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Catalytic Asymmetric Synthesis of γ-Substituted Vinyl Sulfones

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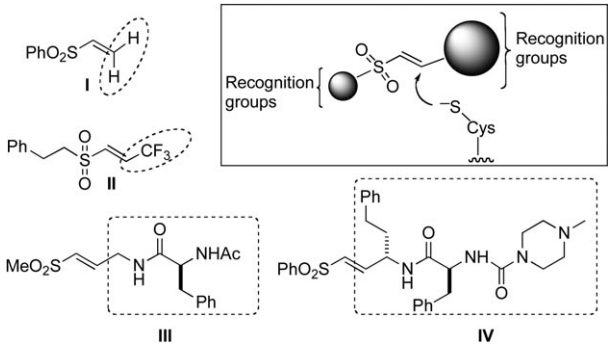
Dedicated to Professor Antonio García Martinez on the occasion of his 70th birthday

Abstract: A fast new entry for the stereoselective construction of γ-substituted vinyl sulfones is presented. The key for success is the use of a readily available chiral secondary amine catalyst that allows the use of base-sensitive β-nitroethyl sulfones as masked β-sulfonyl vinyl anions in conjugate additions. The method performed in a three-step one-pot operation gives access to a great variety of vinyl sulfones in good yields and with excellent enantioselectivities. The method has also been extended to other relatively base-sensitive β-electron-withdrawing-substituted nitroalkanes to afford products with manifold functionality, providing a quick entry to very attractive synthetic intermediates for organic synthesis.

Keywords: amino acids · asymmetric synthesis · iminium activation · nitroalkanes · sulfones

Introduction

Antibiotics have a long standing history of success in the treatment of bacterial infections. Nevertheless, due to the antibiotic resistance increase, a great effort toward the identification and validation of new drugs that target essential and, specially, virulence factors is of crucial interest.[1] Structurally diverse vinyl sulfones have recently been shown to potently inhibit a variety of enzymatic processes providing unique properties for drug design and medicinal chemistry (Scheme 1).[2] For instance, vinyl sulfones **I** and **II** behave as effective inhibitors of sortases[3a] and tyrosine phosphatases[3b] and **III**[4] and **IV**[5] of cysteine proteases, respectively.



Scheme 1. Representative examples of structurally diverse small vinyl sulfone enzyme inhibitors.

Strikingly, whereas the inhibition mechanism is generally accepted as a 1,4-conjugate addition of the thiol group of the cysteine active site to the vinyl sufones, much less known is about the structural requirements for an effective enzyme recognition.

Recent findings, by McCafferty[3a] and Zhang,[3b] support the notion that even the simple phenyl vinyl sulfone **I** holds promise for in vivo applications and shows that further elaboration of vinyl sulfone scaffolds are expected to lead to the identification of more specific inhibitors. In addition, several vinyl sulfones have recently been identified, by using high-throughput screens, that have provided insight into the mechanism of microbial pathogenesis.[6] Despite their biological interest and their chemical versatility in asymmetric synthesis,[7] the preparation of vinyl sulfones almost remains restricted to the addition of sulfonyl-stabilized carbanions to the corresponding carbonyl compound.[2a,7] Herein, we report a practical synthetic methodology for the preparation of vinyl sulfones bearing a γ-stereogenic center that could help to fulfill this gap.

Results and Discussion

Challenges and working plan: We envisioned that base-promoted addition of β-nitroethyl sulfones[8] to the proper carbon-centered electrophile, inter alia α,β-unsaturated carbonyl compounds,[9] followed by nitrous acid elimination[10] would represent a practical short stereoselective route to functionalized γ-substituted vinyl sulfones (Scheme 2). First, both the carbon–carbon bond and the new stereogenic center would be generated concurrently in a single synthetic operation, a notable advantage over traditional methods. Second, new vinyl sulfone scaffolds with different substitution patterns would be made feasible from simple and readi-

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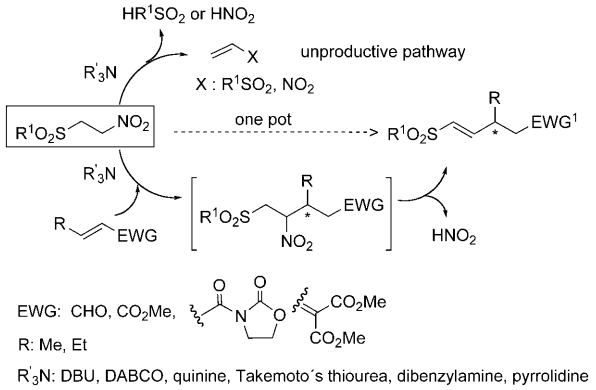


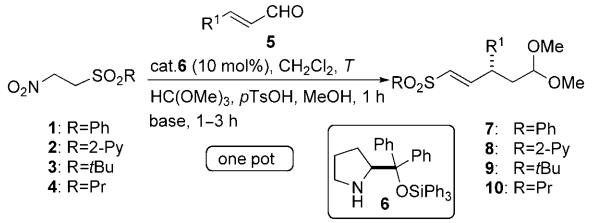
Scheme 2. Conjugate addition of formal β-sulfonyl vinyl anions to π-deficient olefins. EWG: CHO, CO_2Me; R: Me, Et; R_3N: DBU, DABCO, quinine, Takemoto's thiourea, dibenzylamine, pyrrolidine.

ly available achiral starting materials. Third, the process might be realized in a one-pot operation that would be attractive from the economy viewpoint, and finally, the resulting products would broaden the pool of available vinyl sulfones as synthetic intermediates and as potential protease inhibitors.

Two critical issues to consider in the realization of this goal are 1) the ability of the catalyst to promote the formation of the carbon–carbon bond before any elimination of nitrous and/or sulfinic acid in the starting β-nitroethylsulfone may occur[11] and 2) the tendency of α,β-unsaturated sulfones to undergo base-promoted isomerization to β,γ-unsaturated products.[12] Thus, initial experiments to assess this crucial point by using β-nitroethylsulfone **1** (R^1 = Ph) and several π-deficient olefin/amine base combinations revealed that products from the conjugate addition of phenyl sulfinic acid were in fact produced for most of the combinations screened (Scheme 2). For instance, in reactions of 2-pentenal, methyl 2-butenoate, and crotonoyl oxazolidinone, employing catalytic amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the addition of phenyl sulfinic acid was exclusively produced, whereas 1,4-diazobicyclo[2.2.2]octane (DABCO), quinine, and the Takemoto's thiourea[13] afforded mixtures of variable complexity.[14] Gratifyingly, further screening led to the identification of secondary amines, such as pyrrolidine and dibenzylamine, as successful promoters of the reaction of **1** with 2-pentenal to afford the addition product cleanly. This result suggested that the reaction should proceed through the activation of the enal acceptor by in situ generation of the corresponding iminium species rather than Brønsted base-promoted addition. Early observations that carbon–carbon bond-forming reactions, including conjugate additions, may be efficiently promoted by using iminium catalysis[15] provided further support for this proposal.

Catalyst screening and conditions: Upon the above assumption, we examined the ability of chiral secondary amines to promote the reaction enantioselectively and, to our delight, standard chiral pyrrolidines were found to be effective.[16] The optimum results were achieved by using catalyst **6**, which proved to be the most efficient for both β-alkyl and β-aryl-substituted α,β-enals.[17] Thus, treatment of 2-pentenal with a slight excess of β-nitroethyl sulfone **1** in the presence of 10 mol% of **6**, in methylene chloride at room temperature, and subsequent one-pot protection of the resulting aldehyde adduct and base-promoted nitrous acid elimination furnished **7a** in 79% yield and 94% *ee*. As illustrated in Table 1, the method is tolerant with a range of aldehydes

Table 1. γ-Substituted vinyl sulfones from nitroethyl sulfones **1**–**4** and enals **5** promoted by **6**.[a]



Entry	Sulfone	Enal, R^1	T [°C], t [h][b]	Yield [%][c]	*ee* [%][d]
1	**1**	**5a**, Et	RT, 2	**7a** 79	94
2		**5b**, Me	RT, 1	**7b** 71	94
3		**5c**, *n*Bu	RT, 2	**7c** 90	95
4		**5d**, *i*Pr[e]	RT, 15	**7d** 60	95
5		**5e**, *n*Oct[f]	RT, 15	**7e** 80	93
6		**5f**, Ph	0, 24	**7f** 67	98
7		**5g**, 4-Cl-C_6H_4	0, 24	**7g** 56	98
8		**5h**, 4-Me-C_6H_4	0, 24	**7h** 57	97
9		**5i**, 4-MeO-C_6H_4	0, 48	**7i** 60	94
10	**2**	**5a**, Et	RT, 1	**8a** 62	95
11		**5d**, *i*Pr	RT, 24	**8d** 51	96
12		**5e**, *n*Oct[g]	RT, 6	**8e** 92	94
13		**5f**, Ph	0, 24	**8f** 70	93
14	**3**	**5a**, Et	RT, 15	**9a** 40[h]	96
15	**4**	**5a**, Et	RT, 15	**10a** 75	93

[a] Reactions carried out at 0.5 mmol enal scale by using 1.3–1.5 equiv of β-nitroethylsulfone, 10 mol% catalyst **6** in CH_2Cl_2 (1 mL). Nitrous acid elimination was carried out by employing DBU for adducts with alkyl substituents and $Mg(OMe)_2$ for aromatic substituents. [b] Reaction time for the β-nitroethyl sulfone addition. [c] Yield of isolated product. [d] *ee* was determined by chiral HPLC analysis. [e] Reaction carried out at the 4 mmol scale. [f] 5 mol% catalyst. [g] Reaction carried out at 2 mmol scale. [h] Adduct **9a** partially decomposes during purification.

with varying steric demand to give vinyl sulfones with no loss of efficiency or enantiocontrol. Aliphatic enals, independent of the chain length, reacted within a few hours at room temperature, whereas aromatic ones required somewhat longer reaction times and lower temperatures, typically 0°C. Whilst DBU-promoted nitrous acid elimination was tolerant for β-alkyl-substituted adducts, a milder base, such as magnesium methoxide, was required for β-aromatic-substituted adducts.[18]

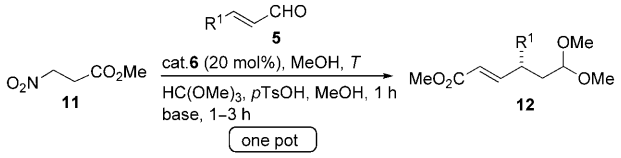
This approach also appears to be general with respect the sulfone moiety. β-Nitroethyl(2-pyridyl)sulfone (**2**) reacts with both aliphatic and aromatic enals in the presence of 10% mol of catalyst **6** to afford, after aldehyde protection and nitrous acid elimination, vinyl sulfones **8** with good overall yields and excellent enantiomeric excesses. Likewise,

β-nitroethylalkylsulfones behaved as β-sulfonyl vinyl anion equivalents in such a reaction to provide the corresponding γ-substituted vinyl sulfones **9** and **10** with equal chemical and stereochemical efficiency than their aromatic counterparts.[19] The catalyst loading, on the other hand, could be reduced to 5 mol% (Table 1, entry 5), whereas the use of 1 mol% of **6** resulted in a considerable decrease in both yield and enantioselectivity. Of practical interest, reactions can be run at the 10 mmol scale without compromising selectivity or yield (R = Ph, R^1 = Oct, 90% yield, 93% *ee*).

The mild reaction conditions employed allow base-sensitive β-nitroethylsulfones to act, for the first time, as formal practical vinyl anions in a process that provides sulfones with different substitution patterns at the sulfone moiety, with good overall yields over the three steps and enantiomeric excesses in the 93–98% range. The fact that small vinyl sulfone inhibitors of serine, cysteine, and threonine proteases,[2,20] as well as those that specifically block the sortase-catalyzed transpeptidation reaction are highly appealing, strongly supports the utility of this method to increase the pool of available sulfones, especially with regard to substitution patterns distinct to those derived from (native) α-amino acids.

Scope and versatility: Further exploration revealed that this approach is also applicable to other related vinyl anion equivalents. For example, methyl β-nitro propanoate **11** reacts with α,β-enals in the presence of catalyst **6** to afford, after aldehyde protection and nitrous acid elimination, adducts **12** with very high chemical efficiency over the three steps (Table 2).

Table 2. Representative γ-substituted crotonates prepared.[a]

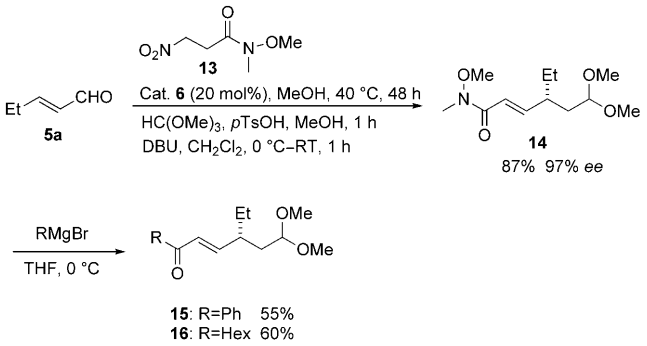


Entry	Enal, R^1	T [°C], t [h][b]	Yield [%][c]	*ee* [%][d]
1	**5a**, Et	40, 24	**12a** 79	92
2	**5c**, *n*Bu	40, 48	**12c** 92	91
3	**5e**, *n*Oct[e]	40, 48	**12e** 88	96
4	**5f**, Ph	10, 24	**12f** 67	93

[a] Reactions carried out at 0.5 mmol enal scale by using 1.3 equiv of **11** (2.0 equiv for enal **5f**), 20 mol% catalyst **6** in MeOH (1 mL). Nitrous acid elimination was carried out by employing DBU for adducts with alkyl substituents and $Mg(OMe)_2$ for aromatic substituents. [b] Reaction time for the addition of **11**. [c] Yield of isolated product. [d] *ee* determined by chiral HPLC analysis. [e] Reaction carried out at 4 mmol scale.

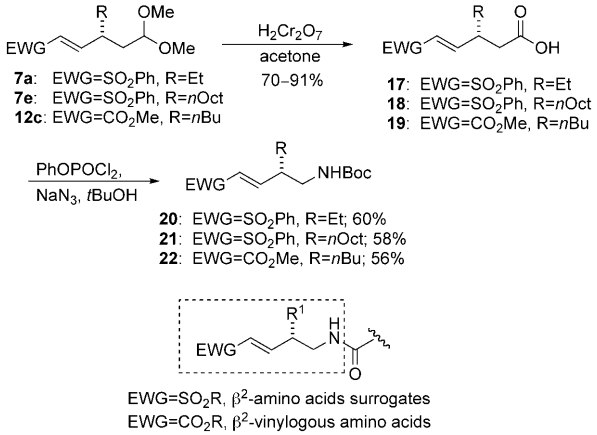
It is worth noting the different reactivity displayed by β-nitroethyl sulfones **1**–**4** and methyl β-nitro propanoate **11** in the present reaction. Whilst β-nitroethyl sulfones appear to be quite sensitive to the reaction conditions, probably as a result of its high tendency to eliminate the corresponding sulfinic acid, **11** allows the conjugate addition to be carried out at 40°C to afford the products in a reasonably short reaction time.[21] Most significantly, under these conditions, the reaction proceeds with good yields and without loss of enantioselectivity.

To expand the scope of this concept, we prepared the β-nitropropanamide **13**[22] with the hope that β-acyl vinyl derivatives might be prepared by simply adding Grignard reagents to a common single intermediate.[23] Once again, the conjugate addition of **13** to the enal **5a** carried out by employing standard conditions, as described for the addition of methyl β-nitropropanoate **11**, afforded adduct **14** in very high chemical and stereochemical efficiency over the three steps (Scheme 3). The α,β-unsaturated ketones **15** and **16** were obtained by treatment of intermediate **14** with the corresponding aryl/alkyl Grignard reagents.



Scheme 3. Conjugate addition of β-nitroethyl Weinreb amides to α,β-enals.

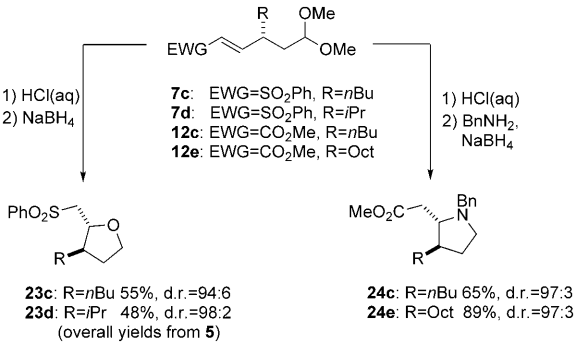
The distinct functionality of the resulting adducts gives additional versatility to this procedure. For instance, simple elaboration of the acetal group in adducts **7** and **12**, as shown in Scheme 4, provided vinyl sulfones **20** and **21** and α,β-unsaturated ester **22**. Compounds that, to the best of our knowledge, constitute new vinylogous amino sulfone and amino acid scaffolds. Additionally, as already shown for peptides containing vinylogous amino acids,[24] these new types of β^2-vinylogous amino acids could exhibit intramolec-



Scheme 4. Preparation of surrogates of β^2-amino acids.

ular specific interactions and provide defined secondary structures when incorporated into peptides.[25,26]

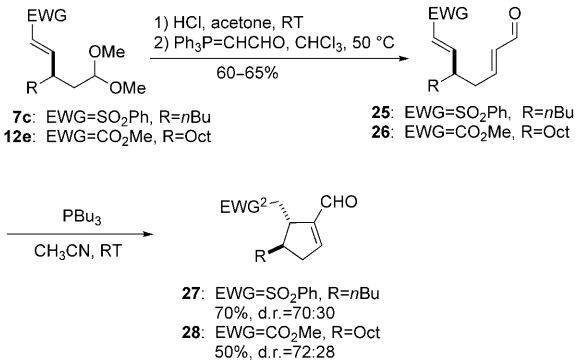
Synthetic applications: In addition to the interest in vinyl sulfone scaffolds for potential drug development, their chemical utility was also explored. We anticipated that acetal hydrolysis and aldehyde reduction in the adducts would provide configurationally defined tetrahydrofuran products as a result of a concurrent intramolecular oxa-Michael reaction,[27] the stereochemistry of which should be dictated by the resident stereocenter in the starting adduct (Scheme 5). For instance, aldehyde deprotection in adducts



Scheme 5. Application of adducts **7** and **12** in the synthesis of enantioenriched 2,3-disubstituted tetrahydrofurans and 3-substituted homoprolines. d.r.: diastereomeric ratio.

7c and **7d** provided the corresponding aldehydes that were subjected to reduction with $NaBH_4$ to afford **23c** and **23d** and, as expected, with excellent diastereomeric ratios. Therefore, this procedure opens a simple way of access to 2,3-disubstituted tetrahydrofurans that nicely complements previously reported asymmetric methodology.[28] Likewise, aldehyde deprotection in **12c** and **12e**, subsequent imine formation, and reduction gave **24c** and **24e** in good overall yields and, essentially, as single diastereomers. Thus, the approach also provides a concise stereocontrolled access to 3-substituted β^3-homoprolines, a class of β-amino acids that may be of interest in the field of β-peptide foldamers.[25,29] In each case, the configuration of the newly created stereogenic center was determined by NOE experiments that showed a 1,2-*trans* relationship between the two substituents of the respective heterocyclic ring.[14]

The present study is also interesting in that acetal deprotection and Wittig olefination provides Rauhut–Currier building blocks that allow the establishment of the effect of a stereogenic center upon reaction stereochemistry. Thus, by following Roush[30] and Krishe[31] cycloisomerization of substrates **25** and **26**, 4,5-disubstituted cyclopentene carbaldehydes may be accessed in diastereomeric ratios of up to 75:25 (Scheme 6).[32] Therefore, this method provides an attractive and quick entry for the stereoselective synthesis of suitable substrates to expand the Rauhut–Currier reaction.[33]



Scheme 6. Intramolecular cycloisomerization towards 4,5-disubstituted cyclopentane carbaldehydes.

Conclusion

In summary, we have presented an operationally simple method for the conjugate addition of β-nitroethylsulfones as bench-storable readily available new formal β-sulfonyl vinyl anions.[34] The method bears several advantages: 1) it is performed in a one-pot three-step operation without the need for intermediate isolation, 2) no chiral materials are required, except the pyrrolidine catalyst that is employed in substoichiometric quantities, 3) very high chemical efficiency is attained, and 4) it provides a broad range of vinyl sulfone scaffolds, important targets for potential drug development. The key of this method is the ability of the catalyst to promote the C–C bond construction before any nitrous acid and/or sulfinic acid elimination in the starting reagents may occur, an aspect that further expands the field of iminium catalysis. Interestingly, the method may also be extended to other relatively base-sensitive β-electron-withdrawing-substituted nitroalkanes to afford products with manifold functionality, and provides a quick entry to building blocks that are very attractive for organic synthesis.

Experimental Section

General considerations: All catalytic reactions were carried out in round-bottomed vials stopped with a septum and provided with efficient magnetic stirring. All solvents were of p. a. quality and were dried by standard procedures prior to use if necessary. Unless otherwise specified, materials were obtained from commercial sources and used without purification. Purification of reaction products was carried out by flash column chromatography by using silica gel 60 (0.040–0.063 mm, 230–400 mesh). Visualization was accomplished with UV light and a solution obtained by admixing in 470 mL of water ammonium molybdate (21.0 g), cerium sulphate (1.0 g), and concentrated sulphuric acid (31 mL), followed by heating. Melting points were determined with a Buchi SMP-20 capillary apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker Advance-DPX-300. The chemical shifts are reported in ppm relative to $CDCl_3$ ($\delta = 7.26$ ppm) for ^1H NMR spectra and relative to the central resonances of $CDCl_3$ ($\delta = 77.23$ ppm) for ^{13}C NMR spectra. Optical rotations were recorded on a Jasco P-2000 polarimeter. Analytical HPLC was performed on Waters 600E device and Hewlett Packard series 1050 chromatographs, equipped with diode array UV detector by using capilary columns (25 cm). MS spectra were

recorded on an ESI-ion trap mass spectrometer (Agilent 1100 series LC/MSD, SL model). α,β-Unsaturated aldehydes **5g** and **5h**[35] and methyl 3-nitropropionate **11**[36] were prepared according to reported procedures. The synthesis of β-nitroethylsulfones (**1–4**), catalyst **6**, β-nitropropanamide **13**, ketones **15** and **16**, as well as the characterization data for compounds **17–19**, **20–22**, **23**, **24**, **25**, **26**, **27**, **28**, and **29** are described in the Supporting information.

General procedure for the synthesis of adducts 7–10: The corresponding β-nitroethylsulfone (**1–4**) (0.65 mmol, 1.3 equiv for aliphatic enals; 0.75 mmol, 1.5 equiv for aromatic enals) was added to a solution of catalyst **6** (0.05 mmol, 0.1 equiv) and the corresponding enal **5** (0.5 mmol, 1 equiv) in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred at the indicated temperature and when enal consumption was detected by ^{1}H NMR spectroscopy, MeOH (2.5 mL), $HC(OMe)_3$ (0.11 mL, 1 mmol, 2 equiv), and *p*-toluensulfonic acid (0.02 g, 0.1 mmol, 0.2 equiv) were successively added. The reaction mixture was stirred at room temperature, typically for 1 h, and then subjected to the following protocol: Method A (for aliphatic enals): DBU (0.15 mL, 1 mmol, 2 equiv) was added at 0 °C and the reaction mixture was stirred for 1 h while reaching room temperature. Method B (for aromatic enals): $Mg(OMe)_2$ (0.26 g, 6 equiv, 3 mmol) was added and the reaction mixture was stirred at 40 °C for 2 h (for adduct **8f**, 4 equiv $Mg(OMe)_2$, room temperature). Then, HCl (0.1 N, 2 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3× 5 mL). The combined organic phases were dried ($MgSO_4$) and the solvent eliminated to afford the crude product, which was purified by flash column chromatography (eluent mixtures EtOAc/hexanes).

(*R*,*E*)-5,5-Dimetoxy-3-ethyl-1-phenylsulfonylpent-1-ene (7a): The title compound was prepared according to the general procedure by starting from enal **5a** (0.050 mL, 0.5 mmol). Yield: 0.118 g (79%); yellow oil; $[\alpha]_D^{25} = -5.6$ ($c = 1.12$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.92$–7.82 (m, 2H), 7.65–7.47 (m, 3H), 6.79 (dd, $J = 9.4$, 15.1 Hz, 1H), 6.31 (d, $J = 15.1$ Hz, 1H), 4.22 (dd, $J = 4.8$, 6.9 Hz, 1H), 3.23 (s, 3H), 3.21 (s, 3H), 2.35–2.23 (m, 1H), 1.83–1.75 (m, 1H), 1.66–1.31 (m, 3H), 0.83 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.2$, 140.9, 133.3, 130.7, 129.3, 127.5, 102.7, 53.1, 52.9, 39.8, 36.7, 27.2, 11.5 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20; 0.75 mL min^{-1}, 210 nm): t_R(major) = 26.5, t_R(minor) = 21.1 min; 94% *ee*; HRMS (TOF MS CI): *m*/*z*: calcd for $C_{17}H_{27}O_4S$: 327.1630 $[M+C_2H_5]^+$; found: 327.1616.

(*R*,*E*)-5,5-Dimetoxy-3-methyl-1-phenylsulfonylpent-1-ene (7b): The title compound was prepared according to the general procedure by starting from enal **5b** (0.041 mL, 0.5 mmol). Yield: 0.101 g (71%); yellow oil; $[\alpha]_D^{25} = -26.9$ ($c = 0.60$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.95$–7.78 (m, 2H), 7.69–7.44 (m, 3H), 6.95 (dd, $J = 7.1$, 15.1 Hz, 1H), 6.29 (dd, $J = 1.1$, 15.1 Hz, 1H), 4.30 (t, $J = 5.8$ Hz, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 2.63–2.52 (m, 1H), 1.73–1.69 (m, 2H), 1.09 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.4$, 140.9, 133.5, 129.4, 127.8, 102.7, 53.1, 38.5, 32.6, 19.4 ppm; Chiral HPLC (Chiralpak IC column; hexane/*i*PrOH 95:5; 1.0 mL min^{-1}, 210 nm): t_R(major) = 111.1, t_R(minor) = 107.9 min; 94% *ee*; HRMS (TOF MS CI): *m*/*z*: calcd for $C_{16}H_{25}O_4S$: 313.1474 $[M+C_2H_5]^+$; found: 313.1482.

(*R*,*E*)-3-Butyl-5,5-dimetoxy-1-phenylsulfonylpent-1-ene (7c): The title compound was prepared according to the general procedure by starting from enal **5c** (0.580 mL, 4.0 mmol). Yield: 1.175 g (90%); yellow oil; $[\alpha]_D^{25} = -4.2$ ($c = 0.78$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$–7.77 (m, 2H), 7.64–7.40 (m, 3H), 6.75 (dd, J = 9.5,15.1 Hz, 1H), 6.26 (d, $J = 15.1$ Hz, 1H), 4.17 (dd, $J = 5.1$, 6.5 Hz, 1H), 3.18 (d, $J = 1.0$ Hz, 3H), 3.16 (d, $J = 0.9$ Hz, 3H), 2.35–2.25 (m, 1H), 1.81–1.48 (m, 2H), 1.47–1.03 (m, 6H), 0.79 ppm (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.6$, 141.0, 133.3, 130.5, 129.3, 127.6, 102.8, 53.1, 52.9, 38.3, 37.2, 34.0, 29.2, 22.6, 13.9 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20; 0.75 mL min^{-1}, 210 nm): t_R (major) = 18.7, t_R (minor) = 15.5 min; 95% *ee*; elemental analysis calcd (%) for $C_{17}H_{26}O_4S$ (326.45): C 62.55, H 8.03, S 9.82; found: C 62.40, H 8.21, S 10.21.

(*S*,*E*)-5,5-Dimetoxy-3-isopropyl-1-phenylsulfonylpent-1-ene (7d): The title compound was prepared according to the general procedure by starting from enal **5d** (0.060 mL, 0.5 mmol). Yield: 0.094 g (60%); yellow oil; $[\alpha]_D^{25} = -12.8$ ($c = 0.42$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.97$–7.79 (m, 2H), 7.65–7.44 (m, 3H), 6.82 (dd, $J = 10.0$, 15.0 Hz, 1H), 6.30 (d, $J = 15.1$ Hz, 1H), 4.16 (dd, $J = 4.3$, 7.5 Hz, 1H), 3.23 (s, 3H), 3.19 (s, 3H), 2.25–2.10 (m, 1H), 1.88–1.80 (m, 1H), 1.78–1.50 (m, 2H), 0.87 ppm (dd, $J = 6.8$, 10.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.0$, 141.2, 133.4, 131.6, 129.5, 127.7, 103.2, 53.5, 52.9, 44.6, 34.6, 32.1, 20.5, 19.3 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20; 0.75 mL min^{-1}, 210 nm): t_R(major) = 21.7, t_R(minor) = 17.2 min; 95% *ee*; HRMS (TOF MS CI): *m*/*z*: calcd for $C_{18}H_{29}O_4S$: 341.1787 $[M+C_2H_5]^+$; found: 341.1770.

(*R*,*E*)-5,5-Dimetoxy-3-octyl-1-phenylsulfonylpent-1-ene (7e): The title compound was prepared according to the general procedure by starting from enal **5e** (0.220 mL, 1.0 mmol). Yield: 0.306 g (80%); yellow oil; $[\alpha]_D^{25} = -7.82$ ($c = 1.01$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$–7.87 (m, 2H), 7.65–7.47 (m, 3H), 6.79 (dd, $J = 9.5$, 15.1 Hz, 1H), 6.29 (d, $J = 15.1$ Hz, 1H), 4.21 (dd, $J = 4.8$, 6.9 Hz, 1H), 3.23 (s, 3H), 3.21 (s, 3H), 2.43–2.26 (m, 1H), 1.82–1.74 (m, 1H), 1.64–1.54 (m, 1H), 1.50–1.07 (m, 14H), 0.88 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 150.6, 141.0, 133.4, 130.5, 129.4, 127.6, 102.7, 53.2, 52.9, 38.4, 37.2, 34.4, 31.9, 29.5, 29.5, 29.3, 27.17, 22.8, 14.2 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 85:15; 0.75 mL min^{-1}, 210 nm): t_R(major) = 17.9, t_R(minor) = 15.2 min; 93% *ee*; HRMS (TOF MS CI): *m*/*z*: calcd for $C_{23}H_{39}O_4S$: 411.2569 $[M+C_2H_5]^+$; found: 411.2573.

(*R*,*E*)-5,5-Dimetoxy-3-phenyl-1-phenylsulfonylpent-1-ene (7f): The title compound was prepared according to the general procedure by starting from enal **5f** (0.063 mL g, 0.5 mmol). Yield: 0.116 g (67%); yellow oil; $[\alpha]_D^{25} = -22.39$ ($c = 0.14$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$–7.82 (m, 2H), 7.67–7.48 (m, 3H), 7.40–7.23 (m, 3H), 7.20–7.08 (m, 3H), 6.28 (dd, $J = 1.4$, 15.1 Hz, 1H), 4.14 (dd, $J = 5.0$, 6.7 Hz, 1H), 3.70–3.62 (m, 1H), 3.28 (s, 3H), 3.24 (s, 3H), 2.18–1.96 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.0$, 140.8, 140.2, 133.5, 130.5, 129.4, 129.2, 128.0, 127.8, 127.6, 102.4, 53.5, 53.0, 43.9, 37.8 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20; 0.75 mL min^{-1}, 235 nm): t_R(major) = 34.1, t_R(minor) = 28.6 min; 98% *ee*; HRMS (TOF MS CI): *m*/*z*: calcd for $C_{21}H_{27}O_4S$: 375.1630 $[M+C_2H_5]^+$; found: 375.1638.

(*R*,*E*)-5,5-Dimetoxy-3-(4-chloro)phenyl-1-phenylsulfonylpent-1-ene (7g): The title compound was prepared according to the general procedure by starting from enal **5g** (0.083 g, 0.5 mmol). Yield: 0.107 g (56%); yellow oil; $[\alpha]_D^{25} = -13.85$ ($c = 0.65$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.93–7.82 (m, 2H), 7.70–7.51 (m, 2H), 7.3–7.26 (m, 3H), 7.17–7.04 (m, 3H), 6.28 (dd, $J = 1.4$, 15.1 Hz, 1H), 4.14 (dd, $J = 4.9$, 6.7 Hz, 1H), 3.70–3.63 (m, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 2.18–1.94 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 148.3$, 140.6, 138.7, 133.6, 130.9, 129.5, 129.4, 129.3, 127.8, 102.3, 53.5, 53.1, 43.2, 37.7 ppm; Chiral HPLC (Chiralpak IC column; hexane/*i*PrOH 50:50; 0.5 mL min^{-1}, 235 nm): t_R(major) = 27.7, t_R(minor) = 26.9 min; 98% *ee*; HRMS (TOF MS CI): *m*/*z*: calcd for $C_{21}H_{26}O_4SCl$: 409.1240 $[M+C_2H_5]^+$; found: 409.1256.

(*R*,*E*)-5,5-Dimetoxy-3-(4-methyl)phenyl-1-phenylsulfonylpent-1-ene (7h): The title compound was prepared according to the general procedure by starting from enal **5h** (0.073 g, 0.5 mmol). Yield: 0.103 g (57%); yellow oil; $[\alpha]_D^{25} = -23.34$ ($c = 0.36$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.91–7.76 (m, 2H), 7.65–7.44 (m, 3H), 7.14–7.00 (m, 5H), 6.24 (dd, $J =$ 1.4, 15.1 Hz, 1H), 4.12 (dd, $J = 4.9$, 6.7 Hz, 1H), 3.64–3.57 (m, 1H), 3.26 (s, 3H), 3.22 (s, 3H), 2.34 (s, 3H), 2.13–1.91 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.3$, 140.9, 137.3, 137.1, 133.5, 130.3, 129.9, 129.4, 127.8, 127.8, 102.4, 53.5, 53.0, 43.5, 37.8, 21.2 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20; 0.75 mL min^{-1}, 235 nm): t_R-(major) = 33.8, t_R(minor) = 24.9 min; 97% *ee*; HRMS (TOF MS CI): *m*/*z*: calcd for $C_{22}H_{29}O_4S$: 389.1787 $[M+C_2H_5]^+$; found: 389.1786.

(*R*,*E*)-5,5-Dimetoxy-3-(4-methoxy)phenyl-1-phenylsulfonylpent-1-ene (7i): The title compound was prepared according to the general procedure by starting from enal **5i** (0.081 g, 0.5 mmol). Yield: 0.113 g (60%); yellow oil; $[\alpha]_D^{25} = -8.0$ ($c = 0.82$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.87$–7.79 (m, 2H), 7.62–7.48 (m, 3H), 7.14–7.00 (m, 3H), 6.87–6.83 (m, 2H), 6.23 (dd, $J = 1.4$, 15.1 Hz, 1H), 4.12 (dd, $J = 4.9$, 6.8 Hz, 1H), 3.79 (s, 3H), 3.62–3.55 (m, 1H), 3.25 (s, 3H), 3.21 (s, 3H), 2.14–1.88 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.0$, 149.4, 140.8, 133.5, 132.0, 130.2, 129.4, 129.0, 127.8, 114.6, 102.4, 55.5, 53.5, 53.0, 43.0, 37.8 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20;

0.75 mL min^{-1}, 235 nm): t_R(major) = 61.9, t_R(minor) = 46.5 min; 94% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{22}H_{29}O_5S$: 405.1736 $[M+C_2H_5]^+$; found: 405.1739.

(*R*,*E*)-5,5-Dimetoxy-3-ethyl-1-(2-pyridyl)sulfonylpent-1-ene (8a): The title compound was prepared according to the general procedure by starting from enal **5a** (0.058 mL, 0.50 mmol). Yield: 0.136 g (62%); yellow oil; $[\alpha]_D^{25} = -4.5$ ($c = 0.95$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.70 (d, $J = 4.7$ Hz, 1H), 8.08 (d, $J = 7.9$ Hz, 1H), 7.93 (td, $J = 1.7$, 7.8 Hz, 1H), 7.49 (ddd, $J = 1.1$, 4.7, 7.6 Hz ,1H), 6.90 (dd, $J = 9.4$, 15.2 Hz, 1H), 6.52 (dd, $J = 0.5$, 15.2 Hz, 1H), 4.28 (dd, $J = 4.7$, 7.1 Hz, 1H), 3.23 (s, 3H), 3.22 (s, 3H), 2.42–2.25 (m, 1H), 1.84–1.76 (m, 1H), 1.67–1.31 (m, 3H), 0.84 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.9$, 153.4, 150.4, 138.3, 128.1, 127.2, 121.9, 102.8, 53.2, 53.1, 40.3, 36.8, 27.3, 11.6 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 70:30; 0.75 mL min^{-1}, 210 nm): t_R(major) = 22.1, t_R(minor) = 16.2 min; 95% *ee*; elemental analysis calcd (%) for $C_{14}H_{21}NO_4S$ (299.12): C 56.16, H 7.07, N 4.68, S 10.71; found: C 56.65, H 7.57, N 5.15, S 10.97.

(*S*,*E*)-5,5-Dimetoxy-3-isopropyl-1-(2-pyridyl)sulfonylpent-1-ene (8d): The title compound was prepared according to the general procedure by starting from enal **5d** (0.075 mL, 0.75 mmol). Yield: 0.080 g (51%); pale-yellow oil; $[\alpha]_D^{25} = -6.2$ ($c = 1.04$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.70$ (d, $J = 4.7$ Hz, 1H), 8.09 (dt, $J = 1.0$, 7.9 Hz, 1H), 7.93 (td, $J = 1.7$, 7.8 Hz, 1H), 7.49 (ddd, $J = 1.1$, 4.7, 7.6 Hz, 1H), 6.94 (dd, $J = 10.0$, 15.2 Hz, 1H), 6.50 (d, $J = 15.2$ Hz, 1H), 4.23 (dd, $J = 4.1$, 7.8 Hz, 1H), 3.24 (s, 3H), 3.21 (s, 3H) 2.33–2.19 (m, 1H), 1.91–1.81 (m, 1H), 1.79–1.54 (m, 2H), 0.88 ppm (dd, $J = 6.8$, 10.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.8$, 152.0, 150.2, 138.1, 128.6, 127.0, 121.7, 102.9, 53.2, 52.7, 44.8, 34.3, 31.8, 20.3, 19.1 ppm; Chiral HPLC (Chiralpak AS-H column; hexane:*i*PrOH 80:20; 0.75 mL min^{-1}, 210 nm): t_R(major) = 27.6, t_R(minor) = 20.4 min; 96% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{14}H_{20}NO_3S$: 282.1164 $[M+H-CH_3OH]^+$; found: 282.1164.

(*R*,*E*)-5,5-Dimetoxy-3-octyl-1-(2-pyridyl)sulfonylpent-1-ene (8e): The title compound was prepared according to the general procedure by starting from enal **5e** (0.396 mL, 2.0 mmol). Yield: 0.705 g (92%); yellow oil; $[\alpha]_D^{25} = -2.7$ ($c = 1.45$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.66$ (d, $J = 4.7$ Hz, 1H), 8.04 (d, $J = 7.9$ Hz, 1H), 7.90 (td, $J = 1.7$, 7.8 Hz, 1H), 7.46 (ddd, $J = 1.1$, 4.7, 7.6 Hz, 1H), 6.86 (dd, $J = 9.5$, 15.2 Hz, 1H), 6.47 (d, $J = 15.2$ Hz, 1H), 4.23 (dd, $J = 4.7$, 7.1 Hz, 1H), 3.19 (s, 3H), 3.18 (s, 3H) 2.48–2.30 (m, 1H), 1.81–1.70 (m, 1H), 1.62–1.51 (m, 1H), 1.47–1.32 (m, 2H), 1.27–1.07 (m, 12H), 0.82 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.8$, 153.6, 150.2, 138.2, 127.8, 127.1, 121.8, 102.7, 53.1, 52.9, 38.7, 37.1, 34.3, 31.9, 29.5, 29.5, 29.2, 27.0, 22.7, 14.2 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20; 0.75 mL min^{-1}, 210 nm): t_R(major) = 23.4, t_R(minor) = 19.1 min; 94% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{19}H_{30}NO_3S$: 352.1946 $[M+H-CH_3OH]^+$; found: 352.1955.

(*R*,*E*)-5,5-Dimetoxy-3-phenyl −1-(2-pyridyl)sulfonylpent-1-ene (8f): The title compound was prepared according to the general procedure by starting from enal **5f** (0.063 mL, 0.50 mmol). Yield: 0.121 g (70%); yellow oil; $[\alpha]_D^{25} = +3.0$ ($c = 0.18$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.71 (d, $J = 4.7$ Hz, 1H), 8.05 (d, $J = 7.9$ Hz, 1H), 7.92 (td, $J = 1.7$, 7.8 Hz, 1H), 7.50 (ddd, $J = 1.1$, 4.7, 7.6 Hz, 1H), 7.36- 7.14 (m, 6H), 6.52 (dd, $J =$ 1.4, 15.2 Hz, 1H), 4.17 (dd, $J = 5.2$, 6.6 Hz, 1H), 3.75–3.65 (m, 1H), 3.27 (s, 3H), 3.23 (s, 3H), 2.18–1.98 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.7$, 151.8, 150.4, 140.1, 138.3, 129.2, 128.1, 127.9, 127.6, 127.2, 122.0, 102.3, 53.4, 53.0, 44.2, 37.7 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20; 0.75 mL min^{-1}, 210 nm): t_R(major) = 50.6, t_R(minor) = 40.6 min; 93% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{17}H_{18}NO_3S$: 316.1007 $[M+H-CH_3OH]^+$; found: 316.0995.

(*R*,*E*)-5,5-Dimetoxy-3-ethyl-1-*tert*-butylsulfonylpent-1-ene (9a): The title compound was prepared according to the general procedure by starting from enal **1a** (0.050 mL, 0.5 mmol). Yield: 0.050 g (40%); yellow oil; $[\alpha]_D^{25} = -6.0$ ($c = 0.94$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.70$ (dd, $J = 9.3$, 15.2 Hz, 1H), 6.24 (dd, $J = 0.7$, 15.2 Hz, 1H), 4.33 (dd, $J = 4.8$, 6.9 Hz, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 2.44–2.30 (m, 1H), 1.86–1.76 (m, 1H), 1.70–1.39 (m, 3H), 1.36 (s, 9H), 0.90 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.4$, 124.2, 102.9, 58.5, 53.4, 53.0, 40.4, 36.9, 27.5, 23.6, 11.7 ppm; Chiral HPLC (Chiralpak AD-H column; hexane/*i*PrOH 98:2; 0.75 mL min^{-1}, 210 nm): t_R(major) = 27.3, t_R(minor) = 34.4 min; 96% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{12}H_{23}O_3S$: 247.1368 $[M+H-CH_3OH]^+$; found: 247.1363.

(*R*,*E*)-5,5-Dimetoxy-3-ethyl-1-propylsulfonylpent-1-ene (10a): The title compound was prepared according to the general procedure by starting from enal **5a** (0.050 mL, 0. 50 mmol). Yield: 0.099 g (75%); yellow oil; $[\alpha]_D^{25} = -11.0$ ($c = 1.04$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.69$ (dd, $J = 9.3$, 15.2 Hz, 1H), 6.24 (d, $J = 15.2$ Hz, 1H), 4.30 (dd, $J = 4.9$, 6.7 Hz, 1H), 3.27 (s, 6H), 2.96–2.86 (m, 2H), 2.39–2.25 (m, 1H), 1.87–1.72 (m, 3H), 1.67–1.32 (m, 3H), 1.04 (t, $J = 7.4$ Hz, 3H), 0.87 ppm (t, $J =$ 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.5$, 128.3, 102.8, 56.7, 53.3, 52.9, 40.0, 36.2, 27.3, 16.5, 13.2, 11.6 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 80:20; 0.75 mL min^{-1}, 210 nm): t_R(major) = 30.3, t_R(minor) = 26.7 min; 93% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{11}H_{21}O_3S$: 233.1211 $[M+H-CH_3OH]^+$; found: 233.1216.

General procedure for the synthesis of adducts 12 and 14: The same procedure described for the preparation of adducts **7**-**10** was followed by employing 20 mol% catalyst **6**.

(*R*,*E*)-Methyl 4-ethyl-6,6-dimethoxyhex-2-enoate (12a): The title compound was prepared according to the general procedure by starting from enal **5a** (0.050 mL, 0.5 mmol). Yield: 0.085 g (79%); yellow oil; $[\alpha]_D^{25} =$ −19.7 ($c = 1.34$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.74$ (dd, $J =$ 9.4, 15.7 Hz, 1H), 5.81 (d, $J = 15.7$ Hz, 1H), 4.30 (dd, $J = 4.4$, 7.4 Hz, 1H), 3.73 (s, 3H), 3.30 (s, 3H), 3.28 (s, 3H), 2.31–2.16 (m, 1H), 1.83–1.72 (m, 1H), 1.66–1.28 (m, 3H), 0.86 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.2$, 152.7, 121.4, 103.0, 53.0, 53.0, 51.6, 40.5, 37.1, 27.6, 11.6 ppm; Chiral HPLC (Chiralpak OD-H OD column; hexane/*i*PrOH 99:1; 0.30 mL min^{-1}, 209.8 nm): t_R(major) = 38.3, t_R(minor) = 49.8 min; 92% *ee*.

(*R*,*E*)-Methyl 4-(2,2-dimethoxyethyl)oct-2-enoate (12c): The title compound was prepared according to the general procedure by starting from enal **5c** (0.072 mL, 0.5 mmol). Yield: 0.113 g (92%); pale-yellow oil; $[\alpha]_D^{25} = -7.5$ ($c = 1.08$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.72$ (dd, $J = 9.5$, 15.6 Hz, 1H), 5.78 (d, $J = 15.7$ Hz, 1H), 4.29 (dd, $J = 4.4$, 7.4 Hz, 1H), 3.70 (s, 3H), 3.27 (s, 3H), 3.26 (s, 3H), 2.36–2.22 (m, 1H), 1.80–1.69 (m, 1H), 1.61–1.49 (m, 1H), 1.48–1.14 (m, 6H), 0.84 ppm (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.1$, 153.0, 121.1, 102.7, 52.9, 52.8, 51.6, 38.8, 37.4, 34.4, 29.3, 22.8, 14.1 ppm; Chiral HPLC (Chiralpak OD OD-H column; hexane/*i*PrOH 99:1; 0.30 mL min^{-1}, 209.8 nm): t_R(major) = 33.0, t_R(minor) = 40.5 min; 91% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{12}H_{22}O_3$: 213.1491 $[M+H-CH_3OH]^+$; found: 213.1485.

(*R*,*E*)-Methyl 4-(2,2-dimethoxyethyl)dodec-2-enoate (12e): The title compound was prepared according to the general procedure by starting from enal **5e** (0.110 mL, 0.5 mmol). Yield: 0.138 g (88%); colorless oil; $[\alpha]_D^{25} = +2.0$ ($c = 0.3$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.75$ (dd, $J = 9.5$, 15.6 Hz, 1H), 5.81 (d, $J = 15.6$ Hz, 1H), 4.31 (dd, $J = 4.4$, 7.4 Hz, 1H), 3.73 (s, 3H), 3.30 (s, 3H), 3.29 (s, 3H), 2.40–2.25 (m, 1H), 1.83–1.71 (m, 1H), 1.64–1.55 (m, 1H), 1.24 (s, 14H), 0.87 ppm (t, $J =$ 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.2$, 153.1, 121.2, 103.0, 53.1, 53.0, 51.6, 38.9, 37.5, 34.8, 32.1, 29.8, 29.7, 29.5, 27.2, 22.9, 14.3 ppm; Chiral HPLC (Chiralpak OD OD-H column; hexane:*i*PrOH 99:01; 0.30 mL min^{-1}, 209.8 nm): t_R(major) = 31.5, t_R(minor) = 37.2 min; 96% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{19}H_{37}O_4$: 329.2692 $[M+C_2H_5]^+$; found: 329.2708.

(*R*,*E*)-Methyl 6,6-dimethoxy-4-phenylhex-2-enoate (12f): The title compound was prepared according to the general procedure by starting from enal **5f** (0.063 mL, 0.5 mmol). Yield: 0.086 g (67%); yellow oil; $[\alpha]_D^{25} = +$ 1.9 ($c = 0.60$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.18 (m, 5H), 7.10 (dd, $J = 7.7$, 15.7 Hz, 1H), 5.83 (dd, $J = 1.3$, 15.7 Hz, 1H), 4.22 (t, $J = 5.9$ Hz, 1H), 3.73 (s, 3H), 3.67–3.57 (m, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 2.17–1.99 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.1$, 151.4, 141.5, 129.1, 128.0, 127.2, 120.8, 102.5, 53.2, 52.9, 51.7, 44.4, 37.8 ppm; Chiral HPLC (Chiralpak OD OD-H column; hexane/*i*PrOH 99:01; 0.30 mL min^{-1}, 209.8 nm): t_R(major) = 76.9, t_R(minor) = 66.2 min; 93% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{14}H_{17}O_3$: 233.1178 $[M+H-CH_3OH]^+$; found: 233.1177.

(*R,E*)-4-Ethyl-*N*-6,6-trimethoxy-*N*-methylhex-2-enamide (14): The title compound **14** was prepared according to the general procedure by starting from enal **5a** (0.100 mL, 1.00 mmol). Yield: 0.214 g (87%); pale-yellow oil; $[\alpha]_D^{25} = -17.2$ ($c = 1.10$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.75$ (dd, $J = 9.4$, 15.4 Hz, 1H), 6.40 (d, $J = 15.4$ Hz, 1H), 4.34 (dd, $J = 4.3$, 7.6 Hz, 1H), 3.69 (s, 3H), 3.31 (s, 3H), 3.29 (s, 3H), 3.24 (s, 3H), 2.35–2.21 (m, 1H), 1.84–1.73 (m, 1H), 1.66–1.56 (m, 1H), 1.56–1.30 (m, 2H), 0.87 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 167.0, 150.8, 119.3, 103.1, 61.9, 53.1, 53.0, 40.6, 37.2, 32.6, 27.7, 11.7 ppm; Chiral HPLC (Chiralpak AS-H column; hexane/*i*PrOH 98:02; 0.70 mL min^{-1}, 209.8 nm): t_R(major) = 26.0, t_R(minor) = 22.8 min; 97% *ee*; HRMS (TOF MS CI): *m/z*: calcd for $C_{14}H_{28}NO_4$: 274.2018 $[M+C_2H_5]^+$; found: 274.2024.

General procedure for the preparation of surrogates of β-aminoacids 20–22: Jones reagent[37] (1.5 equiv) was added dropwise to a solution of the corresponding adduct in acetone (10 mL mmol^{-1}) at 0°C. The reaction mixture was then stirred at room temperature for 15 h. Excess isopropanol was added and the mixture stirred for an additional 2 h. Then, the mixture was filtered and the solvent was removed in the filtrate. The residue was dissolved in EtOAc and washed with HCl (2N). The aqueous phase was extracted twice with EtOAc and then the organic layers were combined and dried ($MgSO_4$). The organic solvent was eliminated to afford the corresponding carboxylic acids **17–19** that were purified by column chromatography (eluent mixtures EtOAc/hexanes). Phenyl dichlorophosphate (2.0 equiv) was added to a stirred suspension of the corresponding carboxylic acid (1 equiv), pyridine (5 equiv), and sodium azide (2 equiv) in dry CH_2Cl_2 (6 mL mmol^{-1}) at 20°C. The reaction mixture was stirred for 15–24 h at 20°C and then the solvent was removed under an argon atmosphere. The crude product was dissolved in dry *t*BuOH (6 mL mmol^{-1}) and the solution heated to reflux for 2 h. Then, the solvent was eliminated and the crude compound was purified by column chromatography by using EtOAc/hexanes mixtures.

General procedure for the synthesis 2,3-disubstituted tetrahydrofurans 23: HCl (6N, 3 mL mmol^{-1}) was added to a solution of the corresponding crude adduct **7** in acetone (6 mL mmol^{-1}) at room temperature and the reaction mixture was stirred for 1 h. Then, H_2O (3 mL mmol^{-1}) was added and the organic solvent eliminated under reduced pressure and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and the solvent eliminated to afford the crude aldehyde in quantitative yield. $NaBH_4$ (4 equiv) in EtOH (3 mL mmol^{-1}) was added to a solution of the corresponding aldehyde in EtOH (5 mL mmol^{-1}) at −20°C. The reaction mixture was stirred for 24–48 h, quenched with H_2O, and the organic solvent eliminated under reduced pressure. The aqueous phase was extracted with CH_2Cl_2, the combined organic layers dried ($MgSO_4$), and the solvent eliminated to afford the crude product that was purified by flash column chromatography (eluent mixtures EtOAc/hexanes) to afford the pure 2,3-disubstituted tetrahydrofuran.

General procedure for the synthesis of 3-substituted homoprolines 24: HCl (6N, 3 mL mmol^{-1}) was added to a solution of the corresponding adduct **12** in acetone (6 mL mm^{-1}ol) at room temperature and the reaction mixture was stirred for 1 h. Then, H_2O (3 mL mm^{-1}ol) was added, the organic solvent eliminated under reduced pressure, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and the solvent eliminated to afford the crude aldehyde in quantitative yield. Anhydrous $MgSO_4$ was added to a solution of the corresponding aldehyde (1 equiv) and benzyl amine (1 equiv) in dry CH_2Cl_2 (2 mL mmol^{-1}). The reaction mixture was stirred at room temperature and when aldehyde consumption was detected by ^{1}H NMR spectra, EtOH (12.0 mL mmol^{-1}) was added. Then, $NaBH_4$ (1.1 equiv) was added at 0°C and the reaction mixture was stirred for 3 h, quenched with H_2O, and the organic solvent eliminated under reduced pressure. The aqueous phase was extracted with CH_2Cl_2, the combined organic layers dried ($MgSO_4$), and the solvent eliminated to afford the crude product that was purified by flash column chromatography (eluent mixtures EtOAc/hexanes) to afford the corresponding pure 3-substituted homoproline.

General procedure for the synthesis of 4,5-disubstituted cyclopentane carbaldehydes (27, 28): HCl (6N, 3 mL mmol^{-1}) was added to a solution of the corresponding crude adduct (**7c**, **8e**) in acetone (6 mL mmol^{-1}) at room temperature and the reaction mixture was stirred for 1 h. Then, H_2O (3 mL mmol^{-1}) was added, the organic solvent eliminated under reduced pressure, and the aqueous phase was extracted with CH_2Cl_2 (2× 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent eliminated to afford the crude aldehyde in quantitative yield. The aldehyde was added dropwise in $CHCl_3$ (1.7 mL) at 0°C to a solution of formylmethylenetriphenylphosphorane (0.417 g, 1.38 mmol, 2 equiv) in $CHCl_3$ (5 mL). The resulting mixture was stirred at the same temperature for 2 h, warmed up to 50°C, and stirred for 24 h. Upon reaction completion, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (eluent mixtures EtOAc/hexanes 50:50) to afford the corresponding pure aldehyde (**25**/**26**) as an *E*/*Z* mixture. Tributylphosphine (0.008 mL, 0.032 mmol, 0.2 equiv) was added to a solution of the corresponding aldehyde (0.16 mmol) in CH_2Cl_2 (1 mL) and the reaction mixture was stirred at room temperature for 15 h. Then, H_2O (3 mL) was added, the organic solvent eliminated under reduced pressure, and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent eliminated to afford the corresponding pure cyclopentane carbaldehyde.

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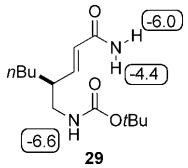

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