

# Highly Enantioselective Direct Michael Addition of Nitroalkanes to Nitroalkenes Catalyzed by Amine–Thiourea Bearing Multiple Hydrogen-Bonding Donors

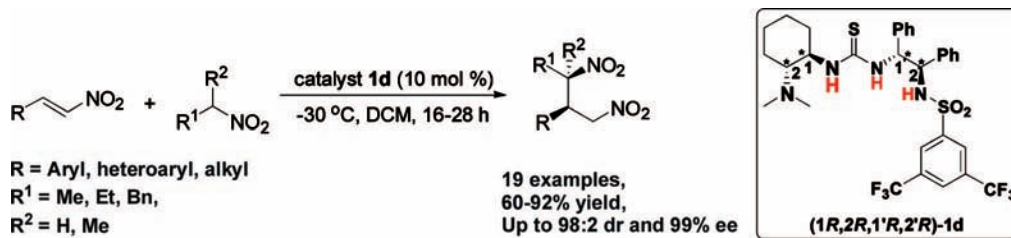
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## ABSTRACT



A highly diastereoselective and enantioselective Michael addition of nitroalkanes to nitroalkenes has been achieved by chiral bifunctional amine–thiourea catalyst bearing multiple hydrogen-bonding donors. This catalytic system performs well over a broad scope of substrates, furnishing various 1,3-dinitro compounds in high diastereoselectivity (up to 98:2) and excellent enantioselectivity (up to 99% ee) under mild conditions. Multiple hydrogen bonding donors play a significant role in accelerating reactions, improving diastereoselectivities and enantioselectivities.

The conjugate addition of stabilized carbanions to electron-deficient  $\alpha,\beta$ -unsaturated compounds is one of the fundamental carbon–carbon bond-forming reactions in organic synthesis and offers an extremely powerful tool for the synthesis of highly functionalized organic molecules.<sup>1–3</sup> The asymmetric addition using various nitroalkanes as excellent Michael donors<sup>4</sup> or nitroalkenes as prominent Michael acceptors<sup>5</sup> has been extensively investigated due to the strong electron-withdrawing property of the nitro group and its facile transformations to highly valuable nitro-containing building blocks.<sup>6</sup> However, only three studies<sup>7</sup> existed on the catalytic asymmetric direct Michael addition of nitroalkanes to nitroalkenes for a limited substrate scope despite the fact that

the generated 1,3-dinitro compounds bearing two contiguous stereogenic centers can be readily converted to chiral 1,3-diamines, which are of great importance and synthetic potential.<sup>8</sup> This problem is partially due to extreme difficulty of suppressing the unfavored subsequent oligomerization to achieve high chemoselectivity and enantio-/diastereo-

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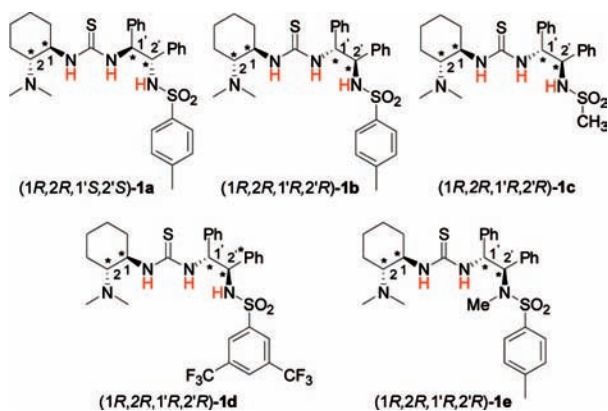
(3) For recent reviews of organocatalytic asymmetric Michael addition, see: (a) Almasi Almaçsi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, 18, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, 40, 3726. (d) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (e) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, 42, 1688.

<sup>†</sup> Wuhan University.

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(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.

selectivity.<sup>7b</sup> Two chiral metal complex catalyzed asymmetric Michael additions of nitroalkanes to nitroalkenes have been reported by Du using Zn(II)/bis(oxazoline) or bis(thiozoline)<sup>9</sup> and Feng using La(III)/*N,N'*-dioxide complexes,<sup>10</sup> respectively. Wang's seminal work showed that organocatalysis also provides a possible approach to this challenging reaction despite the lower reactivity of the cinchona alkaloid catalysts employed.<sup>11</sup> Despite these important contributions, the direct asymmetric Michael addition of nitroalkanes to nitroalkenes is still in its infancy and the development of a new and efficient catalytic system showing high reactivity and enantio-/diastereoselectivity for a broad scope of substrates is still in great demand. Herein, we report a highly syn-selective (up to 98:2) and excellent enantioselective (up to 99% ee) Michael addition of nitroalkanes to nitroalkenes catalyzed by bifunctional amine–thiourea bearing multiple hydrogen-bonding donors (Figure 1).<sup>12,13</sup>



**Figure 1.** Amine–thioureas bearing multiple hydrogen-bonding donors.

Our initial investigation began with the reaction of nitroethane **3a** with nitroolefin **2a**, and the representative

results are summarized in Table 1. It is noteworthy that only 2.3:1 syn-selectivity and 74% enantioselectivity were achieved for **3a** by using the modified cinchona alkaloid organocatalyst in 6 days.<sup>7a,11</sup> To our delight, the reaction was finished in 8–12 h at room temperature with those fine-tunable organocatalysts **1a–d**, and **1d** was revealed as the best catalyst in terms of diastereoselectivity and enantioselectivity (Table 1, entries 1–4). This finding is in agreement with our recently developed amine–thiourea-catalyzed nitro-Mannich reaction and Michael addition reaction.<sup>12</sup> No addition product was observed when using methylated **1e** as the catalyst, which further indicates that the multiple hydrogen bonding donors play a significant role in this efficient system (Table 1, entry 5). A study of reaction with **1d** in various solvents identified PhMe and ether as suitable alternatives to DCM (Table 1, entries 6–12). Interestingly, this Michael addition reaction could also be carried out under neat conditions affording 78:22 dr and 89% ee (Table 1, entry 13). Reducing the temperature to –30 °C in DCM led to full conversion with 98:2 diastereoselectivity and 97% ee for the major syn-diastereomer within 16 h (Table 1, entry 14). A comparable result (96:4 dr and 97% ee) was still achieved even when catalyst loading was reduced to 5 mol % (Table 1, entry 15). The current catalysis demonstrated significant improvements over the previous reported catalytic systems that gave lower diastereo-/enantioselectivity or required longer reaction time (2–6 d).<sup>7a,9–11</sup>

The asymmetric Michael addition of nitroethane **3a** to various nitroolefins **2** in the presence of organocatalyst **1d** was investigated under the optimized experimental conditions. As shown in Table 2, a wide array of aromatic nitroolefins **2a–j**, which bear electron-rich, electron-neutral, or electron-withdrawing groups, reacted smoothly with nitroethane **3a** to afford the corresponding product **4aa–ja** in good yields and with high levels of diastereoselectivity (84:16–98:2) and enantioselectivity (94–99% ee) (Table 2, entries 1–10). It appears that the position and the electronic

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**Table 1.** Screening Studies of Organocatalytic Asymmetric Michael Addition Reaction of Nitroalkane **3a** to Nitroalkene **2a**<sup>a</sup>

entry	catalyst	<i>x</i> (mol %)	solvent	<i>T</i> (°C)	<i>t</i> (h)	yield <sup>b</sup> (%)	syn/anti <sup>c</sup>	ee <sup>d,e</sup> (%)
1	<b>1a</b>	10	DCM	rt	12	89	66:24	26
2	<b>1b</b>	10	DCM	rt	12	84	73:27	73
3	<b>1c</b>	10	DCM	rt	11	85	78:22	79
4	<b>1d</b>	10	DCM	rt	8	87	73:27	83
5	<b>1e</b>	10	DCM	rt				
6	<b>1d</b>	10	DCM	0	12	91	83:17	93
7	<b>1d</b>	10	Et <sub>2</sub> O	0	24	89	86:14	89
8	<b>1d</b>	10	acetone	0	14	88	88:12	83
9	<b>1d</b>	10	PhMe	0	15	85	84:16	91
10	<b>1d</b>	10	CH <sub>3</sub> Cl	0	10	89	80:20	80
11	<b>1d</b>	10	EtOAc	0	12	85	73:27	81
12	<b>1d</b>	10	MeCN	0	15	92	80:20	77
13	<b>1d</b>	10	EtNO <sub>2</sub>	0	13	88	78:22	89
14	<b>1d</b>	10	DCM	−30	16	87	98:2	97
15	<b>1d</b>	5	DCM	−30	24	81	96:4	97

<sup>a</sup> Unless otherwise noted, the reactions was carried out with 0.15 mmol of **2a**, 0.6 mmol of **3a** in 0.6 mL of solvent. <sup>b</sup> Isolated yield. <sup>c</sup> Syn/anti ratio was determined by HPLC analysis except entries 1–4 which were calculated from the isolated two diastereomers. <sup>d</sup> Determined by chiral HPLC analysis. <sup>e</sup> The configuration of **4aa** was determined to be (2*R*,3*R*) by comparing the optical rotation with that of the reported data.

**Table 2.** Asymmetric Direct Michael Addition Reaction of Nitroalkanes **3** to Nitroalkenes **2** Using Organocatalyst **1d**<sup>a</sup>

entry	R	<b>3</b>		Prod	yield <sup>b</sup> (%)	dr <sup>c</sup> syn/anti	ee <sup>d</sup> (%)
		R <sup>1</sup>	R <sup>2</sup>				
1	Ph ( <b>2a</b> )	Me	H ( <b>3a</b> )	<b>4aa</b>	87	98:2	97
2	<i>p</i> -Me-Ph ( <b>2b</b> )	Me	H ( <b>3a</b> )	<b>4ba</b>	89	92:8	97
3	<i>o</i> -Me-Ph ( <b>2c</b> )	Me	H ( <b>3a</b> )	<b>4ca</b>	92	91:9	98
4	<i>p</i> -MeO-Ph ( <b>2d</b> )	Me	H ( <b>3a</b> )	<b>4da</b>	91	91:9	94
5	<i>m</i> -MeO-Ph ( <b>2e</b> )	Me	H ( <b>3a</b> )	<b>4ea</b>	89	93:7	96
6	<i>o</i> -Cl-Ph ( <b>2f</b> )	Me	H ( <b>3a</b> )	<b>4fa</b>	87	93:7	95
7	<i>m</i> -Cl-Ph ( <b>2g</b> )	Me	H ( <b>3a</b> )	<b>4ga</b>	83	88:12	96
8	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>2h</b> )	Me	H ( <b>3a</b> )	<b>4ha</b>	92	84:16	99
9	<i>p</i> -F-Ph ( <b>2i</b> )	Me	H ( <b>3a</b> )	<b>4ia</b>	90	85:15	95
10	1-Naphthyl ( <b>2j</b> )	Me	H ( <b>3a</b> )	<b>4ja</b>	91	91:9	97
11	2-Furyl ( <b>2k</b> )	Me	H ( <b>3a</b> )	<b>4ka</b>	85	80:20	92
12	Cinnamyl ( <b>2l</b> )	Me	H ( <b>3a</b> )	<b>4la</b>	88	82:18	89
13	<i>i</i> Pr ( <b>2m</b> )	Me	H ( <b>3a</b> )	<b>4ma</b>	60	55:45	80 <sup>e</sup>
14	Ph ( <b>2a</b> )	Et	H ( <b>3b</b> )	<b>4ab</b>	92	95:5	96
15	<i>p</i> -Me-Ph ( <b>2b</b> )	Et	H ( <b>3b</b> )	<b>4bb</b>	89	97:3	99
16	<i>o</i> -MeO-Ph ( <b>2c</b> )	Et	H ( <b>3b</b> )	<b>4cb</b>	90	95:5	94
17	<i>o</i> -Cl-Ph ( <b>2f</b> )	Et	H ( <b>3b</b> )	<b>4fb</b>	88	96:4	93
18	Ph ( <b>2a</b> )	Bn	H ( <b>3c</b> )	<b>4ac</b>	89	96:4	95
19	Ph ( <b>2a</b> )	Me	Me ( <b>3d</b> )	<b>4ad</b>	88	—	64 <sup>f</sup>

<sup>a</sup> Unless otherwise noted, the reactions was carried out with 0.15 mmol of **2** and 0.6 mmol of **3** in 0.6 mL of solvent. <sup>b</sup> Isolated yield. <sup>c</sup> Syn/anti ratio was determined by HPLC analysis. <sup>d</sup> Determined by chiral HPLC analysis. <sup>e</sup> In 48 h. <sup>f</sup> The reaction was carried out at rt in 20 h without solvent.

property of the substituents on the aromatic rings have a very limited effect on the enantioselectivities. Heteroaromatic system **2k** was also a viable substrate as α,β-unsaturated nitroolefin **2l** (Table 2, entries 11 and 12). The relatively

challenging aliphatic nitroolefin **2m** also worked in this catalytic system and gave rise to the product in good enantioselectivity albeit lower diastereoselectivity (Table 2, entry 13). The potential of this catalytic approach is further

demonstrated by the reaction of other nitroalkanes (**3b** and **3c**) with nitroolefins to afford the corresponding products in high diastereoselectivities (95:5–97:3) and excellent enantioselectivities (93–99% ee) for the major syn diastereomer (Table 2, entries 14–18). Noticeably, the sterically hindered 2-nitropropane **3d** was also able to undergo the Michael addition affording the product in 88% yield with 64% ee in 20 h (Table 2, entry 19).<sup>14</sup> To the best of our knowledge, this is the best result for asymmetric direct Michael addition of nitroalkanes to nitroalkenes reported so far in terms of reaction rate, enantio-/diastereoselectivity, and substrate scope.

In conclusion, we have described a highly efficient organocatalyzed direct Michael addition of nitroalkanes to nitroalkenes by chiral bifunctional amine–thiourea catalyst

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(14) Only one protocol has been reported to achieve moderate yield and enantioselectivity for this branched substrate in 6 days; see ref 11.

bearing multiple hydrogen-bonding donors. This catalytic system performs well over a broad scope of substrates, furnishing various 1,3-dinitro compounds in high diastereoselectivity (up to 98:2) and excellent enantioselectivity (up to 99% ee) under mild conditions. The mechanistic origin of the high enantiocontrol and future application of this methodology are ongoing in our laboratory.

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**Supporting Information Available:** Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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