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# Pyrrolidine based chiral organocatalyst for efficient asymmetric Michael addition of cyclic ketones to β-nitrostyrenes

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ABSTRACT

An efficient asymmetric Michael addition of cyclic ketones to β-nitrostyrenes using secondary diamine as an organocatalyst derived from L-proline and (*R*)-α-methylbenzyl amine has been described. This pyrrolidine based catalyst **1** was found to be very effective to synthesize various γ-nitrocarbonyl compounds in good yield (up to 81%) with excellent stereoselectivity (up to >99:1 dr and >99% ee).



One of the most powerful and more economical approach for the preparation of wide variety of enantiomerically enriched compounds is through asymmetric organocatalysis.[1] The ease of functionalization, eliminating the use of toxic transition metals and mild reaction conditions are the distinguished features of this methodology.[2] Barbas[3] and List[4] independently reported the first organocatalytic addition of ketones to *trans* β-nitrostyrenes using L-proline as a catalyst with good yields, but very low enantioselectivities (0–23%). Since then the tremendous use of organocatalysis, offering high stereoselective transformations of versatile starting materials using easy procedures and mild conditions is on the rise. Organocatalysts have also been used in the synthesis of natural products such as (+)-Augustureine,[5a] (−)-brasoside[5b] and chiral baclofen,[5c,d] a potent GABAs receptor agonist that is used for the treatment of spinal cord injury-induced spasm. A large number of chiral amine derivatives derived from aminoacids have been developed to affect several highly useful transformations, including aldol, Mannich and Michael reactions, α-alkylations of carbonyl compounds, β-functionalizations of α,β unsaturated carbonyl compounds, Diel–Alder reactions, epoxidation reactions and many more.[6–10] The asymmetric Michael addition[11] involving α-enolizable ketones to electron deficient nitroolefins, has received much attention because the corresponding adducts, γ-nitro carbonyl compounds, constitute important building blocks in organic synthesis.[12] Many efficient and selective organocatalysts[13] have been employed for this reaction such as aminomethyl pyrrolidine, amine thiourea, pyrrolidinyltetrazole, pyrrolidine sulfonamide, chiral primary-secondary diamines, prolinamides etc. and significant improvement in diastereoselectivity and enantioselectivity has been documented.

Preliminary results were reported by Pansare and Kirby[14] on the application of pyrrolidine-based secondary–secondary diamine as catalyst for ketone–nitroalkene conjugate addition reaction and the role of catalyst-nitroalkene hydrogen bonding in the stereoselectivity of these reactions. In addition, the structural investigation for the stereoselectivity of conformationally constrained as well as conformationally flexible analogues of prolinamides,[15] synergically provides a foresight to synthesize and evaluate chiral L-pyrrolidine based diamine **1** as an organocatalyst. Although the corresponding amide **2**[15] has shown excellent yield and diastereoselectivity, but the observed enantioselectivity was up to 81%. A distinct trend in enantioselectivity and reactivity versus catalyst side chain p$K_a$ value was established by Yu et al.[16] and this interestingly reveals that higher p$K_a$ value in the catalyst's side chain favours higher enantioselectivity and reactivity (Fig. 1). Theoretical studies have also implied the role of hydrogen bonding and/or the steric interactions in deciding the stereoselectivity.[17] We explored the use of conformationally flexible chiral secondary–secondary diamine **1** as the organocatalyst, which was found to have higher p$K_a$ value for side chain (p$K_a$ = 34),[18] in Michael addition reactions of ketones with substituted β-nitrostyrenes and found that the corresponding γ-nitroketones are obtained in good yield with high stereoselectivity up to >99% ee and >99:1 dr.

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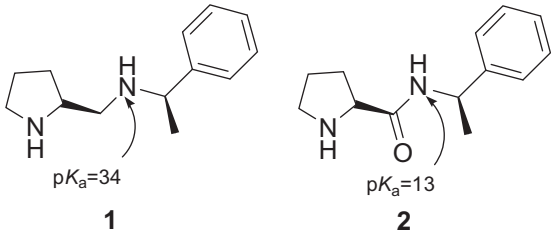



**Figure 1.** Side chain p$K_a$ values of organocatalyst **1** and the earlier known catalyst **2**.

The chiral catalyst **1** was easily prepared according to Scheme 1. Commercially available L-proline was reacted with Boc-anhydride[19] and the *N*-Boc protected proline **3** was activated towards nucleophilic attack by reaction with ethyl chloroformate and then treated with (*R*)-α-methyl benzylamine in the presence of triethyl amine to afford the corresponding amide **4** in 85% yield.[20] *N*-Boc deprotection with formic acid[20] and further reduction of amide **2** by $LiAlH_4$[21] afforded the desired chiral catalyst **1** in 40% overall yield.

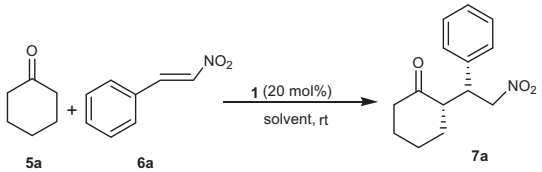
The activity of catalyst **1** was investigated by using cyclohexanone (**5a**) and β-nitrostyrene (**6a**) under different solvent conditions (Table 1). Initial trials using 20 mol % of catalyst **1** in chloroform at room temperature and without any other additive gave the desired Michael adduct **7a** in 53% yield with high *syn* diastereoselectivity (99:1 dr) and good enantioselectivity (98% ee) (Table 1, entry 1).

Best results were obtained in toluene with improved yield and stereoselectivity (Table 1, entry 6). The reaction proceeded to moderate extent in solvents like THF, $Et_2O$ and DMF (Table 1, entries 3–5) while in protic polar solvents, that is methanol and ethanol (Table 1, entries 7 and 8) only trace amount of the Michael adduct was formed. In most of the solvents, high enantioselectivity was observed irrespective of the yield.

Next, using toluene as solvent, the effect of catalyst loading was examined and the results are summarized in Table 2. A decrease in catalyst loading resulted in lowering of yield even after prolonging the reaction time, without affecting stereoselectivity (Table 2, entries 1 and 2). Increase in catalyst loading, that is up to 30 mol % did not show any synergic effect on reaction time, yield and stereoselectivity (Table 2, entry 4). Hence, the use of 20 mol % of catalyst **1** and toluene as a solvent at room temperature provided the best optimized reaction conditions.

To further explore the scope of this asymmetric Michael reaction, various nitro-olefins and cyclic ketones were investigated and the results are shown in Table 3. The catalyst **1** was tolerant to a broad range of nitro-olefins derived from aromatic systems bearing electron-donating as well as electron-withdrawing groups with different substitution patterns (Table 3). The furyl and napthyl derivatives of nitrostyrenes afforded the corresponding products **7f** and **7g** in good yield but somewhat decreased enantiomeric excess (Table 3, entries 6, 7). However, in case of cyclopenta-

**Table 1**
Screening of solvents[a]



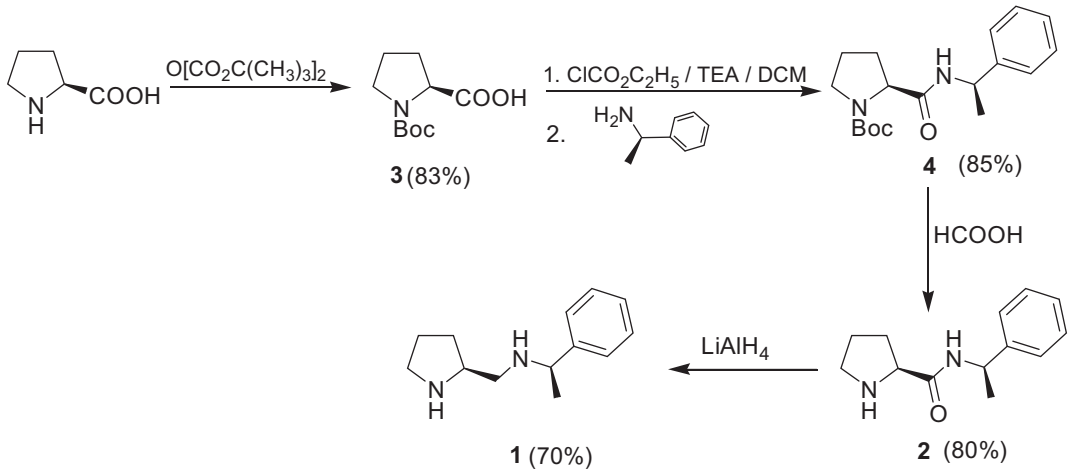

| Entry | Solvent | Time (h) | Yield[b] (%) | ee[c] (%) | dr[d] (*syn/anti*) |
|---|---|---|---|---|---|
| 1 | $CHCl_3$ | 24 | 53 | 98 | 99:1 |
| 2 | DCE | 24 | 58 | 98 | 99:1 |
| 3 | THF | 36 | 49 | 99 | 99:1 |
| 4 | $Et_2O$ | 36 | 44 | >99 | 99:1 |
| 5 | DMF | 36 | 32 | 99 | 98:2 |
| 6 | Toluene | 24 | 68 | >99 | >99:1 |
| 7 | MeOH | 36 | Traces | — | — |
| 8 | EtOH | 36 | Traces | — | — |

[a] Reaction conditions: nitrostyrene (1.6 mmol), cyclohexanone (3.2 mmol), catalyst **1** (20 mol %), solvent (10.0 mL), rt.
[b] Isolated yield.
[c] Determined by chiral HPLC using Chiralpak AS-H column.
[d] Determined by $^1H$ NMR analysis of crude sample.

**Table 2**
Effect of catalyst loading[a]

| Entry | Catalyst **1** (mol %) | Time (h) | Yield[b] (%) | ee[c] (%) | dr[d] (*syn/anti*) |
|---|---|---|---|---|---|
| 1 | 5 | 48 | 41 | 99 | 99:1 |
| 2 | 10 | 36 | 61 | 99 | 99:1 |
| 3 | 20 | 24 | 68 | >99 | >99:1 |
| 4 | 30 | 24 | 70 | >99 | >99:1 |

[a] Reaction conditions: nitrostyrene (1.6 mmol), cyclohexanone (3.2 mmol), toluene (10.0 mL), rt.
[b] Isolated yield.
[c] Determined by chiral HPLC using Chiralpak AS-H column.
[d] Determined by $^1H$ NMR analysis of crude sample.




**Scheme 1.** Synthesis of catalyst **1**.