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Asymmetric Michael addition reactions of aldehydes to β-nitrostyrenes catalyzed by (*S*)—*N*-(D-prolyl-L-prolyl)-1 -triflicamido-3 -phenylpropan-2-amine

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ABSTRACT

In an attempt to improve the catalytic ability of (*S*)—*N*-(D-prolyl)-1-triflicamido-3-phenylpropan-2-amine, a catalyst previously reported by us for the asymmetric Michael addition of aldehydes to β-nitrostyrenes, 4 new molecules were designed and synthesized by increasing the distance between the triflicamide group and the secondary amino group in the catalyst. Under the optimized reaction conditions (*S*)—*N*-(D-prolyl-L-prolyl)-1-triflicamido-3-phenylpropan-2-amine exhibited high and improved catalytic activity and stereoselectivity at a lower catalyst loading (3 mol%). In the studies done with a large number of aldehydes and β-nitrostyrenes, the Michael adducts were obtained in high yields (up to 94%) and with excellent enantioselectivities (up to 98% ee) and with good to excellent diastereoselectivities (up to 98:2 dr).

1. Introduction

Proline is used extensively for asymmetric aldol [1] and Mannich reactions [2] and the products are obtained with high selectivity. However, Michael addition reactions catalyzed by proline is not a useful reaction as the stereoselectivity is poor [3]. This has resulted in the development of a number of catalysts for the asymmetric Michael addition reaction of carbonyl compounds [4]. Of particular interest has been the reaction between aldehydes and nitroalkenes. Starting with the triflicamide catalyst reported by Wang et al. [5], a number of very useful catalysts have been prepared [6]. Lately, attention has been given largely to peptide-based catalysts containing a prolinamide unit [7,8]. The works of Wennemers [9], Lecouvey [10] and Martín [11] have received great attention and has made this otherwise difficult asymmetric transformation a synthetic possibility. Recently, we developed a series of compounds based on Wang's catalyst and established that if a suitable linker is introduced between the secondary amino group of proline and the NHTf (triflicamide) group that acts as the hydrogen bond donor, the catalytic activity is improved at room temperature [12]. Encouraged by these results, and wanting to explore the utility of triflicamides derived from proline, we developed a new catalyst viz. (*S*)—*N*-(D-prolyl)-1-triflicamido-3-phenylpropan-2-amine (**1**) [13] Catalyst **1** (Fig. 1) can be considered as a combination of the triflicamide catalysts of Miura [14] and the dipeptide catalyst developed by Tsogoeva [15]. Catalyst **1** was fairly good in terms of enantioselectivity and in terms of the yield of products formed. It was also able to catalyze the reactions of hindered aldehydes. However, the reactions required at least 24 h to complete and 10 mol% of the catalyst was required [13]. Our earlier report has indicated that an optimal length between the secondary amino group and the hydrogen bond donor in the catalyst is very important for the successful catalysis of asymmetric Michael addition reaction of aldehydes and nitroalkenes by proline-derived molecules [12]. Therefore, it was assumed that a straight forward way to improve the catalytic ability of **1** is to increase the distance between the secondary amino group and the -NHTf group. Accordingly, four molecules **2**, **3**, **4** and **5** were designed (Fig. 1). Molecule **2** has an extended alkyl chain in comparison with catalyst **1**, while molecules **3**, **4** and **5** have an additional proline residue incorporated. The last three molecules are designed by varying the stereochemistry of the two proline residues. These molecules were studied for

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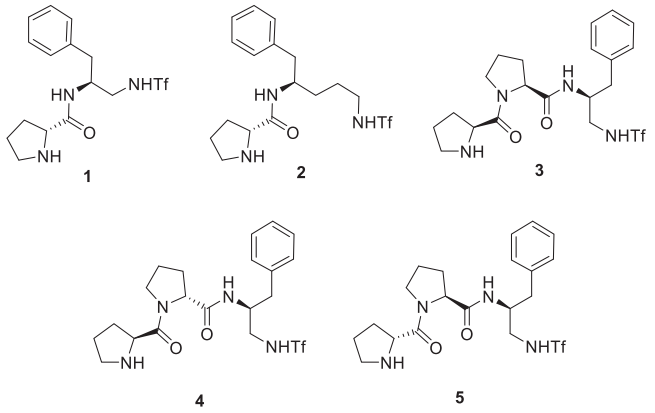
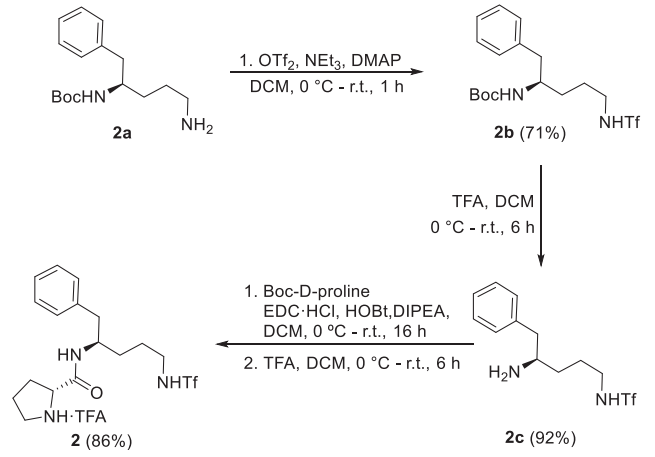


Fig. 1. Catalyst **1** and its variations **2**, **3**, **4** and **5**.



Scheme 1. Synthesis of **2**.

the ability to catalyze the Michael addition reaction of aldehydes with β-nitrostyrenes at rt. The molecule **5** was found to be the best catalyst and here we report those results.

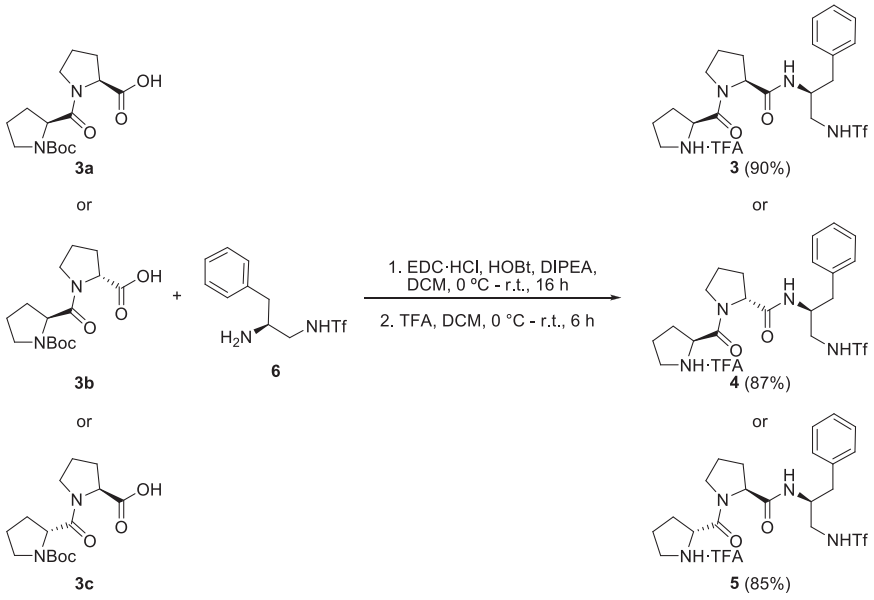
2. Results and discussion

The synthesis of molecule **2** started from the amine **2a**, which was synthesized from commercially available *N*-Boc-L-phenylalaninal, as reported by Liu [16]. The primary amine **2a** was treated with triflic anhydride to get the compound **2b** and the *N*-Boc group was removed using TFA in dry dichloromethane to get the amine **2c** (Scheme 1). Coupling of **2c** and Boc-D-proline under standard peptide coupling conditions using EDC·HCl in the presence of HOBt and DIPEA (DCM, 0 °C - rt) and subsequent removal of the *N*-Boc group yielded **2** as its TFA salt (Scheme 1).

Compounds **3**, **4** and **5** were prepared as their TFA salts by coupling (*S*)-1-triflicamido-3-phenylpropan-2-amine (**6**) with the dipeptide derivatives **3a**, **3b**, and **3c**, respectively and subsequently removing the *N*-Boc groups (Scheme 2). The amine **6** was synthesized from L-phenylalaninol using the procedure reported by Miura [13].

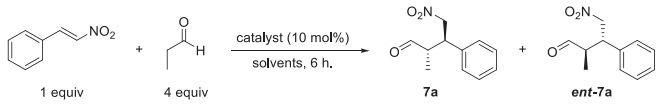
The studies were initiated by carrying out the reaction of propanal with β-nitrostyrene at room temperature in the presence of 10 mol% of catalysts **2**, **3**, **4** and **5** in various solvents (Table 1). The reactions were monitored through TLC and after the complete disappearance of β-nitrostyrene the products were isolated through column chromatography, the diastereomeric ratio was calculated from ^{1}H NMR spectra of the crude reaction mixture and the enantiomeric excess was estimated through chiral HPLC. The chromatograms were compared with that of a racemic mixture of **7a** and *ent*-**7a**, which were prepared by carrying out the reaction in the presence of DL-proline.

As expected, on using catalysts **2** and **5**, the major enantiomer formed was **7a** and on using catalysts **3** and **4**, the major enantiomer formed was ***ent*-7a**. The stereochemistry of the products depends on the stereochemistry of the pyrrolidine ring involved in the formation of the enamine with propanal and the results were consistent with those reported earlier [11,12]. A comparison between the activity of these catalysts in aliphatic (entries 1–5) and aromatic solvents (entries 6, 7 and 8) reveals that the catalysts exhibited better activity in aromatic solvents, both in terms of yields and stereoselectivity. Reactions done in a 1:1 mixture of isopropyl alcohol and chloroform (entry 1) produced the poorest results. Comparing these results with those of the reactions in chloroform (entry5) indicates that isopropyl alcohol has a negative



Scheme 2. Synthesis of compounds **3**, **4** and **5**.

Table 1
Screening of catalysts and Solvents.



entry	solvent	(yield %)[a] and ee[b] of the major products formed with each catalyst							
		catalyst 2[e,h]	syn:anti[c]	catalyst 3[d]	syn:anti[c]	catalyst 4[d]	syn:anti[c]	catalyst 5[e]	syn:anti[c]
1	IPA: $CHCl_3$ (1:1)	(85) 49	80:20	(89) 60	82:18	(94) 44	72:28	(95) 41	65:35
2	THF	(55) 74	83:17	(78) 86	71:29	(86) 70	76:24	(84) 80	80:20
3	DCM	(68) 76	81:19	(82) 85	80:20	(90) 80	73:27	(88) 86	78:22
4	ACN	(72) 33	75:25	(80) 77	81:19	(92) 52	71:29	(93) 80	89:11
5	$CHCl_3$	(75) 86	76:24	(84) 88	78:22	(89) 85	75:25	(90) 87	75:25
6	benzene	(80) 89	85:15	(86) 92	82:18	(89) 92	78:22	(88) 94	83:17
7	toluene	(78) 90	82:18	(82) 92	80:20	(88) 94	80:20	(85) 94	82:18
8	xylene	(81) 91	78:22	(88) 93	86:14	(90) 93	80:20	(90) 95	86:14
9[f]	xylene	(65) 91	80:20	(85) 93	87:13	(88) 93	76:24	(85) 95	83:17
10[g]	xylene	(54) 91	76:24	(81) 92	85:15	(84) 93	78:22	**(82) 95**	81:19

[a] Isolated yield after column chromatography.
[b] *ee* as determined by chiral HPLC analysis using a Chiralpak IC- Column.
[c] diastereomeric ratio is calculated from ^{1}H NMR spectra of the crude reaction mixture.
[d] major product is *ent*-**7a**.
[e] major product is **7a**.
[f] 5 mol% of catalyst with 3 equiv. of propanal were used and reaction time 15 h.
[g] 3 mol% of catalyst with 3 equiv. of propanal were used and reaction time is 24 h.
[h] reaction time is 12 h.

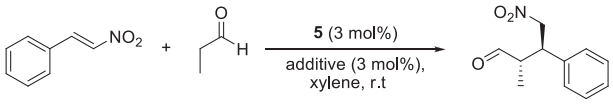
effect on the catalysis. It was interesting to note that reactions using catalyst **3** and **5** were comparable in terms of selectivity in aliphatic solvents. Reactions in THF and chloroform favored the use of catalyst **3** (entries 2 and 5), while those in dichloromethane and acetonitrile favored catalyst **5** (entries 3 and 4). However, these differences were not substantial. All of the catalysts gave consistently good selectivity in the three aromatic solvents studied. The yields for reactions using catalyst **2** were noticeably lower. Among all the conditions and catalysts studied, the reaction using **5** in xylene was found to be the best, which yielded **7a** in 90% yield as a diastereomeric mixture with 86% syn and 14% anti isomers and with 95% ee (entry 8). The reactions using catalysts **3**, **4** and **5** were complete in 6 h, which is a substantial improvement over that of catalyst **1**, reported earlier. Catalyst **2** was the slowest to react under these reaction conditions and the reactions took 12 h for completion. In an effort to reduce the amount of catalysts used and the number of equivalents of propanal, all the reactions were performed with 5 and 3 mol% of catalysts and with 3 equiv. of propanal (entries 9 and 10). It was found that the reaction times increased from 6 h to 15 h and 24 h with 5 and 3 mol% of the catalysts, respectively. While there was a sequential, but marginal, reduction in the yields of the products formed, the enantioselectivities were not affected. It was very clear that compound **5** is best among all the catalysts studied. Based on these results, it was decided to continue the studies with 3 mol% of catalyst **5** in xylene.

The addition of an acid to the reaction mixture is expected to improve the catalysis by protonation of the aldehyde leading to a faster generation of the enamines. Accordingly, the reactions were carried out in the presence of 3 mol% of compound **5** and 3 equivalents of propanal in xylene along with 3 mol% of an organic acid (Table 2). It was found that all acids studied, except *p*-TSA and citric acid had a positive effect on the reactivity and selectivity. The addition of benzoic acid, *p*-nitrobenzoic acid and 3,4-dimethoxyphenylacetic acid gave the best results (entries 1, 2 and 6). In the presence of these acids, the enantioselectivity improved from 95% ee to 97% ee, the reactions were slightly faster and there was a noticeable improvement in the yields. Based on these results, an attempt was made to increase the amount of the acid used in anticipation of better results. On using 5 and 10 mol% of benzoic acid as the additive (entries 9 and 10, respectively), the yields improved to 94%, without much improvement in the reaction times and enantioselectivity. The reactions with 5 and 10 mol% of benzoic acid were identical. Therefore, it was decided to continue the studies with 5 mol% of benzoic acid as the additive for the reactions done in the presence of catalyst **5**.

The scope of catalyst **5** was examined by carrying out the reaction of several aldehydes with various nitroalkenes at the optimized conditions (3 mol% of **5**, 5 mol% of benzoic acid, rt, xylene) with 3 equivalents of the aldehydes (Table 3). Initial studies were directed at the reaction of straight chain aldehydes with β-nitrostyrene to understand the effect of increasing chain length on the reactivity (entries 1–6). The reactions proceeded in high yields (85–94%) and with good diastereoselectivity (up to 98:2 dr) and good to excellent enantioselectivity (92–97% ee). The reaction of propanal is the most effective and an increase in the chain length decreases the reactivity and selectivity. Subsequently, reaction of propanal with various β-nitrostyrene derivatives were performed (entries 7–11 and 1). All of these reactions consistently gave good enantioselectivity, while the diastereoselectivity remained moderate in most cases. The reactions were repeated with butanal (entries 12–16) and pentanal (entries 17–20) and all the products showed very good ee and were isolated in good yields, but were obtained with moderate diastereoselectivity. The highest selectivity was obtained for the reactions of propanal with 4-fluoro-β-nitrostyrene and 2-chloro-β-nitrostyrene (entries 7 and 9) and the lowest selectivity was obtained for the reaction between pentanal and 4-methoxy-β-nitrostyrene (entry 20).

In comparison with catalyst **1** that we reported earlier, compound **5** showcases a substantial improvement. The catalyst loading could be brought down from 10 mol% to 3 mol% and the number of equivalents of aldehydes required was reduced to 3. The reactions catalyzed by **5** are faster and the selectivity is comparable if not better. Catalyst **5** is a very good catalyst, especially for the reactions of long chain aliphatic aldehydes.

Table 2
Influences of additives on Michael addition of propanal and β-nitrostyrenes.



entry	Additive	time (h)	yield (%)[a]	syn:anti[b]	ee (syn)[c]
1	benzoic acid	20	90	84:16	97
2	4-nitrobenzoic acid	20	88	81:19	97
3	acetic acid	24	82	86:14	96
4	4-nitrophenol	20	88	78:22	95
5	tartaric acid	28	82	80:20	96
6	3,4-dimethoxyphenylacetic acid	20	87	87:13	97
7	citric acid	48	(>10)	nd	nd
8	*p*-TSA	48	(>10)	nd	nd
9[d]	**benzoic acid**	**20**	**94**	**82:18**	**97**
10[e]	benzoic acid	20	94	82:18	97

[a] Isolated yield after column chromatography.
[b] diastereomeric ratio is calculated from ^{1}H NMR spectra of the crude reaction mixture.
[c] *ee* as determined by chiral HPLC analysis using a Chiralpak IC- Column.
[d] 5 mol% of benzoic acid was used.
[e] 10 mol% of benzoic acid was used.

3. Conclusion

In conclusion, a new peptide-based triflicamide organocatalyst (*S*)−*N*-(D-prolyl-L-prolyl)-1 -triflicamido-3 -phenylpropan-2 −amine (**5**) was identified, from a group of four different catalysts, which were designed by modifying compound **1**, a catalyst that we reported earlier for the Michael addition reaction of aldehydes to nitroalkenes. Catalyst **5** resulted in formation of the Michael adducts with very high yields (up to 94%), moderate to good diastereoselectivity (up to 98:2 dr) and excellent enantioselectivity (up to 98% ee). Catalyst **5** is definitely a substantial improvement over the two different catalysts that were previously reported from our group. With catalyst **5**, the catalyst loading could be brought down to 3 mol% from 10 mol% that was required for our previous catalysts and the equivalents of aldehyde required could be brought down to 3 from 4. A relatively poor diastereoselectivity remains as a possible area for improvement while using **5** for such reactions.

4. Experimental section

4.1. General information

All the chemicals were purchased from commercial sources. Anhydrous solvents were used for the reactions. Column chromatography was done with silica gel (particle size 60−120 and 100−200 mesh) purchased from Merck. The absolute configuration of the reaction products was confirmed by HPLC, by comparison with reported data. The enantiomeric ratios were estimated by chiral HPLC analysis and diastereomeric ratios were determined from1H NMR analysis. High performance liquid chromatography (HPLC) was performed on an Agilent Technologies chromatograph (1100 Series), using the specified Daicel chiral column and guard columns with a mixture of hexane and 2-propanol as eluents at 25 °C. Optical rotations were measured using a 5.0 mL cell with a 10 dm path length and are reported as $[\alpha]_D^{25}$ (*c* in g per 100 mL solvent).

4.2. Procedure for the preparation of compound 2b

To a solution of **2a** (2.0 g, 7.19 mmol) in DCM (20 mL) was cooled to 0 °C and triethylamine (2.5 mL, 17.98 mmol, 2.5 equiv) and DMAP (0.26 g, 2.15 mmol, 0.3 equiv) were added to this cold solution. This was followed by a slow addition of trifluoromethanesulfonic anhydride (1.45 mL, 8.62 mmol, 1.2 equiv) over a period of 15 min and the mixture was stirred for 3 h at 0 °C. Reaction was quenched with saturated $NaHCO_3$ solution (10 mL) and was extracted with DCM (2 × 30 mL). Combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and was filtered. Solvents were removed under reduced pressure and the product was purified by column chromatography to get the compound **2b**.

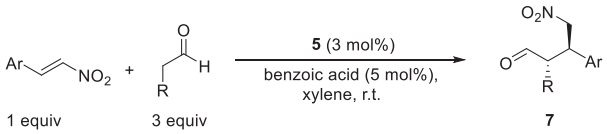
***tert*-butyl (*R*)-(1-phenyl-5-((trifluoromethyl)sulfonamido) pentan-2-yl)carbamate (2b):** Column chromatography (80:20 petroleum ether/EtOAc); White wax (2.0 g, 71%); $[\alpha]_D^{25} = +2.00$ (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.19 (m, 3H), 7.14 (d, $J = 7.1$ Hz, 2H), 6.58 (s, 1H), 4.53−4.36 (m, 1H), 3.91−3.72 (m, 1H), 3.42−3.15 (m, 2H), 2.73 (d, $J = 5.8$ Hz, 2H), 1.66−1.52 (m, 3H), 1.37 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 137.5, 129.3, 128.6, 126.6, 119.7 (q, $J = 321.0$ Hz), 80.0, 50.8, 44.0, 41.6, 31.9, 28.3, 26.3 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3403, 3321, 29305, 1685, 1552, 1445,1368, 1230, 1189, cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$calcd for $C_{17}H_{25}F_3N_2NaO_4S$ 433.1385, found 433.1388.

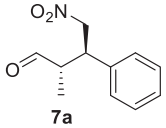
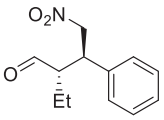
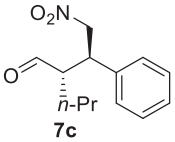
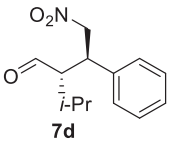
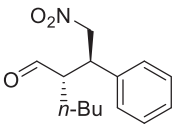
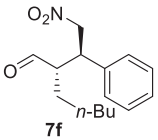
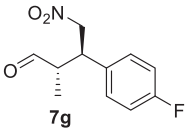
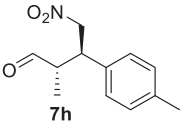
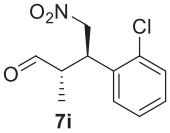
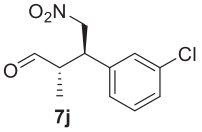
4.3. Procedure for the N-Boc deprotection of 2c

To a stirred solution of *N*-Boc-compound **2b** (1.5 g, 3.65 mmol) in dry DCM (10 mL), TFA (10 mL) was added at 0 °C and the solution was stirred at rt for 6 h. Reaction was monitored through TLC and after the complete disappearance of *N*-Boc-derivatives, the reaction mixture was concentrated under reduced pressure and 2 N NaOH solution was added to get a solution of pH 12. This mixture was extracted with ethyl acetate (3 × 30 mL) and dried over Na_2SO_4 and filtered. Solvents were removed under reduced pressure to get the amine **2c**.

(*R*)-*N*-(4-amino-5-phenylpentyl)-1,1,1-trifluoromethanesulfonamide (2c): White wax, (1.04 g, 92%); $[\alpha]_D^{25} = -3.33$ (*c* 0.60, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 2H), 7.31−7.23 (m, 3H), 7.15 (d, $J = 7.0$ Hz, 2H), 6.61 (d, $J = 15.6$ Hz, 1H), 3.59−3.57 (m, 1H), 3.30−3.02 (m, 2H), 3.02−2.79 (m, 2H), 1.95−1.53 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 129.3, 129.1, 127.8, 119.6 (q, $J = 321.0$ Hz), 53.6, 43.3, 39.0, 28.7, 25.4 ppm;

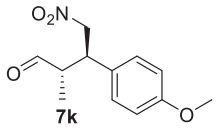
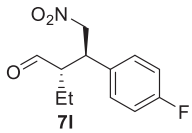
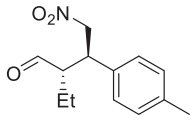
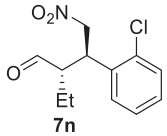
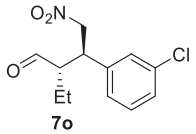
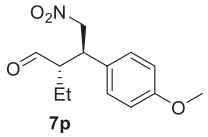
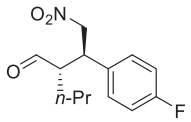
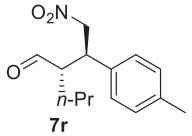
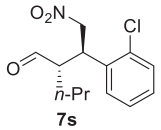
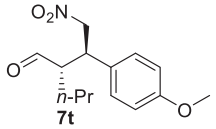
Table 3
Asymmetric Michael additions of aldehydes to β-nitrostyrenes catalyzed by **5**.



entry	Product	time (h)	yield (%)[a]	syn:anti[b]	ee (syn)[c] (%)
1	 **7a**	20	94	82:18	97
2	 **7b**	24	92	92:8	97
3	 **7c**	36	88	90:10	96
4	 **7d**	48	85	98:2	95
5	 **7e**	36	86	96:4	94
6	 **7f**	48	85	95:5	92
7	 **7g**	20	94	83:17	98
8	 **7h**	20	88	84:16	97
9	 **7i**	20	90	82:18	98
10	 **7j**	20	93	82:18	97

(*continued on next page*)

Table 3 (*continued*)

entry	Product	time (h)	yield (%)[a]	syn:anti[b]	ee (syn)[c] (%)
11	 **7k**	20	87	81:19	96
12	 **7l**	24	90	90:10	97
13	 **7m**	24	87	93:7	96
14	 **7n**	24	85	92:8	96
15	 **7o**	24	87	89:11	97
16	 **7p**	24	85	91:9	95
17	 **7q**	36	88	95:5	95
18	 **7r**	36	85	94:6	94
19	 **7s**	36	87	88:12	94
20	 **7t**	36	84	86:14	90

[a] Isolated yield after column chromatography.
[b] diastereomeric ratio is calculated from ^{1}H NMR spectra of the crude reaction mixture.
[c] *ee* as determine by chiral HPLC analysis using a Chiralpak IC-Column.

FTIR (thin film): $\bar{\upsilon}$ = 3420, 3033, 1674, 1522, 1497, 1455, 1370,1229,1144, cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$calcd for $C_{12}H_{18}F_3N_2O_2S$ 311.1041, found 311.1048.

4.4. Procedure for the preparation of compound 3b

To a stirred solution of compound *N*-Boc-D-proline methyl ester (1.0 g, 4.36 mmol, 1 equiv) in dry DCM (20 mL), TFA (10 mL) was

added at 0 °C and the solution was stirred at rt for 5 h. Reaction was monitored through TLC and after the complete disappearance of compound *N*-Boc-D-proline methyl ester, the reaction mixture was concentrated under reduced pressure to get the corresponding amine, which was forwarded for the next step. A solution of the Boc-L-proline (0.98 g, 4.41 mmol, 1.0 equiv) in DCM (20 mL) was cooled to 0 °C. To this solution, EDC·HCl (1.26 g, 6.61 mmol, 1.5 equiv), HOBt (0.9 g, 6.61 mmol, 1.5 equiv) and DIPEA (1.96 mL, 11.02 mmol, 2.5 equiv) were added and was stirred for 15 min. To the cold mixture, the secondary amine (1.06 g, 4.41 mmol, 1.0 equiv) was added as a solution in DCM (5 mL) and the solution was stirred at rt for 16 h. Reaction was monitored through TLC and after the complete disappearance of the amine, the reaction mixture was diluted with DCM (30 mL) and was washed with saturated $NaHCO_3$ solution (10 mL) and then with 1 N $KHSO_4$ solution (10 mL). Crude solution of the prolinamide was washed with brine (30 mL), dried over Na_2SO_4 and was filtered. Solvents were removed under reduced pressure and the product was purified by column chromatography (50:50 petroleum ether/EtOAc) to get the *N*-Boc ester compound, clear oil (1.15 g, 81% Yield) which was forwarded for the ester hydrolysis.

To a stirred solution of *N*-Boc ester compound (1.15 g, 3.52 mmol, 1.0 equiv) in methanol:water (20 mL) was added lithium hydroxide (0.42 g, 17.63 mmol, 5 equiv). The reaction mixture was stirred at rt for 1 h. After the complete disappearance of *N*-Boc ester compound on TLC, the reaction mixture was concentrated under reduced pressure to evaporate solvent and neutralized with saturated $KHSO_4$ solution (25 mL) and extracted with ethyl acetate (2 × 30 mL). Combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and filtered. The solvent were removed under reduced pressure and acid **3b** was purified by column chromatography (90:10 petroleum ether/EtOAc) white wax (0.96 g, 87% Yield).

(*tert*-butoxycarbonyl)-L-prolyl-D-proline (3b): white solid, mp188−190 °C (0.98 g, 72% Yield); $[\alpha]_D^{25} = +29.26$ (*c* 0.41, MeOH); (rotamers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (bs, 1H), 4.70−4.31 (m, 2H), 3.80−3.27 (m, 4H), 2.45−1.85 (m, 8H), 1.44−1.34 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.3, 172.3, 171.9, 155.0, 153.5, 80.7, 80.5, 60.5, 58.0, 57.8, 47.5, 46.9, 46.7, 30.3, 29.2, 28.5, 28.4, 28.2, 28.1, 27.2, 24.9, 24.7, 23.8 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3452, 2975, 2882, 1734, 1650, 1478, 1408,1366, 1331, 1248, 1126 cm-1. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$calcd for $C_{15}H_{25}N_2O_5$313.1763, found 313.1769.

4.5. General procedure for the preparation of N-Boc derivatives 2, 3, 4 and 5

A solution of compound **3a** or **3b** or **3c** (0.6 g, 1.91 mmol, 1.0 equiv) or *N*-Boc- D-proline (0.56 g, 2.60 mmol, 1.0 equiv) in DCM (20 mL) was cooled to 0 °C. To this solution, EDC·HCl (0.75 g, 3.94 mmol, 1.5 equiv), HOBt (0.53 g, 3.94 mmol, 1.5 equiv) and DIPEA (1.14 mL, 6.59 mmol, 2.5 equiv) were added and was stirred for 15 min. To the cold mixture, the primary amine **2c** (0.81 g, 2.60 mmol, 1.0 equiv) or 6 (0.54 g, 1.91 mmol, 1.0 equiv) and was added as a solution in DCM (20 mL) and the solution was stirred at rt for 16 h. Reaction was monitored through TLC and after the complete disappearance of the amine, the reaction mixture was diluted with DCM (40 mL) and was washed with saturated $NaHCO_3$ solution (20 mL) and then with 1 N $KHSO_4$ solution (10 mL). Crude solution of the peptide was washed with brine (40 mL), dried over Na_2SO_4 and was filtered. Solvents were removed under reduced pressure and the products were purified by column chromatography to get the *N*-Boc derivatives of **2** to **5**.

***tert*-butyl (*R*)-2-(((*R*)-1-phenyl-5-((trifluoromethyl)sulfonamido)pentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (*N*-Boc-2):** Column chromatography (70:30 petroleum ether/EtOAc); White wax (1.06 g, 80%); $[\alpha]_D^{25} = +15.0$ (*c* 0.40, MeOH); (rotamers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.20 (m, 3H), 7.15 (d, *J* = 6.9 Hz, 2H), 6.22 (d, *J* = 3.0 Hz, 1H), 4.31−3.98 (m, 2H), 3.68−3.06 (m, 4H), 2.93−2.57 (m, 2H), 2.03−1.54 (m, 8H), 1.41 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 172.6, 155.4, 155.3, 137.7, 137.7, 129.2, 128.6, 128.5, 126.6, 119.6 (q, *J* = 320.5 Hz), 80.66, 80.64, 60.39, 60.34, 49.8, 49.7, 47.2, 44.1, 41.7, 41.5, 32.0, 31.5, 29.7, 29.4, 29.2, 28.45, 28.40, 25.5, 24.5, 22.7 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3301, 3087, 2977, 1670, 1539, 1478, 1412, 1369, 1229, 1178, 1151, cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$calcd for $C_{22}H_{33}F_3N_3O_5S$ 508.2093, found 508.2091.

***tert*-butyl (*S*)-2-((*S*)-2-(((*S*)-1-phenyl-3-((trifluoromethyl)sulfonamido)propan-2-yl)carbamoyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (*N*-Boc-3):** Column chromatography (100% EtOAc); White wax (0.91 g, 83%); $[\alpha]_D^{25} = -25.84$ (*c* 0.41, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.27 (dd, *J* = 13.8, 6.4 Hz, 2H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.20−7.15 (m, 3H), 4.41−4.34 (m, 1H), 4.27−4.10 (m, 2H), 3.61−3.55 (m, 2H), 3.46−3.22 (m, 4H), 2.96−2.83 (m, 2H), 2.15−1.79 (m, 7H), 1.57 (dd, *J* = 13.5, 7.2 Hz, 1H), 1.49 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.8, 155.2, 137.6, 129.1, 128.5, 126.7, 119.5 (q, *J* = 321.8 Hz), 80.3, 61.0, 57.7, 51.6, 47.7, 47.6, 47.3, 37.2, 29.5, 29.2, 28.7, 24.9, 23.8 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3317,3087, 2975, 2925, 1659, 1539, 1455, 1412, 1376, 1333, 1229, 1189, cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M-H]^-$calcd for $C_{25}H_{34}F_3N_4O_6S$ 575.2151, found 575.2152.

***tert*-butyl (*S*)-2-((*R*)-2-(((*S*)-1-phenyl-3-((trifluoromethyl)sulfonamido)propan-2-yl)carbamoyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (*N*-Boc-4):** Column chromatography (100% EtOAc); White wax (0.98 g, 89%); $[\alpha]_D^{25} = +18.96$ (*c* 0.58, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.28−7.16 (m, 5H), 7.14 (s, 1H), 4.54 (dd, *J* = 7.3, 2.3 Hz, 1H), 4.35 (dd, *J* = 7.8, 5.7 Hz, 1H), 4.13−4.04 (m, 1H), 3.87−3.75 (m, 1H), 3.59−3.53 (m, 1H), 3.46−3.24 (m, 4H), 2.98 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.73 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.39−2.29 (m, 1H), 2.16−1.85 (m, 8H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ δ 172.8, 171.5, 155.0, 137.3, 129.0, 128.6, 126.7, 119.8 (q, *J* = 321.5 Hz), 80.5, 60.7, 57.9, 52.1, 47.3, 47.1, 46.0, 37.9, 29.3, 28.5, 27.5, 24.7, 24.4 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3312,3088, 2975, 2931, 1698, 1534, 1497, 1453, 1367, 1335, 1229, 1189, cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M-H]^-$calcd for $C_{25}H_{34}F_3N_4O_6S$ 575.2151, found 575.2154.

***tert*-butyl (*R*)-2-((*S*)-2-(((*S*)-1-phenyl-3-((trifluoromethyl)sulfonamido)propan-2-yl)carbamoyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (*N*-Boc-5):** Column chromatography (100% EtOAc); White wax (0.95 g, 87%); $[\alpha]_D^{25} = -19.0$ (*c* 0.66, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.30−7.16 (m, 5H), 6.85 (d, *J* = 8.7 Hz, 1H), 4.46 (dd, *J* = 8.0, 3.1 Hz, 1H), 4.37−4.26 (m, 2H), 3.81−3.76 (m, 1H), 3.55−3.34 (m, 4H), 3.22−3.13 (m, 1H), 2.93−2.79 (m, 2H), 2.15−1.71 (m, 7H), 1.49 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.8, 155.2, 137.6, 129.1, 128.5, 126.7, 119.9 (q, *J* = 321.6 Hz), 80.3, 61.0, 57.7, 51.6, 47.6, 47.6, 47.3, 37.2, 29.5, 29.2, 28.7, 24.9, 23.9 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3325,3070, 2970, 29551, 1659, 1547, 1478, 1455, 1410, 1365, 1331, 1227, 1156, cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M-H]^-$calcd for $C_{25}H_{34}F_3N_4O_6S$ 575.2151, found 575.2158.

5. General procedure for the *N*-Boc deprotection of *N*-Boc-compound 2 to 5

To a stirred solution of *N*-Boc-derivatives of **2** (1 g, 1.96 mmol) or **3** or **4** or **5** (1 g, 1.73 mmol) in dry DCM (10 mL), TFA (10 mL) was added at 0 °C and the solution was stirred at rt for 6 h. Reaction was monitored through TLC and after the complete disappearance of *N*-Boc-derivatives, the reaction mixture was concentrated under reduced pressure and 2 N NaOH solution was added to get a solution of pH 12. This mixture was extracted with ethyl acetate

(3 × 20 mL) and dried over Na_2SO_4 and filtered. Solvents were removed under reduced pressure to get the peptide catalyst (**2** to **5**).

(*R*)-*N*-((*R*)-1-phenyl-5-((trifluoromethyl)sulfonamido)pentan-2-yl)pyrrolidine-2-carboxamide (2): White wax, (0.69 g, 86%); $[\alpha]_D^{25}$ = +17.50 (*c* 0.40, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (d, *J* = 3.1 Hz, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.54–7.33 (m, 1H), 7.27–7.20 (m, 2H), 7.15 (t, *J* = 6.7 Hz, 2H), 4.56–4.04 (m, 3H), 3.21 (d, *J* = 30.8 Hz, 3H), 2.87 (dd, *J* = 13.4, 4.0 Hz, 1H), 2.61 (dd, *J* = 12.8, 10.1 Hz, 1H), 2.23–2.06 (m, 1H), 1.93–1.75 (m, 1H), 1.61-1-40 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 137.8, 129.2, 128.4, 126.6, 119.7 (q, *J* = 320.9 Hz), 59.6, 51.5, 46.6, 43.9, 41.4, 31.4, 30.3, 26.42, 24.3 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3310, 3087, 2925, 1671, 1565, 1454, 1371, 1229, 1190 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$calcd for $C_{17}H_{25}F_3N_3O_3S$ 408.1569, found 408.1561.

(*S*)-1-(L-prolyl)-N-((*S*)-1-phenyl-3-((trifluoromethyl)sulfonamido)propan-2-yl)pyrrolidine-2-carboxamide (3): White solid (0.74 g, 90%); $[\alpha]_D^{25}$ = −39.02 (*c* 0.41, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.36–7.12 (m, 5H), 4.44 (dd, *J* = 20.4, 5.8 Hz, 1H), 4.25–4.07 (m, 1H), 3.68–3.49 (m, 2H), 3.43–3.18 (m, 5H), 2.94–2.73 (m, 2H), 2.54–2.36 (m, 1H), 2.23–1.76 (m, 7H) ppm; ^{13}C NMR (100 MHz, METHANOL-D3) δ 172.5, 171.7, 167.3, 167.2, 138.1, 137.54, 128.9, 128.2, 126.37, 126.32, 120.1 (q, *J* = 321.5 Hz), 60.6, 59.9, 58.9, 51.4, 47.1, 46.2, 46.0, 37.1, 37.0, 31.9, 29.3, 28.2, 24.5, 23.9, 21.6 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3287,3089, 2957, 2931, 1659, 1544, 1497, 1476, 1455, 1377, 1331, 1229, 1162, 1151, cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$calcd for $C_{20}H_{28}F_3N_4O_4S$ 477.1783, found 477.1778.

(*R*)-1-(L-prolyl)-*N*-((*S*)-1-phenyl-3-((trifluoromethyl)sulfonamido)propan-2-yl)pyrrolidine-2-carboxamide (4): White solid (0.71 g, 87%); $[\alpha]_D^{25}$ = +7.87 (*c* 0.33, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.39–7.03 (m, 5H), 4.45–4.26 (m, 1H), 4.23–4.00 (m, 1H), 3.63 (dt, *J* = 10.1, 7.2 Hz, 1H), 3.49–3.42 (m, 1H), 3.34–317 (m, 4H), 3.15–3.03 (m, 1H), 2.98–2.85 (m, 1H), 2.70–2.61 (m, 1H), 2.41–2.28 (m, 1H), 2.21–1.69 (m, 6H), 1.65–1.53 (m, 1H) ppm; ^{13}C NMR (100 MHz, METHANOL-D4) δ 172.3, 172.0, 169.7, 169.6, 137.9, 129.0, 128.0, 126.1, 120.7 (q, *J* = 323.0 Hz), 60.8, 60.3, 58.9, 58.7, 51.8, 51.4, 47.0, 46.9, 46.5, 46.3, 37.8, 37.5, 29.3, 29.1, 28.5, 24.5, 24.0 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3285,3088, 2957, 2925, 1650, 1549, 1476, 1478, 1457, 1417, 1374, 1280, 1165, 1156, cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$calcd for $C_{20}H_{28}F_3N_4O_4S$ 477.1783, found 477.1771.

(*S*)-1-(D-prolyl)-*N*-((*S*)-1-phenyl-3-((trifluoromethyl)sulfonamido)propan-2-yl)pyrrolidine-2-carboxamide (5): White solid (0.70 g, 85%); $[\alpha]_D^{25}$ = −12.72 (*c* 0.33, MeOH); H NMR (400 MHz, CD_3OD) δ 7.32–7.11 (m, 5H), 4.32 (dd, *J* = 11.2, 8.4 Hz, 1H), 4.27–4.11 (m, 1H), 3.69–3.56 (m, 1H), 3.51–3.45 (m, 1H), 3.39–3.12 (m, 5H), 2.95–2.66 (m, 2H), 2.47–2.30 (m, 1H), 2.25–1.61 (m, 7H) ppm; ^{13}C NMR (100 MHz, METHANOL-D3) δ 172.5, 172.3, 169.7, 169.5, 137.9, 129.1, 128.9, 128.2, 128.0, 126.3, 121.3 (q, *J* = 323.7 Hz), 61.6, 60.1, 59.0, 52.4, 51.6, 47.0, 46.8, 46.5, 46.1, 37.9, 37.2, 29.3, 28.4, 25.2, 24.4, 23.8 ppm; FTIR (thin film): $\bar{\upsilon}$ = 3290,3072, 2965, 2931, 1667, 1534, 1497, 1466, 1417, 1377, 1329, 1266, 1152 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M−H]$^-$calcd for $C_{20}H_{26}F_3N_4O_4S$ 475.1627, found 475.1625.

6. General procedure for the Michael addition of aldehydes to nitroalkenes

To a solution of the aldehyde (1.5 mmol, 3.0 equiv) in 2 mL of the xylene, the nitroalkene (0.5 mmol, 1.0 equiv) and the catalyst **5** (0.007 g, 0.015 mmol, 0.03 equiv) were added and stirred at rt. The reaction was continued until the complete disappearance of nitroalkenes on TLC. The solvent was removed under reduced pressure and Michael adduct were purified by column chromatography. ^{1}H NMR of crude reaction mixtures were taken to determine the diastereomeric ratios, wherever applicable. Purified compounds were subjected to HPLC analysis for the determination of enantiomeric ratios.

Racemic mixtures of the γ-nitro aldehydes were prepared as references for HPLC analysis by carrying out each of the reactions listed in Table 3 in the presence of 20 mol% of DL-proline as the catalyst.

(2*S*,3*R*)-2-methyl-4-nitro-3-phenylbutanal (7a): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.097 g, 94% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.7 Hz, 1H), 7.32 (dd, *J* = 9.9, 4.1 Hz, 3H), 7.18–7.14 (m, 2H), 4.78 (dd, *J* = 6.9, 4.2 Hz, 1H), 4.67 (dd, *J* = 12.6, 9.4 Hz, 1H), 3.80 (dd, *J* = 9.1, 3.5 Hz, 1H), 2.81–2.74 (m, 1H), 0.99 (d, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 136.6, 129.1, 128.2, 128.1, 78.1, 48.5, 44.1, 12.2 ppm; HRMS (ESI-TOF) *m*/*z*: [M−H]$^-$calcd for $C_{11}H_{12}NO_3$ 206.0817, found 206.0827; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.7 mL/min, λ = 254 nm), t_R major = 31.24, t_R minor = 36.42, 97% ee and dr 82:18.

(2*S*,3*R*)-2-ethyl-4-nitro-3-phenylbutanal (7b): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 92% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 2.6 Hz, 1H), 7.35–7.28 (m, 3H), 7.17 (dd, *J* = 5.3, 3.0 Hz, 2H), 4.71 (dd, *J* = 12.8, 5.0 Hz, 1H), 4.62 (dd, *J* = 12.7, 9.7 Hz, 1H), 3.81–3.75 (m, 1H), 2.68–2.65 (m, 1H), 1.52–1.46 (m, 2H), 0.82 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 136.8, 129.2, 128.2, 128.0, 78.6, 55.0, 42.7, 20.4, 10.7 ppm; HRMS (ESI-TOF) *m*/*z*: [M−H]$^-$calcd for $C_{12}H_{14}NO_3$ 220.0974, found 220.0977; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.7 mL/min, λ = 254 nm), t_R major = 21.83, t_R minor = 24.59, 97% ee and dr 92:8.

(*S*)-2-((*R*)-2-nitro-1-phenylethyl)pentanal (7c): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.103 g, 88% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 3.0 Hz, 1H), 7.34–7.28 (m, 3H), 7.16 (dd, *J* = 6.9, 1.6 Hz, 2H), 4.70–4.62 (m, 2H), 3.80–3.73 (m, 1H), 2.72–2.66 (m, 1H), 1.41–1.29 (m, 4H), 0.79 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 136.8, 129.2, 128.2, 128.0, 78.4, 53.8, 43.2, 29.5, 19.8, 14.0 ppm; HRMS (ESI-TOF) *m*/*z*: [M−H]$^-$calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1134; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.8 mL/min, λ = 254 nm), t_R major = 26.95, t_R minor = 31.18, 96% ee and dr 90:10.

(2*S*,3*R*)-2-isopropyl-4-nitro-3-phenylbutanal (7d): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 85% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (d, *J* = 2.4 Hz, 1H), 7.36–7.27 (m, 3H), 7.20–7.16 (m, 2H), 4.66 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.56 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.89 (td, *J* = 10.3, 4.4 Hz, 1H), 2.76 (ddd, *J* = 10.6, 4.1, 2.5 Hz, 1H), 1.75–1.67 (m, 1H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 137.1, 129.2, 128.1, 128.0, 79.0, 58.8, 42.0, 28.0, 21.7, 17.0 ppm; HRMS (ESI-TOF) *m*/*z*: [M−H]$^-$calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.11177; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_R major = 27.07, t_R minor = 30.72, 95% ee and dr 98:2.

(*S*)-2-((*R*)-2-nitro-1-phenylethyl)hexanal (7e): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 86% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.7 Hz, 1H), 7.37–7.28 (m, 3H), 7.16 (d, *J* = 6.9 Hz, 2H), 4.72–4.60 (m, 2H), 3.79–3.73 (m, 1H), 2.72–2.64 (m, 1H), 1.49–1.39 (m, 2H), 1.23–1.12 (m, 4H), 0.77 (t, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 136.8, 129.1, 128.2, 128.0, 78.5, 53.9, 43.2, 28.6, 27.1, 22.5, 13.7 ppm; HRMS (ESI-TOF) *m*/*z*: [M−H]$^-$calcd for $C_{14}H_{18}NO_3$ 248.1287, found 248.1285; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.7 mL/min, λ = 254 nm), t_R major = 22.91, t_R minor = 26.63, 94% ee and dr 96:4.

(*S*)-2-((*R*)-2-nitro-1-phenylethyl)heptanal (7f): Column chromatography (92:8 petroleum ether/EtOAc); Pale yellow oil (0.11 g, 85% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.9 Hz, 1H), 7.35–7.26 (m, 3H), 7.17–7.15 (m, 2H), 4.69 (dd, *J* = 12.8, 5.3 Hz, 1H), 4.62 (dd, *J* = 12.7, 9.5 Hz, 1H), 3.76 (td, *J* = 9.6, 5.2 Hz, 1H), 2.73–2.65

(m, 1H), 1.52–1.37 (m, 3H), 1.19–1.07 (m, 5H), 0.79 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 203.3, 136.8, 129.1, 128.2, 128.0, 78.5, 53.9, 43.2, 31.6, 27.3, 26.1, 22.3, 13.9 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{14}H_{18}NO_3$ 262.1443, found 262.1441; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 92:8, flow rate: 0.6 mL/min, λ = 254 nm), t_R major = 22.92, t_R minor = 26.36, 92% ee and dr 95:5.

(2*S*,3*R*)-3-(4-fluorophenyl)-2-methyl-4-nitrobutanal (7g): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.105 g, 94% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 1.4 Hz, 1H), 7.16–7.12 (m, 2H), 7.05–7.00 (m, 2H), 4.78 (dd, J = 12.7, 5.4 Hz, 1H), 4.66–4.61 (m, 1H), 3.83–3.76 (m, 1H), 2.80–2.71 (m, 1H), 0.99 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 162.4 (d, J = 247.5Hz), 132.4 (d, J = 3.0 Hz), 129.7 (d, J = 8.0 Hz), 116.1 (d, J = 21.5 Hz), 78.2, 48.4, 43.4, 12.2 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{11}H_{11}FNO_3$ 224.0723, found 224.0723; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.8 mL/min, λ = 254 nm), t_R major = 39.74, t_R minor = 44.92, 98% ee and dr 83:17.

(2*S*,3*R*)-2-methyl-4-nitro-3-(p-tolyl)butanal (7h): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.097 g, 88% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 1.8 Hz, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 4.78–4.74 (m, 1H), 4.67–4.62 (m, 1H), 3.79–3.74 (m, 1H), 2.77–2.71 (m, 1H), 2.31 (s, 3H), 0.99 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 137.9, 133.4, 129.8, 127.9, 78.3, 48.5, 43.7, 21.1, 12.1 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{12}H_{14}NO_3$ 220.0974, found 220.0987; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.6 mL/min, λ = 254 nm), t_R major = 34.58, t_R minor = 40.61, 97% ee and dr 84:16.

(2*S*,3*R*)-3-(2-chlorophenyl)-2-methyl-4-nitrobutanal (7i): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.0.108 g, 90% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, J = 1.5 Hz, 1H), 7.40 (dd, J = 7.3, 2.0 Hz, 1H), 7.26–7.23 (m, 2H), 7.21–7.18 (m, 1H), 4.86 (dd, J = 13.1, 9.1 Hz, 1H), 4.80–4.75 (m, 1H), 4.32 (td, J = 9.3, 5.0 Hz, 1H), 3.04–2.94 (m, 1H), 1.02 (d, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 134.56, 134.51, 130.6, 129.3, 127.5, 75.5, 47.8, 40.7, 12.3 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{11}H_{11}ClNO_3$ 240.0427, found 240.0423; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.6 mL/min, λ = 254 nm), t_R major = 20.71, t_R minor = 21.96, 98% ee and dr 82:18.

(2*S*,3*R*)-3-(3-chlorophenyl)-2-methyl-4-nitrobutanal (7j): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.112 g, 93% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, J = 1.6 Hz, 1H), 7.29–7.26 (m, 2H), 7.16 (s, 1H), 7.08–7.04 (m, 1H), 4.78 (dd, J = 12.8, 5.2 Hz, 1H), 4.64 (dd, J = 12.9, 9.4 Hz, 1H), 3.81–3.74 (m, 1H), 2.80–2.72 (m, 1H), 1.00 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 138.8, 135.0, 130.4, 128.5, 128.3, 126.4, 77.8, 48.2, 43.7, 12.3 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{11}H_{11}ClNO_3$ 240.0427, found 240.0426; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.8 mL/min, λ = 254 nm), t_R major = 38.22, t_R minor = 42.89, 97% ee and dr 82:18.

(2*S*,3*R*)-3-(4-methoxyphenyl)-2-methyl-4-nitrobutanal (7k): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.103 g, 87% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 1.7 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.77–4.72 (m, 1H), 4.65–4.60 (m, 1H), 3.77 (s, 3H), 2.75–2.69 (m, 1H), 0.99 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 159.3, 129.1, 128.3, 114.5, 78.4, 55.3, 48.6, 43.4, 12.1 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{12}H_{14}NO_4$ 236.0923, found 236.0920; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_R major = 47.03, t_R minor = 53.59, 96% ee and dr 81:19.

(2*S*,3*R*)-2-ethyl-3-(4-fluorophenyl)-4-nitrobutanal (7l): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.107 g, 90% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 2.4 Hz, 1H), 7.17–7.13 (m, 2H), 7.05–7.00 (m, 2H), 4.72–4.68 (m, 1H), 4.59 (t, J = 6.3 Hz, 1H), 3.81–3.75 (m, 1H), 2.68–2.62 (m, 1H), 1.53–1.45 (m, 2H), 0.82 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 162.3, (d, J = 250 Hz), 132.6 (d, J = 3.1 Hz), 129.7 (d, J = 8.0 Hz), 116.2, (d, J = 22 Hz), 78.6, 54.9, 42.0, 20.4, 10.6 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{12}H_{13}FNO_3$ 238.0879, found 238.0888; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.7 mL/min, λ = 254 nm), t_R major = 20.79, t_R minor = 23.29, 97% ee and dr 90:10.

(2*S*,3*R*)-2-ethyl-4-nitro-3-(p-tolyl)butanal (7m): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.102 g, 87% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 2.9 Hz, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 4.72–4.64 (m, 1H), 4.59 (dd, J = 12.5, 9.7 Hz, 1H), 3.73 (td, J = 9.8, 5.0 Hz, 1H), 2.66–2.60 (m, 1H), 2.31 (s, 3H), 1.53–1.47 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H). ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 137.9, 133.6, 129.8, 127.9, 78.7, 55.1, 42.4, 21.1, 20.4, 10.7 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1134; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.8 mL/min, λ = 254 nm), t_R major = 24.04, t_R minor = 27.75, 96% ee and dr 93:7.

(2*S*,3*R*)-3-(2-chlorophenyl)-2-ethyl-4-nitrobutanal (7n): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.108 g, 85% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, J = 2.4 Hz, 1H), 7.42–7.38 (m, 1H), 7.26–7.19 (m, 3H), 4.85 (dd, J = 12.9, 9.1 Hz, 1H), 4.67 (dd, J = 13.0, 4.7 Hz, 1H), 4.37–4.31 (m, 1H), 2.96–2.91 (m, 1H), 1.60–1.51 (m, 2H), 0.85 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 134.5, 134.4, 130.6, 129.3, 127.5, 76.8, 54.0, 39.2, 20.4, 10.7 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{12}H_{13}ClNO_3$ 254.0584, found 254.0585; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.7 mL/min, λ = 254 nm), t_R major = 23.68, t_R minor = 25.78, 96% ee and dr 92:8.

(2*S*,3*R*)-3-(3-chlorophenyl)-2-ethyl-4-nitrobutanal (7o): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.110 g, 87% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 2.3 Hz, 1H), 7.27 (dd, J = 5.6, 2.0 Hz, 2H), 7.17 (s, 1H), 7.09–7.05 (m, 1H), 4.71 (dd, J = 12.9, 4.7 Hz, 1H), 4.60 (dd, J = 13.0, 9.9 Hz, 1H), 3.80–3.73 (m, 1H), 2.69–2.63 (m, 1H), 1.55–1.46 (m, 2H), 0.84 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 139.0, 135.0, 130.4, 128.5, 128.2, 126.3, 78.2, 54.7, 42.3, 20.7, 10.6 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{12}H_{13}ClNO_3$ 254.0584, found 254.0586; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.8 mL/min, λ = 254 nm), t_R major = 19.73, t_R minor = 22.43, 97% ee and dr 89:11.

(2*S*,3*R*)-2-ethyl-3-(4-methoxyphenyl)-4-nitrobutanal (7p): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.106 g, 85% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 2.5 Hz, 1H), 7.08 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.70–4.65 (m, 1H), 4.56 (dd, J = 12.4, 9.8 Hz, 1H), 3.77 (s, 3H), 3.77–3.59 (m, 1H), 2.65–2.58 (m, 1H), 1.51–1.45 (m, 2H), 0.81 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 159.3, 129.1, 128.6, 114.5, 78.8, 55.3, 55.2, 42.1, 20.4, 10.7 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{16}H_{16}NO_4$ 250.1079, found 250.1080; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.7 mL/min, λ = 254 nm), t_R major = 31.27, t_R minor = 35.09, 95% ee and dr 91:9.

(*S*)-2-((*R*)-1-(4-fluorophenyl)-2-nitroethyl)pentanal (7q): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.11 g, 88% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 2.7 Hz, 1H), 7.16–7.12 (m, 2H), 7.03 (t, J = 8.6 Hz, 2H), 4.68 (dd, J = 12.7, 5.0 Hz, 1H), 4.59 (dd, J = 12.8, 9.8 Hz, 1H), 3.79–3.73 (m,

1H), 2.70–2.63 (m, 1H), 1.47–1.32 (m, 4H), 0.80 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 162.4 (d, J = 246 Hz), 132.6 (d, J = 3.4 Hz), 129.7 (d, J = 8.2 Hz), 116.2 (d, J = 22 Hz),116.34, 116.12, 78.5, 53.8, 42.4, 29.5, 19.7, 14.0 ppm; HRMS (ESI-TOF) m/z: [M−H]$^-$calcd for $C_{13}H_{15}FNO_3$ 252.1036, found 252.1035; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.7 mL/min, λ = 254 nm), t_R major = 19.64, t_R minor = 22.46, 95% ee and dr 95:5.

(*S*)-2-((*R*)-2-nitro-1-(p-tolyl)ethyl)pentanal (7r): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.105 g, 85% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, J = 3.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 4.68–4.58 (m, 2H), 3.72 (td, J = 9.5, 5.3 Hz, 1H), 2.69–2.63 (m, 1H), 2.31 (s, 3H), 1.46–1.28 (m, 4H), 0.79 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 137.9, 133.6, 129.8, 127.9, 78.6, 53.9, 42.9, 29.5, 21.1, 19.8, 14.0 ppm; HRMS (ESI-TOF) m/z: [M−H]$^-$calcd for $C_{14}H_{18}NO_3$ 248.1287, found 248.1281; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.8 mL/min, λ = 254 nm), t_R major = 20.25, t_R minor = 23.71, 94% ee and dr 94:6.

(*S*)-2-((*R*)-1-(2-chlorophenyl)-2-nitroethyl)pentanal (7s): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.116 g, 87% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, J = 2.7 Hz, 1H), 7.42–7.39 (m, 1H), 7.27–7.19 (m, 4H), 4.86 (dd, J = 13.0, 9.3 Hz, 1H), 4.67 (dd, J = 13.1, 4.6 Hz, 1H), 4.35–4.30 (m, 1H), 2.99–2.92 (m, 1H), 1.40–1.27 (m, 4H), 0.82 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 134.6, 134.4, 130.6, 129.3, 127.5, 76.1, 52.9, 39.6, 29.6, 19.8, 14.0 ppm; HRMS (ESI-TOF) m/z: [M−H]$^-$calcd for $C_{13}H_{15}ClNO_3$ 268.0740, found 268.0742; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.7 mL/min, λ = 254 nm), t_R major = 17.71, t_R minor = 19.58, 94% ee and dr 88:12.

(*S*)-2-((*R*)-1-(4-methoxyphenyl)-2-nitroethyl)pentanal (7t): Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.110 g, 84% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, J = 2.7 Hz, 1H), 7.07 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.66–4.55 (m, 2H), 3.78 (s, 3H), 3.69 (dd, J = 9.5, 5.3 Hz, 1H), 2.67–2.61 (m, 1H), 1.43–1.31 (m, 4H), 0.79 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 159.3, 129.1, 128.5, 114.5, 78.7, 55.3, 54.0, 42.5, 29.5, 19.8, 14.0 ppm; HRMS (ESI-TOF) m/z: [M−H]$^-$calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1239; HPLC (Chiralpak-IC column, Hexane:2-Propanol = 90:10, flow rate: 0.6 mL/min, λ = 254 nm), t_R major = 24.34, t_R minor = 28.10, 90% ee and dr 86:14.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132095.

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