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Simple Chiral Pyrrolidine–Pyridine-Based Catalysts for Highly Enantioselective Michael Addition to Nitro Olefins

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Keywords: Asymmetric catalysis / Michael addition / Alkenes / Organocatalysis / Pyrrolidine / Catalyst design

A new class of chiral pyrrolidine–pyridine-based organocatalysts, available from commercially available starting materials, have been synthesized and shown to be very effective catalysts for the asymmetric Michael addition reactions of cyclic/acyclic/aromatic ketones and an aldehyde with nitro olefins, giving excellent yields (up to 99%), diastereoselectivities (*syn*/*anti* = 99:1), and enantioselectivities (up to 99%). Based on the experimental results and ESI-MS analysis of the intermediates, the mode of activity of the organocatalyst with the substrate was deduced.

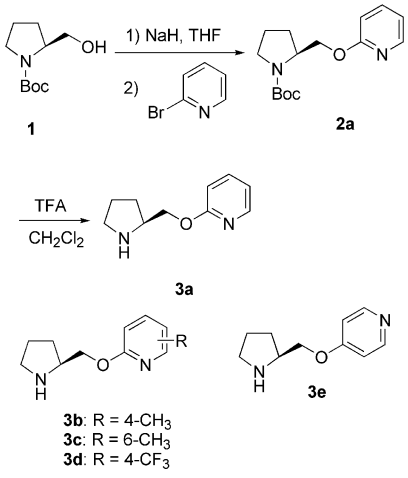
Introduction

The Michael reaction is widely recognized as one of the most important carbon–carbon bond-forming procedures, and it plays an important role in organic synthesis.[1] The development of organocatalysts that promote asymmetric Michael reactions is an attractive area of research.[2] Thus, it is not surprising that chemists pay considerable attention to the development of enantioselective catalytic protocols for this base reaction, aiming at developing more selective and efficient catalytic systems for this synthetically useful transformation. Over the past few years there has been a tremendous increase in research activities directed towards the development of organocatalysts for this asymmetric reaction.[3] Asymmetric Michael addition reactions of ketones or aldehydes to nitro olefins in the presence of L-proline- and pyrrolidine-based catalytic systems have been reported to proceed with poor to good enantioselectivities,[4] and consequently tremendous efforts have been made to find more efficient pyrrolidine-based organocatalysts for use in this transformation.[5]

Most of the catalysts used in the Michael reactions of ketones or aldehydes with nitro olefins give excellent results,[6] but few give good enantioselectivities with both ketones and aldehydes.[7] In nearly all cases, the Michael products were obtained with good results, but the use of ketones was limited to cyclohexanone. Acyclic and aromatic ketones have been little used in this reaction. There are only two reports of pyrrolidine-based catalysts used in the Michael addition of aromatic ketones to nitro olefins, and in both cases very low yields and enantioselectivities were obtained.[4d,8d]

As a result, the design and development of highly active chiral organocatalysts for achieving good results with both ketones and aldehydes in Michael conjugate addition reactions remains a major challenge in synthetic organic chemistry.[8] To the best of our knowledge, there is no universal catalyst that gives both high yield and enantioselectivity for this reaction with cyclic/acyclic/aromatic ketones and aldehydes.

In this paper we report a catalyst that is compatible with various ketones (cyclic/acyclic/aromatic) and an aldehyde, providing excellent yields (up to 99%) and stereoselectivities (up to *syn*/*anti* = 99:1, 99% *ee*). The catalysts are similar in structure to Kotsuki pyrrolidine–pyridine-based catalysts;[8b] they are composed of 2-pyrrolidinyl and 2-pyridyl moieties linked by a methyleneoxy group instead of a meth-



Scheme 1. Synthesis of the catalysts **3**.

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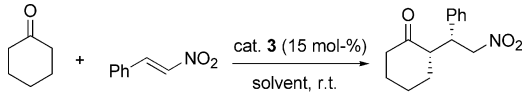
ylene or ethylene spacer and are easier to synthesize and more effective in the enantioselective Michael addition reactions of all kinds of ketones and an acyclic aldehyde to nitro olefins.

A series of pyrrolidine–pyridine catalysts **3** were prepared from the "chiral pool" by using *N*-Boc-L-prolinol as the starting material.[9] The synthetic procedures were quite straightforward; *N*-Boc-L-prolinol was coupled with bromopyridine reagents and then treated with TFA in CH_2Cl_2 to afford the product (for example, **3a**) in 65% total yield from *N*-Boc-L-prolinol (Scheme 1).[10]

Results and Discussion

As can be seen from the results summarized in Table 1, the reaction of cyclohexanone (**4a**) with nitrostyrene (**5a**) was performed at room temperature (20 °C) with 15 mol-% of **3** as the catalyst. All the catalysts tested exhibited good catalytic activity with the corresponding products obtained in excellent chemical yields (Table 1, Entries 1–5). The pyrrolidine–pyridine catalyst **3a** promoted the Michael addition reaction with high diastereoselectivity and enantioselectivity (Table 1, Entry 1). Chiral catalysts **3b**–**3e** also gave good diastereoselectivities, but lower enantioselectivities were obtained than with **3a** (Table 1, Entries 2–5). The catalyst **3c**, containing the 6-methylpyridine moiety, gave mainly the *anti* Michael product, whereas the other catalysts predominantly gave the *syn* products.

Table 1. The effect of catalysts **3** on the asymmetric Michael addition reactions of cyclohexanone and nitrostyrene.[a]



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

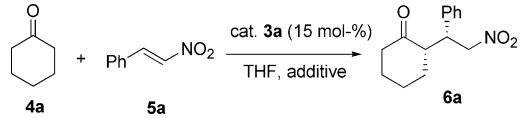
Entry	Catalyst	Solvent	Time [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	**3a**	neat	12	99	94:6	89
2	**3b**	neat	20	97	63:37	81
3	**3c**	neat	48	92	33:67	88
4	**3d**	neat	10	95	60:40	87
5	**3e**	neat	20	97	85:15	88
6	**3a**	H_2O	72	0	–	–
7	**3a**	toluene	72	82	94:6	91
8	**3a**	DMSO	72	68	95:5	86
9	**3a**	$CHCl_3$	72	85	96:4	81
10	**3a**	THF	20	99	97:3	92
11	**3a**	$(CH_3)_3COH$	12	99	94:6	86
12	**3a**	[bmim][PF_4]	72	40	92:8	75

[a] All reactions were conducted in solvent (1 mL) by using **4a** (0.2 mL, 2.0 mmol) and **5a** (30 mg, 0.2 mmol) in the presence of 15 mol-% of the catalyst. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis (Chiralcel AD-H column).

Catalyst **3a** was used as the catalyst of choice and evaluated in different solvents (Table 1, Entries 6–12). The yields and enantioselectivities of the product differed significantly. When H_2O was used as the solvent, no product was obtained. The most polar solvents, DMSO and [bmim][PF_4], both gave poor yields and enantioselectivities (Table 1, Entries 8 and 12). The nonpolar solvent toluene gave a poor yield of 82%. $CHCl_3$ and *tert*-butyl alcohol gave moderate diastereoselectivities and enantioselectivities (Table 1, Entries 9 and 11). The best result was observed when THF was used as the solvent (Table 1, Entry 10: *syn*/*anti* = 97:3, 92% *ee*).

As we had obtained 92% enantioselectivity of the Michael product in THF by using 15 mol-% of **3a**, the effects of some Brønsted acids on the Michael reaction of cyclohexanone (**4a**) and nitrostyrene (**5a**) were examined in the hope of improving the enantioselectivity. As illustrated in Table 2, the enantioselectivities are lower with relatively strong acids such as TFA and *p*TosOH than with weak acids such as PhCOOH and C_6H_5OH. Finally, we found that 2-naphthol was the best weak acid in combination with catalyst **3a** (Table 2, Entry 9: *syn*/*anti* = 98:2, 95% *ee*).

Table 2. Asymmetric Michael addition reactions of cyclohexanone and nitrostyrene catalyzed by **3a** with different additives.[a]



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

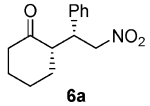
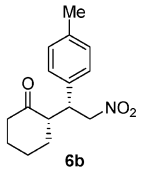
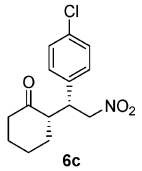
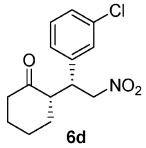
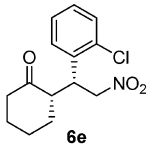
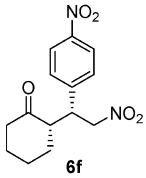
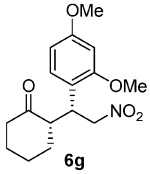
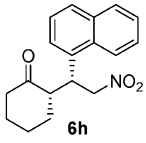
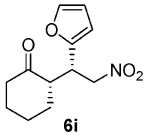
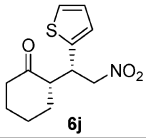
Entry	Additive	Time [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	TFA	24	99	97:3	53
2	PhCOOH	24	99	97:3	90
3	(±)-lactic acid	24	99	97:3	90
4	*p*TosOH	48	20	92:8	73
5	1,4-$(HO)_2C_6H_3$	20	99	95:5	86
6	3,5-$(H_3C)_2C_6H_3OH$	20	99	95:5	88
7	C_6H_5OH	20	99	96:4	85
8	*p*-methylmandelic acid	20	99	97:3	85
9	2-naphthol	20	99	98:2	95
10	1-naphthol	20	98	72:28	85

[a] All reactions were conducted in THF (1 mL) by using **4a** (0.2 mL, 2.0 mmol), **5a** (30 mg, 0.2 mmol), and catalyst **3a** (5.3 mg, 0.03 mmol) in the presence of 5 mol-% of the additive. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis (Chiralcel AD-H column).

Having established the optimal reaction conditions, we then examined the reactions of other nitro olefins to establish the general scope of this asymmetric transformation. As shown in Table 3 (Entries 1–10), high isolated yields were obtained for all the products, regardless of the electronic nature of the aromatic substituents, and in most of the cases we obtained the *syn* products with high diastereoselectivities (>96% *syn*/*anti*) and enantioselectivities (92–99% *ee*).

Other ketones, including cyclic and acyclic ketones, were also examined in the **3a**-catalyzed Michael addition reaction with **5a**, and the products (Table 4, Entries 1–5) were isolated in good yields and with good to excellent enantioselectivities. Cycloheptanone is reported to be less active as a substrate, and the products of Michael reactions with nitro olefins have always been obtained in very low yields

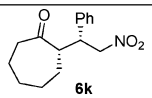
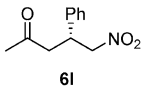
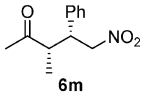
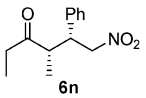
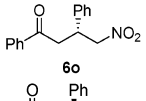
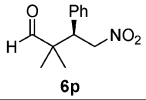
Table 3. Asymmetric Michael addition reactions of cyclohexanone and nitro olefins catalyzed by **3a**.[a]

Entry	Product	Time [h]	Yield [%][b]	*syn/anti*[c]	*ee* [%][d]
1	 **6a**	20	99	98:2	95
2	 **6b**	17	96	99:1	92
3	 **6c**	12	99	98:2	94
4	 **6d**	12	99	95:5	96
5	 **6e**	12	99	99:1	95
6	 **6f**	14	96	94:6	92
7	 **6g**	48	92	97:3	92
8	 **6h**	20	96	97:3	97
9	 **6i**	12	99	97:3	88
10	 **6j**	17	99	96:4	86

[a] Reaction conditions: ketone **4a** (196 mg, 2.0 mmol), nitro olefin (0.2 mmol), 15 mol-% **3a**, 5 mol-% 2-naphthol, and THF (1 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis (Chiralcel AD-H or OD-H column).

and enantioselectivities;[7b,8d,11] however, in this work the highest enantioselectivity was obtained for the reaction with cycloheptanone in the presence of the catalyst **3a** (Table 4, Entry 1). The use of aliphatic ketones in the reaction with nitrostyrene gave similar results (Table 4, Entries 2–4).

Table 4. Asymmetric Michael addition reactions of ketones and nitrostyrene catalyzed by **3a**.[a]

Entry	Product	Time [h]	Yield [%][b]	*syn/anti*[c]	*ee* [%][d]
1	 **6k**	72	65	99:1	99
2	 **6l**	48	85	–	57
3	 **6m**	48	63	96:4	91
4	 **6n**	48	58	98:2	93
5	 **6o**	20	53	–	85
6	 **6p**	72	65	–	81

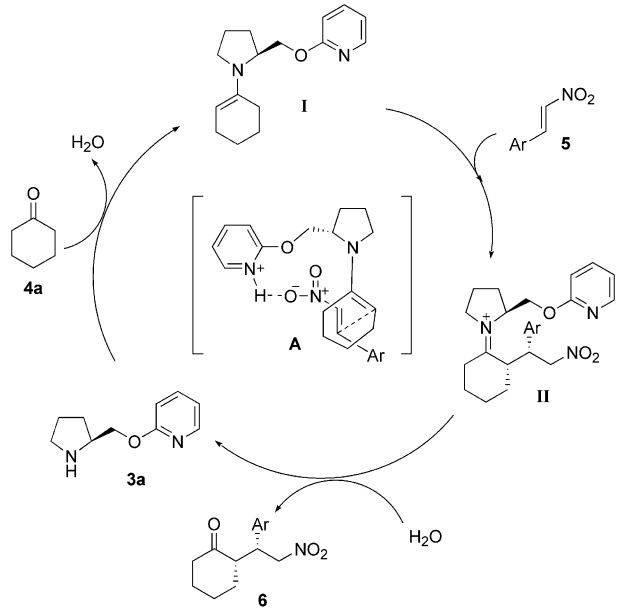
[a] Reaction conditions: ketone **4** (2.0 mmol), nitro olefin (0.2 mmol), 15 mol-% **3a**, 5 mol-% 2-naphthol, and THF (1 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis (Chiralcel AD-H or OD-H column).

The results of a preliminary study demonstrated that **3a** also catalyzed the Michael addition reaction of an aromatic ketone to nitrostyrene (Table 4, Entry 5). Under the reaction conditions described above, the addition of acetophenone to nitrostyrene (**5a**) resulted in the formation of the product in 53% yield and 85% *ee*. This is the best result obtained for the reaction between acetophenone and nitrostyrene catalyzed by a pyrrolidine-based catalyst.[4d,8d] Previously, highly enantioselective Michael additions of aromatic ketones to nitro olefins were only achieved by using chiral bifunctional primary amine–thiourea catalysts.[12]

An aldehyde was also found to be compatible with **3a** under the optimized conditions; the addition of isobutyraldehyde to nitrostyrene (**5a**) gave the desired product in good yield and 81% *ee* (Table 4, Entry 6).

The stereochemistries of the major products **6** were determined to be (2*S*,3*R*) by comparison of their optical rotations with other previous studies.[4–8] The absolute stereochemical results can be explained by an acyclic synclinal transition state, as proposed by Seebach and Golinski.[13] It is accepted that when primary or secondary chiral amines are used as organocatalysts, the reaction proceeds by an enamine pathway. As shown in Scheme 2, the catalyst **3a**

first forms a chiral enamine **I** with cyclohexanone (**4a**), and then a Michael reaction between the enamine-activated **I** and the nitro olefin **5** leads to the formation of the corresponding product **6** via transition state **A**. The catalyst **3a** is regenerated for use in the subsequent catalytic cycle. The existence of the intermediates **I** and **II** in the reaction mixture was confirmed by ESI-MS (Figure 1).



Scheme 2. Proposed mechanism for the **3a**-catalyzed Michael addition reaction.

Conclusions

We have developed a new class of chiral pyrrolidine–pyridine-based organocatalysts that are capable of catalyzing highly enantioselective and diastereoselective nitro-Michael addition reactions. The chiral pyrrolidine–pyridine catalysts were easily prepared from commercially available L-prolinol in only two steps. An exceptionally broad range of ketones (cyclic/acyclic/aromatic), an aldehyde, and a variety of nitro olefins are tolerated in this system. These are the first universal catalysts that can be employed in the Michael addition reactions of all kinds of ketones and nitro olefins to give high yields and good to excellent diastereoselectivities and enantioselectivities. Further investigation into the applications of this organocatalyst in asymmetric catalysis is in progress.

Experimental Section

General: All solvents were purified according to standard procedures. ^{1}H NMR spectra were recorded at 300 or 400 MHz, and ^{13}C NMR spectra were recorded at 75 or 100 MHz with Bruker DPX-300 or AV400 spectrometers. Chemical shifts (δ) were calibrated relative to tetramethylsilane as external reference and are reported in ppm. Coupling constants (J) are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet: t, triplet; m, multiplet. HRMS data were recorded with an IonSpec FT-ICR mass spectrometer with ESI source. Melting points were measured with a RY-I apparatus and are reported uncorrected. Optical rotations were measured with a Perkin–Elmer 341 polarimeter at 20 °C. HPLC analysis was performed with a

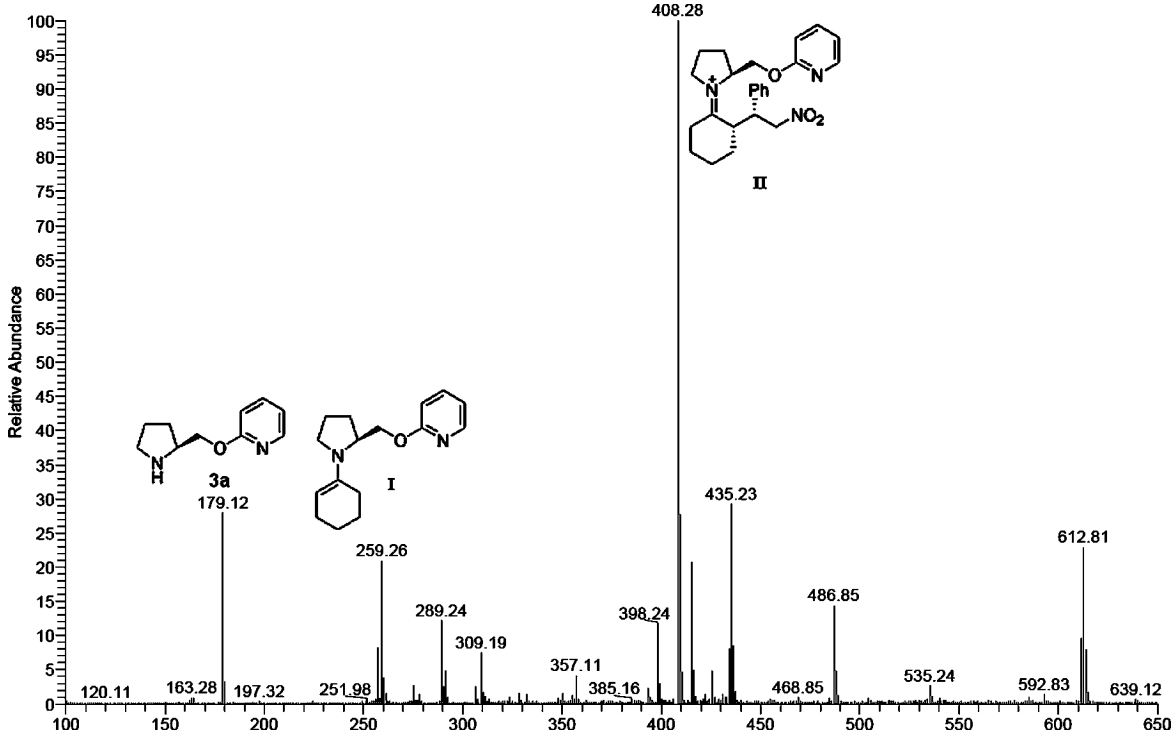


Figure 1. ESI-MS (+) spectra of the intermediates **I** and **II** in the reaction cycle.

Shimadzu CTO-10AS by using a Chiralpak AD-H or an OD-H column purchased from Daicel Chemical Industries.

General Procedure for the Synthesis of Catalysts

(2*S*)-2-[(2-Pyridyloxy)methyl]pyrrolidine (3a): A solution of **1** (3.02 g, 15 mmol) in dry THF (30 mL) under N_2 was cooled to 0 °C and stirred for 10 min. NaH (2.16 g, 90 mmol) was added, and the mixture was stirred for 20 min. The mixture was warmed to room temperature and stirred overnight, and then a solution of 2-bromopyridine (1.7 g, 15 mmol) in THF (5 mL) was added. The mixture was heated at reflux for 24 h. After evaporation of the THF, ethyl acetate (80 mL) was added, and the solution was washed with water (30 mL) and brine (30 mL), and dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography with petroleum ether/ethyl acetate (8:1) to afford 2.9 g (71%) of **2a** as a colorless oil. TFA (8 mL) was added dropwise to a solution of **2a** (1.0 g, 3.6 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight. After removal of the organic solvents under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and then treated with saturated Na_2CO_3 solution (30 mL) at room temperature for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL), and the combined extracts were washed with brine (15 mL) and dried with anhydrous Na_2SO_4. Concentration in vacuo after filtration gave **3a** as a colorless oil (587 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72–1.81 (m, 1 H, CH_2 pyrrolidine), 1.90–1.97 (m, 2 H, CH_2 pyrrolidine), 2.04–2.13 (m, 1 H, CH_2 pyrrolidine), 3.09–3.23 (m, 2 H, CH_2 pyrrolidine), 3.81–3.87 (m, 1 H, CH pyrrolidine), 4.31 (dd, J_1 = 6.8, J_2 = 11.6 Hz, 1 H, OCH_2), 4.51 (dd, J_1 = 3.6, J_2 = 11.6 Hz, 1 H, OCH_2), 6.79 (d, J = 8.4 Hz, 1 H, pyridine), 6.89–6.92 (m, 1 H, pyridine), 7.57–7.62 (m, 1 H, pyridine), 8.10–8.12 (m, 1 H, pyridine) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.29, 27.02, 45.48, 58.25, 65.84, 111.23, 117.49, 139.08, 146.51, 162.98 ppm. HRMS: calcd. for $C_{10}H_{14}N_2ONa^+$ [M + Na]$^+$ 201.0998; found 201.0992. $[\alpha]_D^{20}$ = +33.6 (c = 0.5, CH_2Cl_2). $C_{10}H_{14}N_2O$ (178.23): calcd. C 67.39, H 7.92, N 15.72; found C 67.45, H 7.88, N 15.67.

(2*S*)-2-[(4-Methyl-2-pyridyloxy)methyl]pyrrolidine (3b): Catalyst **3b** was prepared according to the General Procedure to afford the product as a light-yellow solid; yield 92%; m.p. 58–59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52–1.63 (m, 1 H, CH_2 pyrrolidine), 1.71–2.01 (m, 2 H, CH_2 pyrrolidine), 2.28 (s, 3 H, CH_3), 2.95–3.08 (m, 2 H, CH_2 pyrrolidine), 3.54–3.66 (m, 1 H, CH pyrrolidine), 3.83–3.89 (m, 1 H, CH_2 pyrrolidine), 4.16 (dd, J_1 = 10, J_2 = 14.4 Hz, 1 H, OCH_2), 4.33 (dd, J_1 = 5.2, J_2 = 14 Hz, 1 H, OCH_2), 6.58 (s, 1 H, pyridine), 6.70 (d, J = 6.8 Hz, 1 H, pyridine), 7.98 (d, J = 7.2 Hz, 1 H, pyridine) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.90, 25.19, 27.77, 46.34, 57.41, 68.46, 111.17, 118.45, 146.24, 150.00, 164.04 ppm. HRMS: calcd. for $C_{11}H_{16}N_2O_5Na^+$ [M + Na]$^+$ 215.1155; found 215.1162. $[\alpha]_D^{20}$ = +14.1 (c = 0.5, CH_2Cl_2). $C_{11}H_{16}N_2O$ (192.26): calcd. C 68.72, H 8.39, N 14.57; found C 68.78, H 8.33, N 14.59.

(2*S*)-2-[(6-Methyl-2-pyridyloxy)methyl]pyrrolidine (3c): Catalyst **3c** was prepared according to the General Procedure to afford the product as a brown oil; yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.74 (m, 1 H, CH_2 pyrrolidine), 1.85–1.92 (m, 2 H, CH_2 pyrrolidine), 1.97–2.07 (m, 1 H, CH_2 pyrrolidine), 2.43 (s, 3 H, CH_3), 3.03–3.15 (m, 2 H, CH_2 pyrrolidine), 3.66–3.77 (m, 1 H, CH pyrrolidine), 4.24 (dd, J_1 = 6.8, J_2 = 11.6 Hz, 1 H, OCH_2), 4.41 (dd, J_1 = 3.6, J_2 = 11.6 Hz, 1 H, OCH_2), 6.57 (d, J = 8.0 Hz, 1 H, pyridine), 6.74 (d, J = 7.2 Hz, 1 H, pyridine), 7.47 (t, J = 8 Hz, 1 H, pyridine) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.99, 24.05, 26.38, 44.88, 56.86, 66.86, 106.59, 115.37, 138.31, 155.06, 162.02 ppm. HRMS: calcd. for $C_{11}H_{16}N_2OH^+$ [M + H]$^+$ 193.1335; found 193.1339. $[\alpha]_D^{20}$ = –20.0 (c = 0.5, CH_2Cl_2). $C_{11}H_{16}N_2O$ (192.26): calcd. C 68.72, H 8.39, N 14.57; found C 68.65, H 8.34, N 14.53.

(2*S*)-2-{[4-(Trifluoromethyl)-2-pyridyloxy]methyl}pyrrolidine (3d): Catalyst **3d** was prepared according to the General Procedure to afford the product as a colorless oil; yield 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48–1.56 (m, 1 H, CH_2 pyrrolidine), 1.70–1.97 (m, 3 H, CH_2 pyrrolidine), 2.23 (br., 1 H, NH), 2.91–3.04 (m, 2 H, CH_2 pyrrolidine), 3.49–3.56 (m, 1 H, CH pyrrolidine), 4.19 (dd, J_1 = 7.6, J_2 = 10.4 Hz, 1 H, OCH_2), 4.33 (dd, J_1 = 4.4, J_2 = 10.8 Hz, 1 H, OCH_2), 6.98 (s, 1 H, pyridine), 7.04 (d, J = 5.2 Hz, 1 H, pyridine), 8.27 (d, J = 5.2 Hz, 1 H, pyridine) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.36, 27.91, 46.59, 56.95, 69.80, 107.82, 112.18, 123.97, 140.95, 148.18, 164.21 ppm. HRMS: calcd. for $C_{11}H_{13}F_3N_2OH^+$ [M + H]$^+$ 247.1053; found 247.1056. $[\alpha]_D^{20}$ = +9.6 (c = 0.5, CH_2Cl_2). $C_{11}H_{13}F_3N_2O$ (246.23): calcd. C 53.66, H 5.32, N 11.38; found C 53.71, H 5.38, N 11.42.

(2*S*)-2-[(4-Pyridyloxy)methyl]pyrrolidine (3e): Catalyst **3e** was prepared according to the General Procedure to afford the product as a yellow liquid; yield 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48–1.60 (m, 1 H, CH_2 pyrrolidine), 1.73–1.87 (m, 2 H, CH_2 pyrrolidine), 1.92–2.01 (m, 1 H, CH_2 pyrrolidine), 2.34 (br., 1 H, NH), 2.92–3.02 (m, 2 H, CH_2 pyrrolidine), 3.49–3.58 (m, 1 H, CH pyrrolidine), 3.85–3.97 (m, 2 H, OCH_2), 6.79–6.81 (m, 2 H, pyridine), 8.40–8.42 (m, 2 H, pyridine) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.28, 27.97, 46.60, 56.78, 71.28, 110.23, 151.01, 164.89 ppm. HRMS: calcd. for $C_{10}H_{14}N_2ONa^+$ [M + Na]$^+$ 201.0998; found 201.0999. $[\alpha]_D^{20}$ = +9.6 (c = 0.5, CH_2Cl_2). $C_{10}H_{14}N_2O$ (178.23): calcd. C 67.39, H 7.92, N 15.72; found C 67.33, H 7.87, N 15.66.

Typical Experimental Procedure for Asymmetric Michael Addition to Nitro Olefins: 2-Naphthol (1.5 mg, 0.01 mmol) was added to a mixture of catalyst **3a** (5.4 mg, 0.03 mmol) in THF (0.5 mL) at room temperature under air. The reaction mixture was stirred for 10 min, and then cyclohexanone (**4a**; 208 μL, 2.0 mmol) and (*E*)-β-nitrostyrene (**5a**; 30 mg, 0.2 mmol) were added. The homogeneous reaction mixture was stirred at room temperature for 18 h. The reaction mixture was directly loaded onto a silica gel column to afford the Michael adduct **6a** (49 mg, 99%) as a white solid (m.p. 129–130 °C) in a *syn*/*anti* ratio of 98:2 (by ^{1}H NMR). The *ee* was determined by HPLC analysis [Chiralpak AD-H, *i*PrOH/hexane (10:90), 0.5 mL/min, 254 nm, t_r(minor) = 21.8, t_r(major) = 27.0 min] to be 96% *ee*. $[\alpha]_D^{25}$ = –33.7 (c = 0.80, $CHCl_3$).

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