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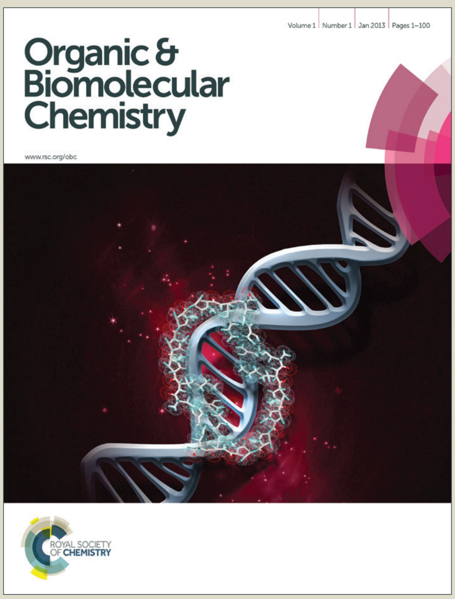

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PAPER

Squaramide-catalysed asymmetric cascade aza-Michael/Michael addition reaction for synthesis of chiral trisubstituted pyrrolidines†

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A bifunctional squaramide catalysed aza-Michael/Michael cascade reaction between nitroalkenes and tosylaminomethyl enones or enoates has been developed. This organocatalytic cascade reaction provides easy access to highly functionalized chiral pyrrolidines with a broad substrate scope, furnishing the desired products in good yields (up to 99%) with good diastereoselectivities (up to 91:9 dr) and excellent enantioselectivities (up to >99% ee) under mild conditions. This protocol provides a straightforward entry to highly functionalized chiral trisubstituted prrolidine derivatives from simple starting materials.

Introduction

The optically active pyrrolidines are widely observed in structural components of numerous naturally occurring alkaloids and biologically active synthetic substances,[1] are increasingly present in pharmaceutical agents,[2] and recently has become ubiquitous in catalysis, finding use as organocatalysts as well as ligands for a broad range of metal-mediated enantioselective protocols.[3] Not surprisingly, the ''privileged'' chiral heterocyclic framework has been widely investigated for new reaction invention.[4] Among these, the strategy of efficient catalytic asymmetric [3+2] cycloaddition reactions,[5] such as the reaction of imino esters with nitroalkenes (scheme 1)[6] that is particularly important in the construction of functionalized pyrrolidinerings, provide a very elegant solution to access stereochemically complex variants. However, the reported direct asymmetric cycloaddition methods mostly rely on chiral auxiliary controlled asymmetric synthesis and transition-metal-catalysed asymmetric dipolar addition reactions.[5,7] In contrast, the methods employing organocatalysed asymmetric processes for the efficient preparation of chiral pyrrolidines are still limited.[8] Recently, we sought to develop a new strategy for the construction of highly functionalized pyrrolidine rings. To the best of our knowledge, the asymmetric synthesis of chiral pyrrolidines via squaramide-catalysed aza-Michael/Michael cascade reactions has rarely been observed. Herein we describe the successful execution of the ideal and demonstrate a simple yet powerful pyrrolidine forming reaction.

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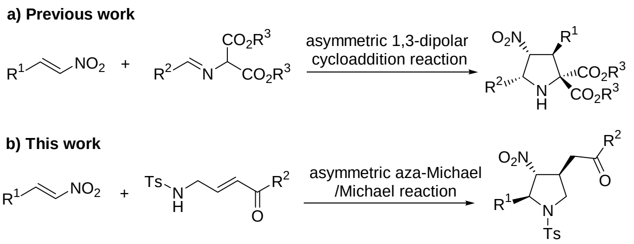
†Electronic Supplementary Information (ESI) available: [Copies of ^{1}H and ^{13}C NMR spectra of new compounds, and HPLC chromatograms]. See DOI: 10.1039/c1ob000000x/

In recent years, organocatalytic cascade or domino reactions have attracted considerable attention, and great progress has been made. Moreover, organocatalysed hetero-Michael cascade reactions, for example aza-Michael,[9] oxa-Michael,[10] and sulfa-Michael cascade reactions,[11] are considered to be highly efficient and facile methods for generating chiral functionalized heterocyclic molecules. As hydrogen-bonding organocatalysts, squaramides[12] have also been successfully used in the organocatalytic cascade reactions.[13] Recently, our laboratory has introduced a mode of [4 + 2] cyclization to generate functionalized tetrahydroquinolines with squaramide catalysts that can enabled the direct cyclization reaction of aromatic 2-aminoenones with nitroalkenes employing one asymmetric cascade aza-Michael/Michael addition strategy.[14] We envisioned this cascade aza-Michael/Michael addition strategy might be employed to design a formal [3 + 2] cyclization for stereoselectively building chiral pyrrolidine rings. So we try to synthesize a series of tandem reaction reagents, alphatic aminomethyl enones or enoates, and design new methods for the synthesis of chiral pyrrolidines. With the aim of expanding our previous studies on the enantioselective synthesis of biologically important molecules, we would like to document an efficient squaramide-catalysed asymmetric cascade aza-Michael/Michael addition reaction for the synthesis of chiral pyrrolidines. As outlined in scheme 1, this one-pot transformation can produce a complex molecular architecture formed with three contiguous stereocenters, which experiences a different process compared with the previously reported work about the synthesis of chiral pyrrolidines.



Scheme1. Preparation of highly functionalized chiral pyrrolidines.

Results and discussion

At the outset of our investigation, a series of organocatalysts (Figure 1) were evaluated in the model reaction of nitrostyrene **1a** and *N*-tosyl aminomethyl enone **2a**. In the presence of quinine-derived squaramide **I** (5 mol%), the reaction provided the desired chiral pyrrolidine **3aa** in 65% yield in CH_2Cl_2 (1.0 mL) at room temprature for 72 h, and with 83:17 dr and 99% ee (Table 1, entry 1) according to the chiral HPLC analysis of the crude product. Encouraged by this important result, we evaluated a small library of organocatalysts for this cascade reaction. Squaramide **II** derived from quinine bearing 4-CF_3 group on the aromatic ring gave a little lower diastereoselectivity and eanantioselectivity (Table 1, entry 2). Squaramide **III** derived from quinine bearing 4-NO_2 group on the aromatic ring afforded the desired adduct with similar eanantioselectivity, but with lower diastereoselectivity (Table 1, entry 3).

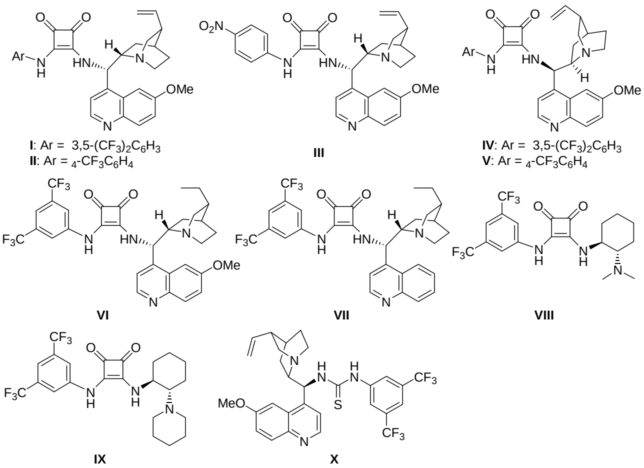
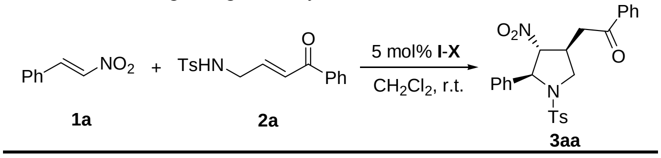


Figure 1. Squaramide and thiourea organocatalysts used in this study.

Squaramides **IV** and **V** derived from quinidine afforded the desired adducts with similar results, but with opposite configuration (Table 1, entries 4 and 5). To our surprise, we noted that a significantly improvement in yield was observed when squaramide **VI** derived from hydroquinine was used (Table 1, entry 6). Squaramides **VII** derived from hydrocinchonidine derivative (Table 1, entry 7) was also evaluated, but no improvements were observed relative to the squaramide **VI**. We then turned our attention to these squaramides **VIII** and **IX** derived from chiral 1,2-diaminocyclohexane (Table 1, entries 8 and 9), but inferior results were observed. For comparison with the used squaramides, the corresponding quinine-derived thiourea **X** was also screened (Table1, entry 10). Unfortunately, a decrease in terms of diastereoselectivity was obtained. At last, we choose hydroquinine-derived squaramide **VI** as the optimal catalyst.

Table 1. Screening of organocatalysts.[a]

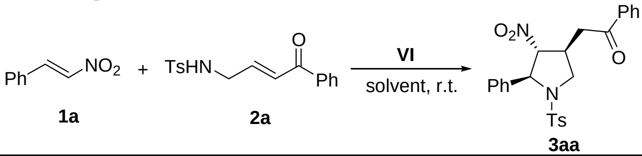


Entry	Catalyst	Yield[b] (%)	*dr*[c]	ee[c] (%)
1	**I**	65	83:17	99
2	**II**	56	82:18	98
3	**III**	69	79:21	99
4	**IV**	66	82:18	–99
5	**V**	63	77:23	–99
6	**VI**	75	84:16	99
7	**VII**	71	84:16	97
8	**VIII**	70	76:24	99
9	**IX**	63	76:24	88
10	**X**	66	76:24	99

[a] Reaction conditions: a mixture of **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (5 mol%) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 72 h. [b]Isolated yield. [c] Determined by chiral HPLC analysis.

Further optimization was carried out using squaramide **VI** as the catalyst. We investigated the effect of solvent, catalyst loading, temperature and the influence of the ratio of two reactants for the optimal reaction conditions. The results are shown in Table 2. The screening of different reaction solvents with 5 mol% catalyst **VI** show that CH_2Cl_2 is the optimal solvent (Table 2, entry 1–7). Then, other parameters such as reaction temperature and catalyst loading were further evaluated. When the model reaction was performed at higher temperature, the yield, enantioselectivity and diastereoselectivity were reduced (Table 2, entry 8). When increasing the catalyst loading, the enantioselectivity or diastereoselectivity of the product **3aa** cannot be further improved (Table 2, entries 9 and 10). When the mol ratio of β-nitrostyrene to *N*-tosyl aminomethyl enone **2a** was increased to 3:1, the product yield was increased to 85% (Table 2, entry 11). After the above reaction condition evaluation, we confirmed that the optimum reaction conditions called for the use of CH_2Cl_2 as solvent and a 10 mol% catalyst loading at room temperature with a 3:1 mol ratio of β-nitrostyrene to *N*-tosyl aminomethyl enone **2a**.

Table 2. Optimization of reaction conditions.[a]



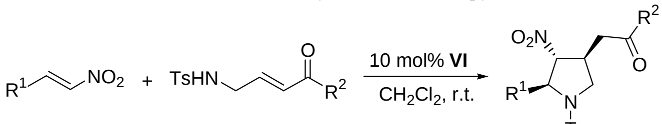
Entry	Solvent	Loading (mol%)	Yield[b](%)	dr[c]	ee[c] (%)
1	CH_2Cl_2	5	75	84:16	99
2	$CHCl_3$	5	72	79:21	98
3	$ClCH_2CH_2Cl$	5	73	83:17	98

4	PhMe	5	62	81:19	96
5	xylene	5	51	82:18	96
6	THF	5	36	78:22	97
7	MeCN	5	22	62:38	99
8[d]	CH_2Cl_2	5	62	81:19	96
9	CH_2Cl_2	10	77	83:17	98
10	CH_2Cl_2	20	76	84:16	96
11[e]	CH_2Cl_2	10	85	84:16	99

[a] Reaction conditions: a mixture of **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst **VI** in 1.0 mL solvent was stirred at room temperature for 72 h. [b]Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was performed at 40 °C for 48 h. [e] 0.6 mmol **1a** was used.

With the optimized conditions in hand, we next examined the scope of the asymmetric cascade reaction for the synthesis of highly functionalized chiral trisubstituted pyrrolidines. As shown in Table 3, a range of electron-poor (entries 2, 3 and 4, 72−84% yield, 81:19−85:15 dr, 97−99% ee) and electron-rich (entries 5 and 6, 43−82% yield, 73:27−85:15 dr, 98−99% ee) substituents were appended to the benzene ring of the β-nitrostyrene. The results show that the electronic nature of the substituents on the aromatic rings have little influence on the cascade process. However, the position of the substituent on the aromatic ring of β-nitrostyrene has an evident effect on enantioselectivity.

Table 3. Scope of asymmetric cascade aza-Michael/Michael addition for synthesis of chiral pyrrolidines.[a]



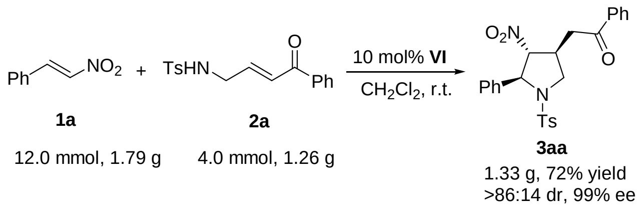
1a-f **2a-i** **3aa-an**

Entry	R^1	R^2	Product	Yield[b] (%)	dr[c]	ee[c] (%)
1	Ph	Ph	**3aa**	85	84:16	99
2	4-ClC_6H_4	Ph	**3ba**	79	85:15	98
3	3-BrC_6H_4	Ph	**3ca**	72	81:19	97
4	4-BrC_6H_4	Ph	**3da**	84	85:15	99
5	2-MeC_6H_4	Ph	**3ea**	43	73:27	98
6	4-MeC_6H_4	Ph	**3fa**	82	85:15	>99
7	2-furyl	Ph	**3ga**	79	80:20	97
8	2-thienyl	Ph	**3ha**	81	79:21	>99
9	phenylethyl	Ph	**3ia**	72	80:20	79
10	cyclohexyl	Ph	**3ja**	47	88:12	95
11	Ph	4-FC_6H_4	**3ab**	69	88:12	>99
12	Ph	4-ClC_6H_4	**3ac**	80	88:12	>99
13	Ph	4-BrC_6H_4	**3ad**	82	89:11	97
14	Ph	4-MeC_6H_4	**3ae**	85	86:14	98
15	Ph	3-$MeOC_6H_4$	**3af**	83	85:15	98
16	Ph	4-$MeOC_6H_4$	**3ag**	84	86:14	99
17	Ph	2-naphthyl	**3ah**	83	86:14	98
18	4-BrC_6H_4	4-BrC_6H_4	**3dd**	82	86:14	98
19[d]	Ph	Me	**3ai**	99	91:9	77
20[d]	Ph	OEt	**3aj**	99	53:47	92/56
21[e]	Ph	OEt	**3aj**	99	55:45	84/56
22[d]	Ph	O*t*Bu	**3ak**	99	57:43	74/80

[a] Reaction conditions: a mixture of **1** (0.6 mmol), **2** (0.2 mmol), catalyst **VI** (10 mol%) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 60–96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was performed for 30 h. [e] The reaction was performed with catalyst **X** (10 mol%) in PhMe (1.0 mL) at room temperature for 30 h.

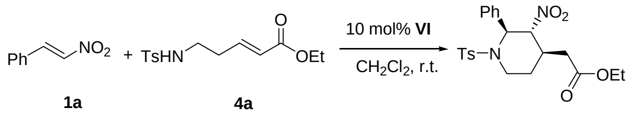
As shown in entry 5, the diastereoselectivity and yield were both reduced when the *o*-methylnitrostyrene reacted with *N*-tosyl aminomethyl enone **2a**, but the enantioselectivity can be maintained. Additionally, heterocyclic substrates were also amenable to this cascade reaction and afforded the corresponding products with comparable enantioselectivity and yields, but in lower diastereoselectivity (entries 7 and 8, 79–81% yield, 79:21–80:20 dr, 97–99% ee). There was a significant decline in diastereo- and enantioselectivity when phenylethyl substituted β-nitrostyrene was used as the reactant (entry 9, 72% yield, 80:20 dr, 79% ee). Moreover, the diastereo- and enantioselectivity are maintained for the less reactive cyclohexyl substituted β-nitrostyrene with large steric hindrance (entry 10, 47% yield, 88:12 dr, 95% ee), but with diminished yield. Then, a variety of tosylaminomethyl enones or enoates **2** were tested. Among them, **2b–g** with different substituents on the aromatic ring (entries 11–16, 69–85% yield, 86:14–89:11 dr, 97–99% ee), whatever electron-withdrawing and electron-donating substituents and the position of the substituents in the benzene ring, all can react smoothly with β-nitrostyrene **1a** to afford the corresponding products **3ab–3ag** in good diastereoselectivities and yields with excellent enantioselectivities. Two reactions that 2-naphthyl substituted enone **2h** reacted with β-nitrostyrene **1a** (entry 17, 83% yield, 86:14 dr, 98% ee) and 4-bromo substituted *N*-tosylaminomethyl enone **2d** reacted with 4-bromo substituted β-nitrostyrene **1d** (entry 18, 82% yield, 86:14 dr, 98% ee) were also evaluated, the results both are satisfactory. The alkyl enone **2i** (entry 19, 99% yield, 91:9 dr, 77% ee) dramatically increases the product yield as compared to aryl enone, which may be due to smaller sterically hinderance that was advantageous to the nucleophilic addition of nitroalkane to enone. In addition, we also examined two 4-tosylamino but-2-enoates **2j** and **2k** (entries 20 and 22, 99% yield, 53:47, 57:43 dr, 92/56, 74/80% ee). These substrates exhibited much higher reactivity and provided the corresponding products in excellent yields and good enantioselectivities, but with drastically diminished diastereoselectivities. In order to determine the absolute configurations of products **3**, entry 21 (99% yield, 55:45 dr, 84/56% ee) was performed with the optimal reaction conditions reported in the literature.[15] Compared with the reported data, the product **3aj** has the same NMR data. The absolute configuration of the major isomer of **3aj** was thus determined to be (3'*S*, 4*R*, 5'*S*) according to optical rotation comparision with literature, and the absolute configurations of other products **3** were assigned by analogy to major isomer of **3aj**.

To demonstrate the synthetic potential of this asymmetric cascade methodology, a gram-scale synthesis of **3aa** was performed (Scheme 2). The reaction proceeded smoothly affording the corresponding product in moderate yield and with higher diastereoselectivity and comparable enantioselectivity than 0.2 mmol-scale reaction.



Scheme 2. The gram-scale preparation of **3aa**.

Because the 4-tosylamino but-2-enoates exhibited so high reactivity, we qustioned if we can develop a aza-Michael/Michael cascade strategy to synthesize highly functionalized chiral piperidines. 5-tosylamino pent-2-enoates **4a** was synthesized and reacted with β-nitrostyrene **1a** under our optimal reaction conditions (Scheme 3). Unfortunately, the reaction did not take place as judged by TLC analysis.



Scheme 3. An attempt of asymmetric cascade aza-Michael/Michael addition for synthesis of chiral piperidine.

Conclusions

In summary, we have developed an efficient highly asymmetric cascade aza-Michael/Michael reaction catalysed by a chiral bifunctional tertiary amine-squaramide catalyst for the synthesis of chiral pyrrolidines. The reaction proceeds in good isolated yield and diastereoselectivity with excellent enantiocontrol. Salient features of the present protocol include a wide substrates range (diverse nitroalkenes, tosylaminomethyl enones and enoates), simple starting materials and amenability to gram-scale synthesis. Further investigations involving the application of this catalytic approach and catalysts are currently underway in our group and will be reported in due course.

Experimental

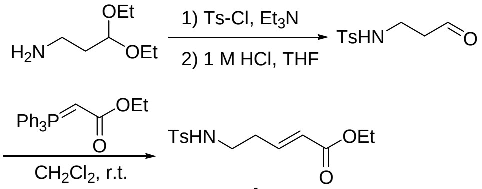
General Methods

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was performed with silica gel (200–300 mesh). Melting points were determined with an XT–4 melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with a Bruker Avance 400 MHz spectrometer. Chemical shifts were reported in δ (ppm) units relative to tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were measured at 100 MHz; chemical shifts were reported in ppm relative to TMS with the solvent resonance as internal standard. Infrared spectra were obtained with a Bruker ALPHA-P spectrometer or a Perkin Elmer Spectrum One spectrometer. High resolution mass spectra (Electron spray ionization) were measured with a Bruker APEX IV Fourier-Transform mass spectrometer. Enantiomeric excesses were determined by chiral HPLC analysis using an Agilent 1200 LC instrument with a Daicel Chiralpak IB or AD-H column.

Materials

Chiral squaramide catalysts **I**, **II**, **IV**, **V**, **VII**, **VIII** and **IX**,[16] **III**,[17] **VI**,[18] and chiral thiourea catalyst **X**,[19] nitroalkenes,[20] tosylaminomethyl enones and enoates[21] were prepared according to the reported procedures.

Synthesis of (*E*)-Ethyl 5-(4-methylphenylsulfonamido)pent-2-enoate (4a)



4a

To a solution of 1-amino-3,3-diethoxyaminopropane (7.36 g, 50.0 mmol) in CH_2Cl_2 (200 mL) was added Et_3N (8.30 mL, 60.0 mmo). The solution was cooled to 0 °C and *p*-toluenesulfonyl chloride (10.5 g, 55.0 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was added over 30 min. The resulting mixture was allowed to warm to room temperature and treated with saturated aqueous NH_4Cl solution. The layers were separated, the organic layer was extracted with CH_2Cl_2, dried over sodium sulfate, and concentrated to a yellow oil. The crude sulfonamide was dissolved in THF (100 mL), treated with 1 M HCl (50 mL), and stirred at room temperature about 3 h. Upon complete consumption of the acetal as judged by TLC analysis (petroleum ether/EtOAc 1:1), EtOAc (100 mL) was added and the layers were separated. The organic layer was washed (H_2O, brine), dried over Na_2SO_4 and concentrated. Purification by column chromatography (petroleum ether/EtOAc 3:1 to 2:1) gave the tosylamino propaldehyde as a pale yellow solid (10.5 g, 77%). Wittig reagent (5 mmol, 1 equiv) was added to a solution of tosylamino propaldehyde (5 mmol, 1 equiv) in CH_2Cl_2 (30 mL) in round bottom flask. The solution was stirred at room temperature for 30 h. After concentration under reduced pressure, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 3:1) to afford **4a** (1.37 g, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.4 Hz, 2H, ArH), 7.22 (d, J = 8.4 Hz, 2H, ArH), 6.71 (dt, J_1 = 15.6 Hz, J_2 = 7.2Hz, 1H, =CH), 5.71 (d, J = 15.6 Hz, 1H, =CH), 5.24 (t, J = 6.2 Hz, 1H, NH), 4.07 (q, J = 7.2 Hz, 2H, CH_2), 2.98 (q, J = 6.8 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.29 (q, J = 6.8 Hz, 2H, CH_2), 1.18 (t, J = 7.0 Hz, 3H, CH_3) ppm.

General procedure for asymmetric aza-Michael/Michael cascade reactions

To a dried small bottle were added **2** (0.2 mmol), catalyst **I** (12.6 mg, 0.02 mmol, 10 mol %) in CH_2Cl_2 (1.0 mL). The mixture was stirred at room temperature for 15 min, and **1** (0.6 mmol) was then added. After stirring at room temperature for 60–96 h, the reaction mixture was concentrated and directly purified by silica gel column chromatography to afford the desired product **3**.

2-((3*S*,4*R*,5*S*)-4-Nitro-5-phenyl-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3aa). The title compound **3aa** was obtained according to the general procedure as a colorless solid (78.6 mg, 85% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 65:35, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 14.4 min, t_{minor} = 16.9 min; minor diastereomer: t_R = 20.3, 33.3 min; 84:16 dr, 99% ee. M.p. 33–35 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.71 (m, 4H, ArH), 7.57 (t, J = 7.2 Hz, 1H, ArH), 7.45–7.32 (m, 9H, ArH), 5.33 (d, J = 4.8 Hz, 1H, CH), 4.78 (t, J = 5.4 Hz, 1H, CH), 4.18 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.46 (dd, J_1 = 11.6 Hz, J_2 = 6.8 Hz, 1H, CH_2), 3.21 (dd, J_1 = 21.0 Hz, J_2 = 8.6 Hz, 1H, CH_2), 3.09–2.97 (m, 2H, CH_2 + CH), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 144.3, 138.7, 135.8, 133.72, 133.66, 129.9, 129.0, 128.7, 128.4, 127.8, 127.7, 126.2, 96.2, 66.9, 53.2, 39.5, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 3063, 3031, 2962, 2923, 1721, 1683, 1597, 1550, 1494, 1449, 1411, 1349, 1305, 1213, 1159, 1090, 1028, 1000, 910, 813, 729, 689, 664, 604, 585, 544 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{25}N_2O_5S$ [M + H]$^+$ 465.14787, found 465.14673.

2-((3*S*,4*R*,5*S*)-5-(4-Chlorophenyl)-4-nitro-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3ba). The title compound **3ba** was obtained according to the general procedure as a colorless solid (78.4 mg, 79% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 14.2 min, t_{minor} = 18.8 min; minor diastereomer: t_R = 28.2, 51.3 min; 85:15 dr, 98% ee. M.p. 51–53 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 2H, ArH), 7.70 (d, J = 8.4 Hz, 2H, ArH), 7.59–7.55 (m, 1H, ArH), 7.43 (t, J = 7.8 Hz, 2H, ArH), 7.37–7.31 (m, 6H, ArH), 5.24 (d, J = 5.2 Hz, 1H, CH), 4.75 (dd, J_1 = 6.8 Hz, J_2 = 5.2 Hz, 1H, CH), 4.16 (dd, J_1 = 11.4 Hz, J_2 = 7.4 Hz, 1H, CH_2), 3.45 (dd, J_1 = 11.6 Hz, J_2 = 7.6 Hz, 1H, CH_2), 3.21 (dd, J_1 = 17.8 Hz, J_2 = 5.0 Hz, 1H, CH_2), 3.11–2.96 (m, 2H, CH + CH_2), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 144.5, 137.2, 135.8, 134.4, 133.8, 133.4, 130.0, 129.2, 128.8, 127.8, 127.7, 95.8, 66.3, 53.1, 39.4, 39.2, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1682, 1597, 1552, 1491, 1411, 1348, 1305, 1213, 1159, 1089, 1034, 1012, 999, 907, 837, 812, 751, 688, 665, 585, 574, 545 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{24}ClN_2O_5S$ [M + H]$^+$ 499.10890, found 499.10849.

2-((3*S*,4*R*,5*S*)-5-(3-Bromophenyl)-4-nitro-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3ca). The title compound **3ca** was obtained according to the general procedure as a yellow oil (77.8 mg, 72% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 10.9 min, t_{minor} = 13.6 min; minor diastereomer: t_R = 12.4, 16.8, 19.8 min; 81:19 dr, 97% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 2H, ArH), 7.60 (d, J = 8.0 Hz, 2H, ArH), 7.47 (t, J = 7.2 Hz, 1H, ArH), 7.43 (s, 1H, ArH), 7.35–7.32 (m, 3H, ArH), 7.26–7.22 (m, 3H, ArH), 7.16–7.10 (m, 1H, ArH), 5.19 (d, J = 5.2 Hz, 1H, CH), 4.68 (t, J = 6.2 Hz, 1H, ArH), 4.12 (dd, J_1 = 11.6 Hz, J_2 = 7.6 Hz, 1H, CH_2), 3.34 (dd, J_1 = 11.2 Hz, J_2 = 8.0 Hz, 1H, CH_2), 3.14 (dd, J_1 = 17.6 Hz, J_2 = 4.8 Hz, 1H, CH_2), 3.03–2.88 (m, 2H, CH + CH_2), 2.35 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 144.5, 140.9, 135.7, 133.7, 133.5, 131.6, 130.5, 129.9, 129.2, 128.7, 127.8, 127.6, 125.1, 95.7, 66.1, 53.0, 39.5, 39.5, 21.5 ppm; IR (ATR): $\tilde{\nu}$ 1682, 1596, 1551, 1474, 1348, 1305, 1261, 1212, 1158, 1089, 1073, 1015, 997, 884, 811, 787, 752, 688, 665, 578, 544 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{24}BrN_2O_5S$ [M + H]$^+$ 543.05838, found 543.05829.

2-((3*S*,4*R*,5*S*)-5-(4-Bromophenyl)-4-nitro-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3da). The title compound **3da** was obtained according to the general procedure as a yellow solid (90.8 mg, 84% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 14.6 min, t_{minor} = 21.5 min;

minor diastereomer: t_R = 32.0, 56.1 min; 85:15 dr, 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.2 Hz, 2H, ArH), 7.69 (d, J = 8.4 Hz, 2H, ArH), 7.57 (t, J = 7.4 Hz, 1H, ArH), 7.48–7.41 (m, 4H, ArH), 7.34 (d, J = 8.0 Hz, 2H, ArH), 7.29 (d, J = 8.4 Hz, 2H, ArH), 5.22 (d, J = 5.2 Hz, 1H, CH), 4.75 (dd, J_1 = 6.8 Hz, J_2 = 5.6 Hz, 1H, CH), 4.16 (dd, J_1 = 11.4 Hz, J_2 = 7.4 Hz, 1H, CH_2), 3.44 (dd, J_1 = 11.6 Hz, J_2 = 7.6 Hz, 1H, CH_2), 3.21 (dd, J_1 = 17.6 Hz, J_2 = 4.8 Hz, 1H, CH_2), 3.11–2.96 (m, 2H, CH + CH_2), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 144.5, 137.7, 135.7, 133.8, 133.4, 132.1, 130.0, 128.7, 128.0, 127.8, 127.7, 122.5, 95.7, 66.3, 53.0, 39.4, 39.2, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 2960, 2899, 1682, 1596, 1551, 1487, 1410, 1348, 1304, 1264, 1212, 1159, 1089, 1072, 1033, 1009, 907, 855, 834, 811, 751, 688, 665, 586, 573, 544 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{25}H_{24}BrN_2O_5S$ [M + H]$^+$ 543.05838, found 543.05747.

2-((3*S*,4*R*,5*S*)-4-Nitro-5-(*o*-tolyl)-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3ea). The title compound **3ea** was obtained according to the general procedure as a yellow oil (41.2 mg, 43% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: $t_{majo\ r}$= 10.0 min, t_{minor} = 12.8 min; minor diastereomer: t_R = 14.2, 36.4 min; 73:27 dr, 98% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.6 Hz, 2H, ArH), 7.60 (d, J = 8.4 Hz, 2H, ArH), 7.47 (t, J = 7.4 Hz, 1H, ArH), 7.40–7.31 (m, 3H, ArH), 7.24 (d, J = 8.0 Hz, 2H, ArH), 7.17–7.06 (m, 3H, ArH), 5.45 (d, J = 4.4 Hz, 1H, CH), 4.66 (t, J = 5.0 Hz, 1H, CH), 4.09 (dd, J_1 = 11.0 Hz, J_2 = 7.4 Hz, 1H, CH_2), 3.47 (dd, J_1 = 11.0 Hz, J_2 = 6.2 Hz, 1H, CH_2), 3.28–2.89 (m, 3H, CH + CH_2), 2.35 (s, 3H, CH_3), 2.25 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 144.1, 136.9, 135.8, 135.1, 133.7, 131.1, 129.7, 128.7, 128.3, 127.8, 127.6, 126.5, 95.4, 64.3, 53.2, 40.0, 39.7, 21.5, 19.2 ppm; IR (ATR): $\tilde{\nu}$ 1683, 1597, 1550, 1449, 1349, 1305, 1262, 1211, 1159, 1090, 1000, 909, 813, 755, 731, 688, 664, 586, 546 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{26}H_{27}N_2O_5S$ [M + H]$^+$ 479.16352, found 479.16224.

2-((3*S*,4*R*,5*S*)-4-Nitro-5-(*p*-tolyl)-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3fa). The title compound **3fa** was obtained according to the general procedure as a colorless solid (88.7 mg, 82% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 14.1 min; minor diastereomer: t_R = 19.0, 61.0 min; 85:15 dr, >99% ee. M.p. 43–45°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 2H, ArH), 7.71 (d, J = 8.0 Hz, 2H, ArH), 7.56 (t, J = 7.0 Hz, 1H, ArH), 7.42 (t, J = 7.6 Hz, 2H, ArH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 7.30 (d, J = 7.6 Hz, 2H, ArH), 7.16 (d, J = 7.6 Hz, 2H, ArH), 5.24 (d, J = 5.2 Hz, 1H, CH), 4.76 (t, J = 5.6 Hz,1H, CH), 4.15 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.45 (dd, J_1 = 11.2 Hz, J_2 = 6.8 Hz, 1H, CH_2), 3.22–2.96 (m, 3H, CH + CH_2), 2.44 (s, 3H, CH_3), 2.34 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 144.3, 138.3, 135.8, 135.7, 133.7, 133.6, 129.9, 129.6, 128.7, 127.9, 127.7, 126.1, 96.3, 66.9, 53.2, 39.6, 39.4, 21.6, 21.1 ppm; IR (ATR): $\tilde{\nu}$ 2920, 1682, 1597, 1551, 1514, 1411, 1348, 1305, 1271, 1212, 1159, 1090, 1034, 999, 908, 832, 811, 752, 706, 689, 664, 581, 542 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{26}H_{27}N_2O_5S$ [M + H]$^+$ 479.16352, found 479.16287.

2-((3*S*,4*R*,5*R*)-5-(Furan-2-yl)-4-nitro-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3ga). The title compound **3ga** was obtained according to the general procedure as a yellow oil (71.5 mg, 79% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{minor} = 11.6 min, t_{major} = 12.0 min; minor diastereomer: t_R = 14.2, 17.0, 22.1 min; 80:20 dr, 97% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H, ArH), 7.65 (d, J = 8.4 Hz, 2H, ArH), 7.58 (t, J = 7.4 Hz, 1H, ArH), 7.45 (t, J = 7.6 Hz, 2H, ArH), 7.30 (d, J = 8.0 Hz, 2H, ArH), 7.28 (dd, J_1 = 6.0 Hz, J_2 = 0.8 Hz, 1H, ArH), 6.50 (d, J = 3.2 Hz, 1H, ArH), 6.34 (dd, J_1 = 3.2 Hz, J_2 = 1.6 Hz, 1H, ArH), 5.39 (d, J = 4.0 Hz, 1H, CH), 5.00 (dd, J_1 = 5.6 Hz, J_2 = 3.6 Hz, 1H, CH), 4.08 (dd, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.43–3.35 (m, 2H, CH_2), 3.24–3.14 (m, 2H, CH + CH_2), 2.42 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 150.0, 144.1, 143.1, 135.9, 133.9, 133.7, 129.8, 128.7, 127.9, 127.5, 110.8, 110.0, 92.3, 60.4, 52.6, 39.9, 39.6, 21.5 ppm; IR (ATR): $\tilde{\nu}$ 1681, 1597, 1552, 1449, 1345, 1275, 1214, 1159, 1090, 1011, 1000, 930, 912, 813, 748, 688, 664, 587, 546 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{23}H_{23}N_2O_6S$ [M + H]$^+$ 455.12713, found 455.12686.

2-((3*S*,4*R*,5*R*)-4-Nitro-5-(thiophen-2-yl)-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3ha). The title compound **3ha** was obtained according to the general procedure as a yellow oil (75.9 mg, 81% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{minor} = 13.6 min, t_{major} = 15.1 min; minor diastereomer: t_R = 17.2, 18.3, 20.4, 37.0 min; 79:21 dr, >99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 7.2 Hz, 2H, ArH), 7.73 (d, J = 8.0 Hz, 2H, ArH), 7.57 (t, J = 7.4 Hz,1H, ArH), 7.44 (t, J = 7.8 Hz, 2H, ArH), 7.33 (d, J = 8.4 Hz, 2H, ArH), 7.26 (dd, J_1 = 5.8 Hz, J_2 = 1.2Hz, 1H, ArH), 7.10 (d, J = 3.6 Hz, 1H, ArH), 6.96 (dd, J_1 = 4.8 Hz, J_2 = 3.6 Hz, 1H, ArH), 5.61 (d, J = 4.4 Hz, 1H, CH), 4.88 (dd, J_1 = 6.6 Hz, J_2 = 4.6 Hz, 1H, CH), 4.14 (dd, J_1 = 11.6 Hz, J_2 = 7.6 Hz, 1H, CH_2), 3.41 (dd, J_1 = 11.6 Hz, J_2 = 7.6 Hz, 1H, CH_2), 3.30 (dd, J_1 = 17.6 Hz, J_2 = 5.2 Hz, 1H, CH_2), 3.17–2.99 (m, 2H, CH + CH_2), 2.44 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 144.4, 142.6, 135.8, 133.74, 133.68, 129.9, 128.7, 127.9, 127.7, 127.3, 126.0, 125.9, 96.0, 63.2, 52.8, 39.7, 39.6, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1681, 1596, 1551, 1492, 1447, 1349, 1305, 1275, 1213, 1158, 1089, 1032, 989, 907, 838, 813, 751, 706, 689, 665, 583, 544 cm^{-1}; HRMS (ESI): m/z calcd. for $C_{23}H_{23}N_2O_5S_2$ [M + H]$^+$ 471.10429, found 471.10490.

2-((3*S*,4*R*,5*S*)-4-nitro-5-phenethyl-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3ia). The title compound **3ia** was obtained according to the general procedure as a yellow oil (70.9 mg, 72% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 70:30, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 11.4 min, t_{minor} = 13.5 min; minor diastereomer: t_R = 14.7, 19.3, 20.6, 21.4 min; 80:20 dr, 79% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 7.2 Hz, 2H, ArH), 7.62 (d, J = 8.4 Hz, 2H, ArH), 7.46 (d, J = 8.0 Hz, 2H, ArH), 7.31–7.28 (m, 4H, ArH), 7.25–7.20 (m, 4H, ArH), 4.60 (dd, J_1 = 6.4 Hz, J_2 = 4.4 Hz, 1H, CH_2), 4.30 (t, J = 6.6 Hz, 1H, CH), 4.13–4.09 (m, 1H, CH), 3.95 (dd, J_1 = 11.8 Hz, J_2 = 7.4 Hz, 1H,

CH_2), 3.29–3.22 (m, 2H, CH_2), 3.10 (dd, J_1 = 18.0 Hz, J_2 = 8.4 Hz, 1H, CH_2), 2.89–2.81 (m, 1H, CH_2), 2.77–2.68 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.15–2.06 (m, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 144.2, 140.1, 135.8, 133.8, 129.9, 128.8, 128.7, 128.6, 128.5, 127.9, 127.7, 126.2, 93.2, 63.5, 52.7, 39.5, 39.3, 36.9, 31.5, 21.5 ppm; IR (KBr): 3028, 2959, 2929, 2872, 1727, 1688, 1598, 1581, 1552, 1496, 1471, 1450, 1349, 1288, 1278, 1219, 1163, 1123, 1093, 1075, 1013, 1001, 815, 749, 700, 691, 665, 631, 590, 550 cm^{-1}; HRMS (ESI): *m/z* calcd. for $C_{27}H_{29}N_2O_5S$ [M + H]$^+$ 493.17917, found 493.18017.

2-((3*S*,4*R*,5*S*)-5-Cyclohexyl-4-nitro-1-tosylpyrrolidin-3-yl)-1-phenylethanone (3ja). The title compound **3ja** was obtained according to the general procedure as a colorless oil (44.2 mg, 47% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 8.0 min, t_{minor} = 8.8 min; minor diastereomer: t_R = 11.7, 20.6 min; 88:12 dr, 95% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.76 (m, 4H, ArH), 7.51 (t, *J* = 6.8 Hz, 1H, ArH), 7.38 (t, *J* = 7.0 Hz, 2H, ArH), 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 4.56 (t, *J* = 6.2 Hz, 1H, CH), 4.22 (br s, 1H, CH), 4.10 (dd, J_1 = 12.6 Hz, J_2 = 7.8 Hz, 1H, CH_2), 3.22 (dd, J_1 = 18.0 Hz, J_2 = 2.0 Hz, 1H, CH_2), 2.97–2.87 (m, 2H, CH + CH_2), 2.35 (s, 3H, CH_3), 1.78–1.72 (m, 4H, CH_2), 1.66–1.53 (m, 2H, CH_2), 1.19–1.08 (m, 4H, CH_2), 1.03–0.94 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 144.2, 135.9, 134.7, 133.7, 130.0, 128.8, 127.9, 127.8, 91.4, 68.3, 53.1, 42.7, 41.0, 39.0, 29.3, 27.8, 26.1, 25.9, 25.8, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1683, 1597, 1550, 1448, 1344, 1304, 1262, 1231, 1214, 1158, 1089, 1019, 989, 810, 751, 689, 664, 588, 543 cm^{-1}; HRMS (ESI): *m/z* calcd. for $C_{25}H_{31}N_2O_5S$ [M + H]$^+$ 471.19482, found 471.19456.

1-(4-Fluorophenyl)-2-((3*S*,4*R*,5*S*)-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)ethanone (3ab). The title compound **3ab** was obtained according to the general procedure as a colorless solid (66.6 mg, 69% yield). HPLC (Daicel Chiralpak IB, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 31.0 min; minor diastereomer: t_R = 22.7, 25.7 min; 88:12 dr, >99% ee. M.p. 35–37 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, J_1 = 8.8 Hz, J_2 = 5.4 Hz, 2H, ArH), 7.63 (d, *J* = 8.0 Hz, 2H, ArH), 7.35–7.22 (m, 7H, ArH), 6.99 (t, *J* = 8.6 Hz, 2H, ArH), 5.23 (d, *J* = 5.2 Hz, 1H, CH), 4.69 (t, *J* = 5.6 Hz,1H, CH), 4.07 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.36 (dd, J_1 = 11.8 Hz, J_2 = 7.0 Hz, 1H, CH_2), 3.08 (dd, J_1 = 20.8 Hz, J_2 = 8.4 Hz, 1H, CH_2), 3.09–2.98 (m, 2H, CH + CH_2), 2.47 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 166.0 (d, $^1J_{C-F}$ = –254.5 Hz), 144.3, 138.6, 133.6, 130.5 (d, $^3J_{C-F}$ = 9.3 Hz), 129.9, 129.0, 128.4, 127.7, 126.2, 115.8 (d, $^2J_{C-F}$ = 21.8 Hz), 96.1, 66.9, 53.1, 39.40, 39.36, 21.5 ppm; IR (ATR): $\tilde{\nu}$ 1683, 1596, 1551, 1506, 1452, 1410, 1349, 1305, 1261, 1229, 1156, 1089, 1013, 992, 910, 832, 811, 763, 732, 698, 662, 604, 580, 543 cm^{-1}; HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}FN_2O_5S$ [M + H]$^+$ 483.13845, found 483.13708.

1-(4-Chlorophenyl)-2-((3*S*,4*R*,5*S*)-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)ethanone (3ac). The title compound **3ac** was obtained according to the general procedure as a colorless solid (79.5 mg, 80% yield). HPLC (Daicel Chiralpak IB, *n*-hexane/2-propanol = 70:30, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 24.8 min; minor diastereomer: t_R = 17.5, 20.5 min; 88:12 dr, >99% ee. M.p. 34–35 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 4H, ArH), 7.41–7.30 (m, 9H, ArH), 5.31 (d, *J* = 5.2 Hz, 1H, CH), 4.77 (t, *J* = 5.6 Hz, 1H, CH), 4.15 (dd, J_1 = 11.4 Hz, J_2 = 7.4 Hz, 1H, CH_2), 3.43 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.15 (dd, J_1 = 21.0 Hz, J_2 = 8.2 Hz, 1H, CH_2), 3.05–2.92 (m, 2H, CH + CH_2), 2.44 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 144.3, 140.2, 138.6, 134.1, 133.6, 129.9, 129.2, 129.02, 128.97, 128.5, 127.7, 126.2, 96.0, 66.9, 53.0, 39.4, 39.3, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1683, 1589, 1551, 1492, 1452, 1400, 1349, 1306, 1273, 1212, 1159, 1090, 1031, 990, 909, 812, 766, 731, 698, 662, 571, 544, 529 cm^{-1}; HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}ClN_2O_5S$ [M + H]$^+$ 499.10890, found 499.10862.

1-(4-Bromophenyl)-2-((3*S*,4*R*,5*S*)-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)ethanone (3ad). The title compound **3ad** was obtained according to the general procedure as a colorless solid (88.9 mg, 82% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 21.6 min, t_{minor} = 24.0 min; minor diastereomer: t_R = 34.3, 68.8 min; 89:11 dr, 97% ee. M.p. 51–52 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H, ArH), 7.62 (d, *J* = 8.8 Hz, 2H, ArH), 7.55 (d, *J* = 8.8 Hz, 2H, ArH), 7.42–7.31 (m, 7H, ArH), 5.31 (d, *J* = 4.8 Hz, 1H, CH), 4.76 (dd, J_1 = 6.0 Hz, J_2 = 5.2 Hz, 1H, CH_2), 4.15 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.44 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.15 (dd, J_1 = 21.0 Hz, J_2 = 8.2 Hz, 1H, CH_2), 3.05–2.92 (m, 2H, CH + CH_2), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 144.4, 138.6, 134.5, 133.6, 132.1, 129.9, 129.3, 129.0, 128.5, 127.7, 126.2, 96.1, 66.9, 53.1, 39.5, 39.3, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1682, 1584, 1551, 1493, 1348, 1305, 1275, 1262, 1159, 1089, 1070, 1031, 988, 811, 750, 698, 665, 571, 543 cm^{-1}; HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}BrN_2O_5S$ [M + H]$^+$ 543.05838, found 543.05814.

2-((3*S*,4*R*,5*S*)-4-Nitro-5-phenyl-1-tosylpyrrolidin-3-yl)-1-(*p*-tolyl)ethanone (3ae). The title compound **3ae** was obtained according to the general procedure as a colorless solid (81.2 mg, 85% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 15.1 min, t_{minor} = 16.9 min; minor diastereomer: t_R = 21.9, 35.9 min; 86:14 dr, 98% ee. M.p. 41–42 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 2H, ArH), 7.67 (d, *J* = 8.4 Hz, 2H, ArH), 7.44–7.31 (m, 7H, ArH), 7.21 (d, *J* = 8.0 Hz, 2H, ArH), 5.32 (d, *J* = 4.8 Hz, 1H, CH), 4.78 (d, *J* = 5.6 Hz, 1H, CH), 4.17 (dd, J_1 = 11.4 Hz, J_2 = 7.0 Hz, 1H, CH_2), 3.45 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.17 (dd, J_1 = 20.8 Hz, J_2 = 8.4 Hz, 1H, CH_2), 3.06–2.93 (m, 2H, CH + CH_2), 2.44 (s, 3H, CH_3), 2.39 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 144.7, 144.3, 138.7, 133.7, 133.4, 129.9, 129.4, 129.0, 128.4, 128.0, 127.7, 126.2, 96.2, 67.0, 53.2, 39.6, 39.4, 21.63, 21.59 ppm; IR (ATR): $\tilde{\nu}$ 2921, 1678, 1605, 1551, 1494, 1451, 1408, 1349, 1305, 1271, 1232, 1182, 1159, 1119, 1090, 1030, 998, 912, 809, 762, 737, 699, 662, 605, 581, 543 cm^{-1}; HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_2O_5S$ [M + H]$^+$ 479.16352, found 479.16349.

1-(3-Methoxyphenyl)-2-((3*S*,4*R*,5*S*)-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)ethanone (3af). The title compound **3af** was obtained according to the general procedure as a colorless solid (82.0 mg, 83% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 55:45, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 13.3 min, t_{minor} = 15.1 min; minor diastereomer: t_R = 21.7, 56.3 min; 85:15 dr, 98% ee. M.p. 38–40 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 2H, ArH), 7.43–7.31 (m, 10H, ArH), 7.12–7.09 (m, 1H, ArH), 5.32 (d, J = 4.8 Hz, 1H, CH), 4.78 (dd, J_1 = 6.2 Hz, J_2 = 5.0 Hz, 1H, CH), 4.17 (dd, J_1 = 11.6 Hz, J_2 = 7.6 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 3.45 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.18 (dd, J_1 = 20.6 Hz, J_2 = 8.2 Hz, 1H, CH_2), 3.08–2.95 (m, 2H, CH + CH_2), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 159.9, 144.3, 138.7, 137.1, 133.7, 129.9, 129.7, 129.0, 128.5, 127.7, 126.2, 120.4, 120.3, 112.1, 96.2, 66.9, 55.4, 53.1, 39.6, 39.5, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1682, 1597, 1583, 1551, 1487, 1452, 1430, 1348, 1305, 1288, 1257, 1199, 1158, 1120, 1090, 1031, 993, 860, 813, 787, 760, 737, 699, 685, 664, 571, 543 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{26}H_{27}N_2O_6S$ [M + H]$^+$ 495.15843, found 495.15864.

1-(4-Methoxyphenyl)-2-((3*S*,4*R*,5*S*)-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)ethanone (3ag). The title compound **3ag** was obtained according to the general procedure as a colorless solid (82.9 mg, 84% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 55:45, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 18.8 min, t_{minor} = 23.8 min; minor diastereomer: t_R = 25.5, 49.0 min; 86:14 dr, 99% ee. M.p. 39–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 9.2 Hz, 2H, ArH), 7.72 (d, J = 8.0 Hz, 2H, ArH), 7.43–7.31 (m, 7H, ArH), 6.88 (d, J = 9.2 Hz, 2H, ArH), 5.31 (d, J = 4.8 Hz, 1H, CH), 4.78 (dd, J_1 = 6.2 Hz, J_2 = 5.0 Hz, 1H, CH), 4.16 (dd, J_1 = 11.4 Hz, J_2 = 7.4 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 3.45 (dd, J_1 = 11.4 Hz, J_2 = 7.0 Hz, 1H, CH_2), 3.13 (dd, J_1 = 20.8 Hz, J_2 = 8.4 Hz, 1H, CH_2), 3.05–2.91 (m, 2H, CH + CH_2), 2.44 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 163.9, 144.3, 138.7, 133.7, 130.2, 129.9, 129.0, 128.9, 128.4, 127.7, 126.2, 113.9, 96.3, 67.0, 55.5, 53.2, 39.6, 39.1, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1672, 1598, 1550, 1510, 1455, 1420, 1348, 1306, 1260, 1236, 1158, 1112, 1089, 1026, 1009, 988, 910, 830, 812, 763, 699, 662, 605, 574, 543 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{26}H_{27}N_2O_6S$ [M + H]$^+$ 495.15843, found 495.15828.

1-(Naphthalen-2-yl)-2-((3*S*,4*R*,5*S*)-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)ethanone (3ah). The title compound **3ah** was obtained according to the general procedure as a colorless solid (85.3 mg, 83% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 20.9 min, t_{minor} = 23.9 min; minor diastereomer: t_R = 30.9, 73.7 min; 86:14 dr, 98% ee. M.p. 45–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H, ArH), 7.90–7.83 (m, 4H, ArH), 7.73 (d, J = 8.0 Hz, 2H, ArH), 7.62–7.52 (m, 2H, ArH), 7.44 (d, J = 7.2 Hz, 2H, ArH), 7.39–7.31 (m, 5H, ArH), 5.35 (d, J = 4.8 Hz, 1H, CH), 4.83 (dd, J_1 = 6.8 Hz, J_2 = 5.2Hz, 1H, CH), 4.20 (dd, J_1 = 11.4 Hz, J_2 = 7.8 Hz, 1H, CH_2), 3.49 (dd, J_1 = 11.6 Hz, J_2 = 7.6 Hz, 1H, CH_2), 3.33 (dd, J_1 = 17.6 Hz, J_2 = 5.2 Hz, 1H, CH_2), 3.17 (dd, J_1 = 17.6 Hz, J_2 = 8.4 Hz, 1H, CH_2), 3.11–3.05 (m, 1H, CH), 2.42 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 144.3, 138.7, 135.7, 133.7, 133.1, 132.3, 129.9, 129.8, 129.5, 129.0, 128.8, 128.7, 128.5, 127.8, 127.7, 127.0, 126.2, 123.3, 96.2, 67.0, 53.2, 39.6, 39.5, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1676, 1627, 1597, 1550, 1494, 1470, 1349, 1305, 1276, 1185, 1159, 1123, 1090, 1027, 992, 909, 856, 812, 749, 698, 662, 583, 544 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{29}H_{27}N_2O_5S$ [M + H]$^+$ 515.16352, found 515.16356.

1-(4-Bromophenyl)-2-((3*S*,4*R*,5*S*)-5-(4-bromophenyl)-4-nitro-1-tosylpyrrolidin-3-yl)ethanone (3dd). The title compound **3dd** was obtained according to the general procedure as a colorless solid (101.3 mg, 82% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 22.3 min, t_{minor} = 27.8 min; minor diastereomer: t_R = 37.3, 131.6 min; 86:14 dr, 98% ee. M.p. 55–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.6 Hz, 2H, ArH), 7.55 (d, J = 8.4 Hz, 2H, ArH), 7.46 (d, J = 8.0 Hz, 2H, ArH), 7.37 (d, J = 8.0 Hz, 2H, ArH), 7.25 (d, J = 8.0 Hz, 2H, ArH), 7.19 (d, J = 8.8 Hz, 2H, ArH), 5.12 (d, J = 5.2 Hz, 1H, CH), 4.65 (t, J = 6.2 Hz, 1H, CH), 4.04 (dd, J_1 = 11.4 Hz, J_2 = 7.4 Hz, 1H, CH_2), 3.34 (dd, J_1 = 11.4 Hz, J_2 = 7.8 Hz, 1H, CH_2), 3.08 (dd, J_1 = 17.6 Hz, J_2 = 4.8 Hz, 1H, CH_2), 2.99–2.83 (m, 2H, CH + CH_2), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 144.6, 137.6, 134.4, 133.3, 132.05, 132.01, 129.9, 129.3, 129.0, 128.0, 127.6, 122.5, 95.5, 66.3, 52.9, 39.2, 39.1, 21.6 ppm; IR (ATR): $\tilde{\nu}$ 1682, 1585, 1551, 1486, 1398, 1347, 1304, 1275, 1211, 1159, 1090, 1070, 1034, 1008, 988, 907, 810, 750, 706, 665, 586, 572, 544 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{23}Br_2N_2O_5S$ [M + H]$^+$620.96889, found 620.96729.

1-((3*S*,4*R*,5*S*)-4-Nitro-5-phenyl-1-tosylpyrrolidin-3-yl)propan-2-one (3ai). The title compound **3ai** was obtained according to the general procedure as a colorless solid (79.3 mg, 99% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 19.7 min, t_{minor} = 23.2 min; minor diastereomer: t_R = 10.5, 13.2 min; 91:9 dr, 77% ee. M.p. 46–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2H, ArH), 7.29–7.23 (m, 7H, ArH), 5.17 (br s, 1H, CH), 4.79 (d, J = 5.2 Hz, 1H, CH), 3.92 (t, J = 6.6 Hz, 1H, CH), 3.11–3.01 (m, 2H, CH_2), 2.41–2.29 (m, 5H, CH_2 + CH_3), 1.97 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.3, 143.9, 138.7, 133.7, 129.6, 128.9, 128.4, 127.7, 126.1, 93.6, 67.1, 51.0, 40.3, 35.5, 29.8, 21.5 ppm; IR (ATR): $\tilde{\nu}$ 1716, 1550, 1495, 1476, 1347, 1161, 1120, 1091, 1011, 815, 763, 703, 683, 662, 604, 569, 547 cm^{-1}; HRMS (ESI): *m*/*z* calcd. For $C_{20}H_{23}N_2O_5S$ [M + H]$^+$ 403.13222, found 403.13279.

Ethyl 2-((3*S*,4*R*,5*S*)-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)acetate (3aj). The title compound **3aj** was obtained according to the general procedure as a yellow oil (85.2 mg, 99% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 60:40, flow rate 1.0 mL/min, detection at 254 nm): for major diastereomer: 92% ee, t_{major} = 9.1 min, t_{minor} = 11.2 min; minor diastereomer: 56% ee, t_{minor} = 13.8 min, t_{major} = 18.1 min; 53:47 dr. For major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62

(d, J = 8.0 Hz,1H, ArH), 7.58 (d, J = 8.0 Hz, 1H, ArH), 7.30–7.23 (m, 7H, ArH), 5.22 (d, J = 5.2 Hz, 1H, CH), 4.68 (t, J = 6.0 Hz, 1H, CH), 4.02–3.94 (m, 3H, CH_2), 3.38 (dd, J_1 = 11.4 Hz, J_2 = 8.2 Hz, 1H, CH_2), 2.80–2.73 (m, 1H, CH), 2.43–2.30 (m, 4H, $CH_2 + CH_3$), 2.22 (dd, J_1 = 8.0 Hz, J_2 = 5.6 Hz, 1H, CH_2), 1.12 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 144.3, 138.4, 133.8, 129.8, 128.9, 128.4, 127.6, 126.2 95.8, 67.0, 61.1, 52.7, 39.8, 34.9, 21.5, 14.0 ppm. For minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.0 Hz, 1H, ArH), 7.58 (d, J = 8.0 Hz, 1H, ArH), 7.30–7.23 (m, 7H, ArH), 5.20 (s, 1H, CH), 4.82 (d, J = 5.6 Hz, 1H, CH), 4.02–3.94 (m, 3H, CH_2), 3.15 (t, J = 10.0 Hz, 1H, CH_2), 3.07–3.01 (m, 1H, CH), 2.43–2.30 (m, 4H, $CH_2 + CH_3$), 2.22 (dd, J_1 = 8.0 Hz, J_2 = 5.6 Hz, 1H, CH_2), 1.12 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 144.0, 138.7, 133.6, 129.6, 128.9, 128.4, 127.7, 126.0, 93.7, 67.3, 61.1, 51.1, 36.5, 31.5, 21.5, 14.0 ppm.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)acetate (3ak).** The title compound **3ak** was obtained according to the general procedure as a colorless solid (90.8 mg, 99% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): for major diastereomer: 74% ee, t_{major} = 11.6 min, t_{minor} = 13.3 min; minor diastereomer: 80% ee, t_{major} = 10.2 min, t_{minor} = 14.2 min; 57:43 dr. M.p. 28–30 °C; For major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.4 Hz, 1H, ArH), 7.67 (d, J = 8.4 Hz, 1H, ArH), 7.38–7.31 (m, 7H, ArH), 5.24 (s, 1H, CH), 4.90 (d,J = 5.6 Hz, 1H, CH), 4.07–4.00 (m, 1H, CH_2), 3.20 (dd, J_1 = 11.2 Hz, J_2 = 8.8 Hz, 1H, CH_2), 3.15–3.05 (m, 1H, CH), 2.44 (s, 3H, CH_3), 2.41–2.34 (m, 1H, CH_2), 2.29 (dd, J_1 = 17.2 Hz, J_2 = 6.8 Hz, 1H, CH_2), 1.38 (s, 9H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 144.0, 138.7, 133.6, 129.6, 128.9, 128.4, 127.7, 126.0, 93.7, 81.8, 67.3, 51.1, 36.6, 32.5, 27.8, 21.5 ppm. For minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.4 Hz, 1H, ArH), 7.67 (d, J = 8.4 Hz, 1H, ArH), 7.38–7.31 (m, 7H, ArH), 5.28 (d, J = 5.2 Hz, 1H, CH), 4.74 (dd, J_1 = 6.8 Hz, J_2 = 5.2 Hz, 1H, CH), 4.07–4.00 (m, 1H, CH_2), 3.45 (dd, J_1 = 11.6 Hz, J_2 = 8.0 Hz, 1H, CH_2), 2.86–2.77 (m, 1H, CH), 2.44 (s, 3H, CH_3), 2.41–2.34 (m, 1H, CH_2), 2.18 (dd, J_1 = 17.4 Hz, J_2 = 7.8 Hz, 1H, CH_2), 1.38 (s, 9H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 144.2, 138.4, 133.8, 129.8, 128.9, 128.4, 127.6, 126.1, 95.9, 81.8, 67.0, 52.7, 40.0, 36.3, 27.8, 21.5 ppm. IR (ATR): $\tilde{\nu}$ 1725, 1552, 1454, 1350, 1278, 1258, 1152, 1091, 1029, 1009, 946, 842, 814, 765, 751, 699, 644, 582, 545 cm^{-1}; HRMS (ESI): *m*/*z* calcd. For $C_{23}H_{29}N_2O_6S$ $[M + H]^+$ 461.17408, found 461.17460.

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