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Organocatalyst-mediated enantioselective intramolecular Michael addition of aldehydes to vinyl sulfones

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

Chiral amines with a hydrogen bond donor promote the intramolecular conjugate addition of aldehydes to vinyl sulfones. Chiral cyclic sulfone-aldehydes are obtained in good yields with an ee of up to 82%.

1. Introduction

During the last decade, asymmetric organocatalysis has gained considerable attention[1] and remarkable progress has been made since the pioneering reports of the proline intermolecular aldol reaction[2] and iminium ion catalysis concept.[3] For stereoselective C–C bond formation, Michael addition via enamine activation represents a very powerful method.[4] Moreover, different withdrawing groups on the Michael acceptors have been well described in aminocatalysis including ester,[5] carbonyl[6] and nitro groups.[7] More recently, much effort has been made to apply organocatalytic asymmetric conjugate addition to more challenging Michael acceptors such as vinyl phosphonates[8] and vinyl sulfones.[9] The intermolecular Michael reaction has been well studied while intramolecular versions have received less attention. To the best of our knowledge, the catalytic amine-mediated intramolecular Michael addition has only been reported with enals or enones.[10] Expanding the scope of Michael acceptors in the intramolecular reaction still remains a challenge. Herein we wish to report the first organocatalyst-mediated enantioselective intramolecular Michael addition of aldehydes to vinyl sulfone.

2. Results and discussion

Vinyl sulfones are very useful intermediates in organic[11] and medicinal chemistry.[12] This functional group can be used, for example, in cycloaddition reactions or Michael additions. In the last decade, our group has developed various methodologies for the Michael addition of aldehydes to vinyl sulfones catalysed by organic molecules such as *N*-*i*Pr-2,2′-bipyrrolidine (*i*-PBP),[9a] aminal pyrrolidine[9c] and diphenylprolinol silyl ether.[9b] Recently, Lu and Palomo et al. also reported the organocatalytic addition of aldehydes and ketones to vinyl sulfones.[13] In all of these examples, the intermolecular addition of carbonyl compounds is performed on a bis-activated substrate, these two activating groups are needed to ensure good reactivities. Our goal was to carry out an intramolecular version of this reaction on vinyl mono-sulfones. Indeed, we hoped that the intramolecular reaction would favour the cyclisation avoiding the use of two activating groups.

To investigate this intramolecular Michael reaction, we synthesised different substrates **5** bearing an aldehyde functionality and a vinyl mono-sulfone moiety (Schemes 1 and 2). Compounds **5a–e** were obtained starting from commercially available lactones **1a** and **1b** which were first reduced by DIBAL-H (Scheme 1). Then, the resulting aldehydes were protected with 1,3-propanedithiol to afford compounds **2a** and **2b**. Oxidation of alcohols to aldehydes **3a** and **3b** was achieved using the complex SO_3–pyridine in the presence of DMSO and triethylamine. To obtain the vinyl sulfone derivatives, we decided to perform a Horner–Wadsworth–Emmons olefination of these aldehydes with various sulfonyl phosphonates.

To this end, we prepared phosphonates **11b–d** by a nucleophilic substitution reaction of the commercially available diethyl iodomethylphosphonate **9** with aromatic thiols **8b–d** (Scheme 3). Then, thioethers **10a–d** were oxidised to the corresponding sulfones **11** with oxone. With these phosphonates in hand, we performed the olefination in THF using NaH as a base, and sulfones **4a–e** were isolated in good yields. Finally, the removal of the dithiane moiety gave rise to the desired vinyl mono-sulfone aldehydes **5a–e** in good yields (Scheme 1).

Substrates **5f** and **5g** could be prepared without protection of the aldehyde functional group, but in modest yields in a two-step procedure (Scheme 2). Reduction of the starting lactones with DIBAL-H gave the corresponding aldehydes that were directly reacted with phosphonate **11a** in the Horner–Wadsworth–Emmons olefination. The resulting olefins **6** and **7** were then oxidised with

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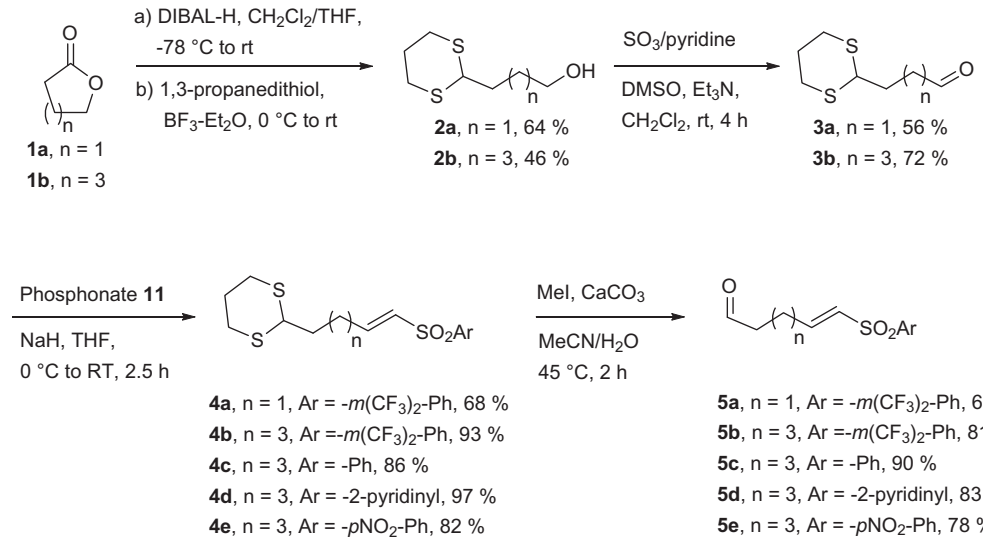
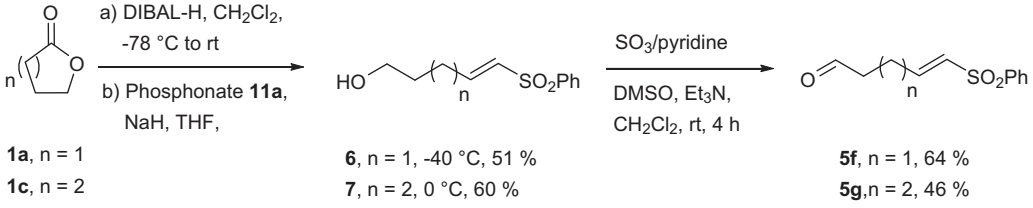
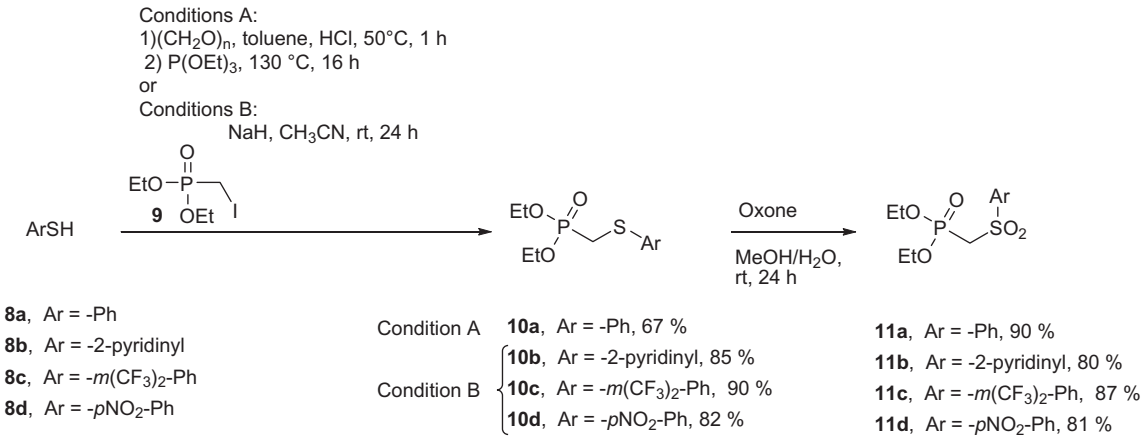


Scheme 1.



Scheme 2.



Scheme 3.

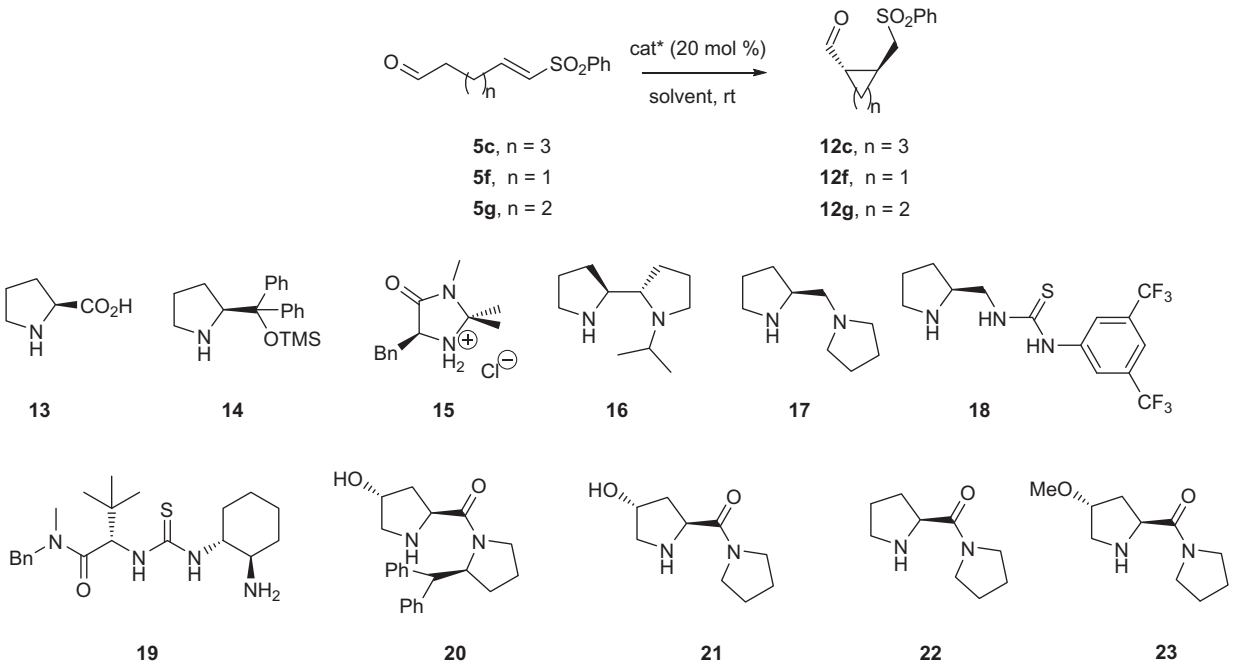
SO_3–pyridine complex to furnish aldehydes **5f** and **5g** with 64% and 46% yield, respectively.

The activity of a series of catalysts was then studied using mono-phenylsulfone aldehydes **5** having various alkyl chain lengths (Scheme 4). The results are summarised in Table 1.

We first evaluated the intramolecular Michael reaction of **5c** using a catalytic amount of L-proline **13**. Unfortunately, no cyclisation product **12c** was observed. We then treated compound **5c** with the prolinol silyl ether **14**, which is an effective catalyst for the intermolecular version of this transformation,[9b] but no reaction occurred. Next we investigated MacMillan's imidazolidinone **15**. Although it proved to be very efficient to promote the asymmetric intramolecular Michael reaction of aldehydes to enones or enals,[10b] no desired product was formed in our reaction.

Next, we focused on chiral diamines. With our catalyst *i*-PBP **16**, adduct **12c** was obtained in a good yield but with a very low enantiomeric excess (Table 1, entry 1). Reaction performed with the 1-pyrrolidinylmethylpyrrolidine **17** afforded the cyclic sulfone-aldehyde **12c** in moderate yield and a good *trans*-diastereoselectivity, but a modest enantioselectivity (entry 2).

Quite recently, it was found by Chen et al.[9e] that amine–thioureas can promote the Michael addition of α-substituted cyanoacetate to vinyl sulfones. The authors proposed that the sulfone group was activated by a double-hydrogen-bonding interaction between the NH of the thiourea and the sulfone. This report led us to examine catalysts bearing a hydrogen bond donor functionality. For this purpose, we performed the intramolecular Michael addition reaction catalysed by thioureas **18** and **19.** After a prolonged



Scheme 4.

reaction time, compound **12c** was obtained in moderate yield and selectivity (entries 3 and 4). Then, we turned our attention to other bifunctional catalysts *trans*-4-hydroxyprolylamides **20** and **21** (bearing a H-bond donor and a secondary amine) which were described as very efficient catalysts in the asymmetric addition of an aldehyde to a nitroalkene.[14] As described, we carried out the intramolecular reaction in *i*-PrOH with catalyst **20**. After a week at room temperature the expected product was isolated in modest yield, good diastereoselectivity and encouraging enantioselectivity (entry 5). Screening various solvents with this organocatalyst **20** proved that dichloromethane gave the highest activity and enantioselectivity (entries 5–7). When the reaction was conducted with another *trans*-4-hydroxyprolylamide **21**, a modest yield was observed but the sulfone aldehyde **12c** was obtained with a promising 71% ee (entry 8). Finally we tested this reaction with substrates **5f** and **5g**; cyclobutane and cyclopropane adducts were not formed (entries 9 and 10).

We have reported the first intramolecular Michael addition of an aldehyde to a vinyl mono-phenylsulfone but the major problem of this transformation is a very long reaction time. To overcome this problem, we hoped that substitution on the sulfone by an electron-withdrawing group would accelerate the reaction.[13d] For this purpose, compound **5b**, bearing CF_3 groups on the phenylsulfone, was treated with catalyst **20** under the same conditions as previously described. As expected, the cyclic sulfone-aldehyde **12b** was isolated in a good yield in only 6 h (vs 4 days), with comparable selectivity (Table 2, entry 1). The shorter reaction time led us to run the experiment at lower temperatures to increase the stereoselectivity (entries 5–7). The best result was achieved at −15 °C and the adduct **12b** was isolated in good yield and enantioselectivity (82% ee, entry 7).

The efficiency of this withdrawing group lead us to perform the cyclisation of the adduct **5a** but the enhanced reactivity of the vinyl-sulfone is not efficient enough to promote the formation of a cyclopropane ring (entry 8).

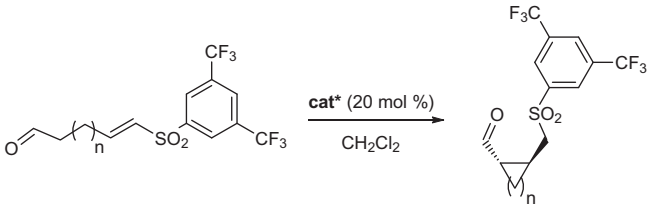
As mentioned above, Chen et al. proposed that sulfones could be activated by a thiourea via a hydrogen-bonding interaction. We

Table 1
Screening of catalysts in the intramolecular Michael addition

Ent.	Substrate	Cat.	Solvent	Time days	Yield (%)	dr *anti*/*syn*	ee (%)
1	**5c**	**16**	$CHCl_3$	1	70	90/10	5
2	**5c**	**17**	*i*-PrOH	2	52	92/8	42
3	**5c**	**18**	Benzene	7	54	89/11	58
4	**5c**	**19**	CH_2Cl_2/H_2O	7	70	91/9	41
5	**5c**	**20**	*i*-PrOH	7	50	90/10	52
6	**5c**	**20**	Toluene	16	62	89/11	62
7	**5c**	**20**	CH_2Cl_2	4	52	90/10	65
8	**5c**	**21**	CH_2Cl_2	4	24	93/7	71
9	**5f**	**20**	CH_2Cl_2	7	nr[a]	—	—
10	**5g**	**20**	CH_2Cl_2	7	nr[a]	—	—

[a] No reaction.

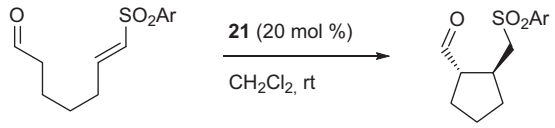
Table 2
Intramolecular conjugate addition to activated vinyl sulfone



Ent.	Substrate	Cat.	Temp.	Time	Yield (%)	dr *anti*/*syn*	ee (%)
1	**5b**	**20**	rt	6 h	80	91/9	65
2	**5b**	**21**	rt	24 h	80	—[b]	67
3	**5b**	**23**	rt	30 d	43[a]	—[b]	40
4	**5b**	**22**	rt	9 d	57[a]	—[b]	0
5	**5b**	**20**	0 °C	5 d	65	85/15	72
6	**5b**	**21**	0 °C	4 d	64	95/5	77
7	**5b**	**21**	−15 °C	4 d	75	86/14	82
8	**5a**	**20**	rt	7 d	nr[c]	—	—

[a] Conversion determined by ^1H NMR.
[b] Not determined.
[c] No reaction.

Table 3
Scope of the intramolecular Michael addition



5b, Ar =-*m*$(CF_3)_2$-Ph
5c, Ar = -Ph
5d, Ar = -2-pyridinyl
5e, Ar = -*p*NO_2-Ph

12b, Ar =-*m*$(CF_3)_2$-Ph
12c, Ar = -Ph
12d, Ar = -2-pyridinyl
12e, Ar = -*p*NO_2-Ph

Entry	Substrate	Time	Yield (%)	dr *anti*/*syn*	ee (%)
1	**5b**[a]	4 d	75	86/14	82
2	**5c**	4 d	24	93/7	71
3	**5d**	2 d	50	93/7	67
4	**5e**[b]	2.5 h	76	83/17	72

[a] Reaction carried out at −15 °C.
[b] Reaction with 30 mol % of **21**.

hypothesise that catalyst **20** or **21** could also activate adduct **5** by a hydrogen-bonding interaction between the hydroxyl group and the sulfone moiety. To evaluate this hypothesis, we performed the reaction with catalyst **22**, without a hydroxyl group, and catalyst **23**, with a methoxy substituent. In these cases, the reactions were very slow (Table 2, entries 3 and 4), and even after 9 or 30 days, the reaction was not completed and the cyclised product was obtained as a racemic mixture with catalyst **22**. These results indicate that the reaction is accelerated with catalysts bearing hydrogen bond donors, thus confirming that sulfones might be activated by a hydrogen bond interaction.

The generality of the present intramolecular Michael addition to various substituted sulfone was examined, and the results are summarised in Table 3.

Whatever might be the substituents on the sulfone, the diastereoselectivity and enantioselectivity are in the same range (83/17–93/7 dr and 67–82% *ee*). Moreover, the reaction is faster with nitrophenyl sulfone than with pyridyl sulfone.

3. Conclusion

In conclusion, we have disclosed the first organocatalytic intramolecular Michael addition of aldehydes bearing various vinyl sulfones in good yield and with good enantioselectivity and diastereoselectivity. In the intermolecular version, no reaction occured with mono vinyl phenylsulfone whereas in the intramolecular version, full conversion was observed. This reaction was promoted by readily available *trans*-4-hydroxyprolylamide **21**, and the catalytic reaction might involve an activation of the sulfone by a hydrogen-bonding interaction.

4. Experimental part

4.1. General methods

Solvents were dried by filtration over alumina previously activated at 350 °C during 12 h under nitrogen before use. Evolution of the reaction was followed with TLC (visualisation by UV $KMnO_4$ or PMA staining). Flash chromatography was performed using silica gel 32–63 μm, 60 Å. NMR spectra were recorded in $CDCl_3$ on Bruker AMX-300, -400 or -500 spectrometers. Chemical shift (δ) is given in ppm relative to residual deuterated solvent. Coupling constants are reported in hertz. Enantiomeric excesses were determined by chiral-SFC measurement on a Berger SFC with the stated column. Gradient programs are described as follows: initial methanol concentration (%)—initial time (min)—percent gradient of methanol (%/min)—final methanol concentration (%)—retention times R_T are given in minutes.

Sulfones **11a**,[16] **11b**[17] and **11c**[18] were prepared according to the reported procedures.

4.1.1. Diethylphosphorylmethyl 4-(nitro)phenyl sulfone 11d

To a room temperature solution of NaH (192 mg, 60% in mineral oil, 4.8 mmol) in CH_3CN under argon atmosphere, 4-nitrobenzenethiol (775 mg, 4 mmol) was added dropwise. After 20 min, the iodomethylphophonate (1.22 g, 4.4 mmol) was added and the mixture was stirred at room temperature for a day. After quenching the reaction with water (30 mL), the mixture was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford the corresponding sulfane **10d** which was used directly in the next step.

To a stirred solution of sulfane **10d** (950 mg, 2.82 mmol) in a 1/1 mixture MeOH/H_2O (40 mL) was slowly added oxone (17.4 g, 28.2 mmol) and the corresponding mixture was stirred at room temperature for a day. Then, MeOH was evaporated, the residue was dissolved in CH_2Cl_2 (100 mL) and filtered through Celite. To the resulting solution water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was washed with a saturated solution of NaCl (3 × 100 mL) and dried over Na_2SO_4. Purification by flash column chromatography on silica gel gave sulfone (730 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J* = 9.0 Hz, 1H), 4.19 (m, 4H), 3.81 (d, *J* = 16.7 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 145.1, 130.2, 124.2, 63.7 (d, *J* = 6.4 Hz), 53.9 (d, *J* = 139.0 Hz), 16.3 (d, *J* = 6.4 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ = 10.5. MS (ESI): *m/z* = 338 $[M+H]^+$. HRMS (ESI): calcd $C_{11}H_{17}NO_7PS$ $[M+H]^+$ 338.0457, found 338.0459.

4.1.2. 3-(1,3-Dithian-2-yl)propan-1-ol (2a)

DIBAL-H (28 mL, 27.8 mmol) was added to a solution of γ-butyrolactone (1.8 mL, 23.2 mmol) in Et_2O (25 mL) at −78 °C. After 3 h MeOH (3 mL) was added to the solution followed by brine (2 mL). The solution was allowed to warm to room temperature, diluted with Et_2O and a gel appeared. The gel was filtered on a pad of Celite with Et_2O. Solvents were removed under reduced pressure. The crude product was diluted with Et_2O (100 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the lactol which was directly used in the next step.

To a solution of lactol (840 mg, 9.54 mmol) in $MeNO_2$ (80 mL), 1,3-propanedithiol (1.9 mL, 19 mmol) was added followed by $BF_3{\cdot}Et_2O$ (3.6 mL, 28.6 mmol) at 0 °C. The reaction was stirred for 1 h at this temperature and then water and Et_2O were added. The organic phase was separated and washed with brine and then dried over Na_2SO_4. The solvents were removed by vaccuo. Purification by flash column chromatography on silica gel (EtOAc/pentane 4:6) gave dithiane **2b** as a colourless oil (1.26 g, 64% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (t, *J* = 6.5 Hz, 1H), 3.65–3.68 (m, 2H), 2.80–2.91 (m, 4H), 2.08–2.14 (m, 1H), 1.76–1.88 (m, 5H), 1.40 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.0, 47.3, 31.9, 30.4, 29.7, 25.9. HRMS (ESI): calcd $C_7H_{14}OS_2$ $[M]^+$ 178.0486, found 178.0484. Spectroscopic data are in agreement with the literature.[15]

4.1.3. 5-(1,3-Dithian-2-yl)pentan-1-ol 2b

To a solution of ε-caprolactone (2.8 g, 24.25 mmol, 1 equiv) in dry CH_2Cl_2/THF (1:1) (150 mL) was added dropwise Dibal-H (25 mL, 1 M in hexane, 25 mmol, 1.03 equiv) at −78 °C and stirred for 15 min. The reaction mixture was then allowed to warm to room temperature, the reaction was quenched with Et_2O (100 mL) and H_2O (30 mL) and the reaction mixture was stirred

until it became a translucent white gel. The solution was further diluted with Et_2O (100 mL), and Celite was added and then stirred until the solution became clear. The resulting mixture was filtered and concentrated under reduced pressure. The crude product was diluted with Et_2O (100 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give lactol which was diluted in dry CH_2Cl_2 (100 mL) and used directly for the next step.

To a solution of lactol (2.81 mmol, 24.25 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was successively added 1,3-propanedithiol (2.86 g, 26.4 mmol, 1.1 equiv) and $BF_3{\cdot}Et_2O$ (4.5 mL, 36 mmol, 1.5 equiv) dropwise at 0 °C. After 1.5 h, the reaction was quenched with satd aq $NaHCO_3$ (200 mL). The biphasic mixture was stirred for 30 min. at room temperature and then extracted with CH_2Cl_2 (4×80 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc/c-Hex, 1:4) gave dithiane **2b** (2.32 g, 46% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.05 (t, J = 7.1 Hz, 1H), 3.64 (t, J = 6.6 Hz, 2H), 2.91–2.78 (m, 4H), 2.15–2.01 (m, 1H), 1.92–1.73 (m, 3H), 1.64–1.50 (m, 4H), 1.38–1.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.9, 60.6, 47.8, 35.6, 32.6, 30.7, 26.6, 26.2, 25.6. MS (EI): 206.

4.2. General procedure for the oxidation of the alcohol

To a solution of alcohol **2** (1 equiv, 11 mmol) in dry CH_2Cl_2 (22 mL) were successively added DMSO (10 equiv), freshly distilled triethylamine (10 equiv) and SO_3/pyridine (5 equiv) at room temperature. The resulting mixture was stirred 4 h at room temperature and then diluted with Et_2O (150 mL), and water was added (150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (c-Hex/EtOAc, 2:1) afforded aldehyde **3**.

4.2.1. 3-(1,3-Dithian-2-yl)ethanal 3a

The oxidation reaction was performed according to the general procedure with alcohol **2a** (7.07 mmol) to afford aldehyde **3a** (700 mg, 56%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1H), 4.03 (t, J = 7.1 Hz, 1H), 2.85–2.82 (m, 4H), 2.70 (dt, J = 7.1 and 1.0 Hz, 2H), 2.14–2.07 (m, 3H), 1.87–1.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 60.3, 46.1, 40.7, 29.8, 27.6, 25.7. HRMS (ESI): calcd $C_7H_{13}OS_2$ $[M+H]^+$ 177.0418, found 177.0402.

4.2.2. 5-(1,3-Dithian-2-yl)butanal 3b

The oxidation reaction was performed according to the general procedure with alcohol **2b** (11.3 mmol) to afford aldehyde **3b** (1.65 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1H), 4.06–4.02 (m, 1H), 2.91–2.79 (m, 4H), 2.47–2.43 (m, 2H), 2.15–2.08 (m, 1H), 1.90–1.80 (m, 3H), 1.74–1.52 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.5, 47.5, 43.8, 35.4, 30.7, 26.3, 26.2, 21.8. MS (EI): 204. HRMS (ESI): calcd $C_9H_{17}OS_2$ $[M+H]^+$ 205.0715, found 205.0717.

4.3. General procedure for the Horner–Wadsworth–Emmons reaction

To a solution of phosphonate **11** (1.4 equiv) in THF (30 mL) was added NaH (1.4 equiv) at 0 °C. After stirring for 0.5 h, this solution was added to aldehyde **3** (1 equiv) dissolved in THF (20 mL). Then, the ice bath was removed and the solution was stirred at room temperature until completion of the reaction. Then saturated NH_4Cl solution and Et_2O were added. The aqueous phase was extracted with Et_2O (3×50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated. Purification by flash column chromatography on silica gel (c-Hex/EtOAc, 8:2) afforded the alkene.

4.3.1. 2-[4-(3,5-Bis(trifluoromethyl)phenylsulfonyl)but-3-enyl]-[1,3]-dithiane 4a

The Wittig Horner reaction was performed according to the general procedure with phosphonate **11c** and aldehyde **3a** (1.23 mmol) to afford alkene **4a** (350 mg, 68%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 2H), 8.11 (s, 1H), 7.13 (dt, J = 6.8 Hz, 1H), 6.39 (d, J = 15.1 Hz, 1H), 3.99 (t, J = 6.9 Hz, 1H), 2.81–2.84 (m, 4H), 2.54 (q, J = 7.3 Hz, 2H), 2.08–2.15 (m, 1H), 1.93–199 (m, 2H), 1.81–1.99 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149, 143.7, 133.2 (q, J^2_{C-F} = 35 Hz,), 129.9, 128.2, 127.1, 122.5 (q, J^1_{C-F} = 274 Hz), 46.4, 33.1, 30.2, 28.8, 25.8, HRMS (ESI): calcd $C_{16}H_{17}F_6O_5S_3$ $[M+H]^+$ 451.0330, found 451.0289.

4.3.2. 2-[6-(3,5-Bis-trifluoromethyl-phenylsulfonyl)hex-5-enyl]-[1,3]dithiane 4b

The Wittig Horner reaction was performed according to the general procedure with phosphonate **11c** and aldehyde **3b** (1.23 mmol) to afford alkene **4b** (550 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (s, 2H), 8.11 (s, 1H), 7.14 (dt, J = 6.8 and 15.1 Hz, 1H), 6.36 (d, J = 15.1 Hz, 1H), 4.02 (t, J = 6.8 Hz, 1H), 2.85 (m, 4H), 2.33 (m, 2H), 2.12 (m, 1H), 1,74–1.87 (m, 3H), 1.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.2, 143.7, 133.2 (q, J^2_{C-F} = 34 Hz, 2C), 129.2, 128.1, 126.9, 122.4 (q, J^1_{C-F} = 273 Hz, 2C), 47.2, 35.0, 31.4, 30.5, 27.0, 25.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 62.8. MS (ESI) m/z: 479 $[M+H]^+$ HRMS (ESI): calcd $C_{18}H_{21}O_2F_6S_3$ $[M+H]^+$ 479.0602, found 479.0616.

4.3.3. 2-[6-(Phenylsulfonyl)hex-5-enyl]-[1,3]dithiane 4c

The Wittig Horner reaction was performed according to the general procedure with phosphonate **11a** and aldehyde **3b** (5.13 mmol) to afford alkene **4c** (1.5 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.91 (m, 2H), 7.68–7.31 (m, 3H), 7.07–7.04 (m, 1H), 6.39–6.34 (d, 1H, J = 20.1 Hz), 4.08–4.03 (m, 1H), 2.95–2.86 (m, 4H), 2.31–2.09 (m, 3H), 1.91–1.81 (m, 3H), 1.75–1.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =146.7, 139.9, 133.3, 130.6, 129.30, 127.6, 47.3, 35.0, 31.3, 30.5, 27.2, 26.0, 26.0. MS (EI): 342. HRMS (ESI): calcd $C_{16}H_{22}O_2S_3$ $[M+H]^+$ 343.0854, found 343.0867.

4.3.4. 2-[6-(Pyridine-2-sulfonyl)hex-5-enyl]-[1,3]dithiane 4d

The Wittig Horner reaction was performed according to the general procedure with phosphonate **11b** and aldehyde **3b** (522 mg, 2.56 mmol) to afford alkene **4d** (853 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (d, J = 4.6 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.94 (td, J = 1.7 and 7.8 Hz, 1H), 7.52 (m, 2H), 7.11 (dt, J = 6.7 and 15.2 Hz, 1H), 6.55 (d, J = 15.1 Hz, 1H), 4.02 (t, J = 6.9 Hz, 1H), 2.84 (m, 4H), 2.31 (m, 2H), 2.04–2.17 (m, 1H), 1,73–1.90 (m, 3H), 1.53 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5, 150.3, 149.7, 138.2, 127.9, 127.0, 121.9, 47.3, 35.1, 31.6, 30.5, 27.1, 26.0. MS (ESI): 344 $[M+H]^+$. HRMS (ESI): calcd $C_{15}H_{22}NO_2S_3$ $[M+H]^+$ 344.0807, found 344.0803.

4.3.5. 2-((*E*)-6-(4-Nitrophenylsulfonyl)hex-5-enyl)-1,3-dithiane 4e

The Wittig Horner reaction was performed according to the general procedure with phosphonate **11d** and aldehyde **3b** (1 mmol) to afford alkene **4e** (320 mg, 82%).[1]H NMR (300 MHz, $CDCl_3$): δ = 8.38 (d, J = 8.9 Hz, 2H), 8.07 (d, J = 8.9 Hz, 2H), 7.08 (dt, J = 6.9 and 15.1 Hz, 1H), 6.33 (d, J = 15.1 Hz, 1H), 4.00 (t, J = 6.7 Hz, 1H), 2.82 (m, 4H), 2.29 (m, 2H), 2.04–2.17 (m, 1H), 1,73–1.88 (m, 3H), 1.51 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5, 149.7, 146.5, 129.6, 129.0, 128.7, 124.5, 47.3, 35.0, 31.4,

30.5, 27.0, 25.9. MS (ESI): 388 $[M+H]^+$. HRMS (EI): calcd $C_{16}H_{21}NO_4S_3$ $[M]^+$ 387.0630, found 387.0633.

4.4. General procedure for the deprotection of the dithiane

A stirred mixture of dithiane **4** (1 equiv), MeI (10.3 equiv) and $CaCO_3$ (5.2 equiv) in $MeCN/H_2O$ (9:1) was heated to 45 °C for 3 h, cooled to room temperature and concentrated under reduced pressure. The residue was diluted in AcOEt and water. The organic phase was separated and the aqueous phase was extracted with AcOEt. Then, the organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (c-Hex/EtOAc, 8:2) afforded aldehyde **5**.

4.4.1. (*E*)-5-(3,5-Bis-(trifluoromethyl) phenylsulfonyl)pent-4-enal 5a

Deprotection of the dithiane **4a** (350 mg, 0.77 mmol, 1 equiv) was performed according to the general procedure to give aldehyde (190 mg, 68%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1H), 8.30 (s, 2H), 8.10 (s, 1H), 7.12 (dt, J = 15.0 and 6.6 Hz, 1H), 6.39 (dt, J = 15.0 and 1.4 Hz, 1H), 2.72 (t, J = 6.9 Hz, 2H), 2.61 (q, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 148.5, 143.6, 133.4 (q, J^2_{C-F} = 35 Hz, 2C), 130.2, 128.3, 127.3, 122.6 (q, J^1_{C-F} = 274 Hz, 2C), 41.3, 24.1.

4.4.2. (*E*)-7-(3,5-Bis-trifluoromethylphenylsulfonyl)hept-6-enal 5b

Deprotection of the dithiane **4b** (380 mg, 0.795 mmol, 1 equiv) was performed according to the general procedure to give the aldehyde (250 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (s, 1H), 8.33 (s, 2H), 8.12 (s, 1H), 7.15 (dt, J = 6.7 and 15.1 Hz, 1H), 6.37 (d, J = 15.1 Hz, 1H), 2.47 (t, J = 12.8 Hz, 2H), 2.35 (q, J = 6.6 Hz, 2H), 1.49–1.66 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.6, 149.8, 143.7, 133.2 (q, J^2_{C-F} = 35 Hz, 2C), 129.4, 128.0, 127.0, 122.4 (q, J^1_{C-F} = 274 Hz, 2C), 43.4, 31.5, 26.9, 21.3. MS (ESI) *m/z*: 389 $[M+H]^+$. HRMS (ESI): calcd $C_{15}H_{15}O_3F_6S_2$ $[M+H]^+$ 389.0646, found 389.0651.

4.4.3. (*E*)-7-(Phenylsulfonyl)hept-6-enal 5c

Deprotection of the dithiane **4c** (610 mg, 1.62 mmol, 1 equiv) was performed according to the general procedure to afford the aldehyde (400 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.78 (s, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.57–7.60 (m, 3H), 7.00 (m, 1H), 6.37 (d, J = 15.1 Hz, 1H), 2.48 (t, J = 7.0 Hz, 2H), 2.30 (q, J = 7.0 Hz, 2H), 1.67–1.53 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.8, 146.2, 140.6, 133.3, 130.9, 129.3, 127.8, 43.4, 31.2, 27.1, 21.4. MS (EI): 252. HRMS (ESI): calcd $C_{13}H_{16}O_3S$ $[M+H]^+$ 253.0892, found 253.0884.

4.4.4. (*E*)-7-(Pyridine-2-sulfonyl)hept-6-enal 5d

Deprotection of the dithiane **4d**(150 mg, 0.437 mmol, 1 equiv) was performed according to the general procedure to give the aldehyde (92 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 8.73 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.94 (dt, J = 1.7 and 7.8 Hz, 1H), 7.52 (dd, J = 4.7 and 7.6 Hz, 1H), 7.10 (dt, J = 6.7 and 15.2 Hz, 1H), 6.56 (d, J = 15.1 Hz, 1H), 2.46 (t, J = 6.9 Hz, 2H), 2.35 (q, J = 7.3 Hz, 2H), 1.51–1.71 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.9, 158.4, 150.3, 149.3, 138.2, 128.1, 127.1, 121.8, 43.5, 31.5, 27.0, 21.4. HRMS (ESI): calcd $C_{12}H_{16}O_3NS$ $[M+H]^+$ 254.085, found 254.0842.

4.4.5. (*E*)-7-(4-Nitro-phenylsulfonyl)hept-6-enal 5e

Deprotection of the dithiane **4e** (225 mg, 0.58 mmol, 1 equiv) was performed according to the general procedure to give the aldehyde (134 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.73 (s, 1H), 8.36 (d, J = 8.6 Hz, 2H), 8.06 (d, J = 8.6 Hz, 2H), 7.07 (dt, J = 6.7 and 15.1 Hz, 1H), 6.37 (d, J = 15.1 Hz, 1H), 2.46 (t, J = 6.8 Hz, 2H), 2.30 (q, J = 7.0 Hz, 2H), 1.47–1.67 (m, 2H), 1.60–1.67 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.8, 150.5, 149.2, 146.4, 129.6, 129.0, 124.5, 43.4, 31.4, 26.9, 21.3.

4.4.6. (*E*)-4-(Phenylsulfonyl)but-3-en-1-ol 6

DIBAL-H (28 mL, 27.8 mmol) was added to a solution of γ-butyrolactone (1.8 mL, 23.2 mmol) in Et_2O (25 mL) at −78 °C. After 3 h MeOH (3 mL) was added to the solution followed by brine (2 mL). The solution was allowed to warm to room temperature, diluted with Et_2O and a gel appeared. The gel was filtered on a pad of Celite with Et_2O. Solvents were removed under reduced pressure. The crude product was diluted with Et_2O (100 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the lactol which was directly used in the next step.

NaH (115 mg, 4.8 mmol) was washed with hexane (5 mL) and dissolved in THF (20 mL).Then phosphonate **11a** (1.4 g, 4.8 mmol) dissolved in THF (20 mL) was added to NaH at 0 °C. The solution was stirred for 30 min at room temperature and then added to the lactol (380 mg, 4.35 mmol) dissolved in THF (20 mL) at −40 °C. After 2 h 30 min at this temperature the reaction was quenched with a solution of NH_4Cl satd and extracted with Et_2O, washed with water and brine and then dried (Na_2SO_4). Purification by flash column chromatography on silica gel (Et_2O 100%) gave alcohol **6** (500 mg, 51% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.94 (m, 1H), 7.52–7.69 (m, 3H), 7.07 (dt, J = 15.1, 6.8 Hz, 1H), 6.39–6.44 (m, 1H), 3.71 (t, J = 6.2 Hz, 2H), 2.39–2.45 (m, 2H), 1.78 (q, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 140.9, 133.6, 131.1, 129.6, 127.9, 61.9, 30.7, 28.2. HRMS (ESI): calcd $[M+H]^+$ $C_{17}H_{14}OS_2$ 178.0486, found 178.0484.

4.4.7. (*E*)-5-(Phenylsulfonyl)pent-4-en-1-ol 7

To a solution of δ-valerolactone (0.93 mL, 9.99 mmol) in CH_2Cl_2 (30 mL) at −78 °C was slowly added DIBAL-H (12 mL, 12.00 mmol). After 1 h 30 min stirring at this temperature the reaction was quenched with MeOH (3 mL) and brine (3 mL). The cold bath was removed, the solution was diluted with EtOAc and then a gel appeared which was filtered and washed with EtOAc. The solvents were removed under reduced pressure .The crude product was diluted with EtOAc (100 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the lactol which was used directly in the next step.

NaH (142 mg, 5.92 mmol) was added to phosphonate **11a** (1.73 mg, 5.92 mmol) dissolved in THF (20 mL) at 0 °C. The solution was stirred for 30 min at this temperature. Then the solution was added to the lactol (550 mg, 5.39 mmol) dissolved in THF (15 mL) at 0 °C. The ice bath was removed and the solution was stirred for 3 h. The reaction was quenched with NH_4Cl sat (15 mL) and the reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). Purification by flash column chromatography on silica gel (Et_2O 100%) gave alcohol **7** (765 mg, 60% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.87 (m, 1 H), 7.64–7.67 (m, 1H), 7.50–7.60 (m, 1H), 7.04 (dt, J = 14.9 and 6.7 Hz, 1H), 6.32 (dt, J = 14.9 and 1.6 Hz, 1H), 3.61–3.64 (m, 2H), 2.26–2.28 (m, 2H), 1.54–1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 140.6, 133.4, 130.5, 129.3, 127.5, 62.2, 31.9, 31.2, 24.0. HRMS (ESI): calcd $C_{12}H_{17}O_3S$ $[M+H]^+$ 241.0892, found 241.0892.

4.4.8. (*E*)-4-(Phenylsulfonyl)but-3-enal 5f

The oxidation reaction was performed according to the general procedure with alcohol **6** (0.9 mmol.) to afford aldehyde **5f** (137 mg, 64%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.94 (m, 2H), 7.58–7.70 (m, 3H), 7.03 (dt, J = 15.2 and

6.7 Hz, 1H), 6.42 (dt, J = 15.2 and 1.5 Hz, 1H), 2.66–2.70 (m, 2H), 2.55–2.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 144.5, 140.4, 133.6, 131.7, 129.4, 127.7, 41.5, 23.8. HRMS (ESI): calcd $C_{11}H_{13}O_3S$ $[M+H]^+$ 225.0579, found 225.0570.

4.4.9. (*E*)-5-(Phenylsulfonyl)pent-4-enal 5g

The oxidation reaction was performed according to the general procedure with alcohol **7** (0.9 mmol.) to afford aldehyde **5g** (340 mg, 46%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 7.92–7.95 (m, 2H), 7.66–7.71 (m, 1H), 7.58–7.63 (m, 2H), 7.00 (dt, J = 6.7and 15.0 Hz, 1H), 6.40 (dt, J = 1.5 and 15.0 Hz, 1H), 2.54 (dt, J = 1.1 and 7.3 Hz, 2H), 2.31–2.37 (m, 2H), 1.85 (q, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 145.6, 140.5, 133.5, 131.4, 129.4, 127.7, 42.9, 30.6, 20.0. HRMS (ESI): calcd $C_{12}H_{15}O_3S$ $[M+H]^+$ 239.0736, found 239.0739.

4.5. General procedure for the intramolecular conjugate addition

To a solution of vinyl sulfone **5** (0.1 mmol) in solvent (2.5 mL) was added a catalyst (20 mol %) at rt. The evolution of the reaction was controlled by TLC until completion of the reaction. The organic solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography on silica gel (c-Hex/EtOAc, 8:2) to give cyclopentane **12**.

4.5.1. 2-Phenylsulfonylmethyl-cyclopentane carbaldehyde 12c

Intramolecular conjugate addition was performed according to the general procedure with sulfone **5c** (25 mg, 0.1 mmol) in dichloromethane with catalyst **20** (6.8 mg, 0.02 mmol) at room temperature for four days to afford compound **12c** (13 mg, 52%). The enantiomeric excess was determined by SFC (chiralcel OB column, 2 mL/min, 200 bar, MeOH 10%-2-1-25%, 30 °C), R_T: 4.26, 7.56. $[\alpha]_D^{20} = -5.5$ (c 0.3, 65% ee, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (d, 1H, J = 1.7 Hz), 7.92–7.90 (m, 2H), 7.66–7.51 (m, 3H), 3.25–3.10 (m, 2H), 2.74–2.63 (m, 2H), 2.12–2.05 (m, 1H), 1.92–1.86 (m, 2H), 1.78–1.70 (m, 1H), 1.69–1.52 (m, 1H), 1.48–1.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3, 139.6, 134.1, 129.6, 128.2, 60.7, 57.1, 34.4, 33.2, 26.6, 24.9. HRMS (ESI): calcd $C_{13}H_{16}O_3S$ $[M+H]^+$ 253.0892, found 253.0883.

4.5.2. 2-(3,5-Bis-Trifluoromethyl-phenylsulfonylmethyl)-cyclopentane carbaldehyde 12b

Intramolecular conjugate addition was performed according to the general procedure with sulfone **5b** (39 mg, 0.1 mmol) in dichloromethane with catalyst **21** (4 mg, 0.02 mmol) at −15 °C for four days to afford compound **12b** (30 mg, 75%). The enantiomeric excess was determined by SFC (chiralcel OD column, 2 mL/min, 200 bar, MeOH 1%-10-1-15%, 30 °C), R_T: 2.75, 3.08. $[\alpha]_D^{20} = +0.5$ (c 1.54, 82% ee, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.70 (s, 1H), 8.39 (s, 2H), 8.18 (s, 1H), 3.22 (m, 2H), 2.75 (m, 2H), 2.13 (m, 1H), 1.98 (m, 1H), 1.91 (m, 1H), 1.76 (m, 1H), 1.43–1.66 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.6, 142.2, 133.0 (q, J = 35 Hz), 128.7, 127.5, 122.0 (q, J = 274 Hz), 60.5, 56.7, 33.5, 33.1, 26.6, 24.6 ppm. MS (ESI): 389 $[M+H]^+$. HRMS (ESI): calcd $C_{15}H_{15}O_3F_6S_2$ $[M+H]^+$ 389.0646, found 389.0657.

4.5.3. 2-(Pyridine-2-sulfonylmethyl)cyclopentane carbaldehyde 12d

Intramolecular conjugate addition was performed according to the general procedure with sulfone **5d** (25 mg, 0.1 mmol) in dichloromethane with catalyst **21** (4 mg, 0.02 mmol) at room temperature for 2 days to afford compound **12d** (12 mg, 50%). The enantiomeric excess was determined by SFC (chiralcel OB column, 2 mL/min, 200 bar, MeOH 2%-10-1-15%, 30 °C), R_T: 10.01, 10.57. $[\alpha]_D^{25} = -10.3$ (c 0.57, 67% ee, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 8.75 (d, J = 4.1 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.56 (m, 1H), 3.51 (m, 2H), 2.73 (m, 2H), 2.09 (m, 1H), 1.88 (m, 2H), 1.72 (m, 1H), 1.42–1.61 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.1, 157.4, 150.3, 138.3, 127.5, 122.2, 56.8, 56.0, 34.0, 33.1, 26.4, 24.7 ppm. MS (ESI): 254 $[M+H]^+$. HRMS (ESI): calcd $C_{12}H_{16}O_3NS$ $[M+H]^+$254.085, found 254.0839.

4.5.4. 2-(4-Nitro-phenylsulfonylmethyl)-cyclopentane carbaldehyde 12e

Intramolecular conjugate addition was performed according to the general procedure with sulfone **5e** (26.2 mg, 0.088 mmol) in dichloromethane with catalyst **21**(5.2 mg, 0.03 mmol) at room temperature during 2.5 h to afford compound **12e** (20 mg, 76%). The enantiomeric excess was determined by SFC (chiralcel OB column, 2 mL/min, 200 bar, MeOH 10%-2-1-25%, 30 °C), R_T: 9.41, 12.41. $[\alpha]_D^{25} = -0.7$ (c 0.74, 72% ee, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 8.44 (d, J = 8.6 Hz, 2H), 8.13 (d, J = 8.6 Hz, 2H), 3.14–3.33 (m, 2H), 2.63–2.76 (m, 2H), 2.14 (m, 1H), 1.61–1.93 (m, 3H), 1.40–1.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.8, 151.0, 144.9, 129.7, 124.6, 60.4, 56.8, 33.7, 33.1, 26.6, 24.6. HRMS (ESI): calcd $C_{13}H_{15}O_5NSNa$ $[M+Na]^+$ 320.0568, found 320.0577.

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