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## Enzymatic Resolution and Decarboxylative Functionalization of $\alpha$ -Sulfinyl Esters

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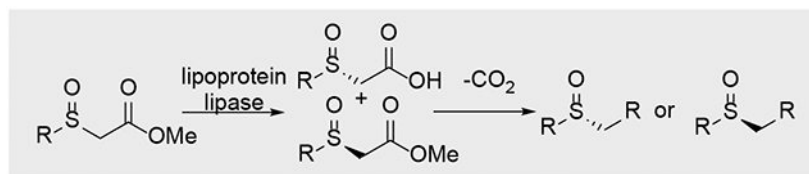
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### Abstract

$\alpha$ -Sulfinyl esters can be readily prepared through thiol substitution of  $\alpha$ -bromo esters followed by oxidation to the sulfoxide. Enzymatic resolution with lipoprotein lipase provides both the unreacted esters and corresponding  $\alpha$ -sulfinyl carboxylic acids in high yields and enantiomeric ratios. Subsequent decarboxylative halogenation, dihalogenation, trihalogenation and cross-coupling gives rise to functionalized sulfoxides. The method has been applied to the asymmetric synthesis of a potent inhibitor of 15-prostaglandin dehydrogenase.

### Graphical Abstract



Enzymatic resolution of  $\alpha$ -sulfinyl esters gives recovered ester and  $\alpha$ -sulfinyl acid in high enantiomeric purity. Decarboxylative functionalization provides access to a wide range of optically active sulfoxides in both enantiomeric forms.

### Keywords

decarboxylation; halogenation; lipase; resolution; sulfoxides

## Introduction

Optically active sulfoxides are important components of pharmaceutical agents, natural products,<sup>[1]</sup> chemical reagents<sup>[2]</sup> chiral auxiliaries,<sup>[3]</sup> and ligands for asymmetric catalysis.<sup>4</sup> Biologically active sulfoxides include the bicyclic octapeptide  $\alpha$ -amanitin was isolated from the death-cap mushroom and found to potently inhibit RNA Pol II (Figure 1).<sup>[5]</sup> Carmaphycin A, produced by a marine cyanobacteria, inhibits the proteasome with  $IC_{50} = 2.5$  nM,<sup>[6]</sup> while ustiloxin G is a cyclopeptide fungal metabolite that potently inhibits rice germination.<sup>[7]</sup> Stereodefined sulfoxides also appear in approved drugs, including the stimulant armodafinil<sup>[8]</sup> and the proton pump inhibitors esomeprazole and dexlansoprazole.<sup>[9]</sup> We became interested in this area in connection with our efforts to identify inhibitors of 15-prostaglandin dehydrogenase (15-PGDH), an enzyme that metabolizes several prostaglandins, including PGE<sub>2</sub>, PGF<sub>2</sub> $\alpha$ , and PGI<sub>2</sub>.<sup>[10]</sup> In this context, the sulfoxide SW209415 inhibits 15-PGDH with low nM  $IC_{50}$  values, and the *R*-isomer is >100-fold more potent than the *S*-enantiomer.<sup>[11]</sup>

The stereospecificity of inhibition by SW209415 and the broader role of sulfoxides in biologically active small molecules highlights the importance of stereoselective syntheses of sulfoxides.<sup>12</sup> Asymmetric, catalytic oxidations of sulfides have been developed, with several reports describing first-row transition metal complexes that use peroxide oxidants.<sup>[13]</sup> The best enantioselectivities are generally achieved with aryl thioethers, with dialkyl sulfoxides being formed with lower selectivity. Chiral phosphoric acids and their derivatives catalyze highly enantioselective oxidation of a range of sulfides. However, these catalysts require multistep syntheses, and their high molecular weight could limit their applicability. Enzymes and cell extracts have been used to kinetically resolve sulfoxides through reduction to the sulfide.<sup>[14]</sup> High enantioselectivities can be obtained with this method, but only one enantiomer is generally accessible.

We considered an approach to optically active  $\alpha$ -sulfinyl carboxylates that would involve kinetic resolution of the corresponding ester **1** (Table 1). Recent advances in decarboxylative functionalization could provide a way to convert  $\alpha$ -sulfinyl acids **2** to a wide variety of functionalized sulfoxides.<sup>[15]</sup> Many kinetic resolutions of sulfoxides have been described, but most of them involve selective oxidation of one sulfoxide enantiomer to the corresponding achiral sulfone.<sup>[16],[17]</sup> By contrast, lipase resolution could provide both enantiomers in easily separated, highly enantioenriched form.<sup>[18]</sup> Pioneering research from Burgess and Henderson demonstrated enzymatic hydrolysis of sulfinyl esters,<sup>[19]</sup> but the enzyme used in that work, *Pseudomonas* K-10, is no longer readily available.

## Results and Discussion

We evaluated lipases and esterases from various sources using the cyclohexyl sulfoxide **1a** as a test substrate (Table S1).<sup>[20]</sup> Of the 16 enzymes tested, five gave >30% conversion, but only lipoprotein lipase from *Burkholderia* sp. (EC 3.1.1.3) gave >35% ee. Under optimized conditions, the ester **1a** could be recovered in 46% yield on gram scale as a single enantiomer from the reaction mixture by simple extraction (Table 1). Monitoring the reaction by <sup>1</sup>H NMR spectroscopy indicated a nearly perfect kinetic resolution with 50%

conversion and selectivity factor  $E > 1000$ .<sup>21</sup> Acidification of the aqueous phase allowed recovery of the corresponding acid **2a** in 30% yield with 99% ee. A brief survey of the reaction scope showed encouraging generality. The same major enantiomer was hydrolyzed with all sulfoxides, but the R and S designations and optical rotation signs vary based on substituents' priority and UV absorption. Both cyclic and linear alkyl sulfoxides were resolved with high efficiency and selectivity, although the acids **2a** and **2b** decomposed on prolonged storage. The success of dialkyl sulfoxides distinguishes this approach from many asymmetric oxidation methods. Similarly, electronic factors did not influence reactivity or selectivity with aryl-substituted sulfoxides, as illustrated by the similar yields and ee's obtained with electron rich (**1d/2d**), electron neutral (**1c/2c**, **1e/2e**) or electron poor aryl groups (**1f/2f**, **1g/1g**). Substrate **1h** represents an interesting example that is chiral by virtue of two different ester groups. The methyl ester was hydrolyzed with high chemo- and enantio-selectivity to provide diester **1h** and ester/acid **2h** in 99 and 89% ee, respectively.

Facile interconversion of the  $\alpha$ -sulfinyl acid and ester allows access to either enantiomer of sulfoxide (Scheme 1), which is a distinguishing characteristic of this method compared to prior enzymatic approaches to sulfoxides. Hydrolysis of the ester with LiOH and esterification of the acid with diazomethane both proceed cleanly and without racemization. In general, ee determination was easier on the esters while many of the derivatizations highlighted below used the acid derived from the unreacted ester recovered from the enzymatic resolution.

To expand the range of optically active sulfoxides accessible through enzymatic resolution of  $\alpha$ -sulfinyl carboxylates, we explored decarboxylative functionalization. Coupling of enantioenriched acids **2** to pyriothione (**3**) with a dicyclohexyl carbodiimide provided an intermediate Barton ester (Scheme 2). Irradiation of a solution of the ester in CBrCl<sub>3</sub> or iodoform (250W, white light) promoted decarboxylative halogenation.<sup>[22]</sup> The bromomethyl sulfoxides (**4**) were formed in good-excellent yields while the iodomethyl sulfoxides (**5**) were isolated in moderate yields. In all cases, complete retention of optical purity was observed.

The halogenation conditions of Scheme 2 were not successful for chlorination. CCl<sub>4</sub> and related solvents were not effective for the chlorination, and NCS and other chlorinating reagents gave no desired product. As an alternative, we considered resolving the  $\alpha$ -chloro- $\alpha$ -sulfinyl esters directly (Table 2). The racemates (**6**) could be synthesized as a ~1:1 mixture of diastereomers by chlorinating the  $\alpha$ -thioether with NCS prior to formation of the sulfoxide with *m*-CPBA (see the Supporting Information). Enzymatic resolution at pH 7.5 proceeded slowly, with recovered **6a** showing only 39% ee after 72h. We hypothesized that one diastereomer might be processed more quickly than the other isomer, and that raising the pH might allow a dynamic kinetic resolution to proceed. Consistent with this expectation, **6a** was isolated in >99% ee after only 18 h when the reaction was performed at pH 9.5. In general, pH 8.6 was optimal for aryl sulfoxides, and pH 9.5 worked for alkyl sulfoxides. The chlorosulfinyl esters **6** and acid **7** were isolated as ~1:1 mixtures of diastereomers with high optical purity. The exception was the cyclohexyl sulfoxide **7a**, which decomposed upon attempted isolation. Heating the  $\alpha$ -chloro- $\alpha$ -sulfinyl acids **7** in the presence of Cs<sub>2</sub>CO<sub>3</sub>

promoted decarboxylation and provided the chloromethyl sulfoxides **8** in good yield and excellent ee.

A similar strategy could be used to access dihalomethyl sulfoxides (Scheme 3). Resolved  $\alpha$ -sulfinyl esters could be dichlorinated or dibrominated with N-halosuccinimide (**9**, **10**). Hydrolysis of the ester with LiOH returned the dihalosulfoxides **11** and **12**.

The dihalogenation described in Scheme 3 proceeded cleanly from the resolved esters. However, attempts to translate these conditions to the corresponding  $\alpha$ -sulfinyl acid generally led to complex mixtures of mono-, di- and trihalogenated products with variable levels of racemization (Table S5). Optimization efforts identified DMSO as an effective solvent for stereoretentive decarboxylative tribromination (Scheme 4). A set of alkyl and aryl sulfoxides all reacted cleanly in the presence of excess N-bromosuccinimide. Monitoring the reaction by LC/MS indicated that the reaction likely proceeds by way of dibromination followed by decarboxylation and the final bromination. Related reactions with NCS or NIS gave <10% of the desired trihalogenated products.

Decarboxylative cross-coupling reactions have emerged as effective strategies for C—C bond formation.<sup>[23]</sup> We explored decarboxylative cross-electrophile coupling using redox active esters derived from optically active  $\alpha$ -sulfinyl acetates following a procedure developed by the Weix group (Table 3).<sup>[24]</sup> First, the acids were coupled N-hydroxyphthalimide. Next, the crude esters were subjected to reductive coupling conditions with iodobenzene in the presence of a Ni catalyst and a dipyrindyl ligand (dtbpy). The corresponding benzyl sulfoxides were formed rapidly in high yield from aryl-substituted  $\alpha$ -sulfinyl acids. A linear alkyl sulfoxide (**2b**) also participated effectively, but the phthalimide ester derived from cyclohexyl sulfoxide **2a** was unstable, while the unsymmetrical ester derived from **2h** could not be formed. In all cases, the decarboxylative coupling proceeded without loss of enantioenrichment.

To demonstrate the utility of the enzymatic resolution and decarboxylative functionalization, we synthesized a novel inhibitor of 15-PGDH. Previous syntheses of this inhibitor class relied on preparative HPLC over a chiral stationary phase, which was both time consuming and wasteful.<sup>[11a]</sup> As shown in Scheme 5, aldol condensation of imidazole aldehyde **15** with methyl ketone **16** provided the enone **17**. Annulation with cyanothioacetamide generated the thiopyridine **18**. Alkylation with either (*R*)- or (*S*)-**4a** provided the enantiomeric sulfoxides **19**. Final cyclization constructed the thienopyridine core without racemization. The two enantiomers were tested for their ability to inhibit recombinant human 15-PGDH. (*R*)-**20** was found to be a potent inhibitor with IC<sub>50</sub> values approaching the limit of detection of this assay.<sup>[10a]</sup> By contrast, (*S*)-**20** was more than 100-fold less active, highlighting the importance of preparing the sulfoxides in single isomer form.

## Conclusion

Lipase resolutions are scalable and operationally simple. The resolved ester can be isolated in nearly pure form through extraction, and the acid of the opposite enantiomer can similarly be obtained through extraction after acidification. Finally, decarboxylative functionalization

can proceed with retention of stereochemistry, thereby providing access to a wide range of optically active sulfoxides.

## Experimental Section

Representative procedure: To a solution of ester ( $\pm$ )-**1a** (1.5 g, 7.35 mmol) in toluene (7.5 mL) were added phosphate buffer (60 mL of pH 7.5, 0.05 M) and lipoprotein lipase from *Burkholderia sp.* (EC 3.1.1.3, 150 mg, 10 wt%). This heterogeneous mixture was stirred at 25 °C for 18 h. The mixture was filtered through celite to remove the enzyme and extracted with EtOAc (3  $\times$  40 mL). Evaporation of the solvent and flash chromatography gave enantioenriched ester derivative (*R*)-**1a** (0.69 g, 46%). Ee was determined to be >99% by HPLC (See SI). Acetic acid (15.0 mL) was added and aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  50 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and removal of the solvent gave acid (*S*)-**2a** (0.42 g, 30%). Ee was determined following conversion to the methyl ester, as described below.

Under a nitrogen atmosphere, a solution of (trimethylsilyl)diazomethane (2.0 M solution in diethyl ether, 21 mmol) was added to a solution of the acid derivative **2a** (2.1 mmol) in dry MeOH (3.0 mL) at 0 °C. The resulting mixture was warmed slowly to rt and stirred overnight. After completion of the reaction, the solvent was removed in vacuo. Purification by ISCO flash column chromatography afforded the ester derivative (*S*)-**2a** in quantitative yield.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

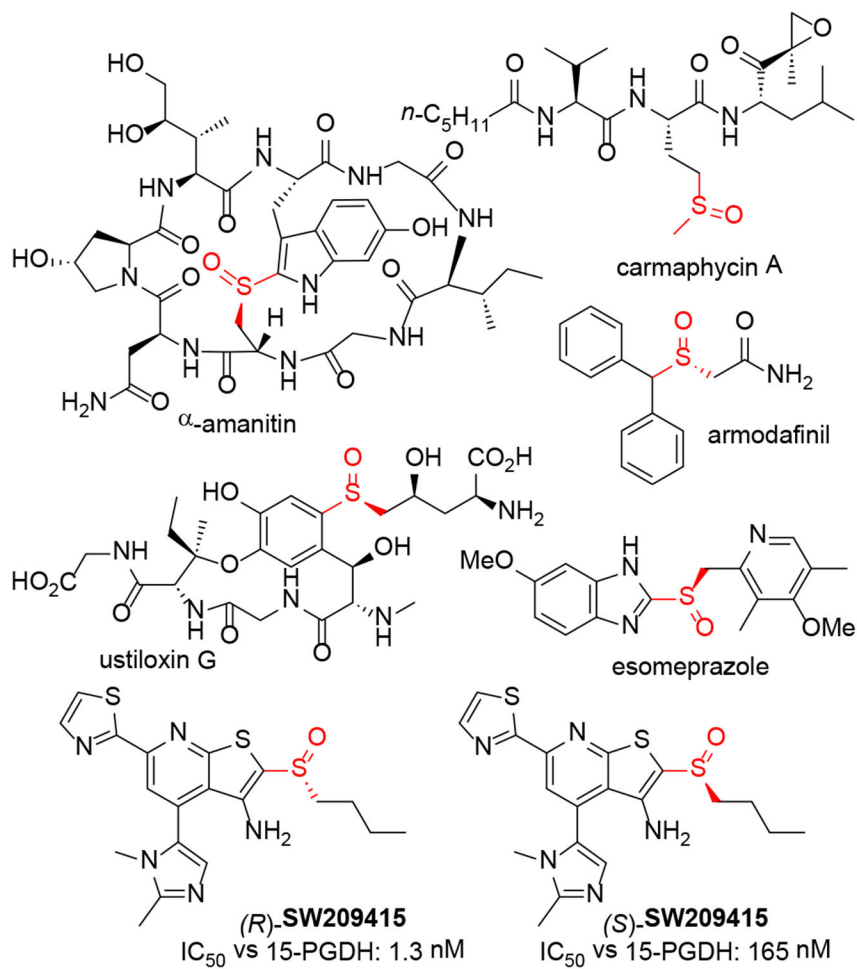
## Acknowledgements

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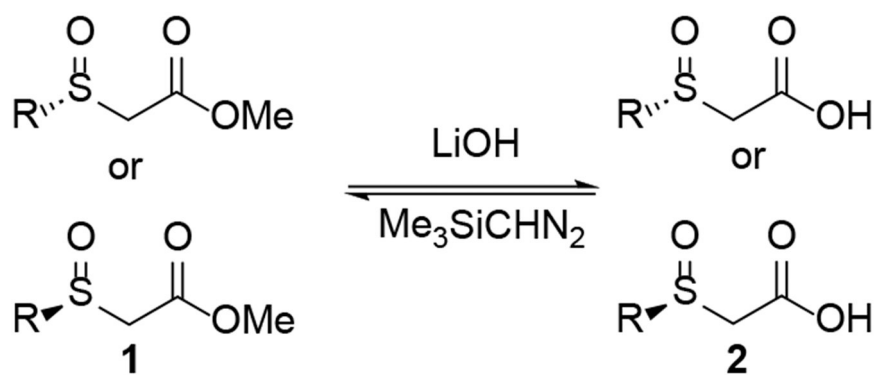
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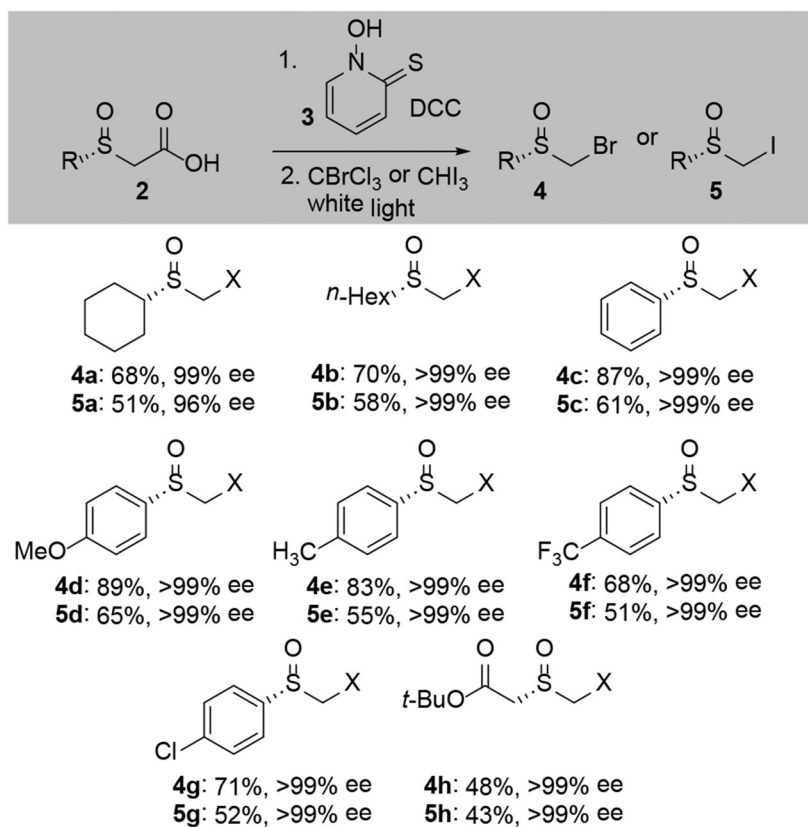
**Figure 1.**  
Representative sulfoxide containing natural products and pharmaceutical agents.



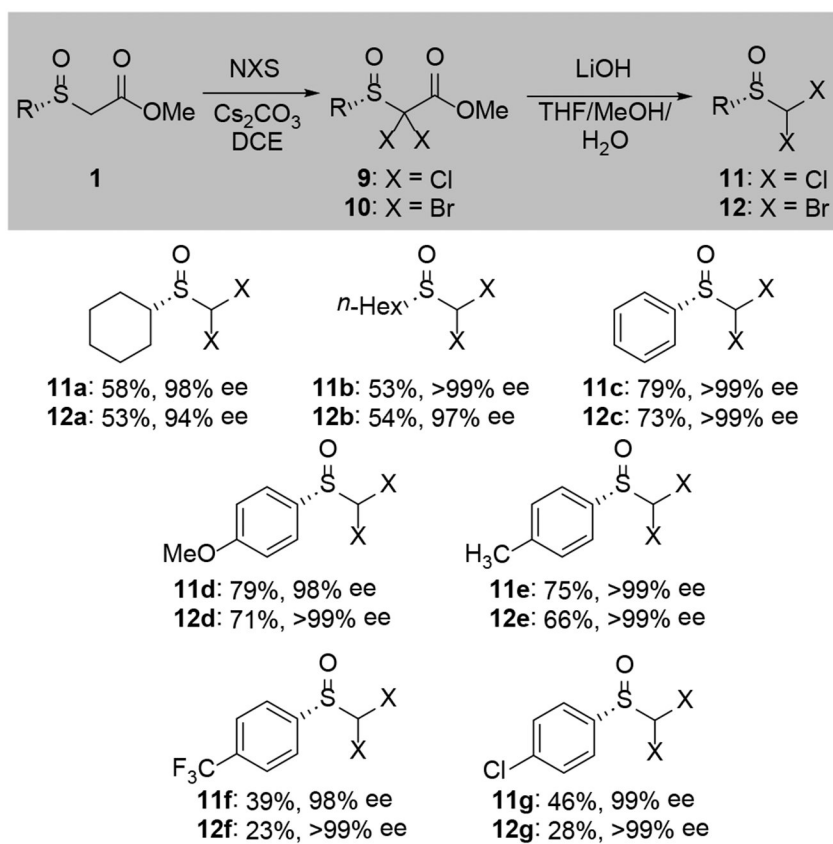
**Scheme 1.**

Ester/acid interconversion allows access to both sulfoxide enantiomers.

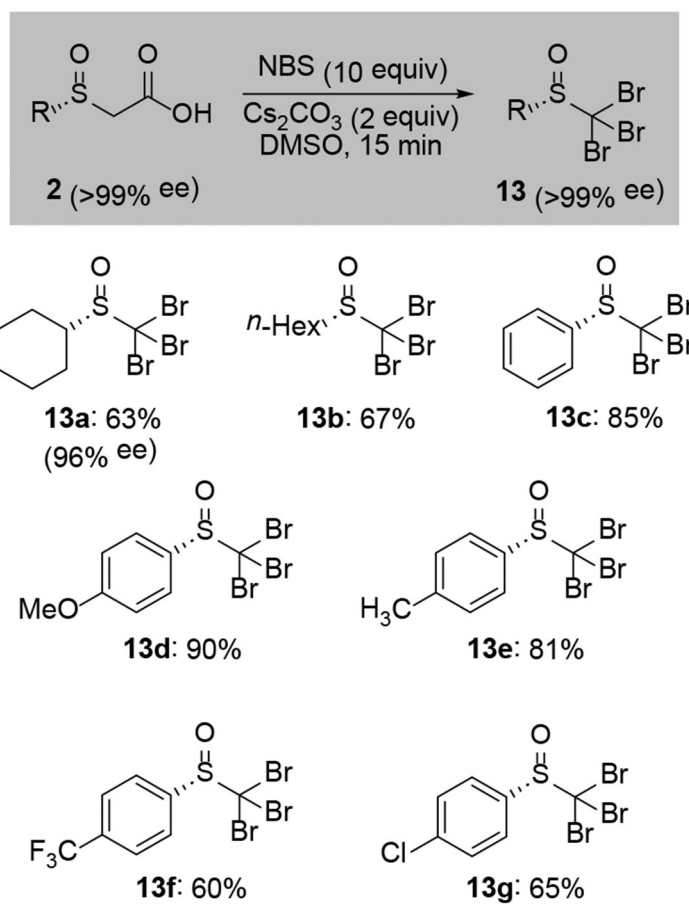




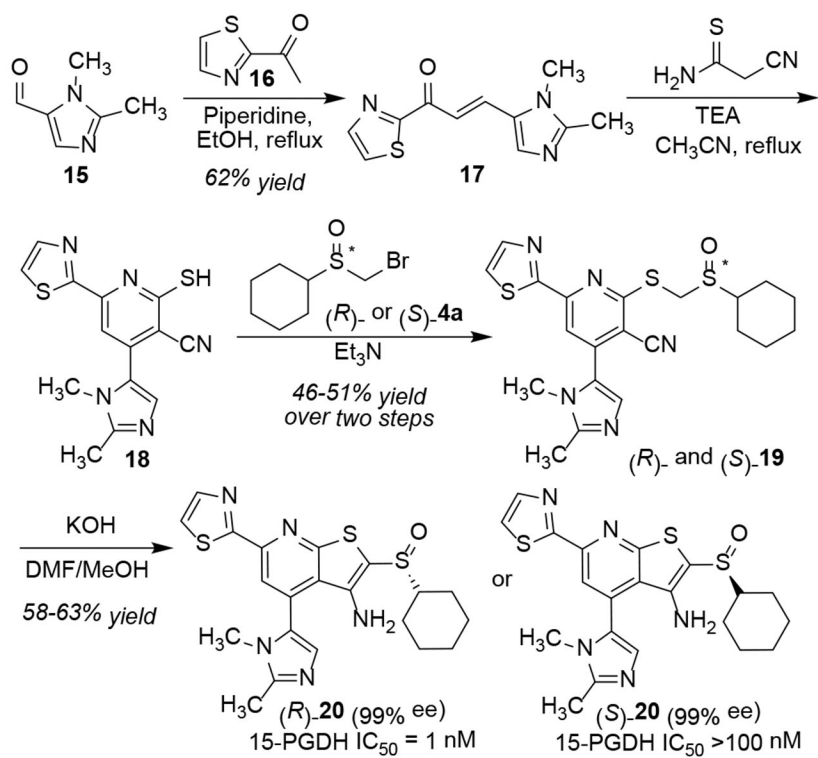
**Scheme 2.**  
Decarboxylative halogenation of  $\alpha$ -sulfinyl carboxylic acids.

**Scheme 3.**

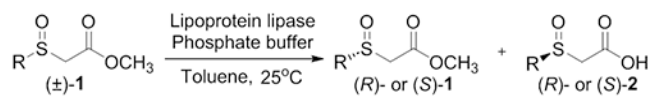
Synthesis of dihalosulfoxides. [a] Isolated yield over 2 steps.



**Scheme 4.**  
Tribromination of  $\alpha$ -sulfinyl acids.

**Scheme 5.**

Asymmetric synthesis of sulfoxide inhibitors of 15-prostaglandin dehydrogenase (15-PGDH).

**Table 1.**Enzymatic resolution of  $\alpha$ -sulfinyl carboxylates.<sup>[a]</sup>

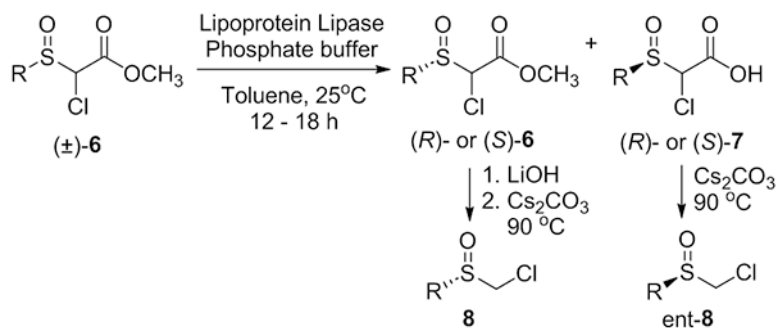
Entry	Cmpd	R	Buffer pH	Time (h)	% Yield 1 (% ee)	% Yield 2 (% ee)
1 <sup>[b]</sup>	1a/2a		7.5	16	46 (>98)	30 (99)
2 <sup>[b]</sup>	1b/2b	<i>n</i> -Hex	9.0	12	46 (>98)	32 (>99)
3	1c/2c		7.5	16	48 (>99)	35 (>99)
4	1d/2d		7.5	15	47 (>99)	36 (96)
5	1e/2e		7.5	15	46 (>99)	35 (>99)
6	1f/2f		8.6	14	45 (>99)	33 (>99)
7	1g/2g		7.5	16	45 (>99)	33 (98)
8 <sup>[b],[c]</sup>	1h/2h		9.5	60	44 (>99)	30 (89)

<sup>[a]</sup> Reactions on a 1 g scale with 10 wt% lipoprotein lipase from *Burkholderia sp.*, 8:1 50 mM phosphate buffer:toluene unless otherwise noted.

<sup>[b]</sup> 30 wt% lipase.

<sup>[c]</sup> 100 mM phosphate buffer.

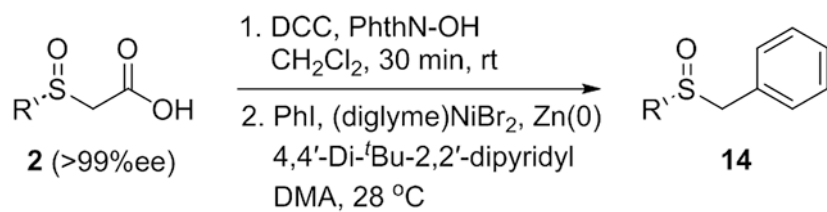
Table 2.

Asymmetric synthesis of chloromethyl sulfoxides.[<sup>a</sup>]

Entry	R	pH	% Yield 6 (% ee)	% Yield 7 (% ee)	% Yield 8 (% ee)
1 <sup>[b]</sup>		9.5	39 (>99)	unstable	--
2 <sup>[b]</sup>	<i>n</i> -Hex	9.5	41 (>99)	28 (99)	( <i>S</i> )-8b 65 (99)
3		8.6	46 (>99)	35 (>99)	( <i>S</i> )-8c: 81 (98) ( <i>R</i> )-8c: 78 (99)
4		8.6	42 (>99)	32 (90)	( <i>S</i> )-8d 80 (99)
5		8.6	41 (>99)	30 (93)	( <i>S</i> )-8e 73 (97)
6		8.6	40 (>99)	25 (95)	( <i>S</i> )-8f 66 (>99)
7		8.6	40 (>99)	31 (98)	( <i>S</i> )-8g 81 (>99)

[<sup>a</sup>] Reactions on a 0.1-0.2 g scale with 20 wt% enzyme, 8:1 50 mM phosphate buffer : toluene unless otherwise noted.

[<sup>b</sup>] 100 mM phosphate buffer.

**Table 3.**Decarboxylative cross couplings of  $\alpha$ -sulfinyl acids.

Entry	Cmpd	R	Time (h)	Yield <b>14</b> (%)	Ee <b>14</b> (%)
1 <sup>[a]</sup>	<b>14a</b>		--	--	--
2	<b>14b</b>	<i>n</i> -Hex	4	68	>99
3	<b>14c</b>		2	70	>99
4	<b>14d</b>		2	71	>99
5	<b>14e</b>		2	67	>99
6	<b>14f</b>		2	65	>99
7	<b>14g</b>		2	67	>99
8 <sup>[b]</sup>	<b>14h</b>		--	--	--

<sup>[a]</sup>Phthalimide ester unstable.<sup>[b]</sup>Phthalimide ester not formed.