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Enantioselective Organocatalytic Michael Addition Reactions between *N*-Heterocycles and Nitroolefins

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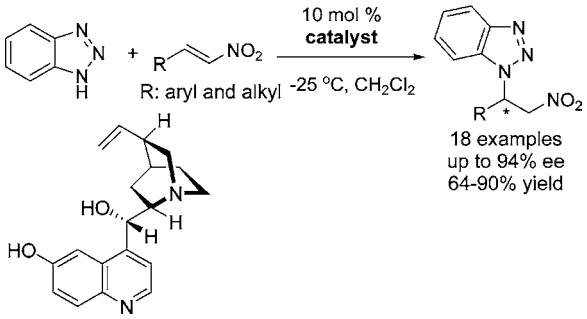
ABSTRACT



A method for Michael addition of *N*-heterocycles to nitroolefins has been developed. The process is promoted by a cinchona alkaloid derivative to give Michael adducts in moderate to high enantioselectivities.

Because of their broad application to organic and medicinal chemistry as well as material science,[1,2] nitrogen-containing heterocycles and their derivatives have been the focus of numerous synthetic efforts. Conjugate addition reactions of nitrogen-centered heterocyclic nucleophiles to electron-deficient olefins serve as a powerful preparative method in the area of heterocyclic chemistry. While an asymmetric version of this Michael addition process would furnish enantiomerically enriched adducts, to date reports of this reaction are sparse. For example, Jacobsen et al. have developed highly enantioselective Michael additions of HN_3, HCN, electron deficient nitrile derivatives, and oximes to α,β-unsaturated ketones and imides that are promoted by a chiral [Al-salen] complex.[3] More recently, this group disclosed that *N*-heterocycles can be used as nucleophiles in this process.[4] In another report, Miller described the use of peptides as a catalyst for the asymmetric conjugate addition of HN_3 to imides.[5]

Nitroolefins are attractive Michael acceptors because the strongly electron withdrawing[6] nitro group can be readily transformed into a variety of functionalities.[7a] We envisioned that weakly nucleophilic *N*-heterocycles, such as benzotriazole, triazole, and tetrazole, would participate as Michael donors in catalytic conjugate addition reactions with nitro-

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olefins. Recently, a number of observations have been made of asymmetric organocatalytic reactions involving nitroalkenes as Michael acceptors.[7−12] Among these, processes catalyzed by bifunctional proline and its derivatives,[8] cinchona alkaloids and their derivatives,[11] and amine thioureas[9,10,12] are notable examples.

Organocatalysts should be particularly useful for promoting these reactions because of their operational simplicity and environmental friendliness.[13] To explore new types of substrates and increase the pool of available templates for catalytic asymmetric Michael addition reactions, we recently explored a new approach in which organocatalysts are employed to promote Michael additions of *N*-heterocycles to electron-deficient nitroalkenes. Below, we present the results of this effort which show that these processes take place in good yields and with high levels of enantioselectivity. The Michael adducts produced in these reactions can be potentially exploited in the synthesis of biologically important substances.[1,2,14]

In an exploratory study, six bifunctional organocatalysts, including cinchona alkaloids **I**−**IV**[11] and amine thioureas **V**[11e] and **VI**,[12] were screened for their ability to promote Michael addition reaction of benzotriazole **1a** and *trans*-*β*-nitrostyrene **2a** in CH_2Cl_2 at room temperature (Figure 1 and

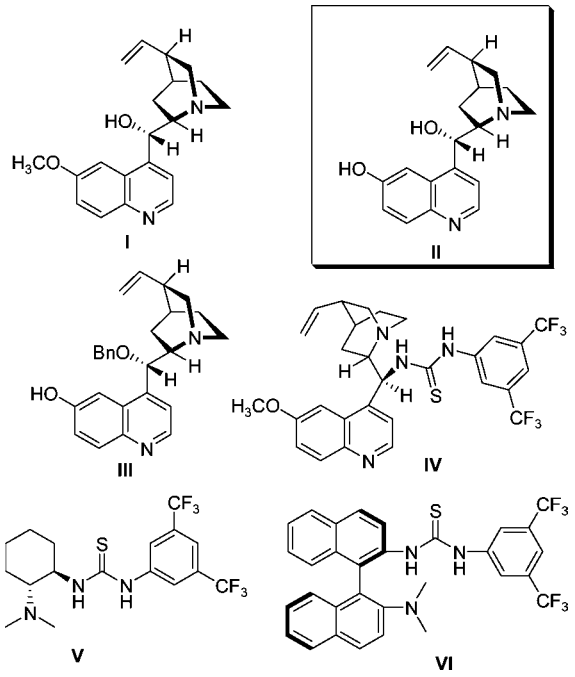
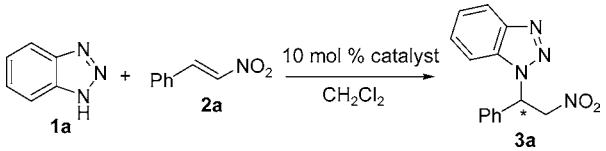


Figure 1. Screened organocatalysts

Table 1). The results showed that all of the catalysts **I**−**VI** exhibited high activity and that the Michael adduct **3a** was formed in good yields (79−88%) in all cases. An interesting finding was that the N1 addition product **3a** was produced exclusively with all catalysts. This contrasts with the results of the chiral [Al-salen] complex promoted Michael addition reactions which afford both N1 and N2 adducts.[4] Among

Table 1. Catalytic Asymmetric Michael Addition Reactions of 1H-Benzo[*d*][1,2,3]triazole (**1a**) and *trans*-*β*-Nitrostyrene (**2a**)[a]



entry	catalyst	*t* (h)	*T* (°C)	yield (%)[b]	ee (%)[c]
1	**I**	12	rt	86	rac[d]
2	**II**	3	rt	87	53
3	**II**	8	0	84	57
4	**II**	24	−25	81	70
5	**II**	72	−25	69	67[e]
6	**II**	120	−50	62	68
7	**III**	5	rt	80	13
8	**IV**	6	rt	88	44
9	**V**	8	rt	85	41
10	**VI**	8	rt	79	26

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.21 mmol) and **2a** (0.19 mmol) in the presence of 10 mol % of an organocatalyst in 2.0 mL of CH_2Cl_2 for the specified time. [b] Isolated yields after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Racemic isomer. [e] 5 mol % of catalyst used.

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(9) For Takemoto's amine thiourea catalysts, see: (a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119 and cited references therein. (b) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807. (c) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898.

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(12) Recently, we have developed binaphthyl-based amine thioureas for asymmetric organocatalytic reactions, see: (a) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (b) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.

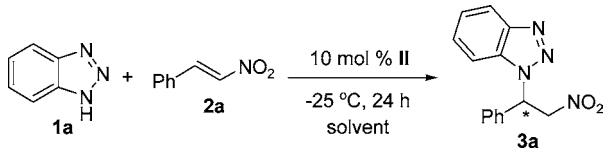
(13) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: New York, 2005.

(14) Triazole moieties are important pharmacophores and can be found in many drugs such as Alprazolam, a major agent for the treatment of anxiety, Fluconazole, an antifungal agent, and nucleoside-based Ribavirin, an antiviral drug. Tetrazoles have often been used as bioequivalent replacements for CO_2H in pharmacologically active compounds due to their favorable physicochemical properties.

those tested, catalyst **II** has the most favorable characteristics in terms of reaction time (3 h) and enantioselectivity (53% ee) (Table 1, entry 2). Examination of the structures of **I**−**III** revealed that the hydroxyl groups in the catalysts played a significant role in controlling enantioselectivity. The reaction promoted by catalyst **II**, which contains two OH groups, proceeds with higher ee than those catalyzed by **I** and **III**, both of which bear only one OH group (entries 1 and 7). Lower ee values were observed for processes promoted by the amine thioureas **IV**−**VI** despite the fact that these reactions took place in higher yields (entries 8 to 10). On the basis of these results, we selected organocatalyst **II** for further investigation.

In studies of the addition reaction promoted by **II** aimed at optimizing reaction conditions, we found that lowering the temperature to −25 °C results in an improved enantioselectivity without a significant lowering of yield and an increase in time (Table 1, entry 4). A much longer reaction time (120 h) was required without enhancing enantioselectivity when the reaction temperature was −50 °C (entries 6). Also, no advantage was gained when catalyst loading was reduced (5 mol %, entry 5). Solvent effects were also probed and it was found that CH_2Cl_2 was ideal for this process (Table 2).

Table 2. Effect of Solvent on the Catalytic Asymmetric Michael Addition Reaction of 1H-Benzo[*d*][1,2,3]triazole (**1a**) and *trans*-*β*-Nitrostyrene (**2a**)[a]

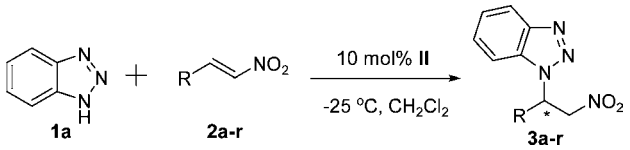


entry	solvent	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	81	70
2	THF	83	59
3	Et_2O	65	52
4	anisole	68	67
5	toluene	83	65
6	$ClCH_2CH_2Cl$	74	70
7	DMF	57	0

[a] Unless specified, see footnote *a* in Table 1 and the Supporting Information for reaction conditions. [b] Isolated yields after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak AS-H).

The conjugate addition reactions of nitrogen heterocycle **1a** with a variety of nitroolefins **2** under optimized conditions (10 mol % of **II**, at −25 °C in CH_2Cl_2) were investigated (Table 3). The results showed that in general the reactions took place efficiently (64−90%) with moderate to excellent levels of enantioselectivity (57−94% ee). Aromatic nitroolefins, bearing both electron-withdrawing (Table 3, entries 3, 7, and 8) and electron-donating substituents (entries 2, 4−6, and 10) on the phenyl ring, participated in this reaction but the substitution pattern on the aromatic ring has a significant affect on enantioselectivity. Reactions of nitro-

Table 3. Catalyst **II** Promoted Michael Addition Reactions of Benzotriazole **1a** to *trans*-*β*-Nitrostyrenes **2a**−**r**[a]

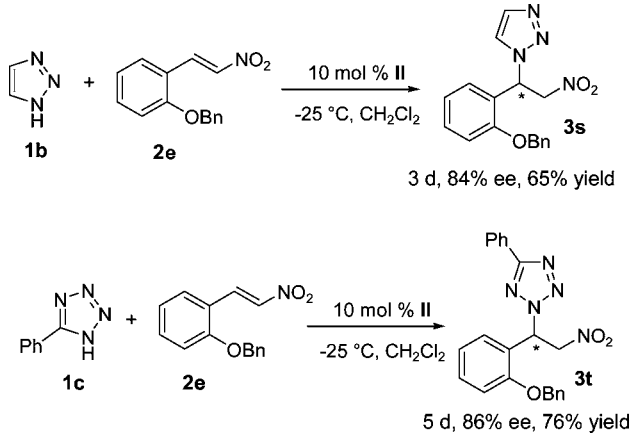


entry	R	adduct	*t* (h)	yield (%)[b]	ee (%)[c]
1	Ph	**3a**	24	87	70
2	4-CH_3-C_6H_4	**3b**	96	70	72
3	4-Cl-C_6H_4	**3c**	36	74	70
4	4-BnO-C_6H_4	**3d**	48	73	78
5	2-BnO-C_6H_4	**3e**	48	87	92
6	2,3-$(MeO)_2$-C_6H_3	**3f**	84	77	80
7	2-(4-NO_2-$PhCO_2$)-C_6H_4	**3g**	36	73	84
8	2-($PhCO_2$)-C_6H_4	**3h**	36	75	94
9	2-Ph-C_6H_4	**3i**	36	90	86
10	2-(4-Cl-PhS)-C_6H_4	**3j**	36	83	90
11	2-naphthalene	**3k**	96	64	67
12	2-thiophene	**3*l***	48	79	80
13	2-(*N*-Cbz)-pyrrole	**3m**	48	80	94
14	4-*N*-trityl-1*H*-imidazole	**3n**	96	77	81
15	$PhCH_2CH_2$	**3o**	48	83	57
16	$(CH_3)_2CHCH_2$	**3p**	36	67	68
17	*n*-C_5H_{11}	**3q**	24	78	65
18	*n*-C_6H_{13}	**3r**	24	76	64

[a] Unless specified, see footnote *a* in Table 1 and the Supporting Information for reaction conditions. [b] Isolated yield after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or AD).

olefins with substituents at the para position (entries 2−4) occurred with relatively low enantioselectivities (70−78% ee), but higher enantioselectivity (80−94% ee) accompanied reactions of substrates with substituents at the *o*-phenyl position (entries 5−10). The **II**-catalyzed processes were also applicable to heterocyclic thiophene-, pyrrole-, and imidazole-substituted nitroolefins (entries 11−14), with good yields (64−80%) and good to high enantioselectivities (64−94% ee) being common. Aliphatic nitroalkenes **2o**−**r** as

Scheme 1. Catalyst **II** Promoted Michael Addition Reactions of *N*-Heterocycles **1b** and **1c**



Michael acceptors were also evaluated for the processes and it was found that the reactions took place in moderate enantioselectivities (57−68% ee) and good yields (67−83%) (entries 15−18). It seems that the steric hindrance arising from the chains of these aliphatic nitroalkenes has a marginal effect on the enantioselectivities of the processes.

In our preliminary effort, the reactivity of other nitrogen heterocycles in this Michael reaction was evaluated (Scheme 1). It was found that both 1*H*-[1,2,3]triazole **1b** and 5-phenyl-1*H*-tetrazole **1c** served as Michael donors in conjugate additions to *β*-nitrostyrene **2e** which took place in good yields (65% and 76%, respectively), high ee (84% and 85%, respectively), and excellent regioselectivities. Unfortunately, the process for purines was very slow (<10% yield after 3 d).

In summary, the new catalytic Michael addition reaction, using the cinchona alkaloid derivative **II**, described above serves as a convenient method to prepare efficiently a wide range of new *N*-hetereocycles with good to high enantiomeric enrichments. A range of nitroolefins and *N*-hetereocycles can be employed in the process. Further investigation of the scope of the Michael reaction and its mechanistic details and its application to the synthesis of biologically important compounds is underway.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR HRMS data for products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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