Enantioselective Nitrocyclopropanation of \( \alpha,\beta \)-Unsaturated-\( \alpha \)-cyanoimides Catalyzed by Bifunctional Thiourea

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

Key words: asymmetric organocatalysis, cyclopropanation, Michael addition, \( \alpha,\beta \)-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-nitrocyclopropanecarboxylic derivatives.\(^4a\) 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 bromonitrilemethane to \( \alpha,\beta \)-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 \( \alpha,\beta \)-unsaturated imides with bifunctional thiourea 1.\(^5\) We envisioned that if the same reaction with bromonitrilemethane proceeds efficiently, there is a chance that the Michael adduct obtained A would cyclize concurrently via the organocatalyzed intramolecular SN2 reaction, to give the desired 2-nitrocyclopropanecarboxylic acids stereoselectively. However, simple \( \alpha,\beta \)-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 \( \alpha \)-position of the substrates to possibly activate the Michael acceptor (Figure 1). In this report, we describe highly enantioselective organocatalyzed cyclopropanation with the use of novel Michael acceptors 4.

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Figure 1 Concept of the cyclopropanation of \( \alpha \)-cyano-\( \alpha,\beta \)-unsaturated compounds catalyzed by bifunctional thiourea 1.

We initially examined the preparation of the requisite \( \alpha \)-cyano-\( \alpha,\beta \)-unsaturated ester, ketone, sulfone, and imides 4a-e from benzaldehyde 2a and several \( \alpha \)-substituted nitriles 3a-e (Table 1).\(^5\) The treatment of 2a and ester 3a with either ZnO\(^7\) or AcOH/morpholine provided the desired 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). 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.

Table 1  Knoevenagel condensation of benzaldehyde 2a and α-cyanoc compounds 3a-e.

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<thead>
<tr>
<th>entry</th>
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<td>B</td>
<td>7</td>
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<td>3b</td>
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<td>3e</td>
<td>C</td>
<td>25</td>
<td>4e</td>
<td>72</td>
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</table>

Method A: AcOH (10 mol%), morpholine (10 mol%), toluene, Dean-Stark; Method B: ZnO (5.0 eq), DMF, room temperature; Method C: thiourea 1 (10 mol%), toluene, reflux. 

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 (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, and the absolute configuration at C3 of 5a-e was assigned to be (R) according to our previous report.

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 equiv of inorganic bases such as NaHCO3 and K2CO3 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, Et3N 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 Et3N. 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 diastereoisomer 7e, which was an C3 epimer of 5e, in a ratio of 63:37 (entry 6). The relative configuration of 7e was deduced from the 1H NMR spectrum. 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.
We finally investigated the scope of this catalytic reaction with several α,β-unsaturated α-cyanoimides 4f-4k bearing different aryl groups as the β-substituent under the optimized conditions (Table 4).

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 (m-, p-) 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 Et₃N.

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

Acknowledgment

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References


(5) Jones, G. White needles; Rf = 0.54 (Hexane:EtOAc, 1:1); m.p 186-188°C; 1H NMR (500 MHz, CDCl3): δ 9.38, H: 3.77, N: 9.52. Found C: 69.57, H: 3.81, N: 9.55. 295 [MH+, 10], 154 [100]. Anal. Calcd for C17H11FN2O2 C: 69.57, H: 3.81, N: 9.55.

(6) 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-phenylacyloyl)-2-fluorobenzamide (4e)
White needles; Rf = 0.54 (Hexane:EtOAc, 1:1); M.p 186-188°C; 1H NMR (500 MHz, CDCl3): δ = 9.96 (d, J = 16.3 Hz, 1H) 8.47 (s, 1H), 8.16 (td, J = 6.3, 1.7 Hz, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.65-7.60 (m, 2H), 7.55 (dd, J = 8.0, 7.2 Hz, 2H), 7.36 (td, J = 7.7, 7.2 Hz, 1H), 7.25 (dd, J = 12.0, 8.0 Hz).

13C NMR (126 MHz, CDCl3): δ = 161.5, 161.0 (2C), 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 = 395 [MH⁺, 10], 154 [100].


(10) o-Fluorobenzimide is a better substrate for asymmetric Michael addition than non-substituted benzimide due to the intramolecular hydrogen bond between imide proton and fluoroo atom, see: Inokuma, T.; Nagamoto, Y.; Sakamoto, S.; Miyabe, H.; Takasu, K.; Takemoto, Y. Heterocycles 1987, 24, 537.

(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 methanalysis [cat. Et(OAc)2], 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 Et3N. 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 1H 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 triethylamine (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/AcOEt (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-phenylcyclopropanecarboxylic acid-catalyzed 2-fluorobenzamide (5e) (Major Diastereomer)
White amorphous; Rf = 0.48 (Hexane:EtOAc, 1:1); [α]D 26 -19.01 (c 0.71, CHCl3). 1H NMR (500 MHz, CDCl3): δ = 9.41 (d, J = 16.3 Hz, 1H), 8.14 (dt, J = 6.0, 1.7 Hz, 1H), 7.64-7.67 (m, 1H), 7.48-7.40 (m, 5H), 7.36 (dd, J = 7.7, 7.4 Hz, 1H), 7.23 (dd, J = 12.3, 8.4 Hz, 1H), 5.41 (d, J = 6.4 Hz, 1H). 13C NMR (126 MHz, CDCl3): δ = 161.9, 161.8, 160.8 (d, J = 24 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 (CHCl3): δ 3400 (NH), 1280 (C=O), 1128 (C=O). MS (FAB+): m/z = 352 [M–H, 20]. HRMS (FAB-): m/z calcd for C18H11FN3O4 [M–H–]: 352.0733; found: 352.0699. HPLC: Daicel Chiralcel AS-H. Hexane–iPrOH, 90:10, 1 mL min⁻¹, 254 nm: tR (minor) = 67.8 min; tR (major) = 76.1 min.

1-Cyano-2-nitro-3-phenylcyclopropanecarboxylic acid-catalyzed 3-fluorobenzamide (7e) (Minor Diastereomer)
Brown oil; Rf = 0.40 (Hexane:EtOAc, 1:1); [α]D 26 +91.9 (0.19, CHCl3). 1H NMR (500 MHz, CDCl3): δ = 9.35 (d, J = 15.8 Hz, 1H), 8.10 (dt, J = 6.6, 1.4 Hz, 1H), 7.61-7.65 (m, 1H), 7.27-7.36 (m, 5H), 7.26 (dd, J = 10.1, 6.0 Hz, 1H), 7.19 (dd, J = 8.3, 4.0 Hz, 1H), 5.79 (d, J = 6.6 Hz, 1H), 4.45 (d, J = 6.6 Hz, 1H). 13C NMR (126 MHz, CDCl3): 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 (CHCl3): δ 3400 (NH), 2244 (CN), 1699 (C=O), 1617 (NO2), 1559 (C=O). MS (FAB+): m/z = 352 [M–H, 100]. HRMS (FAB+): m/z calcd for C18H11FN3O4 [M–H]: 352.0733; found 352.0722. HPLC: Daicel Chiralcel AS-H. Hexane–iPrOH, 90:10, 1 mL min⁻¹, 254 nm: tR (minor) = 90.6 min; tR (major) = 103.9 min.
Graphical Abstract
Enantioselective Nitrocyclopropanation of α,β-Unsaturated-α-cyanoimides Catalyzed by Bifunctional Thiourea

\[ \text{RCON} + \text{O} \xrightarrow{\Delta} \text{RCON} + \text{O} \xrightarrow{\text{thiourea}} \text{RCON} + \text{O} \xrightarrow{\text{thiourea}} \text{RCON} + \text{O} \]

98-99% ee