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A highly enantioselective organocatalyst for the Michael addition of cyclic ketones to nitroolefins

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Dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—Enantiomerically pure triamine **2**, which catalyses the Michael addition of cyclic ketones to nitroolefins with high diastereoselectivity (up to 99:1) and enantioselectivity (up to 91% ee), was designed and prepared.
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1. Introduction

Organocatalyzed asymmetric synthesis has received great attention due to it being environmentally benign and fundamentally interesting.[1] Asymmetric Michael addition of nucleophiles to nitroolefins generates very useful chiral building blocks for organic synthesis.[2] The development of efficient organocatalysts for this reaction is, therefore, of fundamental importance. Recently, a highly enantioselective Michael reaction of malonates to nitroolefins has been reported, using chiral thiourea bifunctional organocatalysts.[3] A considerable amount of effort has been invested in the discovery of chiral organocatalysts for direct Michael addition of ketone or aldehydes to nitroolefins,[4–11] however only a few of the chiral organocatalysts show high enantioselectivity.[7,9–11] Thus, the discovery of new efficient organocatalysts is highly desirable. Readily available chiral diamine **1** has been evaluated for catalyzing the Michael addition, but shows moderate diastereo- and enantioselectivity.[6] Herein, we report a chiral triamine **2**, which contains a skeleton similar to that of diamine **1**, to catalyze the Michael addition with high diastereoselectivity and enantioselectivity (Fig. 1).

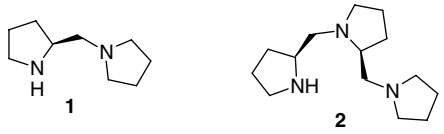

Figure 1. Organocatalysts for the Michael addition.

2. Results and discussion

The synthesis of **2** commenced with a condensation of Cbz-proline **3** with pyrrolidine in the presence of stoichiometric amounts of EDCI and HOBt to generate **4** in 83% yield. Hydrogenolysis of **4** in the presence of 10% Pd/C deprotected the *N*-Cbz group to provide **5** in a nearly quantitative yield. Coupling of **5** with Cbz-proline using EDCI and HOBt, afforded **6** in 81% yield. After removal of the protecting group and a subsequent reduction with lithium aluminum hydride, the target organocatalyst **2** was obtained in 45% yield (Scheme 1).

With organocatalyst **2** in hand, we first investigated the effect of the solvents on the catalytic performance with the Michael addition of cyclohexanone to nitrostyrene as a model reaction. The reaction was performed in different organic solvents at 20 °C in the presence of 15 mol % organocatalyst **2**. As shown in Table 1, both diastereo- and enantioselectivity are highly dependent on the solvent. It was found that toluene and diethyl ether are the solvents of choice. Although high enantioselectivity was observed for the reaction in DMSO, a slightly lower diastereoselectivity than those in toluene and diethyl ether was provided. A small amount of

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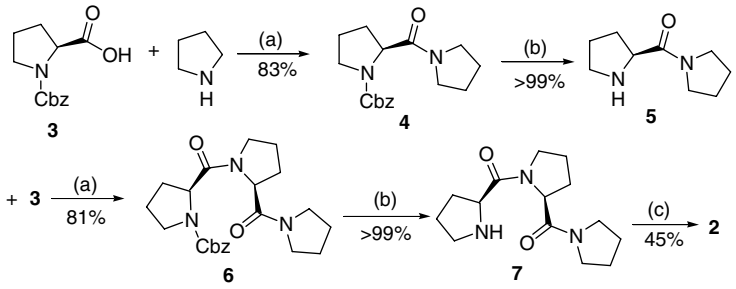
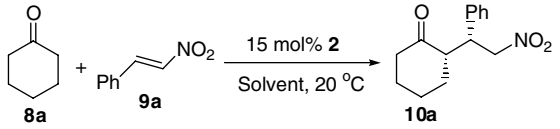


Scheme 1. Preparation of organocatalyst **2**. Reagents and conditions: (a) EDCI, HOBt, NMM, CH_2Cl_2, rt, 24 h; (b) Pd/C (10%), H_2 (1 atm), MeOH, 50 °C, 5 h; (c) $LiAlH_4$, THF, reflux, 2.5 days.

Table 1. Solvent screening[a]



Entry	Solvent	Time (d)	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee[d] (%)
1	THF	4	75	94:6	70
2	$CHCl_3$	5	60	9:1	59
3	Toluene	3	65	97:3	82
4	DCE	4	50	95:5	76
5	Et_2O	3	75	98:2	83
6	DMF	2	50	95:5	71
7	DMSO	2	42	96:4	82
8	Toluene	5	83	28:1	84[e]

[a] The reaction of cyclohexanone (1.0 mL), nitrostyrene (0.25 mmol), and **2** (0.038 mmol) was performed in a solvent (2.0 mL).
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude product.
[d] Determined by HPLC.
[e] The reaction was performed at 0 °C.

improvement in enantioselectivity (84% ee) was induced by performing the reaction at a reduced temperature (entry 8).

It has been reported that addition of an acid to the reaction can enhance the catalytic activity of the organocatalyst for Michael addition.[7a,9] Several sulfonic and carboxylic acids were surveyed for their effect on the organocatalyst **2** catalyzed Michael addition of cyclohexanone **8a** to nitrostyrene **9a**. As indicated in Table 2, the addition of an acid improved the reaction efficiency. Generally, a faster reaction with a higher stereochemical outcome than those in the absence of the acid additive (Table 1, entry 8) was obtained. The increased enantioselectivity of 90% and high diastereoselectivity of >98:2 were observed in the presence of 7.5 mol % (+)-camphor sulfonic acid (entry 4). The use of (−)-camphor sulfonic acid as an additive led to the product with a high diastereoselectivity of >98:2 and enantioselectivity of 85% ee (entry 5), indicating that the chirality of the stereogenic center of the acid had little effect on the enantioselectivity and diastereoselectivity.

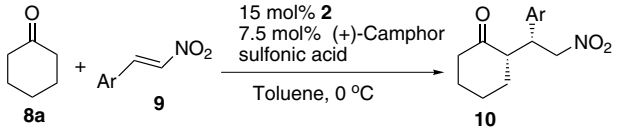
Under the optimized reaction conditions, the Michael addition of cyclohexanone to a range of nitro-olefins was examined. As can be seen in Table 3, the yield varied as the substituent on the nitrostyrenes changed, but the diastereo- and enantioselectivity are to some degree independent of this substituent (entries 1–6). Enantioselectivities of 90–91% ees were observed for all the substituted nitrostyrenes regardless of the electronic- and sterical properties of the substituents. The Michael addition to 2-(2-nitro-vinyl)-thiophene also led to formation of **10g** with high diastereoselectivity of 96:4 and enantioselectivity of 90% ee (entry 7).

Table 2. Effect of the acid on the Michael addition of cyclohexanone to nitrostyrene catalyzed by organocatalyst **2**[a]

Entry	Acid	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee[d] (%)
1	$C_6H_5CO_2H$	92	>98:2	85
2	4-$NO_2C_6H_4CO_2H$	94	>98:2	89
3	4-$MeC_6H_4SO_2H$	86	>98:2	85
4	(+)-Camphor sulfonic acid	95	>98:2	90
5	(−)-Camphor sulfonic acid	94	>98:2	85
6	CF_3CO_2H	85	>98:2	88

[a] The reaction of cyclohexanone (1.0 mL), nitrostyrene (0.25 mmol), **2** (0.038 mmol), and acid (0.019 mmol) in toluene (2.0 mL) was performed at 0 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude product.
[d] Determined by HPLC.

Table 3. Michael addition of cyclohexanone with nitroolefins[a]



Entry	Ar (**9**)	Time (d)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	Ph (**9a**)	3	95	>98:2	90
2	2-$NO_2C_6H_4$ (**9b**)	5	86	>98:2	90
3	3-$NO_2C_6H_4$ (**9c**)	3	88	>98:2	90
4	2-ClC_6H_4 (**9d**)	3.5	99	>98:2	91
5	4-ClC_6H_4 (**9e**)	4	88	97:3	90
6	4-BrC_6H_4 (**9f**)	3	90	>98:2	90
7	C_4H_3S (**9g**)	3.5	81	96:4	90

[a] The reaction of cyclohexanone (1.0 mL), nitrostyrene (0.25 mmol), **2** (0.038 mmol), and (+)-camphor sulfonic acid (0.019 mmol) in toluene (2.0 mL) was performed.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude product.
[d] Determined by HPLC.

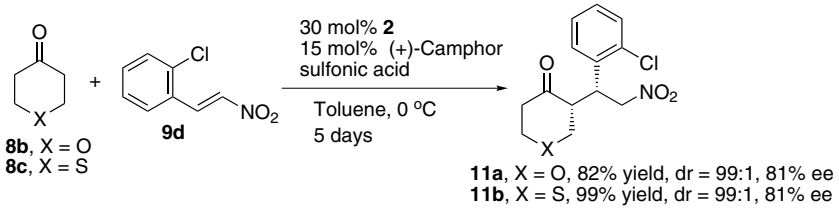


Figure 2. Michael addition of ketones to **9d**.

Two cycloketones **8b** and **8c** were reacted with **9d** in the presence of 30 mol % organocatalyst **2** to give the corresponding products **11a** and **11b** in 82% and 99% yields with perfect diastereoselection of 99:1 and good enantioselectivities (81% ee) (Fig. 2).

Since the relative and absolute configurations of the product generated from **2** catalyzed Michael addition are the same as those observed with diamine **1** as a catalyst,[6] a transition state similar to the diamine **1** catalyzed Michael addition was proposed for **2** catalyzed Michael addition (Fig. 3). The R group occupies a larger space than a pyrrolidine to more efficiently shield the *si*-face of an enamine double bond,[12] which might be a possible reason for the high stereochemical outcome.

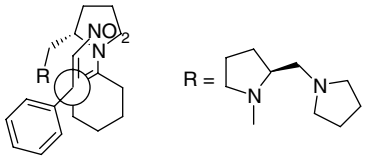


Figure 3. Proposed transition state.

3. Conclusion

In conclusion, we have designed and prepared a chiral triamine **2**, which effectively catalyzed the Michael addition of cyclohexanone and its analogues to nitroolefins in high yields with excellent diastereo- and enantioselectivity. The application of this catalyst to other reactions is currently underway.

Acknowledgements

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