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Enantio- and diastereoselective Michael addition reactions of α-cyanoketones to nitroalkenes catalyzed by binaphthyl-derived organocatalyst

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ABSTRACT

The catalytic enantioselective and diastereoselective Michael addition reactions promoted by chiral bifunctional organocatalysts are described. The treatment of α-cyanoketones with nitroalkenes under mild reaction conditions afforded the corresponding γ-niro α-cyanoketones with excellent diastereoselectivities (up to *syn*/*anti* >99/1) and excellent enantioselectivities (up to 99% ee).

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One of the ultimate goal and challenges in organic synthesis is the development of catalytic asymmetric construction of highly functionalized organic molecules containing an all-carbon quaternary stereogenic center by asymmetric catalysis.[1] The Michael addition reaction is widely recognized as one of the most general and versatile methods for formation of C–C bonds in organic synthesis,[2] and the development of enantioselective catalytic protocols for this reaction has been a subject of intensive research.[3] In addition to the great success catalyzed by metal complexes, the powerful and environmentally friendly organocatalyst-mediated asymmetric Michael reaction has been explored intensively in recent years.[4,5] Michael reaction of nucleophiles to nitroalkenes represents a direct and most appealing approach to chiral nitroalkanes that are versatile intermediates in organic synthesis, which can be transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen etc.[6] Extensive studies have been devoted to the development of asymmetric conjugate addition using α-substituted 1,3-dicarbonyl compounds as pronucleophiles for the construction of an quaternary stereogenic center.[7] However, related transformations using α-cyanocarbonyl compounds have been less explored.[8,9] The rich chemistry of functional group interconversion of nitriles allows for the elaboration of the conjugate addition products. Recently, Deng, Shibasaki and our groups have reported a highly enantio- and diastereoselective Michael or Mannich reaction of α-cyanoketones, catalyzed by chiral metal complexes and organocatalysts.[10] Although a number of catalytic enantioselective Michael additions of various active methines to nitroalkenes have reported, up to now there is one example of Michael additions α-cyanoketones to nitroalkenes was reported by Lu with moderate enantiselectivity.[11] This addition reaction could provide a highly attractive, convergent approach toward optically active γ-amino nitriles and γ-amino carbonyl compounds. Bifunctional organocatalysts possessing a combination of hydrogen-bonding donors and chiral tertiary amines have been developed for activation of both electrophilic and nucleophilic components. They have emerged as powerful tools for the enantioselective formation of carbon–carbon bond and carbon–heteroatom bonds.[4]

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[12] we recently reported chiral amine-thiourea **I** (Fig. 1) to be a highly selective catalyst for the enantioselective Michael addition reaction of active methines.[13] Herein, we wish to describe the direct enantioselective Michael addition reaction of α-cyanoketones with nitroalkenes catalyzed by using bifunctional organocatalysts bearing both central and axial chiral elements.

To determine suitable reaction conditions for the catalytic enantioselective Michael addition reaction of α-cyanoketones, we initially investigated the reaction system with 2-cyano-1-indanone (**1a**) and nitrostyrene (**2a**) in the presence of 10 mol % of catalyst in toluene at room temperature. We first examined the impact of the structure of catalysts **I**–**VI** on enantioselectivities (15–75% ee, Table 1, entries 1–6). The best results have been obtained with catalyst **VI**. These results indicate that the strength and steric hindrance of the multiple hydrogen-bonding donor may play

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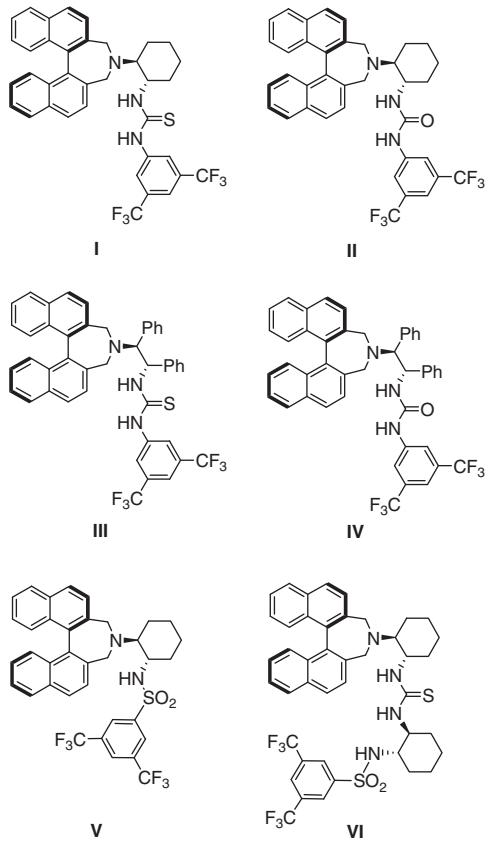
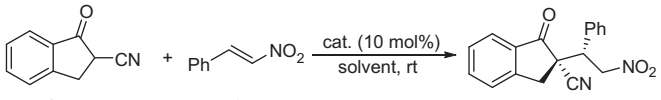


Figure 1. Structures of chiral binaphthyl-derived organocatalysts.

Table 1
Optimazation of the reaction conditions



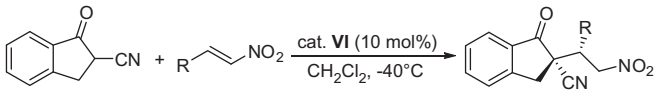
1a 2a 3a

Entry	Cat.	solvent	Time (h)	Yield[a] (%)	dr[b] (%)	Ee[c] (%)
1	**I**	Toluene	1	95	56:44	40
2	**II**	Toluene	1	98	67:33	15
3	**III**	Toluene	1	93	70:30	67
4	**IV**	Toluene	1	95	60:40	58
5	**V**	Toluene	3	92	52:48	30
6	**VI**	Toluene	1	95	68:32	75
7	**VI**	CH_3CN	7	87	56:44	37
8	**VI**	THF	3	89	65:35	43
9	**VI**	CH_2Cl_2	2	95	74:26	79
10	**VI**	CH_2Br_2	2	95	63:37	79
11	**VI**	DCE	2	93	70:30	79
12[d]	**VI**	CH_2Cl_2	11	98	90:10	89
13[e]	**VI**	CH_2Cl_2	11	98	97:3	97

[a] Combined yield of both diastereomers.
[b] Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis.
[c] Enantiopurity of major diastereomer was determined by HPLC analysis using a chiralpak IB column.
[d] This reaction was carried out at −20 °C.
[e] This reaction was carried out at −40 °C.

important roles in the catalytic activity and the level of enantioselectivity achieved.[14] Concerning the solvent (entries 6–11), the use of halogenated solvents gave the best results in the yield and the enantiomeric excess (entries 9–11). Lowering the temperature to

Table 2
Variation of the nitroalkenes **2**



1a 2 3

Entry	**2**, R	Time (h)	Yield[a] (%)	dr[b] (%)	Ee[c] (%)
1	**2a**, C_6H_5	11	**3a**, 98	97:3	97
2	**2b**, 4-FC_6H_4	24	**3b**, 95	98:2	97
3	**2c**, 4-ClC_6H_4	24	**3c**, 98	93:7	97
4	**2d**, 2-ClC_6H_4	42	**3d**, 97	72:28	95
5	**2e**, 4-BrC_6H_4	24	**3e**, 98	94:6	97
6	**2f**, 2-BrC_6H_4	40	**3f**, 97	68:32	95
7	**2g**, 4-MeC_6H_4	24	**3g**, 98	96:4	97
8	**2h**, 4-$MeOC_6H_4$	24	**3h**, 98	96:4	97
9	**2i**, 3-$NO_2C_6H_4$	12	**3i**,, 90	96:4	97
10	**2j**, 2-$NO_2C_6H_4$	40	**3j**, 97	70:30	93
11	**2k**, 2-furyl	54	**3k**, 90	86:14	92
12	**2l**, 2-thienyl	10	**3l**, 97	90:10	95
13	**2m**, 1-naphthyl	10	**3m**, 96	98:2	95
14	**2n**, $PhCH_2CH_2$	10	**3n**, 93	97:3	93
15	**2o**, *i*-Bu	12	**3o**, 97	97:3	91
16	**2p**, *n*-Bu	94	**3p**, 95	99:1	93

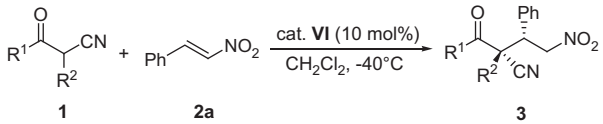
[a] Combined yield of both diastereomers.
[b] Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis.
[c] Enantiopurity of major diastereomer was determined by HPLC analysis using chiralpak IA (for **3b**, **3h**, and **3j**) and IB (for **3a**, **3c**–**g**, **3i**, **3k**, and **3l**–**p**) columns.

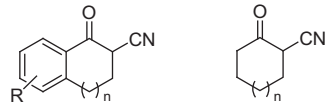
−40 °C with catalyst **VI** improved the diastereoselectivity (*syn*/*anti* = 97/3) and enantioselectivity (97% ee, entry 13). We then explored the possibility of using a wide range of nitroalkene derivatives **2** with α-cyanoketone **1a** in the presence of 10 mol % of catalyst **VI** in THF −40 °C (Table 2). A range of electron-donating and withdrawing substitutions on the aryl ring of the nitrostyrenes **2b**–**j** provided reaction products in high yields (90–99%), high to excellent diastereoselectivities (*syn*/*anti* = 68/32–99/1), and excellent enantioselectivities (92–97%). *meta*- and *para*-substituted nitrostyrenes gave excellent diastereoselectivities. However, *ortho*-substituted nitrostyrenes gave moderate diastereoselectivities. Heteroaryl- and naphthyl-substituted nitroalkenes **2k**–**m** provided products with high selectivity (entries 11–13). The aliphatic nitroalkenes system, including 1-nitro-4-phenyl-1-butene (**2n**) and 4-methyl-1-nitropent-1-ene (**2o**), and 1-nitrohexene (**2p**), was also acceptable starting materials and provided corresponding Michael adducts with high yields and excellent enantioselectivities (entries 14–16).

To examine the generality of the catalytic enantioselective Michael addition reaction of α-cyanoketones **1** by using chiral bifunctional organocatalyst **VI**,[16] we studied the Michael addition reaction of various α-cyanoketones **1b**–**i** with nitrostyrene (**2a**). As it can be seen by the results summarized in Table 3, the corresponding γ-nitro-α-cyanoketones **3q–x** were obtained in excellent yields and enantioselectivities. The cyclic α-cyanoketones **1a–g**, with cyclic aromatic ketones **1a–d**, and cyclic aliphatic ketones **1e–g**, reacted with nitrostyrene (**2a**) to give the corresponding γ-nitro-α-cyanoketones **3a–q** in 95–98% yields and 92–99% ee (Table 3, entries 1–7). Acyclic α-cyanoketones **1h–i** reacted with nitrostyrene (**2a**) to afford the γ-nitro-α-cyanoketones **3r–o** with 95 and 85% ee (Table 3, entries 8–9). The absolute configuration of adducts **3** has been determined for some derivatives by comparison of their optical and HPLC properties with literature values.[11]

To determine the absolute configuration of the generated stereogenic center by chemical correlation, the Michael adduct **3a** was readily converted into the corresponding methyl ester **4a** without loss of enantioselectivity (Scheme 1). The absolute configuration of **4a** was established by comparison of the optical rotation and chiral HPLC analysis with previously reported values.[11,15]

Table 3
Variation of the α-cyanoketones **1**

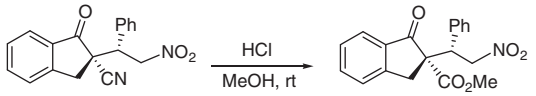




1a : n = 0, R = H
1b : n = 0, R = 5-MeO
1c : n = 0, R = 5,6-$(MeO)_2$
1d : n = 1, R = H
1e : n = 0
1f : n = 1
1g : n = 2
1h : R^1 = Ph, R^2 = Ph
1i : R^1 = Me, R^2 = Ph

Entry	1	Time (h)	Yield[a] (%)	dr[b] (%)	Ee[c] (%)
1	**1a**	11	**3a**, 98	97:3	97
2	**1b**	24	**3q**, 95	95:5	97
3	**1c**	24	**3r**, 98	97:3	97
4	**1d**	42	**3s**, 97	98:2	99
5	**1e**	24	**3t**, 98	>99:1	99
6	**1f**	40	**3u,** 97	90:10	95
7	**1g**	24	**3v**, 98	>99:1	92
8[d]	**1h**	24	**3w**, 98	79:21	95
9	**1i**	24	**3x**, 89	80:20	85

[a] Combined yield of both diastereomers.
[b] Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis.
[c] Enantiopurity of major diastereomer was determined by HPLC analysis using chiralpak AD–H (for **3u**), IA (for **3v**–**x**), IB (for **3a** and **3q**–**r**), IC (for **3s**), and chiralcel OD–H (for **3t**) columns.
[d] This reaction was carried out at −70 °C.



Scheme 1. Determination of the absolute configuration of **3a** by chemical correlation: synthesis of the known **4a**.

In conclusion, we have developed a highly efficient catalytic enantioselective Michael addition reaction of α-cyanoketones using chiral bifunctional organocatalyst bearing multiple hydrogen-bonding donors. The desired γ-nitro-α-cyanoketones were obtained in good to high yields, and excellent enantioselectivities (up to 99% ee) were observed for all the substrates examined in this work. We believe that this method provides a practical entry for the preparation of chiral γ-nitro-α-cyanoketone derivatives. Further study of these new bifunctional organocatalysts in other asymmetric reactions is being under investigation.

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16. *Synthesis of bifunctional organocatalyst* ***VI***: To a solution of *N*-((1*S*,2*S*)-2-aminocyclohexyl)-3,5-bis(trifluoromethyl)benzene-sulfonamide (185 mg, 0.6 mmol) in anhydrous THF (2 mL) was added (*R*)-4-((1*S*,2*S*)-2-isothiocyanatocyclohexyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1′,2′-e]azepine (217 mg, 0.5 mmol). The mixture was stirred at room temperature for 60 h and then it was concentrated in vacuo. The residue was purified by column chromatography (EtOAc–Hexane, 1:5) to give catalyst **VI** (129 mg, 32%) as a yellow solid. $[\alpha]_D^{26} = -71.46$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–1.90 (m, 16H), 2.46–2.59 (m, 2H), 3.17–3.26 (m, 1H), 3.58–3.75 (m, 4H), 4.00–4.17 (m, 1H), 6.33 (br s, 1H), 7.17–7.33 (m, 4H), 7.40–7.62 (m, 4H), 7.90–7.98 (m, 4H), 8.06 (s, 1H), 8.45 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.0, 24.3 (×2), 25.1, 26.9, 29.6, 28.6, 32.6, 33.2, 34.0, 51.2 (×2), 56.5, 60.1, 68.0, 122.6 (q, J_{C-F} = 271.7 Hz), 125.7, 125.9, 127.0, 127.4, 128.1, 128.8, 131.9 (q, J_{C-F} = 34.0 Hz), 130.7, 131.2, 133.0, 133.2, 133.6, 134.8, 145.4, 183.4; HRMS(ESI) : *m*/*z* calcd for $C_{43}H_{43}F_6N_4O_2S_2$ $[M+H]^+$: 825.2732.; found 825.2737.*Typical procedure for the Michael addition reaction of α-cyanoketone* ***1a*** *with β-nitrostyrene (****2a****)*: A mixture of 2-cyano-1-indanone (**1a**, 31.4 mg, 0.2 mmol) and catalyst **VI** (16.5 mg, 0.02 mmol) in dichoromethane (0.4 mL) was stirred at room temperature for 5 min and then was cooled to −40 °C. A solution of nitrostyrene (**2a**, 35.8 mg, 0.24 mmol) was added. The reaction mixture was stirred for 11 h at −40 °C. After completion of the reaction, the resulting solution was allowed to warm to room temperature, concentrated in vacuo and the obtained residue was purified by flash chromatography (EtOAc–Hexane, 1:5) to afford the 60.0 mg (98%) of Michael adduct **3a**. *(R)-2,3-dihydro-2-((S)-2-nitro-1-phenylethyl)-1-oxo-1H-indene-2-carbonitrile (****3a****)*: Major diastereoisomer. $[\alpha]_D^{25} = +69.12$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.20 (d, J = 17.9 Hz, 1H), 3.38 (d, J = 17.9 Hz, 1H), 3.73 (dd, J = 4.0 Hz, 11.2 Hz, 1H), 5.14 (dd, J = 11.2 Hz, 13.7 Hz, 1H), 5.65 (dd, J = 4.0 Hz, 13.7 Hz, 1H), 7.39–7.41 (m, 5H), 7.48–7.55 (m, 2H), 7.69–7.77 (m, 1H), 7.86–7.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.6, 46.8, 49.2, 76.2, 118.1, 126.2, 126.4, 128.5, 129.1, 129.4, 129.5, 132.4, 134.8, 137.1, 149.9, 196.2; HRMS (ESI) : *m*/*z* calcd for $C_{18}H_{14}N_2NaO_3$ $[M+Na]^+$: 329.0902.; found 329.0910. HPLC (90:10, *n*-hexane–*i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak IB, (major diastereomer) t_R = 12.65 min (major), 15.24 min (minor), (minor diastereomer) t_R = 20.23 min (minor), 41.17 min (major), 97% ee.