

# Chiral amine-thioureas bearing multiple hydrogen bonding donors: highly efficient organocatalysts for asymmetric Michael addition of acetylacetone to nitroolefins†

Chun-Jiang Wang,\* Zhi-Hai Zhang, Xiu-Qin Dong and Xiao-Jun Wu

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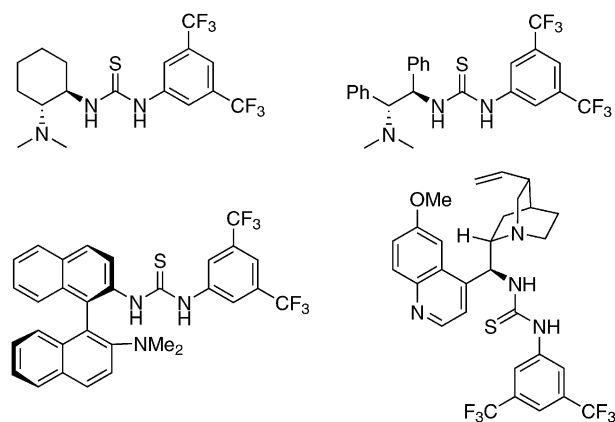
**New bifunctional organocatalysts amine-thioureas bearing multiple hydrogen bonding donors were synthesized and applied in catalytic asymmetric Michael addition of acetylacetone to aryl and alkyl nitroolefins. Multiple hydrogen bonding donors play a significant role in accelerating reactions, improving yields and enantioselectivities.**

Recently, the design and application of organocatalysts have received much attention due to asymmetric organocatalysis emerging as a powerful and environmentally friendly methodology for the catalytic production of the valuable synthetic building blocks.<sup>1</sup> Impressive progress has been made in the development of small chiral molecules bearing hydrogen bonding donors for a diverse range of reactions with high enantioselectivities attributed to their strong activation of carbonyl or nitro groups through efficient double hydrogen bonding interactions.<sup>2</sup> Of the developed organocatalysts, bifunctional amine-thioureas have been proved to be powerful and have been applied successfully in asymmetric Michael addition reactions<sup>3</sup> (Fig. 1). Nonetheless, catalyst loading of as high as 20–30 mol% and long reaction times are usually required to achieve good isolated yields and high enantioselectivities for amine-thiourea catalyzed asymmetric reactions.<sup>1d,4</sup> Therefore, the development of highly efficient chiral amine-thiourea catalysts, which show high enantioselectivity and fast reaction rate for a broad scope of substrates at low catalyst loading, is still in great demand.

Considering the importance of the double hydrogen bonding interactions between the thiourea moiety and substrates in amine-thiourea catalyzed asymmetric reactions,<sup>5</sup> we envisioned that amine-thioureas bearing multiple hydrogen bonding donors as shown in Scheme 1 could facilitate forming more hydrogen bonds<sup>6</sup> and thereby significantly enhance their catalytic activity and overcome the drawback of high catalyst loading. *To the best of our knowledge, this strategy has not yet been applied in the design and synthesis of chiral amine-thiourea organocatalysts.*<sup>7</sup> Herein, we report a new class of amine-thiourea catalysts bearing multiple hydrogen bonding donors which efficiently catalyze asymmetric Michael addition of acetylacetone to nitroolefins with both high yields and high

enantioselectivities up to 99% ee using as low as to 0.1–1 mol% catalyst loading.

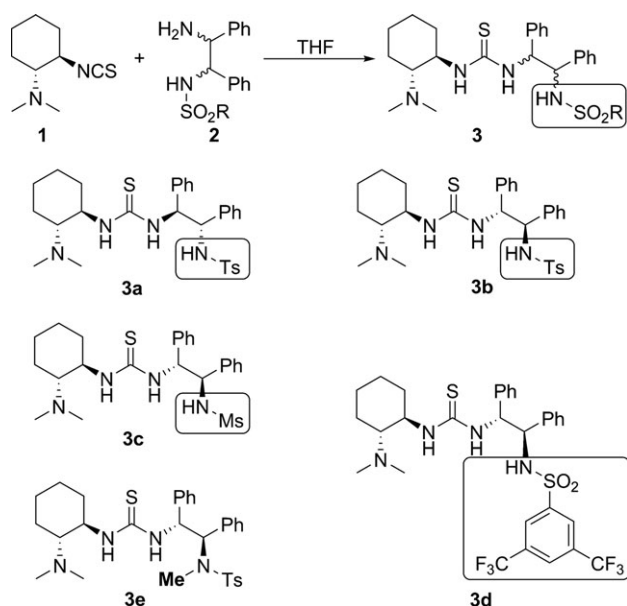
In the presence of 10 mol% **3a–d**, the reaction of nitroolefin (**4a**) with acetylacetone (**5**) was initially examined under different conditions. The results are summarized in Table 1. To our delight, the newly designed catalysts exhibited high catalytic efficiency. The reactions were finished in less than 0.5 h at room temperature when ether was used as the solvent.<sup>8</sup> Chiral catalyst **3a** promoted the reaction with a high yield of 97% but a moderate enantioselectivity (76% ee, entry 1). Gratifyingly, its isomer catalyst **3b** afforded a superior level of enantioselectivity with the same sense of asymmetric induction (93% ee, entry 2). This indicates that the (*R,R*)-1,2-diphenylethenediamine moiety matched the (*R,R*)-cyclohexanediamine moiety and the configurations of the products were determined mainly by the latter, but the enantioselective control could be greatly enhanced by the former. Replacing the Ts group of **3b** with a less bulky group (Ms) decreased the enantioselectivity (89% ee) due to the steric flexibility of catalyst **3c** (entry 3). The highest enantioselectivity of 97% ee was observed with **3d** as catalyst (entry 4), which is presumably attributed to the presence of the additional stronger hydrogen bonding donor from sulfonamide  $\text{NHSO}_2\text{Ar}$  with two electron-withdrawing groups  $\text{CF}_3$  on the aromatic ring. The change of solvents has a remarkable effect on the enantioselectivity and catalytic activity. In polar solvents, the reaction became sluggish and displayed lower ee presumably due to the competitive activation of **4a** between **3d** and the



**Fig. 1** Examples of reported chiral bifunctional amine-thiourea catalysts.

College of Chemistry and Molecular Sciences, Wuhan University, 430072, China. E-mail: cjwang@whu.edu.cn; Fax: +86 (0)2768754067; Tel: +86 (0)2765241880

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**Scheme 1** Synthesis of amine-thiourea catalysts bearing multiple hydrogen bonding donors.

protic solvent such as methanol (entry 5), or the reduced activity of **3d** caused by strongly H-bonding acceptor solvents such as DMSO, MeCN and THF (entries 6, 7 and 8). In contrast, **3d** in nonpolar or less polar solvents, such as DCM, PhMe and ether, efficiently promoted the reaction in high yield with good to excellent enantioselectivities within less than 1 h (entries 4, 9 and 10). Ether was the best solvent of choice and 97% ee was obtained. Reducing the reaction temperature from room temperature to 0 and  $-20^{\circ}\text{C}$  did not improve the enantioselectivities (entries 11 and 12). Further optimization showed that high yield and enantioselectivity and fast reaction rate remained when the reaction was performed with as low as 1 mol% of catalyst loading (entry 14). Even when the catalyst loading was reduced to 0.1 mol%, a comparable result (95% ee, 85% yield) was still achieved with extended reaction time (entry 15).<sup>9</sup>

Under the optimized experimental conditions, the scope of the reaction was explored (Table 2). A variety of aryl nitroolefins (**4a–k**) reacted smoothly with acetylacetone (**5**) to afford the corresponding products (**6a–k**) in high yields (87–97%) and excellent enantioselectivities (95–99% ee) in the presence of 1 mol% of catalyst **3d** at room temperature within 1–2 h. It appears that the position and the electronic property of the substituents on the aromatic rings have a very limited effect on the enantioselectivities. Noticeably, alkyl nitroolefins also work well in this reaction with 1–5 mol% catalyst loading: alkyl nitroolefins with sterically hindered or unhindered substituents (**4l–n**) led to similar enantioselectivities of 82–85% ee (entries 12–15). *To the best of our knowledge, no example of the asymmetric addition of acetylacetone to alkyl nitroolefins has been described so far, probably due to the fact that they are less reactive than aryl nitroolefins.*<sup>10</sup> Actually, extended reaction time and 5 mol% catalyst loading were needed to complete the reactions compared with needing only 0.1–1 mol% catalyst and 1–2 h for aryl nitroolefins.

Interestingly, this Michael addition reaction could also be carried out without solvent. Mixing nitroolefin (**4a**) with

**Table 1** Screening studies of organocatalytic asymmetric Michael addition of acetylacetone and nitroolefins<sup>a</sup>

| Entry | Catalyst             | Solvent           | Temp/ $^{\circ}\text{C}$ | t/h | Yield (%) <sup>b</sup> | ee (%) <sup>c,d</sup> |
|-------|----------------------|-------------------|--------------------------|-----|------------------------|-----------------------|
| 1     | <b>3a</b> (10 mol%)  | Et <sub>2</sub> O | Rt                       | 0.5 | 97                     | 76                    |
| 2     | <b>3b</b> (10 mol%)  | Et <sub>2</sub> O | Rt                       | 0.5 | 96                     | 93                    |
| 3     | <b>3c</b> (10 mol%)  | Et <sub>2</sub> O | Rt                       | 0.5 | 96                     | 89                    |
| 4     | <b>3d</b> (10 mol%)  | Et <sub>2</sub> O | Rt                       | 1   | 97                     | <b>97</b>             |
| 5     | <b>3d</b> (10 mol%)  | MeOH              | Rt                       | 17  | 69                     | 18                    |
| 6     | <b>3d</b> (10 mol%)  | DMSO              | Rt                       | 16  | 72                     | 0                     |
| 7     | <b>3d</b> (10 mol%)  | MeCN              | Rt                       | 10  | 90                     | 86                    |
| 8     | <b>3d</b> (10 mol%)  | THF               | Rt                       | 5   | 96                     | 35                    |
| 9     | <b>3d</b> (10 mol%)  | DCM               | Rt                       | 0.5 | 97                     | 89                    |
| 10    | <b>3d</b> (10 mol%)  | PhMe              | Rt                       | 0.5 | 97                     | 95                    |
| 11    | <b>3d</b> (10 mol%)  | Et <sub>2</sub> O | 0                        | 0.5 | 97                     | 98                    |
| 12    | <b>3d</b> (10 mol%)  | Et <sub>2</sub> O | $-20$                    | 2   | 96                     | 97                    |
| 13    | <b>3d</b> (2 mol%)   | Et <sub>2</sub> O | Rt                       | 1   | 97                     | 97                    |
| 14    | <b>3d</b> (1 mol%)   | Et <sub>2</sub> O | Rt                       | 1   | 97                     | <b>97</b>             |
| 15    | <b>3d</b> (0.1 mol%) | Et <sub>2</sub> O | Rt                       | 10  | 81                     | <b>95</b>             |

<sup>a</sup> Unless otherwise noted, the reaction was carried out with 0.15 mmol of **4a** and 0.30 mmol of **5** in 0.35 mL of solvent. <sup>b</sup> Isolated yield.

<sup>c</sup> Enantiomeric excesses were determined by chiral HPLC analysis.

<sup>d</sup> The absolute configuration of the product was determined as *R* by comparing the optical rotation with the reported date.<sup>8</sup>

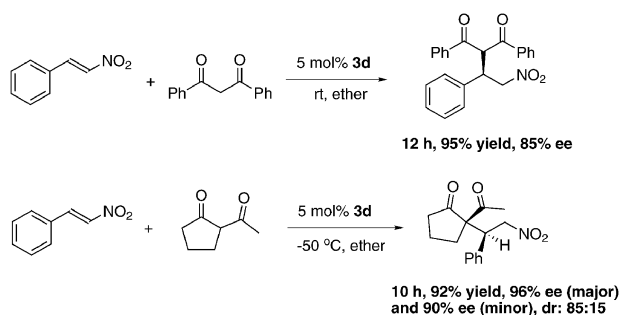
acetylacetone (**5**) (1:2 ratio) in the presence of 1 mol% **3d** afforded the product in >99% yield with 94% ee within 2 h.<sup>11</sup>

The asymmetric Michael addition of other diketones to nitroolefin **4a** using **3d** as a catalyst was also investigated. As

**Table 2** Asymmetric Michael addition of acetylacetone to nitroolefins (**4**) catalyzed by organocatalyst **3d**<sup>a</sup>

| Entry           | R                              | Yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |
|-----------------|--------------------------------|------------------------|---------------------|
| 1               | Ph ( <b>4a</b> )               | 97                     | 97                  |
| 2               | 4-MePh ( <b>4b</b> )           | 96                     | 95                  |
| 3               | 2-MePh ( <b>4c</b> )           | 95                     | 98                  |
| 4               | 4-MeOPh ( <b>4d</b> )          | 93                     | 98                  |
| 5               | 3-MeOPh ( <b>4e</b> )          | 96                     | 97                  |
| 6               | 2-MeOPh ( <b>4f</b> )          | 97                     | 95                  |
| 7               | 3-ClPh ( <b>4g</b> )           | 87                     | 98                  |
| 8               | 4-BrPh ( <b>4h</b> )           | 97                     | 95                  |
| 9               | 3-BrPh ( <b>4i</b> )           | 96                     | 96                  |
| 10              | 2-BrPh ( <b>4j</b> )           | 97                     | 96                  |
| 11              | 4-FPh ( <b>4k</b> )            | 96                     | <b>99</b>           |
| 12 <sup>d</sup> | Amyl ( <b>4l</b> )             | 85                     | 85                  |
| 13 <sup>d</sup> | <i>i</i> -Propyl ( <b>4m</b> ) | 81                     | 81                  |
| 14 <sup>e</sup> | <i>i</i> -Propyl ( <b>4m</b> ) | 80                     | 83                  |
| 15 <sup>d</sup> | <i>i</i> -Butyl ( <b>4n</b> )  | 83                     | 82                  |

<sup>a</sup> Unless otherwise noted, the reactions were carried out with 0.15 mmol of **4** and 0.30 mmol of **5** in 0.35 mL of ether within 1–2 h. <sup>b</sup> Isolated yield. <sup>c</sup> Enantiomeric excesses were determined by chiral HPLC analysis. <sup>d</sup> 5 mol% catalyst was used and the reactions completed in 16–28 h. <sup>e</sup> 1 mol% catalyst was used and the reaction completed in 36 h.



**Scheme 2** Asymmetric Michael addition of other diketones to nitroolefin **4a** catalyzed by **3d**.

shown in Scheme 2, 1,3-diphenylpropane-1,3-dione gave the desired product in 95% yield with 85% ee, which is the first report using this diketone in this asymmetric Michael addition. Unsymmetrical 2-acetylcyclopentanone also worked well to give the desired products with good diastereoselectivity (85:15) and excellent enantioselectivity (96 and 90% ee for the major and the minor diastereomer respectively) which is comparable with the two best results reported in the literature.<sup>5d,12</sup>

In order to evaluate the role of the multiple hydrogen bonding donors played in this system, a control experiment was carried out using 10 mol% **3e** as catalyst (Scheme 1) in which the sulfonamide NMeSO<sub>2</sub>Ts is methylated. In the Michael addition of acetylacetone to **4a**, the reaction became sluggish and the corresponding product was formed in 80% yield with only 68% ee even in 16 h. This indicates that the third NH of sulfonamide on the 1,2-diphenylethenediamine moiety indeed play a significant role in this Michael addition reaction.<sup>13</sup>

In conclusion, a new class of bifunctional amine-thiourea catalysts bearing multiple hydrogen bonding donors was synthesized and evaluated for their ability to catalyze the Michael addition of acetylacetone to nitroolefins. We found that multiple hydrogen bonding donors play a key role in accelerating reactions, improving yields and improving enantioselectivities. Further investigation of the efficacy of these organocatalysts in other catalytic asymmetric reactions and the design of new bifunctional catalysts bearing multiple hydrogen bonding donors are ongoing in our lab and will be reported in due course.

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