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Effective and recyclable dendritic catalysts for the direct asymmetric Michael addition of aldehydes to nitrostyrenes

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Abstract—Direct catalytic enantio- and diastereoselective Michael addition reaction of aldehydes to nitrostyrenes is described using a series of recyclable chiral 2-trimethylsilanyloxy-methyl-pyrrolidine-based dendritic catalysts. Good yields (up to 82%), and high diastereoselectivities (up to *syn*/*anti* = 95/5) and enantioselectivities (up to 99% ee) have been obtained.

1. Introduction

The Michael addition reaction is widely recognized as one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1] Great efforts have been made to develop the stoichiometric and catalytic systems for this type of transformation, which is still spurring on research activities.[2] In particular, the Michael addition of a carbon nucleophile to nitroalkenes is a useful synthetic method for the preparation of nitroalkanes,[2c] which are versatile synthetic intermediates owing to the various possible easy transformations of the nitro group into other useful functional groups, such as amino groups and nitrile oxides. In recent years, considerable attention has been focused on the asymmetric Michael reactions of nitroalkenes, providing the Michael adducts with high enantioselectivities. For example, cinchona-alkaloid derivatives catalyzed the reaction of malonates or β-ketoesters with nitroalkenes in high yields and excellent enantioselectivities.[3] Similar results were also achieved by using chiral bifunctional thiourea catalysts.[4] Direct catalytic Michael addition reactions of unmodified ketones or aldehydes to nitroalkenes have been reported using pyrrolidinyltetrazole,[5] aminomethylpyrrolidine,[6] or 2,2′-bipyrrolidine as efficient catalysts.[7] Barbas III[8] and List[9] independently described a proline-catalyzed Michael reaction of ketones to nitroalkenes. Oriyama et al. used (*S*)-homoproline to catalyze this reaction with high diastereoselectivity and moderate enantioselectivity.[10] Kotsuki et al. had discovered a new class of chiral pyrrolidine–pyridine conjugate base catalysts for this asymmetric Michael addition reaction.[11a] Meanwhile, Wang et al. developed pyrrolidine sulfonamide to catalyze this reaction, which was highly diastereoselective and enantioselective.[11b] Hayashi et al. reported a diphenylprolinol silyl ether which was promoted asymmetric. Although the catalyst loading was relatively high, Michael reaction of aldehydes and nitroalkenes provided excellent results.[12]

On the other hand, dendrimers as well-defined macromolecules with controllable structures have triggered increasing attention on their applications in catalysis since dendritic catalysts have the advantages of total solubility and may be analyzed with routine spectroscopic techniques.[13] Moreover, the globular shapes of higher generation dendritic catalysts are suitable for membrane filtration[14] or selective precipitation under specific conditions.[15] Recently, we reported the synthesis of a series of new dendritic catalysts and their application in the catalytic asymmetric reactions.[16] Being interested in the development of mild and convenient methodologies of asymmetric reactions using recyclable catalysts, we herein report the highly enantio- and diastereoselective Michael addition reactions of aldehydes to nitrostyrenes using the polyether dendritic chiral 2-trimethylsilanyloxy-methyl-pyrrolidine derivatives as catalysts.

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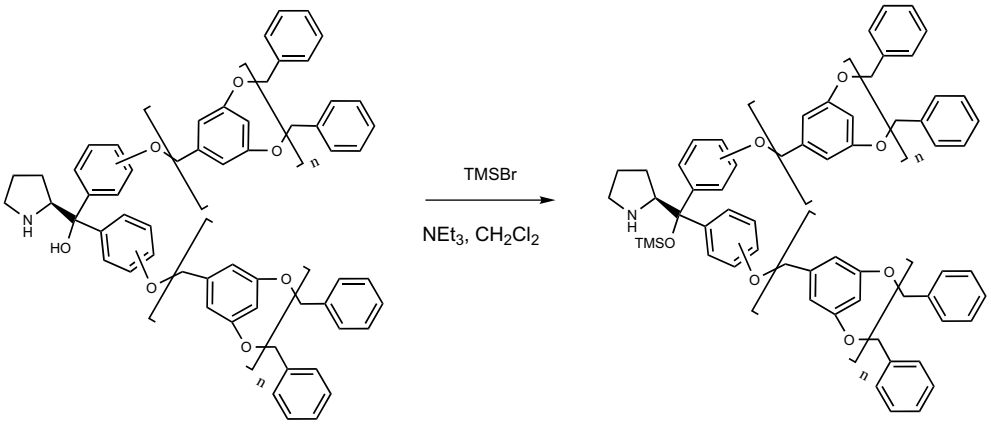
2. Results and discussion

A series of chiral dendrimers **1**–**4** were synthesized according to our previously published method.[17a,c] A mixture of these dendritic alcohols, trimethylsilyl bromide, and triethylamine as a base in dichloromethane was stirred for 3 h to afford the corresponding silyl ethers **5**–**8** in high yields (Scheme 1). These catalysts were purified by flash column chromatography and characterized by ^{1}H NMR spectroscopy, MALDI mass spectrometry, and elemental analysis. All the results were in full agreement with the proposed structures.

In preliminary studies, the Michael addition reaction of isovaleraldehyde **9a** with nitrostyrene **10a** in the presence of these dendritic catalysts **5**–**8** under various reaction conditions was investigated with the results shown in Table 1. After adding aldehyde **9a** and nitrostyrene **10a** in CCl_4, the mixture was stirred at room temperature for 3 d in the presence of 10 mol % of catalyst **5**. The addition product 2-isopropyl-4-nitro-3-phenyl-butyraldehyde **11a** was isolated in excellent enantioselectivity (99% ee), good yield (86%), and moderate diastereoselectivity (dr: 80:20) (Table 1, entry 1). The *para*-substituted second generation dendritic catalyst **6** gave a comparable result (Table 1, entry 2).

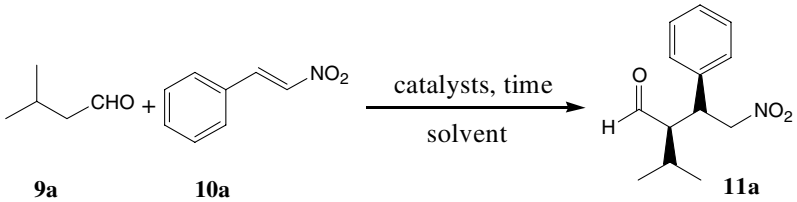


1 (n = 1, *para*-position)
2 (n = 2, *para*-position)
3 (n = 3, *para*-position)
4 (n = 2, *meta*-position)

5 (n = 1, *para*-position)
6 (n = 2, *para*-position)
7 (n = 3, *para*-position)
8 (n = 2, *meta*-position)

Scheme 1.

Table 1. Optimizing the conditions for asymmetric Michael reactions catalyzed by dendritic ligands[a]



9a **10a** **11a**

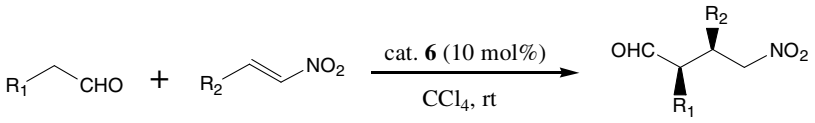
Entry	Catalyst	*T* (°C)	Solvent	*t* (d)	Yield (%)[b]	dr (*syn*/*anti*)[c]	ee (%)[d]
1	**5**	20	CCl_4	3	86	80/20	99
2	**6**	20	CCl_4	3	81	81/19	99
3	**8**	20	CCl_4	3	70	89/11	97
4	**7**	20	CCl_4	4	59	82/18	99
5	**8**	0	CCl_4	6	30	92/8	99
6	**6**	0	CCl_4	6	41	93/7	99
7	**6**	20	CCl_4/hexane = 1/1	3	43	72/28	99
8	**6**	20	CH_2Cl_2	3	61	74/26	99
9	**6**	20	Toluene	4	50	87/13	99
10[e]	**6**	20	CCl_4	5	41	91/9	99

[a] Unless otherwise stated, all the reactions were performed with 10 mol % catalyst loading, **9a**/**10a** = 10/1.
[b] Isolated yields.
[c] Determined by the analysis of ^{1}H NMR spectra.
[d] Reported values refer to the *syn* isomer and were determined by chiral HPLC.
[e] The catalytic loading was 5 mol %.

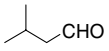
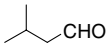
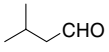
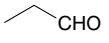
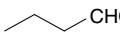
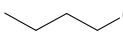
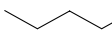
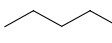
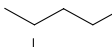
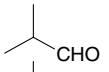
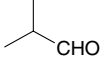
Higher diastereoselectivity was observed when the *meta*-substituted catalyst **8** was employed, but the yield and enantioselectivity were lower (Table 1, entry 3). Although relatively good diastereoselectivity and excellent enantioselectivity were obtained with the third generation dendritic catalyst **7**, the reaction rate was slower and the product yield was moderate owing to poor solubility of the catalyst in the solvent (Table 1, entry 4). The reaction performed at 0 °C can increase the diastereoselectivity with a much longer reaction time (Table 1, entries 5 and 6). When the reaction was carried out in CCl_4/hexane = 1/1 (v/v) and CH_2Cl_2, the diastereoselectivity was reduced to a moderate level with the slow reaction rate (Table 1, entries 7 and 8). Compared with CH_2Cl_2, the addition reaction performed in toluene gave a surprising increase in diastereoselectivity along with a moderate yield (Table 1, entry 9). Additional studies indicated that reducing the catalytic loading did not affect the diastereo- or enantioselectivity, but reduced the product yield (Table 1, entry 10). Thus, using catalyst **6** in CCl_4 at room temperature was found to be the best protocol for the direct asymmetric Michael addition reactions of aldehydes to nitrostyrenes.

With the optimal reaction conditions, we examined the Michael addition reactions of a series of unmodified aldehydes with nitrostyrenes in order to establish the scope of the reactions. All the reactions were performed in CCl_4 at room temperature with 10 mol % of catalyst **6**. The results are summarized in Table 2. It should be emphasized that the level of diastereo- and enantiocontrol for all reactions was outstanding. In almost all of the examples (Table 2, entries 1–11), after reacting for the indicated time, the Michael adducts were obtained with good yields (up to 82%), excellent enantioselectivities (up to 99% ee), and good diastereoselectivities (up to *syn*/*anti* 95/5). When isovaleraldehyde was used as Michael donor and nitrostyrene as an acceptor, product **11a** was obtained with 81% yield, 81/19 dr and 99% ee (Table 2, entry 1). An electron-withdrawing substituent on the phenyl of nitrostyrene gave a comparable enantioselectivity, albeit with a slight increase in diastereoselectivity and an apparently reduced yield (Table 2, entry 2). Nitrostyrene with a more bulky group (naphthyl) afforded excellent enantioselectivity and diastereoselectivity along with an accelerated reaction rate (Table 2, entry 3). Higher diastereoselectivity was achieved with increasing bulkiness of the substituents on the aldehyde donor in the order Me < Et < *n*-C_3H_7 < *n*-C_4H_9 < *n*-C_5H_{11}, although the varieties were very slight (Table 2, entries 4–9). Conversely, the reaction rate and yields decreased in that order, which can be attributed to bulk of the substituents and the activity of aldehydes. It was obvious that all the substrates afforded the adducts in nearly enantiomerically pure form except for the *n*-valeraldehyde (Table 2, entry 6). However, when *n*-valeraldehyde was reacted with a nitrostyrene with an electron-donating group on the phenyl ring, the enantiomeric excess was increased to 99% (Table

Table 2. Michael addition of unmodified aldehydes to nitro olefins



9 **10** **11**

Entry	**9**	R_2	Product	Time	Yield (%)[a]	dr (*syn*/*anti*)[b]	ee (%)[c]
1		Ph	**11a**	3 d	81	81/19	99
2		4-BrPh	**11b**	4 d	60	85/15	99
3		α-Naphthyl	**11c**	50 h	71	89/11	99
4		Ph	**11d**	4 h	79	91/9	99
5		Ph	**11e**	30 h	80	92/8	99
6		Ph	**11f**	30 h	75	93/7	97
7		4-MeOPh	**11g**	2 d	78	90/10	99
8		Ph	**11h**	2 d	73	92/8	99
9		Ph	**11i**	36 h	82	95/5	99
10		Ph	**11j**	6 d	80	—	89
11		4-BrPh	**11k**	6 d	42	—	77

[a] Isolated yields.
[b] Determined by the analysis of ^{1}H NMR spectra.
[c] Reported values refer to the *syn* isomer and were determined by chiral HPLC.

2, entry 7). Isobutyraldehyde was found to be a poor nucleophile. In this reaction, the products were obtained with only moderate enantioselectivities (89% and 77%, ee respectively), when nitrostyrene and 1-bromo-4-((*E*)-2-nitrovinyl) benzene independently were used as the substrates (Table 2, entries 10 and 11); however, they were improved compared with the small organocatalyst diphenylprolinol silyl ethers.[12] To account for the present high enantio- and diastereoselective Michael addition reactions, we propose that the *anti* enamine, with its double bond orientated away from the di(polyether dendrimer)siloxymethyl group, would be formed selectively and would react with nitrostyrene via an acyclic synclinal transition state proposed by Seebach and Golinski,[17] which is similar to Hayashi's results.[12]

To demonstrate the significant advantage of dendritic catalysts that can be easily separated from substrates and products through precipitation, owing to different solubilities in methanol, we recovered these dendritic ligands by the precipitation method. After the reaction, dry methanol was added to the reaction mixture, and catalyst **6** precipitated almost quantitatively and recovered via filtration. The recovered catalyst was reused to catalyze the Michael addition reaction of isovaleraldehyde and nitrostyrene. The results are shown in Table 3. Obviously, the recovered catalyst **6** could be reused at least five times with only a slight loss of activity.

Table 3. Recycling use of dendritic catalyst **6** in asymmetric Michael addition reactions

Run	Time (d)	Yield (%)[a]	dr (*syn*/*anti*)[b]	ee (%)[c]
1	5	81	81/19	99
2	5	70	80/20	99
3	5	72	81/19	99
4	5	74	79/21	98
5	5	65	75/25	99

[a] Isolated yields.
[b] Determined by the analysis of ^{1}H NMR spectroscopy.
[c] Reported values refer to the *syn* isomer and were determined by HPLC on a chiral stationary phase.

3. Conclusion

In conclusion, we synthesized a new series of recyclable chiral 2-trimethylsilanyloxy-methyl-pyrrolidine-based dendritic catalysts for the Michael addition reaction of various unmodified aldehydes with various nitrostyrenes. Good yields, high diastereoselectivities, and excellent enantioselectivities were achieved. This study extends the catalytic scope of our chiral dendritic ligands, which were highly efficient and easily separable. Further studies on the applications of the dendritic ligands are underway.

4. Experimental

4.1. General

All reactions were carried out under a dry argon atmosphere. CCl_4 was freshly distilled from CaH_2 before use. Analytical TLC was done on precoated silica gel plates. Column chromatography was conducted with 300–400 mesh silica gel. ^{1}H NMR spectra were recorded on 300 MHz spectrometers. Chemical shifts of ^{1}H NMR spectra were recorded relative to tetramethylsilane ($\delta = 0$). Analytical high performance liquid chromatography (HPLC) was done using a chiral column (4.6 mm × 25 cm, Chiralcel OD, OB, OJ, or Chiralpak AD). Optical rotations were measured on a polarimeter.

4.1.1. Synthesis of catalysts 5–8. Dendritic prolinols **1**–**4** were synthesized according to our previous reported method.[17] Prolinol (0.2 mmol) was dissolved in dichloromethane (5 mL). To this solution, triethylamine (0.52 mmol) and TMSBr (0.52 mmol) were added. Then the mixture was allowed to stir for 3 h at room temperature under argon atmosphere. The resulting solution was evaporated and purified by silica gel chromatography employing CH_2Cl_2/acetone (1/1) as an eluent to give the corresponding dendritic silyl ether ligands **5**–**8**.

4.1.1.1. Catalyst 5 (*n* = 1). Yield (92%) white foam, mp 46–47 °C; $[\alpha]_D^{20} = -25.2$ (*c* 0.30, $CHCl_3$); IR (film) 3358, 3032, 2918, 1597, 1507, 1453, 1159 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.071 (s, 9H), 1.51–1.81 (m, 5H), 2.90–3.10 (m, 2H), 4.22 (t, $J = 6.5$ Hz, 1H), 4.82 (s, 4H), 4.95 (s, 8H), 6.45–6.59 (m, 7H), 6.72–6.87 (m, 5H); MALDI MS (IAA): *m*/*e* 873.5 ([M−OTMS+H]$^+$); Anal. Calcd for $C_{62}H_{63}NO_7Si$: C, 77.39; H, 6.60; N, 1.46. Found: C, 77.50; H, 6.52; N, 1.45.

4.1.1.2. Catalyst 6 (*n* = 2). Yield (89%) white foam, mp 57–59 °C; $[\alpha]_D^{21} = -9.7$ (*c* 0.50, $CHCl_3$); IR (film) 3353, 2917, 1596, 1508, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.002 (s, 9H), 1.41–1.82 (m, 5H), 2.61–3.18 (m, 2H), 4.09 (t, $J = 7.4$ Hz, 1H), 5.05 (s, 16H), 6.63–6.65 (m, 6H), 6.67–6.76 (m, 12H), 6.99–7.01 (m, 3H), 7.35–7.51 (m, 45H); MALDI MS (IAA): *m*/*e* 1722.2 ([M−OTMS+H]$^+$); Anal. Calcd for $C_{118}H_{111}NO_{15}Si$: C, 78.25; H, 6.18; N, 0.77. Found: C, 77.98; H, 6.18; N, 0.64.

4.1.1.3. Catalyst 7 (*n* = 3). Yield (85%) white foam, mp 61–63 °C; $[\alpha]_D^{21} = -5.3$ (*c* 0.80, $CHCl_3$); IR (film) 3400, 3032, 2931, 1598, 1506, 1452, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 9H), 1.41–1.56 (m, 5H), 2.91–3.09 (m, 2H), 4.10 (t, $J = 7.7$ Hz, 1H), 4.93 (s, 28H), 4.97 (s, 32H), 6.51–6.55 (m, 4H), 6.63–6.65 (m, 28H), 6.80–6.83 (m, 4H), 7.21–7.37 (m, 84H) ; MALDI MS (IAA): *m*/*e* 3418.2 ([M−OTMS+H]$^+$); Anal. Calcd for $C_{230}H_{207}NO_{31}Si$: C, 78.72; H, 5.95; N, 0.40. Found: C, 78.73; H, 5.84, N, 0.59.

4.1.1.4. Catalyst 8 (*n* = 2). Yield (92%) white foam, mp 58–59 °C; $[\alpha]_D^{21} = -9.7$ (*c* 0.50, $CHCl_3$); IR (film) 3357, 2918, 1596, 1507, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.01 (s, 9H), 1.31–1.90 (m, 5H), 2.51–2.89 (m, 2H), 4.21 (t, $J = 7.5$ Hz, 1H), 5.02 (s, 12H), 5.10 (s, 16H), 6.60–6.61 (m, 5H), 6.73–6.75 (m, 12H), 6.99–7.11 (m, 4H), 7.34–7.51 (m, 45H); MALDI MS (IAA): *m*/*e* 1722.5 ([M−OTMS+H]$^+$); Anal. Calcd for $C_{118}H_{111}NO_{15}Si$: C, 78.25; H, 6.18; N, 0.77. Found: C, 78.09; H, 6.27; N, 0.65.

4.2. General experimental procedure for the dendritic ligand catalyzed Michael addition reaction of unmodified aldehydes with nitrostyrenes

Catalyst **6** (0.025 mmol, 44 mg) was added to a solution of nitrostyrene (0.25 mmol) in CCl_4 (2 mL). The aldehyde (2.5 mmol) was then added to this solution in one portion. The mixture was stirred at room temperature under an argon atmosphere. After the addition reaction was complete (followed by TLC), the mixture was treated with methanol (10 mL) and filtered. The dendrimeric catalyst was washed several times with methanol and 38 mg (86.4%) catalyst was recovered. The resulting solution was evaporated and purified by flash chromatography to give corresponding products **11a**–**11k**.

4.2.1. (2*R*,3*S*)-2-Isopropyl-4-nitro-3-phenylbutanal 11a.[12] Yield: 81%; $[\alpha]_D^{24.3} = +53.1$ (*c* 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.26 (m, 3H), 7.10 (m, 2H), 4.73–4.46 (m, 2H), 3.93–3.79 (m, 1H), 2.70 (d, $J = 10.2$ Hz, 1H), 1.62 (dd, $J = 13.5$, 6.6 Hz, 1H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.80 (d, $J = 6.9$ Hz, 3H). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak AD, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{major} 8.5 min and t_{minor} 9.4 min.

4.2.2. (2*R*,3*S*)-3-(4-Bromophenyl)-2-isopropyl-4-nitrobutanal (11b). Yield: 60%; $[\alpha]_D^{22.2} = +36.2$ (*c* 1.60, $CHCl_3$); mp 105–106 °C; IR (KBr) $\nu = 2964$, 1718, 1553, 1379, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (d, $J = 2.4$ Hz, 1H), 7.48 (dd, $J = 8.4$, 1.5 Hz, 2H), 7.07 (dd, $J = 8.4$, 1.5 Hz, 2H) 4.71–4.65 (m, 1H), 4.58–4.50 (m, 1H), 3.88 (m, 1H), 2.77–2.73 (m, 1H), 1.70 (m, 1H), 1.10 (dd, $J = 7.2$, 1.2 Hz, 3H), 0.86 (dd, $J = 7.2$, 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 203.8, 136.2, 132.3, 129.7, 122.1, 78.6, 58.5, 41.4, 27.9, 21.6, 16.9; Anal. Calcd for $C_{13}H_{16}BrNO_3$: C, 49.70; H, 5.13; N, 4.46. Found: C, 49.89; H, 5.04; N, 4.24. Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak AD, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{major} 16.2 min and t_{minor} 22.4 min.

4.2.3. (2*R*,3*S*)-2-Isopropyl-3-(naphthalen-1-yl)-4-nitrobutanal 11c.[12] Yield: 71%; $[\alpha]_D^{22.5} = +49.5$ (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.17 (br s, 1H), 7.87 (d, $J = 7.5$ Hz, 1H), 7.80 (d, $J = 7.8$ Hz), 7.60–7.32 (m, 4H), 4.82 (m, 3H), 3.06 (br s, 1H), 1.76 (s, 1H), 1.12 (d, $J = 6.3$ Hz, 3H), 0.83 (d, $J = 6.3$ Hz, 3H). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak OD-H, ^{i}PrOH/hexane 20/80), UV 254 nm, flow rate 0.5 mL/min, t_{minor} 42.7 min and t_{major} 46.7 min.

4.2.4. (2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal 11d.[12] Yield: 80%; $[\alpha]_D^{22.3} = +29.7$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, $J = 1.5$ Hz, 1H), 7.36–7.15 (m, 5H), 4.83–4.64 (m, 2H), 3.87–3.77 (m, 1H), 2.83–2.72 (m, 1H), 1.00 (d, $J = 6.9$ Hz, 3H). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak OD-H, ^{i}PrOH/hexane 7/93), UV 237 nm, flow rate 1.0 mL/min, t_{minor} 43.6 min and t_{major} 60.1 min.

4.2.5. (2*R*,3*S*)-2-Ethyl-4-nitro-3-phenylbutanal 11e.[12] Yield: 81%; $[\alpha]_D^{23.7} = +59.6$ (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, $J = 2.7$ Hz, 1H), 7.26 (m, 5H), 4.84–4.59 (m, 2H), 3.85–3.75 (m, 1H), 2.68 (m, 1H), 1.53 (m, 1H), 0.83 (t, $J = 7.5$ Hz, 3H). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak AD, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{major} 12.2 min and t_{minor} 13.7 min.

4.2.6. (*R*)-2-((*S*)-2-Nitro-1-phenylethyl)pentanal 11f.[12] Yield: 76%; $[\alpha]_D^{23.8} = +69.1$ (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, $J = 1.2$ Hz, 1H), 7.34–7.16 (m, 5H), 4.64 (m, 2H), 3.82–3.74 (dd, $J = 15.3$, 9.0 Hz, 1H), 2.71 (t, $J = 8.7$ Hz, 1H), 1.49–1.19 (m, 4H), 0.80 (d, $J = 6.9$ Hz, 3H). Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak OD-H, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 22.9 min and t_{major} 28.3 min.

4.2.7. (*R*)-2-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)pentanal 11g.[13b] Yield: 78%; $[\alpha]_D^{22.1} = +47.2$ (*c* 1.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, $J = 3.5$ Hz, 1H), 7.02 (d, $J = 5.1$ Hz, 2H), 6.80 (d, $J = 5.1$ Hz, 2H), 4.59 (m, 2H), 3.72 (s, 3H), 3.63 (m, 1H), 2.59 (m, 1H), 1.45–1.24 (m, 4H), 0.81 (t, $J = 4.5$ Hz, 3H). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak OD-H, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 38.7 min and t_{major} 42.6 min.

4.2.8. (*R*)-2-((*S*)-2-Nitro-1-phenylethyl)hexanal 11h.[13b] Yield: 74%; $[\alpha]_D^{24.6} = +35.5$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, $J = 2.4$ Hz, 1H), 7.34 (m, 3H), 7.18 (m, 2H), 4.74–4.60 (m, 2H), 3.81–3.73 (ddd, $J = 15.0$, 9.9, 5.4 Hz, 1H), 2.73–2.66 (m, 1H), 1.51–1.10 (m, 6H), 0.78 (t, $J = 6.3$ Hz, 3H). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak OD-H, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 23.3 min and t_{major} 26.4 min.

4.2.9. (*R*)-2-((*S*)-2-Nitro-1-phenylethyl)heptanal 11i.[13b] Yield: 82%; $[\alpha]_D^{24.0} = +34.1$ (*c* 2.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.24–7.09 (m, 5H), 4.71–4.52 (m, 2H), 3.71 (m, 1H), 2.62 (m, 1H), 1.34–1.09 (m, 8H), 0.73 (s, 3H). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak OD-H, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 20.3 min and t_{major} 24.8 min.

4.2.10. (*R*)-2,2-Dimethyl-4-nitro-3-phenylbutanal 11j.[14] Yield: 80%; $[\alpha]_D^{21.5} = +5.6$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.30–7.19 (m, 5H), 4.86 (t, $J = 12.9$ Hz, 1H), 4.70 (d, $J = 12.9$ Hz, 1H), 3.80 (d, $J = 11.7$ Hz, 1H), 1.13 (s, 3H), 1.00 (s, 3H). Enantiomeric excess: 89%, determined by HPLC (Daicel Chiralpak AS, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 0.5 mL/min, t_{minor} 35.7 min and t_{major} 37.4 min.

4.2.11. (*R*)-3-(4-Bromophenyl)-2,2-dimethyl-4-nitrobutanal 11k. Yield: 42%; $[\alpha]_D^{24.1} = +8.1$ (*c* 0.60, $CHCl_3$); mp 105–106 °C; IR (KBr) $\nu = 2973$, 1724, 1553, 1378, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.48 (d, $J = 8.1$ Hz, 2H), 7.10 (d, $J = 8.1$ Hz, 2H) 4.78 (m, 2H),

3.75 (d, $J = 11.1$ Hz, 1H), 1.12 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 203.7, 134.6, 131.9, 130.7, 122.2, 76.1, 48.1, 48.0, 21.7,18.9; Anal. Calcd for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.70; N, 4.67. Found: C, 48.00; H, 4.62; N, 4.42. Enantiomeric excess: 77%, determined by HPLC (Daicel Chiralpak AD, ^{i}PrOH/hexane 10/90), UV 254 nm, flow rate 0.5 mL/min, t_{major} 21.6 min and t_{minor} 27.1 min.

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