

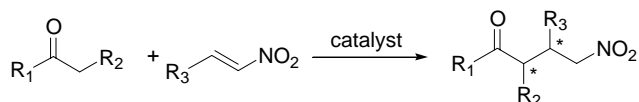
# Recent Advances in Asymmetric Organocatalytic Michael Additions to Nitroalkenes

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## ABSTRACT



Organocatalysis mediated by chiral amine and thiourea derivatives for the asymmetric conjugate addition of carbon nucleophiles to nitroalkenes is described. Advances in this area include a broader substrate scope with regard to both nucleophilic and electrophilic partners, in addition to increased yields (up to 98%), dr's (<95:5) and ee's (up to 99%).

The Michael addition reaction is an important method for the generation of new C-C bonds and is a valuable tool in organic synthesis. Recently, there has been a significant interest in the development of an asymmetric organocatalytic variant of the Michael addition reaction that utilizes nitroalkenes as Michael acceptors.<sup>1</sup> Stimulated interest in this area is attributed to the versatility of the chiral nitroalkane products, which can undergo facile conversion of the nitro functionality to other synthetically useful functional groups.<sup>2</sup> In addition, there is continual need for effective environmentally friendly catalysts.

The most successful approaches in the asymmetric conjugate addition of carbon nucleophiles to nitroalkenes have employed enantiopure catalysts/additives, or have been auxiliary controlled.<sup>1</sup> The use of auxiliaries has been shown to be an effective method for providing good yields, with high diastereo- and enantioselectivity; however further manipulation is required. Both organic

and metal mediated catalytic procedures have been extensively investigated but are often limited by substrate scope and/or low diastereo- and enantioselectivities.<sup>3,4</sup>

Described herein are recent advances in organocatalytic asymmetric conjugate addition reactions of carbonyl compounds to nitroalkenes. The latest publications in this area have utilized organocatalysts containing chiral amines with thiourea moieties, or diamines. In addition, a new class of 3,3'-bimorpholine derivatives has also been developed. The results of these

<sup>3</sup> For recent organocatalytic examples see: (a) Xu, Y.; Zou, W.; Sundén, H.; Ibrahim, I.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348*, 418–424. (b) Zhu, M-K.; Cun, L-F.; Mi, A-Q.; Jiang, Y-Z.; Gong, L-Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491–493. (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215. (d) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, *4*, 611–614. (e) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas III, C. F. *Synthesis* **2004**, 1509–1521. (f) Ishii, T.; Fujioka, Y. S.; Hiyoshizo, K. *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559.

<sup>4</sup> For metal catalyzed example see: (a) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958–9959. (b) Wantanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T.; *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149. (c) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701.

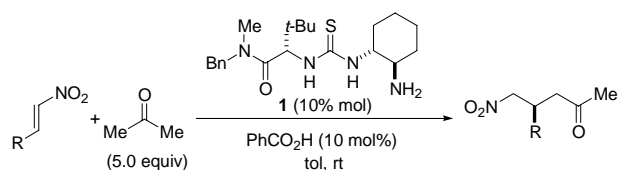
<sup>1</sup> Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.

<sup>2</sup> Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

systems and origins of the observed selectivities will be discussed.

Bifunctional thiourea derivatives are effective in mediating organocatalysis for a variety of organic transformations.<sup>5</sup> Takemoto and coworkers reported the first example of a thiourea catalyst bearing a chiral amino group, which promoted the conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes in good yield and with good enantioselectivities.<sup>6</sup> More recently, direct conjugate addition of ketones to nitroalkenes using a bifunctional thiourea catalyst (**1**) has been developed by Jacobsen and coworkers (Table 1).<sup>7</sup> High yields and enantioselectivities were obtained when acetone was treated with aromatic, and heteroaromatic nitroalkenes (entries 1-5). Noteworthy, is the success of  $\beta$ -substituted aliphatic alkenes which afforded products in good yield with high enantioselectivity (entries 6-8). The addition of acid, in small amounts, prevented bisalkylation byproducts.

**Table 1.** Enantioselective Addition of Acetone to Nitroalkenes using Jacobsen's Thiourea Catalyst **1**



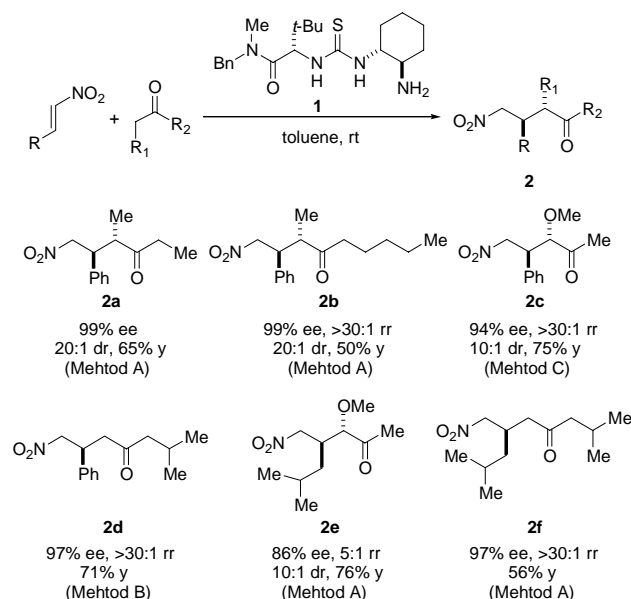
entry	R	yield (%)	ee (%)
1	Ph	93	99
2	4-MeOC <sub>6</sub> H <sub>4</sub>	88	99
3	4-MeC <sub>6</sub> H <sub>4</sub>	87	97
4	2-furyl	88	99
5	2-thienyl	94	96
6 <sup>a</sup>	Me	70	98
7 <sup>a</sup>	<i>n</i> -Bu	78	95
8 <sup>a</sup>	<i>i</i> -Bu	81	94

<sup>a</sup> Results obtained using 15 mol% of **1** and 2 mol% of PhCO<sub>2</sub>H.

Impressively, catalyst **1** demonstrated a bias toward activation of ethyl ketones affording regio- and diastereoselective products, **2a-2e**, containing adjacent tertiary stereocenters (Scheme 1). When aliphatic ketones were treated with nitrostyrene, excellent enantioselectivity and diastereoselectivity was obtained (**2a**, **2b**, **2d**,) in modest yields. Methoxyacetone was also an effective Michael donor, however a decrease in diastereoselectivity was observed (**2c**, **2e**). The more sterically hindered methyl isopropyl ketone afforded a single product with high enantioselectivity (**2f**). Jacobsen's thiourea catalyst has provided exceptional results when acetone is treated with various nitroalkenes,

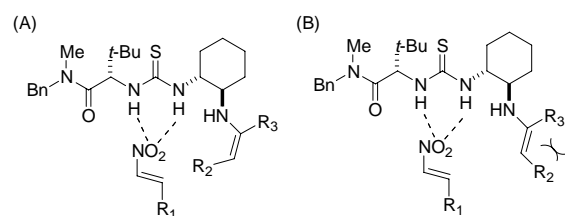
however, when more complex ketones were employed moderate yields were obtained.

**Scheme 1.** Asymmetric Additions of Ketones to Nitroalkenes using Catalyst **1**



<sup>a</sup>rr = regioisomer ratio. Method A: 20 mol% of **1**, 2 mol% of PhCO<sub>2</sub>H, 1.5-5.0 equiv of ketone. Method B: 10 mol% of **1**, 1.5 equiv of ketone. Method C: 20 mol% of **1**, 2.0 equiv of ketone.

The proposed mechanism of Jacobsen's thiourea catalyst involves activation of the ketone through formation of an enamine on the primary amine of catalyst **1** while the thiourea moiety is thought to interact with the nitroalkene through hydrogen bonding of the nitro group (Figure 1). The anti-selectivity arises from formation of a *Z*-enamine intermediate, which is further supported from results obtained by Tsogoeva and Wei where formation of an *E*-enamine intermediate provided syn-selective products.<sup>8</sup>



**Figure 1.** Proposed intermediates. (A) Favored *Z*-enamine. (B) Disfavored *E*-enamine.

<sup>5</sup> Connon, S. J. *Chem. Eur. J.* **2006**, DOI: 10.1002/chem.200501076.

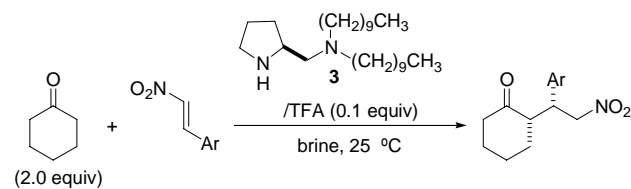
<sup>6</sup> Okino, T.; Hoashi, Y.; Furukawa, X. X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

<sup>7</sup> Huang, H.; Jacobsen, E. R. *J. Am. Chem. Soc.* **2006**, DOI: 10.1021/ja0620890.

<sup>8</sup> Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451–1453.

Barbas III and coworkers have developed a small chiral organic diamine catalyst, which catalyzes the Michael addition of ketones and aldehydes to  $\beta$ -nitrostyrenes in water/brine without the use of organic cosolvents.<sup>9</sup> When TFA was added to the reaction a greater yield was obtained due to an increase in enamine formation. Using this method, various  $\beta$ -nitrostyrenes were treated with cyclohexanone to afford *syn* selective products (Table 2). Excellent yields and diastereoselectivity was observed in entries 1–4, however entry 5, containing an aryl nitro functionality, afforded modest yield and selectivity.

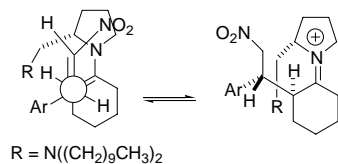
**Table 2.** Asymmetric Addition of Cyclohexanone to Various  $\beta$ -Nitrostyrenes using Barbas's Diamine Catalyst **3**



entry	R	yield (%)	<i>syn:anti</i>	ee (%)
1	Ph	93	95:5	89
2	4-MeOC <sub>6</sub> H <sub>4</sub>	98	96:4	83
3	2-furyl	94	96:4	86
4	2-naphthyl	99	98:2	97
5	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	57	74:26	83

<sup>a</sup>Conditions: amine catalyst **3** (0.05 mmol), TFA (0.05 mmol), cyclohexanone (1.0 mmol), and  $\beta$ -nitrostyrene (0.5 mmol) in brine (0.5 mL) at 25 °C with vigorous stirring.

The high *syn* selectivity observed is explained through the acyclic synclinal model where by there are favorable electrostatic interactions between the partially positive nitrogen of the enamine and the partially negative nitro group in the transition state (Figure 2).<sup>10,3f</sup> Approach from the less hindered *Si* face provides the observed stereochemistry.

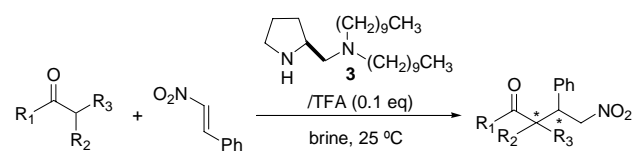


**Figure 2.** Proposed synclinal transition state.

To further expand the scope of this system a variety of aldehydes and ketones were employed (Table 3). Cyclic ketones (entries 1, 2) provided the best results, with good diastereoselection and enantioselection, however a linear

ketone provided low enantioselectivity (entry 3). All carbon quaternary centers were obtained (entries 4–6) in good yield although the diastereo- and enantioselectivities were diminished. These results are similar to those obtained in organic solvents.<sup>11</sup> Diamine catalyst **3** is an effective catalyst in brine, providing simple reaction conditions. In addition, this method can be scaled to multigram quantities, which could be advantageous for pharmaceutical and industrial processes. High yields and diastereomeric ratios were generally obtained in this system, however ee's tended to be more variable and reaction times were generally long (up to 96 h).

**Table 3.** Asymmetric Addition of Ketones and Aldehydes to Nitrostyrene using Barbas's Diamine Catalyst



entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	yield (%)	<i>syn:anti</i>	ee (%) <sup>b</sup>
1		-(CH <sub>2</sub> ) <sub>4</sub> -	H	93	95:5	89
2		-(CH <sub>2</sub> ) <sub>3</sub> -	H	96	77:23	80
3	Me	H	H	87		32
4	H	Me	Me	76		76
5	H	Me	Et	74	59:41	74
6	H	Me	Pr	97	61:30	64

<sup>a</sup>Conditions: catalyst **3** (0.05 mmol), TFA (0.05 mmol), ketone or aldehyde (1.0 mmol), and nitrostyrene (0.5 mmol) in brine (0.5 mL) at 25 °C with vigorous stirring. <sup>b</sup>(2*S*)-*syn*-isomers were obtained in entries 1–3, and (2*R*)-*syn*-isomers were obtained in entries 4–6.

Recently, a new organocatalyst has been developed by Alexakis and coworkers that consists of a C<sub>2</sub>-symmetric 3,3'-bimorpholine structure containing an *N*-alkyl moiety.<sup>12</sup> Normally, pyrrolidine-based catalysts tend to be more effective than six-membered cyclic amines, making this system an interesting and exciting new advancement.<sup>3</sup> To evaluate the effectiveness of this new *N*-*i*Pr-3*S*,3'*S*-bimorpholine (*i*PBM) catalyst, various aliphatic aldehydes were treated with nitrostyrene to afford *syn* selective products in good enantiomeric excess (Table 4). In general, good yields and diastereomeric ratios were obtained when smaller groups were present on the aldehyde (entries 1, 4–7). With bulkier groups (entries 2, 3) no reaction occurred with nitrostyrene due to increased steric hindrance.

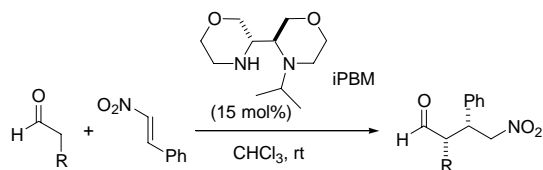
<sup>9</sup> Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967.

<sup>10</sup> Betancort, J. M.; Barbas III, C. F. *Org. Lett.* **2001**, *3*, 3737–3740.

<sup>11</sup> Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas III, C. F. *Org. Lett.* **2004**, *6*, 2527–2530

<sup>12</sup> Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, DOI: 10.1021/ol0607490.

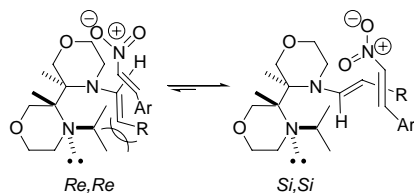
**Table 4.** Asymmetric Addition of Aliphatic Aldehydes to Nitrostyrene using Alexakis's *i*PBM Catalyst



entry	R	yield (%)	<i>syn:anti</i>	ee (%)
1	<i>i</i> Pr	85	94:6	88
2	<i>t</i> Bu	—	—	—
3	Me,Me	—	—	—
4	<i>n</i> Pr	88	83:17	89
5	<i>c</i> Hex	88	95:5	90
6	Me	90	82:18	74
7 <sup>a</sup>	Me	86	90:10	80

<sup>a</sup> Reaction maintained at  $-3^{\circ}\text{C}$ .

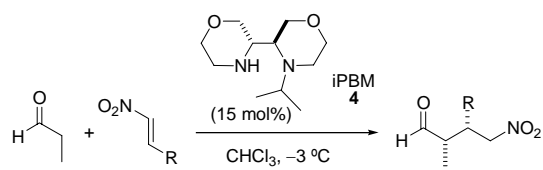
Similar to diamine catalyst **3** (Figure 2), the proposed mechanism involves formation of an *E*-enamine intermediate that reacts with the nitroalkene through a synclinal transition state affording *syn* selective products (Figure 3). The presence of the bulky isopropyl group on the amine of catalyst **3** disfavors formation of the *Z*-enamine intermediate, and shields the *Re,Re* face, leading to attack on the less hindered *Si,Si* face, and provides the observed *syn* adducts.



**Figure 3.** Proposed transition state for *i*PBM

Various nitroalkenes were also examined with propionaldehyde to further expand the scope of this method (Table 5). The reaction proceeded, in general, with high yields, and diastereo- and enantioselectivity when aromatic nitroalkenes were employed (entries 1–4). Catalyst **4** was not as effective with an aliphatic nitroalkene (entry 5) providing low selectivities and yield. This new *N*-*i*Pr-3,3'-bimorpholine organocatalyst **4** has been successful in the conjugate addition of various aldehydes to aromatic nitroalkenes with high diastereomeric ratios and enantiomeric excess, however, long reaction times were required.

**Table 4.** Asymmetric Addition of Propionaldehyde to Nitroalkenes Catalyzed by **4**



entry	R	yield (%)	<i>syn:anti</i>	ee (%)
1	Ph	86	90:10	80
2	2-thienyl	89	89:11	79
3	4-ClPh	84	80:20	75
4	4-MeOPh	81	84:16	78
5	<i>c</i> Hex	23	85:15	85

In summary, new organocatalytic systems have been developed for the asymmetric conjugate addition of carbonyl compounds to nitroalkenes. These reported results are exciting, providing an increase in substrate scope, robust reaction conditions, and generally high diastereomeric ratios and enantiomeric excess. Although improvements in reaction rates are still needed the effectiveness of these organocatalysts will promote additional research efforts in this area.