Asymmetric Michael Addition of Aromatic Ketones to Nitroolefins Catalyzed by Simple Chiral Bifunctional Primary Amine-Thioureas

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Abstract: Simple chiral primary amine-thiourea catalysts derived from chiral 1,2-diphenylethylenediamine were found to catalyze direct Michael addition of aromatic ketones to nitroolefins with good enantioselectives (up to 86% ee) and excellent yields (up to 97%) for a broad range of substrates and successfully used in the preparation of (R)-Balcofen.

Keywords: Organocatalyst, Michael addition, aromatic ketones, nitroolefins, primary-amine thiourea.

INTRODUCTION

Michael addition reaction is proved as one of the most powerful C-C bond forming reactions, which plays a very important role in organic synthesis [1]. Conjugate addition of carbon-centered nucleophiles to nitroalkenes represents a direct and most appealing approach to nitroalkanes which could undergo variant transformations, such as α-alkylation, reduction to amino-containing compounds, and Nef. reaction (the conversion of nitroalkanes into the corresponding carbonyl compounds in the presence of acid) to aldehydes and ketones [2]. Direct asymmetric Michael addition of ketones and aldehydes to activated olefins has received considerable interests in recent years due to its atom economy and flexible operation conditions [3], in particular with the development of organocatalysts [4] since List and Barbas first reported the proline promoted aldol reactions [5].

Actually, impressive progresses have been made in the development of small molecular thiourea bifunctional catalysts [6]. Secondary amine thiourea catalysts are proved to be effective to Michael addition of aliphatic ketones and aldehydes to nitroolefins through enamine [7] and hydrogen bond activation [8]. However, the applications of aromatic ketones as direct nucleophilic donors still remain limited due to their lower activities and stereotically bulky hindrance. Only very few examples have been presented [9]. Jacobsen's group first reported chiral primary amine-thiourea catalysts promoted asymmetric addition of acetophenone to nitrostyrene [9b], while no further substrate scope of aromatic ketones was investigated. Later, Ma's group designed and synthesized a new class of saccharide-substituted primary amine–thiourea bifunctional catalysts [9a] by four steps, and used as efficient organocatalysts (up to 99% yield and 97% ee) for the asymmetric Michael addition of aromatic ketones to nitroolefins. Very recently, Feng and co-workers [9g] also reported a new class of chiral primary-secondary diamine catalysts derived from bispidine and their applications in the same addition in high yields and enantioselectivities.

Herein, we wish to report a very simple kind of primary amine-thiourea bifunctional catalysts represented by catalyst **2** shown in Fig. (**1**), just prepared by simple reaction of chiral 1,2-Diphenylethylenediamine with isothiocyanate, as an efficient bifunctional catalyst for the direct asymmetric Michael addition of a broad spectrum of aromatic ketones with nitroolefins in good enantioselectivities (up to 86% ee) and excellent yields (up to 97%). To the best of our knowledge, this simple primary amine thiourea catalyst has not attracted enough attention except one case recently reported by Melchiorre [10]. During the preparation of this manuscript, Wu's group reported the same chiral primary amine-thiourea **2** as an efficient catalyst for the analogous addition of aromatic ketones to more conjugated nitrodienes [9i], and before this submission of our work, Xu's group reported the analogous results [9j].

RESULT AND DISCUSSION

In the initial study, primary amine-thiourea catalysts **1** and **2** were tested for the Michael addition of acetophenone to nitrostyrene in the presence of acid additive in dichloromethane and the results are summarized in Table **1**. The addition was performed in the presence of 20 mol % of catalyst **2** and 20 mol% of 4-nitrobenzoic acid and afforded 69% yield and 77% ee (entry 4), while catalyst **1** gave only 25% yield and 69% ee (entry 2). To improve yield and enantioselectivity, a series of solvents were investigated (Table **1**). In general, the enantioselectivity was slightly higher in aprotic solvents (entries 4-8, 13, 14) than in protic solvents (entries 10, 12). In *i*-PrOH, excellent yield (89%) and good enantioselectivity (74% ee) were obtained (entry 10). This asymmetric Michael addition was also performed in pure water [9g, 11] and moderate yield and enantioselectivity (entry 12) were obtained even though nitrostyrene is slightly soluble in water. A survey of solvents

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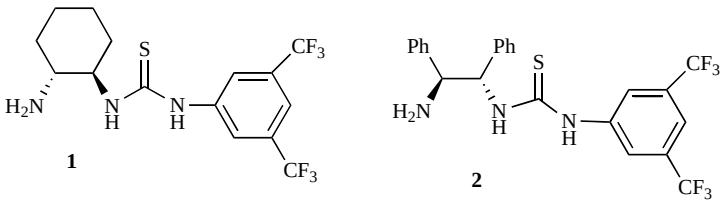
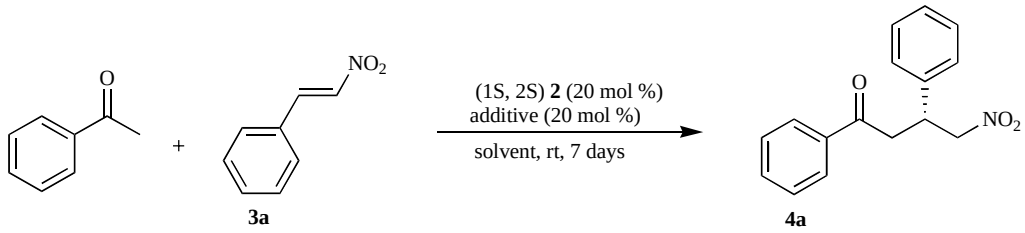


Fig. (1). Chiral primary amine-thiourea bifunctional catalyst.

Table 1. Asymmetric Michael Addition of Acetophenone to Nitrostyrene[a]



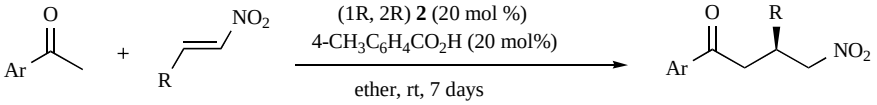
Entry	Cat.	Additive	Solvent	Yield(%)[b]	ee(%)[c]
1	1	TFA	DCM	N.D.[d]	N.D.[d]
2	1	4-$NO_2C_6H_4CO_2H$	DCM	25	69(S)
3	2	TFA	DCM	N.D.[d]	N.D.[d]
4	2	4-$NO_2C_6H_4CO_2H$	DCM	69	77(R)
5	2	4-$NO_2C_6H_4CO_2H$	$CHCl_3$	65	84(R)
6	2	4-$NO_2C_6H_4CO_2H$	Cyclohexane	27	75(R)
7	2	4-$NO_2C_6H_4CO_2H$	Toluene	45	80(R)
8	2	4-$NO_2C_6H_4CO_2H$	o-Xylene	45	80(R)
9	2	4-$NO_2C_6H_4CO_2H$	CH_3CN	35	69(R)
10	2	4-$NO_2C_6H_4CO_2H$	i-PrOH	89	74(R)
11	2	4-$NO_2C_6H_4CO_2H$	DMF	12	29(R)
12	2	4-$NO_2C_6H_4CO_2H$	H_2O	52	72(R)
13	2	4-$NO_2C_6H_4CO_2H$	THF	26	83(R)
14	2	4-$NO_2C_6H_4CO_2H$	Et_2O	70	80(R)
15	2	4-$NO_2C_6H_4CO_2H$	Et_2O	25	85(R)[e]
16	2	HCO_2H	Et_2O	12	84(R)
17	2	$C_6H_5CH_2CO_2H$	Et_2O	93	83(R)
18	2	4-$CH_3C_6H_4CO_2H$	Et_2O	97	82(R)
19	2	4-$OHC_6H_4CO_2H$	Et_2O	91	82(R)
20	2	3-$OHC_6H_4CO_2H$	Et_2O	80	79(R)
21	2	2-$OHC_6H_4CO_2H$	Et_2O	89	78(R)
22	2	4-$ClC_6H_4CO_2H$	Et_2O	95	79(R)
23	2	$HO_2CC_6H_4CO_2H$	Et_2O	45	83(R)
24	2	$PhCO_2H$	Et_2O	87	80(R)

[a]The reaction was conducted with 0.02 mmol (0.2 eq) of (1S, 2S) **2**, 0.1 mmol (1 eq) of nitrostyrene, 0.5 mmol (5 eq) of acetophenone and 0.02 mmol (0.2 eq) of additive in 0.5 mL ether for seven days at room temperature.
[b]Isolated yield.
[c]The ee values were determined by HPLC and the configuration was assigned by comparison of retention time and specific rotation with the literature [9a].
[d]Not Determinated.
[e]4Å MS added.

in Table **1** indicated that ether is a suitable candidate for the addition of acetophenone to nitrostyrene. In ether, catalyst **2** afforded 70% yield and 80% ee (entry 14). To further improve the yield and enantioselectivity, several additives were also investigated. The additives have obvious effects on the yields of the Michael adducts. When strong acids, typically TFA used as additive (entries 1, 3), no desired product was observed. Satisfyingly, the reaction was performed smoothly in ether in the presence of 20 mol% of catalyst **2** and 20 mol% of 4-methylbenzoic acid and 97% yield, 82% ee (entry 18) were obtained. Benzoic acid could also give a satisfying result with 93% yield and 83% ee (entry 17). Other reaction parameters such as amount of acetophenone were also investigated, but no superoir results were obtained. Decreasing temperature to zero centigrade slightly increased enantioselectivity, while the reaction rate and the desired yield were dramatically decreased. The addition of 4 Å MS, generally exerting extra active effects in analogous system [9e], has negative effect on the yield (only 25%), even though the enantioselectivity was slightly increased (entry 15). Through extensive screening, the optimized reaction conditions were found to be 20 mol% of catalyst **2** and 20 mol% of 4-methylbenzoic acid, 5 eq. acetophenone, and ether as a solvent at room temperature.

The optimal protocol was expanded to a variety of aromatic ketones and nitroolefins and the results are shown in Table **2**, excellent yields (up to 97%) and good enantioselectivities (73-86% ee) were obtained. The electronic properties and steric hindrance of the substituents on the aromatic ring of nitroolefins have no obvious effects on the enantioselectivities (entries 1-12), but greatly affected the yields. Generally, higher yields were obtained with nitroolefins bearing electron-withdrawing substituents (entries 5-11) than those bearing electron-donating groups (entries 2-4). The reaction was obviously detarted (34% yield) when 3,4,5–trimethoxy nitrostyrene used as acceptor (entry 3). Good enantioselectivities (82-86% ee) were obtained for a broad spectrum of nitrolefins bearing electron-withdrawing or donating groups. The positions of

Table 2. Scope of Substrates[a]



3 **4**

Entry	Ar	R	Yield(%)[b]	ee(%)[c]
1	Ph	Ph	4a-97	82(R)[d]
2	Ph	4-$CH_3C_6H_4$	4b-78	86(S)
3	Ph	3,4,5-tri-$CH_3OC_6H_4$	4c-34	86(S)
4	Ph	4-$CH_3OC_6H_4$	4d-68	81(S)
5	Ph	4-ClC_6H_4	4e-95	84(S) (99)[e]
6	Ph	4- ClC_6H_4	4e-92	85(R)[d](99)[e]
7	Ph	2-ClC_6H_4	4f-80	82(S)
8	Ph	2-BrC_6H_4	4g-93	85(S)
9	Ph	4-BrC_6H_4	4h-92	83(S)
10	Ph	3-FC_6H_4	4i-90	83(S)
11	Ph	4-FC_6H_4	4j-90	85(S)
12	Ph	1-naphthyl	4k-53	82(S)
13	4-$CH_3C_6H_4$	Ph	4l-77	82(S)
14	4-$CH_3OC_6H_4$	Ph	4m-85	82(S)
15	4-ClC_6H_4	Ph	4n-54	83(S)
16	3-ClC_6H_4	Ph	4o-76	73(S)
17	4-BrC_6H_4	Ph	4p-86	80(S)
18	3-BrC_6H_4	Ph	4q-81	75(S)
19	4-FC_6H_4	Ph	4r-58	82(S)
20	2-naphthyl	Ph	4s-87	74(S)

[a]The reaction was conducted with 0.04 mmol (0.2 eq) of (1R,2R) **2**, 0.2 mmol (1 eq) of nitrostyrene, 1.0 mmol (5 eq) of acetophenone and 0.04 mmol (0.2 eq) of additive in 1.0 mL ether for seven days at room temperature.
[b]Isolated yield.
[c]The ee values were determined by HPLC and and the configuration was assigned by comparison of retention time and specific rotation with the literature [9a,9g,9h].
[d](1S,2S) **2** was used.
[e]after single recrystallization(see supporting information).

substituents on nitroolefins were also tested. Whether para, meta or ortho electron–withdrawing substituted nitroolefins used, good enantioselectivities and yields (entries 5-11) were obtained in each case. Furthermore, the scope of other aromatic ketones was also screened. It was found that various aromatic methyl ketones may take part in this addition and afford good yields (54-87 %) and enantioselectivities (73-83% ee) (entries 13-20). Aromatic ketones with electron-donating sbustitutents (entries 13, 14) exhibited comparable or even better enantioselectivities than those with electron withdrawing substituents (entries 15-19). The position of the substitutented group of the aromatic ketones obviously affected the enantioselectivities (entries 15-18). To the best of all, even the bulky β-acetonaphone could also smoothly react and afford satisfying results (entry 20).

Importantly, we have sensed the applications and significances of our process in specific chiral pharmaceuticals or related intermediates because of their generallity and representations, and especially, most of the target products are solid and can be easily recrystallized to afford enantiopure ones. All this may provide mutiple approaches and choices for chiral pharmaceutical preparations. Typically, the optical pure enantiomer of (R)-**4e** with 85% ee (entry 6, Table **2**) can be easily purified after single recrystallization from EtOAc-hexane (1:20) with good yield and (R)-baclofen may be synthesized by further Baeyer-Villiger oxidation and reduction according to the literature [12] as outlined in Scheme **1**. Notably, in the same way, the optical pure (S)-baclofen enantiomer could also be prepared.

In conclusion, we have found a very simple kind of bifuntional primary amine-thiourea catalysts derived from chiral 1,2-diphenylethylenediamine can effectively catalyze the direct Michael addition of aromatic ketones to nitroolefins with a broad spectrum of substrates in excellent yields (up to 97%) and good enantioselectivities (up to 86% ee). This may provide multiple approaches and choices for chiral pharmaceutical preparations. Applications of our catalytic system and the efficacy of the cataylsts in other asymmetric reactions are going on in our laboratory.

EXPERIMENTAL SECTION

General

All regents were obtained from commercial supplier without further purification. Commercial grade solvent was dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz (Bruker Avance). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0 ppm) for ^{13}C NMR spectroscopy. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. High-resolution mass spectra were obtained with the micrOTOF-QⅡ10203 mass spectrometer. Recations were monitored by TLC and visualized with ultraviolet light. Enantiomeric excess was determined by HPLC analysis on chiralpak AD-H or whelk-01 columns. IR spectra were recorded on a ThermoFisher Nicolet Avatar 360 FTIR spectrometer on a KBr beamsplitter. Optical rotations were measured at 589 nm at 20 ^{o}C.

General Procedure for Asymmetric Michael Addition of Aryl Ketones to Nitroolefins

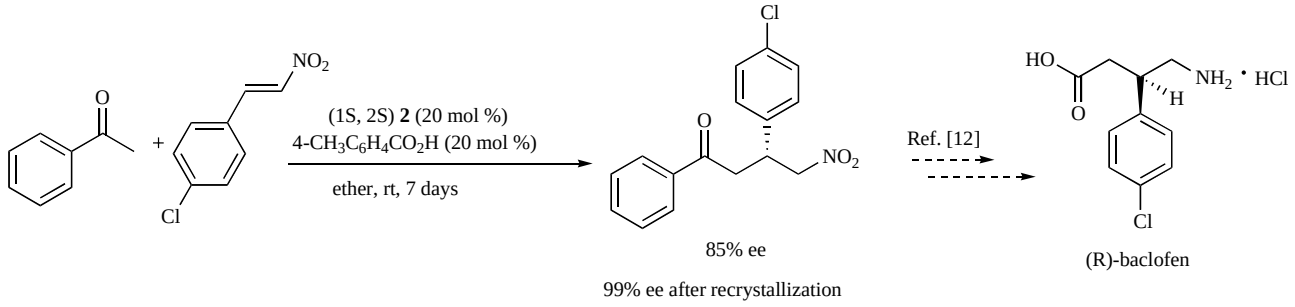
Aromatic ketone (1.0 mmol, 5 equiv), nitroolefin (0.2 mmol, 1equiv), **2** (0.04 mmol, 0.2 equiv), and 4-$CH_3C_6H_4CO_2H$ (0.04 mmol, 0.2 eq) were stirred in 1.0 mL ether at room temperature for seven days. The reaction was monitored by TLC analysis. After flash chromatography on silica gel (petroleum petroleum/EtOAc), the corresponding product **4** was obtained. **4a, 4b, 4d-4g, 4j-4n, 4p, 4r, 4s** were known compounds [9a, 9g, 9h].

Compound (S)-4c

White solid; 34% yield;^{1}H NMR (300 M, $CDCl_3$): δ 7.93 (d. *J* = 7.2 Hz, 2H), 7.61-7.56 (m, 1H), 7.49-7.44 (m, 2H), 6.46 (s, 2H), 4.83 (dd, *J* = 12.6, 6.6 Hz, 1H), 4.68 (dd, *J* = 12.6, 8.1 Hz, 1H), 4.19-4.14 (m, 1H), 3.91 (s, 6H), 3.81 (s, 3H) 3.45-3.40 (m, 2H); ^{13}C NMR (75 M, $CDCl_3$): δ 196.9, 153.5, 136.4, 134.7, 133.6, 128.7, 127.9, 126.4, 104.6, 79.4, 60.7, 56.2, 41.6, 39.7 ppm. IR (KBr): ν 3342, 3004, 2925, 2846, 1678, 1591, 1540, 1513, 1460, 1422, 1378, 1365, 1322, 1276, 1246, 1129, 1000, 831, 696 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{19}H_{21}NNaO_6$ ($[M+Na]^+$) = 382.1261, Found 382.1261.

Compound (S)-4h

White solid; 92% yield; ^{1}H NMR (300 M, $CDCl_3$): δ 7.92 (d, *J* = 12 Hz, 2H), 7.58-7.55 (m, 1H), 7.48-7.43 (m, 4H), 7.18-7.16 (m, 2H), 4.82 (dd, *J* = 12.6, 6.3 Hz, 1H), 4.66 (dd,



Scheme 1. Enantioseletive synthesis of (R)-baclofen.

J = 12.6, 9.0 Hz, 1H), 4.25-4.15 (m, 1H) 3.44-3.41 (m, 2H); ^{13}C NMR (75M, $CDCl_3$): δ 196.4, 138.1, 136.2, 133.6, 132.1, 129.2, 128.8, 127.9, 121.8, 79.2, 41.3, 38.7 ppm. IR(KBr): ν 3349, 3083, 2958, 2921, 1683, 1537, 1488, 1424, 1371, 1269, 1231, 1010, 825, 771, 753, 690, 628, 571 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{16}H_{14}BrNNaO_3$ ($[M+Na]^+$) = 370.0052, Found 370.0049.

Compound (S)-4i

White solid; 90% yield; ^{1}H NMR (300 M, $CDCl_3$): δ 7.93 (d. *J* = 7.5 Hz, 2H), 7.58-7.56 (m, 1H), 7.49-7.43 (m, 2H), 7.31-7.26 (m, 1H), 7.09-6.97 (m, 3H), 4.84(dd, *J* = 12.6, 6.6 Hz, 1H), 4.68 (dd, *J* = 12.6, 8.1 Hz, 1H), 4.29-4.21 (m, 1H), 3.49-3.42 (m, 2H).^{13}C NMR (300 M, $CDCl_3$): δ 196.4, 164.6, 141.6, 136.2, 133.6, 130.7, 129.1, 128.7, 127.9, 123.2, 115.0, 79.2, 41.3, 38.9 ppm. IR (KBr): ν 3361, 3062, 2919, 1687, 1614, 1546, 1487, 1449, 1368, 1269, 1225, 1149, 1002, 893, 794, 701, 685, 624 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{16}H_{14}FNNaO_3$ ($[M+Na]^+$) = 310.0853, Found 310.0850.

Compound (S)-4o

Oil; 76% yield; ^{1}H NMR (300 M, $CDCl_3$): δ 7.87-7.77 (m, 2H), 7.52-7.26 (m, 7H), 4.82 (dd, J = 12.3, 6.9 Hz, 1H), 4.69 (dd, *J* = 12.3, 7.8 Hz, 1H), 4.26-4.17 (m, 1H), 3.48-3.36 (m, 2H) ppm; ^{13}C NMR (300 M, $CDCl_3$): δ 195.6, 138.8, 137.9, 135.1, 133.4, 130.0, 129.1, 128.1, 127.9, 127.6, 126.0, 79.4, 41.6, 39.2 ppm. IR (KBr): ν 3066, 3031, 1689, 1551, 1454, 1425, 1378, 1203, 1078, 999, 784, 765, 700, 680 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{16}H_{14}ClNNaO_3$ ($[M+Na]^+$) = 326.0560, Found 326.0554.

Compound (S)-4q

Oil; 81% yield; ^{1}H NMR (300 M, $CDCl_3$): δ 8.03 (s, 1H), 7.84-7.67 (m, 2H), 7.36-7.26 (m, 6H), 4.82 (dd, *J* = 12.3, 6.9Hz, 1H), 4.69 (dd, *J* = 12.3, 7.5Hz, 1H), 4.26-4.16 (m, 1H),3.43-3.41 (m, 2H) ppm; ^{13}C NMR (300 M, $CDCl_3$): δ 195.5, 138.8, 138.0, 136.4, 131.1, 130.3, 129.1, 127.9, 127.4, 126.5, 123.0, 79.4, 41.6, 39.2 ppm. IR (KBr): ν 3064, 3031, 2917, 1688, 1551, 1422, 1378, 1224, 1201, 1068, 955, 783, 763, 700, 680 $cm.^{-1}$ HRMS (ESI-TOF) calcd for $C_{16}H_{14}BrNNaO_3$ ($[M+Na]^+$) = 370.0043, Found 370.0049.

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