Asymmetric Conjugate Addition of Unmodified Propionaldehyde to *β*-Nitrostyrenes Catalyzed by Readily Available Proline-Based Dipeptidols

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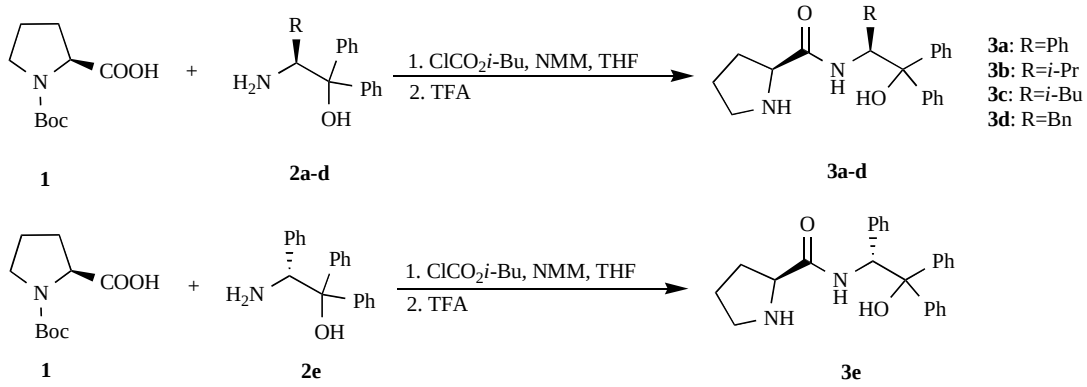
Abstract: Organocatalytic asymmetric additions of unmodified aldehydes to *β*-nitrostyrenes are important carbon-carbon bond formation reactions and have become very attractive recently, because they are metal-free and environmentally benign. This work employed a series of *L*-proline-based diphenyl dipeptidols to catalyze this reaction. The results showed that these dipeptidols were effective organocatalysts with the yield up to 99%. **3a** was optimal with the highest enantioselectivity up to 75% and dr (*syn*/*anti*) up to 94/6. In addition, the mechanism of this asymmetric reaction is also discussed.

Keywords: Asymmetric conjugate addition, propionaldehyde, *β*-nitrostyrene, proline-based dipeptidol, organocatalysis, enantioselectivity.

1. INTRODUCTION

Conjugate addition reaction is one of the most important carbon-carbon bond-forming reactions [1]. Asymmetric conjugate addition of aldehydes to *β*-nitrostyrenes could produce versatile chiral *γ*-nitro aldehydes which could be easily transferred into a wide range of synthetically interesting compounds such as optically active *γ*-amino alcohols, *γ*-amino acids, and *γ*-nitro acids [2]. Nowadays, organocatalytic direct asymmetric reactions of unmodified aldehydes with *β*-nitrostyrenes have become attractive because they are metal-free and environmentally benign [3]. Since Barbas III disclosed the first case of organocatalytic asymmetric conjugate addition of unmodified aldehydes to *β*-nitrostyrenes catalyzed by proline-derived diamines [4], there have been many effective organocatalysts reported [5]. These chiral catalysts include diamines [6], fluorous (*S*)-pyrrolidine sulfonamides [7], proline-derived tetrazoles [8], proline and substituted prolines [9], thioureas [10], simple dipeptides [11], silylated prolinol and its derivatives [12], chiral ionic liquid [13], prolinal dithioacetals [14], amino alcohol derivatives [15] and etc. It is suggested that an enamine transition state forms in the reaction process, which is similar to the organocatalyzed asymmetric aldol reactions. Thus many organocatalysts successfully applied to direct aldol reactions could also be used in asymmetric conjugation reactions, such as *L*-proline and others [3a]. Recently, proline-based dipeptidol derivatives were reported by Singh to catalyze the asymmetric aldol reactions efficiently [16]. But their use in the conjugate reaction has not yet been disclosed. We presumed that this kind of catalysts could also be used in this reaction [5a]. Herein we describe these diphenyl dipeptidols as organocatalysts in this reaction.



Scheme 1. Synthesis of *L*-proline-based diphenyl dipeptidols **3a**-**3e**.

2. RESULTS AND DISCUSSION

As shown in Scheme **1**, these catalysts could be easily prepared according to the typical procedure. Boc-*L*-proline was condensed with a series of *L*-diphenyl-amino-alcohols *via* the mixed anhydride method. Catalyst **3e** was prepared by using *D*-diphenyl-phenylglycinol instead. Then trifluoro-

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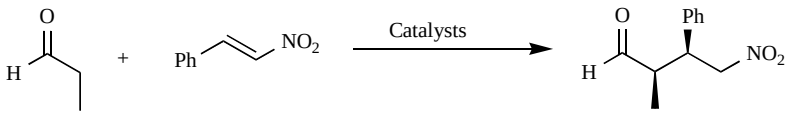
Table 1. Asymmetric Catalytic Addition of Unmodified Propionaldehyde to *β*-Nitrostyrene [17]



Entry	Catalyst	Solvent	Additive	Temperature	*T* (d)	Yield (%)[a]	dr (*syn* / *anti*)[b]	ee (%)[c]
1	**3a** (20 mol %)	Toluene	No	rt.	8	98	87/13	53
2	**3a** (20 mol %)	*c*-hexane	No	rt.	7	49	92/8	56
3	**3a** (20 mol %)	*n*-hexane	No	rt.	3	97	89/11	60
4	**3a** (20 mol %)	$CHCl_3$	No	rt.	4	95	93/7	29
5	**3a** (20 mol %)	MeOH	No	rt.	4.5	58	87/13	33
6	**3a** (20 mol %)	THF	No	rt.	4.5	51	88/12	26
7	**3a** (20 mol %)	NMP	No	rt.	8	88	81/19	12
8	**3a** (20 mol %)	*n*-hexane	H_2O (5 eq.)	rt.	4	80	91/9	42
9	**3a** (20mol %)	*n*-hexane	Et_3N (0.2 eq.)	rt.	3	54	75/25	43
10	**3a** (20 mol %)	*n*-hexane	TFA (0.2 eq.)	rt.	3	Trace	-	-
11	**3a** (20 mol %)	*n*-hexane	*m*-nitrophenol (0.2 eq.)	rt.	6	53	89/11	51
12	**3a** (10 mol %)	*n*-hexane	No	rt.	6	88	89/11	58
13	**3b** (10 mol %)	*n*-hexane	No	rt.	3	98	90/10	34
14	**3c** (10mol %)	*n*-hexane	No	rt.	2	99	92/8	38
15	**3d** (10 mol %)	*n*-hexane	No	rt.	1	99	91/9	29
16	**3e** (10 mol %)	*n*-hexane	No	rt.	5	85	90/10	57
17	**3a** (30 mol %)	*n*-hexane	No	rt.	2	96	90/10	56
18	**3a** (20 mol %)	*n*-hexane	No	0 °C	4	90	90/10	57

[a]Isolated yield.
[b]Determined by ^{1}H NMR spectra.
[c]Ee stands for enantioselectivity, determined by Chiral HPLC using Chiralcel OD-H column.

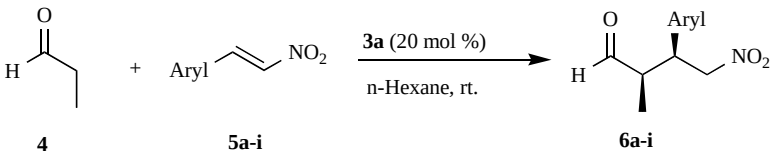
acetic acid was employed to deprotect the Boc group to achieve catalysts **3a**-**3e**.

The reaction of propionaldehyde with *β*-nitrostyrene in the presence of **3a** (20 mol %) in various solvents was investigated initially. The results showed that (Table **1**, entries 1-7) non-polar solvents were superior to polar solvents. *n*-hexane, *cyclo*-hexane and toluene had nearly the same effect on enantioselectivity but *n*-hexane gave the fastest reaction rate. No significant improvement in the enantioselectivity was observed with some additives (Table **1**, entries 8-11). As for chiral organocatalysts **3a**-**3d** (Table **1**, entries 12-15), all of them were efficient catalysts and gave high yield with good diastereoselectivity, and **3a** gave the best enantioselectivity. Interestingly, **3e** gave almost the same diastereoselectivity and enantioselectivity as **3a** did (Table **1**, entries 12 and 16). It seems that the configuration of the diphenyl amino alcohol has non-impact on the diastereoselectivity and enantioselectivity which are thoroughly determined by *L*-proline segment. **3d** gave the fastest rate, but achieved the poorest enantioselectivity value. There was no significant improvement in enantioselectivity by increasing the loading of the catalyst (Table **1**, entries 3, 12 and 17). Lowering temperature did not lead to higher enantioselectivity but a much longer reaction time (Table **1**, entry 18).

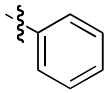
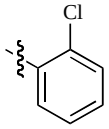
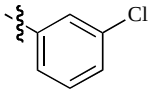
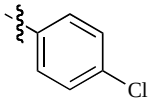
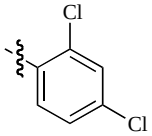
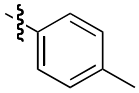
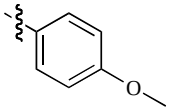
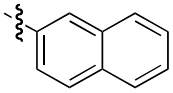
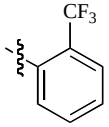
The conjugate addition of propionaldehyde to various *β*-nitrostyrenes were carried out with the above optimized reaction conditions as shown in Table **2**. Those *β*-nitrostyrenes with substitutions on the phenyl ring had a worse solubility in this solvent system, so a little toluene was added to make them dissolve. Generally, **3a** was an efficient catalyst with yield up to 97%, dr up to 94/6 and enantioselectivity up to 75%. Some structural effects on diastereoselectivity and enantioselectivity were observed. *para*-Chloro substituted nitrostyrene gave the highest enantioselectivity up to 75%. *ortho*-Chloro, *meta*-Chloro substituted and naphthyl nitrostyrenes also afforded good enantioselectivity. 2,4-Dichloro substituted nitrostyrene got the highest dr but low enantioselectivity. Others achieved only moderate enantioselectivity.

It is supposed that an enamine transition state is formed in the catalytic process [5a]. As depicted in Fig. (**1**), the *E*-enamine would be generated between the amine group of the pyrrolidine circle and propionaldehyde, while the hydroxyl and amide groups might activate *β*-nitrostyrene by forming two hydrogen bonds, so relatively more stable *Re*-rotamer *E*-enamine is formed mainly. On account of the hydrogen bonds and the bulky diphenyl groups of the catalyst, the catalytic process would take place preferentially by the enamine attack to the less hindered *Si* face of the *β*-

Table 2. Direct Michael Addition of Propionaldehyde to Various *β*-Nitrostyrenes[a]



4 **5a-i** **6a-i**

Entry	Aryl	*T* (d)	Yield (%)[b]	dr (*syn* / *anti*)[c]	ee (%)[d]	Config.[e]
1		3	97	89/11	60	(2*R*,3*S*)
2		7	81	92/8	58	(2*R*,3*S*)
3		7	74	92/8	61	(2*R*,3*S*)
4		7	70	89/11	75	(2*R*,3*S*)
5		9	50	94/6	33	(2*R*,3*S*)
6		9	77	85/15	42	(2*R*,3*S*)
7		9	50	86/14	44	(2*R*,3*S*)
8		9	61	89/11	56	(2*R*,3*S*)
9		9	70	90/10	46	(2*R*,3*S*)

[a]The reaction was carried out in the presence of 20 mol % loading of catalyst **3a** in 1ml *n*-hexane under room temperature. 1.0 ml toluene was introduced to make the substrate soluble into the mixture in entries 2-6 and 9 whereas 0.4ml toluene was introduced into the reaction mixture in entries 7-8.
[b]Isolated yield.
[c]Determined by ^{1}H NMR spectra.
[d]Ee stands for enantioselectivity, determined by HPLC using a Chiralcel OD-H column in entry 1 whereas using a Chiralpak AS column in other cases.
[e]The major isomer's configuration of *syn* isomer was determined by comparison with reported retention time of the major peak on chiral HPLC [4(a), 12(c)].

nitrostyrenes and produce *syn* isomers mainly. The absolute conformation of main adducts should be (2*R*,3*S*) isomers.

3. CONCLUSIONS

In conclusion, we have successfully employed a series of efficient chiral diphenyl dipeptidols as organocatalysts for the direct asymmetric Michael addition of unmodified propionaldehyde to various *β*-nitrostyrenes. They behaved more active in non-polar solvent with yield up to 99% and catalyst **3a** was the optimal with the enantioselectivity (up to 75%).

4. EXPERIMENTAL

4.1. General

Solvents were dried and distilled according to established procedures. Reactions were monitored by thin layer chro-

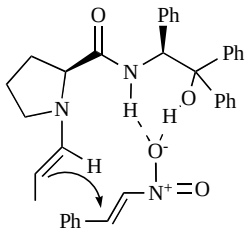


Fig. (1). The supposed transition state.

matography (TLC), Column chromatography purifications were carried out using silica gel. All reagents were purchased from commercial corporations. ^{1}H NMR spectra were measured on Bruker Am 400 MHz and DRX-200 MHz spectrometers (NMR in $CDCl_3$ with TMS as an internal standard). Optical rotations were recorded on a Perkin–Elmer 341 polarimeter. The enantioselectivity value determination was carried out using chiral HPLC with Chiralpak AS or Chiralcel OD-H column on Waters® 600 with a 2996 UV detector.

4.2. Preparation of Catalysts 3a-3e

4.2.1. General Procedure for the Synthesis of Catalysts 3a-e

N-methyl morpholine (1.21 mL, 11mmol) was added to a solution of *N*-Boc-*L*-proline (2.153 g, 10 mmol) in dry THF (40 mL) at -15 °C. Then isobutyl chloroformate (1.439 mL, 11mmol) was added dropwise and the solution was stirred at the same temperature for 6 min. Then, optically pure amino alcohol **2a** (2.834 g, 9.8 mmol) in dry THF was added and the resulting solution was stirred at the same temperature for 2 h. And then let the reaction stir at room temperature overnight. The whole solution was filtered. Washed the precipitate with ethyl acetate, combined the organic solvents and evaporated to dryness. The crude product was dissolved in ethyl acetate again, washed successively with 0.1 M HCl, water, 0.1 M NaOH and brine, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by recrystalisation with ethyl acetate to give Boc-protected dipeptidol. TFA (9 mL) was slowly introduced into this Boc-protected dipeptidol in dry DCM (9 ml) at 0 °C and the resulting solution was stirred at room temperature for 12 h. Excess TFA was carefully neutralized by adding 2 M Na_2CO_3 and the whole mixture was extracted with ethyl acetate three times. The combined organic layer was dried and the solvent was removed under reduced pressure to obtain the product. Pure product was achieved by recrystalisation with ethyl acetate/petroleum.

4.2.2. Diphenyl L-*prolyl*-L-*phenyl glycinol (3a)*

Prepared according to the general procedure to afford the product **3a** as a white solid; yield 81%; Mp: 210-212 °C. $[\alpha]_D^{20}$= +85° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (m, 2 H), 1.79 (m, 1 H), 1.95 (m, 1 H), 2.21 (s, 2 H), 2.66 (m, 1 H), 2.87 (m, 1 H), 3.66 (dd, 1 H, *J* = 9.2 Hz, 4.8 Hz), 7.07-7.34 (m, 15 H), 9.16 (s, 1 H). ESI-MS: ($C_{25}H_{26}N_2O_2$-H_2O+H^+) *calcd*. 369, found 369.

4.2.3. Diphenyl L-*prolyl*-L-*valinol (3b)*

Prepared according to the general procedure to afford the product **3b** as a white solid; yield 79%. Mp: 207-209 °C. $[\alpha]_D^{20}$= -95° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80-0.98 (m, 6 H), 1.48-1.62 (m, 3 H), 1.95 (m, 2 H), 2.33 (s, 1 H), 2.82 (m, 1 H), 2.94 (m, 1 H), 3.61 (m, 1 H), 4.69 (d, 1H, *J* = 12 Hz), 7.10-7.31 (m, 3 H), 7.49-7.53 (m, 4 H), 8.20 (d, 1H, *J* = 9.6 Hz). ESI-MS: ($C_{22}H_{28}N_2O_2$ + H^+) *calcd*. 353, found 353, ($C_{22}H_{28}N_2O_2$-H_2O) *calcd*. 335, found 335.

4.2.4. Diphenyl L-*prolyl*-L-*leucinol (3c)*

Prepared according to the general procedure to afford the product **3c** as a white solid; yield 83%. Mp: 198-200 °C. $[\alpha]_D^{20}$= -40° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81-1.17 (m, 6 H), 1.22 (m, 2 H), 1.35-1.55 (m, 3 H), 1.85 (m, 2 H), 2.60 (m, 2 H), 2.83 (m, 1 H), 3.53 (q, 1 H, *J* = 3.6 Hz), 4.65 (t, 1 H, 10 Hz), 7.10-7.31 (m, 6 H), 7.54-7.98 (m, 4 H), 7.99 (d, 1 H, *J* = 8.8 Hz). ESI-MS: ($C_{23}H_{30}N_2O_2$ + H^+) *calcd*. 367, found 367.

4.2.5. Diphenyl L-*prolyl*-L-*phenyl alaniol (3d)*

Prepared according to the general procedure to afford the product **3d** as a white solid; yield 78%. Mp: 190-192 °C; $[\alpha]_D^{20}$= -91° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (m, 1 H), 1.21 (m, 1 H), 1.35 (m, 1 H), 1.79 (m, 1 H), 2.09 (s, 1 H), 2.41 (m, 1 H), 2.71 (m, 1 H), 2.83 (d, 1 H, *J* = 14.2 Hz), 3.21 (dd, 1 H, *J* = 14 Hz, 11.2 Hz), 3.49 (dd, 1 H, 9.2 Hz, 4.8 Hz), 4.60 (m, 1 H), 7.07-7.29 (m, 9 H), 7.34-7.38 (m, 2 H), 7.56-7.58 (m, 1 H), 7.68-7.70 (m, 1 H), 8.03 (d, 8.4 Hz). ESI-MS: ($C_{26}H_{28}N_2O_2$ + H^+) *calcd*. 401, found 401.

4.2.6. Diphenyl L-*prolyl*-D-*1-phenyl-glycinol (3e)*

Prepared according to the general procedure to afford the product **3e** as a white solid; yield 72%. Mp: 191-194 °C. $[\alpha]_D^{20}$= +109° (*c* 1.0, DMF). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (m, 2 H), 1.76-2.04 (m, 4 H), 2.61-2.90 (m, 2 H), 3.61 (m, 1 H), 7.08-7.33 (m, 15 H), 9.15 (s, 1 H). ESI-MS: ($C_{25}H_{26}N_2O_2$ + H^+) *calcd*. 387, found 387. ($C_{25}H_{26}N_2O_2$-H_2O+H^+) *calcd*. 369, found 369.

4.3. General Procedure for the Direct Asymmetric Conjugate Addition of Propionaldehyde to β-Nitrostyrenes

Propionaldehyde (5 mmol) was added into the mixture of *β*-nitrostyrene (0.5 mmol) and catalyst **3a** (0.1 mmol) in *n*-hexane (1 mL). The reaction vessel was wrapped in aluminium foil, and the resulting solution was stirred under an argon atmosphere for the appropriate time and at the temperature indicated in the schemes. The reaction was then quenched with aq. NH_4Cl solution and the product was extracted three times with ethyl acetate. The organic fractions were dried with Na_2SO_4 and the volatiles were removed on a rotary evaporator. The products were purified by preparative chromatography on silica gel (DCM/*n*-hexane, 1:1). The configurations of the products were determined by comparison of the major isomer retention time on chiral HPLC with the reported data. The enantiomeric excess was measured by HPLC with Chiralpak AS or Chiralcel OD-H.

4.3.1. (2R,3S)-2-Methyl-4-nitro-3-phenylbutanal (6a)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined by NMR to be 85/15. The enantioselectivity was measured by HPLC (Chiralcel OD-H, 10% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ = 220 nm). Retention time: 24.9 min (*syn*, minor), 38.1 min (*syn*, major), enantioselectivity (*syn*) 60%. Comparing to the reported retention time of the *syn* isomer: major peak 29.63 min, minor peak 37.58 min [4a], configuration of **6a** was assigned to be (2*R*,3*S*). ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.71 (d, 1H, *J* = 1.7 Hz), 7.26-7.35 (m, 3 H), 7.14-7.19 (m, 2 H), 4.62-4.85 (m, 2 H), 3.75-3.87 (m, 1 H), 2.73-2.82 (m, 1 H), 1.00 (d, 3H, *J* = 7.3 Hz).

4.3.2. (2R,3S)-2-Methyl-4-nitro-3-(2-Chlorophenyl)butanal (6b)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 92/8. The enantioselectivity was measured by HPLC (Chiralpak AS, 10% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ =220 nm). Retention time: 21.9 min (*syn*, major), 27.1 min (*syn*, minor), enantioselectivity (*syn*) 58%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.73 (d, 1 H, *J* = 1.6 Hz), 7.42 (m, 1 H), 7.21 (m, 3 H), 4.73-4.93 (m, 2 H), 4.3-4.4 (m, 1 H), 2.97-3.05 (m, 1 H), 1.03 (d, 3 H, *J* = 7.4 Hz).

4.3.3 (2R,3S)-2-Methyl-4-nitro-3-(3-Chlorophenyl)butanal (6c)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 92/8. The enantioselectivity was measured by HPLC (Chiralpak AS, 10% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ = 220 nm). Retention time: 27.6 min (*syn*, major), 32.2 min (*syn*, minor), enantioselectivity (*syn*) 61%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.69 (d, 1 H, *J* = 1.5 Hz), 7.03-7.29 (m, 4 H), 4.64 (dd, *J* = 9.2, 11.0 Hz), 4.79 (dd, *J* = 5.6, 12.9 Hz), 3.71-3.83 (m, 1 H), 2.71-2.80 (m, 1 H), 1.00 (d, 3 H, *J* = 7.3 Hz).

4.3.4. (2R,3S)-2-Methyl-4-nitro-3-(4-Chlorophenyl)butanal (6d)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 89/11. The enantioselectivity was measured by HPLC (Chiralpak AS, 10% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ = 220 nm). Retention time: 30 min (*syn*, major), 32.7 min (*syn*, minor), enantioselectivity (*syn*) 75%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.70 (d, 1 H, *J* = 1.5 Hz), 7.32 (d, 2 H, *J* = 10 Hz), 7.11 (d, 2 H, *J* = 8.5 Hz), 4.58-4.84 (m, 2 H), 3.73-3.85 (m, 1 H), 2.71-2.80 (m, 1 H), 1.01 (d, 3 H, *J* = 7.3 Hz).

4.3.5. (2R,3S)-2-Methyl-4-nitro-3-(2,4-Dichlorophenyl) butanal (6e)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 94/6. The enantioselectivity was measured by HPLC (Chiralpak AS, 10% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ = 220 nm). Retention time: 19.2 min (*syn*, major), 23.8 min (*syn*, minor), enantioselectivity (*syn*) 33%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.73 (d, 1 H, *J* = 1.4 Hz), 7.12-7.45 (m, 3 H), 4.71-4.91 (m, 2 H), 4.2-4.3 (m, 1 H), 2.93-3.07 (m, 1 H), 1.00 (d, 3 H, *J* = 7.4 Hz).

4.3.6. (2R,3S)-2-Methyl-4-nitro-3-(4-methylphenyl)butanal (6f)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 85/15. The enantioselectivity was measured by HPLC (Chiralpak AS, 10% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ = 220 nm). Retention time: 20.0 min (*syn*, major), 21.0 min (*syn*, minor), enantioselectivity (*syn*) 42%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.71 (d, 1 H, *J* = 1.7 Hz), 7.02-7.26 (m, 4 H), 4.59-4.79 (m, 2 H), 3.74-3.83 (m, 1 H), 2.70-2.79 (m, 1 H), 2.32 (s, 3 H), 1.00 (d, 3 H, *J* = 7.2 Hz).

4.3.7. (2R,3S)-2-Methyl-4-nitro-3-(4-methoxyphenyl)butanal (6g)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 86/14. The enantioselectivity was measured by HPLC (Chiralpak AS, 10% 2-propanol in *n*-hexane, flow1.0 mL/min, λ = 220 nm). Retention time: 48.2 min (*syn*, minor), 73.2 min (*syn*, major), enantioselectivity (*syn*) 44%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.70 (d, 1 H, *J* = 1.7 Hz), 7.08 (d, 2 H, *J* = 8.7 Hz), 6.86 (d, 2 H, *J* = 8.8 Hz), 4.57-4.81 (m, 2 H), 3.73-3.78 (m, 4 H), 2.69-2.77 (m, 1 H), 0.99 (d, 3 H, *J* = 7.3 Hz).

4.3.8. (2R,3S)-2-Methyl-4-nitro-3-naphthylbutanal (6h)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 89/11.The enantioselectivity was measured by HPLC (Chiralpak AS, 10% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ = 220 nm). Retention time: 32.8 min (*syn*, major), 36.5 min (*syn*, minor), enantioselectivity (*syn*) 56%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.78 (d, 1 H, *J* = 1.7 Hz), 8.14 (s, 1 H), 7.79-7.91 (m, 2 H), 7.34-7.60 (m, 4 H), 4.86-4.96 (m, 2 H), 4.73-4.85 (m, 1 H), 3.00-3.04(m, 1 H), 0.99 (d, 3 H, *J* = 7.3 Hz).

4.3.9. (2R,3S)-2-Methyl-4-nitro-3-(2-trifluoromethylphenyl) butanal (6i)

Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 90/10. The enantioselectivity was measured by HPLC (Chiralpak AS, 10% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ = 220 nm). Retention time: 14.5 min (*syn*, major), 16.2 min (*syn*, minor), enantioselectivity (*syn*) 46%. Comparing to the reported retention time of the *syn* isomer: major peak 14.5 min, minor peak was not observed [12c], configuration of **6i** was assigned to be (2*R*,3*S*). ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.75 (d, 1 H, *J* = 1.8 Hz), 7.33-7.74 (m, 4 H), 4.66-4.90 (m, 2 H), 4.09-4.15 (m, 1 H), 3.03-3.11 (m, 1 H), 0.99 (d, 3 H, *J* = 7.4 Hz).

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[17] We also observed that the same configurational product as propionaldehyde was afforded when butyraldehyde was employed as substrate to reaction with *β*-nitrostyrene. Its enantioselectivity is 51% whereas *syn*/*anti* is 83/17. The product could be characterized as follows:
(2*R*,3*S*)-2-Ethyl-4-nitro-3-phenylbutanal. Prepared according to the general procedure. A mixture of diastereoisomers was obtained; *syn*/*anti* ratio was determined to be 83/17. The enantioselectivity was measured by HPLC (Chiralpak AD-H, 1% 2-propanol in *n*-hexane, flow 1.0 mL/min, λ = 220 nm). Retention time: 23.5 min (*syn*, major), 27.7 min (*syn*, minor), enantioselectivity (*syn*) 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (d, 1 H, J = 2.6 Hz,), 7.28-7.36 (m, 3 H), 7.17-7.19 (m, 2 H), 4.72 (dd, 1 H, J = 12.8, 4.9 Hz), 4.63 (dd, 1 H, J =12.8, 9.7 Hz), 3.80 (ddd, 1 H, J = 9.7, 9.7, 4.9 Hz), 2.65-2.71 (m, 1 H), 1.50-1.58 (m,2 H), 0.83 (dd, 3 H, J = 7.5, 7.5 Hz).