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Application of L-prolinamides as highly efficient organocatalysts for the asymmetric Michael addition of unmodified aldehydes to nitroalkenes

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ABSTRACT

The asymmetric Michael addition of aldehydes to nitroolefins was investigated using a combination of L-prolinamide derivatives and various acidic additives. (*S*)-1,1′-Bi-2-naphthol was found to be the most effective co-catalyst and afforded the nitroaldehyde products with excellent yields (up to 95%), enantiomeric excesses (up to 99%) and diastereoselectivity ratios (up to 99:1).

1. Introduction

Organocatalysis is recognized as a convenient and highly useful synthetic method in both research and industry because of its operational simplicity, ready availability of catalysts, environmental consciousness, low toxicity of the organic catalysts, (compared to the corresponding transition metal species) and the high efficiency and selectivity attained in many organocatalytic transformations under mild reaction conditions, which meet the current requirements for practical organic synthesis.[1]

The organocatalytic asymmetric Michael addition of ketones or aldehydes to nitroolefins is one of the most powerful and efficient methods for the preparation of enantiomerically enriched nitroalkanes. These Michael adducts are versatile building blocks due to the various possible transformations of the nitro functionality into other useful functional groups, such as amines, nitrile oxides, ketones, and carboxylic acids.[2]

Ever since Barbas[3] and List[4] independently published their own pioneering studies on the asymmetric Michael addition reactions using L-proline as the catalyst with good yields but very low enantioselectivities, a variety of organocatalysts have been synthesized and studied for the direct addition of ketones and aldehydes to β-nitrostyrenes. Among the most popular organocatalysts, pyrrolidine-based chiral compounds have been found to be highly successful for asymmetric organic transformations. The notable feature of these catalysts is that they contain a hydrogen-bond donor group attached to a pyrrolidine ring at the 2- or 4-position. Representative examples in this area include chiral pyrrolidinyl triazole,[5] tetrazole,[6] aminomethylpyrrolidine,[7] 2,2-bipyrrolidine,[8] pyrrolidine-pyridine,[9] pyrrolidine sulfonamide,[10] pyrrolidine-thiourea,[11] diphenylprolinol ether,[12] ionic liquid supported pyrrolidine-based catalysts,[13] and others,[14] which have been found to be highly successful for asymmetric organic transformations and significantly improved efficiencies and stereoselectivities have been obtained. Despite the excellent results achieved from previous studies, the development of an efficient organocatalyst for the direct asymmetric Michael additions of ketones and aldehydes to β-nitroalkenes remains a challenge in asymmetric synthesis.

2. Results and discussion

Over the course of our studies on the synthesis of chiral receptors equipped with various functionalities to aid their catalytic activities[15] and enantiomeric recognition properties,[16] we recently synthesized a series of L-proline-based chiral receptors[17] and investigated their recognition abilities for carboxylic acids by ^{1}H NMR spectroscopy (Fig. 1).

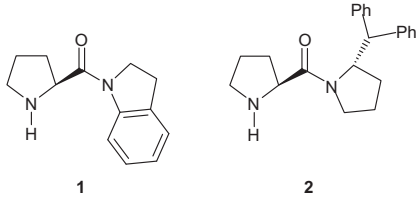

Figure 1. Structures of proline derived organocatalysts.

It was expected that these pyrrolidine-type receptors could also serve as organocatalysts for the enantioselective Michael reactions of aldehydes and ketones with nitrostyrenes. To address this possibility, we herein report the catalytic properties of these L-proline-derived receptors for the enantioselective Michael

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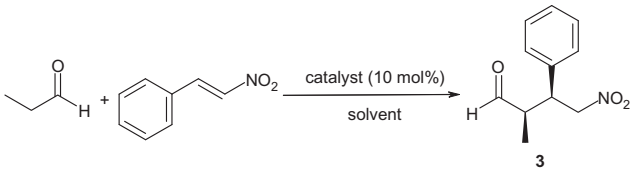
Table 1
Optimization of reaction conditions



Entry	Catalyst	Solvent	Time (d)	Yield[a] (%)	d.r.[b]	*ee*[c] (%)
1	**1**	*i*-PrOH	3	95	62:38	33
2	**1**	CCl_4	3	90	80:20	55
3	**1**	$CHCl_3$	4	70	63:37	42
4	**1**	DMF	4	60	87:13	32
5	**1**	Toluene	3	80	74:26	60
6	**1**	CH_2Cl_2	4	85	75:25	38
7	**1**	THF	3	65	70:30	41
8	**1**	H_2O	4	70	65:35	45
9	**2**	DMF	4	55	82:18	27
10	**2**	*i*-PrOH	3	70	65:35	35
11	**2**	$CHCl_3$	4	74	77:23	57
12	**2**	CH_2Cl_2	4	90	78:22	62
13	**2**	THF	3	90	79:21	48
14	**2**	Toluene	4	85	62:38	75
15	**2**	CCl_4	3	95	79:21	70
16	**2**	H_2O	3	75	70:30	55

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^1H NMR of crude product and/or HPLC analysis. The absolute configuration was determined by comparison with the literature data.
[c] Determined by chiral HPLC analysis (Chiralpak OD-H).

addition of aldehydes with β-nitrostyrenes, which is one of the most important C–C bond forming reactions in organic chemistry. To the best of our knowledge, this is the first application of prolinamides **1** and **2** as organocatalysts using co-catalysts for the stereoselective direct Michael addition of aldehydes to nitroalkenes.

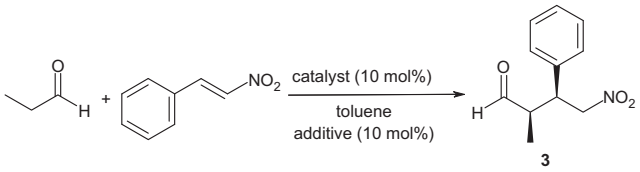
We initially focused on solvent effects in the Michael reactions at ambient temperature; the Michael addition of propionaldehyde to β-nitrostyrene was selected as a model reaction in the presence of organocatalysts (10 mol %) **1** and **2**.

As can be seen from the results shown in Table 1, the use of polar solvents, such as H_2O, DMF, and *i*-PrOH afforded the addition product in moderate to excellent yields, but poor diastereo and enantioselectivities (Table 1, entries 1, 4, 8–10, and 16) were observed. This may be due to the fact that the polar solvents interact with the organocatalysts through hydrogen bonding to weaken the activation ability of **1** and **2** toward the reaction. Despite higher diastereoselectivities and yields being achieved, poor enantioselectivities were observed when the reactions were carried out in CH_2Cl_2, $CHCl_3$, and THF (Table 1, entries 3, 6, 7, and 11–13). It is noteworthy that the Michael reactions proceeded smoothly in non-polar toluene, to generate the products in excellent yields (80–85%) with moderate to good enantioselectivities (60–75% ee) and diastereoselectivities (Table 1, entries 5 and 14). Interestingly, the results in CCl_4 resemble those in toluene, with the sole exception of the slightly low enantioselectivities achieved in CCl_4 (Table 1, entries 2 and 15). The main reason for the moderate stereoselectivities with catalysts **1** and **2** may be attributed to the lack of hydrogen bond donors, such as a hydroxyl or amide hydrogen.[18] As reported earlier,[19] a hydroxyl group in an organocatalyst plays a crucial role in the addition reaction; it was expected that an appropriate co-catalyst containing an acidic hydroxyl group could also be used to improve the catalytic efficiency in the presence of prolinamides **1** and **2**. Therefore, we tested a series of chiral and achiral co-catalysts in toluene for the asymmetric addition reactions to further improve the reactivities and enantioselectivities.

It is interesting to note that the chemical yields and stereoselectivities were changed to different extents, depending on the nature of the additive used. With the use of AcOH and *p*-TsOH as additives, catalysts **1** and **2** promoted the addition with improved enantioselectivities of 75–92% *ee*s, but the resulting chemical yields were significantly decreased (Table 2, entries 3, 4, 11, and 12).

Similar diastereoselectivities, but poor chemical yields and enantioselectivities were observed when the additive was replaced with (*S*)-phenyl glycine (Table 2, entries 2 and 10). The use of trifluoroacetic acid (TFA) afforded only trace amounts of the products

Table 2
Substrate scope of the asymmetric Michael addition of propionaldehyde to *trans*-β-nitrostyrene



Entry	Catalyst	Additive	Time (d)	Yield[a] (%)	d.r. [b]	ee[c] (%)
1	**1**	None	3	80	74:26	60
2	**1**	(*S*)-phenyl glycine	4	55	76:24	51
3	**1**	AcOH	4	45	63:37	85
4	**1**	*p*-TsOH	4	35	83:17	75
5	**1**	TFA	nd[d]			
6	**1**	(*S*)-1,1′-bi-2-naphthol	4	65	93:7	84
7	**1**	(*R*)-1,1′-bi-2-naphthol	4	62	88:12	72
8	**1**	*rac*-1,1′-bi-2-naphthol	4	64	90:10	80
9	**2**	None	4	85	62:38	75
10	**2**	(*S*)-phenyl glycine	3	75	67:33	56
11	**2**	AcOH	3	70	72:28	85
12	**2**	*p*-TsOH	3	50	66:34	92
13	**2**	TFA	nd[c]			
14	**2**	(*S*)-1,1′-bi-2-naphthol	3	80	87:13	95
15	**2**	(*R*)-1,1′-bi-2-naphthol	3	78	85:15	90
16	**2**	*rac*-1,1′-bi-2-naphthol	3	77	86:14	92

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^1H NMR of the crude product and/or HPLC analysis.
[c] Determined by chiral HPLC analysis (Chiralpak OD-H). The absolute configuration was determined by comparison with the literature data.
[d] Not determined.

(Table 2, entries 5 and 13), implying that the strong acid is not suited for use as the co-catalyst. The combination of prolinamides **1** and **2** and (*S*)-1,1′-bi-2-naphthol exhibited efficient organocatalytic activity and the adducts were afforded with high enantioselectivities (up to 95% *ee*, Table 2, entries 6 and 14).

The (*R*)- and *rac*-1,1′-bi-(2-naphthol) compounds were also employed as chiral additives to observe any changes in the enantioselectivity or absolute configuration. However, very similar results were obtained in both cases with slight decreases in the rate and stereoselectivity of the reaction (Table 2, entries 7, 8, 15, and 16). This may be due to the fact that (*R*)-binaphthol acts as the mismatched pair regarding the catalyst while (*S*)-binaphthol acts as the matched pair.

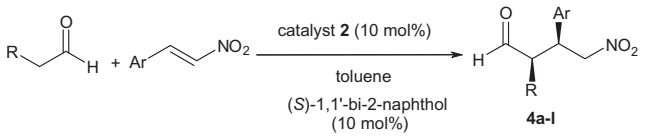
With the optimal reaction conditions realized, we proceeded to examine a variety of nitroalkenes reacting with aldehydes in order to establish the general utility of this asymmetric transformation (Table 3).

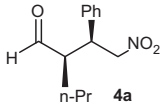
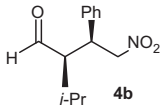
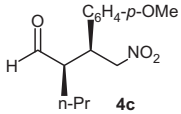
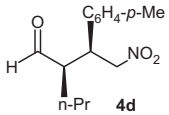
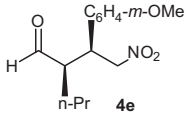
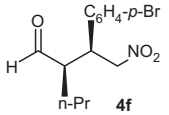
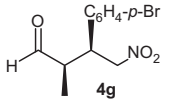
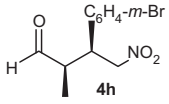
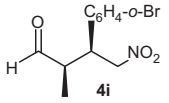
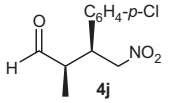
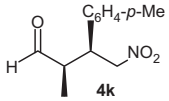
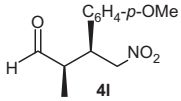
In all cases, Michael reactions were conducted in toluene at room temperature in the presence of 10 mol % of catalyst **2** and 10 mol % of (*S*)-1,1′-bi-2-naphthol and the substrates were completely converted into the addition products.

The results indicate that the aromatic nitroalkenes reacted well with aldehyde donors to give the desired products with high yields and stereoselectivities (up to 95%, and 99% *ee*). Aromatic nitroolefins, which possess either neutral (Table 3, entries 1 and 2), electron-donating (Table 3, entries 3, 5, and 12), or electron-withdrawing groups (Table 3, entries 6–10) slightly affected the enantioselectivity and yield.

The high diastereoselectivities and excellent enantioselectivities can be explained by the transition model proposed originally by Seebach and Golinski[20] as shown in Figure 2. In this model, the pyrrolidine moiety of catalyst **2** reacts with the unmodified aldehyde to form a nucleophilic enamine and the co-catalyst (*S*)-1,1′-bi-2-naphthol activates the nitro group through hydrogen bonding to organize a favorable transition model. The *anti*-enamine double bond is away from the bulky substituent at the 2-position of the pyrrolidine ring and the attack of this enamine onto the less hindered *si* face of the nitrostyrene leads to the formation of the observed major enantiomer of the *syn*-diastereomer. The higher enantioselectivity in the reaction with **2** instead of **1** as the organocatalyst could be attributed to the presence of an additional chiral group attached to the pyrrolidine ring at the 2-position.

Table 3
Michael reactions of α-monosubstituted aldehydes to *trans*-nitrostyrenes catalyzed by **2**



Entry	Product	Time (d)	Yield[a] (%)	d.r.[b]	*ee*[c] (%)
1	 **4a**	3	70	83:17	74
2	 **4b**	2	90	99:1	87
3	 **4c**	1	85	89:11	96
4	 **4d**	1	80	100	99
5	 **4e**	1	83	96:4	82
6	 **4f**	1	87	99:1	85
7	 **4g**	2	83	72:28	99
8	 **4h**	2	95	97:3	68
9	 **4i**	2	90	84:16	98
10	 **4j**	2	81	99:1	68
11	 **4k**	2	78	82:18	89
12	 **4l**	2	85	77:23	90

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^1H NMR of crude product and/or HPLC analysis.
[c] Determined by chiral HPLC analysis (Chiralpak OD-H or AD-H). The absolute configuration was determined by comparison with the literature data.

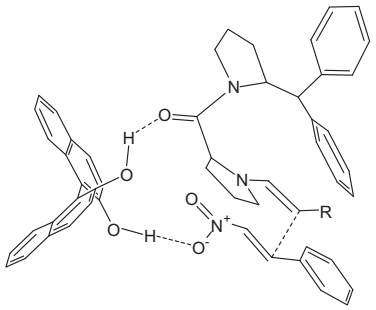


Figure 2. Proposed transition state.

3. Conclusion

In conclusion, a new pyrrolidine-based organocatalytic system has been developed for the asymmetric Michael addition reactions of aldehydes to nitroolefins using L-prolinamides as catalysts and (*S*)-1,1′-bi-2-naphthol as a co-catalyst. The combination of compound **2** and (*S*)-1,1′-bi-2-naphthol exhibits a high catalytic activity and generates the corresponding products with high chemical yields and high to excellent levels of diastereo- and enantioselectivities. Further studies of this catalytic system in other asymmetric C–C bond forming processes are currently underway.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants (Hz), integration. The HPLC measurements were carried out on Agilent 1100 equipment connected with Chiralpak Daicel AD-H and OD-H columns. Analytical TLC was performed using Merck prepared plates (silica gel 60 F254 on aluminum). Flash chromatography separations were performed on a Merck Silica Gel 60 (230–400 mesh). All starting materials and reagents used were of standard analytical grade from Fluka, Merck and Aldrich and used without further purification. Dichloromethane was dried ($CaCl_2$), distilled from CaH_2 and stored over molecular sieves. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent employed was anhydrous $MgSO_4$. The spectra and other data were consistent with the reported values.

4.2. Synthesis of catalysts

Chiral catalysts **1** and **2** were obtained by following the literature procedure.[17]

4.3. Typical procedure for the addition of aldehydes to nitrostyrenes

To a mixture of catalyst (0.01 mmol), (*S*)-1,1′-bi-2-naphthol (0.01 mmol), and nitroolefin (1 mmol) in toluene (1 mL) was added the carbonyl compound (1.5 mmol). The reaction mixture was stirred at room temperature until the nitroolefin was completely consumed (monitored by TLC). After evaporation of the solvent under vacuum, the residue was separated by flash chromatography over silica gel (petroleum ether/ethyl acetate = 10:1) to give the Michael adduct. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD-H or OD-H columns. The absolute configuration of products **3**, **4a**–**l** was determined by comparison with the literature data: **3**,[13b] **4a**,[21] **4b**,**c**,**g**–**l**,[14c] **4d**,**f**,[12i] **4e**.[12h]

4.3.1. (2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal 3

Compound **3** was prepared according to the general procedure from propanal and *trans*-β-nitrostyrene to provide the title compound (80% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 7.36–7.15 (m, 5H), 4.80 (dd, 1H, J = 12.8 and 5.6 Hz), 4.68 (dd, 1H, J = 12.8 and 9.2 Hz), 3.81 (dt, 1H, J = 9.2 and 5.6 Hz), 2.81–2.73 (m, 1H), 1.00 (d, 3H, J = 7.6 Hz). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hexane/*i*-PrOH 90:10, UV 254 nm, 1 ml/min, *syn*-isomer: t_{minor} = 23.7 min and t_{major} = 32.6 min, *anti*-isomer: t_{minor} = 27.9 min and t_{major} = 37.9 min; 95 % *ee*.

4.3.2. (*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]pentanal 4a

Compound **4a** was prepared according to the general procedure from pentanal and *trans*-β-nitrostyrene to provide the title compound (70% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.74 (d, 1H, J = 2.2 Hz), 7.41–7.32 (m, 3H), 7.24–7.22 (m, 2H), 4.75 (dd, 1H, J = 4.4 and 10.2 Hz), 4.69 (dd, 1H, J = 4.7 and 10.2 Hz), 3.83 (dt, 1H, J = 4.3 and 7.8 Hz), 2.75 (tt, 1H, J = 2.6 and 7.6 Hz), 1.56–1.47 (m, 1H), 1.44–1.32 (m, 2H), 1.25–1.17 (m, 1H), 0.84 (t, 3H, J = 5.7 Hz). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hexane/*i*-PrOH 80:20, UV 254 nm, 1 ml/min, *syn*-isomer: t_{minor} = 11.8 min and t_{major} = 14.4 - min, *anti*-isomer: t_{minor} = 13.2 min and t_{major} = 20.0 min; 74 % *ee*.

4.3.3. (2*R*,3*S*)-2-Isopropyl-4-nitro-3-phenylbutanal 4b

Compound **4b** was prepared according to the general procedure from isobutyraldehyde and *trans*-β-nitrostyrene to provide the title compound (90% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.86 (d, 1H, J = 2.4 Hz), 7.35–7.10 (m, 5H), 4.68–4.43 (m, 2H), 3.83 (dt, 1H, J = 10.4 and 4.4 Hz,), 2.75–2.69 (m, 1H), 1.68–1.62 (m, 1H), 1.10 (d, 3H, J = 7.2 Hz), 0.86 (d, 3H, J = 7.2 Hz). The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane/*i*-PrOH 97:3, UV 254 nm, 0.4 ml/min, *syn*-isomer: t_{major} = 28.2 min and t_{minor} = 33.1 min, *anti*-isomer: t_{major} = 26.5 min; 87 % *ee*.

4.3.4. (2*R*,3*S*)-2-Propyl-4-nitro-3-(4-methoxyphenyl)butanal 4c

Compound **4c** was prepared according to the general procedure from pentanal and *trans*-1-methoxy-4-(2-nitrovinyl) benzene to provide the title compound (85% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.69 (d, 1H, J = 2.8 Hz), 7.07 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.73–4.55 (m, 2H), 3.78–3.68 (m, 1H), 2.69–2.62 (m, 1H), 1.55–1.10 (m, 4H), 0.78 (t, 3H, J = 7.6 Hz). The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane/*i*-PrOH 95:5, UV 254 nm, 0.5 ml/min, *syn*-isomer: t_{major} = 22.9 min and t_{minor} = 28.0 min, *anti*-isomer: t_{minor} = 25.8 min and t_{major} = 26.9 min; 96 % *ee*.

4.3.5. (2*R*,3*S*)-2-Propyl-4-nitro-3-(4-methylphenyl)butanal 4d

Compound **4d** was prepared according to the general procedure from pentanal and *trans*-1-methyl-4-(2-nitrovinyl) benzene to provide the title compound (80% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (d, 1H, J = 2.8 Hz), 7.13 (d, 2H, J = 8.0 Hz), 7.04 (d, 2H, J = 8.0 Hz), 4.66 (dd, 1H, J = 12.8 and 5.6 Hz), 4.60 (dd, 1H, J = 12.8 and 9.6 Hz), 3.72 (dt, 1H, J = 9.6 and 5.2 Hz), 2.69–2.59 (m, 1H), 2.31 (s, 3H), 1.60–1.10 (m, 4H), 0.79 (d, 3H, J = 7.2 Hz). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hexane/*i*-PrOH 85:15, UV 254 nm, 1 ml/min, *syn*-isomer: t_{minor} = 13.9 min and t_{major} = 15.4 min, *anti*-isomer: t_{major} = 21.9 min; 99 % *ee*.

4.3.6. (2*R*,3*S*)-2-Propyl-4-nitro-3-(3-methoxyphenyl)butanal 4e

Compound **4e** was prepared according to the general procedure from pentanal and *trans*-1-methoxy-3-(2-nitrovinyl) benzene to provide the title compound (83% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.69 (d, 1H, J = 2.8 Hz), 7.28–7.23 (m, 1H), 6.84–6.71 (m, 3H), 4.71–4.60 (m, 2H), 3.79 (s, 3H), 3.80–3.70 (m, 1H), 2.72–2.65, (m, 1H), 1.56–1.10 (m, 4H), 0.81 (t, 3H, J = 7.2 Hz). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hexane/*i*-PrOH 90:10, UV 220 nm, 1 ml/min, *syn*-isomer: t_{minor} = 23.4 min and t_{major} = 59.1 min, *anti*-isomer: t_{major} = 28.0 min; 82 % *ee*.

4.3.7. (2*R*,3*S*)-2-Propyl-4-nitro-3-(4-bromophenyl)butanal 4f

Compound **4f** was prepared according to the general procedure from pentanal and *trans*-1-bromo-4-(2-nitrovinyl) benzene to provide the title compound (87% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.3 (d, 1H, J = 2.4 Hz), 7.10 (d, 2H, J = 6.8 Hz), 6.66 (d, 2H, J = 6.8 Hz), 4.46–4.15 (m, 2H), 3.37 (dt, 1H, J = 10.0 and 5.2 Hz), 2.42–2.26 (m,1H),1.35–0.75 (m, 4H), 0.42 (t, 3H, J = 7.2 Hz). The enantiomeric excess was determined by HPLC

(Chiralcel OD-H), Hexane/*i*-PrOH 90:10, UV 254 nm, 1 ml/min, *syn*-isomer: t_{minor} = 21.8 min and t_{major} = 24.3 min, *anti*-isomer: t_{major} = 26.4 min; 85 % *ee*.

4.3.8. (2*R*,3*S*)-(4-Bromophenyl)-2-methyl-4-nitrobutanal 4g

Compound **4g** was prepared according to the general procedure from propanal and *trans*-1-bromo-4-(2-nitrovinyl) benzene to provide the title compound (83% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.67 (d, 1H, J = 1.1 Hz), 7.45 (d, 1H, J = 8.4 Hz), 7.03 (d, 1H, J = 8.4 Hz), 4.57–4.80 (m, 2H), 3.71–3.81 (m, 1H), 2.67–2.81 (m, 1H), 0.98 (d, 3H, J = 7.3 Hz). The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane/*i*-PrOH 95:5, UV 254 nm, 0.5 ml/min, *syn*-isomer: t_{major} = 32.7 min and t_{minor} = 47.1 min, *anti*-isomer: t_{minor} = 38.3 min and t_{major} = 42.8 min; 99 % *ee*.

4.3.9. (2*R*,3*S*)-(3-Bromophenyl)-2-methyl-4-nitrobutanal 4h

Compound **4h** was prepared according to the general procedure from propanal and 1-bromo-3-(2-nitrovinyl)-benzene to provide the title compound (95% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.69 (s, 1H), 7.43 (d, 1H, J = 7.9 Hz), 7.33 (s, 1H), 7.30–7.18 (m, 1H), 7.12 (d, 1H, J = 7.9 Hz), 4.79 (dd, 1H, J = 1.3 and 12.9 Hz), 4.65 (dd, 1H, J = 9.6 and 12.8 Hz), 3.88–3.70 (m, 1H), 2.86–2.70 (m, 1H), 1.01 (d, 3H, J = 7.2 Hz). The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane/*i*-PrOH 95:5, UV 254 nm, 0.5 ml/min, *syn*-isomer: t_{major} = 28.9 min and t_{minor} = 32.0 min, *anti*-isomer: t_{minor} = 21.1 min and t_{major} = 22.1 min; 68 % *ee*.

4.3.10. (2*R*,3*S*)-(2-Bromophenyl)-2-methyl-4-nitrobutanal 4i

Compound **4i** was prepared according to the general procedure from propanal and 1-bromo-2-(2-nitrovinyl)-benzene to provide the title compound (90% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 7.60 (d, 1H, J = 8.0 Hz), 7.36–7.28 (m, 1H), 7.24–7.12 (m, 2H), 4.86–4.78 (m, 1H), 4.77 (dd, 1H, J = 4.8 and 12.9 Hz), 4.46–4.38 (m, 1H), 3.02–2.96 (m, 1H), 1.04 (d, 3H, J = 7.4 Hz). The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane/*i*-PrOH 95:5, UV 254 nm, 0.5 ml/min, *syn*-isomer: t_{major} = 23.6 min and t_{minor} = 26.9 min, *anti*-isomer: t_{minor} = 28.3 min and t_{major} = 30.4 min; 98 % *ee*.

4.3.11. (2*R*,3*S*)-(4-Chlorophenyl)-2-methyl-4-nitrobutanal 4j

Compound **4j** was prepared according to the general procedure from propanal and 1-chloro-4-(2-nitrovinyl)-benzene to provide the title compound (81% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70 (d, 1H, J = 1.5 Hz), 7.32 (d, 2H, J = 10 Hz), 7.11 (d, 2H, J = 8.5 Hz), 4.58–4.84 (m, 2H), 3.73–3.85 (m, 1H), 2.71–2.80 (m, 1H), 1.01 (d, 3H, J = 7.3 Hz). The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hexane/*i*-PrOH 95:5, UV 254 nm, 0.5 ml/min, *syn*-isomer: t_{major} = 30.5 min and t_{minor} = 39.8 min; 68 % *ee*.

4.3.12. (2*R*,3*S*)-3-(4-Methylphenyl)-2-methyl-4-nitrobutanal 4k

Compound **4k** was prepared according to the general procedure from propanal and *trans*-1-methyl-4-(2-nitrovinyl) benzene to provide the title compound (78% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 7.14 (d, 2H, J = 8.0 Hz), 7.05 (d, 2H, J = 8.0 Hz), 4.84–4.72 (m, 1H), 4.66 (dd, 1H, J = 3.2 and 12.6 Hz), 3.82–3.70 (m, 1H), 2.80–2.72 (m, 1H), 2.32 (s, 3H), 1.00 (d, 3H, J = 7.2 Hz). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hexane/*i*-PrOH 90:10, UV 254 nm, 1 ml/min, *syn*-isomer: t_{minor} = 20.3 min and t_{major} = 25.3 min, *anti*-isomer: t_{major} = 30.8 min; 89 % *ee*.

4.3.13. (2*R*,3*S*)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal 4l

Compound **4l** was prepared according to the general procedure from propanal and *trans*-1-methoxy-4-(2-nitrovinyl) benzene to provide the title compound (85% yield) after flash column chromatography on silica gel (petroleum ether/ethyl acetate = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70 (d, 1H, J = 1.7 Hz), 7.08 (d, 2H, J = 8.7 Hz), 6.84 (d, 2H, J = 8.8 Hz), 4.59–4.77 (m, 2H), 3.72–3.80 (m, 4H), 2.69–2.77 (m, 1H), 0.95 (d, 3H, J = 7.3 Hz). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hexane/*i*-PrOH 90:10, UV 254 nm, 1 ml/min, *syn*-isomer: t_{minor} = 28.8 min and t_{major} = 30.6 min, *anti*-isomer: t_{major} = 36.6 min and t_{minor} = 38.6 min; 90 % *ee*.

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