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Organocatalytic Asymmetric Mannich/Aza-Michael Cascade Reaction of δ-Formyl-α,β-unsaturated Ketones with Cyclic *N*-Sulfimines: Enantioselective Synthesis of Benzosulfamidate-Fused Pyrrolidines

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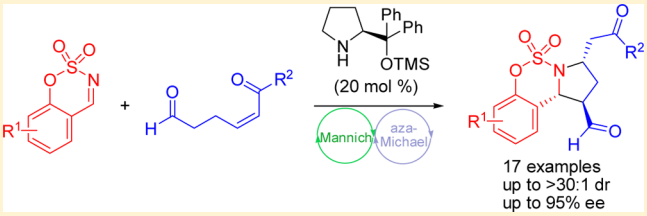
Supporting Information

ABSTRACT: A catalytic highly enantioselective Mannich/aza-Michael cascade reaction of δ-formyl-α,β-unsaturated ketones with cyclic *N*-sulfimines, promoted by diphenylprolinol TMS ether as an organocatalyst, has been developed for the synthesis of chiral benzosulfamidate-fused pyrrolidines, which generated in good yields and with high diastero- and enantioselectivities. Further chemical transformations have been performed with chiral benzosulfamidate-fused pyrrolidines



INTRODUCTION

Pyrrolidine is a well-known privileged scaffold commonly encountered in many biologically active natural products and synthetic pharmaceutical compounds.[1] This scaffold is also widely used as a ligand as well as an organocatalyst in asymmetric synthesis for a variety of enantioselective transformations[2] and as a synthetic building block or intermediate to construct heterocyclic compounds.[3] In view of their potent biological activities and unique structural features, the highly selective synthesis of chiral pyrrolidines is increasingly attracting considerable interest from synthetic chemists, and therefore numerous synthetic approaches have been developed.[4]

On the other hand, cyclic sulfamidates, 1,2,3-oxathiazolidine 2,2-dioxides, have become a very interesting class of heterocyclic compounds that exhibit important biological activities such as antibiotic, antiviral, anticancer, anticonvulsant, antiobesity, antiarthritis, and antiosteoporosis activities.[5] They also play an important role in the synthesis of various biologically and chemically valuable alkylamines.[6] Therefore, it is very desirable to develop concise methods for the synthesis of sulfamidate heterocycles. Several reactions employing cyclic *N*-sulfimines as substrates, which are readily accessible and stable imines,[7] including allylation, annulation, cycloaddition, and the Mannich reaction, have been developed to synthesize cyclic sulfamidate molecules.[8,9] Notably, cyclic sulfamidate-fused heterocycles have received little attention. Hence, we have become very interested in the development of new and efficient methods for the synthesis of cyclic sulfamidate-fused heterocycles, especially an organocatalytic asymmetric version.

Two examples of enantioselective organocatalytic strategies have been explored to access chiral cyclic sulfamidate-fused heterocycles.[8a,b] In 2013, He and co-workers investigated an enantioselective [4 + 2] cycloaddition of cyclic *N*-sulfimines and acyclic enones using a cinchona alkaloid-derived chiral primary amine as organocatalyst, giving sulfamidate-fused 2,6-disubstituted piperidin-4-ones in good yields (60−85%) and with excellent diastereo- and enantioselectivities (>19:1 dr and 90−97% ee, Scheme 1a). Alternatively, Guo and co-workers developed a phosphine-catalyzed enantioselective [3 + 2] cycloaddition process for cyclic *N*-sulfimines with allenoates to provide sulfamidate-fused dihydropyrroles in moderate to good yields (45−91%) and enantioselectivities (31−97% ee, Scheme 1b). A catalytic cycloaddition reaction was used for the synthesis of cyclic sulfamidate-fused heterocycles in the above two cases. Encouraged by this work, we designed a novel synthesis of chiral benzosulfamidate-fused pyrrolidines employing cyclic *N*-sulfimines as substrates (Scheme 1c). In this strategy, we envisaged that the catalytic Mannich reaction of cyclic *N*-sulfimines with δ-formyl-α,β-unsaturated ketones would be readily followed by an intramolecular aza-Michael ring closure reaction. If the chiral amine catalyst works properly, this reaction system will provide an asymmetric cascade reaction model to rapidly construct chiral pyrrolidine rings containing benzosulfamidates.[10]

RESULTS AND DISCUSSION

On the basis of our previous successful studies on asymmetric cascade reactions for the rapid construction of complex molecules,[11] we chose diarylprolinol silyl ethers as the chiral amine catalysts to activate the aldehyde group in the δ-formyl-α,β-unsaturated ketones and generate nucleophilic enamine intermediates. The initial exploration was carried out by reacting *cis*-6-oxo-6-phenylhex-4-enal **1a** and benzoxathiazine

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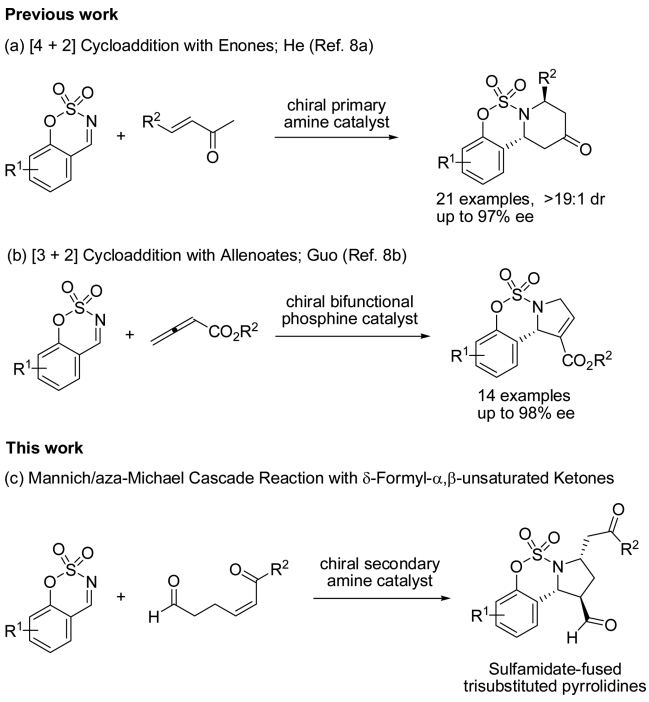
Scheme 1. Catalytic Enantioselective Cycloaddition of Cyclic *N*-Sulfimines

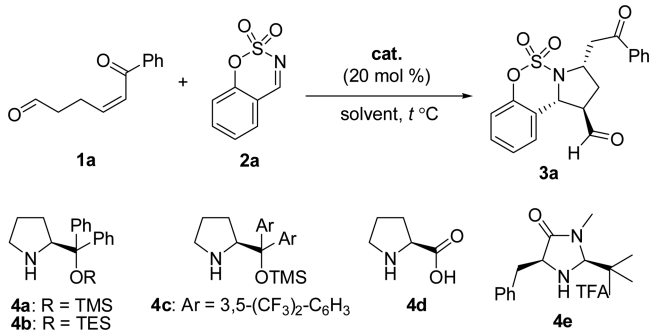


2,2-dioxide **2a** as model substrates using (*s*)-2-(diphenyl-((trimethylsilyl)oxy)methyl)pyrrolidine **4a** (20 mol %) as catalyst in dichloromethane at room temperature (Table 1, entry 1). Gratifyingly, the cascade reaction proceeded smoothly affording benzosulfamidate-fused pyrrolidine **3a** in 76% yield with high enantioselectivity (81% ee).

Encouraged by this promising result, the reaction was performed at different temperatures in an attempt to improve the enantioselectivity. A lower reaction temperature provided a better stereocontrol. Thus, when the reaction was carried out at −40 °C, the desired product was obtained in good yield and with excellent enantioselectivity (91% ee) and diastereoselectivity (10:1 dr) although the reaction time increased (Table 1, entry 3). To optimize the reaction efficiency further, various organocatalysts were subsequently examined. Both diarylprolinol silyl ether organocatalysts **4b** and **4c** afforded the desired cascade adducts with excellent enantioselctivities (Table 1, entries 4 and 5). However, proline **4d** and Macmillan catalyst **4e** gave disappointing results (Table 1, entries 6 and 7). Although catalyst **4c** showed the best enantioselectivity (92% ee), a longer reaction time (96 h) was required; therefore, **4a** was chosen as the catalyst for further optimization of the reaction conditions.

A solvent survey revealed that the reaction medium has a substantial impact on the conversion efficiency and stereoselectivity of the reaction (Table 1, entries 8−16). Chloroform, 1,2-dichloroethane, toluene, acetonitrile, and THF all proved to be effective solvents but afforded slightly lower enantioselectivities than dichloromethane. In contrast, protic solvents such as MeOH and EtOH were found unsuitable for this reaction, providing low yields and unsatisfying enantioselectivities. The best results were obtained with EtOAc and Et_2O (Table 1, entries 12 and 14, respectively). Both solvents were used as the reaction medium in the following cascade reactions, depending on the nature of the substrates.

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	solvent	temp (°C)	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	CH_2Cl_2	rt	2	76	7:1	81
2	**4a**	CH_2Cl_2	0	2	72	9:1	83
3	**4a**	CH_2Cl_2	−40	6	80	10:1	91
4	**4b**	CH_2Cl_2	−40	8	67	12:1	85
5	**4c**	CH_2Cl_2	−40	96	64	12:1	92
6	**4d**	CH_2Cl_2	−40	120	61	12:1	27
7	**4e**	CH_2Cl_2	−40	96	-[e]	nd	nd
8	**4a**	$CHCl_3$	−40	8	78	15:1	86
9	**4a**	$ClCH_2H_2Cl$	−30	24	93	8:1	80
10	**4a**	toluene	−40	8	82	9:1	82
11	**4a**	CH_3CN	−40	24	85	6:1	84
12	**4a**	EtOAc	−40	24	78	9:1	93
13	**4a**	THF	−40	48	72	5:1	89
14	**4a**	Et_2O	−40	24	84	10:1	93
15	**4a**	MeOH	−40	48	42	5:1	57
16	**4a**	EtOH	−40	48	58	7:1	70

[a]The reactions were carried out in solvent (0.2 M) with *cis*-**1a** (0.2 mmol) and **2a** (0.24 mmol) in the presence of 20 mol % catalyst at the given temperature. [b]Isolated yield after chromatographic purification. [c]Determined by ^1H NMR analysis of the crude product. [d]Determined by chiral-phase HPLC analysis after Wittig reaction to the corresponding ester (e.g., Ph_3PCHCO_2Me). [e]No reaction. nd = Not determined.

With the optimized reaction conditions in hand (1 equiv of *cis*-**1**, 1.2 equiv of **2**, and 20 mol % of catalyst **4a** in Et_2O or EtOAc at −40 °C), the substrate scope and generality of the reaction were investigated (Table 2). First, diverse *cis*-*δ*-formyl-*α*,*β*-unsaturated ketones **1** were screened against benzoxathiazine 2,2-dioxide **2a**. In general, the reactions of all the substrates in Et_2O smoothly afforded the corresponding benzosulfamidate-fused pyrrolidines in good yields (71−95%) with good to excellent diastereo- and enantioselectivities (8:1−14:1 dr, 82−93% ee). The electronic nature of the aromatic R^1 group only slightly affected the reaction yields and stereoselectivities, with both electron-donating (Table 2, entries 2−5) and electron-withdrawing (Table 2, entries 6 and 7) substituents being well tolerated. Moreover, meta-substituents generally led to higher reaction activities and enantioselectivities than para-substituents did (**3b** vs **3c**; **3d** vs **3e**). However, *cis*-*δ*-formyl-*α*,*β*-unsaturated ketone having an aliphatic R1 group (*n*-butyl group) did not react with benzoxathiazine 2,2-dioxide **2a** under the optimized reaction conditions.

Encouraged by the excellent results obtained from the use of *cis*-*δ*-formyl-*α*,*β*-unsaturated ketones, the scope of our strategy was further extended. The reactions of several functionalized cyclic *N*-sulfimines **2** were carried out in EtOAc under the optimized reaction condition (Table 2, entries 8−17). Here EtOAc was used because the solubility of these substituted

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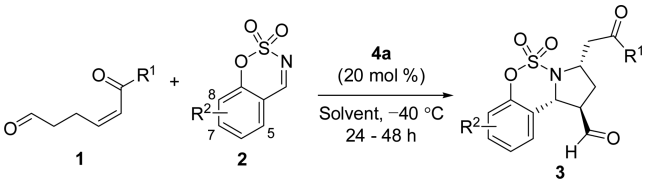
Table 2. Substrate Scope of the Reaction[a]



1 2 3

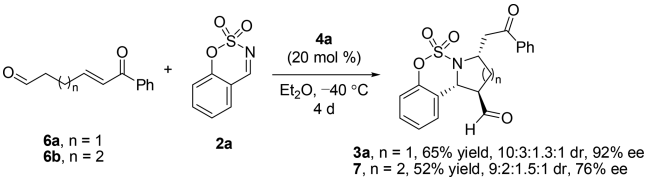
entry	R^1	R^2	solvent	3	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	H	Et_2O	**3a**	78	10:1	93
2	*p*-MeC_6H_4	H	Et_2O	**3b**	71	10:1	85
3	*m*-MeC_6H_4	H	Et_2O	**3c**	76	14:1	91
4	*p*-$MeOC_6H_4$	H	Et_2O	**3d**	74	8:1	85
5	*m*-$MeOC_6H_4$	H	Et_2O	**3e**	95	12:1	88
6	*p*-FC_6H_4	H	Et_2O	**3f**	82	13:1	82
7	*p*-ClC_6H_4	H	Et_2O	**3g**	79	10:1	84
8	Ph	6-Me	EtOAc	**3h**	79	20:1	88
9	Ph	7-Me	EtOAc	**3i**	85	12:1	83
10	Ph	6-OMe	EtOAc	**3j**	79	15:1	90
11	Ph	7-OMe	EtOAc	**3k**	96	25:1	90
12	Ph	8-OMe	EtOAc	**3l**	83	16:1	92
13	Ph	6-F	EtOAc	**3m**	74	>30:1	88
14	Ph	6-Cl	EtOAc	**3n**	72	16:1	87
15	Ph	6-Br	EtOAc	**3o**	79	>30:1	92
16	Ph	6,8-Cl	EtOAc	**3p**	72	25:1	91
17	Ph	6,8-Br	EtOAc	**3q**	74	>30:1	94

[a]The reactions were carried out in solvent (0.2 M) with **1a** (0.2 mmol) and **2a** (0.24 mmol) in the presence of 20 mol % catalyst at the given temperature. [b]Isolated yield after chromatographic purification. [c]Determined by ^1H NMR analysis of the crude mixture. [d]Determined by chiral-phase HPLC analysis after Wittig reaction to the corresponding ester (e.g., Ph_3PCHCO_2Me).

cyclic *N*-sulfimines **2** was not good in Et_2O. When functionalized cyclic *N*-sulfimines **2** reacted with *cis*-6-oxo-6-phenylhex-4-enal **1a**, the cascade reaction products were obtained in good yields with good to excellent stereocontrol (12:1−30:1 dr, 83−94% ee), regardless of the electronic nature, bulkiness, or position of the substituent on the phenyl ring of the *N*-sulfimines. Cyclic *N*-sulfimines bearing functional groups in the 8-position led to slightly higher enantioselectivities compare to those with functional groups in other positions (Table 2, entries 12, 16, and 17).

In addition, *trans*-formyl-α,β-unsaturated ketones were employed for this asymmetric cascade reaction under the optimal reaction conditions (Scheme 2). To our delight,

Scheme 2. Enantioselective Mannich/Aza-Michael Cascade Reaction with *trans*-Formyl-α,β-unsaturated Ketones



6a, n = 1
6b, n = 2

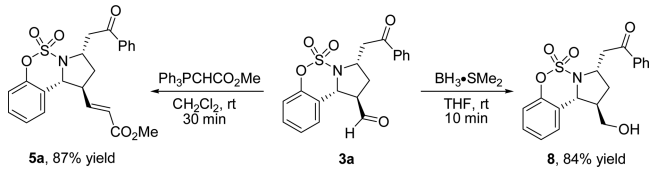
2a

3a, n = 1, 65% yield, 10:3:1.3:1 dr, 92% ee
7, n = 2, 52% yield, 9:2:1.5:1 dr, 76% ee

trans-6-oxo-6-phenylhex-4-enal **6a** exhibited similar enantioselectivity to *cis*-6-oxo-6-phenylhex-4-enal **1a**, giving the desired benzosulfamidate-fused pyrrolidine **3a** in good yield with high enantioselectivity (92% ee); however, the reaction required more time and provided more diastereomers with only moderate diastereoselectivity (10:3:1.3:1 dr). Interestingly, the reaction of *trans*-ε-formyl-α,β-unsaturated phenylketone **6b** proceeded smoothly to give benzosulfamidate-fused piperidine **7** in 52% yield with moderate stereocontrol (9:2:1.5:1 dr, 76% ee).

The aldehyde functional group present in the product provides many opportunities for derivatization. For example, the reaction of **3a** with methyl(triphenylphosphoranylidene)-acetate provided Wittig product **5a** in 87% yield. Moreover, the aldehyde group could be selectively reduced to the corresponding alcohol **8** in 84% yield (Scheme 3).

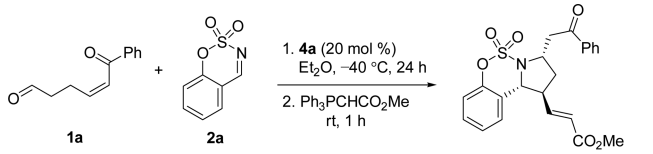
Scheme 3. Synthetic Transformations



5a, 87% yield **3a** **8**, 84% yield

Once the Mannich/aza-Michael cascade reaction to give chiral benzosulfamidate-fused pyrrolidine followed by the Wittig reaction had been demonstrated, we were confident that a sequential one-pot cascade reaction procedure would provide benzosulfamidate-fused pyrrolidine derivatives with high enantioselectivities. The cascade reaction between *cis*-6-oxo-6-phenylhex-4-enal **1a** and benzoxathiazine 2,2-dioxide **2a** was carried out in the presence of 20 mol % of catalyst **4a** for 24 h under the optimized reaction condition, followed by the addition of methyl(triphenylphosphoranylidene)acetate (1.2 equiv) in situ (Scheme 4). The benzosulfamidate-fused

Scheme 4. One-Pot Enantioselective Mannich/Aza-Michael Addition and in Situ Wittig Cascade Reaction



1a **2a**

5a, 61% yield, 10:1 dr, 91% ee

pyrrolidine product was obtained in 61% yield with excellent sterocontrol (10:1 dr, 91% ee).

To prove the absolute configuration of prepared benzosulfamidate-fused pyrrolidines **3**, a single crystal of benzosulfamidate-fused pyrrolidine derivatized methyl ester **5o**, obtained from the Wittig reaction of product **3o**, was subjected to X-ray diffraction analysis after crystallization from CH_2Cl_2/hexane double layer. The X-ray diffraction data show that benzosulfamidate-fused pyrrolidine **5o** has an 8*S*,10*S*,11*R* configuration (Scheme 5a).[12]

Based on the experimental results, the mechanism of this reaction is depicted in Scheme 5b. The catalyst **4a** activates *cis*-6-oxo-6-phenylhex-4-enal **1a**, forming the highly reactive eanamine intermediate **8**. This then reacts with benzoxathiazine 2,2-dioxide **2a** in a Mannich/aza-Michael cascade reaction to produce intermediate **10**. In this cascade process, the first Mannich reaction step preferentially affords the intermediate with the 8*S*,10*S*-configuration, due to the enamine attacking the imine moiety from the *Re* face, and is followed by aza-Michael reaction via a *Si*-face attack. Subsequent hydrolysis yields benzosulfamidate-fused pyrrolidine **3a** and regenerated catalyst **4a**.

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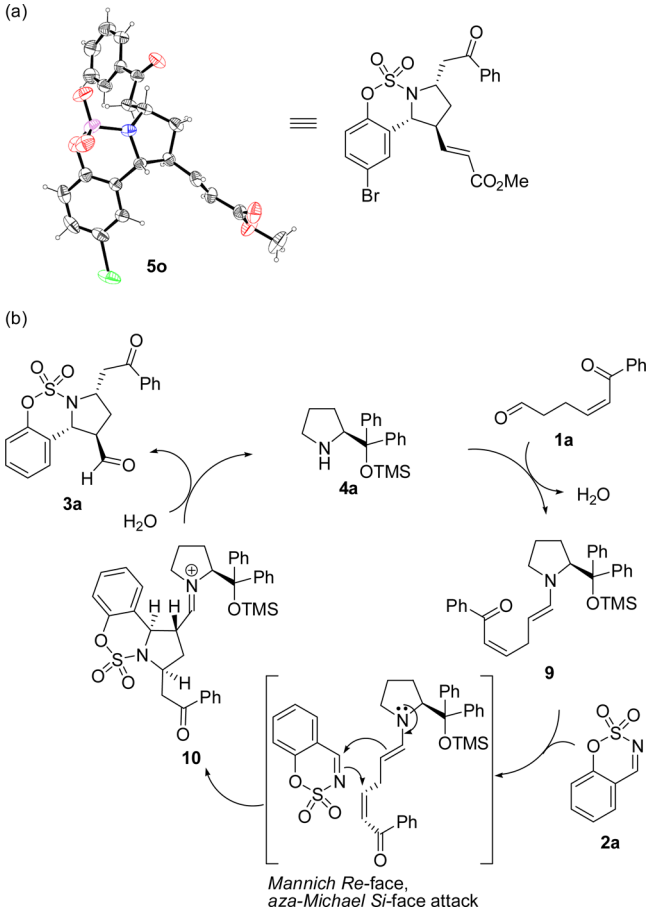
Scheme 5. (a) X-ray Structure of 5o with Thermal Ellipsoids at the 50% Probability Level and (b) the Proposed Mechanism



CONCLUSION

We have developed a highly enantioselective Mannich/aza-Michael cascade reaction with cyclic *N*-sulfimines for the synthesis of chiral benzosulfamidate-fused pyrrolidines. The organocatalytic reaction of *cis*-*δ*-formyl-*α*,*β*-unsaturated ketones with cyclic *N*-sulfimines, promoted by diphenylprolinol TMS ether as organocatalyst, generated chiral benzosulfamidate-fused pyrrolidines in good yields with high diastereo- and enantioselectivities. This methodology will allow the preparation of highly substituted pyrrolidine-based architectures for pharmaceutically attractive heterocyclic compounds.

EXPERIMENTAL SECTION

General Information. Organic solvents were distilled prior to use. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Developed chromatograms were visualized by fluorescence quenching and with anisaldehyde stain. ^{1}H and ^{13}C NMR spectra were recorded (400 MHz for ^{1}H and 100 MHz for ^{13}C) and were internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (*δ* ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on an FT IR spectrometer and are reported in wave numbers. Optical rotations were taken on a digital polarimeter. High-resolution mass spectroscopy (HRMS) was performed with an electron impact ionization (EI-magnetic sector) mass spectrometer. Enantiomeric excesses were determined using an HPLC instrument with Chiralpak columns as noted. *δ*-Formyl-*α*,*β*-unsaturated ketones,[13] *ε*-formyl-*α*,*β*-unsaturated ketones,[14] and cyclic *N*-sulfimines[15] were prepared according to the literature.

General Procedure for Asymmetric Mannich/Aza-Michael Cascade Reaction of *δ*-Formyl-*α*,*β*-unsaturated Ketones with Cyclic *N*-Sulfimines. To a solution of *δ*-formyl-*α*,*β*-unsaturated ketone **1** (0.2 mmol) in Et_2O (1 mL) was added catalyst **4a** (0.04 mmol). The solution was stirred at −40 °C for 10 min, and then cyclic *N*-sulfimine **2** (0.24 mmol) was added in one portion. The reaction mixture was stirred at −40 °C until *δ*-formyl-*α*,*β*-unsaturated ketone **1** was completely consumed, as determined by TLC. Then the resulting mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography with 10−30% EtOAc/hexanes as eluent to afford desired product **3**.

3a: 58 mg, yield 78%, colorless oil; $[\alpha]_D^{22}$ = +20.6 (*c* = 0.21, $CHCl_3$); 93% ee; R_f 0.4 (50% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.89 (d, *J* = 1.2 Hz, 1H), 7.93−7.86 (m, 2H), 7.58 (dd, *J* = 10.5, 4.3 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.35 (dd, *J* = 11.5, 4.1 Hz, 1H), 7.23 (td, *J* = 7.6, 1.1 Hz, 1H), 7.14−7.06 (m, 2H), 5.53 (d, *J* = 6.6 Hz, 1H), 4.68 (ddt, *J* = 11.2, 5.4, 2.7 Hz, 1H), 4.04 (dd, *J* = 16.0, 2.7 Hz, 1H), 3.47 (dt, *J* = 9.7, 7.9 Hz, 1H), 2.76 (dd, *J* = 16.0, 11.4 Hz, 1H), 2.50−2.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.9, 197.1, 150.2, 135.9, 133.9, 129.6, 128.9, 128.2, 126.4, 126.2, 123.1, 118.9, 59.8, 59.0, 57.9, 39.0, 31.6; IR (neat) 2922, 1724, 1679, 1485, 1449, 1394, 1198, 1172, 1102 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{19}H_{17}NO_5S$: 371.0827, found: 371.0792; Chiralpak IA column and IA guard column (10% *i*-PrOH:hexanes, 1.0 mL/min flow, *λ* = 254 nm); major-isomer t_r = 23.8 min and minor-isomer t_r = 25.2 min.

3b: 55 mg, yield 71%, colorless oil; $[\alpha]_D^{22}$ = +51.2 (*c* = 0.12, $CHCl_3$); 85% ee; R_f 0.4 (50% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.89 (d, *J* = 1.3 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.37−7.32 (m, 1H), 7.27−7.21 (m, 3H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.53 (d, *J* = 6.6 Hz, 1H), 4.66 (ddd, *J* = 11.2, 7.1, 3.9 Hz, 1H), 4.02 (dd, *J* = 15.7, 2.9 Hz, 1H), 3.47 (dt, *J* = 10.3, 9.1 Hz, 1H), 2.71 (dd, *J* = 15.7, 11.5 Hz, 1H), 2.47−2.42 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.9, 196.7, 150.2, 144.9, 133.5, 129.6 (two peaks overlapping), 128.4, 126.4, 126.1, 123.1, 118.9, 59.8, 59.1, 57.9, 39.0, 31.6, 21.7; IR (neat) 2923, 1725, 1674, 1605, 1485, 1451, 1394, 1198, 1172, 1102 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{20}H_{19}NO_5S$: 385.0984, found: 385.0967; Chiralpak IA column and IA guard column (10% *i*-PrOH:hexanes, 1.0 mL/min flow, *λ* = 254 nm); major-isomer t_r = 25.4 min and minor-isomer t_r = 28.5 min.

3c: 59 mg, yield 76%, colorless oil; $[\alpha]_D^{22}$ = +42.4 (*c* = 0.19, $CHCl_3$); 91% ee; R_f 0.4 (50% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.89 (d, *J* = 1.3 Hz, 1H), 7.73−7.65 (m, 2H), 7.41−7.33 (m, 3H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.53 (d, *J* = 6.6 Hz, 1H), 4.67 (dtd, *J* = 8.1, 5.5, 2.8 Hz, 1H), 4.03 (dd, *J* = 15.8, 2.8 Hz, 1H), 3.54−3.42 (m, 1H), 2.74 (dd, *J* = 15.8, 11.4 Hz, 1H), 2.44 (dt, *J* = 7.0, 4.8 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.9, 197.3, 150.2, 138.8, 135.9, 134.7, 129.6, 128.8, 128.7, 126.4, 126.2, 125.5, 123.1, 118.9, 59.8, 59.0, 57.9, 39.2, 31.6, 21.4; IR (neat) 2923, 1725, 1677, 1584, 1485, 1451, 1394, 1190, 1172, 1102 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{20}H_{19}NO_5S$: 385.0984, found: 385.0995; Chiralpak IA column and IA guard column (7% *i*-PrOH:hexanes, 1.0 mL/min flow, *λ* = 254 nm); major-isomer t_r = 23.2 min and minor-isomer t_r = 27.4 min.

3d: 59 mg, yield 74%, colorless oil; $[\alpha]_D^{22}$ = +73.8 (*c* = 0.23, $CHCl_3$); 85% ee; R_f 0.3 (50% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.89 (d, *J* = 1.2 Hz, 1H), 7.91−7.86 (m, 2H), 7.34 (td, *J* = 7.4, 3.7 Hz, 1H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.96−6.91 (m, 2H), 5.53 (d, *J* = 6.6 Hz, 1H), 4.71−4.59 (m, 1H), 4.00 (dd, *J* = 15.4, 2.2 Hz, 1H), 3.87 (s, 3H), 3.49 (dt, *J* = 11.4, 7.5 Hz, 1H), 2.67 (dd, *J* = 15.4, 11.5 Hz, 1H), 2.52−2.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

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δ 198.0, 195.5, 164.1, 150.1, 130.7, 129.6, 129.0, 126.4, 126.2, 123.2, 118.9, 114.1, 59.7, 59.3, 58.0, 55.6, 38.8, 31.5; IR (neat) 2921, 1725, 1669, 1597, 1575, 1511, 1451, 1393, 1259, 1198, 1169, 1102, 1025 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{20}H_{19}NO_6S$: 401.0933, found: 401.0947; Chiralpak IB column and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 30.0 min and minor-isomer t_r = 33.0 min.

3e: 76 mg, yield 95%, colorless oil; $[\alpha]_D^{22}$ = +18.9 (*c* = 0.22, $CHCl_3$); 88% ee; R_f 0.3 (50% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (d, *J* = 1.2 Hz, 1H), 7.50−7.42 (m, 2H), 7.36 (dd, *J* = 15.7, 7.8 Hz, 2H), 7.23 (td, *J* = 7.6, 1.1 Hz, 1H), 7.16−7.10 (m, 2H), 7.07 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.53 (d, *J* = 6.6 Hz, 1H), 4.67 (ddd, *J* = 11.1, 7.0, 3.9 Hz, 1H), 4.04 (dd, *J* = 15.7, 2.8 Hz, 1H), 3.85 (s, 3H), 3.48 (dt, *J* = 10.5, 9.2 Hz, 1H), 2.73 (dd, *J* = 15.7, 11.5 Hz, 1H), 2.45 (dd, *J* = 9.4, 3.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 196.9, 160.0, 150.1, 137.2, 129.9, 129.6, 126.4, 126.2, 123.1, 120.9, 120.5, 118.9, 112.3, 59.8, 59.1, 57.9, 55.5, 39.3, 31.5; IR (neat) 2926, 1725, 1679, 1597, 1582, 1486, 1451, 1394, 1256, 1197, 1172, 1103, 1036 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{20}H_{19}NO_6S$: 401.0933, found: 401.0921; Chiralpak IB column and IB guard column (7% *i*-PrOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 38.4 min and minor-isomer t_r = 49.2 min.

3f: 64 mg, yield 82%, colorless oil; $[\alpha]_D^{22}$ = +33.9 (*c* = 0.24, $CHCl_3$); 82% ee; R_f 0.4 (50% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (d, *J* = 1.3 Hz, 1H), 7.97−7.90 (m, 2H), 7.35 (ddd, *J* = 8.2, 7.5, 0.8 Hz, 1H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 7.17−7.10 (m, 3H), 7.07 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.53 (d, *J* = 6.6 Hz, 1H), 4.72−4.60 (m, 1H), 4.01 (dd, *J* = 15.8, 2.8 Hz, 1H), 3.54−3.42 (m, 1H), 2.73 (dd, *J* = 15.9, 11.3 Hz, 1H), 2.54−2.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 195.4, 166.2 (d, J^1 = 256.4 Hz), 150.1, 132.4, 131.0 (d, J^3 = 9.5 Hz), 129.6, 126.4, 126.2, 123.0, 118.9, 116.1 (d, J^2 = 22.0 Hz), 59.8, 58.9, 57.8, 39.1, 31.6; IR (neat) 2926, 1725, 1680, 1596, 1507, 1485, 1451, 1394, 1198, 1172, 1156, 1101, 995 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{19}H_{16}FNO_5S$: 389.0733, found: 389.0750; Chiralpak IB column and IB guard column (7% *i*-PrOH:hexanes, 1.0 mL/min flow, λ = 254 nm); minor-isomer t_r = 21.7 min and major-isomer t_r = 23.7 min.

3g: 64 mg, yield 79%, colorless oil; $[\alpha]_D^{22}$ = +50.9 (*c* = 0.33, $CHCl_3$); 84% ee; R_f 0.4 (50% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (d, *J* = 1.3 Hz, 1H), 7.87−7.81 (m, 2H), 7.47−7.41 (m, 2H), 7.35 (dd, *J* = 11.5, 4.1 Hz, 1H), 7.23 (td, *J* = 7.6, 1.1 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.52 (d, *J* = 6.6 Hz, 1H), 4.69−4.58 (m, 1H), 4.00 (dd, *J* = 16.0, 2.2 Hz, 1H), 3.47 (dt, *J* = 10.1, 7.5 Hz, 1H), 2.73 (dd, *J* = 16.0, 11.3 Hz, 1H), 2.53−2.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 195.8, 150.1, 140.5, 134.2, 129.6(two peaks overlapping), 129.3, 126.4, 126.2, 123.0, 118.9, 59.8, 58.8, 57.8, 39.1, 31.6; IR (neat) 2928, 1725, 1680, 1588, 1486, 1451, 1394, 1198, 1172, 1091, 994 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{19}H_{16}ClNO_5S$: 405.0438, found: 405.0441; Chiralpak IA column and IA guard column (10% *i*-PrOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 31.1 min and minor-isomer t_r = 34.4 min.

3h: 61 mg, yield 79%, colorless oil; $[\alpha]_D^{22}$ = +38.3 (*c* = 0.16, $CHCl_3$); 88% ee; R_f 0.4 (40% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (d, *J* = 1.3 Hz, 1H), 7.93−7.86 (m, 2H), 7.59 (ddd, *J* = 8.7, 2.5, 1.2 Hz, 1H), 7.46 (dd, *J* = 10.6, 4.8 Hz, 2H), 7.13 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 5.50 (d, *J* = 6.5 Hz, 1H), 4.72−4.62 (m, 1H), 4.04 (dd, *J* = 16.0, 2.8 Hz, 1H), 3.47 (dt, *J* = 10.5, 8.8 Hz, 1H), 2.76 (dd, *J* = 16.0, 11.4 Hz, 1H), 2.51−2.41 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 197.1, 148.1, 136.1, 135.9, 133.9, 130.2, 128.9, 128.2, 126.5, 122.6, 118.6, 59.7, 59.0, 57.9, 39.0, 31.6, 20.9; IR (neat) 2924, 1726, 1679, 1597, 1490, 1449, 1394, 1202, 1183, 1110 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{20}H_{19}NO_5S$: 385.0984, found: 385.1014; Chiralpak IB column and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 18.8 min and minor-isomer t_r = 21.0 min.

3i: 65 mg, yield 85%, colorless oil; $[\alpha]_D^{22}$ = +61.6 (*c* = 0.16, $CHCl_3$); 83% ee; R_f 0.4 (50% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, *J* = 1.3 Hz, 1H), 7.93−7.87 (m, 2H), 7.59 (dd, *J* = 10.5, 4.3 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.01 (dd, *J* = 20.6, 8.0 Hz, 2H), 6.88 (s, 1H), 5.48 (d, *J* = 6.5 Hz, 1H), 4.71−4.62 (m, 1H), 4.04 (dd, *J* = 16.0, 2.3 Hz, 1H), 3.49−3.38 (m, 1H), 2.76 (dd, *J* = 16.0, 11.4 Hz, 1H), 2.45 (dt, *J* = 8.8, 7.2 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 197.1, 150.0, 140.2, 135.9, 133.9, 128.9, 128.2, 127.0, 126.1, 119.9, 119.1, 59.7, 59.0, 57.9, 39.1, 31.6, 21.1; IR (neat) 2924, 1726, 1679, 1597, 1504, 1449, 1393, 1195, 1102, 1001 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{20}H_{19}NO_5S$: 385.0984, found: 385.0978; Chiralpak IA column and IA guard column (15% *i*-PrOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 14.8 min and minor-isomer t_r = 17.5 min.

3j: 63 mg, yield 79%, colorless oil; $[\alpha]_D^{22}$ = +63.1 (*c* = 0.33, $CHCl_3$); 90% ee; R_f 0.3 (50% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, *J* = 1.1 Hz, 1H), 7.94−7.86 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 9.1 Hz, 1H), 6.87 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 5.48 (d, *J* = 6.6 Hz, 1H), 4.72−4.60 (m, 1H), 4.04 (dd, *J* = 16.0, 2.7 Hz, 1H), 3.77 (s, 3H), 3.47 (dd, *J* = 16.5, 9.7 Hz, 1H), 2.77 (dd, *J* = 16.0, 11.4 Hz, 1H), 2.45 (dd, *J* = 9.7, 3.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 197.1, 157.3, 143.8, 135.95, 133.9, 128.9, 128.2, 123.8, 119.9, 115.2, 110.9, 59.9, 59.0, 57.8, 55.8, 38.9, 31.6; IR (neat) 2939, 1727, 1680, 1597, 1490, 1449, 1393, 1282, 1253, 1174, 1128, 1033, 1001 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{20}H_{19}NO_6S$: 401.0933, found: 401.0934; Chiralpak IB column and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 24.7 min and minor-isomer t_r = 29.6 min.

3k: 77 mg, yield 96%, colorless oil; $[\alpha]_D^{24}$ = +37.6 (*c* = 0.26, $CHCl_3$); 90% ee; R_f 0.3 (50% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, *J* = 1.3 Hz, 1H), 7.95−7.87 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 5.45 (d, *J* = 6.4 Hz, 1H), 4.73−4.62 (m, 1H), 4.03 (dd, *J* = 16.1, 2.3 Hz, 1H), 3.82 (s, 3H), 3.42 (dt, *J* = 9.8, 7.5 Hz, 1H), 2.78 (dd, *J* = 16.0, 11.4 Hz, 1H), 2.45 (dd, *J* = 12.9, 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 197.1, 160.3, 150.9, 136.0, 133.89, 128.9, 128.2, 127.1, 114.8, 112.9, 103.8, 59.5, 59.0, 58.0, 55.7, 39.1, 31.6; IR (neat) 2918, 1725, 1679, 1624, 1597, 1578, 1505, 1448, 1393, 1292, 1239, 1197, 1157, 1093, 1028 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{20}H_{19}NO_6S$: 401.0933, found: 401.0929; Chiralpak IB column and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 24.5 min and minor-isomer t_r = 33.4 min.

3l: 67 mg, yield 83%, colorless oil; $[\alpha]_D^{24}$ = +38.4 (*c* = 0.31, $CHCl_3$); 92% ee; R_f 0.3 (50% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, *J* = 1.3 Hz, 1H), 7.92 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.58 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.46 (dd, *J* = 9.8, 5.6 Hz, 2H), 7.15 (t, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 5.52 (d, *J* = 6.7 Hz, 1H), 4.66 (ddt, *J* = 11.1, 5.5, 2.6 Hz, 1H), 4.14−4.05 (m, 1H), 3.91 (s, 3H), 3.55−3.44 (m, 1H), 2.76 (dd, *J* = 15.7, 11.5 Hz, 1H), 2.48−2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 197.2, 148.8, 139.8, 135.9, 133.0, 128.9, 128.3, 125.9, 124.0, 117.3, 111.8, 59.9, 59.1, 57.9, 56.3, 39.1, 31.5; IR (neat) 2933, 1725, 1679, 1597, 1582, 1479, 1394, 1319, 1274, 1199, 1159, 1074, 1001 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{20}H_{19}NO_6S$: 401.0933, found: 401.0908; Chiralpak IB column and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 25.4 min and minor-isomer t_r = 31.2 min.

3m: 58 mg, yield 74%, colorless oil; $[\alpha]_D^{24}$ = +43.2 (*c* = 0.31, $CHCl_3$); 88% ee; R_f 0.4 (40% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, *J* = 0.9 Hz, 1H), 7.94−7.87 (m, 2H), 7.64−7.56 (m, 1H), 7.47 (dd, *J* = 10.6, 4.8 Hz, 2H), 7.10−7.02 (m, 2H), 6.91−6.83 (m, 1H), 5.50 (d, *J* = 6.7 Hz, 1H), 4.74−4.64 (m, 1H), 4.02 (dd, *J* = 16.0, 2.2 Hz, 1H), 3.54−3.42 (m, 1H), 2.76 (dd, *J* = 16.0, 11.4 Hz, 1H), 2.55−2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 196.9, 159.8 (d, J^1 = 247.0 Hz), 146.0, 135.9, 134.0, 128.9, 128.2, 124.7 (d, J^3 = 7.2 Hz), 120.6 (d, J^3 = 8.3 Hz), 116.7 (d, J^2 = 23.7 Hz), 113.2 (d, J^2 = 25.0 Hz), 59.6, 59.0, 57.8, 38.8, 31.5; IR (neat) 2923, 1726, 1678, 1597, 1485, 1449, 1396, 1258, 1200, 1162, 1123, 1095, 1000 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{19}H_{16}FNO_5S$: 389.0733, found: 389.0702; Chiralpak IB column

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and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 16.5 min and minor-isomer t_r = 19.7 min.

3n: 58 mg, yield 72%, colorless oil; $[\alpha]_D^{22}$ = +66.8 (c = 0.17, $CHCl_3$); 87% ee; R_f 0.4 (40% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (d, J = 0.7 Hz, 1H), 7.93−7.85 (m, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.32 (dd, J = 9.1, 2.1 Hz, 1H), 7.15−7.09 (m, 1H), 7.03 (d, J = 8.8 Hz, 1H), 5.51 (d, J = 6.6 Hz, 1H), 4.74−4.63 (m, 1H), 4.00 (dd, J = 16.2, 2.5 Hz, 1H), 3.55−3.42 (m, 1H), 2.76 (dd, J = 16.0, 11.4 Hz, 1H), 2.58−2.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 196.8, 148.7, 135.9, 134.0, 131.4, 129.8, 128.9, 128.2, 126.5, 124.7, 120.4, 59.5, 59.1, 57.8, 38.8, 31.6; IR (neat) 2927, 1725, 1678, 1597, 1475, 1396, 1198, 1170, 1110, 1000 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{19}H_{16}ClNO_5S$: 405.0438, found: 405.0455; Chiralpak IA column and IA guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); minor-isomer t_r = 34.3 min and major-isomer t_r = 51.5 min.

3o: 71 mg, yield 79%, colorless oil; $[\alpha]_D^{24}$ = +32.3 (c = 0.16, $CHCl_3$); 92% ee; R_f 0.4 (30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, J = 0.7 Hz, 1H), 7.93−7.86 (m, 2H), 7.59 (dt, J = 8.7, 1.2 Hz, 1H), 7.46 (dd, J = 10.8, 5.0 Hz, 3H), 7.25 (dd, J = 2.3, 0.9 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 5.51 (d, J = 6.5 Hz, 1H), 4.72−4.63 (m, 1H), 3.99 (dd, J = 16.0, 2.4 Hz, 1H), 3.54−3.43 (m, 1H), 2.76 (dd, J = 16.0, 11.4 Hz, 1H), 2.53−2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 196.8, 149.2, 135.9, 134.0, 132.7, 129.4, 128.9, 128.2, 125.1, 120.7, 118.9, 59.35, 59.1, 57.7, 38.8, 31.6; IR (neat) 2921, 1724, 1678, 1597, 1474, 1396, 1198, 1171, 1111, 1000 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{19}H_{16}BrNO_5S$: 448.9933, found: 448.9929; Chiralpak IB column and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 16.4 min and minor-isomer t_r = 18.6 min.

3p: 63 mg, yield 72%, white solid; mp 61−62 °C; $[\alpha]_D^{23}$ = +69.4 (c = 0.32, $CHCl_3$); 91% ee; R_f 0.3 (30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, J = 0.6 Hz, 1H), 7.94−7.87 (m, 2H), 7.65−7.58 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.43 (dd, J = 2.4, 0.7 Hz, 1H), 7.03 (dd, J = 2.4, 1.0 Hz, 1H), 5.51 (d, J = 6.7 Hz, 1H), 4.69 (t, J = 9.0 Hz, 1H), 4.02 (dd, J = 15.9, 2.0 Hz, 1H), 3.55−3.42 (m, 1H), 2.75 (dd, J = 15.8, 11.3 Hz, 1H), 2.61−2.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 196.7, 145.0, 135.8, 134.1, 131.2, 130.2, 129.0, 128.2, 126.01, 125.0, 124.8, 59.6, 59.2, 57.8, 38.8, 31.5; IR (neat) 2927, 1726, 1678, 1597, 1567, 1447, 1402, 1325, 1201, 1168, 1128, 1001 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{19}H_{15}Cl_2NO_5S$: 439.0048, found: 439.0022; Chiralpak IB column and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 21.2 min and minor-isomer t_r = 24.5 min.

3q: 78 mg, yield 74%, white solid; mp 76−78 °C; $[\alpha]_D^{23}$ = +52.7 (c = 0.34, $CHCl_3$); 94% ee; R_f 0.3 (30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, J = 0.5 Hz, 1H), 7.93−7.89 (m, 2H), 7.74 (dd, J = 2.2, 0.7 Hz, 1H), 7.65−7.58 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.20 (dd, J = 2.2, 1.0 Hz, 1H), 5.52 (d, J = 6.6 Hz, 1H), 4.74−4.65 (m, 1H), 4.02 (dd, J = 15.8, 2.1 Hz, 1H), 3.55−3.43 (m, 1H), 2.74 (dd, J = 15.8, 11.3 Hz, 1H), 2.58−2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 196.7, 146.4, 135.8(two peaks overlapping), 134.1, 129.0, 128.4, 128.3, 126.4, 118.8, 113.8, 59.5, 59.2, 57.8, 38.8, 31.5; IR (neat) 2925, 1724, 1677, 1596, 1555, 1440, 1402, 1324, 1198, 1159, 1115, 1000 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{19}H_{15}Br_2NO_5S$: 526.9038, found: 526.9009; Chiralpak IB column and IB guard column (5% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 31.2 min and minor-isomer t_r = 35.9 min.

Synthesis of Compounds 5a, 5o, 7, and 8. To a solution of compound **3a** (37 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added methyl (triphenylphosphoranylidene)acetate (40 mg, 0.12 mmol). The solution was stirred at room temperature for 30 min. Then, the resulting mixture was concentrated in vacuo and purified by flash column chromatography with 15% EtOAc/hexanes as eluent to afford desired product **5a** as a colorless oil (37 mg, 87% yield). $[\alpha]_D^{22}$ = +18.0 (c = 0.22, $CHCl_3$); 93% ee; R_f 0.4 (30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.88 (m, 2H), 7.63−7.54 (m, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.35 (dt, J = 8.5, 4.3 Hz, 1H), 7.20 (d, J = 4.1 Hz, 2H), 7.10 (dd, J = 16.4, 8.3 Hz, 2H), 6.08 (d, J = 15.6 Hz, 1H), 5.01 (d, J = 7.3 Hz, 1H), 4.65 (t, J = 7.7 Hz, 1H), 4.03 (dd, J = 16.1, 2.0 Hz, 1H), 3.80 (s, 3H), 3.42−3.30 (m, 1H), 2.84 (dd, J = 16.1, 11.3 Hz, 1H), 2.26 (dtd, J = 19.9, 12.4, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 166.0, 150.0, 146.6, 136.1, 133.8, 129.5, 128.9, 128.2, 125.9, 125.7, 123.7, 123.5, 119.0, 77.4, 77.1, 76.7, 64.4, 58.7, 52.0, 48.9, 39.8, 37.1; IR (neat) 3026, 2951, 1720, 1681, 1598, 1580, 1485, 1450, 1395, 1315, 1198, 1173, 1135, 1102, 1039, 992 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{22}H_{21}NO_6S$: 427.1090, found: 427.1081; Chiralpak IA column and IA guard column (10% i-PrOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 23.9 min and minor-isomer t_r = 28.2 min.

To a solution of compound **3o** (68 mg, 0.15 mmol) in CH_2Cl_2 (0.5 mL) was added methyl (triphenylphosphoranylidene)acetate (60 mg, 0.18 mmol). The solution was stirred at room temperature for 30 min. Then the resulting mixture was concentrated in vacuo and purified by flash column chromatography with 20% EtOAc/hexanes as eluent to afford desired product **5o** as a colorless oil (70 mg, 92% yield). $[\alpha]_D^{22}$ = +46.8 (c = 0.32, $CHCl_3$); 92% ee; R_f 0.5 (30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.86 (m, 2H), 7.63−7.54 (m, 1H), 7.51−7.42 (m, 3H), 7.31 (dd, J = 2.3, 0.8 Hz, 1H), 7.08 (dd, J = 15.6, 8.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 6.17−6.06 (m, 1H), 4.98 (d, J = 7.1 Hz, 1H), 4.71−4.57 (m, 1H), 3.98 (dd, J = 16.1, 2.1 Hz, 1H), 3.81 (s, 3H), 3.36 (td, J = 16.0, 7.5 Hz, 1H), 2.82 (dd, J = 16.1, 11.3 Hz, 1H), 2.27 (dtd, J = 19.6, 12.3, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 165.9, 149.1, 146.1, 136.0, 133.9, 132.7, 128.9, 128.5, 128.2, 125.4, 123.8, 120.8, 118.5, 77.4, 77.1, 76.7, 64.0, 58.9, 52.0, 48.7, 39.5, 37.2; IR (neat) 2946, 2853, 1715, 1674, 1699, 1473, 1391, 1371, 1317, 1241, 1194, 1165, 1133, 1035 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{22}H_{20}BrNO_6S$: 505.0195, found: 505.0169; Chiralpak IB column and IB guard column (10% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); major-isomer t_r = 16.4 min and minor-isomer t_r = 18.6 min.

To a solution of *trans*-ε-formyl-α,β-unsaturated ketone **6b** (62 mg, 0.3 mmol) in Et_2O (1.5 mL) was added catalyst **4a** (20 mg, 0.06 mmol). The solution was stirred at −40 °C for 10 min, and then cyclic *N*-sulfimine **2** (67 mg, 0.36 mmol) was added in one portion. The reaction mixture was stirred at −40 °C for 4 days until *trans*-ε-formyl-α,β-unsaturated ketone **6b** was complete consumed. Then the resulting mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography with 20% EtOAc/hexanes as eluent to afford desired product **7** as a colorless oil (60 mg, 52% yield). $[\alpha]_D^{27}$ = +55.9 (c = 0.62, $CHCl_3$); 76% ee; R_f 0.4 (50% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 9.85 (s, 1H), 8.03−7.83 (m, 1H), 7.77−7.72 (m, 1H), 7.57−7.39 (m, 4H), 7.29 (d, J = 7.7 Hz, 1H), 7.24 (d, J = 6.7 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 5.85 (d, J = 2.0 Hz, 1H), 4.55−4.36 (m, 1H), 3.46 (dd, J = 15.4, 2.6 Hz, 1H), 3.36−3.14 (m, 1H), 2.65 (dd, J = 15.4, 11.9 Hz, 1H), 2.28−2.14 (m, 1H), 2.06−1.77 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.5, 196.8, 152.4, 135.9, 133.7, 130.5, 128.8, 128.2, 125.6, 124.5, 121.2, 118.6, 53.5, 52.3, 45.5, 37.7, 24.0, 15.3; IR (neat) 2924, 2852, 1726, 1680, 1597, 1580, 1482, 1449, 1389, 1284, 1192, 1166, 1098, 1067, 1049, 1001 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{20}H_{19}NO_5S$: 385.0984, found: 385.1008. To determine the enantiomeric excess using HPLC analysis, the isolated products was reacted with methyl (triphenylphosphoranylidene)acetate to afford the corresponding ester. Chiralpak IB column and IB guard column (5% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); minor-isomer t_r = 38.5 min and major-isomer t_r = 45.2 min.

To a solution of compound **3a** (37 mg, 0.1 mmol) in THF (0.5 mL) was added borane dimethyl sulfide complex (9.5 μL, 0.1 mmol). The solution was stirred at room temperature for 10 min, and MeOH was added until bubbling no longer occurred. Then the resulting mixture was concentrated in vacuo and purified by flash column chromatography with 20% EtOAc/hexanes as eluent to afford desired product **8** as a colorless oil (31 mg, 84% yield). $[\alpha]_D^{25}$ = +55.2 (c = 0.69, $CHCl_3$); R_f 0.3 (50% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.83 (m, 2H), 7.59−7.53 (m, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.22 (td, J = 7.6, 1.2 Hz, 1H), 7.05 (dd, J = 8.2, 1.1 Hz, 1H), 5.09 (d, J = 5.1 Hz, 1H),

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4.66−4.51 (m, 1H), 4.04−3.93 (m, 2H), 3.86 (dd, J = 10.3, 8.0 Hz, 1H), 2.99−2.85 (m, 1H), 2.69 (dd, J = 15.7, 11.5 Hz, 1H), 2.16−1.92 (m, 3H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 150.4, 136.1, 133.7, 129.2, 128.8, 128.2, 127.2, 125.8, 124.1, 118.5, 77.3, 77.0, 76.7, 65.1, 64.1, 59.2, 48.3, 39.3, 33.4; IR (neat) 2924, 2852, 1726, 1680, 1597, 1580, 1449, 1389, 1284, 1192, 1166, 1067, 1049, 1001 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{19}H_{19}NO_5S$: 373.0984, found: 373.0962.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01533.

X-ray crystallographic analysis of **5o**, copies of ^{1}H and ^{13}C NMR spectra, and HPLC analysis (PDF)

X-ray crystallographic data for **5o** (CIF)

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The authors declare no competing financial interest.

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