# A chiral thioureido acid as an effective additive for enantioselective organocatalytic Michael additions of nitroolefins†

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**A novel and effective organocatalytic system consisting of pyrrolidinyl-thioimidazole and a chiral thioureido acid efficiently catalyzed the asymmetric Michael addition reactions of ketones to nitroolefins to afford the adducts with high diastereoselectivities (up to 99 : 1) and excellent enantioselectivities (up to 99% ee).**

The organocatalytic asymmetric Michael addition reaction of ketones to nitroolefins is widely recognized as one of the most important carbon–carbon bond-forming reactions in organic synthesis. Following the development of L-proline as an efficient and powerful catalyst,[1] impressive progress has been made in the development of efficient organocatalysts for the asymmetric Michael reaction. With the growing attention focused on the importance of the pyrrolidine motif in the activation of the carbonyl group in the enamine intermediate, a series of pyrrolidine derivatives was synthesized and successfully applied to asymmetric Michael addition reactions.[2] The introduction of acid additives has been shown to be usually necessary for high activities of the pyrrolidine-derived catalysts. A variety of Brønsted acids, such as PhCOOH,[3] AcOH,[4] *p*TsOH,[5] salicylic acid,[6] TFA,[7] *n*-butyric acid[8] and 2,4-dinitrobenzenesulfonic acid,[9] have been applied to Michael reactions, thereby enhancing the yields of the adducts. However, these additives are mostly achiral and have their limitations in improving the enantiopurities of the products. Very recently, a new concept, asymmetric counteranion-directed catalysis (ACDC), has been introduced as an efficient strategy for enantioselective transformations.[10] In ACDC, chiral counteranions can help to conduct asymmetric catalytic reactions that proceed through cationic intermediates. Despite impressive progress in the use of this strategy in enantioselective reactions, there is further need for high-performance chiral additives.

In our previous work, we showed that pyrrolidinyl-thioimidazole **1** could efficiently catalyze the asymmetric Michael addition reactions of ketones to nitroolefins in the presence of inorganic or organic acids.[6b,11] Herein, we present further improvements in this organocatalytic system, which uses a series of novel chiral thioureido acids **2** as additives (Fig. 1). On the basis of the ACDC strategy, we envisioned that these acids could not only activate the catalyst, but also enhance the enantioselectivities of these Michael reactions by asymmetric inducement.

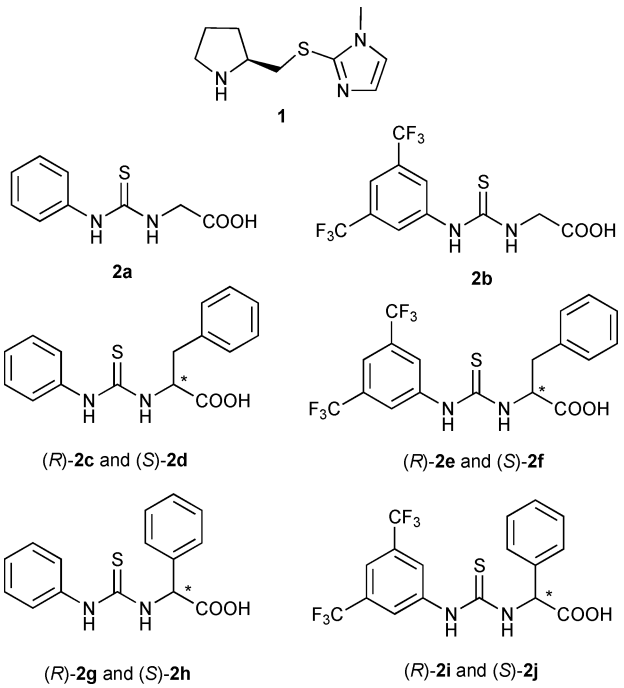
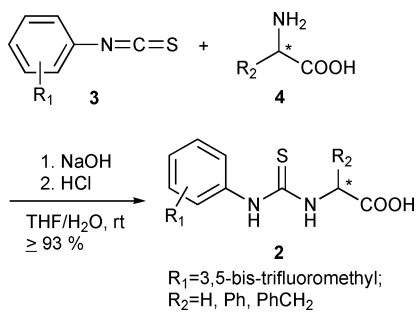



**Fig. 1** Chiral pyrrolidinyl-thioimidazole and thioureido acids.

Thioureido acids **2** were easily prepared from isothiocyanates **3** and amino acids **4** by treatment with NaOH in THF–$H_2O$ and subsequent adjustment of the pH with aqueous HCl (Scheme 1).




**Scheme 1** Synthesis of the chiral thioureido acids **2**.

The direct asymmetric Michael addition of cyclohexanone to *trans*-β-nitrostyrene in $CHCl_3$ at room temperature was examined in the presence of 5 mol% of organocatalyst **1** with a series of chiral thioureido acids **2**. The results are summarized in Table 1.

The asymmetric Michael addition of cyclohexanone **5** to *trans*-β-nitrostyrene **6** was catalyzed by **1** without the additive to afford product **7** in 55% yield and 71% ee (entry 1). With the addition of hydrobromic acid, catalyst **1** promoted the addition with improved

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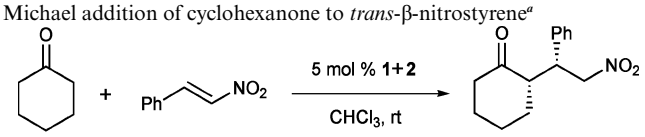
**Table 1** Organocatalyzed asymmetric Michael addition of cyclohexanone to *trans*-β-nitrostyrene[a]




**5** **6** **7**

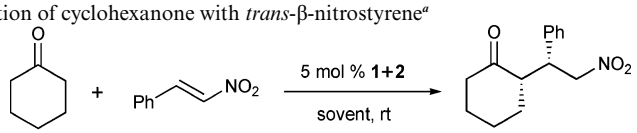
| Entry | Additive | Time/days | Yield[b] (%) | dr[c] *syn*/*anti* | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | — | 8 | 55 | 90 : 10 | 71 |
| 2 | HBr | 8 | 50 | 88 : 12 | 82 |
| 3 | PhCOOH | 6 | 90 | 83 : 17 | 78 |
| 4 | **2a** | 4 | 85 | 92 : 8 | 77 |
| 5 | **2b** | 4 | 80 | 90 : 10 | 71 |
| 6 | **2c** | 2 | 96 | 95 : 5 | 97 |
| 7 | **2d** | 4 | 92 | 89 : 11 | 86 |
| 8 | **2e** | 3 | 93 | 98 : 2 | 93 |
| 9 | **2f** | 4 | 91 | 98 : 2 | 87 |
| 10 | **2g** | 4 | 94 | 97 : 3 | 86 |
| 11 | **2h** | 4 | 90 | 93 : 7 | 80 |
| 12 | **2i** | 4 | 90 | 95 : 5 | 87 |
| 13 | **2j** | 4 | 88 | 94 : 6 | 83 |

[a] All reactions were conducted in $CHCl_3$ (5 mL) using **5** (1 mmol) and **6** (0.5 mmol) in the presence of 5 mol% of the catalysts. [b] Determined by GC with *n*-butyl 4-hydroxybenzoate as an internal standard. [c] Determined by GC–MS. [d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H, hexane–*i*-PrOH = 90 : 10).

enantioselectivity of 82% ee, but the resulting reaction yield was only 50% (entry 2). The use of benzoic acid, in place of an inorganic acid, accelerated the reaction and enhanced the yield (90%), but decreased the ee value to 78% (entry 3). Similar results were obtained when the additive was replaced with non-chiral thioureido acids **2a** and **2b** (entries 4 and 5). Gratifyingly, the chiral thioureido acid additives **2c–j** exhibited excellent activities and the adducts were afforded with high yields (up to 96%) and high enantioselectivities (up to 97% ee) (entries 6–13). These results indicated that chiral thioureido acids **2** could act in a dual role, not only activating the catalyst **1** (presumably by providing the acidic proton), but also inducing chiralityby hydrogen bonding. More excitingly, the additives **2c**, **2e**, **2g** and **2i**, all having an (*R*)-configuration (entries 6, 8, 10 and 12), showed better efficiency than (*S*)-thioureido acids **2d**, **2f**, **2h** and **2j** (entries 7, 9, 11 and 13), which further illuminates the synergistic effects of the chiral thioureido acids.

The effects of solvents on the reaction of cyclohexanone with *trans*-β-nitrostyrene were also studied. As shown in Table 2, in polar solvents, the catalyst system **1**+**2c** exhibited poor activity and the products were obtained with moderate enantioselectivities (71–90%) (entries 1–8). This indicated that polar solvents may interact

**Table 2** Effects of solvents on the reaction of cyclohexanone with *trans*-β-nitrostyrene[a]

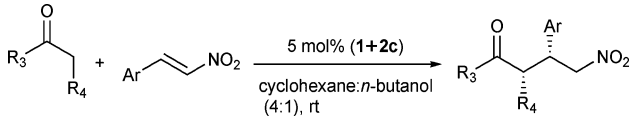



**5** **6** **7**

| Entry | Solvent | Time/days | Yield[b] (%) | dr[c] *syn*/*anti* | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | DMSO | 8 | 83 | 92 : 8 | 71 |
| 2 | DMF | 8 | 80 | 91 : 9 | 86 |
| 3 | $CH_3OH$ | 8 | 92 | 92 : 8 | 69 |
| 4 | Isopropanol | 3 | 95 | 90 : 10 | 86 |
| 5 | *n*-Butanol | 3 | 94 | 98 : 2 | 90 |
| 6 | $CH_2Cl_2$ | 3 | 95 | 93 : 7 | 85 |
| 7 | $CHCl_3$ | 2 | 96 | 95 : 5 | 97 |
| 8 | $ClCH_2CH_2Cl$ | 2 | 96 | 93 : 7 | 90 |
| 9 | Ethyl ether | 3 | 96 | 98 : 2 | 90 |
| 10 | Dioxane | 8 | 73 | 97 : 3 | 99 |
| 11 | Isopropyl ether | 8 | 92 | 90 : 10 | 99 |
| **12** | **Cyclohexane–*n*-butanol (4 : 1)** | **0.5** | **97 (94[e])** | **97 : 3** | **98** |
| 13 | Cyclohexane–$CHCl_3$ (4 : 1) | 1.5 | 95 | 98 : 2 | 95 |
| 14 | Cyclohexane–*i*-propanol (4 : 1) | 1 | 96 | 98 : 2 | 94 |

[a] All reactions were conducted using **6** (1 mmol) and **7** (0.5 mmol) in the presence of 5 mol% of catalyst **1** and additive **2c**. [b] Determined by GC with *n*-butyl 4-hydroxybenzoate as an internal standard. [c] Determined by GC–MS. [d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H, hexane–*i*-PrOH = 90 : 10). [e] Isolated yield.

**Table 3** Michael addition reactions of ketones to nitroolefins[a]




| Entry | Product | | Yield[b] (%) | dr[c] *syn*/*anti* | ee[d] (%) |
|---|---|---|---|---|---|
| | $R_3$, $R_4$ | Ar | | | |
| 1 | -$(CH_2)_4$- | *p*-$MeOC_6H_4$ | 93 (88[e]) | 96 : 4 | 99 |
| 2 | -$(CH_2)_4$- | *m*-$MeOC_6H_4$ | 96 (92[e]) | 95 : 5 | 99 |
| 3 | -$(CH_2)_4$- | *p*-$MeC_6H_4$ | 94 (90[e]) | 98 : 2 | 90 |
| 4 | -$(CH_2)_4$- | *o*-$BrC_6H_4$ | 93 | 94 : 6 | 92 |
| 5 | -$(CH_2)_4$- | *o*-$NO_2C_6H_4$ | 92 | 96 : 4 | 86 |
| 6 | -$(CH_2)_4$- | *p*-$CF_3C_6H_4$ | 85 | 94 : 6 | 87 |
| 7 | -$(CH_2)_4$- | 2-Naphthyl | 92 | 85 : 15 | 89 |
| 8 | -$(CH_2)_4$- | 2-Furanyl | 95 | 94 : 6 | 87 |
| 9 | -$(CH_2)_4$- | 2-Thienyl | 94 | 93 : 7 | 95 |
| 10 | H, *i*-Pr | Ph | 90 | 79 : 21 | 70 |
| 11 | $CH_3$, H | Ph | 95 | — | 64 |
| 12 | $CH_3$, *i*-Pr | Ph | 90 | — | 71 |
| 13 | $CH_3$, Et | Ph | 91 | 89 : 11 | 74 |
| 14 | -$(CH_2)_3$- | Ph | 67 | — | 87 |
| 15 | -$(CH_2)_5$- | Ph | 40 | — | 40 |
| 16 | -$CH_2CH_2SCH_2$- | Ph | 90 (86[e]) | 97 : 3 | 78 |
| 17 | -$CH_2CH_2OCH_2$- | Ph | 92 (87[e]) | 95 : 5 | 59 |
| 18 | -$CH_2CH$(*t*-Bu)$CH_2$- | Ph | 95 (90[e]) | 90 : 10 | 97 |

[a] All reactions were conducted in cyclohexane (4 mL) and *n*-butanol (1 mL) using ketones (1 mmol) and nitroolefins (0.5 mmol) in the presence of 5 mol% of catalyst **1**+**2c**. [b] Determined by GC with *n*-butyl 4-hydroxybenzoate as an internal standard. [c] Determined by GC–MS. [d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H, hexane–*i*-PrOH = 90 : 10). [e] Isolated yields.

with **2c** through hydrogen bonding to weaken the activation ability of **2c** towards the reaction. Although the enantiopurities of the products increased to 99% ee in dioxane and isopropyl ether, the reaction times and yields were disappointing (entries 10 and 11). This was probably due to the difficulties in dissolution of the polar catalyst system **1**+**2c** in such nonpolar solvents. Therefore, the use of mixed solvents was examined (entries 12, 13 and 14). In cyclohexane–*n*-butanol, the results were improved and the reactants were rapidly converted to the desired product with excellent yield (97%), high diastereoselectivity (97 : 3) and enantioselectivity (98% ee).

Having established these optimized conditions, reactions with a variety of ketones and nitroolefins were explored, and the results are summarized in Table 3. First, different nitroolefins were probed and the reactions reached completion, affording good yields of up to 96%. Nitroolefins bearing electron-donating aryl groups afforded the desired adducts with higher selectivities (dr up to 98 : 2, ee up to 99%) (entries 1–3) than those bearing electron-withdrawing aryl groups (entries 4–7). Furthermore, 2-(2-nitrovinyl)furan and 2-(2-nitrovinyl)thiophene also worked well in the reaction and gave the corresponding products with high selectivities in excellent yields (entries 8 and 9). Moreover, the asymmetric additions of the aliphatic aldehydes and ketones to *trans*-β-nitrostyrene were examined (entries 10–18). In the presence of the catalyst system **1**+**2c**, isovaleraldehyde was efficiently converted to the desired adduct in 90% yield and 70% enantioselectivity (entry 10). The use of the aliphatic ketones in the reaction with *trans*-β-nitrostyrene gave similar results (entries 11–13). Cyclopentanone (entry 14) and cycloheptanone (entry 15) were less active as substrates, providing yields of 67% and 40%, and enantioselectivities of 87% and 40% ee, respectively. At the same time, tetrahydrothiopyran-4-one and tetrahydropyran-4-one reacted smoothly with *trans*-β-nitrostyrene to provide the products in excellent yields, and with high diastereoselectivities and moderate enantioselectivities (entries 16 and 17). 4-*tert*-Butylcyclohexanone was also a suitable substrate in a Michael addition reaction with *trans*-β-nitrostyrene and led to the product in excellent yield of 95% with an ee value of 97% (entry 18).

To account for the high performance of the Michael addition reactions using the designed catalyst system, an enamine activation model combined synergistically with the effect of ACDC is proposed as shown in Fig. 2 using cyclohexanone and *trans*-β-nitrostyrene as an example. When the stable ionic pair is formed, the carboxyl group and two N–H bonds of the (*R*)-thioureido acids are oriented in the same direction. The thiourea moiety then activates the nitro group of the nitroolefin through hydrogen bonding, enhancing the electrophilicity of the nitroolefin, while the pyrrolidine activates the ketone by forming an enamine intermediate. The enamine is favored to attack the nitroolefin from

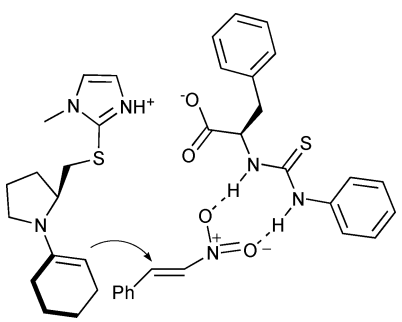



**Fig. 2** Possible transition state model.

the *re*-face, affording the desired adduct. The observed solvent dependency of the reaction enantioselectivities may be due to the stability of the ion pair allowing the counteranion to influence the chiral environment of the transition state.

In summary, a new organocatalytic system composed of a pyrrolidinyl-thioimidazole catalyst and a chiral thioureido acid additive has been designed and applied successfully to a series of asymmetric Michael addition reactions. A large range of Michael adducts was obtained with excellent yields and high selectivities using various ketone and nitroolefin substrates, which suggests that this novel organocatalytic system may find wide application in the asymmetric Michael reactions of nitroolefins. Further investigations of the applications of this organocatalytic system in other asymmetric reactions are in progress.

## Acknowledgements

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