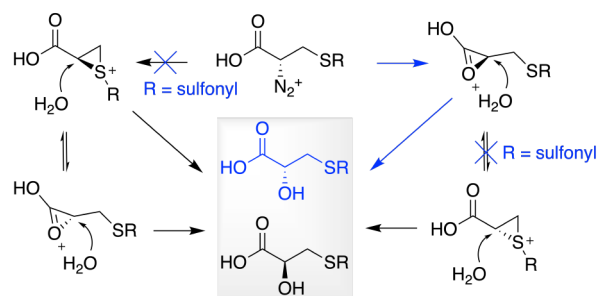


Figure 5. Mechanistic rationale for retention of configuration and stereochemical fidelity in the diazotization of *S*-sulfonyl-cysteines.

with the α -lactone by substitution at the α -position. Any variation in the sequence of substitution events could lead to erosion in the *er*. Likewise, preventing episulfonium formation should improve the *er* (blue pathway). We propose that the anomeric effect decreases the nucleophilicity of the sulfonyl sulfur, destabilizing the undesired episulfonium and favoring the α -lactone pathway.

The anomeric effect can help rationalize the higher enantiomeric ratio of the products observed in preparation of the α -chloro derivative **13**; hydrochloric acid likely protonates the thiosulfonate oxygens to a greater extent than sulfuric acid, increasing the anomeric effect. Alternatively, the steric bulk of the thiosulfonate may also contribute to the stereochemical fidelity of this transformation. Repulsive interactions between the sulfonyl oxygens and the carbonyl oxygen could minimize undesired nucleophilic substitution at the α -position after diazonium formation (Figure 5a).

In conclusion, we have enabled preparation of enantiomerically enriched sulfur-containing α -hydroxy and α -chloro acid building blocks by diazotization of *S*-sulfonyl-cysteines. Key to the success of this investigation was the use of a thiosulfonate protecting group and optimization of the reaction conditions by a 2² factorial DoE. We posit that the thiosulfonate protecting group enables this transformation by rendering the sulfur in cysteine resistant to the oxidizing reaction conditions and by attenuating sulfur's nucleophilicity by the anomeric effect.

EXPERIMENTAL SECTION

General Remarks. Reagents were used as supplied commercially without further purification. Solvents were dried and sparged with Argon using a solvent purification system prior to use. Reactions were run under inert atmosphere except where otherwise noted. Thin-layer chromatography (TLC) was performed using 0.2 mm coated glass silica gel plates and visualized using either ultraviolet light or staining with KMnO₄ solution. Purification by column chromatography over silica gel was performed on a Biotage Isolera flash chromatography system using SNAP KP-Sil or RediSep Rf Gold normal-phase columns. All NMR spectra were collected on Bruker instruments. Spectra reported with field strength of 400 MHz were collected using a two-channel Bruker Avance-III HD Nanobay spectrometer

operating at 400.09 MHz. Spectra reported with field strength of 500 MHz were collected using a three-channel Bruker Avance Neo spectrometer operating at 500.34 MHz. Both spectrometers were equipped with a 5 mm liquid-nitrogen-cooled Prodigy broad band observe (BBO) cryoprobe. Chemical shifts (δ) are reported in units of ppm, relative to the residual solvent peak, which was adjusted to match reported values.²⁹ Individual peaks are assigned multiplicity with the following definitions: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Reported NMR data follow the general format: Nuclei NMR (resonance frequency, reference solvent) chemical shift (multiplicity, coupling constants, integration). High-resolution mass spectrometry data was recorded using an Agilent Technologies 6545 Q-TOF LC/MS. Samples were directly injected using a mobile phase of 0.1% formic acid in acetonitrile. Infrared (IR) resonances were observed using an Agilent Cary 630 FTIR spectrometer. IR samples were prepared as solutions in dichloromethane then loaded onto a diamond surface, with the exception of compounds **5** and **6** which were observed in solid form. Enantiomeric ratio was assessed by HPLC using an Agilent 1290 Infinity II series instrument equipped with a chiral column. For each compound, a racemic standard was prepared to identify retention times for each enantiomer. Method details are described separately for each compound. Optical rotation was measured using a Jasco Model 1010 Polarimeter configured with a standard 589 nm Sodium D line at ambient temperature of 23 °C (c = grams of material/100 mL) and a standard glass cell of 3 mm width and 1 dm length.

Safety Considerations. Mixing solutions of sodium nitrite with solutions of strong acid (hydrochloric acid or sulfuric acid) may generate noxious NO_x fumes. Take care to mix these reagents slowly; use the indicated quantities of each reagent according to the reported procedures, and always perform reactions in a working fume hood. This safety precaution is relevant to the preparation of compounds **5** and **6** and all diazotization products. Methylating agent trimethylsilyldiazomethane TMSCH₂N₂ should be used with great caution. Carefully review safety documentation prior to use and always perform reaction in a fume hood with proper personal protective equipment. Increasing the scale beyond what is reported herein is not recommended by the authors. Take care when washing syringes and needles used for reagent addition, as gas evolution will occur. This safety recommendation is relevant to the preparation of compounds **9** and **13**.

General Screening Procedure for Amino Acid Diazotization. All optimization data (OFAT and DoE data) reported for amino acid diazotizations of cysteine derivatives and valine was collected according to the following general procedure: amino acid starting material (0.25 mmol) was dissolved in aqueous acid (0.5–2 M stock solution, stoichiometry as indicated) and added to a 2 dram glass vial equipped with a magnetic stirrer. Cosolvent and/or additional DI water was added to achieve indicated cosolvent mixture and starting material concentration, and the mixture was cooled in an ice–water bath for 5 min. A 1 M aqueous solution of sodium nitrite (as indicated) was added with stirring. The vial was *not* capped but left open to ambient atmosphere. The reaction was allowed to warm slowly to room temperature and stirred for the indicated reaction time (1–24 h). Ethyl acetate (1.5 mL) was added directly to the vial. The vial was shaken vigorously, then the layers were allowed to separate. The organic layer was separated, and this extraction procedure was repeated 4 times. The combined organic fractions were dried (MgSO₄) then filtered through cotton. Benzyl benzoate (0.25 mmol) was added, and then the solvent was removed under reduced pressure. The resulting mixture was analyzed by ¹H NMR with a 25 s relaxation delay in (CD₃)₂SO to calculate an assay yield for the transformation. The results of OFAT and DoE optimization experiments are tabulated and summarized in the [Supporting Information](#).

Preparation of S-(Methylsulfonyl)-L-cysteine (5). L-Cysteine hydrochloride monohydrate (7.02 g, 40 mmol) was dissolved in 40 mL of 2 N HCl (aq) in a 250 mL Erlenmeyer flask then cooled in an ice–water bath. Note: precisely 3 equiv of HCl is required, so if L-cysteine is used in place of HCl salt, use 40 mL of 3 N HCl. With

stirring, sodium nitrite (2.76 g, 40 mmol) dissolved in 20 mL DI water was added dropwise, and the deep red solution was stirred open to ambient atmosphere for 40 min. Sodium methane sulfinate (8.17 g, 80 mmol) dissolved in 20 mL of DI water was added by pipet, rapidly, with stirring. An additional 2 mL of DI water was used to complete the transfer. The solution was stirred on ice for 3.5 h, replenishing ice as needed, then additional sodium methane sulfinate (2.04 g, 20 mmol) dissolved in 20 mL of DI water was added rapidly. The solution was stirred for a further 30 min, until the red color disappeared. The resulting suspension was filtered using a sintered glass funnel (medium porosity). Washing the isolated solid with 60 mL each of DI water, acetone, and diethyl ether, followed by drying under high vacuum afforded the title compound as a fine white powder (4.76 g, 23.9 mmol, 60%). ¹H NMR (400 MHz, D₂O): δ 4.47 (dd, J = 6.8, 4.5 Hz, 1H), 3.85 (dd, J = 15.7, 4.5 Hz, 1H), 3.74 (dd, J = 15.7, 6.8 Hz, 1H), 3.55 (s, 3H). ¹³C{¹H} NMR (100 MHz, D₂O): δ 169.5, 52.6, 49.6, 34.8. HRMS (ESI-QTOF) m/z : [M + Na]⁺ calcd for C₄H₉NO₄S₂Na, 221.9865; found, 221.9871. IR 3243, 3035, 2987, 2913, 2802, 2621, 2103, 1991, 1578, 1490, 1404, 1342, 1290, 1254, 1192, 1117, 1044, 956, 888, 856, 801, 753, 693 cm⁻¹. Specific rotation [α]_D²⁵ = -48.7 (c 1.1, H₂O)

Preparation of S-(Phenylsulfonyl)-L-cysteine (6). L-Cysteine hydrochloride monohydrate (5.27 g, 30 mmol) was dissolved in 30 mL of 2 N HCl (aq) in a 250 mL Erlenmeyer flask then cooled in an ice–water bath. Note: precisely 3 equiv of HCl are required, so if L-cysteine is used in place of HCl salt, use 40 mL of 3 N HCl. With stirring, sodium nitrite (2.07 g, 30 mmol) dissolved in 20 mL of DI water was added dropwise, and the deep red solution was stirred open to ambient atmosphere for 40 min, and then a solution of sodium benzene sulfinate (9.85 g, 60 mmol) in 20 mL DI water was added dropwise with stirring. Solids immediately start to form. The solution was warmed to room temperature to disperse solids (the product began collecting on the magnetic stirrer). Stirring was continued at rt until all of the red color disappeared (about 3 h). The suspension was briefly cooled in an ice bath, then filtered using a sintered glass funnel (medium porosity, note that filtering will take hours if fine porosity is used), and washed with approximately 60 mL each of DI water, acetone, and diethyl ether to afford the title compound as a fluffy white solid (4.97 g, 19.0 mmol, 63%). ¹H NMR (400 MHz, CD₃OD): δ 8.01 (dd, J = 7.7, 1.7 Hz, 2H), 7.80 (t, J = 7.4 Hz, 1H), 7.70 (t, J = 7.7 Hz, 2H), 4.36 (dd, J = 7.0, 4.9 Hz, 1H), 3.59 (dd, J = 15.3, 5.0 Hz, 1H), 3.54 (dd, J = 15.3, 7.0 Hz, 1H). ¹³C{¹H} NMR (100 MHz, CD₃OD): δ 169.4, 144.7, 135.9, 131.0, 128.3, 53.4, 35.8. HRMS (ESI-QTOF) m/z : [M + Na]⁺ calcd for C₉H₁₁NO₄S₂Na, 284.0022; found, 284.0022. IR 3276, 2973, 2923, 2688, 2199, 2117, 1932, 1617, 1577, 1437, 1396, 1349, 1311, 1255, 1187, 1140, 1069, 929, 848, 757, 717, 684 cm⁻¹. Specific rotation [α]_D²⁵ = -97.1 (c 0.10, MeOH).

Preparation of (R)-2-Hydroxy-3-((methylsulfonyl)thio)propanoic Acid (7). Amino acid **5** (199.2 mg, 1.0 mmol) was dissolved in 8 mL of 0.5 M sulfuric acid (aq) in a 50 mL round-bottom flask and cooled in an ice–water bath. The reaction was run open to ambient atmosphere. After 5 min of stirring, a solution of sodium nitrite (276 mg, 4.0 mmol) in DI water (3 mL) was added dropwise with stirring. Additional DI water (1 mL) was used to complete the transfer. The solution was warmed to room temperature gradually over 4 h. The reaction mixture was transferred to a separatory funnel, and saturated sodium sulfate solution (8 mL) was added. The aqueous layer was extracted four times with ethyl acetate (4 × 5 mL). The combined organic extracts were dried (MgSO₄) then filtered using a sintered glass funnel (medium porosity). The solvent was removed under reduced pressure at 30 °C, then concentrated three times with hexanes, and dried under high vacuum to yield the title compound as a waxy yellow solid (119 mg, 0.59 mmol, 59%, 96:4 er). ¹H NMR (400 MHz, (CD₃)₂SO): δ 4.34 (dd, J = 6.9, 4.3 Hz, 1H), 3.53 (s, 3H), 3.52 (dd, J = 13.8, 4.3 Hz, 1H), 3.41 (dd, J = 13.8, 7.0 Hz, 1H). ¹³C{¹H} NMR (100 MHz, (CD₃)₂SO): δ 173.2, 69.0, 50.4, 40.1. HRMS (ESI-QTOF) m/z : [M + Na]⁺ calcd for C₄H₈O₅S₂Na, 222.9705; found, 222.9702. IR 3412, 3010, 2931, 2612, 1734, 1430, 1403, 1306, 1280, 1227, 1167, 1127, 1079, 1005,

956, 914, 860, 776, 742 cm^{-1} . Specific rotation $[\alpha]_{\text{D}}^{23} = -33.5$ (c 0.23, MeOH).

Preparation of (R)-1-Methoxy-3-((methylsulfonyl)thio)-1-oxopropan-2-yl Benzoate (7b). The hydroxy acid **7** was derivatized as described for chiral HPLC analysis: **7** (50 mg, 0.25 mmol) was dissolved in dry methanol (2 mL), heated to 60 °C, and stirred overnight. The solvent was removed under reduced pressure. The crude residue was diluted with ethyl acetate, washed with dilute sodium bicarbonate, and then dried (MgSO_4). The solvent was removed under reduced pressure. The resulting oil (ca. 0.23 mmol) was dissolved in 5 mL of dry dichloromethane in a flame-dried round-bottom flask and then cooled in an ice–water bath. To the solution was added triethylamine (39 μL , 0.28 mmol), followed by benzoyl chloride (32 μL , 0.28 mmol) and 4-dimethylaminopyridine (5.6 mg, 0.05 mmol). The mixture was warmed to room temperature overnight, and then the reaction was quenched with ammonium chloride. The layers were separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were washed with dilute HCl and then dried (MgSO_4). The resulting residue was purified by flash column chromatography (7–40% EtOAc/hexanes, $R_f = 0.14$, 25% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3): δ 8.11–8.05 (m, 2H), 7.68–7.56 (m, 1H), 7.48 (dd, $J = 8.5$, 7.1 Hz, 2H), 5.65 (dd, $J = 7.0$, 4.1 Hz, 1H), 3.86 (dd, $J = 14.8$, 4.1 Hz, 1H), 3.82 (s, 3H), 3.74 (dd, $J = 14.8$, 7.1 Hz, 1H), 3.37 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 168.2, 165.5, 134.0, 130.1, 128.7, 128.7, 71.2, 53.2, 51.2, 37.2. HRMS (ESI-QTOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{15}\text{O}_6\text{S}_2$, 319.0305; found, 319.0307. IR 3007, 1754, 1726, 1601, 1452, 1319, 1268, 1177, 1134, 1109, 1071, 1026, 957, 745, 713 cm^{-1} . Specific rotation $[\alpha]_{\text{D}}^{23} = +28.9$ (c 1.7, CHCl_3). Enantiomeric ratio 96:4. HPLC chromatograms and method information for assessment of enantiomeric ratio are included in the Supporting Information.

Preparation of Methyl (R)-2-Hydroxy-3-((phenylsulfonyl)thio)propanoate (9). Amino acid **6** (261.3 mg, 1.0 mmol) was dissolved in 4 mL of 1 M sulfuric acid in a 50 mL round-bottom flask equipped with a magnetic stirrer. The reaction was run open to ambient atmosphere. The mixture was cooled in an ice–water bath; 4 mL of acetone was then added. Sodium nitrite (276 mg, 4.0 mmol) was dissolved in DI water (3 mL) and then added dropwise, using additional DI water for rinsing (1 mL). The solution was warmed to room temperature gradually over 4 h. The reaction mixture was transferred to a separatory funnel. Saturated sodium sulfate was added (8 mL), and then the aqueous layer was extracted with ethyl acetate (4 \times 5 mL). The combined organic extracts were dried (MgSO_4) and then filtered using a sintered glass funnel (medium porosity). The solvent was removed under reduced pressure. The resulting yellow oil containing **8** was dissolved in dry methanol in a flame-dried round-bottom flask and stirred for 48 h at rt. The solvent was removed under reduced pressure, and the resulting residue was purified by flash column chromatography (7–40% EtOAc/hexanes) to yield a yellow oil (168 mg, 0.61 mmol, 61%, 97:3 er). Alternatively, the crude oil containing **8** was methylated with TMSCH_2N_2 (see Safety Considerations) according to a general procedure¹² and purified analogously (143.2 mg, 0.52 mmol, 52%). ^1H NMR (500 MHz, CDCl_3): δ 8.02–7.84 (m, 2H), 7.70–7.61 (m, 1H), 7.55 (dd, $J = 8.4$, 7.0 Hz, 2H), 4.42 (dd, $J = 6.3$, 4.1 Hz, 1H), 3.75 (s, 3H), 3.49 (dd, $J = 14.0$, 4.1 Hz, 1H), 3.30 (dd, $J = 14.0$, 6.3 Hz, 1H), 3.23 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 172.4, 144.5, 134.0, 129.5, 127.1, 69.2, 53.2, 39.7. HRMS (ESI-QTOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_{12}\text{O}_5\text{S}_2\text{Na}$, 299.0018; found, 299.0023. IR 3487, 3065, 2955, 1736, 1447, 1404, 1322, 1218, 1179, 1134, 1096, 1076, 1013, 969, 847, 755, 716, 685 cm^{-1} . Specific rotation $[\alpha]_{\text{D}}^{23} = +7.8$ (c 0.57, CHCl_3). Enantiomeric ratio 97:3. HPLC chromatograms and method information for assessment of enantiomeric ratio are included in the Supporting Information.

Preparation of Allyl (R)-2-Hydroxy-3-((methylsulfonyl)thio)propanoate (10). Hydroxy acid **7** (2.12 g, 10.6 mmol) was suspended in dry toluene (10 mL) in a flame-dried 50 mL round-bottom flask. Allyl alcohol (2.9 mL, 42 mmol) was added with stirring. Sulfuric acid (4 drops) was added, and the reaction was

heated to 70 °C. Note that the thiosulfonate degrades when heated to refluxing temperatures, or above approximately 85 °C. A reflux condenser was attached, and the reaction was stirred for 2 h, turning pale yellow in color. The reaction mixture was transferred to a separatory funnel, diluted with ethyl acetate, and then washed with half sat. NaHCO_3 . The aqueous layer was extracted with ethyl acetate, and then the combined organic layers were washed with an aqueous solution of saturated sodium chloride and dried (MgSO_4). The solvent was removed under reduced pressure, and the resulting oil was purified by flash column chromatography on silica gel (10–100% EtOAc/hexanes, $R_f = 0.38$, 50:50 EtOAc/hexanes) to yield the title compound as a yellow oil (1.49 g, 6.20 mmol, 60%). ^1H NMR (400 MHz, CDCl_3): δ 5.90 (ddt, $J = 16.6$, 10.4, 5.9 Hz, 1H), 5.39–5.25 (m, 2H), 4.69 (dt, $J = 6.0$, 1.3 Hz, 2H), 4.56 (dd, $J = 6.0$, 3.8 Hz, 1H), 3.66 (dd, $J = 14.8$, 3.8 Hz, 1H), 3.53 (dd, $J = 14.8$, 5.9 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 171.8, 130.9, 120.0, 69.9, 67.1, 50.9, 40.2. HRMS (ESI-QTOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_7\text{H}_{12}\text{O}_5\text{S}_2\text{Na}$, 263.0018; found, 263.0022. IR 3477, 3011, 2930, 1735, 1648, 1449, 1411, 1312, 1185, 1128, 1093, 995, 956, 744 cm^{-1} . Specific rotation $[\alpha]_{\text{D}}^{23} = -56.2$ (c 2.5, CHCl_3).

Preparation of Allyl (R)-2-Hydroxy-3-((phenylsulfonyl)thio)propanoate (11). The title compound was prepared by the method described for **10**, starting from the crude hydroxy acid intermediate **8** described in the preparation of **9** on a 3.2 mmol scale. The crude oil was purified by flash column chromatography ($R_f = 0.49$, 50:50 EtOAc/hexanes) to yield the title compound as a pearly yellow solid (381 mg, 40% over 2 steps from **6**). A single crystal was grown for X-ray analysis by dissolving the material in a minimal amount of diethyl ether, layering with hexanes, and allowing to stand at room temperature for 48 h. ^1H NMR (500 MHz, CDCl_3): δ 7.97–7.91 (m, 2H), 7.69–7.62 (m, 1H), 7.56 (dd, $J = 8.5$, 7.1 Hz, 2H), 5.90 (ddt, $J = 16.4$, 10.4, 5.9 Hz, 1H), 5.42–5.26 (m, 2H), 4.67 (qdt, $J = 12.9$, 5.9, 1.4 Hz, 2H), 4.45 (dd, $J = 6.3$, 4.1 Hz, 1H), 3.51 (dd, $J = 14.1$, 4.1 Hz, 1H), 3.34 (dd, $J = 14.0$, 6.3 Hz, 1H), 2.77 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 171.8, 144.6, 134.1, 131.1, 129.5, 127.2, 119.9, 69.3, 67.1, 39.8. HRMS (ESI-QTOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{O}_5\text{S}_2\text{Na}$, 325.0175; found, 325.0177. IR 3482, 3067, 2948, 1736, 1648, 1582, 1447, 1415, 1322, 1243, 1203, 1139, 1095, 1075, 997, 937, 755, 715, 684 cm^{-1} . Specific rotation $[\alpha]_{\text{D}}^{23} = +6.3$ (c 0.54, CHCl_3). Melting point range 39–42 °C.

Preparation of Methyl (R)-2-Chloro-3-((phenylsulfonyl)thio)propanoate (13). Amino acid **6** (261 mg, 1.0 mmol) was dissolved in 4 mL of 4 M HCl (aq) in a 25 mL round-bottom flask equipped with a magnetic stirrer. The reaction was run open to ambient atmosphere. The mixture was cooled in an ice–water bath, and then 4 mL of acetone was added. Solid sodium nitrite (276 mg, 4.0 mmol) was added in portions with stirring. The solution was gradually warmed to rt over 2 h. The reaction mixture was transferred to a separatory funnel and diluted with 8 mL of saturated sodium sulfate (aq). The aqueous mixture was extracted with ethyl acetate (4 \times 5 mL). The combined organic layers were dried (MgSO_4), then filtered into a flame-dried 100 mL round-bottom flask, and concentrated under reduced pressure. The resulting yellow oil containing **12** was suspended in 1:1 anhydrous methanol/toluene (14 mL) and cooled in an ice–water bath with stirring. The mixture was capped with a rubber septum and vented with a needle. A solution of TMSCH_2N_2 (2.0 M in diethyl ether) was added dropwise through the septum until gas evolution ceased and yellow color persisted (approximately 2.5 mL, 5 mmol). The mixture was then stirred for 5 min at rt, and the reaction was quenched with 10 mL of 10% aqueous acetic acid (continue adding acetic acid until nitrogen evolution ceases). The biphasic mixture was carefully transferred to a separatory funnel, and 1 mL of 4 M HCl was added. The aqueous phase was extracted with EtOAc (4 \times 20 mL). The combined organic fractions were dried (MgSO_4) and concentrated under reduced pressure at 40 °C and then diluted with toluene and concentrated twice more. The resulting oil was purified by flash column chromatography over silica gel (4–40% EA/hexanes, $R_f = 0.4$ in 50:50 EtOAc/hexanes) to yield the title compound as a yellow oil (219 mg, 0.74 mmol, 74%, 99:1 er). ^1H NMR (400 MHz, CDCl_3): δ

8.01–7.84 (m, 2H), 7.75–7.65 (m, 1H), 7.59 (t, $J = 7.6$ Hz, 2H), 4.52 (dd, $J = 8.8, 5.8$ Hz, 1H), 3.80 (s, 3H), 3.56 (dd, $J = 14.7, 8.7$ Hz, 1H), 3.36 (dd, $J = 14.7, 5.8$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 168.3, 144.2, 134.4, 129.7, 127.2, 53.6, 53.5, 38.7. HRMS (ESI-QTOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_{11}\text{ClO}_4\text{S}_2\text{Na}$, 316.9679; found, 316.9678. IR 3064, 2999, 2956, 1742, 1582, 1447, 1404, 1325, 1275, 1226, 1198, 1139, 1077, 999, 972, 892, 834, 754, 715, 684 cm^{-1} . Specific rotation $[\alpha]_{\text{D}}^{23} = +80.1$ (c 0.92, CHCl_3). Enantiomeric ratio 99:1. HPLC chromatograms and method information for assessment of enantiomeric ratio are included in the [Supporting Information](#).

Preparation of Methyl (R)-3-(tert-Butyldisulfaneyl)-2-hydroxypropanoate (14). Thiosulfonate **9** (276.3 mg, 1.0 mmol) was dissolved in 15 mL of anhydrous dichloromethane in a flame-dried 50 mL round-bottom flask equipped with a magnetic stirrer. The solution was cooled in an ice–water bath, and 2-methyl-2-propanethiol (200 μL , 1.8 mmol) was added. The solution was warmed to rt, and triethylamine (140 μL , 1.0 mmol) was added. The pale yellow mixture was stirred for 5 min, then diluted with dichloromethane, and transferred to a separatory funnel. The organic layer was washed with 10 mL of 1 M HCl (aq). The aqueous layer was extracted with dichloromethane, and then the combined organic layers were washed with an aqueous solution of saturated sodium chloride (10 mL) and dried (MgSO_4). The solvent was removed under reduced pressure, and the resulting clear oil was purified by flash column chromatography over silica gel (3–35% EtOAc/hexanes, $R_f = 0.43$, 30:70 EtOAc/hexanes) to yield the title compound as a clear oil (120.4 mg, 0.50 mmol, 50%). ^1H NMR (400 MHz, CDCl_3): δ 4.49 (td, $J = 6.3, 4.0$ Hz, 1H), 3.82 (s, 3H), 3.17 (dd, $J = 13.7, 4.0$ Hz, 1H), 3.06 (d, $J = 6.2$ Hz, 1H), 3.02 (dd, $J = 13.7, 6.4$ Hz, 1H), 1.34 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 173.4, 69.5, 52.7, 48.1, 44.9, 29.8. HRMS (ESI-QTOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_8\text{H}_{16}\text{O}_3\text{S}_2\text{Na}$, 247.0433; found, 247.0434. IR 3448, 2962, 1724, 1456, 1362, 1217, 1164, 1088, 1018, 914, 832, 768, 669 cm^{-1} . Specific rotation $[\alpha]_{\text{D}}^{23} = +10.0$ (c 0.48, CHCl_3).

Diazotization of L-Cystine: Preparation of Thiirane-2-carboxylic Acid and Acrylic Acid. L-Cystine (60.1 mg, 0.25 mmol) was dissolved in 2 mL of 0.5 M sulfuric acid (aq) in a 2 dram vial then cooled in an ice–water bath. The reaction was run open to ambient atmosphere. Sodium nitrite (1 mL of a 1 M aqueous solution) was added dropwise with stirring. The mixture was warmed to room temperature overnight. Saturated sodium sulfate (1 mL) was added, and then the mixture was extracted 4 times with diethyl ether. The combined organic fractions were dried (MgSO_4) and filtered, and then they were concentrated under reduced pressure (200 Torr, rt). Note that material was not dried under high vacuum, because this results in polymerization and loss of acrylic acid. For yield determination, benzyl benzoate (23.7 μL , 0.13 mmol) was added as an NMR internal standard; the mixture was suspended in $(\text{CD}_3)_2\text{SO}$ and analyzed by ^1H NMR using a 25 s relaxation delay. A mixture of two products was observed: thiirane-2-carboxylic acid (ca. 51%) and acrylic acid (ca. 19%), as identified by ^1H NMR relative to reported spectra.^{30,31} The mixture of products could not be separated because of instability of the material upon concentration (likely polymerization). Tabulated correlations observed by ^1H – ^1H COSY and ^1H – ^{13}C HSQC NMR are included in the [Supporting Information](#). Thiirane-2-carboxylic acid: ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$): δ 12.90 (s, 1H), 3.42 (t, $J = 5.6$ Hz, 1H), 2.70 (d, $J = 5.6$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $(\text{CD}_3)_2\text{SO}$): 171.4, 29.2, 23.5. HRMS (ESI-QTOF) m/z : $[\text{M}-\text{H}]^-$ calcd for $\text{C}_3\text{H}_3\text{O}_2\text{S}$, 102.9859; found, 102.9693. Acrylic acid: ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$): δ 12.90 (s, 1H), 6.26 (dd, $J = 17.3, 1.8$ Hz, 1H), 6.08 (dd, $J = 17.3, 10.3$ Hz, 1H), 5.88 (dd, $J = 10.3, 1.8$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $(\text{CD}_3)_2\text{SO}$): 166.9, 130.7, 129.5.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.joc.9b02630](https://doi.org/10.1021/acs.joc.9b02630).

Supplementary graphs and tables; crystallographic data; and copies of ^1H , ^{13}C NMR spectra and HPLC chromatograms for relevant compounds (PDF)

Crystallographic data for **11** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tfj@mit.edu

ORCID

Timothy F. Jamison: [0000-0002-8601-7799](https://orcid.org/0000-0002-8601-7799)

Notes

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation.

The authors declare no competing financial interest.

CCDC 1949213 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. 1122374. The authors thank the Bill and Melinda Gates Foundation (Medicines For All Institute, OPP1176590) for research funding. The authors thank Dr. Peter Müller (MIT) for X-ray crystallography data and Dr. Bruce Adams (MIT) for ^1H – ^{13}C HSQC experiment optimization.

■ REFERENCES

- (1) Coppola, G. M.; Schuster, H. F. *α -Hydroxy Acids in Enantioselective Syntheses*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2002.
- (2) Humber, D. C.; Jones, M. F.; Payne, J. J.; Ramsay, M. V. J.; Zacharie, B.; Jin, H.; Siddiqui, A.; Evans, C. A.; Tse, H. L. A.; Mansour, T. S. Expedient Preparation of (–)-2'-Deoxy-3'-Thiacytidine. *Tetrahedron Lett.* **1992**, *33*, 4625–4628.
- (3) Biel, M.; Deck, P.; Giannis, A.; Waldmann, H. Synthesis and Evaluation of Acyl Protein Thioesterase 1 (APT1) Inhibitors. *Chem. - Eur. J.* **2006**, *12*, 4121–4143.
- (4) Raza, A. R.; Saddiq, A.; Çakmak, O. Chiral Pool-Based Synthesis of Naphtho-Fused Isocoumarins. *Chirality* **2015**, *27*, 951–957.
- (5) Hu, D. X.; Bielitz, M.; Koos, P.; Ley, S. V. A Total Synthesis of the Ammonium Ionophore, (–)-Enniatin B. *Tetrahedron Lett.* **2012**, *53*, 4077–4079.
- (6) Lücke, D.; Dalton, T.; Ley, S. V.; Wilson, Z. E. Synthesis of Natural and Unnatural Cyclooligomeric Depsipeptides Enabled by Flow Chemistry. *Chem. - Eur. J.* **2016**, *22*, 4206–4217.
- (7) Matthes, D.; Richter, L.; Müller, J.; Denisiuk, A.; Feifel, S. C.; Xu, Y.; et al. *In Vitro* Chemoenzymatic and *In Vivo* Biocatalytic Synthesis of New Beauvericin Analogues. *Chem. Commun.* **2012**, *48*, 5674–5676.
- (8) Albertsson, A.-C.; Varma, I. K. Recent Developments in Ring Opening Polymerization of Lactones for Biomedical Applications. *Biomacromolecules* **2003**, *4*, 1466–1486.
- (9) Rasal, R. M.; Janorkar, A. V.; Hirt, D. E. Poly(Lactic Acid) Modifications. *Prog. Polym. Sci.* **2010**, *35*, 338–356.
- (10) Lu, Y.; Yin, L.; Zhang, Y.; Zhang, Z.; Xu, Y.; Tong, R.; Cheng, J. Synthesis of Water-Soluble Poly(α -Hydroxy Acids) from Living Ring-Opening Polymerization of *O*-Benzyl-L-Serine Carboxyanhydrides. *ACS Macro Lett.* **2012**, *1*, 441–444.

- (11) Sokolsky-Papkov, M.; Agashi, K.; Olaye, A.; Shakesheff, K.; Domb, A. J. Polymer Carriers for Drug Delivery in Tissue Engineering. *Adv. Drug Delivery Rev.* **2007**, *59*, 187–206.
- (12) Hu, D. X.; O'Brien, M.; Ley, S. V. Continuous Multiple Liquid-Liquid Separation: Diazotization of Amino Acids in Flow. *Org. Lett.* **2012**, *14*, 4246–4249.
- (13) Stuhr-Hansen, N.; Padrah, S.; Strömgaard, K. Facile Synthesis of α -Hydroxy Carboxylic Acids from the Corresponding α -Amino Acids. *Tetrahedron Lett.* **2014**, *55*, 4149–4151.
- (14) Koppenhoefer, B.; Schurig, V. (S)-2-Chloroalkanoic Acids of High Enantiomeric Purity from (S)-2-Amino Acids: (S)-2-Chloropropanoic Acid. *Org. Synth.* **1988**, *66*, 151.
- (15) Deeckongkit, S.; You, S.-L.; Kelly, J. W. Synthesis of All Nineteen Appropriately Protected Chiral α -Hydroxy Acid Equivalents of the α -Amino Acids for Boc Solid-Phase Depsi-Peptide Synthesis. *Org. Lett.* **2004**, *6*, 497–500.
- (16) Muhl, C.; Schäfer, O.; Bauer, T.; Räder, H.-J.; Barz, M. Poly(S-Ethylsulfonyl-L-Homocysteine): An α -Helical Polypeptide for Chemoselective Disulfide Formation. *Macromolecules* **2018**, *51*, 8188–8196.
- (17) Schäfer, O.; Huesmann, D.; Muhl, C.; Barz, M. Rethinking Cysteine Protective Groups: S-Alkylsulfonyl-L-Cysteines for Chemoselective Disulfide Formation. *Chem. - Eur. J.* **2016**, *22*, 18085–18091.
- (18) Rojas, A. J.; Pentelute, B. L.; Buchwald, S. L. Water-Soluble Palladium Reagents for Cysteine S-Arylation under Ambient Aqueous Conditions. *Org. Lett.* **2017**, *19*, 4263–4266.
- (19) Hanaya, K.; Ohata, J.; Miller, M. K.; Mangubat-Medina, A. E.; Swierczynski, M. J.; Yang, D. C.; Rosenthal, R. M.; Popp, B. V.; Ball, Z. T. Rapid Nickel(II)-Promoted Cysteine S-Arylation with Arylboronic Acids. *Chem. Commun.* **2019**, *55*, 2841–2844.
- (20) Hope, D. B.; Wälti, M. Synthesis of the α -Hydroxy-Analogues of S-Benzylcysteine and Cysteine. *J. Chem. Soc. C* **1970**, *18*, 2475–2478.
- (21) Burke, H. M.; McSweeney, L.; Scanlan, E. M. Exploring Chemoselective S-to-N Acyl Transfer Reactions in Synthesis and Chemical Biology. *Nat. Commun.* **2017**, *8*, 15655.
- (22) Oae, S.; Fukushima, D.; Kim, Y. H. Multistep Oxidations of the Unsymmetrical Disulfide and Thiolsulfonates: New Evidence for the Formation of the Thionitrite and the Sulfinyl Derivatives as the Intermediates. *Chem. Lett.* **1978**, *7*, 279–280.
- (23) Leonov, A.; Voigt, B.; Rodriguez-Castañeda, F.; Sakhaii, P.; Griesinger, C. Convenient Synthesis of Multifunctional EDTA-Based Chiral Metal Chelates Substituted with an S-Mesylcysteine. *Chem. - Eur. J.* **2005**, *11*, 3342–3348.
- (24) Huesmann, D.; Schäfer, O.; Braun, L.; Klinker, K.; Reuter, T.; Barz, M. Exploring New Activating Groups for Reactive Cysteine NCAs. *Tetrahedron Lett.* **2016**, *57*, 1138–1142.
- (25) Carlson, R. *Design and Optimization in Organic Synthesis*, 1st ed.; Elsevier Science B.V.: Amsterdam, The Netherlands, 1992.
- (26) Hyde, A. M.; Zultanski, S. L.; Waldman, J. H.; Zhong, Y.-L.; Shevlin, M.; Peng, F. General Principles and Strategies for Salting-Out Informed by the Hofmeister Series. *Org. Process Res. Dev.* **2017**, *21*, 1355–1370.
- (27) Defonsi Lestard, M. E.; Ramos, L. A.; Tuttolomondo, M. E.; Ulic, S. E.; Ben Altabef, A. Synthesis and Vibrational Properties of Trifluoromethyl Trifluoromethanesulfonate and Comparison with Covalent Sulfonates. *Vib. Spectrosc.* **2012**, *59*, 40–46.
- (28) Galván, J. E.; Contreras Aguilar, E.; Defonsi Lestard, M. E.; Tuttolomondo, M. E.; Ulic, S. E.; Ben Altabef, A. Theoretical and Experimental Study of a New Thiosulfonate Derivative: Methyl Trifluoromethanesulfonate, $\text{CF}_3\text{SO}_2\text{SCH}_3$. Conformational Transferability in $\text{CX}_3\text{SO}_2\text{S-R}$ Compounds. *Inorg. Chim. Acta* **2017**, *455*, 254–261.
- (29) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29*, 2176–2179.
- (30) Maycock, C. D.; Stoodley, R. J. Studies Related to Thiirans. Part 1. Synthesis of Chiral Thiirancarboxylates. *J. Chem. Soc., Perkin Trans. 1* **1979**, *1*, 1852–1857.
- (31) Yu, H.; Ru, S.; Dai, G.; Zhai, Y.; Lin, H.; Han, S.; Wei, Y. An Efficient Iron(III)-Catalyzed Aerobic Oxidation of Aldehydes in Water for the Green Preparation of Carboxylic Acids. *Angew. Chem., Int. Ed.* **2017**, *56*, 3867–3871.