Asymmetric Michael Addition of Ketones to Nitroolefins Catalyzed by a New Chiral Catalyst

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A new chiral catalyst was synthesized and found that it could catalyze the asymmetric Michael reaction of ketones with nitroolefins smoothly at room temperature, giving the desired adducts in 71 - 92% yields with excellent diastereoselectivities and high enantioselectivities (up to 95% ee).

Key Words: Chiral catalyst, Michael reaction, Nitroolefin, Ketone, Enantioselectivity

Introduction

Chiral asymmetric Michael addition of nucleophiles to nitroolefins affords very useful chiral building blocks in organic synthesis.¹ Many outstanding efforts have been taken into the development of both chiral metal-catalysts^{1,2} and chiral organocatalysts^{1,3} for the nitro-Michael addition. Due to the importance of the nitro-Michael addition and nitro group as a "synthetic chameleon", the development of new chiral catalysts for a highly enantioselective nitro-Michael reaction is still significant. Herein, we wish to report a new chiral multifunctional catalyst for the highly stereoselective Michael addition of nitroolefins with ketones.

As we know, chiral thiourea organocatalysts **1** were applied successfully in the asymmetric Michael reaction of nitroolefins with malonates or ketones.^{4,5,10} Considering that the hydrogen connecting to nitrogen in thiourea may play a key role in the asymmetric nitro-Michael reaction,^{4c-e} we envision to synthesize new catalyst in order to increase its activity as a Brønsted acid catalyst.

Results and Discussion

Aminomethylpyrrolidine **3** can be prepared from L-proline according to the literature method.⁶ It was found that the reaction of **3** with **4**^{7a} in CH₂Cl₂ at room temperature for 5 hr, followed by stirring the resulting mixture with CH₃NH₂ at this temperature for 1 hr, then deprotected by trifluoroacetic acid to afford desired catalyst **2** in 72% yield (Scheme 1).^{7b}

Initially, chiral thiourea organocatalysts **2** were examined in the Michael reaction of cyclohexanone **5a** with *trans*-nitrostyrene **6a**. As Table 1 shows, using 10 mol % **2** in the common solvents such as MeOH, THF, CH₂Cl₂, Toluene, EtOH, CH₃CN and H₂O led to the adduct **7a** in low yields (entries 1-8). Our

experiment showed that adducts **7a** was obtained in moderate yields when DMF or DMSO was used as solvent (entries 9 and 10). Interestingly, using dichloromethane (DCE) as solvent improved both the yield and the enantioselectivity (compare

Scheme 1. Synthesis of chiral catalyst **2**

Table 1. Optimization of the Michael reaction of cyclohexanone with *trans*-nitrostyrene^{2a}

Entry	Solvent	Additive	Time (h)	Yield (%)	d.r. ^b	e.e. ^c (%)
1	MeOH	-	36	11	n.d.	n.d.
2	THF	-	36	16	n.d.	n.d.
3	CH ₂ Cl ₂	-	36	22	n.d.	n.d.
4	Toluene	-	36	9	n.d.	n.d.
5	CHCl ₃	-	36	31	n.d.	n.d.
6	EtOH	-	36	21	n.d.	n.d.
7	CH ₃ CN	-	36	33	n.d.	n.d.
8	H ₂ O	-	36	8	n.d.	n.d.
9	DMF	-	36	56	75/25	68
10	DMSO	-	36	68	80/20	74
11	DCE	-	24	80	85/15	80
12	DCE	TFA	24	87	88/12	84
13	DCE	HCO ₂ H	24	86	90/10	86
14	DCE	CH ₃ CO ₂ H	24	87	92/8	90
15	DCE	PhCO ₂ H	24	92	97/3	95

^aUnless otherwise noted, all reactions were carried out in solvent (1 mL) using **5a** (0.14 mL, 5 equiv.) and **6a** (0.25 mmol, 1 equiv.) in the presence of 10 mol % **2** at rt. ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC analysis (chiralpak AS-H).

entries 1-10 with entry 11). Moreover, under the catalysis of **2** and in DCE solvent conditions, the addition of a catalytic amount of TFA resulted in excellent yield and enantiomeric excess (entry 12-15). When HCO₂H or CH₃CO₂H was employed instead of TFA, the little higher yield and enantioselectivity of **7a** was obtained (compare entry 13, 14 with 12). However, the addition of PhCO₂H led to the remarkable improvement of yield and enantioselectivity (compare entry 15 with 12-14). Thus, the optimal reaction conditions were as follows: the reaction was performed at room temperature with DCE as solvent, 10 mol % benzoic acid was employed as an additive and the amount of chiral catalyst **2** was 10 mol %.

Under the optimal conditions, the Michael reactions of nitroolefins with various ketones were examined (Table 2). It was found that chiral catalyst **2** at 10 mol % loading could catalyze the Michael reaction of *trans*-nitroolefins **6a-f** smoothly with cyclohexanone **5a** at room temperature for 20 - 36 h, giving the adducts **7a-f** in moderate to excellent yields (71 - 92%) with excellent diastereoselectivities. The experimental results also demonstrated that for almost all ketones **5a-e**, the chiral catalyst **2** could result in high enantioselectivities (85 - 94% ee) in the nitro-Michael reaction. The absolute configurations of the adducts **7a-j** were determined by comparison with known literature data.^{3d,10} It can be concluded that chiral catalyst **2** is the same as chiral thiourea catalyst **1** which resulted in good yields and excellent enantioselectivities. This can be rationalized as follows: the hydrogens connecting to nitrogen in this catalyst may also coordinate one or two oxygens of nitro group.^{4c-e}

Experiments

¹H NMR and ¹³C NMR spectra were determined in CDCl₃ or CD₃OD on a Bruker ARX-300 (300 MHz) with TMS as internal standard. Mass spectra were recorded by the ESI method with ThermoFisher Scientific LCQ FLEET mass spectrometer. Melting points (mp) were determined with a digital electrothermal apparatus without further correction. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter. The enantiomeric excesses of Michael adducts **6a-i** were determined by chiral HPLC analysis on Waters 600 under the conditions as follows: Chiralpak AS-H column, hexane / *i*-PrOH = 90/10, λ = 238 nm, flow = 0.7 mL/min. Nitroolefins were prepared according to the literature procedures.⁸

Preparation of catalyst 2. To a solution of S-methyl-*N*-nitro-*N*-phthaloylisothiurea (**4**, 3.00 g, 11.3 mmol) in dichloromethane (20 mL) in an ice-cold bath, Aminomethylpyrrolidine (**3**, 2.26 g, 11.3 mmol) in dichloromethane (10 mL) was added dropwise. The mixture was stirred at room temperature for 3 hr. The resulting solid was filtered off and the filtrate was concentrated under reduced pressure.

The above crude product (2.00 g, 6.45 mmol) and 40% MeNH₂ (in MeOH, 1.00 g, 12.9 mmol) in MeOH (10 mL) was stirred at room temperature for 1 hr. The mixture was concentrated to dryness under reduced pressure and the solid was washed with ether (15 mL), and then dried to give BOC protected product as a white solid, which was dissolved in the mixture of trifluoroacetic acid and dichloromethane (10 mL, v/v = 1:2) and the solution was stirred at room temperature for 3 h. Re-

Table 2. Michael reactions of *trans*-nitroolefins with ketones catalyzed by **2**^a

7	Ar	R ₁	R ₂	Time (h)	Yield (%)	d.r. ^b	ee (%) ^c
a	Ph	(CH ₂) ₃	-	24	92	97/3	95
b	4-ClC ₆ H ₄	(CH ₂) ₃	-	28	86	90/10	90
c	4-MeOC ₆ H ₄	(CH ₂) ₃	-	22	83	96/4	93
d	4-BrC ₆ H ₄	(CH ₂) ₃	-	32	80	93/7	94
e	2-Furyl	(CH ₂) ₃	-	20	88	95/5	90
f	2-BrC ₆ H ₄	(CH ₂) ₃	-	24	83	91/9	91
g	Ph	CH ₃	CH ₃	32	77	97/3	92
h	Ph	H	H	36	79	-	86
i	Ph ₄	(CH ₂) ₂	-	36	71	-	88
j	Ph	CH ₃	H	36	72	-	85

^aAll reactions were carried out in toluene (1 mL) using **4** (0.14 mL, 5 equiv.) and **5** (0.25 mmol, 1 equiv.) in the presence of 10 mol % **2** and 10 mol % PhCO₂H at rt. ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC analysis (Chiralpak AS-H).

moval of solvent gave a residue, which was washed with Et₂O (20 mL), and then filtration led to a solid. To the mixture of the solid in CHCl₃ was added saturated aqueous NaHCO₃ to weak basicity. The organic layer was washed with saturated brine (10 mL × 3) and dried over MgSO₄. Concentration and purification by column chromatography (MeOH/CH₂Cl₂) gave catalyst **2**.

White solid; mp 87 - 90 °C; Yield: 72%. ¹H NMR (300 MHz, CD₃OD) δ 3.72 (s, 3H), 3.37-3.29 (m, 2H), 2.81 (s, 3H), 2.27-2.18 (m, 2H), 2.16-1.95 (m, 3H), 1.89-1.74 (m, 2H). ¹³C NMR (75 MHz, CD₃OD) δ 164.6, 59.7, 51.5, 41.6, 29.2, 24.7, 22.5. MS (ESI, positive) *m/z* 202.5 (M+H). Anal. Calcd. for C₇H₁₅N₃O₂: C, 41.78; H, 7.51; N, 34.80. Found: C, 42.01; H, 7.24; N, 34.18.

Michael reaction of ketones 4 with *trans*-nitroolefins 5: General procedure; The mixture of catalyst **2** (6.0 mg, 0.03 mmol), benzoic acid (3.6 mg, 0.03 mmol) and ketone **5** (4.5 mmol) was stirred at room temperature for 5 min, and then nitroolefin **6** (0.3 mmol) was added. After the reaction was completed (monitored by TLC), the mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (petroleum ether/AcOEt as eluent) to give the adduct **7**.

(S)-2-[(R)-2-Nitro-1-phenylethyl]cyclohexanone (6a):⁹ Yield: 92%; [α]_D²⁵ = -18.2 (*c* = 0.63 in CHCl₃); HPLC analysis: *t*_R (minor) = 19.58 min, *t*_R (major) = 30.62 min, 95% ee. ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.20 (m, 3H), 7.18-7.10 (m, 2H), 4.92 (dd, *J* = 4.7, 12.6 Hz, 1H), 4.64 (dd, *J* = 9.9, 12.3 Hz, 1H), 3.74 (dt, *J* = 4.5, 9.9 Hz, 1H), 2.70-2.60 (m, 1H), 2.50-2.29 (m, 2H), 2.15-2.01 (m, 1H), 1.80-1.45 (m, 4H), 1.31-1.20 (m, 1H).

(S)-2-[(R)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone (6b):¹⁰ Yield: 86%; [α]_D²⁵ = -19.7 (*c* = 0.40 in CHCl₃); HPLC analysis: *t*_R (minor) = 43.61 min, *t*_R (major) = 56.54 min, 90% ee. ¹H NMR (300 MHz, CDCl₃) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.98 (dd, *J* = 4.8, 12.8 Hz, 1H), 4.65 (dd,

$J = 10.0, 12.8$ Hz, 1H), 3.80 (dt, $J = 4.4, 10.0$ Hz, 1H), 2.70–2.60 (m, 1H), 2.50–2.34 (m, 2H), 2.15–2.05 (m, 1H), 1.85–1.52 (m, 4H), 1.29–1.23 (m, 1H).

(S)-2-[(R)-1-(4-Methoxyphenyl)-2-nitroethyl]cyclohexanone (6c):⁹ Yield: 83%; $[\alpha]_{\text{D}}^{25} = -16.7$ ($c = 0.30$ in CHCl_3); HPLC analysis: t_{R} (minor) = 37.55 min, t_{R} (major) = 49.98 min, 93% ee. ^1H NMR (300 MHz, CDCl_3) δ 7.10 (dd, $J = 2.4, 9.3$ Hz, 2H), 6.85–6.75 (m, 2H), 4.93 (dd, $J = 4.8, 12.3$ Hz, 1H), 4.61 (dd, $J = 9.9, 12.3$ Hz, 1H), 3.79 (s, 3H), 3.72 (dt, $J = 4.5, 9.9$ Hz, 1H), 2.70–2.58 (m, 1H), 2.55–2.35 (m, 2H), 2.15–2.00 (m, 1H), 1.85–1.49 (m, 4H), 1.30–1.15 (m, 1H).

(S)-2-[(R)-1-(4-Bromophenyl)-2-nitroethyl]cyclohexanone (6d):¹¹ Yield: 80%; $[\alpha]_{\text{D}}^{25} = -27.7$ ($c = 0.43$ in CHCl_3); HPLC analysis: t_{R} (minor) = 27.76 min, t_{R} (major) = 32.84 min, 94% ee. ^1H NMR (300 MHz, CDCl_3) δ 7.46 (d, $J = 8.7$ Hz, 2H), 7.10 (d, $J = 8.1$ Hz, 2H), 4.95 (dd, $J = 4.5, 12.6$ Hz, 1H), 4.60 (dd, $J = 9.9, 12.6$ Hz, 1H), 3.77 (dt, $J = 4.5, 9.9$ Hz, 1H), 2.70–2.50 (m, 1H), 2.48–2.30 (m, 2H), 2.15–2.00 (m, 1H), 1.90–1.49 (m, 4H), 1.32–1.10 (m, 1H).

(S)-2-[(S)-1-(Furan-2-yl)-2-nitroethyl]cyclohexanone (6e):¹¹ Yield: 88%; $[\alpha]_{\text{D}}^{25} = -15.2$ ($c = 0.40$ in CHCl_3); HPLC analysis: t_{R} (minor) = 32.12 min, t_{R} (major) = 39.36 min, 90% ee. ^1H NMR (300 MHz, CDCl_3) δ 7.35 (m, 1H), 6.30 (dd, $J = 1.8, 3.3$ Hz, 1H), 6.15 (d, $J = 3.3$ Hz, 1H), 4.80–4.60 (m, 2H), 3.97 (dt, $J = 4.8, 9.3$ Hz, 1H), 2.80–2.71 (m, 1H), 2.50–2.25 (m, 2H), 2.25–2.00 (m, 1H), 1.95–1.55 (m, 4H), 1.40–1.23 (m, 1H).

(S)-2-[(R)-1-(2-Bromophenyl)-2-nitroethyl]cyclohexanone (6f):¹¹ Yield: 83%; $[\alpha]_{\text{D}}^{25} = -12.7$ ($c = 0.31$ in CHCl_3); HPLC analysis: t_{R} (minor) = 28.37 min, t_{R} (major) = 34.70 min, 91% ee. ^1H NMR (300 MHz, CDCl_3) δ 7.49 (dd, $J = 1.2, 8.1$ Hz, 1H), 7.25–7.15 (m, 2H), 7.08–7.00 (m, 1H), 4.85–4.70 (m, 2H), 4.30–4.20 (m, 1H), 2.80 (m, 1H), 2.35–2.25 (m, 2H), 2.05–1.97 (m, 1H), 1.75–1.45 (m, 4H), 1.30–1.26 (m, 1H).

(4S, 5R)-4-Methyl-6-nitro-5-phenylhexan-3-one (6g):⁹ Yield: 77%; $[\alpha]_{\text{D}}^{20} = 28.6$ ($c = 0.40$ in CHCl_3); HPLC analysis: t_{R} (minor) = 21.59 min, t_{R} (major) = 26.64 min, 92% ee. ^1H NMR (300 MHz, CDCl_3) δ 7.35–7.20 (m, 3H), 7.18–7.10 (m, 2H), 4.75–4.55 (m, 2H), 3.68 (dt, $J = 4.8, 9.3$ Hz, 1H), 3.05–2.95 (m, 1H), 2.70–2.55 (m, 1H), 2.45–2.35 (m, 1H), 1.06 (t, $J = 7.2$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H).

(R)-5-Nitro-4-phenylpentan-2-one (6h):^{3d} Yield: 79%; $[\alpha]_{\text{D}}^{25} = -22.8$ ($c = 0.51$ in CHCl_3); HPLC analysis: t_{R} (minor) = 41.19 min, t_{R} (major) = 47.07 min, 86% ee. ^1H NMR (300 MHz, CDCl_3) δ 7.40–7.20 (m, 5H), 4.71 (dd, $J = 6.9, 12.3$ Hz, 1H), 4.62 (dd, $J = 7.5, 12.3$ Hz, 1H), 4.05–3.95 (m, 1H), 2.91 (d, $J = 6.9$ Hz, 2H), 2.15 (s, 3H).

(S)-2-[(R)-2-Nitro-1-phenylethyl]cyclopentanone (6i):¹¹ Yield: 71%; $[\alpha]_{\text{D}}^{25} = -19.7$ ($c = 0.60$ in CHCl_3); HPLC analysis: t_{R} (minor) = 35.24 min, t_{R} (major) = 42.28 min, 88% ee. ^1H NMR (300 MHz, CDCl_3) δ 7.40–7.25 (m, 3H), 7.25–7.11 (m, 2H), 5.33 (dd, $J = 5.7, 12.9$ Hz, 1H), 4.71 (dd, $J = 10.2, 12.6$ Hz, 1H), 3.75–3.64 (m, 1H), 2.45–2.30 (m, 2H), 2.25–2.05 (m, 1H), 2.00–1.80 (m, 2H), 1.78–1.55 (m, 1H), 1.53–1.35 (m, 1H).

(R)-6-Nitro-5-phenylhexan-3-one (6j):¹¹ Yield: 72%; $[\alpha]_{\text{D}}^{25} = -10.12$ ($c = 0.35$ in CHCl_3); HPLC analysis: t_{R} (minor) = 17.37 min, t_{R} (major) = 24.15 min, 85% ee. ^1H NMR (300 MHz, CDCl_3)

δ 7.35–7.25 (m, 3H), 7.24–7.20 (m, 2H), 4.75–4.54 (m, 2H), 4.08–3.99 (m, 1H), 2.89 (d, $J = 7.2$ Hz, 2H), 2.45–2.31 (m, 2H), 1.02 (t, $J = 7.2$ Hz, 3H).

Conclusions

In conclusion, we have synthesized a new chiral catalyst **2**. It was found that catalyst **2** could catalyze the asymmetric Michael reaction of ketones with nitroolefins smoothly at room temperature, giving the desired adduct **7a-j** in 71–92% yields with excellent diastereoselectivities (*syn/anti* = 90/10–97/3) and enantioselectivities (up to 95% ee).

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