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Aromatic L-prolinamide-catalyzed asymmetric Michael addition of aldehydes to nitroalkenes

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ABSTRACT

Two chiral aromatic L-prolinamides were synthesized in high overall yield (95%) from *N*-Boc-L-proline and served as organocatalysts in asymmetric Michael reactions of aldehydes to nitroalkenes. Under the optimized reaction conditions, (*S*)-*N*-tritylpyrrolidine-2-carboxamide **4** was found to be a highly efficient organocatalyst for the Michael addition, and the corresponding Michael adducts were obtained in good yields (up to 94%), with excellent enantioselectivities (up to 99% ee) and diastereoselectivities (up to 99:1 dr).

1. Introduction

Asymmetric organocatalysis has emerged as a new, powerful, and environmentally friendly methodology for the catalytic production of enantiomerically pure organic compounds and is also one of the most rapidly growing and competitive research areas in synthetic organic chemistry.[1] The organocatalytic asymmetric Michael addition reaction has attracted growing attention in organic synthesis to form carbon—carbon bonds.[2]

Among the various types of Michael addition, the conjugate addition of aldehydes or ketones with nitroalkenes to afford γ-nitrocarbonyl compounds is especially important for their key role in stereocontrolling steps in the enantioselective synthesis of chiral biologically active compounds and natural products.[3–5] Recently, tremendous effort has been made in developing efficient organocatalysts, including L-proline derivatives,[6] chiral sulfonamides[7] and chiral thioureas.[8] Among, then L-proline **1** and its derivatives, such as (*R*)-diarylprolinol **2**, diarylprolinol silyl ethers, prolinamides, and pyrrolidines, are commonly used in asymmetric catalysis. Prolinamide derivatives have been demonstrated to be excellent reagents in asymmetric enamine organocatalysis.[9] Although these organocatalysts give good results in asymmetric Michael addition reactions, the discovery of environmentally friendly non-metal catalyzed asymmetric organocatalysts in Michael addition reactions is still needed. To the best of our knowledge, there are only a few reports to date of aromatic L-prolinamide derivatives used as organocatalyst in asymmetric Michael addition reactions.[10] We have designed and synthesized chiral aromatic L-prolinamide in high overall yield from *N*-Boc-L-proline, and found that compound **4** was excellent for catalyzing asymmetric Michael additions of aldehydes to nitroalkenes. Herein we report our preliminary results using our self-assembled organocatalysts in direct Michael additions of aldehydes to nitroalkenes (Fig. 1).

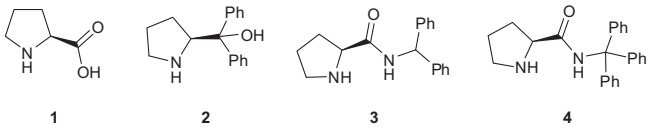

Figure 1. Structure of aromatic L-proline derivative catalysts.

2. Results and discussion

Chiral aromatic L-prolinamides **3** and **4** were easily prepared in two steps from commercially available Boc-L-proline and the corresponding amine component in 95% overall yield (Scheme 1). Boc-L-proline was treated separately with aminodiphenylmethane and tritylamine in the presence of the corresponding additives to afford the protected prolinamides **3a** and **4a**. Deprotection of the Boc group using TFA in dry dichloromethane afforded chiral L-prolinamide catalysts **3** and **4**.

Initially, the Michael reaction of acetaldehyde **5a** and *trans*-β-nitrostyrene **6a** was selected as a model reaction (Table 1). The catalytic properties of L-proline **1**, (*R*)-diphenylprolinol **2**, and catalysts **3** and **4** were evaluated by examining the addition reaction in dichloromethane with 10% benzoic acid as the additive at room

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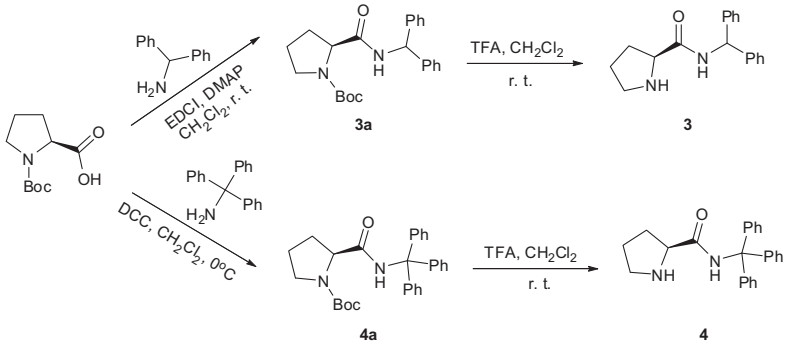
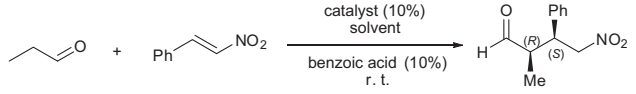


Scheme 1. Synthesis of catalysts **3** and **4**.

Table 1
Screening of the catalysts and solvents[a]

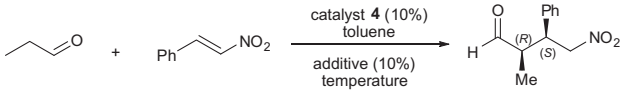


5a 6a 7a

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee(*syn*)[d] (%)
1	**1**	CH_2Cl_2	24	36	66:34	40
2	**2**	CH_2Cl_2	12	54	64:36	92
3	**3**	CH_2Cl_2	24	91	89:11	72
4	**4**	CH_2Cl_2	18	87	67:33	84
5	**4**	$CHCl_3$	18	85	64:33	72
6	**4**	THF	24	67	62:38	54
7	**4**	CH_3CN	36	61	75:25	36
8	**4**	Hexane	36	55	70:30	76
9	**4**	*i*-Propanol	36	54	72:28	43
10	**4**	**Toluene**	**12**	**93**	**74:26**	**85**
11[e]	**4**	Toluene	36	68	70:30	82

[a] All reactions were carried out with **5a** (3.0 mmol), **6a** (1.0 mmol), and benzoic acid (10 mol %) in the presence of catalyst (10 mol %) in solvent (1.0 mL) at room temperature.
[b] Yield of the isolated product.
[c] Determined by ^{1}H NMR analysis of the crude products.
[d] Determined by chiral HPLC. The absolute configuration was established by comparison with literature date.[11]
[e] 5 mol % of catalyst **4** was used.

Table 2
Screening of additives and temperatures[a]



5a 6a 7a

Entry	Additive	*T* (°C)	Time (h)	Yield[b] (%)	*syn*:*anti*[c]	ee(*syn*)[d] (%)
1	None	rt	48	<5	nd	nd
2	H_2O	rt	48	<5	nd	nd
3	Et_3N	rt	48	<5	nd	nd
4	*p*-TSA	rt	48	<10	nd	nd
5	Tartaric acid	rt	48	<10	nd	nd
6	CF_3COOH	rt	48	<10	nd	nd
7	CHOOH	rt	12	94	65:35	70
8	CH_3COOH	rt	18	87	70:30	80
9	PhCOOH	rt	12	93	74:26	85
10[e]	PhCOOH	rt	24	51	65:35	82
11	PhCOOH	0	18	92	70:30	87
12	**PhCOOH**	**−20**	**24**	**91**	**64:36**	**89**
13	PhCOOH	−40	48	59	69:31	91
14	PhCOOH	−78	48	27	67:33	93

[a] All reactions were carried out with **5a** (3.0 mmol) and **6a** (1.0 mmol) in the presence of catalyst **4** (10 mol %) in toluene (1.0 mL).
[b] Yield of the isolated product.
[c] Determined by ^{1}H NMR analysis of the crude products.
[d] Determined by chiral HPLC. The absolute configuration was established by comparison with literature data.[11]
[e] 5 mol % of PhCOOH was used.

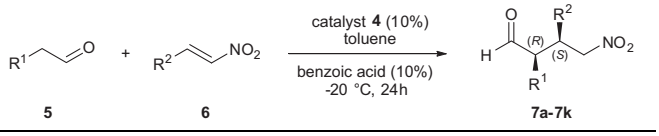
temperature. As shown in Table 1, L-proline could catalyze this reaction, but rather poor yields and stereoselectivity were observed (Table 1, entry 1). Although (*R*)-diarylprolinol **2** could efficiently promote the enantioselectivity (92% ee, entry 2), the moderate yields (54%) were unsatisfactory. Prolinamide **3** was also evaluated (entry 3). Although an excellent yield (91%) was obtained, the enantioselectivity (72% ee) was moderate. When aromatic L-prolinamide **4** was used, the best result was observed with a high yield (87%), good diastereoselectivities (*syn*/*anti* = 67:33) and enantioselectivity (84% ee) (entry 4). According to the above result, catalyst **4** was confirmed to be the most effective catalyst in terms of both the yield and enantioselectivity of the reaction.

To further optimize the reaction conditions, some reaction parameters, including the solvent, additive, temperature, and amount of catalyst were examined, and the results are shown in Tables 1 and 2. A range of typical solvents was first screened in the presence of benzoic acid (10 mol %) and catalyst **4** (10 mol %) at room temperature. Among the solvents screened, toluene (Table 1, entry 9) exhibited the best performance for both the yield (93%) and stereoselectivity (85% ee). Moreover, we examined the influence of catalyst loading on the reaction. When reducing the catalyst loading from 10 mol % to 5 mol %, the reaction rate rapidly decreased from 93% to 68% (entry 11). Next, the effect of a series of different additives was tested and the results are summarized in Table 2. The reaction proceeded very slowly in the absence of acid additives and gave poor yield and enantioselectivity after 48 h (Table 2, entries 1–3). When benzoic acid was used as an acid additive, better results were observed with an excellent yield (93%) and enantioselectivity (85%, ee) (Table 2, entry 9). Although other acid additives, such as HCOOH and CH_3COOH, were beneficial for this reaction, their yields and enantioselectivities were slightly lower than the results with PhCOOH (Table 2, entries 7 and 8). The addition of a strong acid, such as *p*-TSA or TFA, was not favorable to the reaction (Table 2, entries 4 and 6). In addition, when tartaric acid was employed, it gave poor yield and enantioselectivities (Table 2, entry 5). We found that temperature had an important influence on the yield and stereoselectivity of the reaction. It was obvious that good enantioselectivity could be obtained with a low reaction temperature. Based on the overall evaluation, −20 °C was selected to be the optimal reaction temperature.

Thus, the catalytic system consisting of 10 mol % of **4** and 10 mol % of benzoic acid in toluene solution at −20 °C was proposed to be the most efficient conditions for the asymmetric Michael addition of aldehydes to nitrostyrene. Under the above optimized

conditions, the scope of the asymmetric Michael addition was investigated by applying different aldehydes and nitrostyrene (Table 3). The results showed that this catalytic system had good compatibility with various aldehydes and nitrostyrene. Products were obtained with good yields (79–94%) and excellent enantioselectivities (89–99%). The steric hindrance of the R^1 group for aliphatic aldehydes increased the diastereoselectivity to a large degree (entries 1–4 and 12–16). Moreover, various styrene-type nitroolefins reacted smoothly with various aldehydes in good to excellent yields (83–94%) and with high enantioselectivity (89–99%) (entries 1–10 and 12–15). Excellent enantioselectivities (93–99% ee) were also observed for the Michael addition of aldehydes to nitroalkenes containing heteroaryl groups (entries 11 and 16).

Table 3
Asymmetric Michael additions of aldehydes to nitroalkenes catalyzed by **4**[a]



5 **6** **7a-7k**

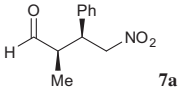
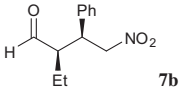
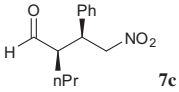
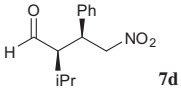
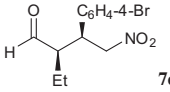
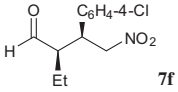
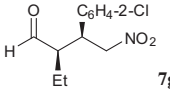
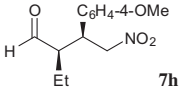
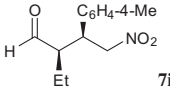
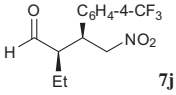
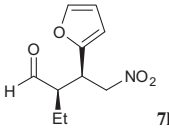
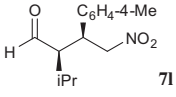
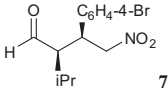
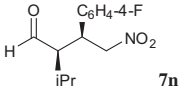
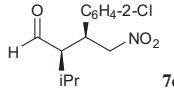
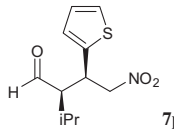
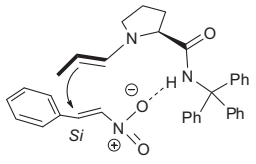
Entry	Product	Yield[b] (%)	*syn*:*anti*[c]	ee (*syn*)[d] (%)
1	 **7a**	91	63:37	89
2	 **7b**	90	61:39	90
3	 **7c**	87	57:43	90
4	 **7d**	79	99:1	96
5	 **7e**	93	61:39	90
6	 **7f**	90	57:43	92
7	 **7g**	83	63:35	89
8	 **7h**	83	65:35	91
9	 **7i**	94	85:15	96
10	 **7j**	92	93:7	89
11	 **7k**	87	84:16	93
12	 **7l**	91	99:1	98
13	 **7m**	92	98:2	99
14	 **7n**	90	96:4	96

Table 3 (*continued*)

Entry	Product	Yield[b] (%)	*syn*:*anti*[c]	ee (*syn*)[d] (%)
15	 **7o**	88	99:1	97
16	 **7p**	89	99:1	99

[a] All reactions were carried out with nitroalkenes (1.0 mmol) and aldehydes (3.0 mmol) in the presence of catalyst **4** (10 mol %) in toluene (1.0 mL) at 0 °C.
[b] Yield of the isolated product.
[c] Determined by ^{1}H NMR analysis of the crude products.
[d] Determined by chiral HPLC. The absolute configuration was established by comparison with literature data.[11]

In order to account for the good enantioselectivity of the reaction, a plausible transition-state model is proposed in Scheme 2. The pyrrolidine activates the aldehyde through the formation of an enamine intermediate, and the nitro group of *trans*-β-nitrostyrene is directed toward the amide group by a hydrogen bond between the NH group of the amide and the nitro group. The enamine formed in situ attacks the *Si* face of the nitroalkene to furnish the Michael adduct. It is noteworthy that the bulky aromatic group is considered to be important with regards to the high catalytic activity and enantioselectivity and diastereoselectivity of the catalyzed reactions. Our previous research[11] and some other literature[12,13] could be used to support the proposed transition-state model.



Scheme 2. Possible transition state of the reaction.

3. Conclusions

In conclusion, we have synthesized two new L-prolinamides **3** and **4** as catalysts from commercially available Boc-L-proline in high yield (95%). These catalysts were found to efficiently catalyze asymmetric Michael addition reactions of aldehydes and nitroalkenes under mild conditions. In the presence of (*S*)-*N*-tritylpyrrolidine-2-carboxamide **4** (10%), the asymmetric Michael addition reaction proved to be applicable to a variety of aldehydes and nitroalkenes, affording the products in high yields of 94%, and with excellent diastereoselectivity (up to 99:1 dr) and enantioselectivity (up to 99%). Further applications of these chiral amides are currently underway in our laboratory.

4. Experimental

4.1. General

Reagents and materials were of the highest commercially available grade and used without further purification. Solvents were purified by standard procedures and distilled before use. The NMR spectra were recorded on a Bruker DRX400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) with TMS as the internal standard, chemical shifts (δ) are expressed in ppm, J values are given in Hz, and deuterated $CDCl_3$ was used as the solvent. High resolution mass spectrometry (HRMS) was recorded on a VG Auto Spec-3000 spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. The mass spectroscopic data were obtained at the Agilent 1100 LC/MSD Trap LC-mass spectrometer. HPLC analysis was performed with a Shimadzu LC-10A instrument equipped with Daicel HPLC columns. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. Column chromatography was performed on silica gel (200–300 mesh). Compounds were visualized by UV and spraying with H_2SO_4 (10%) in ethanol followed by heating.

4.2. Procedure for the synthesis of catalysts 3

4.2.1. Procedure for the synthesis of 3a

To a stirred solution of *N*-*t*-butyloxycarbonyl-L-proline (1.075 g, 5 mmol) in dry dichloromethane (15 mL) was added DMAP (210 mg, 1.5 mmol). The mixture was allowed to stir for 15 min and then cooled to 0 °C after which EDCI (1.22 g, 5.5 mmol) was added. After 20 min, a solution of 1,1-diphenylmethylamine (676 mg,4 mmol) in dichloromethane (15 mL) was added to the above reaction mixture. The resulting solution was stirred at room temperature until complete consumption of the nitroalkene (monitored by TLC). The reaction was quenched with water and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated brine solution (20 mL), followed by drying over Na_2SO_4 and evaporation in vacuo. The crude product was purified by column chromatography to give pure *tert*-butyl (*S*)-2-(benzhydrylcarbamoyl)pyrrolidine-1-carboxylate **3a** as an amorphous powder, 97% yield. $[\alpha]_D^{20} = -78.6$ (c 1.0, $CHCl_3$); IR (KBr) 698, 1160, 1245, 1384, 1540, 1654, 1699, 2974, 3288 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{28}N_2O_3$ $[M+Na]^+$ 403.1992, found 403.1993. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.97 (s, 1H), 7.38–7.24 (m, 10H), 6.24 (d, J = 27.2 Hz, 1H), 4.35 (d, J = 26.8 Hz, 1H), 3.39 (d, J = 59.2 Hz, 1H), 2.42 (s, 1H), 2.19 (s, 1H), 1.88 (s, 3H), 1.46 (s, 5H), 1.32 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 170.8, 156.1, 141.8, 128.6, 128.5, 127.5, 127.2, 127.0, 126.9, 80.5, 61.3, 59.7, 56.7, 47.2, 31.1, 28.3, 27.5, 24.7, 23.9.

4.2.2. Procedure for the synthesis of 3

To a solution of *tert*-butyl (*S*)-2-(benzhydrylcarbamoyl)pyrrolidine-1-carboxylate (4 mmol) in CH_2Cl_2 (10 mL) was added TFA (3 mL). After stirring at 0 °C for 2.5 h, the solution was concentrated under vacuum to leave a glutinous phase. The pH of the mixture was brought to 12 by the addition of 2 M NaOH. The aqueous phase was extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered off and the solvent was evaporated off at low pressure to give a crude residue, which was purified by column chromatography to give pure (*S*)-*N*-benzhydrylpyrrolidine-2-carboxamide **3** as an amorphous powder, 98% yield. $[\alpha]_D^{20} = -59.0$ (c 1.0, $CHCl_3$); IR (KBr) 694, 751, 918, 1106, 1495, 1662, 2851, 2953, 3309 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{20}N_2O$, $[M+H]^+$ 281.1648, found 281.1650. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.42 (d, J = 8.4 Hz, 1H), 7.32–7.19 (m, 10H), 6.21 (d, J = 8.8 Hz, 1H), 3.80–3.76 (m, 1H), 3.25–3.19 (m, 1H), 3.03–2.87 (m, 1H), 2.18–2.08 (m, 1H), 1.99–1.92 (m, 1H), 1.76–1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 174.2, 142.0, 128.6, 128.6, 127.5, 127.3, 127.2, 127.1, 60.6, 56.1, 47.3, 30.8, 26.3.

4.3. Procedure for the synthesis of catalysts 4

4.3.1. Procedure for the synthesis of 4a

A solution of *N*-*t*-butyloxycarbonyl-L-proline (2.58 g, 12 mmol) and tritylamine (2.59 mg, 10 mmol) in dry dichloromethane (15 mL) was allowed to stir for 15 min and then cooled to 0 °C after which a dichloromethane (10 mL) solution of dicyclohexylcarbodiimide (2.678 g, 13 mmol) was added. After 20 min, the resulting solution was stirred at room temperature until the complete consumption of the nitroalkene (monitored by TLC). The reaction was quenched with water and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with saturated brine solution (100 mL), followed by drying over Na_2SO_4 and then evaporated in vacuo. The crude product was purified by column chromatography to give pure *tert*-butyl (*S*)-2-(tritylcarbamoyl)pyrrolidine-1-carboxylate **4a** as an amorphous powder, 96% yield. $[\alpha]_D^{20} = -38.4$ (c 1.0, $CHCl_3$); IR (KBr) 702, 759, 1164, 1392, 1507, 1695, 2925, 2974, 3321 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{32}N_2O_3$ $[M+Na]^+$ 479.2305, found 479.2303. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.31 (s, 1H), 7.27–7.21 (m, 15H), 4.48–4.41 (m, 1H), 3.43–3.37 (m, 2H), 2.31 (s, 1H), 1.81–1.76 (m, 5H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 171.1, 154.1, 144.8, 128.6, 127.9, 126.9, 80.6, 70.2, 58.4, 54.4, 50.1, 47.1, 31.4, 28.4, 28.3, 26.1, 24.6.

4.3.2. Procedure for the synthesis of 4

To a solution of *tert*-butyl (*S*)-2-(tritylcarbamoyl)pyrrolidine-1-carboxylate **4a** (10 mmol) in CH_2Cl_2 (30 mL) was added TFA (10 mL). After stirring at 0 °C for 2.5 h, the solution was concentrated under vacuum to leave a glutinous phase. The pH of the mixture was brought to 12 by the addition of 2 M NaOH. The aqueous phase was extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered off and the solvent was evaporated at low pressure to give a crude residue, which was purified by column chromatography to give pure (*S*)-*N*-tritylpyrrolidine-2-carboxamide **4** as a amorphous powder, 99% yield. $[\alpha]_D^{20} = -27.0$ (c 1.0, $CHCl_3$); IR (KBr) 632, 694, 755, 1094, 1176, 1446, 1491, 1674, 2859, 2921, 3260, 3321 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{24}N_2O$ $[M+Na]^+$ 379.1780, found 379.1778.^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.13 (s, 1H), 7.24–7.14 (m, 15H), 3.70–3.67 (m, 1H), 3.03–2.97 (m, 1H), 2.93–2.88 (m, 1H), 2.05–1.90 (m, 3H), 1.73–1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 173.9, 145.2, 128.6, 127.9, 126.9, 69.4, 61.4, 47.4, 30.5, 26.3.

4.4. General procedure for the enantioselective Michael reaction

To a stirred mixture of the corresponding nitroolefin (1 mmol, 1.0 equiv) in 2 mL of the indicated solvent, the catalyst and benzoic acid were added, after which the mixture was stirred at the indicated temperature for 30 min, then freshly distilled aldehyde (3 mmol, 3.0 equiv) was added. The resulting solution was stirred at the same temperature and monitored by TLC. It was then quenched with ice water (2 mL), and extracted with ethyl acetate (3 × 2 mL). The combined organic phase was dried over Na_2SO_4 and after removing the solvent, the crude product was purified by flash chromatography to afford the corresponding Michael adducts. The enantiomeric excess was determined by chiral HPLC analysis.

4.4.1. (2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal 7a[11]

Pale yellow oil, 91% yield. $[\alpha]_D^{20}$ = +8.3 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 9.53 ((s, 1H), 7.36–7.28 (m, 6H), 7.21–7.16 (m, 4H), 4.82–4.78 (m, 2H), 4.71–4.65 (m, 1H), 3.86–3.78 (m, 2H), 2.83–2.75 (m, 2H), 1.21 (d, *J* = 7.2 Hz, 2H), 0.99 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 202.3, 136.6, 129.1, 129.1, 128.1, 128.1, 78.1, 48.7, 48.4, 44.8, 44.0, 12.1, 11.7; HPLC (Chiralcel OD-H, Hexane:*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 31.9, T_{minor} = 23.9, 89% ee.

4.4.2. (2*R*,3*S*)-2-Ethyl-4-nitro-3-phenylbutanal 7b[11]

Pale yellow oil, 90% yield. $[\alpha]_D^{20}$ = +8.8 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.4 Hz, 1H), 9.48 (d, *J* = 2.8 Hz), 7.36–7.28 (m, 6H), 7.18 (d, *J* = 6.8, 3H), 4.82–4.70 (m, 2H), 4.65–4.60 (m, 1H), 3.83–3.76 (m, 1H), 2.71–2.65 (m, 1H), 2.61–2.55 (m, 1H), 1.76–1.70 (m, 2H), 1.68–1.63 (m, 2H), 1.51 (t, *J* = 11.6 Hz, 2H), 1.48 (t, *J* = 11.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 203.2, 136.8, 129.1, 128.2, 128.2, 128.0, 78.6, 77.9, 55.0, 54.9, 44.1, 42.7, 20.6, 20.4, 11.5, 10.7; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 99: 1, flow rate: 0.8 mL/min, λ = 254 nm), T_{major} = 27.7, T_{minor} = 33.6, 90% ee.

4.4.3. (*R*)-2-((*S*)-2-Nitro-1-phenylethyl)pentanal 7c[11]

Pale yellow oil, 87% yield. $[\alpha]_D^{20}$ = +6.8 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (d, *J* = 2.4 Hz, 1H), 9.47 (d, *J* = 2.8 Hz, 1H), 7.37–7.28 (m, 6H), 7.17 (d, *J* = 7.2, 3H), 4.81–4.72 (m, 2H), 4.70–4.62 (m, 2H), 3.81–3.76 (m, 2H), 2.73–2.71 (m, 1H), 2.68–2.63 (m, 1H), 1.68–0.94 (m, 10H), 0.91 (t, *J* = 18.4 Hz, 2H), 0.80 (t, *J* = 18.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.4, 203.2, 136.8, 136.2, 129.1, 128.2, 128.1, 128.0, 78.4, 77.9, 53.8, 53.3, 44.5, 43.2, 29.6, 29.5, 20.3, 19.8, 14.0, 13.9; HPLC (Chiralcel OD-H, Hexane:*i*-PrOH = 96:4, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 34.3, T_{minor} = 27.9, 90% ee.

4.4.4. (2*R*,3*S*)-2-Isopropyl-4-nitro-3-phenylbutanal 7d[11]

Pale yellow oil, 79% yield. $[\alpha]_D^{20}$ = +25.6 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.36–7.27 (m, 3H), 7.19 (d, *J* = 7.2, 2H), 4.69–4.65 (m, 1H), 4.60–4.55 (m, 1H), 3.93–3.87 (m, 1H), 2.80–2.76 (m, 1H), 1.76–1.59 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 129.4, 129.2, 128.0, 79.0, 58.8, 42.0, 27.9, 21.7, 17.0; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 97: 3, flow rate: 0.5 mL/min, λ = 254 nm), T_{major} = 23.9, T_{minor} = 28.6, 96% ee.

4.4.5. (2*R*,3*S*)-3-(4-Bromophenyl)-2-ethyl-4-nitrobutanal 7e[11]

Pale yellow oil, 93% yield. $[\alpha]_D^{20}$ = +7.6 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 9.49 (d, *J* = 2.4 Hz, 1H), 7.49–7.45 (m, 4H), 7.07 (d, *J* = 8.0, 3H), 4.81–4.70 (m, 2H), 4.62–4.56 (m, 1H), 3.80–3.75 (m, 1H), 2.69–2.65 (m, 1H), 2.60–2.56 (m, 1H), 1.76–1.64 (m, 2H), 1.56–1.46 (m, 2H), 0.99 (t, *J* = 14.8 Hz, 2H), 0.87 (d, *J* = 14.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 202.7, 132.3, 132.2, 130.0, 129.7, 78.3, 54.8, 54.6, 43.4, 42.1, 20.5, 20.3, 11.4, 10.5; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 98.5:1.5, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 31.5, T_{minor} = 48.3, 90% ee.

4.4.6. (2*R*,3*S*)-3-(4-Chlorophenyl)-2-ethyl-4-nitrobutanal 7f[11]

Pale yellow oil, 90% yield. $[\alpha]_D^{20}$ = +9.5 (c 1.0, $CHCl_3$),^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 9.49 (s, 1H), 7.34–7.30 (m,4H), 7.13 (d, *J* = 7.6, 4H), 4.82–4.71 (m, 3H), 4.62–4.57 (m, 1H), 3.84–3.76 (m, 2H), 2.69–2.65 (m, 1H), 2.60–2.58 (m, 1H), 1.78–1.46 (m, 4H), 1.01 (t, *J* = 14.8 Hz, 4H), 0.86 (d, *J* = 14.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 202.7, 129.6, 129.4, 129.3, 78.3, 77.6, 54.8, 54.7, 43.3, 42.0, 20.5, 20.3, 11.4, 10.5; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 98.5:1.5, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 28.7, T_{minor} = 42.8, 92% ee.

4.4.7. (2*R*,3*S*)-3-(2-Chlorophenyl)-2-ethyl-4-nitrobutanal 7g[11]

Pale yellow oil, 84% yield. $[\alpha]_D^{20}$ = +11.8 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$):δ 9.73 (d, *J* = 2.0 Hz, 1H), 9.57 (d, *J* = 2.4 Hz, 1H), 7.43–7.28 (m, 2H), 7.24–7.20 (m, 4H), 4.89–4.76 (m, 2H), 4.71–4.67 (m, 1H), 4.48–4.47 (m, 1H), 4.38–4.33 (m, 1H), 2.95 (s, 1H), 2.80–2.75 (m, 1H), 1.76–1.73 (m, 1H), 1.61–1.52 (m, 3H), 0.98 (t, *J* = 14.8 Hz, 2H), 0.87 (d, *J* = 15.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 202.3, 134.5, 130.6, 129.3, 129.3, 127.5, 76.7, 76.2, 54.5, 54.0, 39.5, 39.2, 29.7, 20.4, 19.9, 11.6, 10.7; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 98.5:1.5, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 17.5, T_{minor} = 19.6, 89% ee.

4.4.8. (2*R*,3*S*)-2-Ethyl-3-(4-methoxyphenyl)-4-nitrobutanal 7h[11]

Pale yellow oil, 83% yield. $[\alpha]_D^{20}$ = +10.4 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.4 Hz, 1H), 9.46 (d, *J* = 2.8 Hz, 1H), 7.10 (d, *J* = 8.8, 3H), 6.88–6.84 (m, 3H), 4.79–4.67 (m, 2H), 4.61–4.55 (m, 1H), 3.79–3.74 (m, 5H), 2.66–2.60 (m, 1H), 2.54–2.52 (m, 1H), 1.75–1.65 (m, 2H), 1.55–1.47 (m, 2H), 1.25 (t, *J* = 14.8 Hz, 1H), 1.00 (d, *J* = 14.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 203.3, 159.3, 129.3, 129.0, 114.5, 78.8, 78.2, 55.2, 55.1, 55.0, 43.5, 42.0, 20.7, 20.3, 11.5, 10.7; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 96:4, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 17.3, T_{minor} = 21.0, 91% ee.

4.4.9. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(*p*-tolyl)butanal 7i[11]

Pale yellow oil, 94% yield. $[\alpha]_D^{20}$ = +13.1 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.66 (d, *J* = 1.6 Hz, 1H), 9.44 (d, *J* = 2.0 Hz), 7.54 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.75–4.68 (m, 1H), 4.62–4.56 (m, 1H), 3.85–3.79 (m, 1H), 2.68–2.65 (m, 1H), 1.50–1.37 (m, 2H), 0.95 (t, *J* = 14.8 Hz, 1H), 0.77 (d, *J* = 14.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 141.1, 128.5, 126.1, 126.1, 78.1, 54.5, 42.3, 20.4, 10.5; HPLC (Chiralcel OD-H, Hexane:*i*-PrOH = 92:8, flow rate: 0.5 mL/min, λ = 254 nm), T_{major} = 40.2, T_{minor} = 34.9, 96% ee.

4.4.10. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(4-(trifluoromethyl)phenyl)-butanal 7j[11]

Pale yellow oil, 92% yield. $[\alpha]_D^{20}$ = +9.8 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.66 (d, *J* = 1.6 Hz, 1H), 9.44 (d, *J* = 4.0 Hz), 7.54 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.75–4.68 (m, 1H), 4.62–4.56 (m, 1H), 3.85–3.79 (m, 1H), 2.69–2.65 (m, 1H), 1.49–1.37 (m, 2H), 0.96 (t, *J* = 14.8 Hz), 0.77 (t, *J* = 14.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 141.1, 128.5, 126.1, 126.1, 78.1, 54.5, 42.3, 20.4, 10.5; HPLC (Chiralcel AS-H, Hexane:*i*-PrOH = 93:7, flow rate: 0.5 mL/min, λ = 254 nm), T_{major} = 27.2, T_{minor} = 29.6, 89% ee.

4.4.11. (2*R*,3*R*)-2-Ethyl-3-(furan-2-yl)-4-nitrobutanal 7k[11]

Pale yellow oil, 87% yield. $[\alpha]_D^{20}$ = +17.2 (*c* 1.0, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 9.61 (s), 7.37 (s, 1H), 6.31 s, 1H), 6.20 (s, 1H), 4.75–4.65 (m, 3H), 4.05–3.99 (m, 1H), 2.79–2.74 (m, 1H), 1.58–1.52 (m, 2H), 0.99 (t, *J* = 14.8 Hz, 1H), 0.90 (d, *J* = 14.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 202.4, 150.1, 142.7, 110.5, 110.4, 109.0, 108.8, 76.2, 76.0, 53.6, 53.4, 37.7, 37.0, 20.5, 20.0, 11.6, 10.9; HPLC (Chiralcel AS-H, Hexane:*i*-PrOH = 96:4, flow rate: 0.5 mL/min, λ = 254 nm), T_{major} = 39.4, T_{minor} = 35.3, 93% ee.

4.4.12. (2*R*,3*S*)-2-Isopropyl-4-nitro-3-(*p*-tolyl)butanal 7l

Pale yellow oil, 91% yield. $[\alpha]_D^{20}$ = +66.1 (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 9.93 (d, *J* = 2.1 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 4.68–4.65 (m, 1H), 4.58–4.54 (m, 1H), 3.90–3.85 (m, 1H), 2.77–2.74 (m, 1H), 2.34 (s, 3H), 1.76–1.73 (m, 1H), 1.00 (d, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.9, 138.2, 134.4, 130.2, 128.2, 79.5,

59.2, 42.0, 28.3, 22.1, 21.5, 17.4; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 97:3, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 11.6, T_{minor} = 10.8, 98% ee.

4.4.13. (2*R*,3*S*)-3-(4-Bromophenyl)-2-isopropyl-4-nitrobutanal 7m

Pale yellow oil, 92% yield. $[\alpha]_D^{20}$ = +92.5 (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 9.92 (d, *J* = 2.0 Hz,1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 4.70–4.67 (m, 1H), 4.57–4.52 (m, 1H), 3.90–3.86 (m, 1H), 2.78–2.74 (m, 1H), 1.72–1.69 (m, 1H), 1.12 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.3, 136.6, 132.8, 130.1, 122.5, 79.1, 58.9, 41.8, 28.4, 22.0, 17.4; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 97:3, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 32.9, T_{minor} = 27.5, 99% ee.

4.4.14. (2*R*,3*S*)-3-(4-Fluorophenyl)-2-isopropyl-4-nitrobutanal 7n

Pale yellow oil, 90% yield. $[\alpha]_D^{20}$ = +78.3 (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.17 (t, *J* = 13.5 Hz, 2H), 7.04 (t, *J* = 16.9 Hz, 2H), 4.69–4.66 (m, 1H), 4.56–4.52 (m, 1H), 3.91–3.89 (m, 1H), 2.71–2.70 (m, 1H), 1.19–1.09 (m, 3H), 0.94–0.86 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.5, 204.4, 163.7, 161.7, 130.4, 130.0, 129.9, 116.7, 116.5, 79.4, 59.1, 58.9, 41.8, 41.6, 28.3, 22.1, 22.0, 17.3; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 97:3, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 18.2, T_{minor} = 15.9, 96% ee.

4.4.15. (2*R*,3*S*)-3-(2-Chlorophenyl)-2-isopropyl-4-nitrobutanal 7o

Pale yellow oil, 88% yield. $[\alpha]_D^{20}$ = +107.1 (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 9.93 (s,1H), 7.43 (d, *J* = 7.0 Hz,1H), 7.27–7.20 (m, 3H), 4.87–4.83 (m, 1H), 4.69–4.66 (m, 1H), 4.45 (s, 1H), 3.12 (s, 1H), 1.79–1.74 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.6, 135.0, 131.1, 129.7, 127.9, 18.1, 58.0, 30.1, 28.8, 22.1, 18.2; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 99:1, flow rate: 0.7 mL/min, λ = 254 nm), T_{major} = 19.0, T_{minor} = 19.9, 97% ee.

4.4.16. (2*R*,3*R*)-2-Isopropyl-4-nitro-3-(thiophen-2-yl)butanal 7p

Pale yellow oil, 89% yield. $[\alpha]_D^{20}$ = +29.3 (*c* 1.0, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 9.90 (d, *J* = 2.5 Hz,1H), 7.51–7.48 (m,1H), 7.28 (s, 2H), 6.95–6.94 (m, 1H), 4.67–4.54 (m, 2H), 4.10–4.06 (m, 1H), 2.79–2.76 (m, 1H), 1.82–1.76 (m, 1H), 1.14–1.10 (m, 3H), 0.98–0.89 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.7, 138.0, 127.5, 126.7, 123.7, 79.1, 63.7, 59.3, 45.2, 37.9, 28.4, 27.0, 22.0, 17.7; HPLC (Chiralcel AD-H, Hexane:*i*-PrOH = 96:4, flow rate: 1.0 mL/min, λ = 254 nm), T_{major} = 22.0, T_{minor} = 28.5, 99% ee.

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