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Asymmetric Michael addition of aldehydes to nitroolefins catalyzed by L-prolinamide derivatives using phenols as co-catalysts

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ABSTRACT

The asymmetric Michael addition of aldehydes to nitroolefins was investigated using L-prolinamide derivatives of 2-(2′-piperidinyl)pyridine as catalyst and a variety of phenols as co-catalyst. Extensive screening toward the effect of prolinamides, phenols, and solvents on this transformation revealed that a combination of (*S*)-2-(2′-piperidinyl)pyridine-derived *trans*-4-hydroxy-L-prolinamide **2c**, (*S*)-1,1′-bi-2-naphthol, and dichloromethane was a promising system. This system was shown to be amenable to a rich variety of aldehydes and nitroolefins and afforded the nitroaldehyde products with excellent yield, enantiomeric excess (up to 99%) and diastereoselectivity ratio (up to 99/1), even in the case of 1 mol % catalyst loading and 1.5 equiv of aldehydes.

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1. Introduction

The organocatalytic asymmetric Michael addition reaction has attracted rapidly growing attention as one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1] Among a broad range of such conversions, the addition of aldehydes to nitroolefins is of great interest owing to the importance of the resulting bifunctional nitroaldehydes as valuable intermediates. Since Betancort and Barbas first reported the asymmetric Michael addition of aldehydes to nitroolefins catalyzed by (*S*)-2-(morpholinomethyl)-pyrrolidine,[2] a number of efficient catalytic systems have been developed. For instance, Hayashi et al. and Wang et al. developed a pyrrolidine-based diphenylprolinol silyl ether[3] and a sulfonamide,[4] respectively, with high enantio- and diastereoselectivity. Recently, Palomo et al. presented a highly efficient organocatalyst containing the simple structure of *trans*-4-hydroxyprolylamide.[5] However, the requirements for high catalyst loading (5–20 mol %) and a large excess of aldehyde (up to 10 equiv), as well as the limited suitability for substrate scope in these systems handicapped their practical applications. To overcome these problems, a range of catalysts derived from piperazine,[6] 4,4′-disubstituted-L-proline,[7] and a tripeptide[8] were developed, which not only expanded the catalyst library but also enhanced the catalytic efficiency. Moreover, Ma et al. and Alexakis et al. found that diphenylprolinol silyl ether was highly effective in water media.[9] Despite the contributions from their pioneering studies, the development of new organocatalyst systems aimed at lowering the catalyst loading and the amount of aldehydes, and expanding the general applicability is still highly desirable in the area of aldehydes and nitroolefins addition reactions.

It was demonstrated that the pyrrolidine motif presented an attractive option for the catalytic asymmetric Michael reaction of aldehydes to nitroolefins.[10] Herein, we have prepared a series of prolinamides (Fig. 1, **2a**–**d**) from the readily available enantiomerically pure 2-(2′-piperidinyl)pyridine **1**[11] and investigated their catalytic properties. After extensive optimization of the reaction conditions, we found that the combination of **2c** and (*S*)-1,1′-bi-2-naphthol was highly selective for the asymmetric addition, giving rise to dr and ee values higher than 95/5 and 95%, respectively,

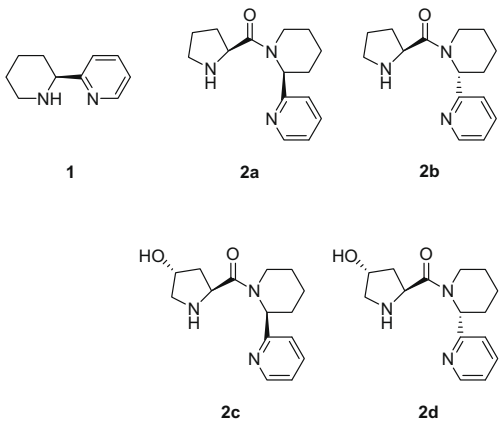

Figure 1. Structure of 2-(2′-piperidinyl)pyridine-derived organocatalysts.

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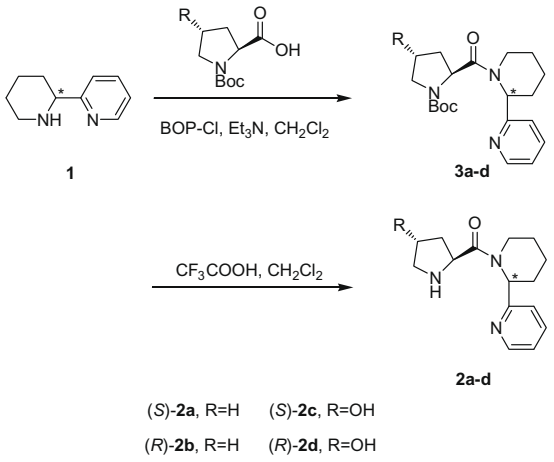


Scheme 1. Synthesis of organocatalysts **2a–d**.

for a variety of aldehydes and nitroolefins. Most importantly, the new catalytic system was very effective, affording the products in over 92% yield with only 1 mol % catalyst loading and 1.5 equiv of aldehydes with a reaction time shorter than 24 h.

2. Results and discussion

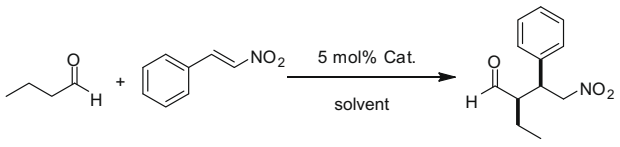
Catalysts **2a–d** were synthesized as outlined in Scheme 1. 2-(2′-Piperidinyl)pyridine **1** was prepared according to the procedures described previously by us,[11] and then treated with various Boc-protected prolines in the presence of BOP-Cl and Et_3N to afford the protected prolinamides **3a–d**.[12] Removal of the Boc group in **3a–d** using CF_3COOH in dichloromethane solution gave the desired products **2a–d**.[13] It should be noted that a couple of inseparable rotamers can be observed in the NMR spectra of **2a–d** due to hindered rotation around a C–N bond.[14]

With the five organocatalysts **1** and **2a–d** in hand, we initiated the study of the asymmetric Michael addition reactions. At the outset, the catalytic properties of the catalysts were evaluated by examining the addition reaction of butyraldehyde **4a** to *trans*-β-nitrostyrene **5a** in a molar ratio of 1.5:1 in dichloromethane (Table 1, entries 1–5). In the presence of 5 mol % catalyst, product **6a** was formed in high yield. Good diastereoselectivity was observed for the five catalysts, but the enantioselectivity was relatively low. However, the pyrrolidine motif in the catalysts plays an important role in the selectivity. Catalyst **1** without the pyrrolidine moiety almost lost its selectivity with only 10% ee (entry 1). In contrast, catalysts **2a–d** containing the pyrrolidine moiety gave rise to a significant enhancement of the enantioselectivity. Moreover, the introduction of hydroxyl group at the 4-position of the pyrrolidine led to a large increase in both diastereo- and enantioselectivity (**2c** vs **2a**, and **2d** vs **2b**). This result can probably be attributed to the directing effect of the hydroxyl group via the H-bonding interaction with the nitro group in the nitroolefins.[5,15] The dependence of the selectivity on the configurations of the 2-(2′-piperidinyl)pyridine unit in the catalysts was also observed. Catalysts **2a** and **2c** derived from (*S*)-2-(2′-piperidinyl)pyridine displayed a higher selectivity than **2b** and **2d** derived from (*R*)-2-(2′-piperidinyl)pyridine (entries 2 vs 3, and 4 vs 5).

We then screened the effect of solvents and temperatures on the outcome of the asymmetric transformation based on catalyst **2c** (Table 1, entries 6–13). It was observed that the addition reaction in the solvents of *i*-PrOH, MeOH, CH_3CN, DMF, dioxane, THF, and H_2O (entries 6–12) was not better than that in CH_2Cl_2 (entry 4). Polar DMF and dioxane retarded the reaction, which resulted in a trace amount of product, even when stirring the reaction mixture for 3 days (entries 9 and 10). Interestingly, a decrease of temperature from room temperature to 0 °C led to an increase of the ee value from 78% to 85%, although the reaction time was elongated to 40 h for complete conversion (entry 13).

To further improve the reactivity and enantioselectivity, we introduced a series of co-catalysts in the asymmetric addition reactions. Since our results demonstrated that the hydroxyl group in catalysts **2c** and **2d** was crucial for the addition reaction, which was also verified by other groups,[5,15,16] it was believed that a proper co-catalyst with the hydroxyl group could be used to improve

Table 1
Initial screening for the asymmetric Michael addition of butyraldehyde **4a** to *trans*-β-nitrostyrene **5a**[a]

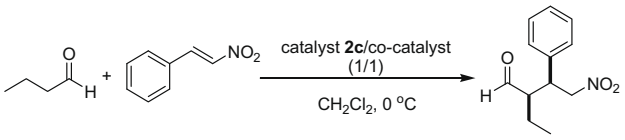


4a **5a** **6a**

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*) (%)
1	**1**	CH_2Cl_2	12	91	90/10	10
2	**2a**	CH_2Cl_2	24	94	86/14	56
3	**2b**	CH_2Cl_2	48	86	80/20	35
4	**2c**	CH_2Cl_2	24	97	91/9	78
5	**2d**	CH_2Cl_2	40	91	90/10	48
6	**2c**	*i*-PrOH	24	92	87/13	48
7	**2c**	MeOH	24	95	85/15	45
8	**2c**	CH_3CN	30	90	93/7	52
9	**2c**	DMF	72	Trace	n.d.[e]	n.d.[e]
10	**2c**	1,4-Dioxane	72	Trace	n.d.[e]	n.d.[e]
11	**2c**	THF	24	82	95/5	72
12	**2c**	H_2O	12	92	92/8	57
13[f]	**2c**	CH_2Cl_2	40	96	91/9	85

[a] Unless stated otherwise, conditions: **4a**/**5a** = 1.5, room temperature.
[b] Isolated yield of mixture of *syn*/*anti* based on nitrostyrene.
[c] Diastereomeric ratio, determined by chiral HPLC analysis. The relative and absolute configurations of **6a** were determined by comparison with the literature data.[2]
[d] Enantiomeric excess, determined by chiral HPLC analysis in comparison with authentic racemic material.
[e] Not determined.
[f] The reaction temperature is 0 °C.

Table 2
Effect of co-catalysts on the Michael addition of butyraldehyde **4a** to *trans*-β-nitrostyrene **5a** catalyzed by organocatalyst **2c**[a]



4a 5a 6a

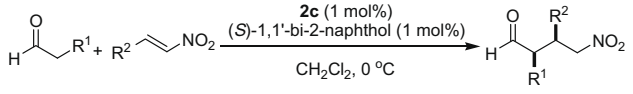
Entry	Co-catalyst	Mol % cat.	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*) (%)
1	*p*-TsOH	5	30	n.r.[e]	—	—
2	4-$CF_3C_6H_4OH$	5	22	92	91/9	87
3	4-$CH_3C_6H_4OH$	5	36	95	88/12	89
4	3-$NH_2C_6H_4OH$	5	42	87	92/8	87
5	4-BrC_6H_4OH	5	26	95	92/8	87
6	2,6-(*t*-Bu)$_2$-4-$CH_3C_6H_4OH$	5	42	83	89/11	87
7	2,3-$(CH_3)_2C_6H_4OH$	5	42	91	96/4	88
8	2-OHC_6H_4OH	5	20	95	96/4	92
9	3-OHC_6H_4OH	5	20	93	95/5	93
10	(*rac*)-1,1′-Bi-2-naphthol	5	15	93	92/8	92
11	(*R*)-1,1′-Bi-2-naphthol	5	20	93	92/8	90
12	(*S*)-1,1′-Bi-2-naphthol	5	8	97	97/3	97
13	(*S*)-1,1′-Bi-2-naphthol	1	24	95	97/3	97
14	(*S*)-1,1′-Bi-2-naphthol	0.5	75	90	97/3	97
15	(*S*)-1,1′-Bi-2-naphthol	0.1	75	Trace	n.d.[f]	n.d.[f]
16[g]	(*S*)-1,1′-Bi-2-naphthol	0	72	n.r.[e]	—	—

[a] All reactions were conducted in CH_2Cl_2 using **4a** (1 equiv) and **5a** (1.5 equiv).
[b] Isolated yield of a mixture of *syn*/*anti* based on nitrostyrene.
[c] Diastereomeric ratio, determined by chiral HPLC analysis. The relative and absolute configurations of **6a** were determined by comparison with the literature data.[2]
[d] Enantiomeric excess, determined by chiral HPLC analysis in comparison with authentic racemic material.
[e] No reaction.
[f] Not determined.
[g] Only 10 mol % (*S*)-1,1′-bi-2-naphthol was used.

the catalytic efficiency. Thus, a variety of OH-containing co-catalysts were examined at 0 °C in CH_2Cl_2 (Table 2). Here the molar ratio of the co-catalyst to **2c** was fixed at 1:1. It was observed that addition of *p*-TsOH completely suppressed the reaction (entry 1), implying that the strong acid is not suited for use as the co-catalyst. The addition of *p*-trifluoromethylphenol shortened the reaction time from 40 to 22 h, and led to a slight increase of the selectivity (entry 2 in Table 2 vs entry 13 in Table 1). Similarly, other mono-phenols (entries 3–7) weakly increased the dr and ee values, indicating that the effect of these co-catalysts on the transformation can be negligible. Most interestingly, the replacement of mono-phenols with *o*- or *m*-benzenediol or 1,1′-bi-2-naphthol clearly improved the catalytic efficiency as well as the selectivity (entries 8–12). It was shown that a combination of catalyst **2c** and (*S*)-1,1′-bi-2-naphthol afforded the product **6a** with the highest enantiomeric excess 97% and diastereoselectivity ratio 97/3 in 97% yield within 8 h (entry 12). Significantly, when reducing the catalyst loading from 5 mol % to 1 mol %, this catalytic system still displayed high efficiency and good selectivity (entry 13 vs entry 12). The conversion can be completed 24 h. When the catalyst loading was further lowered, the reaction rate was rapidly decreased (entries 14 and 15). The effect of the molar ratio of (*S*)-1,1′-bi-2-naphthol and **2c** was also studied. It was found that lowering the ratio led to a decrease of the selectivity, in contrast, increasing the ratio did not improve the selectivity. It should be mentioned that (*S*)-1,1′-bi-2-naphthol itself cannot catalyze the addition reaction (entry 16).

Thus, the catalytic system consisting of 1 mol % of **2c** and 1 mol % of (*S*)-1,1′-bi-2-naphthol in CH_2Cl_2 solution at 0 °C is proposed as the most efficient condition for the asymmetric Michael addition of aldehydes to nitroolefins. Under these conditions, a broad range of aldehydes and nitroolefins were exposed to the asymmetric addition reactions (Table 3). It was proven that this catalytic system exhibited very good compatibility with various aldehydes (entries 1–3), aliphatic nitroolefin (entry 13), and a number of aromatic nitroolefins possessing electron-rich (entries 4–6), electron-deficient (entries 7–10), heterocyclic (entries 11 and 12), and sterically demanding groups (entry 9). In all cases, the substrates were completely converted into the addition products within 24 h with excellent diastereo- and enantioselectivity.

Table 3
Michael addition of aldehydes to nitroolefins catalyzed by **2c**/(*S*)-1,1′-bi-2-naphthol[a]



4 5 6

Entry	R^1	R^2	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)	Product
1	Et	Ph	95	97/3	97	**6a**
2	*n*-C_4H_9	Ph	93	95/5	96	**6b**
3	*i*-Pr	Ph	96	98/2	98	**6c**
4	Et	4-MeC_6H_4	94	98/2	96	**6d**
5	Et	4-$MeOC_6H_4$	92	96/4	97	**6e**
6	Et	3-$MeOC_6H_4$	95	98/2	95	**6f**
7	Et	4-BrC_6H_4	96	99/1	>99	**6g**
8	Et	3-$NO_2C_6H_4$	93	97/3	96	**6h**
9	Et	2-$NO_2C_6H_4$	92	>99/1	96	**6i**
10	Et	4-ClC_6H_4	95	97/3	96	**6j**
11	Et	2-Thienyl	93	>99/1	95	**6k**
12	Et	2-Furyl	95	95/5	98	**6l**
13	*n*-Pr	$PhCH_2CH_2$	93	>99/1	99	**6m**

[a] Unless stated otherwise, conditions: **4**/**5** = 1.5, *T* = 5 °C, 24 h.
[b] Isolated yield of a mixture of *syn*/*anti* based on nitroolefins.
[c] Diastereomeric ratio, calculated from the ^{1}H NMR spectrum of the product. The absolute stereochemistry of compounds **6a**, **6b**, **6c**, **6e**, **6g**, **6j**, **6k**, and **6m** was determined by comparison with known literature data.[2,4,6,8,16d,19] The absolute configurations of the remaining Michael adducts were assigned by comparison with analogous compounds.
[d] Enantiomeric excess, determined by chiral HPLC analysis in comparison with authentic racemic material.

In order to account for the high performance of the Michael addition reactions using the catalytic system of **2c** and (*S*)-1,1′-bi-2-naphthol, we proposed an enamine activation transition state model. In this model, there should be a synergistic effect of the co-catalyst. Figure 2 shows an example of the transition state using butyraldehyde and *trans*-β-nitrostyrene as substrates. In this case the pyrrolidine activates the aldehyde by forming an enamine intermediate. It is easy to see that one face of the enamine double bond in the intermediate is efficiently shielded due to the steric hindrance of the bulky amide moiety.[17] At the same time, the hydrogen-bonds are favorable to form between the two O–H groups of the (*S*)-1,1′-bi-2-naphthol, the nitro group of the nitroolefin and the hydroxyl group of the catalyst. The hydrogen-bonding interactions not only activate the nitro group of the nitroolefin and enhance the electrophilicity of the nitroolefin, but also direct the nitroolefin to approach the less hindered enamine face, affording the desired adduct.[5,15,16]

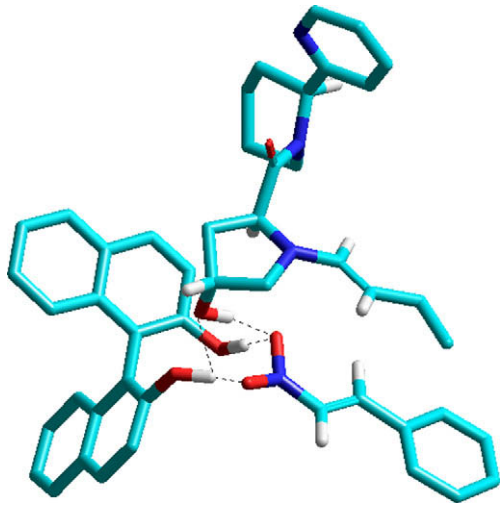


Figure 2. Proposed transition state of **2c** and (*S*)-1,1′-bi-2-naphthol-catalyzed Michael addition reaction.

3. Conclusions

In conclusion, we have developed a new catalytic system for the asymmetric Michael addition reaction of aldehydes and nitroolefins using 2-(2′-piperidinyl)pyridiyl prolinamides as a catalyst and (*S*)-1,1′-bi-2-naphthol as a co-catalyst. This system was proven to be applicable to a variety of aldehydes and nitroolefins, affording the products in excellent yields of over 92% with only 1 mol % of catalyst loading and low substrate ratio (aldehyde/nitroalkene = 1.5/1). Moreover, the system exhibited very high diastereo- and enantioselectivity with dr and ee values up to 99/1 and 99%, respectively. Consequently, the excellent catalytic efficiency, high diastereo- and enantioselectivity, and the broad applicability of the catalytic system presented in this work render this system an attractive option for the asymmetric Michael addition of aldehydes and nitroolefins. Further improvements of the present system in other types of reactions are currently underway.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded in deuterium chloroform or DMSO on a Bruker spectrometer with TMS as an internal standard. Optical rotations were measured on a Perkin Elmer 341LC polarimeter in an 1 dm tube. HPLC utilized a Shimadzu LC-6AD pump, a Shimadzu SPD-10A UV detector, and Shimadzu Class-VP system controller software. Separations were carried out on Chiralcel OD or AD analytical column with hexane/2-propyl alcohol as eluent. TLC was performed on aluminum TLC-layers Silica gel GF-254 and detected by UV light (254 and 365 nm). Silica gel (100–200 mesh) was used for column chromatography. All reactions were carried out under an argon atmosphere unless otherwise stated. All reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use. 2-(2′-Piperidinyl)pyridine **1**[11] and Boc-protected proline[18] were obtained as previously described, and matched the reported characteristics.

4.2. Typical experimental procedure for the direct Michael reaction

To a mixture of catalyst **2c** (0.01 mmol), (*S*)-1,1′-bi-2-naphthol (0.01 mmol), and nitroolefin (1 mmol) in dichloromethane (1 mL) was added carbonyl compound (1.5 mmol) under cooling with an ice-bath. The reaction mixture was stirred until the nitroolefin was completely consumed (monitored by TLC).

It was then quenched with 1 M HCl (1 mL), and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified over silicagel by flash column chromatography (eluent: petroleum ether/ethyl acetate = 20/1–5/1, v/v) to afford the desired Michael adducts **6a–6m** for further analysis.

4.2.1. (2*R*,3*S*)-2-Ethyl-4-nitro-3-phenylbutanal 6a

Prepared from butanal and *trans*-β-nitrostyrene according to the general procedure. $[\alpha]_D^{20} = +26.6$ (*c* 0.94, $CHCl_3$). Spectroscopic data are in agreement with the published data.[2] The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 3% 2-propanol in hexane, flow 0.5 mL/min, λ = 254 nm): t_R: (*syn*, major) = 15.6 min, (*syn*, minor) = 17.0 min.

4.2.2. (2*R*)-[(*S*)-2-Nitro-1-phenylethyl]hexanal 6b

Prepared from hexanal and *trans*-β-nitrostyrene according to the general procedure. $[\alpha]_D^{20} = +42.2$ (*c* 0.24, $CHCl_3$). Spectroscopic data are in agreement with the published data.[2,16d] The enantiomeric excess was determined by HPLC (Chiralpak OD-H, 3% 2-propanol in hexane, flow 1 mL/min, λ = 254 nm): t_R: (*syn*, minor) = 21.7 min, (*syn*, major) = 28.5 min.

4.2.3. (2*R*,3*S*)-2-(Methylethyl)-4-nitro-3-phenylbutanal 6c

Prepared from isobutyraldehyde and *trans*-β-nitrostyrene according to the general procedure. $[\alpha]_D^{20} = +45.2$ (*c* 0.45, $CHCl_3$). Spectroscopic data are in agreement with the published data.[16d] The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 3% 2-propanol in hexane, flow 0.4 mL/min, λ = 254 nm): t_R: (*syn*, major) = 30.8 min, (*syn*, minor) = 37.9 min.

4.2.4. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(4-tolyl)butanal 6d

Prepared from butanal and 1-methyl-4-(2-nitrovinyl)benzene according to the general procedure. $[\alpha]_D^{20} = +14.0$ (*c* 1.40, $CHCl_3$). Major diastereoisomer (*syn*): ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.4 Hz, 1H), 7.14 (d, *J* = 7.8 Hz 2H), 7.06 (d, *J* = 7.8 Hz 2H), 4.69 (dd, *J* = 12.6, 4.8 Hz, 1H), 4.60 (dd, *J* = 12.6, 10.2 Hz, 1H), 3.75 (ddd, *J* = 9.6, 9.6, 4.8 Hz, 1H), 2.66–2.62 (m, 1H), 2.32 (s, 3H), 1.53–1.48(m, 2H), 0.83 (dd, *J* = 7.8, 7.8 Hz, 3H). The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 3% 2-propanol in hexane, flow 0.5 mL/min, λ = 254 nm): t_R: (*syn*, major) = 23.5 - min, (*syn*, minor) = 28.8 min.

4.2.5. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(4-methoxyphenyl)butanal 6e

Prepared from butanal and 1-methoxy-4-(2-nitrovinyl)benzene according to the general procedure. $[\alpha]_D^{20} = +16.6$ (*c* 0.58, $CHCl_3$).

Spectroscopic data are in agreement with the published data.[6] The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 5% 2-propanol in hexane, flow 0.8 mL/min, λ = 254 nm): t_R: (*syn*, major) = 32.4 min, (*syn*, minor) = 37.8 min.

4.2.6. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(3-methoxyphenyl)butanal 6f

Prepared from butanal and 1-methoxy-3-(2-nitrovinyl)benzene according to the general procedure. $[\alpha]_D^{20} = +27.2$ (*c* 0.12, CH_2Cl_2). Major diastereoisomer (*syn*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.7 Hz, 1H), 7.28–7.25 (m, 1H), 6.83 (m, 1H), 6.76 (m, 1H), 6.71 (s, 1H), 4.70 (dd, *J* = 12.6, 5.1 Hz, 1H), 4.61 (dd, *J* = 12.6, 9.6 Hz, 1H), 3.80 (s, 3H), 3.76 (ddd, *J* = 9.9, 9.9, 5.1 Hz, 1H), 2.69–2.61 (m, 1H), 1.54–1.51 (m, 2H), 0.84 (t, *J* = 7.5 Hz, 3H). The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 5% 2-propanol in hexane, flow 0.8 mL/min, λ = 254 nm): t_R: (*syn*, major) = 19.3 min, (*syn*, minor) = 20.9 min.

4.2.7. (2*R*,3*S*)-3-(4-Bromophenyl)-2-ethyl-4-nitrobutanal 6g

Prepared from butanal and 1-bromo-4-(2-nitrovinyl)benzene according to the general procedure. $[\alpha]_D^{20} = +30.5$ (*c* 1.0, CH_2Cl_2). Spectroscopic data are in agreement with the published data.[8] The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 5% 2-propanol in hexane, flow 1.0 mL/min, λ = 254 nm): t_R: (*syn*, major) = 11.8 min, (*syn*, minor) = 15.3 min.

4.2.8. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(3-nitrophenyl)butanal 6h

Prepared from butanal and 1-nitro-3-(2-nitrovinyl)benzene according to the general procedure. $[\alpha]_D^{20} = +17.8$ (*c* 0.45, $CHCl_3$). Major diastereoisomer (*syn*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (d, *J* = 1.8 Hz, 1H), 8.21–8.18 (m, 1H), 8.11(s, 1H), 7.58–7.56 (m, 2H), 4.82 (dd, *J* = 13.2, 4.8 Hz, 1H), 4.69 (dd, *J* = 13.2, 10.2 Hz, 1H), 3.96 (ddd, *J* = 9.9, 9.9, 4.5 Hz, 1H), 2.84–2.76 (m, 1H), 1.59–1.45 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H). The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 5% 2-propanol in hexane, flow 0.8 mL/min, λ = 254 nm): t_R: (*syn*, major) = 21.8 min, (*syn*, minor) = 26.8 min.

4.2.9. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(2-nitrophenyl)butanal 6i

Prepared from butanal and 1-nitro-2-(2-nitrovinyl)benzene according to the general procedure. $[\alpha]_D^{20} = +72.5$ (*c* 0.32, $CHCl_3$). Major diastereoisomer (*syn*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (d, *J* = 2.4 Hz, 1H), 7.91–7.88 (m, 1H), 7.65–7.60 (m, 1H), 7.51–7.40 (m, 2H), 4.92 (dd, *J* = 13.5, 9 Hz, 1H), 4.74 (dd, *J* = 13.5, 4.2 Hz, 1H), 4.42 (ddd, *J* = 9, 9, 4.2 Hz, 1H), 3.03–2.94 (m, 1H), 1.63–1.44 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 5% 2-propanol in hexane, flow 0.8 mL/min, λ = 254 nm): t_R: (*syn*, major) = 42.8 min, (*syn*, minor) = 43.9 min.

4.2.10. (2*R*,3*S*)-3-(4-Chlorophenyl)-2-ethyl-4-nitrobutanal 6j

Prepared from butanal and 1-chloro-4-(2-nitrovinyl)benzene according to the general procedure. $[\alpha]_D^{20} = +17.7$ (*c* 0.20, $CHCl_3$). Spectroscopic data are in agreement with the published data.[8] The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 5% 2-propanol in hexane, flow 0.8 mL/min, λ = 254 nm): t_R: (*syn*, major) = 19.9 min, (*syn*, minor) = 27.0 min.

4.2.11. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(thien-2-yl)butanal 6k

Prepared from butanal and *trans*-2-(2-nitrovinyl)thiophene according to the general procedure. $[\alpha]_D^{20} = +27.1$ (*c* 0.16, $CHCl_3$). Spectroscopic data are in agreement with the published data.[19] The enantiomeric excess was determined by HPLC (Chiralpak AD-H, 5% 2-propanol in hexane, flow 0.5 mL/min, λ = 254 nm): t_R: (*syn*, major) = 30.0 min, (*syn*, minor) = 36.7 min.

4.2.12. (2*R*,3*S*)-2-Ethyl-4-nitro-3-(2-furyl)butanal 6l

Prepared from butanal and *trans*-2-(2-nitrovinyl)furan according to the general procedure. $[\alpha]_D^{20} = +23.3$ (*c* 2.5, $CHCl_3$). Major diastereoisomer (*syn*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.5 Hz, 1H), 7.37 (d, *J* = 1.2 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.20 (d, *J* = 3 Hz, 1H), 4.70 (d, *J* = 4.8 Hz, 1H), 4.67 (d, *J* = 1.8 Hz, 1H), 4.01 (ddd, *J* = 8.7, 8.7, 5.7 Hz, 1H), 2.80–2.73 (m, 1H), 1.62–1.52 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). The enantiomeric excess were determined by HPLC (Chiralpak AD-H, 5% 2-propanol in hexane, flow 0.5 mL/min, λ = 254 nm): t_R: (*syn*, minor) = 16.2 min, (*syn*, major) = 16.9 min.

4.2.13. *R*-2-[(*R*)-1-Nitro-4-phenylbutan-2-yl]pentanal 6m

Prepared from pentanal and 4-(nitrobut-3-enyl)benzene according to the general procedure. $[\alpha]_D^{20} = +21.5$ (*c* 0.49, $CHCl_3$). Spectroscopic data are in agreement with the published data.[4] The enantiomeric excess was determined by HPLC (Chiralpak OD-H, 3% 2-propanol in hexane, flow 0.8 mL/min, λ = 254 nm): t_R: (*syn*, major) = 22.5 min, (*syn*, minor) = 24.2 min.

4.3. Synthesis of organocatalyst 2c

Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl, 0.33 g, 1.3 mmol) was added to a solution of the *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-L-proline (0.3 g, 1.3 mmol) and triethylamine (0.3 mL, 2.2 mmol) in dichloromethane (3 mL). The suspension was stirred for 30 min under cooling with an ice-bath. Then the (*S*)-2-(2′-piperidinyl)pyridine (0.16 g, 1.0 mmol) solution in dichloromethane (1 mL) and triethylamine (0.15 mL, 1.1 mmol) was added dropwise at the same temperature. It was stirred further for 16 h (0 °C–rt). The mixture was filtered and the filtrate was diluted with 10 mL dichloromethane, washed with saturated aqueous $NaHCO_3$ (5 mL × 2) and brine (5 mL × 2). The aqueous solutions were extracted with further dichloromethane (10 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The intermediate *N*-Boc-pyrrolidine derivative **3c** was obtained in quantitative yield as a white solid, and used without additional purification.

Compound **3c** (0.3 g, 0.8 mmol) was dissolved in 7 mL dichloromethane, to which was added trifluoroacetic acid (2 mL, 26 mmol). The solution was stirred at room temperature for 10 h and then concentrated under reduced pressure to remove excess trifluoroacetic acid. The residue was dissolved in dichloromethane (20 mL) followed by the addition of saturated aqueous Na_2CO_3. The aqueous phase was extracted with further dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, which was further purified by flash column chromatography on silicagel (CH_2Cl_2/MeOH/Et_3N = 10:1:0.1, v/v). The relevant fractions were combined to give pure **2c** as a white solid. Other organocatalysts **2a**, **2b**, and **2d** were also obtained via similar processes. The total yield of **2c** in two steps was 80%: $[\alpha]_D^{20} = -100.0$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR of major rotamer (600 MHz, DMSO-*d*): δ 1.30, 1.50, 1.58, 1.71–1.76, 1.82–1.84, 1.95 (m, 7H), 2.57 (m, 2H), δ 3.03 (m, 1H), δ 3.14 (m, 1H), 3.90 (m, 1H), 4.14 (t, *J* = 7.8 Hz, 1H), 4.20 (m, 1H), 5.70 (d, *J* = 4.2 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.24 (m, 1H), 7.77 (m, 1H), 8.55 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR of major rotamer (150 MHz, DMSO-*d*): δ 19.5, 25.2, 27.1, 40.1, 41.7, 52.5, 55.2, 56.6, 71.5, 121.0, 121.7, 136.8, 149.0, 159.1, 172.6. ^{1}H NMR of minor rotamer (600 MHz, DMSO-*d*): δ 1.30, 1.58, 1.71–1.76, 1.95 (m, 7H), 2.45–2.52 (m, 2H), 2.68 (d, *J* = 13.2 Hz, 1H), 3.14 (m, 1H), 3.84 (m, 1H), 4.20 (m, 1H), 4.40 (d, *J* = 13.2 Hz, 1H), 5.21 (d, *J* = 3.6 Hz, 1H), 7.30 (m, 2H), 7.83 (t, *J* = 7.2 Hz, 1H), 8.60 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR of minor rotamer (150 MHz, DMSO-*d*): δ 19.5, 24.8, 27.6, 38.3, 40.4, 55.2, 55.8, 56.6, 71.6, 121.1, 122.0, 137.1, 149.2, 158.5, 173.1.

4.4. Organocatalyst 2a

Compound **2a** was obtained in a 90% yield from (*S*)-2-(2′-piperidinyl)pyridine and *N*-*tert*-butoxycarbonyl-L-proline (two steps) as a white solid. $[\alpha]_D^{20} = -198.4$ (*c* 0.64, CH_2Cl_2). ^{1}H NMR of major rotamer (600 MHz, $CDCl_3$): δ 1.26 (t, *J* = 6.6 Hz, 1H), 1.57 (m, 1H), 1.65–1.67 (m, 2H), 1.75 (m, 1H), 1.83 (m, 3H) 2.18–2.20 (m, 1H), 2.62 (d, *J* = 13.2 Hz, 1H), 2.93 (q, *J* = 7.8 Hz, 1H), 3.18 (t, *J* = 12.0 Hz, 1H), 3.23 (m, 1H), 3.77 (m, 1H), 4.13 (m, 1H), 5.92 (s, 1H), 7.11–7.13 (m, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 8.56 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR of major rotamer (150 MHz, $CDCl_3$): δ 19.8, 25.8, 26.3, 27.3, 30.6, 42.4, 47.7, 53.3, 58.4, 121.3, 121.5, 136.5, 149.1, 159.4, 173.1. ^{1}H NMR of minor rotamer (600 MHz, $CDCl_3$): δ 1.35 (q, *J* = 12.6 Hz, 1H), 1.55–1.57 (m, 2H), 1.65–1.67 (m, 1H), 1.75 (m, 2H), 1.83 (m, 2H), 2.18–2.21 (m, 1H), 2.67 (t, *J* = 12.6 Hz, 1H), 2.81 (m, 1H), 2.86 (d, *J* = 13.2 Hz, 1H), 3.23 (m, 1H), 3.77 (m, 1H), 4.60–4.63 (m, 1H), 5.14 (s, 1H), 7.20–7.21 (m, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 8.61 (d *J* = 2.4 Hz, 1H); ^{13}C NMR of minor rotamer (150 MHz, $CDCl_3$): δ 19.8, 25.1, 26.6, 27.9, 31.5, 39.1, 47.7, 56.6, 58.3, 121.0, 122.0, 137.0, 149.6, 158.3, 174.3.

4.5. Organocatalyst 2b

Compound **2b** was obtained in a 93% yield from (*R*)-2-(2′-piperidinyl)pyridine and *N*-*tert*-butoxycarbonyl-L-proline (two steps) as a white solid. $[\alpha]_D^{20} = +70.0$ (*c* 1, CH_2Cl_2). ^{1}H NMR of major rotamer (600 MHz, $CDCl_3$): δ 1.51–1.56, 1.58–1.60, 1.68–1.70, 1.79, 1.87 (m, 8H), 2.19 (m, 1H), 2.71–2.77 (m, 1H), 2.91 (m, 1H), 3.12–3.16 (m, 1H), 3.21–3.23 (m, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 4.07 (t, *J* = 6.0 Hz, 1H), 5.94 (s, 1H), 7.13–7.17 (m, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 8.57 (s, 1H); ^{13}C NMR of major rotamer (150 MHz, $CDCl_3$): δ 19.8, 25.9, 26.4, 26.9, 31.2, 42.2, 47.5, 53.6, 58.5, 121.6, 121.7, 136.6, 149.1, 158.9, 173.1. ^{1}H NMR of minor rotamer (600 MHz, $CDCl_3$): δ 1.32 (m, 1H), 1.51–1.56, 1.58–1.60, 1.68–1.70, 1.79, 1.87 (m, 9H), 2.78 (m, 1H), 2.85 (m, 1H), 3.12–3.16 (m, 1H), 4.01 (m, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 5.26 (s, 1H), 7.13–7.17 (m, 2H), 7.68 (m, 1H), 8.62 (s, 1H); ^{13}C NMR of minor rotamer (150 MHz, $CDCl_3$): δ 19.8, 25.3, 26.4, 28.8, 30.7, 39.5, 47.3, 57.2, 58.7, 121.1, 121.9, 136.6, 149.6, 158.9, 173.1.

4.6. Organocatalyst 2d

Compound **2d** was obtained in a 87% yield from (*R*)-2-(2′-piperidinyl)pyridine and *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-L-proline (two steps) as a white solid. $[\alpha]_D^{20} = +61.7$ (*c* 0.47, CH_2Cl_2). ^{1}H NMR of major rotamer (600 MHz, $CDCl_3$): δ 1.42–1.78 (m, 5H), 2.00 (m, 1H), 2.31 (m, 1H), 2.69 (m, 1H), 3.05 (d, *J* = 16.8 Hz, 1H), 3.16 (m, 1H), 3.30 (m, 1H), 3.79 (d, *J* = 19.8 Hz, 1H), 4.44 (t, *J* = 11.4 Hz, 1H), 4.53 (s, 1H), 5.90 (d, *J* = 5.4 Hz, 1H), 7.13–7.20 (m, 2H), 7.67 (m, 1H), 8.57 (d, *J* = 6 Hz, 1H); ^{13}C NMR of major rotamer (150 MHz, DMSO-*d*): δ 19.4, 25.1, 26.9, 38.4, 42.2, 53.3, 53.7, 56.8, 69.8, 121.3, 121.9, 136.9, 149.0, 158.1, 169.1. ^{1}H NMR of minor rotamer (600 MHz, $CDCl_3$): δ 1.42–1.78 (m, 5H), 2.45–2.52 (m, 2H), 1.90 (m, 1H), 2.69 (m, 1H), 2.83 (m, 1H), 2.97 (m, 1H), 3.30 (m, 1H), 4.39 (m, 1H), 4.61 (m, 1H), 5.29 (d, 1H), 7.13–7.20 (m, 2H), 7.68 (m, 1H), 8.60 (d, 1H); ^{13}C NMR of minor rotamer (150 MHz, DMSO-*d*): δ 19.4, 24.7, 28.6, 38.3, 40.0, 53.5, 56.3, 56.7, 69.7, 121.3, 122.1, 137.1, 149.2, 158.2, 168.9.

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