



Highly efficient asymmetric Michael addition of aldehydes to nitroalkenes with 4,5-methano-L-proline as organocatalysts

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ABSTRACT

The 4,5-methano-L-prolines were used as chiral organocatalysts in asymmetric Michael addition of aldehydes to nitroolefins. These proline-like catalysts are unique for their rigid bicyclic structure with a cyclopropane and two H atoms attached to the bridgehead C atoms lying on the same side of the ring. They therefore showed high efficiency in asymmetric Michael addition of aldehydes to nitroolefins. Under the optimal conditions, excellent diastereo- and enantioselectivities (up to 97/3 dr and 98% ee) were obtained in high yields for a series of aldehydes and nitroolefins using only 5 mol % catalyst loading. The methodology features easily available catalysts, high catalytic efficiency and environmentally friendly procedures.

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1. Introduction

The organocatalytic asymmetric Michael addition reaction has attracted rapidly growing attention as one of the most important carbon–carbon bond-forming reactions in organic synthesis.¹ Specifically, the organocatalytic Michael addition of an aldehyde to nitroolefins is of great interest owing to the importance of the resulting bifunctional nitroaldehydes as valuable intermediates.^{1,2} The first organocatalytic asymmetric Michael addition of aldehydes to nitroalkenes was reported by Betancort and Barbas,³ after which extraordinary progress has been sought in order to find more selective and efficient catalytic systems for these Michael reactions.⁴ Even though L-proline, which is a widely distributed amino acid, has been described as a catalyst for asymmetric Michael reactions with aldehydes as the donor, only poor enantioselectivity is typically observed.⁵ After that, the groups of Alexakis,⁶ Wang,^{2f} Hayashi,⁷ Zhao,⁸ Palomo,²ⁱ Jacobsen,^{2h} Chen,⁹ and Loh,¹⁰ among many others,^{11,12} have developed a series of efficient proline-like catalysts to improve the stereoselectivity and substrate scope of this reaction. However, current procedures retain several shortcomings, such as: the low reaction activity, difficulty in obtaining readily available catalysts, high catalyst loading requirements and unsatisfactory results, and further modifications of these proline-like catalysts had to be carried out for excellent

asymmetric catalytic results.^{2,2g–i,3,6–10} The search for highly efficient and easily available proline-like organocatalysts therefore remains a worthwhile endeavor.

The Hanessian group¹³ had reported the synthesis of 4,5-methano-L-prolines and the enzymatic activity of the corresponding *N*-(3-mercaptopropionyl) analogs as inhibitors of angiotensin converting enzyme (Fig. 1). We found that these proline-like compounds are unique for their rigid bicyclic structure with two H atoms attached to the bridgehead C atoms lying on the same side of the ring. The X-ray structure and solid state conformational characteristics of 4,5-methano-L-prolines revealed considerable flattening of the pyrrolidine ring compared to L-proline. To the best of our knowledge, 4,5-methanoproline can surpass the venerable proline in catalyzing conjugate additions of nitroalkanes to cyclic enones in many cases.^{13a} We therefore envisage that they would be good catalysts for asymmetric catalysis in conjugate additions of nitroalkanes to acyclic enones. Herein, we report a highly efficient asymmetric Michael addition of aldehydes to nitroolefins using 4,5-methano-L-prolines as a chiral organocatalyst.



Fig. 1. The structure of *trans*-4,5-methano-L-proline (**1a**) and *cis*-4,5-methano-L-proline (**1b**).

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2. Results and discussion

We first applied **1a** and **1b** in Michael additions of aldehydes to nitroalkenes to determine the effect of different configurations of the catalyst used in the reaction. Thus, the reaction of (*E*)-(2-nitrovinyl) benzene and Propionaldehyde was carried out in the presence of 20 mol % of catalyst loading at room temperature in CH₂Cl₂ (Table 1, entries 1 and 2). However, the *trans*-4,5-methano-*L*-proline **1b** showed low reaction activity even after 48 h (entry 2). To our delight, *cis*-4,5-methano-*L*-proline **1a** resulted in a highly efficient reaction with excellent diastereo- and enantioselectivity, affording *syn*-selective Barbos-Michael reaction products (entry 1).¹⁴ The catalyst loading was then decreased with **1a** as a chiral organocatalyst. Although no obvious influence on the diastereo and enantioselectivity was found, DMAP is somewhat better than others according to a combination of diastereo- and enantioselectivity, and it was used in the following reactions.

Table 1

Influence of catalysts and additives for Michael additions of aldehyde **2a** to nitroalkene **3a**^a

Entry	Catalyst (mol %)	Time (h)	Additive	Yield (%) ^b	Syn/anti ^c	ee (%) ^d
1	1a (20)	36	—	95	94/6	85
2	1b (20)	48	—	37	83/17	73
3 ^e	Proline	72	—	<5	93/7	25
4	1a (10)	72	—	68	93/7	84
5	1a (10)	48	Benzoic acid	45	94/6	92
6	1a (10)	42	CH ₃ CO ₂ H	59	94/6	86
7	1a (10)	72	TsOH	68	93/7	89
8	1a (10)	72	TFA	89	96/4	91
9	1a (10)	3.5	DABCO	95	96/4	94
10	1a (10)	2.5	DMAP	98	95/5	95
11	1a (10)	4	Et ₃ N	96	93/7	94
12	1a (10)	3.5	DBU	95	97/3	93
13	1a (10)	3.5	TMEDA	93	96/3	91
14	1a (10)	5	DIPEA	93	95/5	92
15	1a (10)	3	Pyridine	72	94/6	86
16	1a (5)	6	Et ₃ N	92	88/12	95
17	1a (5)	3	DMAP	96	94/6	93
18	1a (2)	12	Et ₃ N	90	90/10	95
19	1a (2)	14	DMAP	87	84/16	94

^a Reactions were conducted with (*E*)-(2-nitrovinyl)benzene **3** (0.2 mmol) and Propionaldehyde **2** (2.0 mmol) in the presence of catalyst with different additives in CH₂Cl₂ at 20 °C.

^b Isolated yield.

^c Isolated Determined by ¹H NMR spectra of crude products. The relative and absolute configurations of **4aa** were determined by comparison with the literature data.^{12h}

^d Determined by chiral HPLC.

^e Ref. 3 provided the date.

We wanted to further decrease catalyst loading since the high reaction activity was obtained by using basic additives such as Et₃N and DMAP in the presence of 10 mol % catalytic loading. To our delight, when the above reaction was carried out in the presence of 5 mol % **1a**, almost no change was found in diastereoselectivity and enantioselectivity with DMAP as an additive, together with a slight increase in reactivity (entries 16 and 17). However, further decreasing the catalyst loading to 2 mol % resulted in decreased diastereoselectivity and long reaction times (entries 18 and 19). Therefore 5 mol % catalytic loading was adopted in following reactions.

We then investigated the influence of solvents on the reaction and several solvents were effective for this reaction, leading to

excellent catalytic results (Table 2). High yields and excellent enantioselectivity were obtained by using CH₃CN, CH₂Cl₂ and toluene (entries 1–3). CH₂Cl₂ gave better diastereoselectivity but lower enantioselectivity than CH₃CN. CH₃CN was the best solvent according to the reactions activity and stereoselectivity. DMF also afforded high diastereoselectivity and enantioselectivity, but only a moderate yield was obtained (entry 4). *i*-PrOH and THF proved unsuitable for the reaction. As shown in Table 2, reduced diastereo- and enantioselectivity and yields were obtained even with long reaction time (entries 5 and 6).

Table 2

Influence of solvents and temperature for the Michael addition of aldehyde **2a** to nitroalkene **3a** catalyzed by catalyst **1a**^a

Entry	Solvent	Tem. (°C)	Time (h)	Yield (%) ^b	Syn/anti ^c	ee (%) ^d
1	CH ₂ Cl ₂	20	3	96	94/6	93
2	CH ₃ CN	20	3	94	89/11	95
3	Toluene	20	6	93	92/8	90
4	DMF	20	15	73	93/7	91
5	THF	20	23	47	87/13	86
6	<i>i</i> -PrOH	20	36	56	82/18	84
7	CH ₃ CN	0	6	98	96/4	98
8	CH ₃ CN	−20	12	87	94/6	97
9	CH ₂ Cl ₂	0	6	93	95/5	94
10	CH ₂ Cl ₂	−20	12	85	96/4	95

^a Reactions were conducted with (*E*)-(2-nitrovinyl)benzene **3** (0.2 mmol) and Propionaldehyde **2** (2.0 mmol) in the presence of catalyst with DMAP as an additive in solvent at suitable temperature.

^b Isolated yield.

^c Isolated Determined by ¹H NMR spectra of crude products. The relative and absolute configurations of **4aa** were determined by comparison with the literature data.^{12h}

^d Determined by chiral HPLC.

Temperature had a little effect on the reaction, and excellent enantioselectivity and diastereoselectivity were observed from 20 °C to −20 °C (entries 2, 7, 8, 9 and 10). 0 °C was somewhat better than others and was adopted in following reactions.

With the optimal reaction conditions in hand, we surveyed a series of aldehydes. Excellent results was obtained when using linear aldehydes, such as *n*-butyraldehyde, propaldehyde and hexaldehyde (Table 3, entries 1–4). Propaldehyde with decreased steric hindrance gave the best result. As for nonlinear aldehydes, large steric hindrance resulted in lower reaction activity and a 72 h reaction time was required for isovaleraldehyde though excellent stereo- and enantioselectivity were obtained (entry 4). Unfortunately, no reaction occurred when using α -branching aldehydes, such as cyclohexyl formaldehyde and isobutyraldehyde, mainly due to their much larger steric hindrance.

Finally, we examined several kinds of nitroolefins (Table 3, entries 5–17). In the case of aryl-substituted nitroolefins, high yields and excellent diastereo- and enantioselectivity were observed for both electron-withdrawing and electron-donating substituted nitroalkenes (entries 5–11). However, the reaction activity decreased for some electron-withdrawing substituted nitroalkenes (entries 5–7). Replacement of the phenyl ring by a naphthalene ring resulted in excellent dr and ee values together with high yields of products (entries 12 and 13). In addition, this method also allowed the use of heteroaromatic nitroolefins (entries 14–16). Unfortunately, no reaction occurred when using aliphatic nitroalkenes with a cyclohexyl group (entry 17). In short, the present catalytic system is suitable for asymmetric Michael additions of a series of aromatic nitroolefins.

Table 3
Michael addition of aldehydes to nitroolefins catalyzed by **1a**^a

Entry	Product	R ¹	R ²	Time (h)	Yield (%) ^b	Syn/anti ^c	ee (%) ^d
1	4aa	Me	Ph	6	96	94/6	98
2	4ba	Et	Ph	8	98	97/3	97
3	4ca	<i>n</i> -Bu	Ph	18	99	96/4	95
4	4da	<i>i</i> -Pr	Ph	72	97	97/3	95
5	4ab	Me	4-FPh	36	99	92/8	97
6	4ac	Me	4-ClPh	24	97	92/8	97
7	4ad	Me	4-CF ₃ Ph	48	95	88/12	96
8	4ae	Me	4-CH ₃ Ph	27	88	93/7	97
9	4af	Me	4-CH ₃ OPh	26	92	95/5	96
10	4ag	Me	2-CH ₃ OPh	18	93	93/7	96
11	4ah	Me	3-CH ₃ OPh	18	94	94/6	96
12	4ai	Me	1-Naphthyl	28	98	92/8	95
13	4aj	Me	2-Naphthyl	30	97	89/11	96
14	4ak	Me	3-Pyridyl	72	99	66/34	95
15	4al	Me	2-Furyl	72	95	86/14	96
16	4am	Me	2-Thienyl	72	98	87/13	94
17	4an	Me	Cyclohexyl	72	n.r.	—	—
18 ^e	4aa	Me	Ph	20	95	93/7	94

^a Reactions were conducted with nitrostyrene (0.2 mmol) and aldehyde (2.0 mmol) in the presence of catalyst with DMAP as an additive in CH₃CN at 0 °C.

^b Isolated yield.

^c Isolated Determined by ¹H NMR spectra of crude products. The relative and absolute configurations of **4aa** were determined by comparison with the literature data.^{12h}

^d Determined by chiral HPLC.

^e Reactions were conducted with nitrostyrene (4.0 mmol, 596 mg) and Propionaldehyde (40.0 mmol, 2.32 g) in the presence of catalyst with DMAP as an additive in CH₃CN at 0 °C.

To show the practicality of the method, the reaction was tested at a large scale. Thus nitrostyrene (4.0 mmol, 596 mg) was allowed to react with Propionaldehyde (40.0 mmol, 2.32 g) by using the catalyst **1a** (0.2 mmol, 32 mg) with DMAP as an additive in CH₃CN (12.5 mL) at 0 °C. The reaction was complete in 20 h, and the Michael adduct was obtained in 95% yield and 94% ee (Table 3, entry 18).

3. Conclusion

In summary, we have successfully applied the 4,5-methano-*l*-proline in asymmetric Michael additions of aldehydes to nitroolefins. These proline-like catalysts enjoy the merits of easy availability and especially high catalytic efficiency in asymmetric catalysis. As a result, they showed excellent diastereo- and enantioselectivity (up to 97/3 dr and 98% ee) together with high yields in the catalytic reactions. The methodology could also be expanded to a series of aldehydes and nitroolefins with excellent asymmetric catalytic results using **1a** as a chiral organocatalyst. Encouraged by its excellent performance, a broader application is under investigation in our laboratory.

4. Experimental section

4.1. General

All ¹H NMR (400 MHz) spectra were recorded using a Varian MERCURY plus-400 spectrometer with TMS as an internal standard. HRMS was performed on Analysis Center of Shanghai Institute of Technology University. The Enantioselectivity was measured by high performance liquid chromatography (HPLC) using chiral column (Chiralcel OD, AD, AS, OJ, OZ) with hexane/2-propyl alcohol as eluent. Column chromatography was performed using

300–400 mesh silica gel. All commercially available substrates were used as received. Nitroolefins were prepared according to the literature procedures.¹⁵

4.2. General procedure for the Michael addition reaction

The catalyst **1a** (1.27 mg, 0.01 mmol), DMAP (1.22 mg, 0.01 mmol) and propionaldehyde (143 μL, 2.0 mmol) were added to a screw-capped vial containing CH₃CN (1.0 mL) at 0 °C. The reaction mixture was stirred for 5 min, and then appropriate nitroolefin (0.2 mmol) was added. The reaction mixture was stirred at 0 °C until the complete consumption of nitroalkene (monitored by TLC). The solvent was then evaporated and the residue was purified by flash column silica-gel chromatography (PE/EA, 10/1) to provide the corresponding Michael adducts. Diastereoselectivity were measured by ¹H NMR analysis of the crude product. The enantiomeric excess (ee) was determined by chiral-phase HPLC analysis of pure product. The absolute configuration of the products was determined by comparing the values with those previously reported in the literature.^{12h}

4.2.1. (2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal (4aa**).^{12h} From aldehyde **2a** and nitroolefin **3a** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.72 (d, *J*=1.8 Hz, 1H), 7.36–7.14 (m, 5H), 4.85–4.75 (m, 1H), 4.71–4.65 (m, 1H), 3.85–3.72 (m, 1H), 2.86–2.71 (m, 1H), 0.98 (d, *J*=7.2 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hexane/*i*-PrOH=90:10, UV 210 nm, 0.8 mL min^{−1}, syn: *t*_R=48.66 min (major) and *t*_R=31.92 min (minor).**

4.2.2. (2*R*,3*S*)-2-Ethyl-4-nitro-3-phenylbutanal (4ba**).^{12h} From aldehyde **2b** and nitroolefin **3a** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.70 (d, *J*=2.5 Hz, 1H), 7.37–7.13 (m, 5H), 4.74–4.59 (m, 2H), 3.81–3.73 (m, 1H), 2.73–2.65 (m, 1H), 1.57–1.46 (m, 2H), 0.85 (t, *J*=7.5 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex-*i*-PrOH=91:9, UV 230 nm, 0.9 mL min^{−1}, syn: *t*_R=32.94 min (major) and *t*_R=24.72 min (minor).**

4.2.3. (R)-2-((S)-2-Nitro-1-phenylethyl)hexanal (4ca**).^{12h} From aldehyde **2c** and nitroolefin **3a** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.71 (d, *J*=2.7 Hz, 1H), 7.46–7.15 (m, 5H), 4.84–4.58 (m, 2H), 3.86–3.73 (m, 1H), 2.81–2.65 (m, 1H), 1.51–1.07 (m, 6H), 0.79 (t, *J*=6.8 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex-*i*-PrOH 90:10, UV 210 nm, 0.8 mL min^{−1}, syn: *t*_R=28.48 min (major) and *t*_R=21.14 min (minor).**

4.2.4. (2*R*,3*S*)-2-Isopropyl-4-nitro-3-phenylbutanal (4da**).^{12h} From aldehyde **2d** and nitroolefin **3a** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.93 (d, *J*=2.4 Hz, 1H), 7.36–7.25 (m, 3H), 7.23–7.15 (m, 2H), 4.71–4.63 (m, 1H), 4.62–4.53 (m, 1H), 3.93–3.85 (m, 1H), 2.82–2.74 (m, 1H), 1.77–1.66 (m, 1H), 1.08 (d, *J*=7.2 Hz, 3H), 0.88 (d, *J*=7.0 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex-*i*-PrOH 95:5, UV 210 nm, 0.8 mL min^{−1}, syn: *t*_R=27.21 min (major) and *t*_R=25.66 min (minor).**

4.2.5. (2*R*,3*S*)-3-(4-Fluorophenyl)-2-methyl-4-nitrobutanal (4ab**).^{16a} From aldehyde **2a** and nitroolefin **3b** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.71 (d, *J*=1.5 Hz, 1H), 7.21–7.12 (m, 2H), 7.08–6.99 (m, 2H), 4.84–4.73 (m, 1H), 4.67–4.59 (dd, *J*=12.6, 9.6 Hz, 1H), 3.85–3.75 (m, 1H), 2.83–2.66 (m, 1H), 1.00 (d, *J*=7.4 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC**

(Chiralcel AD-H), Hex-*i*-PrOH 97:3, UV 210 nm, 0.9 mL min⁻¹, syn: t_R =22.98 min (major) and t_R =30.85 min (minor).

4.2.6. (2*R*,3*S*)-3-(4-Chlorophenyl)-2-methyl-4-nitrobutanal (4ac).^{12h} From aldehyde **2a** and nitroolefin **3c** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.70 (d, J =1.5 Hz, 1H), 7.36–7.29 (m, 2H), 7.15–7.08 (m, 2H), 4.82–4.72 (m, 1H), 4.65–4.59 (m, 1H), 3.82–3.75 (m, 1H), 2.80–2.70 (m, 1H), 1.00 (d, J =7.2 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hex-*i*-PrOH 97:3, UV 210 nm, 0.9 mL min⁻¹, syn: t_R =24.16 min (major) and t_R =33.93 min (minor).

4.2.7. (2*R*,3*S*)-2-Methyl-4-nitro-3-(4-(trifluoromethyl)phenyl)butanal (4ad).^{16c} From aldehyde **2a** and nitroolefin **3d** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.71 (d, J =1.4 Hz, 1H), 7.62 (d, J =8.2 Hz, 2H), 7.31 (d, J =8.1 Hz, 2H), 4.86–4.80 (m, 1H), 4.74–4.66 (m, 1H), 3.95–3.85 (m, 1H), 2.90–2.75 (m, 1H), 1.00 (d, J =7.4 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hex-*i*-PrOH 90:10, UV 210 nm, 0.8 mL min⁻¹, syn: t_R =11.83 min (major) and t_R =15.00 min (minor).

4.2.8. (2*R*,3*S*)-2-Methyl-4-nitro-3-*p*-tolylbutanal (4ae).^{16b} From aldehyde **2a** and nitroolefin **3e** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.71 (d, J =2.0 Hz, 1H), 7.22–7.08 (m, 4H), 4.82–4.61 (m, 2H), 4.21–4.03 (m, 1H), 2.81–2.71 (m, 1H), 2.36 (s, 3H), 0.95 (d, J =7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane/*i*-PrOH=95:5, UV 210 nm, 0.9 mL min⁻¹, syn: t_R =23.11 min (major) and t_R =24.89 min (minor).

4.2.9. (2*R*,3*S*)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal (4af).^{12h} From aldehyde **2a** and nitroolefin **3f** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.68 (d, J =1.7 Hz, 1H), 7.15–6.97 (m, 2H), 6.9–6.77 (m, 2H), 4.82–4.71 (m, 1H), 4.67–4.59 (m, 1H), 3.78 (s, 3H), 3.75–3.71 (m, 1H), 2.81–2.63 (m, 1H), 0.98 (d, J =7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane/*i*-PrOH=85:15, UV 210 nm, 0.8 mL min⁻¹, syn: t_R =45.56 min (major) and t_R =35.23 min (minor).

4.2.10. (2*R*,3*S*)-3-(2-Methoxyphenyl)-2-methyl-4-nitrobutanal (4ag).^{12h} From aldehyde **2a** and nitroolefin **3g** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.71 (d, J =1.8 Hz, 1H), 7.31–7.23 (m, 1H), 7.07 (dd, J =7.5, 1.7 Hz, 1H), 6.96–6.83 (m, 2H), 4.90–4.81 (m, 1H), 4.77–4.70 (m, 1H), 4.10–3.96 (m, 1H), 3.83 (s, 3H), 3.09–2.91 (m, 1H), 0.93 (d, J =7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane/*i*-PrOH=98:2, UV 210 nm, 0.95 mL min⁻¹, syn: t_R =45.50 min (major) and t_R =43.61 min (minor).

4.2.11. (2*R*,3*S*)-3-(3-Methoxyphenyl)-2-methyl-4-nitrobutanal (4ah).^{12j} From aldehyde **2a** and nitroolefin **4h** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.70 (d, J =1.6 Hz, 1H), 7.26–7.21 (m, 1H), 6.82–6.67 (m, 3H), 4.79–4.73 (m, 1H), 4.68–4.62 (m, 1H), 3.77 (s, 3H), 3.83–3.72 (m, 1H), 2.82–2.69 (m, 1H), 1.00 (d, J =7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OZ-H), Hexane/*i*-PrOH=90:10, UV 210 nm, 0.8 mL min⁻¹, syn: t_R =40.97 min (major) and t_R =35.48 min (minor).

4.2.12. (2*R*,3*S*)-2-Methyl-3-(naphthalen-1-yl)-4-nitrobutanal (4ai).^{12h} From aldehyde **2a** and nitroolefin **3i** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz,

CDCl₃): δ 9.77 (d, J =1.8 Hz, 1H), 8.23–8.05 (m, 1H), 7.90 (d, J =8.0 Hz, 1H), 7.81 (d, J =8.2 Hz, 1H), 7.63–7.34 (m, 4H), 5.00–4.83 (m, 3H), 3.10–2.93 (m, 1H), 0.99 (d, J =7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane/*i*-PrOH=90:10, UV 210 nm, 0.8 mL min⁻¹, syn: t_R =37.14 min (major) and t_R =39.40 min (minor).

4.2.13. (2*R*,3*S*)-2-Methyl-3-(naphthalen-2-yl)-4-nitrobutanal (4aj).^{16d} From aldehyde **2a** and nitroolefin **3j** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.75 (d, J =1.6 Hz, 1H), 7.86–7.78 (m, 3H), 7.68–7.61 (m, 1H), 7.53–7.45 (m, 2H), 7.35–7.24 (m, 1H), 4.91–4.84 (m, 1H), 4.82–4.73 (m, 1H), 4.04–3.92 (m, 1H), 2.93–2.82 (m, 1H), 1.02 (d, J =7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane/*i*-PrOH=90:10, UV 210 nm, 0.8 mL min⁻¹, syn: t_R =34.53 min (major) and t_R =41.53 min (minor).

4.2.14. (2*R*,3*S*)-2-Methyl-4-nitro-3-(pyridin-3-yl)butanal (4ak).^{12j} From aldehyde **2a** and nitroolefin **3k** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.70 (d, J =1.4 Hz, 1H), 8.54–8.45 (m, 2H), 7.52–7.50 (m, 1H), 7.31–7.22 (m, 1H), 4.82–4.79 (m, 1H), 4.71–4.65 (m, 1H), 3.89–3.80 (m, 1H), 2.90–2.77 (m, 1H), 1.01 (d, J =7.4 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OZ-H), Hexane/*i*-PrOH=75:25, UV 210 nm, 0.6 mL min⁻¹, syn: t_R =49.58 min (major) and t_R =61.62 min (minor).

4.2.15. (2*R*,3*R*)-3-(Furan-2-yl)-2-methyl-4-nitrobutanal (4al).^{12h} From aldehyde **2a** and nitroolefin **3m** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.71 (d, J =1.0 Hz, 1H), 7.43–7.30 (m, 1H), 6.31–6.28 (m, 1H), 6.20–6.16 (m, 1H), 4.77–4.66 (m, 2H), 4.12–4.03 (m, 1H), 2.86–2.75 (m, 1H), 1.06 (d, J =7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hexane/*i*-PrOH=90:10, UV 210 nm, 0.8 mL min⁻¹, syn: t_R =24.73 min (major) and t_R =22.85 min (minor).

4.2.16. (2*R*,3*R*)-2-Methyl-4-nitro-3-(thiophen-2-yl)butanal (4am).^{12h} From aldehyde **2a** and nitroolefin **3m** at 0 °C according to the general procedure to give pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.68 (d, J =1.2 Hz, 1H), 7.25–7.21 (m, 1H), 6.97–6.87 (m, 2H), 4.83–4.64 (m, 2H), 4.27–4.12 (m, 1H), 2.90–2.68 (m, 1H), 1.12 (d, J =7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OZ-H), Hexane/*i*-PrOH=98:2, UV 230 nm, 0.95 mL min⁻¹, syn: t_R =84.94 min (major) and t_R =57.27 min (minor).

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2014.08.069>.

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