Enantioselective Nitrocyclopropanation of α,β-Unsaturated α-Cyanoimides Catalyzed by Bifunctional Thiourea

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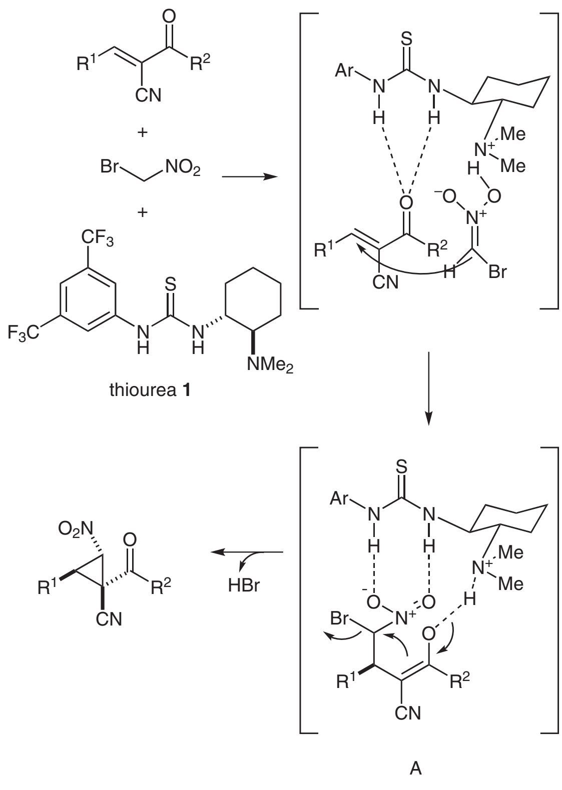
Abstract: The organocatalyzed asymmetric cyclopropanation of bromonitromethane with α-cyano-α,β-unsaturated imides is described. In addition, the same bifunctional thiourea was revealed to be a powerful catalyst for preparing these α-cyanoimides by Knoevenagel condensation.

Key words: asymmetric organocatalysis, cyclopropanation, Michael addition, α,β-unsaturated imides

2-Nitrocyclopropanecarboxylic acid derivatives are now recognized as versatile precursors for biologically active compounds.[1] Furthermore, they are quite useful building blocks for the synthesis of highly functionalized molecular targets.[2] Therefore, the catalytic and enantioselective construction of these motifs is a valuable challenge for synthetic chemists.[3] Asymmetric Michael addition followed by intramolecular nucleophilic substitution is a representative process for this purpose. There have been several reports on the metal-free, organocatalyzed asymmetric synthesis of 2-nitrocyclopropane derivatives.[4] Connon et al. reported the asymmetric cyclopropanation of nitroolefins with 2-iodomalonate via a chiral thiourea-catalyzed Michael addition followed by DBU-mediated intramolecular nucleophilic substitution.[4a] However, the enantioselectivity in these reactions was moderate and environmentally hazardous hexamethylphosphoramide (HMPA) was used in the second step. Recently, Fan et al. successfully applied the combined use of an aminothiourea catalyst and hypervalent iodine such as $PhI(OAc)_2$ to cyclopropanation, although this method was limited to the synthesis of malonate-derived cyclopropanes.[4b] Ley and Cordova independently developed a proline-mediated cyclopropanation of bromonitromethane to α,β-unsaturated ketones or aldehydes.[4c,d] Although these reactions could be used for the efficient synthesis of the desired nitrocyclopropanes, these methods require an additional step for oxidation of the ketone or aldehyde into the corresponding carboxylic acids. Therefore, the development of a more direct and convenient protocol for preparing 2-nitrocyclopropanecarboxylic acids would be a considerable challenge.

We previously reported the enantioselective Michael addition of nitromethane to α,β-unsaturated imides with bifunctional thiourea **1**.[5] We envisioned that if the same reaction with bromonitromethane proceeds efficiently, there is a chance that the obtained Michael adduct **A** would cyclize concurrently via the organocatalyzed intramolecular S_N2 reaction, to give the desired 2-nitrocyclopropanecarboxylic acids stereoselectively. However, simple α,β-unsaturated imides are not sufficiently electrophilic to react with the nucleophile. Therefore, we planned to introduce an additional small electron-withdrawing group such as CN at the α-position of the substrates to possibly activate the Michael acceptor (Scheme 1). In this report, we describe highly enantioselective organocatalyzed cyclopropanation with the use of novel Michael acceptors **4**.



Scheme 1 Concept of the cyclopropanation of α-cyano-α,β-unsaturated compounds catalyzed by bifunctional thiourea **1**

We initially examined the preparation of the requisite α-cyano-α,β-unsaturated ester, ketone, sulfone, and imides **4a–e** from benzaldehyde **2a** and several α-substituted nitriles **3a–e** (Table 1).[6] The treatment of **2a** and ester **3a** with either ZnO[7] or AcOH/morpholine provided the de-

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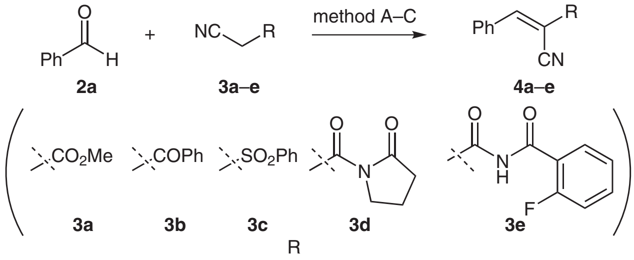
sired product **4a** in moderate yield (entries 1 and 2). In the course of our study on Knoevenagel condensation, we discovered that bifunctional thiourea **1** could be used as a catalyst to give **4a** in better yield than with the typical reaction conditions (entry 3).[8] This reaction was successfully applied to the synthesis of other Michael acceptors to give **4b–e** in good yields (entries 4–7). In addition, the corresponding *E*-isomers were exclusively obtained in all cases.[9]

Table 1 Knoevenagel Condensation of Benzaldehyde **2a** and α-Cyano Compounds **3a–e**

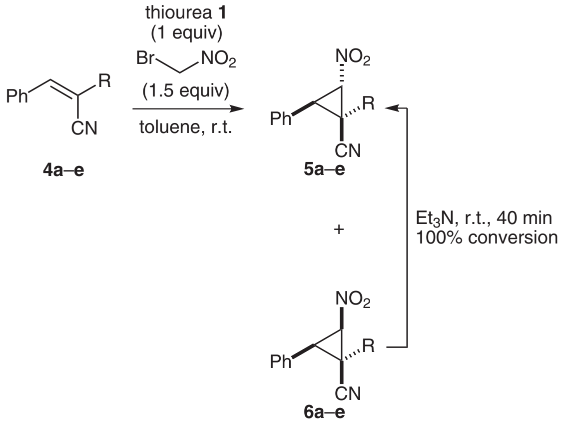


Entry	3	Method[a]	Time (h)	Product	Yield (%)[b]
1	**3a**	A	24	**4a**	54
2	**3a**	B	7	**4a**	22
3	**3a**	C	26	**4a**	68
4	**3b**	C	24	**4b**	85
5	**3c**	C	17	**4c**	88
6	**3d**	C	6	**4d**	59
7	**3e**	C	25	**4e**	72

[a] Method A: AcOH (10 mol%), morpholine (10 mol%), toluene, Dean–Stark; method B: ZnO (5.0 equiv), DMF, r.t.; method C: thiourea **1** (10 mol%), toluene, reflux.
[b] Isolated yield.

With the desired α,β-unsaturated nitriles **4a–e** in hand, we next studied the nitrocyclopropanation of **4a–e** with bromonitromethane in the presence of a stoichiometric amount of thiourea **1** (Table 2). The reaction of both methyl ester **4a** and phenyl ketone took place smoothly at room temperature to give the corresponding nitrocyclopropanes **5a** and **5b** in moderate yields as a single product, respectively, but the enantioselectivities were low to moderate (entries 1 and 2). When α,β-unsaturated sulfone **4c** was used as a substrate, the desired product **5c** was not obtained at all (entry 3). In contrast to these results, the enantioselectivity was considerably improved with α,β-unsaturated oxazolidinone and imide **4d** and **4e**[10] (entries 4 and 5). In the case of **4e**, the major product **5e** was obtained with 97% ee. Although inseparable epimer **6e** was obtained as a minor product, **6e** could be converted into **5e** under basic conditions. The relative configuration of **5d** was determined by X-ray crystallographic analysis,[11,12] and the absolute configuration at C3 of **5a–e** was assigned to be *R* according to our previous report.[5b]

Table 2 Screening of the Substrates



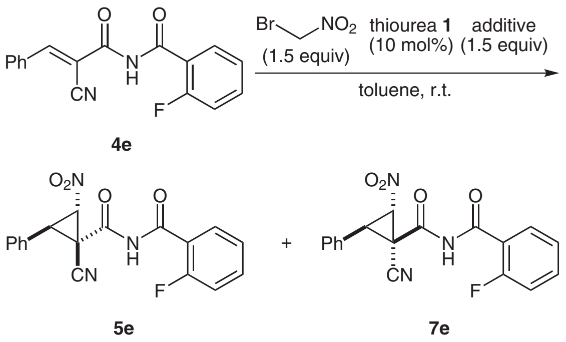
Entry	4	Time (h)	yield (%)[a]	dr (**5**/**6**)[b]	ee of **5**[c]
1	**4a**	26	29	>99:1	11
2	**4b**	24	68	>99:1	47
3	**4c**	24	0	–	–
4	**4d**	6	48	>99:1	71
5	**4e**	25	53	71:29	97

[a] Isolated yield.
[b] Estimated from ^{1}H NMR.
[c] Determined by HPLC.

Based on the ee obtained, we selected **4e** as the optimal Michael acceptor. To reduce the catalytic amount of **1**, we next examined the catalytic asymmetric cyclopropanation of **4e** in the presence of 10 mol% of **1** with several bases (Table 3). As expected, the catalytic reaction with no additional base resulted in the recovery of most of the starting material and gave the cycloadduct **5e** in 11% yield with small amounts of Michael adduct (4%, entry 1). Although the addition of 1.5 equivalents of inorganic bases such as $NaHCO_3$ and K_2CO_3 improved the yield of **5e** to 37% and 27% without producing **6e**, the reaction did not proceed effectively due to the low solubility of the bases in toluene (entries 2 and 3). Furthermore, pyridine was too weak as a base for the reaction (entry 4). After several investigations of bases, Et_3N was found to be the best additive, and gave **5e** in 55% yield as a single product (entry 5). The excellent enantioselectivity of the product was still maintained in the catalytic reaction even with an excess amount of an achiral base such as Et_3N. On the other hand, when the same reaction was performed at lower temperature, the chemical yield was enhanced to 84%, and we obtained a mixture of **5e** and diastereomer **7e**, which was a C3 epimer of **5e**, in a ratio of 63:37 (entry 6). The relative configuration of **7e** was deduced from the ^{1}H NMR spectrum.[13] The mechanism of the generation of **7e** with a decrease in the reaction temperature is unclear at this stage, but might be attributed to deceleration of the cyclization of the Michael adduct at low temperature.[14]

We finally investigated the scope of this catalytic reaction with several α,β-unsaturated α-cyanoimides **4f–k** bearing

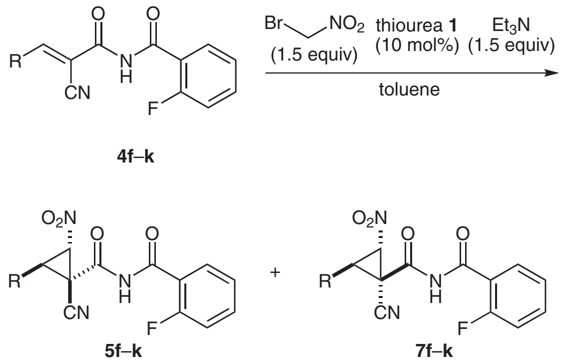
Table 3 Screening of the Additives



Entry	Additive	Time (h)	Total yield (%)[a]	**5e/7e**	ee of **5e** (%)[b]
1	none	24	11	>99:1	97
2	$NaHCO_3$	24	37	>99:1	94
3	K_2CO_3	24	27	>99:1	82
4	pyridine	19	7	>99:1	90
5	Et_3N	2	55	>99:1	96
6[c]	Et_3N	24	84	63:37	97

[a] Isolated yield.
[b] Determined by HPLC.
[c] The reaction was performed at –60 °C.

Table 4 Substrate Scopes



Entry	R	Temp (°C)	Time (h)	Yield of **5** and **7**[a]	ee of **5** (%)[b]
1	4-MeC_6H_4 (**4f**)	–60	24	81 (62:38)	99
2	4-ClC_6H_4 (**4g**)	–20	4	75 (60:40)	98
3	3-ClC_6H_4 (**4h**)	–20	2	80 (50:50)	98
4	2-ClC_6H_4 (**4i**)	–20	1	79 (63:37)	98
5	4-BrC_6H_4 (**4j**)	–20	5	76 (58:42)	98
6	1-naphthyl (**4g**)	–20	1	81 (73:27)	98

[a] Isolated yield.
[b] Determined by HPLC.

different aryl groups as the β-substituent under the optimized conditions (Table 4).[15] Regardless of the electron-withdrawing and electron-donating groups of the aryl group, the catalytic reaction of **4f–g** and **4j** proceeded in good yield without affecting the stereoselectivity (entries 1, 2, and 5). The substituted position (2-, 3-, 4-) of the chloride group did not significantly affect either the chemical yield or the ee (entries 2–4). Furthermore, imide **4k** bearing a naphthyl group could be converted to the corresponding cyclopropane **5k** in excellent ee. Although the diastereoselectivity should be improved, we have developed the thiourea-catalyzed enantioselective cyclopropanation of bromonitromethane and α,β-unsaturated imides **4** in the presence of Et_3N.

In conclusion, we have developed highly reactive and stereoselective Michael acceptors such as **4e–g**. These substrates could be easily prepared by Knoevenagel condensation with bifunctional thiourea. Optically active 2-nitrocyclopropanecarboxylic acids were also synthesized with the same thiourea in excellent enantioselectivities.

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(7) **Knoevenagel Reaction Catalyzed by Thiourea 1**
A mixture of **3e** (40.2 mg, 0.195 mmol), benzaldehyde **2a** (22 μL, 0.215 mmol), and(*rac*)-thiourea **1** (8.1 mg, 0.0195 mmol) in toluene (2.0 mL) was stirred at 80 °C for 25 h. After the reaction mixture was concentrated in vacuo, the residue was purified by silica gel column chromatography with hexane–EtOAc (3:1) to afford **4e** (41.5 mg, 72%) as white needles.
(*E*)-*N*-(2-Cyano-3-phenylacryloyl)-2-fluorobenzamide (4e)
White needles; R_f = 0.54 (hexane–EtOAc, 1:1); mp 186–188 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.96 (d, *J* = 16.3 Hz, 1 H) 8.47 (s, 1 H), 8.16 (td, *J* = 6.3, 1.7 Hz, 1 H), 8.02 (d, *J* = 8.0 Hz, 2 H), 7.65–7.60 (m, 2 H), 7.55 (dd, *J* = 8.0, 7.2 Hz, 2 H), 7.36 (td, *J* = 7.7, 7.2 Hz, 1 H), 7.25 (dd, *J* = 12.0, 8.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.5, 161.0 (2 C), 160.6 (d, *J* = 249 Hz), 158.3, 156.4, 135.6 (d, *J* = 9.9 Hz), 133.9, 132.7, 131.3, 129.2, 125.6 (d, *J* = 3.0 Hz), 116.0 (d, *J* = 10.2 Hz), 116.5 (d, *J* = 24.6 Hz), 116.0, 103.4. IR (KBr): 3364, 1737, 1513, 1289 cm^{-1}. MS–FAB$^+$: *m/z* (%) = 295(10) [MH$^+$], 154 [100]. Anal. Calcd for $C_{17}H_{11}FN_2O_2$C: 69.38, H: 3.77, N: 9.52. Found C: 69.57, H: 3.81, N: 9.55.

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(10) *o*-Fluorobenzimide is a better substrate for asymmetric Michael addition than nonsubstituted benzimide due to the intramolecular hydrogen bond between imide proton and fluoro atom, see: Inokuma T., Nagamoto Y., Sakamoto S., Miyabe H., Takasu K., Takemoto Y.; *Heterocycles*; 2009, in press

(11) CCDC 717740 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) The methanolysis [cat. Er(OTf)$_3$, MeOH, 60 °C] of **4d** and **4e** provided the same product **4a**. Therefore, we concluded that the compounds **4a**, **4d**, and **4e** have the same relative configuration. In addition, the minor product **6e** was converted into **5e** by the treatment with a catalytic amount of Et_3N. The result suggests that **6e** was a C2 epimer of **5e**.

(13) The relative configuration of **7e** was assigned as follows: From the coupling constant of C2 and C3 protons (**5e**: 6.4 Hz, **7e**: 6.6 Hz) in ^{1}H NMR, the relative configuration between the phenyl and nitro group of both **5e** and **7e** was determined to be *trans*. Then, **7e** was deduced to be a C1 epimer of **5e**.

(14) We tried the one-pot process of Knoevenagel reaction and cyclopropanation. But, disappointingly, we obtained the same product **5e** with lower ee (58% yield, 63:37 dr, 17% ee).

(15) **General Procedure for the Thiourea-Catalyzed Nitrocyclopropanation**
To a mixture of **4e** (29.7 mg, 0.1 mmol) and thiourea **1** (4.7 mg, 10 mol%) in toluene (0.1 M) were added bromonitromethane (10 μL, 0.15 mmol) and Et_3N (20 μL, 0.15 mmol) at –60 °C during the indicated period. The reaction mixture was directly purified by silica gel column chromatography with hexane–EtOAc (3:1) to afford **5e** (19 mg, 53%, 97% ee) as white amorphous solids and **7e** (11 mg, 31%, 90% ee) as a brown oil.
1-Cyano-2-nitro-3-phenylcyclopropanecarbonyl)-2-fluorobenzamide (5e; Major Diastereomer)
White amorphous solids; R_f = 0.48 (hexane–EtOAc, 1:1); $[\alpha]_D^{26}$ –19.01 (*c* 0.71, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.41 (d, *J* = 16.3 Hz, 1 H), 8.14 (dt, *J* = 6.0, 1.7 Hz, 1 H), 7.64–7.67 (m, 1 H), 7.48–7.40 (m, 5 H), 7.36 (dd, *J* = 7.7, 7.4 Hz, 1 H), 7.23 (dd, *J* = 12.3, 8.4 Hz, 1 H), 5.41 (d, *J* = 6.4 Hz, 1 H), 4.34 (d, *J* = 6.4 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.9, 161.8, 160.8 (d, *J* = 241 Hz), 159.7, 136.4 (d, *J* = 9.9 Hz), 132.9, 129.6, 129.2 (d, *J* = 24.6 Hz), 128.0, 125.6 (d, *J* = 3.6 Hz), 118.1 (d, *J* = 9.9 Hz), 116.7 (d, *J* = 24.6 Hz), 112.2, 68.4, 37.7, 35.9. IR ($CHCl_3$): 3400 (NH), 2247 (CN), 1699 (C=O), 1617 (NO_2), 1559 (C=O). MS–FAB$^-$: *m/z* (%) = 352(100) [M – H]. HRMS–FAB$^-$: *m/z* calcd for $C_{18}H_{11}FN_3O_4$ [M – H]: 352.0733; found: 352.0699. HPLC: Daicel Chiralcel AS-H; hexane–*i*-PrOH (90:10), 1 mL min^{-1}, 254 nm: t_R(minor) = 67.8 min; t_R(major) = 76.1 min.
1-Cyano-2-nitro-3-phenylcyclopropanecarbonyl)-2-fluorobenzamide (7e; Minor Diastereomer)
Brown oil; R_f = 0.40 (hexane–EtOAc, 1:1); $[\alpha]_D^{26}$ +91.9 (*c* 0.19, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.35 (d, *J* = 15.8 Hz, 1 H), 8.10 (dt, *J* = 6.6, 1.4 Hz, 1 H), 7.61–7.65 (m, 1 H), 7.27–7.36 (m, 5 H), 7.26 (dd, *J* = 10.1, 6.0 Hz, 1 H), 7.19 (dd, *J* = 8.3, 4.0 Hz, 1 H), 5.79 (d, *J* = 6.6 Hz, 1 H), 4.45 (d, *J* = 6.6 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.6, 161.8, 159.4 (d, *J* = 263 Hz), 158.7, 136.5 (d, *J* = 9.9 Hz), 132.9, 129.6, 129.2 (d, *J* = 24.6 Hz), 128.0, 125.6 (d, *J* = 3.6 Hz), 118.4 (d, *J* = 9.9 Hz), 116.6 (d, *J* = 24.6 Hz), 112.5, 65.1, 41.1, 34.1. IR ($CHCl_3$): 3400 (NH), 2244 (CN), 1699 (C=O), 1615 (NO_2), 1563 (C=O). MS–FAB$^-$: *m/z* (%) = 352(20) [M – H]. HRMS–FAB$^-$: *m/z* calcd for $C_{18}H_{11}FN_3O_4$ [M – H]: 352.0733; found: 352.0722. HPLC: Daicel Chiralcel AS-H; hexane–*i*-PrOH (90:10), 1 mL min^{-1}, 254 nm: t_R(minor) = 91.0 min; t_R(major) = 103.9 min.