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Authors: Amol B Gorde and Ramesh Ramapanicker

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Enantioselective Michael Addition Reaction of Aldehydes to β-Nitrostyrenes Catalyzed by (S)-*N*-(D-prolyl)-1-triflicamido-3-phenylpropan-2-amine

Amol B. Gorde,[a] and Ramesh Ramapanicker*[a][b]

Abstract: A new organocatalyst for the asymmetric Michael addition reaction of aldehydes with β-nitrostyrenes is developed by coupling D-proline with (S)-1-triflicamido-3-phenylpropan-2-amine, which in turn is prepared from L-phenylalaninol. The Michael addition products were obtained in very high yields (up to 93%) and with excellent enantioselectivity (up to 97% ee) and high diastereoselectivity (up to >99:1 dr). The catalyst is effective for reactions between α-branched aldehydes and β-nitrostyrenes.

Introduction

Among the various asymmetric transformations catalyzed by proline, the Michael addition reaction is one of the least efficient.[1] As a consequence, asymmetric Michael addition reactions in general and the reaction between aldehydes and nitroolefins in particular have remained as active fields of research.[2] (S)-2-triflicamidomethylpyrrolidine, prepared by the modification of L-proline, was reported as an efficient catalyst for the conjugate addition of carbonyl compounds to nitroolefins at 0 ºC by Wang et al. in 2005 (Figure 1).[3] Peptide derivatives especially those containing proline have gained particular attention as organocatalysts for the reactions of carbonyl compounds.[4] The tripeptides designed by Tsogoeva et al. is among the erliest to be used for asymmetric Michael addition reactions.[5] Among such peptide based catalysts, peptides developed by Wennemers's group are one of the most successful (Figure 1).[6] They carried out a series of studies to understand the mechanisms of these catalytic reactions, including the role of peptide conformations.[7] They have succeeded in overcoming most of the limitations associated with organocatalytic Michael addition reactions. Improved and consistent diastereoselectivity and an improvement in the reactivity of α,α-disubstituted aldehydes are probably the main challenges that remain to be addressed. The success of Wennemers's catalysts has prompted other groups to come up with similar proline containing peptide derivatives as catalysts for asymmetric Michael addition reactions. Among these, Lecouvey's peptides[8] containing a phosphonic acid side chain and the proline-sugar amino acid conjugates by Martín[9] have resulted in excellent yields and very high stereoselectivity (Figure 1). Inspired by the triflicamide catalysts developed by Wang and the peptides of Wennemers, we have recently developed D-prolyl-2-(triflicamidopropyl)pyrrolidine[10] as a very efficient catalyst for the Michael addition reaction between β-nitrostyrenes and aldehydes (Figure 1).

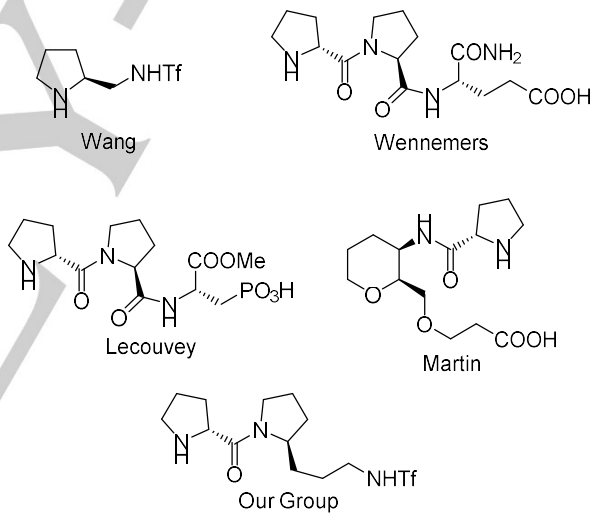

Figure 1. Catalysts previously reported for the Michael addition reaction of aldehydes with nitroolefins.

Apart from Wang's catalyst[3] and the catalyst developed by us recently,[10] those using a triflicamide (-NHTf) group as the H-bond donor for asymmetric Michael addition reactions are rare. Miura et al. used (S)-1-triflicamido-3-phenylpropan-2-amine (**1**), derived from L-phenylalanine as an organocatalyst for asymmetric aldol reactions.[11] However, **1** or its analogues,[12] reported by the same group, have not been used as catalysts for asymmetric Michael addition reactions. In continuation of our efforts to develop catalysts containing a triflicamido group for asymmetric Michael addition reactions at ambient conditions, we assumed that **1** and its L- and D-prolinamides, **2** and **3** respectively, could be interesting candidates to be analyzed (Figure 2). In addition to the use of triflicamide group as the H-bond donor in the catalyst, our investigations were aimed at

[a] Mr Amol B. Gorde and Dr Ramesh Ramapanicker
Department of Chemistry
Indian Institute of Technology Kanpur, Kanpur
Uttar Pradesh – 208016, India
E-mail: rameshr@iitk.ac.in
Webpage: www.ramapanicker.net

[b] Dr Ramesh Ramapanicker
Centre for Environmental Science and Engineering
Indian Institute of Technology Kanpur, Kanpur
Uttar Pradesh – 208016, India

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developing a catalyst that is easier to prepare and that would work at ambient conditions even for the reactions of α,α-disubstituted aldehydes.

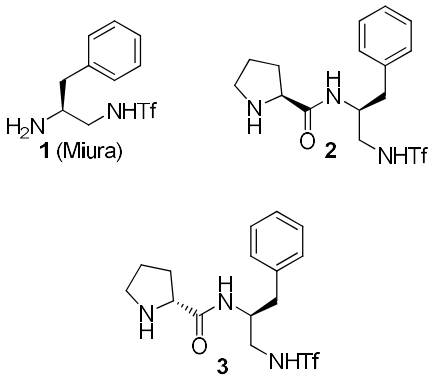
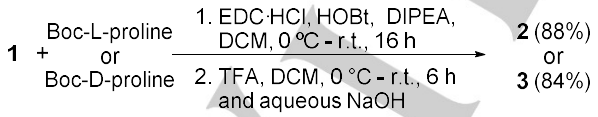


Figure 2. Molecules used as catalysts in this study.

Here we report the results of our findings, which show that compound **3**, a conjugate of D-proline and **1**, is an efficient catalyst for the asymmetric Michael addition reaction of aldehydes to β-nitrostyrenes at ambient reaction conditions. Tsogoeva and coworkers have reported the dipeptide salt H-Pro-Phe-ONa as a catalyst for Michael addition reaction in water with up to 70% ee.[13] The compounds **2** and **3** reported here are the –NHTf analogues of Tsogoeva's catalyst.

Results and Discussion

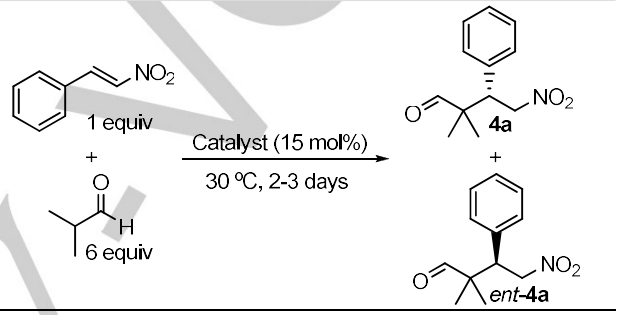
The compound **1** was prepared from L-phenylalaninol as reported by Miura.[9] **1** was coupled with *N*-Boc derivatives of L- and D-proline using standard peptide coupling conditions (EDC·HCl, HOBt, DIPEA, DCM, 0 ºC − rt). Removal of the *N*-Boc group using TFA and treating the salts with aqueous NaOH and extracting to ethyl acetate yielded **2** and **3** from Boc-L- and Boc-D-proline respectively (Scheme 1).



Scheme 1. Synthesis of **2** and **3**.

The catalytic studies were initiated by examining the reaction between isobutyraldehyde and β-nitrostyrene in different solvents at rt (30 ºC) in the presence of 15 mol% of the catalysts **1**, **2** and **3** (Table 1). The reactions were carried out until the complete consumption of β-nitrostyrene as evidenced from TLC of the reaction mixture. The products were isolated through column chromatography, and the enantiomeric excess was estimated through chiral HPLC. The chromatograms were compared with that of a racemic mixture of **4a**, which was prepared by carrying out the reaction in the presence of DL-proline. It was decided that the optimization studies would be done with isobutyraldehyde, a relatively less reactive aldehyde, to ensure that the conditions thus obtained would work for most of the other aldehydes. In general, the reactions of α-branched aldehydes are difficult and reports on their reactions are limited. A notable contribution is from Nugent et al., who developed a three component catalytic system specifically for the reaction of such aldehydes with nitroolefins.[14]

Table 1. Screening of catalysts **1**, **2** and **3**.

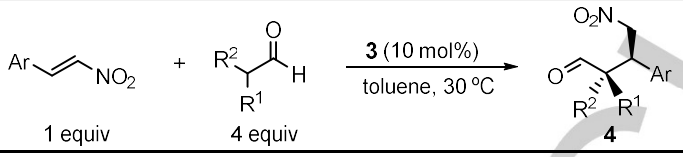


entry	solvent	(yield %)[a] and ee[b] of the major product catalyst **1**[c]	catalyst **2**[c]	catalyst **3**[d]
1	CH_3CN	(81) 10	(73) 13	(68) 40
2	IPA	(86) 44	(80) 33	(90) 42
3	DCM	(65) 78	(48) 60	(60) 84
4	Toluene	(70) 73	(83) 84	(86) 94
5	DMF	(86) 11	(86) 17	(85) 36
6	$CHCl_3$	(78) 83	(75) 68	(84) 87
7	$CHCl_3$:Toluene	(71) 80	(70) 62	(81) 89
8	THF	(68) 47	(56) 61	(76) 80

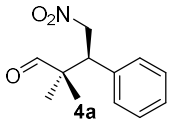
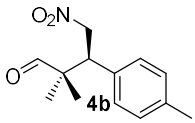
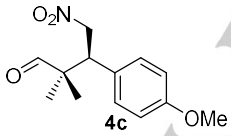
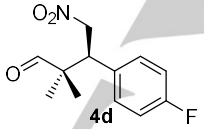
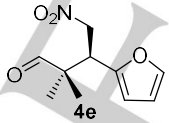
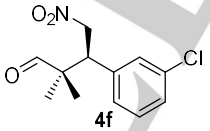
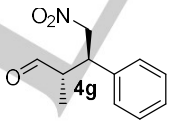
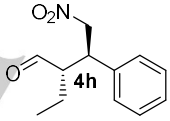
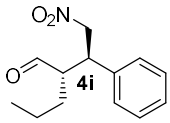
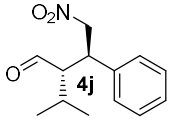
[a] Isolated yield after column chromatography. [b] *ee* as determined by chiral HPLC analysis using a Chiralpak OD-H Column. [c] major product is *ent*-**4a**; [d] major product is **4a**.

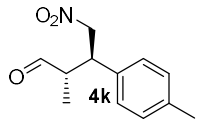
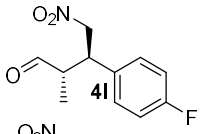
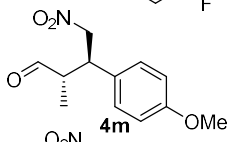
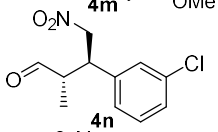
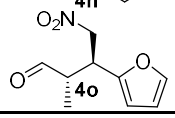
As expected, the major enantiomer formed on using catalysts **1** and **2** was the adduct *ent*-**4a**, and that obtained using **3** was **4a**. This can be explained by the stereochemistry of the amines involved in forming the enamine intermediates. Catalysts **1** and **2** uses amino groups from L-amino acids to react with the aldehyde and gives a product different from that formed using **3**, which uses the secondary amino group of D-proline. The best selectivity for the reactions using **1** was obtained in chloroform (entry 6, Table 1), while the best results using **2** and **3** were obtained in toluene (entry 4, Table 1). The yields were generally high in all the solvents while the enantioselectivity varied widely based on the solvents used. It was evident from the results that catalyst **3** is the most efficient in terms of yield and enatioselectivity achieved in the reactions. Reaction catalyzed by **3** in toluene at rt gave the best results, forming **4a** in 86% yield and with 94% ee (entry 4, Table 1).

Table 2. Reaction of aldehydes with β-nitrostyrenes in the presence of **3**.



1 equiv 4 equiv **4**

entry	reactants	product (**4**)	reaction time	Yield[a]	ee[b]	dr[c]
1	Ar = Ph $R^1 = R^2 = Me$	 **4a**	60 h	82%	94%	---
2	Ar = 4-Me-C_6H_4 $R^1 = R^2 = Me$	 **4b**	60 h	80%	94%	---
3	Ar = 4-OMe-C_6H_4 $R^1 = R^2 = Me$	 **4c**	60 h	85%	93%	---
4	Ar = 4-F-C_6H_4 $R^1 = R^2 = Me$	 **4d**	60 h	83%	94%	---
5	Ar = furyl $R^1 = R^2 = Me$	 **4e**	60 h	91%	96%	---
6	Ar = 3-Cl-C_6H_4 $R^1 = R^2 = Me$	 **4f**	60 h	81%	94%	---
7	Ar = Ph $R^1 = H, R^2 = Me$	 **4g**	36 h	92%	95%	72:28
8	Ar = Ph $R^1 = H, R^2 = Et$	 **4h**	42 h	91%	96%	90:10
9	Ar = Ph $R^1 = H, R^2 = Pr$	 **4i**	42 h	87%	96%	93:7
10	Ar = Ph $R^1 = H, R^2 = i$-Pr	 **4j**	42 h	81%	95%	>99:1

11	Ar = 4-Me-C_6H_4 R^1 = H, R^2 = Me	 **4k**	36 h	93%	95%	73:27
12	Ar = 4-F-C_6H_4 R^1 = H, R^2 = Me	 **4l**	36 h	88%	97%	78:22
13	Ar = 4-OMe-C_6H_4 R^1 = H, R^2 = Me	 **4m**	48 h	92%	95%	82:18
14	Ar = 3-Cl-C_6H_4 R^1 = H, R^2 = Me	 **4n**	36 h	85%	97%	76:24
15	Ar = furyl R^1 = H, R^2 = Me	 **4o**	36 h	93%	95%	79:21

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

We then tried to find out whether it would be possible to lower the amount of the catalyst used as well as to reduce the number of equivalents of the aldehyde required for the reaction, without affecting the efficiency of the reaction. On reducing the amount of catalyst to 10 mol% and then to 5 mol%, the reaction yielded **4a** with 82% and 48% yields respectively with no reduction in ee (94%). While complete consumption of β-nitrostyrene could be observed after 60 h in the former case, unreacted β-nitrostyrene could be recovered from the reaction mixture after 72 h in the latter. On reducing the number of equivalents of isobutyraldehyde to 4 from 6 and keeping the catalyst loading at 10 mol% resulted in completion of the reaction after 60 h and yielded **4a** in 82% yield and with 94% ee. Reducing the number of equivalents of the aldehyde further resulted in incomplete consumption of β-nitrostyrene even after 72 h. Based on these results it was assumed that 10 mol% of the catalyst in the presence of 4 equivalents of the aldehydes and 1 equivalent of β-nitrostyrenes in toluene would be the ideal condition for asymmetric Michael addition reactions using **3** as the catalyst.

Based on the results obtained from the optimization studies, we examined the utility of the catalyst **3** for effecting the reactions between aldehydes and β-nitrostyrenes. Various β-nitrostyrenes (1 equivalent) were treated with different aldehydes (4 equivalents) in toluene at rt (30 ºC) in the presence of **3** (10 mol%). The reactions were carried out until the complete disappearance of the β-nitrostyrenes on TLC after which the products were isolated by column chromatography and enantioselectivity and diastereoselectivity were determined (Table 2). Entries 1 to 6 shows the reactions of isobutyraldehyde with six different nitroolefins, entries 1 and 7-10 show the reaction of β-nitrostyrene with five different aldehydes and entries 7 and 11-15 show the reaction of propanal with six different β-nitrostyrenes. The yields obtained in all the reactions were high (80-93%), while the enantioselectivites were excellent (93-97%). Entries 7-15 show reactions that resulted in the formation of diastereomers. The diastereoselectivity obtained in these reactions were moderate to very high (72:28 – >99:1). As expected, the reactions of isobutyrealdehyde with various β-nitrostyrenes were the slowest, requiring up to 60 h for the complete consumption of the latter (entries 1-6). Propanal reacted the fastest among all the aldehydes studied and the reactions were completed within 36 h, except for the one with 4-methoxy-β-nitrostyrene, which required 48 h (entry 13). The diastereoselectivites were the lowest for reactions involving propanal, while the best diastereoselectivty was observed for the reaction between isovaleraldehyde and β-nitrostyrene (entry 10).

A direct comparison between D-Prolyl-2 -(triflicamidopropyl)pyrrolidine (Figure 1), the catalyst that we have recently reported[10] and **3** reveals that the latter is a better catalyst for two different reasons. One, the preparation of **3** is rather straight forward and is thus more easily accessible. The second and most important observation is the relatively higher enantioselectivity achieved for reactions with *n*-butanal and *n*-pentanal on using **3** as the catalyst. It was observed that the previously reported catalyst resulted in reduced enenatioselectivity with increasing chain length of linear aldehydes. With β-nitrostyrene, the reaction of propanal resulted in 95% ee, while the enantioselectivity reduced to 93% for *n*-butanal and to 86% for *n*-pentanal.[10] However, the enantioselectivity achieved for reactions with all the three aldehydes and β-nitrostyrene were similar when **3** is used as the catalyst (entries 7-9, Table 2). The high enantioselectivity

obtained in all of the reactions studied and especially those using isobutyraldehyde makes catalyst **3** a valuable addition to organocatalysts available for Michael addition reactions. A relatively high catalysts loading (10 mol%) and the need for higher reaction times provide rooms for improvement and warrants for future attempts on structural modification of **3**.

Conclusions

In an effort to develop organocatalysts that use a triflicamide group as the H-bond donor in organocatalytic Michael addition reactions, we have developed a new catalyst **3** by conjugating D-proline with Miura's triflicamide catalyst **1**. Catalyst **3** is found to be substantially better than **1** and proline itself in catalyzing the reactions between aldehydes and β-nitrostyrenes. In comparison with a catalyst that we have reported recently, the preparation of **3** is easier and the results using **3** are more consistent. The high enantioselectivity achieved in all the examples studied, including those with isobutyraldehyde, a hindered α,α-branched aldehyde, makes **3** one of the best catalysts available for Michael addition reactions at ambient conditions. Relatively high catalyst loading, longer reaction times and the requirement of four equivalents of aldehyde are the points to be addressed to establish the utility of **3** or related compounds. We are currently involved in attempts to develop catalysts based on **3** through structural modifications, which would address all of the above concerns..

Experimental Section

All the chemicals used in this study were purchased from commercial sources. Anhydrous solvents prepared using standard procedures were used for the reactions. Column chromatography of the final products were done with silica gel (particle size 60-120 and 100-200 mesh) purchased from Merck. 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 ºC. The absolute configuration of the reaction products was confirmed by HPLC analysis, by comparison with those available in the literature for the same compounds. The enantiomeric ratios were estimated by chiral HPLC analysis and diastereomeric ratios were determined from ^{1}H NMR analysis. Optical rotations were measured using a 5.0 mL cell with 10 dm path length and are reported as $[\alpha]_D^{25}$ (*c* in g per 100 mL solvent).

Procedure for the preparation of catalysts 2 and 3. A solution of Boc-Pro-OH or Boc-D-pro-OH (0.21 g, 1.0 mmol, 1.0 equiv) in DCM (20 mL) was cooled to 0 ºC. To this solution, EDC·HCl (0.28 g, 1.5 mmol, 1.5 equiv), HOBt (0.2 g, 1.5 mmol, 1.5 equiv) and DIPEA (0.43 mL, 2.5 mmol, 2.5 equiv) were added and the solution was stirred for 15 min. To the cold mixture, the primary amine **1** (0.28 g, 1 mmol, 1.0 equiv) was added as a solution in DCM (5 mL) and the mixture 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 (2 × 20 mL) and was washed with saturated $NaHCO_3$ solution (20 mL) and then with 1N $KHSO_4$ (15 mL) solution. 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 products were purified by column chromatography to get the *N*-Boc derivatives of **2** and **3**.

***tert*-butyl (*S*)-2-(((*S*)-1-phenyl-3-((trifluoromethyl)sulfonamido)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (*N*-Boc-2).** Column chromatography (50:50 petroleum ether/EtOAc); White Wax (0.43 g, 90%); $[\alpha]_D^{25}$ = –44 (*c* 0.25, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.2 Hz, 2H), 7.24 – 7.21 (m, 1H), 7.16– 7.14 (m, 2H), 6.48 (d, *J* = 3.5 Hz, 1H), 4.18 – 3.99 (m, 2H), 3.59 – 3.19 (m, 4H), 2.88 (d, *J* = 2.0 Hz, 2H), 2.02 – 1.69 (m, 4H), 1.44 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 156.0, 136.8, 129.0, 128.8, 127.1, 119.8 (q, *J* = 320.5 Hz) 81.3, 60.8, 52.2, 47.3, 46.9, 37.3, 29.0, 28.4, 24.4 ppm; FTIR(thin film): ū = 3301, 3089, 2975, 2931, 1698, 1659, 1534, 1497, 1478, 1455, 1417, 1377, 1331, 1229, 1162, 1151, cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{29}F_3N_3O_5S$ 480.1780, found 480.1789.

***tert*-butyl (*R*)-2-(((*S*)-1-phenyl-3-((trifluoromethyl)sulfonamido)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (*N*-Boc-3).** Column chromatography (60:40 petroleum ether/EtOAc); White Wax (0.41 g, 86%); $[\alpha]_D^{25}$ = +28 (*c* 0.25, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.2 Hz, 2H), 7.24 – 7.15 (m, 3H), 6.42 (d, *J* = 8.1 Hz, 1H), 4.29 – 4.17 (m, 1H), 4.06 – 3.87 (m, 1H), 3.66 – 3.53 (m, 1H), 3.46 – 3.31 (m, 2H), 3.24 (dt, *J* = 13.2, 6.5 Hz, 1H), 2.85 (d, *J* = 6.0 Hz, 2H), 2.06 – 1.89 (m, 3H), 1.83 – 1.75 (m, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 155.8, 136.5, 129.2, 128.8, 127.0, 119.8 (q, *J* = 321.0 Hz), 81.2, 60.7, 51.0, 47.3, 46.6, 37.6, 29.2, 28.4, 24.6 ppm; FTIR(thin film): ū = 3301, 3031, 2990, 2938, 1666, 1597, 1528, 1491, 1460, 1445, 1410, 1377, 1320, 1229, 1162, 1151, cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{29}F_3N_3O_5S$ 480.1780, found 480.1785.

To stirred solutions of the *N*-Boc derivatives of **2** and **3**, (1.0 mmol, 1.00 equiv) in dry DCM (10 mL), TFA (10 mL) was added at 0 °C and the solutions were stirred at rt for 8 h. Reactions were monitored through TLC and after the complete consumption of the starting materials the reaction mixtures were concentrated under reduced pressure and 2N NaOH solution was added to get a solution with pH 12, which were then extracted with ethyl acetate (3 × 30 mL) and dried over anhydrous Na_2SO_4 and filtered. Solvents were removed under reduced pressure to get **2** and **3**.

(*S*)-*N*-(L-prolyl)-1-triflicamido-3-phenylpropan-2-amine (2). White solid, mp 90-92 °C (0.33 g, 88%); $[\alpha]_D^{25}$ = –45.6 (*c* 0.25, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 3.4 Hz, 2H), 7.23 – 7.18 (m, 1H), 7.17 – 7.12 (m, 2H), 4.39 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.03 – 3.94 (m, 1H), 3.54 – 3.47 (m, 1H), 3.40 – 3.27 (m, 3H), 3.00 (dd, *J* = 13.9, 8.4 Hz, 1H), 2.84 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.28 – 2.20 (m, 1H), 1.96 – 1.85 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 136.8, 129.0, 128.7, 127.0, 119.9 (q, *J* = 321.4 Hz),60.1, 53.8, 46.6, 46.0, 36.8, 29.8, 24.4 ppm; FTIR(thin film): ū = 3452, 3062, 2925, 1670, 1578, 1496, 1455, 1374, 1230, 1193, 1147, cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{21}F_3N_3O_3S$ 380.1256, found 380.1259.

(*S*)-*N*-(D-prolyl)-1-triflicamido-3-phenylpropan-2-amine (3). White solid, mp 138-140 °C (0.31 g, 84%); $[\alpha]_D^{25}$ = +6.4 (*c* 0.25, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.47 (s, 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.28 – 7.15 (m, 5H), 4.45 – 4.35 (m, 1H), 4.26–4.20 (m, 1H), 3.54 (dd, *J* = 14.0, 3.4 Hz, 1H), 3.38 – 3.16 (m, 3H), 2.87 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.69 (dd, *J* = 14.0, 9.3 Hz, 1H), 2.17 (ddd, *J* = 14.0, 13.0, 7.3 Hz, 1H), 1.93 – 1.88 (m, 1H), 1.72 – 1.58 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 136.6, 129.2, 128.6, 126.9, 119.7 (q, *J* = 320.9 Hz), 59.6, 52.0, 46.7, 46.6, 38.3, 30.2, 24.2 ppm; FTIR(thin film): ū = 3410, 3069, 2976, 1674, 1610, 1452, 1365, 1340, 1276, 1190, cm^{-1}. HRMS

(ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{21}F_3N_3O_3S$ 380.1256, found 380.1263.

General procedure for the Michael addition of aldehydes to nitroalkenes. Nitroalkenes (0.5 mmol, 1.0 equiv) and the catalyst **3** were added to a stirred solution of the aldehydes (2.0 mmol, 4.0 equiv) in toluene (2 mL) at rt. The solution was stirred until the complete disappearance of the nitroalkenes on TLC. Toluene was removed under reduced pressure and the crude mixtures containing γ-nitro aldehydes **4** were purified by column chromatography. Diastereomeric ratios, wherever applicable, were determined from the ^{1}H NMR of the crude reaction mixtures and enantiomeric ratios were determined by HPLC analysis of the purified compounds.

Initial screening of the catalysts was done using a similar procedure as above, where the solvents and catalysts were varied as required. Racemic mixtures of the γ-nitro aldehydes were prepared for each of those listed in Table 3 by carrying out the reactions in the presence of 20 mol% of DL-proline as the catalyst and were used as references for HPLC analysis.

(*S*)-2,2-dimethyl-4-nitro-3-phenylbutanal (4a). Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil, (0.09 g, 82% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.34 – 7.28 (m, 3H),7.18 (dd, *J* = 7.6, 1.2 Hz, 2H), 4.84 (dd, *J* = 13.0, 11.3 Hz, 1H), 4.68 (dd, *J* = 13.0, 4.2 Hz, 1H), 3.77 (dd, *J* = 11.3, 4.2 Hz, 1H), 1.13 (s, 3H), 1.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 135.3, 129.1, 128.8, 128.2, 76.3, 48.5, 48.3, 21.7, 18.9 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_{12}H_{14}NO_3$ 220.0974, found 220.0977; HPLC (Chiralpak OD-H column, Hexane:2-propanol = 90:10, flow rate: 1 mL/min, λ= 254 nm), t_R minor= 15.10, t_R major= 21.80, 94% ee.

(*S*)-2,2-dimethyl-4-nitro-3-(p-tolyl)butanal (4b). Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.09 g, 80% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 4.81 (dd, *J* = 12.9, 11.4 Hz, 1H), 4.65 (dd, *J* = 12.9, 4.3 Hz, 1H), 3.72 (dd, *J* = 11.3, 4.2 Hz, 1H), 2.30 (s, 3H), 1.11 (s, 3H), 0.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 138.0, 132.2, 129.4, 128.9, 76.4, 48.3, 48.2, 21.6, 21.1, 18.9 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1147 ; HPLC (Chiralpak OD-H column, Hexane:2-Propanol = 90:10, flow rate: 1 mL/min, λ= 254 nm), t_R minor= 11.43, t_R major= 15.28, 94% ee.

(*S*)-3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (4c). Column chromatography (90:10 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 85% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.83 – 4.75 (m, 1H), 4.64 (dd, *J* = 12.8, 4.2 Hz, 1H), 3.77 (s, 3H), 3.71 (dd, *J* = 11.4, 4.3 Hz, 1H), 1.10 (s, 3H), 0.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 159.4, 130.1, 127.1, 114.1, 76.5, 55.3, 48.4, 47.9, 21.6, 18.9 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_{13}H_{16}NO_4$ 250.1079, found 250.1089; HPLC (Chiralpak OD-H column, Hexane:2-Propanol = 90:10, flow rate: 0.9 mL/min, λ = 254 nm), t_R minor= 24.25, t_R major= 33.52, 93% ee.

(*S*)-3-(4-fluorophenyl)-2,2-dimethyl-4-nitrobutanal (4d). Column chromatography (88:12 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 83% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.19 – 7.15 (m, 2H), 7.02 (t, *J* = 8.6 Hz, 2H), 4.81 (dd, *J* = 13.0, 11.5 Hz, 1H), 4.68 (dd, *J* = 13.1, 4.1 Hz, 1H), 3.76 (dd, *J* = 11.4, 4.2 Hz, 1H), 1.11 (s, 3H), 1.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 162.5 (d, *J* = 247.7 Hz), 131.2 (d, *J* = 2.9 Hz), 130.7 (d, *J* = 7.9 Hz), 115.8 (d, *J* = 21.5 Hz), 76.4, 48.3, 47.9, 21.8, 19.0 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_{12}H_{13}FNO_3$ 238.0879, found 238.0877; HPLC (Chiralpak OD-H column, Hexane:2-Propanol = 90:10, flow rate: 1 mL/min, λ = 254 nm), t_R minor= 13.28, t_R major= 21.67, 94% ee.

(*S*)-3-(furan-2-yl)-2,2-dimethyl-4-nitrobutanal (4e). Column chromatography (85:15 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 91% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 6.30 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 4.74 (dd, *J* = 12.9, 11.0 Hz, 1H), 4.57 (dd, *J* = 12.9, 4.0 Hz, 1H), 3.91 (dd, *J* = 11.0, 3.8 Hz, 1H), 1.16 (s, 3H), 1.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 149.8, 142.8, 110.5, 109.7, 74.9, 48.2, 42.3, 21.2, 19.1 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_{10}H_{12}NO_4$ 210.0766, found 210.0760; HPLC (Chiralpak OD-H column, Hexane:2-Propanol = 90:10, flow rate: 0.9 mL/min, λ = 254 nm), t_R minor= 16.45, t_R major= 24.13, 96% ee.

(*S*)-3-(3-chlorophenyl)-2,2-dimethyl-4-nitrobutanal (4f). Column chromatography (85:15 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 81% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 9.51 (s, 1H), 7.29 (dd, *J* = 4.8, 2.0 Hz, 2H), 7.21 (s, 1H), 7.12 – 7.09 (m, 1H), 4.87 – 4.80 (m, 1H), 4.70 (dd, *J* = 13.2, 4.1 Hz, 1H), 3.80 – 3.75 (m, 1H), 1.15 (s, 3H), 1.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 137.7, 134.7, 130.0, 129.3, 128.5, 127.3, 76.1, 48.2, 48.1, 21.9, 19.0 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_{12}H_{13}ClNO_3$ 254.0584, found 254.0583; HPLC (Chiralpak OD-H column, Hexane:2-Propanol = 90:10, flow rate: 0.9 mL/min, λ = 254 nm), t_R minor= 11.06, t_R major= 18.77, 94% ee.

(2*S*,3*R*)-2-methyl-4-nitro-3-phenylbutanal (4g). Column chromatography (85:15 petroleum ether/EtOAc); Pale yellow oil (0.09 g, 92% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.8 Hz, 1H), 7.34 – 7.29 (m, 3H), 7.18 (m, 2H), 4.80 – 4.76 (m, 1H), 4.67 (dd, *J* = 12.6, 9.4 Hz, 1H), 3.83 – 3.78 (m, 1H), 2.81 – 2.75 (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: 0.9 mL/min, λ = 254 nm), t_R major = 22.41, t_R minor = 27.29, 95% ee and 72:28 dr.

(2*S*,3*R*)-2-ethyl-4-nitro-3-phenylbutanal (4h). Column chromatography (85:15 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 91% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 2.6 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.17 (dd, *J* = 5.2, 3.1 Hz, 2H), 4.71 (dd, *J* = 12.6, 5.0 Hz, 1H), 4.62 (dd, *J* = 12.6, 9.7 Hz, 1H), 3.78 (td, *J* = 9.8, 5.1 Hz, 1H), 2.69–2.64 (m, 1H), 1.54 – 1.48 (m, 2H), 0.82 (t, *J* = 7.4 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: 1 mL/min, λ = 254 nm), t_R major= 18.67, t_R minor= 22.04, 96% ee and 90:10 dr.

(*S*)-2-((*R*)-2-nitro-1-phenylethyl)pentanal (4i). Column chromatography (85:15 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 87% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) 9.69 (d, *J* = 2.7 Hz, 1H), 7.35–7.28 (m, 3H), 7.19 – 7.14 (m, 2H), 4.71 – 4.59 (m, 2H), 3.76 (td, *J* = 9.5, 5.4 Hz, 1H), 2.69 (tt, *J* = 9.5, 3.2 Hz, 1H), 1.45 – 1.24 (m, 4H), 0.79 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 136.8, 129.1, 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 = 93:7, flow rate: 1 mL/min, λ = 254 nm), t_R major= 20.15, t_R minor= 24.26, 96% ee and 93:7 dr.

(2S,3R)-2-isopropyl-4-nitro-3-phenylbutanal (4j). Column chromatography (85:15 petroleum ether/EtOAc); Pale yellow oil (0.09 g, 81% 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* = 12.5, 4.4 Hz, 1H), 4.56 (dd, *J* = 12.5, 9.9 Hz, 1H), 3.89 (td, *J* = 10.3, 4.4 Hz, 1H), 2.76 (ddd, *J* = 10.7, 4.1, 2.4 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 7.0 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 234.1117; HPLC (Chiralpak IC column, Hexane:2–Propanol = 99:1, flow rate: 1 mL/min, λ = 254 nm), t_R major= 14.77, t_R minor= 17.40, 95% ee and >99:1 dr.

(2*S*,3*R*)-2-methyl-4-nitro-3-(*p*-tolyl)butanal (4k). Column chromatography (85:15 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 93% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 1.8 Hz, 1H), 7.12 – 7.10 (m, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 4.75 (dd, *J* = 6.7, 3.1 Hz, 1H), 4.67 – 4.61 (m, 1H), 3.76 (dd, *J* = 9.0, 3.3 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.31 (s, 3H), 0.98 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 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: 1 mL/min, λ = 254 nm), t_R major = 20.70, t_R minor = 25.47, 95% ee and 73:27 dr.

(2*S*,3*R*)-3-(4-fluorophenyl)-2-methyl-4-nitrobutanal (4l). Column chromatography (80:20 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 88% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.3 Hz, 1H), 7.18–7.12 (2H), 7.04 – 7.00 (m, 2H), 4.78 – 4.74 (m, 1H), 4.65 – 4.60 (m, 1H), 3.79 (td, *J* = 9.3, 5.3 Hz, 1H), 2.79 – 2.71 (m, 1H), 0.98 (d, *J* = 7.3 Hz, 3H ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 162.4 (d, *J* = 247.3 Hz), 132.4 (d, *J* = 2.9 Hz), 129.7 (d, *J* = 8.2 Hz), 116.1 (d, *J* = 21.7 Hz), 78.2, 48.4, 43.3, 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: 1 mL/min, λ = 254 nm), t_R major= 21.23, t_R minor = 25.00, 97% ee and 78:22 dr.

(2*S*,3*R*)-3-(4-methoxyphenyl)-2-methyl-4-nitrobutanal (4m). Column chromatography (80:20 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 92% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 1.7 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.75 (dd, *J* = 7.5, 2.1 Hz, 1H), 4.65 – 4.59 (m, 1H), 3.77 (s, 3H), 3.76 – 3.72 (m, 1H), 2.76-2.68(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: 1 mL/min, λ = 254 nm), t_R major= 30.43, t_R minor = 35.08, 95% ee and 82:18 dr.

(2*S*,3*R*)-3-(3-chlorophenyl)-2-methyl-4-nitrobutanal (4n). Column chromatography (80:20 petroleum ether/EtOAc); Pale yellow oil (0.10 g, 85% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 1.4 Hz, 1H), 7.28–7.25 (m, 2H), 7.16 (s, 1H), 7.07 – 7.04 (m, 1H), 4.77 (d, *J* = 5.0 Hz, 1H), 4.67 – 4.61 (m, 1H), 3.77 (dd, *J* = 9.2, 4.0 Hz, 1H), 2.82 – 2.74 (m, 1H), 1.01 (d, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 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: 1 mL/min, λ = 254 nm), t_R major= 20.07, t_R minor = 23.61, 97% ee and 76:24 dr.

(2*S*,3*S*)-3-(furan-2-yl)-2-methyl-4-nitrobutanal (4o). Column chromatography (85:15 petroleum ether/EtOAc); Pale yellow oil (0.09 g, 93% Yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 0.8 Hz, 1H), 7.35 (dd, *J* = 3.2, 1.4 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.18 (dd, *J* = 8.5, 3.2 Hz, 1H), 4.71 (dd, *J* = 8.2, 6.9 Hz, 2H), 4.10 – 4.04 (m, 1H), 2.79 (dd, *J* = 7.3, 6.7 Hz, 1H), 1.06 (d, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 149.9, 142.7, 110.5, 108.8, 75.8, 47.1, 37.7, 11.0 ppm; HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_9H_{10}NO_4$ 196.0610, found 196.0625; HPLC (Chiralpak IC column, Hexane:2–Propanol = 90:10, flow rate: 1 mL/min, λ = 254 nm), t_R major= 15.21, t_R minor = 21.05, 95% ee and 79:21 dr.

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Keywords: Michael addition • organocatalysis • aldehydes • nitroalkenes • enantioselectivity

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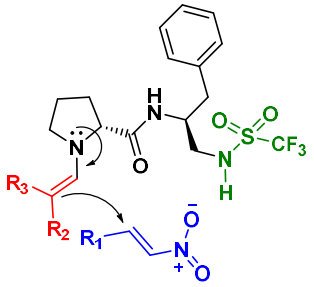
Asymmetric Organocatalysis

A D-prolinamide catalyst containing a triflicamide group as the H-bond donor, for the asymmetric Michael addition reactions of β-nitroalkenes with aldehydes is developed. Very high enantioselectivity and yields are achieved using 10 mol% of the catalyst at rt in toluene.



enantiomeric ratio up to 98.5:1.5
diastereomeric ratio up to >99:1

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Enantioselective Michael Addition Reaction of Aldehydes to β-Nitrostyrenes Catalyzed by (S)-*N*-(D-prolyl)-1-triflicamido-3-phenylpropan-2-amine