# Asymmetric multifunctional organocatalytic Michael addition of nitroalkanes to α,β-unsaturated ketones†

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**Cinchona alkaloid derived primary amine thioureas organo catalyzed Michael addition of nitroalkanes to enones in good yield and up to 98% ee and offered a new way to construct quaternary stereocenters from enones and nitroalkanes.**

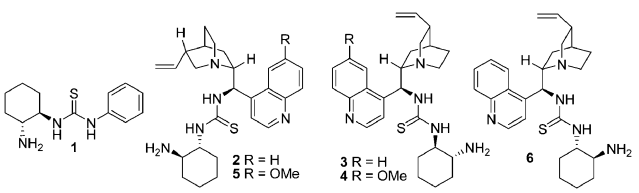
As one of the most important chiral bond-forming processes in organic chemistry, the field of asymmetric organocatalytic Michael addition employing chiral organocatalysts has developed significantly and become the focus of intense research efforts.[1–4] Inspired by one of the key features of enzyme activity, the synergistic cooperation of a number of functional groups, chemists have successfully applied bifunctional organocatalytic strategy in organic synthesis during the past few years.[5] Such bifunctional organocatalysts will help to arrange and activate the different reactants cooperatively, and promote the reaction with high selectivity. However, substrate dependence still remains an important issue in many bifunctional organocatalytic asymmetric reactions. Therefore, we have a high motivation to develop a multifunctional chemical system that can mimic the action of enzymes and effect organic reactions with excellent efficiency and stereoselectivity.

We here describe a new type of organocatalyst consisting of 1,2-diaminocyclohexane and 9-aminocinchona alkaloid derivatives for asymmetric Michael addition of enones. The organocatalysts provide multifunctional groups: a primary amine, which is expected to activate and arrange the enone,[6] and tertiary amine and thiourea helping to activate and arrange the nucleophiles.[7] Based on our design, cinchona alkaloid like derived primary amine thioureas have been synthesized (**2**, **3**, **4**, **5** and **6**). For comparison, a simple primary amine thiourea (**1**) was also prepared (Scheme 1).

We started our investigation using cyclohex-2-enone and nitromethane as substrates and some representative results are displayed in Table 1. Although the Michael addition between aldehydes and nitroalkenes was successfully catalyzed by the primary amine thiourea,[8] the reaction catalyzed by **1** gave a very poor result (entry 1). The main reason might be the fact that nucleophile was not efficiently activated by **1**. An essential enhancement was achieved when the reaction was catalyzed by a cinchona alkaloid derived primary amine thiourea containing a tertiary amine, which was expected to enhance the nucleophilicity of nitromethane. As a result, the Michael addition of nitromethane to enone was highly efficient and enantioselectively catalysed by **2**, **3**, **4** and **5** (entries 2–5). Especially with **3**, up to 92% ee and 92% of conversion were obtained without optimization. These encouraging results indicated that cinchona alkaloid derived primary amine thioureas might be a very efficient tool for this kind of Michael addition.

Optimal reaction conditions were investigated and the results are displayed in Table 1. It was found that the reaction medium had an impact on the conversion and enantioselective induction. The use of methanol afforded only 42% conversion and 55% ee (entry 6), which was in accordance with the reported results.[9] The reaction in DMF also gave low conversion (entry 7).[10] Importantly, the reaction in THF, $CH_3CN$, $Et_2O$, $CH_2Cl_2$, $CHCl_3$ and EtOAc all proceeded with excellent enantioselectivities and good to excellent conversions (entries 8–13) and the best results were obtained in ethyl acetate (entry 13).‡ It should be noted that decreasing solvent dosage resulted in high conversion and slightly decreased enantioselectivies within short times (entries 14–17). Decreasing the catalyst loading also afforded excellent conversion and enantioselectivity (entries 18 and 19). When a catalyst loading of 2 mol% was employed, up to 91% conversion and 95% ee could still be obtained (entry 19). When the catalyst was changed from **3** to **6**, the reaction rate was slowed and the configuration of the adduct was reversed (entry 20). This indicated that the stereochemistry was mainly controlled by the 1,2-diaminocyclohexane motif.

Under the optimized conditions, the scope of the reaction was explored. The results of Michael addition of nitroalkanes to a series of cyclic enones are presented in Table 2. The results showed that the reaction took place efficiently with good to excellent enantioselectivities and good isolated yields. Catalyzed by **3** with a loading of 5 mol%, up to 96% ee and 70% yield were obtained after only 36 h when cyclohex-2-enone reacted with nitromethane (entry 1). The presence of substituents at γ-position on the cyclic enone did not significantly effect the enantioselective induction and yield. The Michael




**Scheme 1** Structures of organocatalysts.

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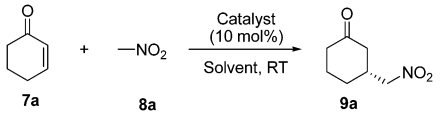
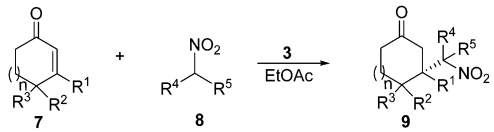
**Table 1** Catalyst and reaction conditions screen for the reaction between **7a** and **8a**[a]




| Entry | Catalyst | Solvent | $t$/h | Conv.[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **1** | Toluene | 48 | 15 | Nd |
| 2 | **2** | Toluene | 48 | 65 | 93 |
| 3 | **3** | Toluene | 48 | 92 | 92 |
| 4 | **4** | Toluene | 48 | 86 | 90 |
| 5 | **5** | Toluene | 48 | 90 | 90 |
| 6 | **3** | MeOH | 48 | 42 | 55 |
| 7 | **3** | DMF | 48 | 41 | 83 |
| 8 | **3** | THF | 48 | 89 | 95 |
| 9 | **3** | $CH_3CN$ | 48 | 83 | 96 |
| 10 | **3** | $Et_2O$ | 48 | 77 | 96 |
| 11 | **3** | $CH_2Cl_2$ | 48 | 81 | 96 |
| 12 | **3** | $CHCl_3$ | 48 | 84 | 95 |
| 13 | **3** | EtOAc | 42 | 95 | 97 |
| 14 | **3** | EtOAc[d] | 24 | 97 | 89 |
| 15 | **3** | EtOAc[e] | 20 | 95 | 95 |
| 16 | **3** | EtOAc[f] | 24 | 92 | 96 |
| 17 | **3** | None | 24 | 95 | 87 |
| 18 | **3**[g] | EtOAc[e] | 30 | 95 | 96 |
| 19 | **3**[h] | EtOAc[e] | 72 | 91 | 95 |
| 20 | **6**[g] | EtOAc[e] | 96 | 76 | −92 |

[a] *Reaction conditions*: a mixture of **7a** (1.0 mmol), **8a** (3.0 mmol), and the catalyst (10 mol%) in the solvent (2.0 mL) was stirred at room temperature for the time given. nd = not detected. [b] Determined by GC. [c] Determined by chiral HPLC. [d] Solvent (0.2 mL). [e] Solvent (0.5 mL). [f] Solvent (1.0 mL). [g] Catalyst (5 mol%). [h] Catalyst (2 mol%).

**Table 2** Asymmetric Michael addition of **8** to cyclic enones **7**[a]




| Entry | $n$ | $R^1$ | $R^2/R^3$ | $R^4$ | $R^5$ | $t$/h | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|---|---|
| 1[d] | 1 | H | H | H | H | 36 | 70 | 96 |
| 2 | 1 | H | Me | H | H | 120 | 85 | 87 |
| 3 | 0 | H | H | H | H | 120 | 70 | 80 |
| 4 | 2 | H | H | H | H | 120 | 25 (30[e]) | 92 |
| 5 | 1 | Me | H | H | H | 120 | 82 | 94 |
| 6[f] | 1 | Pr | H | H | H | 120 | 70 | 94 |
| 7[f] | 1 | Bu | H | H | H | 120 | 72 | 93 |
| 8[f] | 1 | Pentyl | H | H | H | 120 | 79 | 93 |
| 9[d] | 1 | H | H | Me | Me | 96 | 80 | 97 |
| 10[g] | 1 | H | H | Me | H | 48 | 84 | 98, 96 d.r. 2 : 3 |
| 11 | 1 | Me | H | Me | H | 120 | 92 | 95, 90 d.r. 7 : 3 |
| 12 | 1 | H | Me | Me | H | 48 | 92 | 91, 88 d.r. 3 : 2 |

[a] *Reaction conditions*: a mixture of **7** (1.0 mmol), **8** (3.0 mmol) and **3** (10 mol%) in ethyl acetate (0.5 mL) was stirred at room temperature. [b] Isolated yield. [c] Detected on GC or HPLC. [d] Catalyst (5 mol%). [e] Conversion. [f] Catalyst (20 mol%). [g] Catalyst (2 mol%).

adduct was generated with 85% yield and 87% ee from 4,4-dimethylcyclohex-2-enone (entry 2). Both enantioselectivity and conversion of cyclopent-2-enone were lower than that of cyclohex-2-enone.[9,11] The reaction between cyclopent-2-one and nitromethane gave 70% yield and 80% ee in the presence of **3** (entry 3). Cyclohept-2-enone was found to react quite slowly, however the enantioselectivity was still 92% (entry 4).

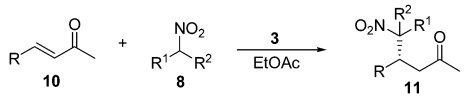
The organocatalytic enantioselective construction of quaternary stereocenters is an important yet challenging task in asymmetric synthesis and still receives the attention of synthetic chemists.[12] Due to steric repulsion, it is difficult to create such centers in a C–C bond-forming event. Moreover, it is also difficult to achieve high levels of enantiotopic face selectivity as a result of the relatively similar steric environments presented by the non-hydrogen substituents. It should be noted that a quaternary chiral carbon center was produced in 90–95% ee and 70–82% isolated yield when 3-substituted cyclohex-2-enone was reacted with nitroalkanes in the presence of **3** (entries 5–8, 11), which had rarely been reported before. It provides a new method for construction of quaternary stereocenters from cyclic enones and nitroalkanes.

It is known that different nitroalkanes have a large effect on the asymmetric induction of the reaction. Fortunately, the use of different nitroalkanes all gave excellent enantioselectivities with the cinchona derived primary amine thiourea **3** (entries 9–12). However, the diastereoselectivity is no higher than the reported results (entries 10–12).[13,14]

To further explore the scope of the reaction, the Michael addition of nitroalkanes to acyclic enones was tested and the results are displayed in Table 3. Most successful organocatalytic Michael addition reactions are limited to cyclic enones.[9–11,15] Jørgensen and co-workers have used imidazoline for the addition of 2-nitropropane to acyclic enone with high enantioselectivity and conversion.[14] However, the addition of nitromethane to acyclic enones has been reported rarely.[5d] With **3**, the Michael addition adducts from aromatic enones (entries 1–7), heteroaromatic enones (entry 8) and the alkyl-substituted enones (entries 9 and 10) were all formed in good to excellent yields with high enantioselectivities. Different substituents can be introduced on the aromatic ring without compromising the yield or enantioselectivity of the reaction (entries 3–7) except nitro group (entry 2). Excellent isolated yield and high enantioselectivity were obtained when nitroethane and 2-nitropropane were used as nucleophile, respectively (entries 11 and 12). Although acyclic enones provided low enantioselectivities compared with cyclic enones, the cinchona alkaloid derived primary amine thioureas were still an efficient tool for the Michael addition of nitroalkanes to acyclic enones.

In summary, we have developed a new type of multifunctional catalysts exhibiting synergistic cooperation to activate and arrange the different reactants, which is efficient tool for the asymmetric Michael addition of nitroalkanes to enones with high efficiency and enantioselectivity. Such cinchona alkaloid derived primary amine thioureas offer a new way to construct quaternary stereocenters from enones and nitroalkanes. Further investigations of the capacity of this methodology are currently underway and the results from these studies will be presented in due course.

**Table 3** Asymmetric Michael addition of **8** to cyclic enones **10**[a]




| Entry | R | $R^1$ | $R^2$ | $t$/h | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1[d] | $C_6H_5$ | H | H | 48 | 90 | 85 |
| 2 | 4-$NO_2C_6H_4$ | H | H | 72 | 60 | 73 |
| 3 | 4-$MeC_6H_4$ | H | H | 72 | 82 | 82 |
| 4 | 2-$MeC_6H_4$ | H | H | 72 | 91 | 84 |
| 5 | 4-$MeOC_6H_4$ | H | H | 72 | 65 | 80 |
| 6 | 2-$MeOC_6H_4$ | H | H | 96 | 70 | 85 |
| 7 | 4-$ClC_6H_4$ | H | H | 72 | 73 | 86 |
| 8 | 2-Thienyl | H | H | 96 | 68 | 78 |
| 9[d] | Pr | H | H | 60 | 93 | 84 |
| 10[d] | Bu | H | H | 60 | 84 | 84 |
| 11[d] | $C_6H_5$ | Me | Me | 48 | 96 | 82 |
| 12 | $C_6H_5$ | Me | H | 48 | 98 | 84, 84 d.r. 1 : 1 |

[a] *Reaction conditions*: A mixture of **10** (1.0 mmol), **8** (3.0 mmol), and **3** (10 mol%) in the solvent (0.5 mL) was stirred at room temperature. [b] Isolated yield. [c] Determined by GC or HPLC. [d] Catalyst (20 mol%).

## Notes and references

‡ General procedure for the Michael addition of nitroalkanes to α,β-unsaturated ketones: To a solution of ethyl acetate (0.5 mL) was added enone **7** or **10** (1.0 mmol), nitroalkane **8** (3.0 mmol) and catalyst **3** (0.10 mmol). The reaction mixture was stirred at room temperature for the time given and then the solvent was removed under vacuum. 1 M hydrochloric acid (5.0 mL) was added and the residue extracted with $CH_2Cl_2$ three times. The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (350–400 mesh) to yield the desired addition product.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