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L-Prolinol as a highly enantioselective catalyst for Michael addition of cyclohexanone to nitroolefins

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ABSTRACT

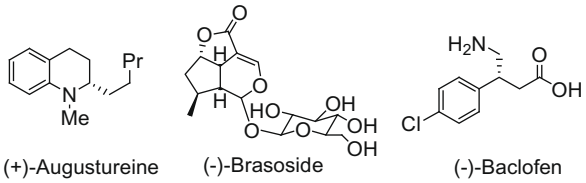
Though many chiral amines such as L-proline and its derivatives have proven to be versatile catalysts in many reactions, L-prolinol was seldom used as organocatalyst for reactions. Herein, we report the first L-prolinol catalyzed asymmetric Michael addition of cyclohexanone to nitroolefins in the presence of benzoic acid to afford Michael adducts with high diastereoselectivities (87:13–>99:1) and enantioselectivities (82–96%).

Organocatalysis has emerged as an extremely useful tool for the preparation of enantiomerically pure compounds in the past few years.[1] Operational simplicity, availability and the non-toxicity of the organic catalysts compared to the corresponding transition-metal species, as well as its high efficiencies and selectivities attained in many organocatalytic transformations made this methodology very attractive for the formation of enantiomerically pure compounds. Organocatalysis has proven its worth in the synthesis of many natural products such as (+)-Augustureine and (−)-brasoside.[2] Recently, Wang developed an efficient, organocatalytic, highly enantioselective, conjugate addition reaction which serves as the key step for a practical 3-step synthesis of chiral baclofen, a potent GABAs receptor agonist that is used for the treatment of spinal cord injury-induced spasm (Fig. 1).[3]

The Michael addition reaction is certainly one of the most general and versatile methods for formation of C–C bonds in organic synthesis.[4] Among all the organocatalytic transformations reported to date, considerable attention has been directed towards the development of organocatalytic asymmetric addition of carbonyl compounds to electron deficient nitroolefins.[5,6] This transformation has useful applications in organic synthesis due to the potential of formation up to three contiguous stereocenters and the high synthetic versatility of the nitro group.[7]

Many chiral amines such as L-proline and its derivatives have proven to be versatile catalysts in many C–C and C-heteroatom bond-forming reactions via enamine or iminium intermediates.[8] For example, Barbas[9], List[10] and Enders[11] independently reported L-proline-catalyzed addition of acetone to *trans*-β-nitrostyrene while Barbas also reported a reaction with cyclopentanone.[13b] In addition, Jørgensen[12], Barbas[13] and Alexakis[14] described the use of chiral imidazoline, aminomethylpyrrolidine and 2,2′-bipyrrolidine derivatives respectively as catalysts for asymmetric Michael addition reaction. Although these catalytic processes provide a unique methodology in asymmetric Michael addition reactions, development of effective catalysts is still very much desired.[15] Much attention has been paid to L-proline and its various derivatives but L-prolinol, first used in the Robinson annulation reaction[16], was rarely reported as an effective and efficient organocatalyst for reactions mainly due to poor results, such as yield, diastereo-, and enantioselectivities.[17]

The activation of the donors and control of asymmetric induction most likely occur through the formation of enamine intermediates.[18] Taking the proposed transition state of L-prolinol-type catalyst[19] into consideration, we envisioned that L-prolinol-cata-



(+)-Augustureine (-)-Brasoside (-)-Baclofen

Figure 1. Examples of natural products synthesized by organocatalysis.

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lyzed reaction of cyclohexanone to nitrostyrene will most probably proceed through similar hydrogen bonding in the transition state. Furthermore, the development of the simple and commercially available L-prolinol as a good organocatalyst will potentially reduce much hassle for stereoselective reactions. It would be an added advantage if the reaction could be carried out under solvent-free conditions. In view of the above advantages, we report the enantioselective organocatalytic Michael addition of cyclohexanone to nitroolefin using L-prolinol as catalyst under neat conditions, as well as the scope of the above-mentioned reaction.

We first performed the Michael addition of cyclohexanone to nitrostyrene in the presence of L-prolinol under neat conditions at room temperature (Table 1, entry 1). Despite the high diastereoselectivity (dr), low yield and enantioselectivity (ee) were obtained. This supported our initial idea and encouraged us to explore the reaction further. Thus, we tried to investigate the effects of the amount of cyclohexanone on the yield, dr and ee of the reaction at room temperature (Table 1, entries 3–5). Increasing the amounts of cyclohexanone is beneficial to both the dr and the ee. However, when cyclohexanone was used in large excess, the yield of the product dropped drastically (Table 1, entry 5). We also noticed that the yield, dr and ee decreased when the amount of benzoic acid was doubled (Table 1, entry 6).

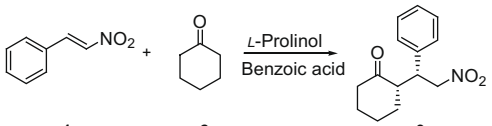
We tried to improve the results further by carrying out the reaction at low temperature. There was a significant improvement in the diastereoselectivity when the reaction was carried out at 0–4 °C (Table 1, entry 7). Next, the catalyst loading was decreased to 20 mol % and the enantioselectivity increased without affecting the yield and dr (Table 1, entry 9). However, the reaction rate was significantly reduced when the catalyst loading was decreased further to 10 mol % (Table 1, entry 11). The impact of cyclohexanone loading on the yield, diastereoselectivity and ee of the reaction was also probed—this time at low temperatures (Table 1, entries 8–10). Highest yield and enantioselectivity was achieved when 10 equiv of cyclohexanone was used. Although 3 equiv of cyclohexanone gave very good dr, the ee values were lower. In view of the above findings and in consideration of the various factors, such as time, yield, dr and ee, the scope of the reaction was explored using the following reaction conditions: 10 equiv of cyclohexanone added to 1 equiv of nitroolefin in the presence of 20 mol % of L-prolinol and benzoic acid at 0–4 °C.

With optimal reaction conditions established, we probed the scope of the reaction for a variety of nitroolefins and the results are summarized in Table 2. In the cases investigated, the Michael adducts were obtained in good to high yields (80–92%), with good to excellent diastereoselectivities (87:13–99:1) and enantioselectivities (82–96%). The Michael reaction between nitrostyrene and cyclohexanone was completed in 3 days and the Michael adduct was obtained in high yield (92%) with excellent diastereoselectivity (98:2) and enantioselectivity (95%) (Table 2, entry 1). The reaction times of *para*-substituted nitrostyrene are generally shorter than the *ortho*- or *meta*-substituted nitrostyrene, probably due to steric and electronic influences. Generally, the position and electronic properties (electron donating or electron withdrawing) of the substituents on the aromatic rings does not seem to affect the diastereo- and enantioselectivity of the addition reaction significantly. (Table 2, entries 3–10) The meta-substituted compounds were observed to give a slightly lower enantioselectivity than the *ortho*- and *para*-substituents. (Table 2, entry 6 and 9) The reaction also gave good results with heterocycles such as furanyl and thienyl compounds (Table 2, entries 11–13). On top of the diastereoselectivity and enantioselectivity of this reaction, **3n** also showed that this reaction is regioselective as cyclohexanone was added selectively on the double bond closer to the nitro group.

Since the relative and absolute configurations of the product generated from L-prolinol is the same as those catalyzed by pyrrolidine sulfonamide,[19] a similar transition state was proposed for L-prolinol-catalyzed Michael addition (Fig. 2).

In conclusion, the first L-prolinol-catalyzed asymmetric Michael additions of cyclohexanone to nitroolefins in the presence of benzoic acid afforded the respective adducts in good to high yields with high diastereoselectivities and enantioselectivities. Regioselectivity of this reaction was also demonstrated. Further investigations on the application of L-prolinol in natural product synthesis is in progress.

Table 1
Optimization of reaction condition[a]

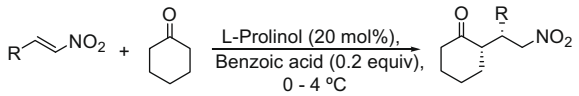


1a 2 3a

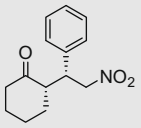
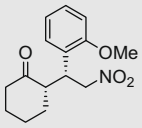
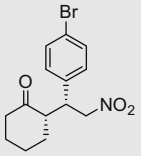
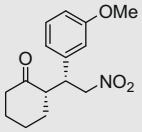
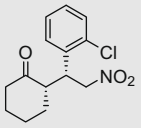
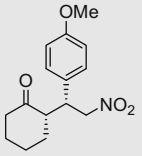
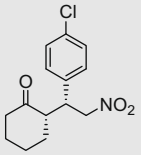
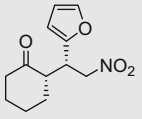
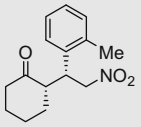
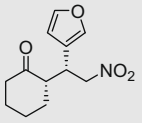
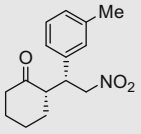
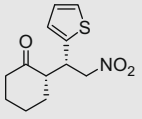
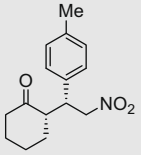
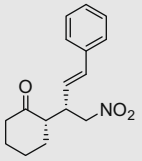
Entry	**2** (equiv)	Catalyst loading (mol%)	Time	Yield[b] (%)	dr[c]	ee[d] (%)
1[e]	3	30	66 h	43	95:5	54
2	3	30	6.25 h	74	91:9	72
3	5	30	6.5 h	78	89:11	87
4	10	30	6.5 h	83	91:9	84
5	20	30	6.5 h	31	94:6	81
6[f]	5	30	16 h	72	86:14	70
7[g]	5	30	42 h	78	>99:1	86
8[g]	3	20	3 days	77	96:4	92
9[g]	5	20	3 days	77	>99:1	91
10[g]	**10**	**20**	**3 days**	**92**	**98:2**	**95**
11[g]	5	10	<26 days	—	—	—

[a] Conditions: Nitrostyrene (0.5 mmol), cyclohexanone, L-prolinol and benzoic acid (1 equiv of catalyst) was added at 0–4 °C unless otherwise stated.
[b] Isolated yields.
[c] Determined by NMR.
[d] Determined by chiral phase HPLC.
[e] No benzoic acid added.
[f] 60 mol % of benzoic acid.
[g] Reaction at 0–4 °C.

Table 2
The generality of reaction of cyclohexanone and nitroolefin[a]



1a-n 2 3a-n

Entry	Adduct **3**	Time (days)	Yield[b] (%)	dr[c]	ee[d] (%)	Entry	Adduct **3**	Time (days)	Yield[b] (%)	dr[c]	ee[d] (%)
1	 **(3a)**	3	92	98:2	95	8	 **(3h)**	8	92	94:6	91
2	 **(3b)**	3	87	98:2[d]	93	9	 **(3i)**	8	83	>99:1[d]	84
3	 **(3c)**	11	80	98:2	90	10	 **(3j)**	6	85	94:6	91
4	 **(3d)**	4	83	93:7	92	11	 **(3k)**	3	90	90:10	93
5	 **(3e)**	11	82	97:3	92	12	 **(3l)**	6	89	>99:1[d]	82
6	 **(3f)**	17	85	95:5	89	13	 **(3m)**	3	92	90:10	94
7	 **(3g)**	7	83	96:4	92	14	 **(3n)**	12	82	97:3[d]	96

[a] Conditions: Nitrostyrene (0.5 mmol), cyclohexanone (5 mmol), in the presence of 20 mol % of L-prolinol and benzoic acid (without solvent) at 0–4 °C.
[b] Isolated yields.
[c] Determined by NMR unless otherwise stated.
[d] Determined by chiral phase HPLC.

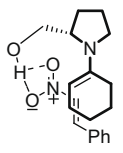


Figure 2. Proposed transition state.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.076.

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