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**PAPER**

# Highly efficient asymmetric Michael addition of aldehyde to nitroolefin using perhydroindolic acid as a chiral organocatalyst†

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Perhydroindolic acids, the by-products obtained in the industrial production of a trandolapril intermediate, were used as chiral organocatalysts in asymmetric Michael addition reactions of aldehydes to nitroolefins. These proline-like catalysts are unique for their rigid bicyclic structure with two H atoms attached to the bridgehead C atoms lying on the opposite side of the ring. They therefore showed high efficiency in asymmetric Michael additions of aldehydes to nitroolefins. Under the optimal conditions, excellent diastereo- and enantioselectivities (up to 99/1 dr and 98% ee) were obtained with high chemical 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 green procedures.

## Introduction

Asymmetric Michael additions as a practical and atom-economic strategy to construct carbon–carbon bonds have drawn much attention for decades.[1] Specifically, the organocatalytic Michael addition of an aldehyde to a nitroalkene is deemed to be one of the most important reactions due to the crucial role of nitroalkanes in organic synthesis.[1,2] In 2001, Barbas first reported the asymmetric Michael addition, by using proline derivatives as catalysts with up to 78% ee, however, when using L-proline and *trans*-4-hydroxyl-L-proline only 25% ee was obtained (Fig. 1).[3] After that, the amine-catalyzed Michael addition (named the Barbas–Michael reaction),[4] has been improved by Hayashi,[5] Zhao,[6] Chan,[7] and Loh[8] by using proline-like catalysts (molecules containing a proline moiety, Fig. 1). However, current procedures retain several shortcomings, such as: the difficulty in obtaining readily available catalysts, high catalytic loading requirements and unsatisfactory results, and further modifications of these proline-like catalysts had to be carried out for excellent asymmetric catalytic results.[2,3,5–7] The search for highly efficient and easily available proline-like organocatalysts therefore remains a worthwhile endeavor.

Recently, we have been committed to developing new and easily available organocatalysts and applying them to various asymmetric transformations.[9] We found that perhydroindolic acid **1a** (Fig. 2), the key intermediate of ACE inhibitor trandolapril, could be obtained from large-scale industrial production. Furthermore, perhydroindolic acids **1b**, **1c**, **1d** (Fig. 2), the by-products of **1a**, are discarded resulting in the waste of resources and environmental pollution.[10] However, these proline-like compounds are unique for their rigid bicyclic structure with two H atoms attached to the bridgehead C atoms lying on the opposite side of the ring. We therefore envisage that they would be good catalysts for asymmetric catalysis. Herein, we report a highly efficient asymmetric Michael addition of aldehydes to nitroolefins using perhydroindolic acid as a chiral organocatalyst.

## Results and discussion

We first applied **1a**–**1d** 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 n-butyraldehyde was carried out in the presence of 20 mol% of catalyst loading at room

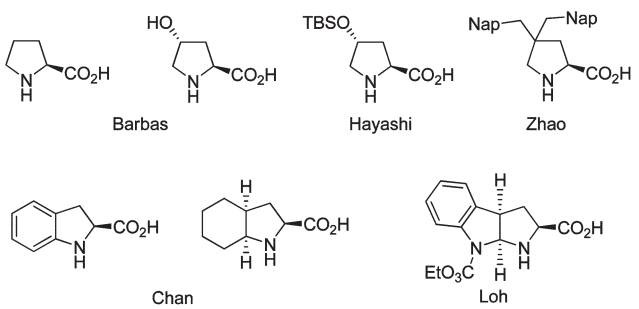


**Fig. 1** The proline-type catalysts.

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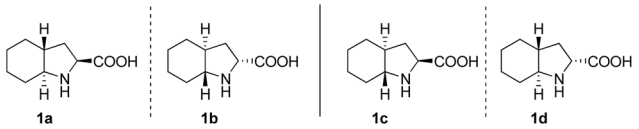
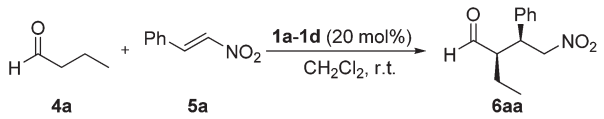



**Fig. 2** Trandolapril intermediate **1a** and its by-products **1b–1d**.

**Table 1** Screening of catalysts **1a–1d** for Michael additions of aldehyde **4a** to nitroalkene **5a**[a]




| Entry | Catalyst | *t* [h] | Yield [%][b] | *syn*/*anti*[c] | ee [%][d] |
|---|---|---|---|---|---|
| 1 | **1a** | 72 | trace | — | — |
| 2 | **1b** | 72 | trace | — | — |
| 3 | **1c** | 72 | 93 | 91/9 | −86 |
| 4 | **1d** | 72 | 95 | 92/8 | 86 |

[a] Reactions were conducted with 0.2 mmol (*E*)-(2-nitrovinyl)benzene and 2 mmol butaldehyde at room temperature in the presence of catalyst with $CH_2Cl_2$ as a solvent. [b] Isolated yield. [c] Determined by $^1H$ NMR spectra of crude products. The relative and absolute configurations of **6aa** were determined by comparison with the literature data.[7] [d] Determined by chiral HPLC.

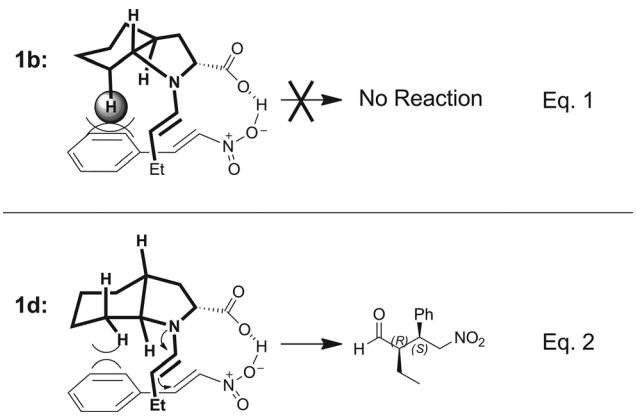
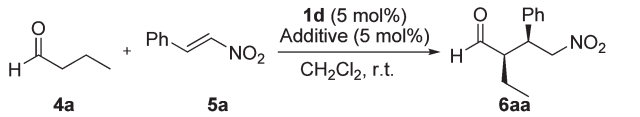



**Fig. 3** A proposed stereochemical pathway for **1b** and **1d**.

temperature in $CH_2Cl_2$ (Table 1). However, the intermediate **1a** and its enantiomer **1b** showed no reaction activity even after 72 h (entries 1 and 2). To our delight, their diastereoisomers, **1c** and **1d**, resulted in a highly efficient reaction with excellent diastereo- and enantioselectivity, affording *syn*-selective Barbas–Michael reaction products (entries 3 and 4).[11]

The difference in reactivity between the utilized catalysts can be explained by the proposed stereochemical pathway shown in Fig. 3 with catalysts **1b** and **1d**. Originally, the n-butyraldehyde reacts with **1b** and **1d** to afford a nucleophilic enamine intermediate whilst the (*E*)-(2-nitrovinyl)benzene is directed toward the carboxylic group by a hydrogen bond, which enhances the electrophilic property of the nitroolefin.[12] The formed enamine

**Table 2** Influence of additives for the Michael addition of aldehyde **4a** to nitroalkene **5a** catalyzed by catalyst **1d**[a]



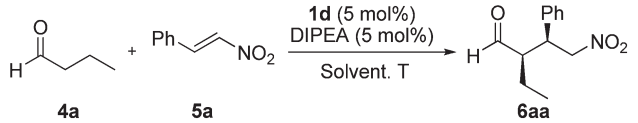

| Entry | Catalyst loading [mol%] | *t* [h] | Additive | Yield/ [%][b] | *syn*/ *anti*[c] | ee[d] [%] |
|---|---|---|---|---|---|---|
| 1 | 10 | 7 d | — | 59 | 93/7 | 85 |
| 2 | 10 | 5 d | TFA | 43 | 91/9 | 92 |
| 3 | 10 | 7 d | Methane sulfonamide | 45 | 93/7 | 86 |
| 4 | 10 | 7 d | $CH_3CO_2H$ | 59 | 93/7 | 89 |
| 5 | 10 | 5 d | Benzoic acid | 68 | 92/8 | 91 |
| 6 | 10 | 3.5 | $Et_3N$ | 97 | 95/5 | 94 |
| 7 | 10 | 3.5 | DIPEA | 95 | 94/6 | 95 |
| 8 | 10 | 3.5 | DBU | 95 | 92/8 | 94 |
| 9 | 10 | 3.5 | TMEDA | 98 | 96/4 | 93 |
| 10 | 10 | 12 | DABCO | 95 | 95/5 | 91 |
| 11 | 10 | 16 | DMAP | 93 | 94/6 | 92 |
| 12 | 10 | 7 d | Pyridine | 72 | 93/7 | 86 |
| 13 | 5 | 7 | $Et_3N$ | 93 | 87/13 | 95 |
| 14 | 5 | 7 | DIPEA | 97 | 93/7 | 95 |
| 15 | 2 | 16 | $Et_3N$ | 94 | 89/11 | 95 |
| 16 | 2 | 72 | DIPEA | 90 | 83/17 | 92 |

[a] Reactions were conducted with 0.2 mmol (*E*)-(2-nitrovinyl)benzene and 2 mmol butaldehyde in the presence of catalyst with different additives in $CH_2Cl_2$ at room temperature. [b] Isolated yield. [c] Determined by $^1H$ NMR spectra of crude products. The relative and absolute configurations of **6aa** were determined by comparison with the literature data.[7] [d] Determined by chiral HPLC.

moiety then tends to attack the double C–C bond of (*E*)-(2-nitrovinyl)benzene to afford the terminal molecule. Accordingly, different catalysts result in different reaction results. With **1b** as a chiral catalyst, much larger steric repulsion will exist between the a-H atom of the cyclohexyl moiety and phenyl group of the activated (*E*)-(2-nitrovinyl)benzene (eqn (1)). The large steric repulsion leads to a relatively long distance between the enamine moiety and double bond of (*E*)-(2-nitrovinyl)benzene and thus no reaction occurs. Alternatively, if **1d** was used as a catalyst, the e-H atom plus upward pointing C atom results in a short distance between the enamine moiety and the double bond of (*E*)-(2-nitrovinyl)benzene (eqn (2)). The reaction can therefore occur readily.

The catalyst loading was then decreased with **1d** as a chiral organocatalyst. No obvious influence was found on the diastereo- and enantioselectivity, but only 59% yield was obtained even after 7 days (Table 2, entry 1). Several bases and acids were chosen as additives with the aim to improve the reaction activity. As shown in Table 2, acidic additives had a slight effect on the reaction (entries 2–5). Compared to acidic additives, many basic additives (entries 5–12) dramatically shortened the reaction time providing excellent yield (up to 97% yield within 3.5 h). It appears that the basic conditions are in favour of the leaving of (*E*)-(2-nitrovinyl)benzene, promoting reaction activity. $Et_3N$ and DIPEA are somewhat better than others according to a combination of diastereo- and enantioselectivity, and they were used in the following reactions.

**Table 3** Influence of solvents and temperature for the Michael addition of aldehyde **4a** to nitroalkene **5a** catalyzed by catalyst **1d**[a]




**4a** **5a** **6aa**

| Entry | Solvent | $T$ [°C] | $t$ [h] | Yield [%][b] | *syn*/*anti*[c] | ee [%][d] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 20 | 7 | 97 | 93/7 | 95 |
| 2 | $CH_3CN$ | 20 | 7 | 91 | 89/11 | 95 |
| 3 | Toluene | 20 | 30 | 90 | 92/8 | 90 |
| 4 | DMF | 20 | 16 | 50 | 93/7 | 92 |
| 5 | THF | 20 | 7 d | 36 | 87/13 | 85 |
| 6 | i-PrOH | 20 | 7 d | 14 | 82/18 | 84 |
| 7 | DCM | 0 | 15 | 95 | 96/4 | 96 |
| 8 | DCM | −20 | 72 | 88 | 93/7 | 97 |

[a] Reactions were conducted with 0.2 mmol (*E*)-(2-nitrovinyl)benzene and 2 mmol butaldehyde in the presence of catalyst with DIPEA as an additive in $CH_2Cl_2$ at suitable temperature. [b] Isolated yield. [c] Determined by $^1$H NMR spectra of crude products. The relative and absolute configurations of **6aa** were determined by comparison with the literature data.[7] [d] Determined by chiral HPLC.

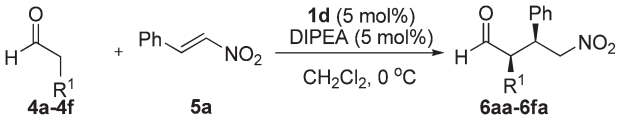
We wanted to further decrease catalyst loading since the high reaction activity was obtained by using basic additives such as $Et_3N$ and DIPEA in the presence of 10 mol% catalytic loading. To our delight, when the above reaction was carried out in the presence of 5 mol% **1d**, almost no change was found in diastereoselectivity and enantioselectivity with DIPEA as an additive, albeit with a slight drop in reactivity (entries 13–14). However, further decreasing the catalyst loading to 2 mol% resulted in decreased diastereoselectivity and long reaction times (entries 15–16). Therefore 5 mol% catalytic loading was adopted in further reactions.

We then investigated the influence of solvents on the reaction and almost all reactions presented excellent catalytic results (Table 3). High yield and excellent enantioselectivity were obtained by using $CH_2Cl_2$, $CH_3CN$ and toluene (entries 1–3). $CH_2Cl_2$ 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 3, reduced diastereo- and enantioselectivity and yield were obtained even with long reaction times (entries 5–6).

Temperature had a little effect on the reaction, and excellent enantioselectivity and diastereoselectivity were observed from 20 °C to −20 °C (entries 1, 7–8). 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 (Table 4). Excellent catalytic behavior was obtained when using linear aldehydes, such as n-butyraldehyde, propaldehyde and hexaldehyde (entries 1–3). 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 was 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.

**Table 4** Exploration of aldehydes for Michael addition catalyzed by catalyst **1b**[a]

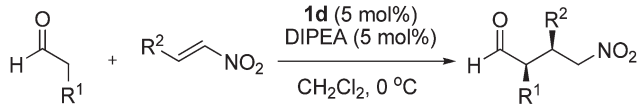



**4a-4f** **5a** **6aa-6fa**

| Entry | Product | $R^1$ | $t$ [h] | Yield [%][b] | *syn*/*anti*[c] | ee [%][d] |
|---|---|---|---|---|---|---|
| 1 | **6aa** | Et | 15 | 95 | 96/4 | 97 |
| 2 | **6ba** | Me | 24 | 97 | 92/8 | 98 |
| 3 | **6ca** | n-Bu | 12 | 98 | 95/5 | 95 |
| 4 | **6da** | i-Pr | 72 | 96 | 97/3 | 95 |

[a] Reactions were conducted with 0.2 mmol (*E*)-(2-nitrovinyl)benzene and 2 mmol propaldehyde in the presence of catalyst with DIPEA as an additive in $CH_2Cl_2$ at 0 °C. [b] Isolated yield. [c] Determined by $^1$H NMR spectra of crude products. The relative and absolute configurations of **6** were determined by comparison with the literature data.[7] [d] Determined by chiral HPLC.

**Table 5** Nitroolefins generality for Michael addition catalyzed by catalyst **1b**[a]




**4** **5** **6**

| Entry | Product | $R^1$ | $R^2$ | $T$ [h] | Yield [%][b] | *syn*/*anti*[c] | ee [%][d] |
|---|---|---|---|---|---|---|---|
| 1 | **6ba** | Me | Ph | 24 | 97 | 92/8 | 98 |
| 2 | **6bb** | Me | 4-ClPh | 10 | 99 | 91/9 | 97 |
| 3 | **6bc** | Me | 3-ClPh | 48 | 95 | 94/6 | 95 |
| 4 | **6bd** | Me | 4-FPh | 16 | 98 | 92/8 | 97 |
| 5 | **6be** | Me | 4-$CF_3$Ph | 12 | 99 | 87/13 | 96 |
| 6 | **6bf** | Me | 4-$CH_3O$Ph | 96 | 96 | 94/6 | 96 |
| 7 | **6bg** | Me | 3-$CH_3O$Ph | 5d | 85 | 93/7 | 96 |
| 8 | **6bh** | Me | 2-$CH_3O$Ph | 96 | 99 | 97/3 | 96 |
| 9 | **6bi** | Me | 2-$CH_3$Ph | 7d | 57 | 93/7 | 97 |
| 10 | **6bj** | Me | 3,4-$(CH_3O)_2$Ph | 7d | 45 | 91/9 | 96 |
| 11 | **6bk** | Me | 1-Naphthyl | 96 | 84 | 92/8 | 95 |
| 12 | **6bl** | Me | 2-Naphthyl | 72 | 93 | 89/11 | 96 |
| 13 | **6bm** | Me | 2-Furyl | 72 | 99 | 86/14 | 96 |
| 14 | **6bn** | Me | 2-Thienyl | 5d | 83 | 87/13 | 94 |
| 15 | **6bo** | Me | 3-Pyridyl | 36 | 99 | 65/35 | 95 |
| 16 | **6bp** | Me | Cyclohexyl | 7d | n.r. | — | — |
| 17 | **6cb** | i-Pr | 4-ClPh | 90 | 98 | 98/2 | 97 |
| 18 | **6cc** | i-Pr | 2-$CH_3O$Ph | 7d | 94 | 99/1 | 96 |

[a] Reactions were conducted with 0.2 mmol (*E*)-(2-nitrovinyl)benzene and 2 mmol propaldehyde in the presence of catalyst with DIPEA as an additive in $CH_2Cl_2$ at 0 °C. [b] Isolated yield. [c] Determined by $^1$H NMR spectra of crude products. The relative and absolute configurations of **6** were determined by comparison with the literature data.[7,8,13] [d] Determined by chiral HPLC.

Finally, we examined several kinds of nitroolefins (Table 5). 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 1–9). However, the reaction activity decreased for some electron-donating substituted nitroalkenes (entries 6–9). The most obvious being the nitroalkene with di-methoxyl groups, which gave only 45% yield of product even after 7 days. However excellent diastereo- and enantioselectivity were also obtained (entry 10). Replacement of the phenyl ring by a naphthalene ring resulted in excellent dr and ee values being obtained with high yields of products (entries 11–12). In addition, this method also allowed the use of heteroaromatic nitroolefins in excellent asymmetric catalytic behavior (entries 13–15). Unfortunately, no reaction occurred when using aliphatic nitroalkenes with a cyclohexyl group (entry 16). It is obvious that the present catalytic system is suitable for asymmetric Michael additions of a series of aromatic nitroolefins.

Isobutyraldehyde with large steric hindrance was also adopted to pursue higher diastereoselectivity. As we expected, up to 99/1 diastereoselectivity were also obtained with excellent enantioselectivity (entries 17, 18). However, long reaction times were needed for the reaction to go to completion.

## Conclusions

In summary, we have successfully applied the by-products of a trandolapril key intermediate 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 99/1 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 **1d** as a chiral organocatalyst. Encouraged by its excellent performance, a broader application is under investigation in our laboratory.

## Experimental section

### General

$^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer with TMS as an internal standard. HRMS was performed on Analysis Center of Shanghai Jiao Tong University. The enantioselectivity was measured by high performance liquid chromatography (HPLC) using Daicel Chiralcel AD-H, OD-H, AS-H, OJ-H and OZ-H columns with hexane/2-propyl alcohol as eluent. Column chromatography was performed using 100–200 mesh silica gel. All commercially available substrates were used as received. Nitroolefins were prepared according to literature procedures.[2d,e,m,14]

### General procedure for the Michael addition

The catalyst **1d** (1.69 mg, 0.01 mmol), DIPEA (1.75 μL, 0.01 mmol) and aldehyde (2 mmol) were dissolved in $CH_2Cl_2$ (1 mL) at 0 °C. The solution was stirred for 5 min, and then the appropriate nitroolefin (0.2 mmol) was added. The reaction mixture was stirred at 0 °C until the complete consumption of nitroolefin (monitored by TLC). The solvent was then evaporated and the residue was purified by flash column silica-gel chromatography (PE/EA = 8/1) to provide the corresponding Michael adducts. Diastereoselectivities were measured by $^1$H NMR analysis of the crude product directly. The enantiomeric excess (ee) was determined by HPLC analysis of samples with different fractions.[15] The absolute configurations of the products were determined by comparing with reported literature data.

**(2*R*,3*S*)-2-Ethyl-4-nitro-3-phenylbutanal (6aa).**[7] From aldehyde **4a** and nitroolefin **5a** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.71 (d, $J$ = 2.5 Hz, 1H), 7.38–7.14 (m, 5H), 4.75–4.58 (m, 2H), 3.83–3.74 (m, 1H), 2.72–2.63 (m, 1H), 1.55–1.45 (m, 2H), 0.83 (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: $t_R$ = 32.96 min (major) and $t_R$ = 24.73 min (minor).

**(2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal (6ba).**[7] From aldehyde **4b** and nitroolefin **5a** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.70 (d, $J$ = 1.8 Hz, 1H), 7.37–7.12 (m, 5H), 4.83–4.75 (m, 1H), 4.72–4.64 (m, 1H), 3.86–3.74 (m, 1H), 2.85–2.70 (m,1H), 0.99 (d, $J$ = 7.2 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: $t_R$ = 48.66 min (major) and $t_R$ = 31.92 min (minor).

**(2*R*,3*S*)-2-Isopropyl-4-nitro-3-phenylbutanal (6ca).**[7] From aldehyde **4c** and nitroolefin **5a** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.92 (d, $J$ = 2.4 Hz, 1H), 7.38–7.25 (m, 3H), 7.21–7.15 (m, 2H), 4.70–4.63 (m, 1H), 4.61–4.53 (m, 1H), 3.94–3.85 (m, 1H), 2.80–2.74 (m, 1H), 1.77–1.66 (m, 1H), 1.09 (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: $t_R$ = 27.20 min (major) and $t_R$ = 25.67 min (minor).

**(*R*)-2-((*S*)-2-Nitro-1-phenylethyl)hexanal (6da).**[7] From aldehyde **4e** and nitroolefin **5a** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.70 (d, $J$ = 2.7 Hz, 1H), 7.44–7.15 (m, 5H), 4.84–4.57 (m, 2H), 3.86–3.72 (m, 1H), 2.81–2.63 (m, 1H), 1.52–1.07 (m, 6H), 0.78 (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 $t_R$ = 21.13 min (minor).

**(2*R*,3*S*)-3-(4-Chlorophenyl)-2-methyl-4-nitrobutanal (6bb).**[7] From aldehyde **4b** and nitroolefin **5b** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.69 (d, $J$ = 1.5 Hz, 1H), 7.36–7.28 (m, 2H), 7.15–7.09 (m, 2H), 4.82–4.73 (m, 1H), 4.68–4.59 (m, 1H), 3.83–3.75 (m, 1H), 2.81–2.70 (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).

**(2*R*,3*S*)-3-(3-Chlorophenyl)-2-methyl-4-nitrobutanal (6bc).**[13a] From aldehyde **4b** and nitroolefin **5c** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.69 (d, $J$ = 1.5 Hz, 1H), 7.32–6.97 (m, 4H), 4.84–4.75 (m, 1H), 4.69–4.61 (m, 1H), 3.82–3.74 (m, 1H), 2.82–2.70 (m, 1H), 1.01 (d, $J$ = 7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OZ-H), Hex–i-PrOH 90 : 10, UV 210 nm, 0.8 mL min$^{-1}$, syn: $t_R$ = 35.05 min (major) and $t_R$ = 29.42 min (minor).

**(2*R*,3*S*)-3-(4-Fluorophenyl)-2-methyl-4-nitrobutanal (6bd).**[13b] From aldehyde **4b** and nitroolefin **5d** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.70 (d, $J$ = 1.5 Hz, 1H), 7.22–7.11 (m, 2H), 7.07–6.99 (m, 2H), 4.83–4.73 (m, 1H), 4.68–4.59 (dd, $J$ = 12.7, 9.6 Hz, 1H), 3.85–3.75 (m, 1H), 2.84–2.66 (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: $t_R$ = 22.99 min (major) and $t_R$ = 30.86 min (minor).

**(2*R*,3*S*)-2-Methyl-4-nitro-3-(4-(trifluoromethyl)phenyl)butanal (6be).**[13d] From aldehyde **4b** and nitroolefin **5e** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.70 (d, $J$ = 1.4 Hz, 1H), 7.61 (d, $J$ = 8.2 Hz, 2H), 7.32 (d, $J$ = 8.1 Hz, 2H), 4.87–4.79 (m, 1H), 4.75–4.65 (m, 1H), 3.96–3.84 (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).

**(2*R*,3*S*)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal (6bf)**[7]**.** From aldehyde **4b** and nitroolefin **5f** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.69 (d, $J$ = 1.7 Hz, 1H), 7.17–6.97 (m, 2H), 6.95–6.77 (m, 2H), 4.82–4.70 (m, 1H), 4.67–4.58 (m, 1H), 3.77 (s, 3H), 3.76–3.71 (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), Hex–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).

**(2*R*,3*S*)-3-(3-Methoxyphenyl)-2-methyl-4-nitrobutanal (6bg).** From aldehyde **4b** and nitroolefin **5g** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.69 (d, $J$ = 1.6 Hz, 1H), 7.27–7.21 (m, 1H), 6.83–6.67 (m, 3H), 4.80–4.73 (m, 1H), 4.69–4.62 (m, 1H), 3.78 (s, 3H), 3.84–3.72 (m, 1H), 2.83–2.69 (m, 1H), 1.00 (d, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 202.4, 160.1, 138.4, 130.3, 120.3, 114.6, 113.1, 78.2, 55.4, 48.6, 44.2, 12.3. HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OZ-H), Hex–i-PrOH 90 : 10, UV 210 nm, 0.8 mL min$^{-1}$, syn: $t_R$ = 40.98 min (major) and $t_R$ = 35.47 min (minor). HRMS (ESI-TOF) Calcd for $C_{12}H_{15}NO_4$ [M − H] 236.0923, Found: 236.0938. IR ($\nu$/cm$^{-1}$): 2970, 2939, 2888, 2839, 2729, 1724, 1601, 1552, 1491, 1456, 1382, 1263, 1161, 1045, 785, 702.

**(2*R*,3*S*)-3-(2-Methoxyphenyl)-2-methyl-4-nitrobutanal (6bh)**[7]**.** From aldehyde **4b** and nitroolefin **5h** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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), Hex–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).

**(2*R*,3*S*)-2-Methyl-4-nitro-3-o-tolylbutanal (6bi).**[13c] From aldehyde **4b** and nitroolefin **5i** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.72 (d, $J$ = 2.0 Hz, 1H), 7.23–7.08 (m, 4H), 4.83–4.61 (m, 2H), 4.22–4.03 (m, 1H), 2.82–2.71 (m, 1H), 2.38 (s, 3H), 0.96 (d, $J$ = 7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hex–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).

**(2*R*,3*S*)-3-(3,4-Dimethoxyphenyl)-2-methyl-4-nitrobutanal (6bj).** From aldehyde **4b** and nitroolefin **5j** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.70 (d, $J$ = 1.9 Hz, 1H), 6.86–6.62 (m, 3H), 4.84–4.72 (m, 1H), 4.69–4.61 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79–3.70 (m, 1H), 2.82–2.68 (m, 1H), 1.02 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.6, 149.4, 148.9, 129.0, 120.3, 111.6, 111.3, 78.5, 56.1, 56.0, 48.8, 43.9, 12.3. HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OJ-H), Hex–i-PrOH 75 : 25, UV 210 nm, 0.6 mL min$^{-1}$, syn: $t_R$ = 80.56 min (major) and $t_R$ = 122.64 min (minor). HRMS (ESI-TOF) Calcd for $C_{13}H_{17}NO_5$ [M − H] 266.1028, Found: 266.1040. IR ($\nu$/cm$^{-1}$): 2968, 2937, 2888, 2839, 1722, 1592, 1552, 1518, 1463, 1381, 1263, 1145, 1026,980, 901, 810, 768.

**(2*R*,3*S*)-2-Methyl-3-(naphthalen-1-yl)-4-nitrobutanal (6bk)**[7]**.** From aldehyde **4b** and nitroolefin **5k** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.76 (d, $J$ = 1.8 Hz, 1H), 8.24–8.05 (m, 1H), 7.89 (d, $J$ = 8.0 Hz, 1H), 7.81 (d, $J$ = 8.2 Hz, 1H), 7.63–7.33 (m, 4H), 5.00–4.82 (m, 3H), 3.10–2.92 (m, 1H), 0.99 (d, $J$ = 7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hex–i-PrOH 90 : 10, UV 210 nm, 0.8 mL min$^{-1}$, syn: $t_R$ = 37.14 min (major) and $t_R$ = 39.39 min (minor).

**(2*R*,3*S*)-2-Methyl-3-(naphthalen-2-yl)-4-nitrobutanal (6bl).**[13a] From aldehyde **4b** and nitroolefin **5l** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 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), Hex–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).

**(2*R*,3*R*)-3-(Furan-2-yl)-2-methyl-4-nitrobutanal (6bm).**[7] From aldehyde **4b** and nitroolefin **5m** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.70 (d, $J$ = 1.0 Hz, 1H), 7.44–7.30 (m, 1H), 6.32–6.28 (m,

1H), 6.21–6.16 (m, 1H), 4.78–4.66 (m, 2H), 4.13–4.03 (m, 1H), 2.87–2.75 (m, 1H), 1.06 (d, $J$ = 7.3 Hz, 3H). HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hex–i-PrOH 90 : 10, UV 210 nm, 0.8 mL min$^{-1}$, syn: $t_R$ = 24.77 min (major) and $t_R$ = 22.84 min (minor).

**(2*R*,3*R*)-2-Methyl-4-nitro-3-(thiophen-2-yl)butanal (6bn)[7].** From aldehyde **4b** and nitroolefin **5n** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 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), Hex–i-PrOH 98 : 2, UV 230 nm, 0.95 mL min$^{-1}$, syn: $t_R$ = 84.95 min (major) and $t_R$ = 57.26 min (minor).

**(2*R*,3*S*)-2-Methyl-4-nitro-3-(pyridin-3-yl)butanal (6bo).** From aldehyde **4b** and nitroolefin **5o** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.68 (d, $J$ = 1.4 Hz. 1H), 8.56–8.45 (m, 2H), 7.54–7.50 (m, 1H), 7.33–7.22 (m, 1H), 4.84–4.79 (m, 1H), 4.73–4.65 (m, 1H), 3.90–3.80 (m, 1H), 2.91–2.77 (m, 1H), 1.01 (d, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.7, 149.9, 149.7, 135.7, 132.8, 124.0, 77.6, 48.1, 41.7, 12.4. HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OZ-H), Hex–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). HRMS (ESI-TOF) Calcd for $C_{10}H_{12}N_2O_3$ [M + H] 209.0926, Found: 209.0925. IR ($\nu$/cm$^{-1}$): 3035, 2974, 2935, 2881, 2854, 2730, 1724, 1576, 1556, 1381, 1025, 814, 717.

**(2*R*,3*S*)-3-(4-Chlorophenyl)-2-isopropyl-4-nitrobutanal (6cb).** From aldehyde **4c** and nitroolefin **5b** at 0 °C according to the general procedure to give white solid (78.2–80.0 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.90 (d, $J$ = 2.2 Hz, 1H), 7.36–7.27 (m, 2H), 7.16–7.08 (m, 2H), 4.71–4.62 (m, 1H), 4.58–4.47 (m, 1H), 3.92–3.83 (m, 1H), 2.78–2.70 (m, 1H), 1.76–1.64 (m, 1H), 1.10 (d, $J$ = 7.2 Hz, 3H), 0.86 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 204.2, 135.8, 134.2, 129.6, 129.5, 78.9, 58.7, 41.5, 28.1, 21.8, 17.1. HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OJ-H), Hex–i-PrOH 85 : 15, UV 210 nm, 0.7 mL min$^{-1}$, syn: $t_R$ = 28.95 min (major) and $t_R$ = 26.76 min (minor). HRMS (ESI-TOF) Calcd for $C_{13}H_{16}ClNO_3$ [M − H] 268.0740, Found: 268.0728. IR ($\nu$/cm$^{-1}$): 3029, 2964, 2934, 2875, 2845, 2742, 1716, 1554, 1492, 1468, 1379, 1087, 1013, 831, 721.

**(2*R*,3*S*)-2-Isopropyl-3-(2-methoxyphenyl)-4-nitrobutanal (6cc).** From aldehyde **4c** and nitroolefin **5c** at 0 °C according to the general procedure to give pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.91 (d, $J$ = 2.4 Hz, 1H), 7.30–7.23 (m, 1H), 7.11 (dd, $J$ = 7.4, 1.7 Hz, 1H), 6.94–6.83 (m, 2H), 4.83–4.75 (m, 1H), 4.61–4.54 (m, 1H), 4.17–4.07 (m, 1H), 3.85 (s, 3H), 3.08–3.02 (m, 1H), 1.74–1.63 (m, 1H), 1.10 (d, $J$ = 7.2 Hz, 3H), 0.84 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 205.1, 157.7, 130.9, 129.4, 124.8, 121.2, 111.4, 77.5, 57.1, 55.5, 39.4, 28.4, 21.9, 17.3. HPLC conditions: The enantiomeric excess was determined by HPLC (Chiralcel OJ-H), Hex–i-PrOH 96 : 4, UV 210 nm, 0.8 mL min$^{-1}$, syn: $t_R$ = 37.63 min (major) and $t_R$ = 31.79 min (minor). HRMS (ESI-TOF) Calcd for $C_{14}H_{19}NO_4$ [M − H] 264.1236, Found: 264.1221. IR ($\nu$/cm$^{-1}$): 2964, 2942, 2875, 2840, 2741, 1716, 1601, 1587, 1552, 1494, 1464, 1381, 1246, 1124, 1026, 756.

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