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Organocatalytic Asymmetric Tandem Michael−Henry Reactions: A Highly Stereoselective Synthesis of Multifunctionalized Cyclohexanes with Two Quaternary Stereocenters

Bin Tan, Pei Juan Chua, Yongxin Li, and Guofu Zhong*

Division of Chemistry & Biological Chemistry, School of Physical and Mathamatical Sciences, Nanyang Technological University, Singapore 637371, Singapore

guofu@ntu.edu.sg

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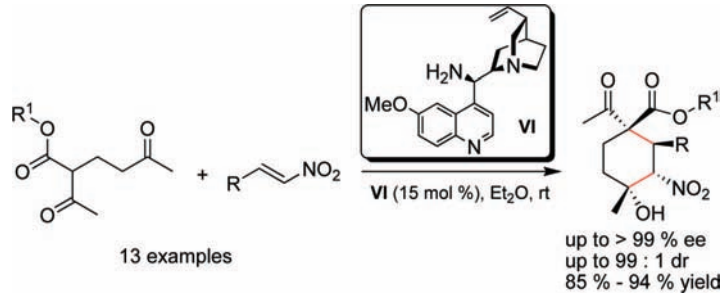
ABSTRACT



A novel organocatalytic asymmetric tandem Michael−Henry reaction catalyzed by 9-amino-9-deoxyepiquinine (VI) has been developed. The reaction was efficiently catalyzed by catalyst VI to give highly functionalized cyclohexanes with four stereogenic carbons including two quaternary stereocenters in excellent enantioselectivities (97 to >99% ee) and high diastereoselectivities (93:7−99:1 dr). Thus, the first organocatalytic asymmetric Henry reaction of common ketones as acceptors is shown.

The asymmetric construction of a quaternary carbon atom represents one of the most challenging and demanding topics in the synthesis of natural products and chiral drugs.[1] The development of efficient methods to access complex molecules with multiple stereogenic centers also continues to be a substantial challenge in both academic research and industrial applications.[2] One approach toward these challenges is the use of catalytic enantioselective cascade reactions,[3] which have emerged as powerful tools to give a rapid increase in molecular complexity from simple and readily available starting materials, thus producing enantioenriched complex compounds in a single operation. Of the developed strategies for asymmetric tandem reactions, organocatalysis provided an efficient protocol.[4] The syntheses of substituted cyclohexenes by applying a three-component

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domino reaction[5a,b] and by a two-component multistep Michael−Henry sequence using pentane-1,5-dial and 2-substituted nitroalkenes[5e] have been described. Although several other elegant organocatalytic tandem reactions have also been reported recently,[6] the development of new methods for the generation of molecules with multiple stereogenic carbons[5] including quaternary centers in a cascade manner remains a big challenge at the forefront of synthetic chemistry.

The Michael addition reaction provides an important tool for the construction of highly functionalized carbon skeletons.[7] In principle, the stereocontrolled conjugate addition of a trisubstituted carbon nucleophile to a prochiral Michael acceptor could provide a one-step construction of such highly congested motifs from simple precursors. However, this requires the catalyst to impart both high enantioselectivity and diastereoselectivity in a sterically demanding intermolecular C−C bond formation that simultaneously creates both the quaternary and tertiary stereocenters. This task has proven to be a formidable challenge. Up to date, there were only a few literatures that reported the 1,4-adducts containing one adjacent quaternary and tertiary stereocenters in both excellent enantioselectivity and diastereoselectivity in the field of organocatalysis[8] and still no report that is related to the formation of two quaternary centers.

The Henry reaction also represents a powerful C−C bond-forming tool, and the resulting nitro alcohol products can be transformed into a number of nitrogen and oxygen-containing derivatives such as nitroalkenes, amino alcohols and amino acids.[9] In addition to substrate-controlled Henry reactions, organocatalytic systems that provide good stereoselectivity have been developed in recent years. However, to the best of our knowledge, there is no report describing the possibility of common ketones used as acceptors with good results. In this paper, we disclose a novel facile organocatalyzed enantioselective tandem Michael-Henry reaction that generates multifunctionalized cyclohexane derivatives with four stereogenic centers including two quaternary stereocenters in excellent enantioselectivities (97 to >99% ee) and diastereoselectivities (up to 99:1 dr).

Readily accessible cinchona alkaloid and derivative catalysts, which were developed recently in several research groups, have been identified as efficient bifunctional organocatalysts in asymmetric Michael reactions[10] and Henry reactions.[11] These results prompted us to explore the feasibility of employing thiourea catalyst **I** (Figure 1) to catalyze

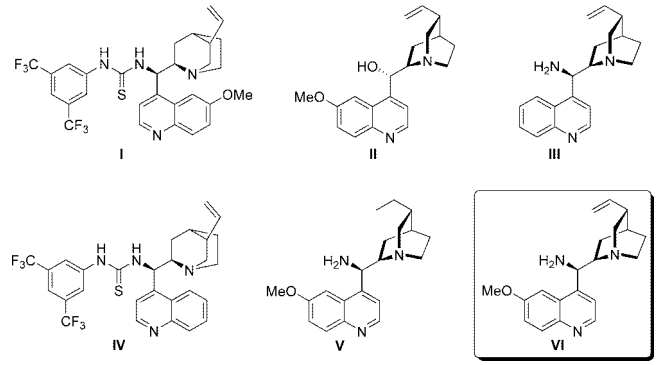

Figure 1. Cinchona alkaloid and derivative catalysts tested in the tandem Michael−Henry reaction.

the tandem Michael−Henry reactions involving a nitroolefin and carbon nucleophiles **1a** containing three carbonyl groups. To our great delight, the tandem Michael−Henry reaction proceeded smoothly to yield the desired cyclohexane product in high yield (85%) and good enantioselctivity (80% ee) and diastereoselctivity (92:8 dr, Table 1, entry 1). To improve the results, different conditions were investigated. However, the results did not change significantly when the reaction

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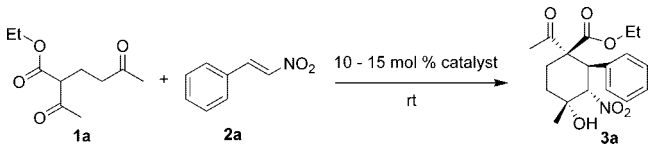
Table 1. Organocatalytic Tandem Michael−Henry Reactions of Ethyl 2-Acetyl-5-oxohexanoate **1a** and *trans*-β-Nitrostyrene[a]



entry	cat.	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**I**	neat	3	85	92:8	80
2	**I**	toluene	8	88	93:7	78
3[e]	**I**	neat	8	86	93:7	77
4	**II**	neat	3	95	85:15	26
5	**III**	neat	3	94	82:18	23
6	**IV**	neat	10	92	78:22	65
7	**V**	neat	18	90	95:5	92
8	**VI**	neat	10	92	95:5	92
9	**VI**	toluene	24	88	97:3	>99
10[f]	**VI**	toluene	18	92	98:2	>99
11[f]	**VI**	Et_2O	16	93	98:2	>99
12[f,g]	**VI**	Et_2O	16	93	98:2	>99

[a] Unless otherwise specified, all of the reactions were carried out using **1a** (0.6 mmol, 1.5 equiv) and **2a** (0.4 mmol, 1.0 equiv) with 10 mol % of catalyst at room temperature (23 °C). [b] Isolated yields. [c] Determined by crude NMR. [d] Determined by chiral HPLC analysis (major isomer). [e] Reaction at 4 °C. [f] 15 mol % of catalyst was used. [g] **1a** (0.4 mmol, 1.0 equiv) and **2a** (0.6 mmol, 1.5 equiv) were used.

was carried out in solvent or when the reaction temperature was decreased (Table 1, entries 2 and 3). As such, we turned our attention to revolutionizing catalysts. After screening the catalysts **II**−**VI** in Figure 1 at room temperature (23 °C) under neat conditions, **V** and **VI** were found to be excellent candidates to catalyze this tandem reaction with the highest stereoselectivity (92% ee, 95:5 dr) among all the tested cases, as shown in the Table 1. Catalyst **VI**[12] was then chosen as catalyst due to the higher yield obtained and its easy synthesis. Further optimization of the reaction conditions revealed that solvents played a very important role in determining the selectivities of the reaction (in toluene or diethyl ether, > 99% ee, 98:2 dr) (Table 1, entries 9−11).

With the optimized reaction conditions at hand, we expanded the scope of the tandem Michael−Henry process by using a variety of nitroolefins in diethyl ether at room temperature. It was discovered that most of the reactions are completed within 24 h with good to excellent yields (85% − 94%), with excellent enantioselectivities (97% to > 99% ee) and diastereoselectivities (93:7−98:2 dr). It appeared that the position and the electronic property of the substituents on aromatic rings have a very limited effect on the stereoselectivities. Regardless of the types of substituents on the aromatic rings, be it electron-withdrawing (Table 2, entries

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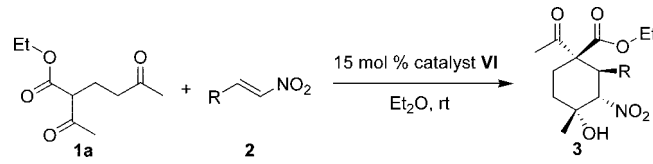
Table 2. Tandem Michael−Henry Reaction of Diketo Ester **1a** and Nitroolefin (**2**) Catalyzed by Catalyst **VI**[a]

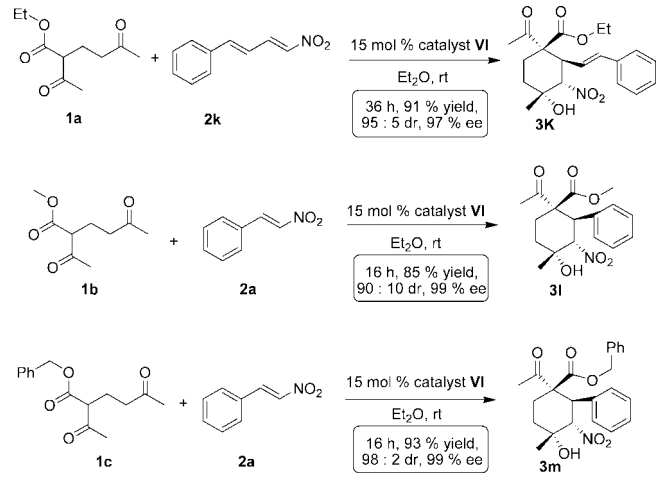


entry	R	**3**	time (h)	yield[b] (%)	dr	ee[c] (%)
1	Ph	**3a**	16	93	98:2	>99
2	4-MeO-C_6H_4	**3b**	24	91	95:5	98
3	4-Me-C_6H_4	**3c**	24	89	96:4	98
4	3-Me- C_6H_4	**3d**	24	90	95:5	99
5	4-Br- C_6H_4	**3e**	30	88	93:7	>99
6	2-Br- C_6H_4	**3f**	20	90	99:1	97
7	4-Cl- C_6H_4	**3g**	24	87	93:7	97
8	2-Cl- C_6H_4	**3h**	24	91	96:4	97
9	2-O_2N- C_6H_4	**3i**	24	94	98:2	97
10	4-CF_3- C_6H_4	**3j**	24	91	95:5	98

[a] All of the reactions were carried out using **1a** (0.4 mmol, 1.0 equiv) and **2** (0.6 mmol, 1.5 equiv) in the presence of 15 mol % of **VI** at room temperature in diethyl ether (0.4 mL). [b] Isolated yields. [c] Determined by chiral HPLC analysis (major isomer).

9 and 10) or electron-donating (entries 2−4), neutral groups (entry 1) and substrates containing a variety of substitution patterns (para, meta, and ortho) participated in this reaction efficiently. The reactions proceeded to afford highly enantioselective adducts. To our surprise, the presence of the nitro group on the aromatic ring did not cause the enantiomeric excess to decrease. This may be attributed to the primary amine group in the catalyst that can selectively capture the two nitro groups. Notably, only one Michael−Henry adduct was obtained from the reaction of nitrodiene **2k** in 97% ee (Scheme 1). Theoretically, both β- and δ-positions of **2k** are

Scheme 1. Tandem Michael−Henry Reactions of **1a** with **2k** and **1b**/**1c** with **2a**



possibly attacked due to the congruous two double bonds, showing the great regioselectivity and enantioselectivity of

this method. Furthermore, the tandem reaction also proceeded smoothly when **1a** was replaced by either **1b** or **1c**, giving excellent stereoselectivities (99% ee) as displayed in Scheme 1.

According to the dual activation model,[8e] the two substrates involved in the reaction are activated simultaneously by catalyst **VI** as shown in Figure 2. Nitroolefins are assumed

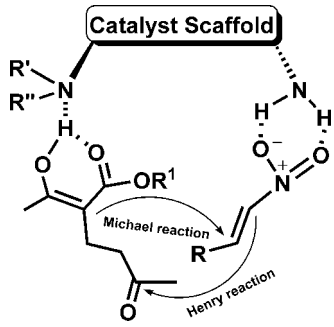


Figure 2. Proposed action of catalyst.

to interact with the primary amine moiety of **VI** via multiple H-bonds, thus enhancing the electrophilic character of the reacting carbon center. The carboanion (adjacent to the nitro group) generated from the Michael addition then attacks the si-face of the carbonyl group to afford Henry products (Figure 2). The stereochemistry was established by X-ray crystallographic determination of **3f** (CCDC 670273) and analysis of NMR data of the products.

In summary, we have developed a novel organocatalytic tandem Michael-Henry reaction. The reaction was efficiently catalyzed by readily available 9-amino-9-deoxyepiquinine (**VI**) to give synthetically useful, highly functionalized chiral cyclohexanes with four stereogenic centers containing two quaternary stereocenters in good to excellent yields (85−94%), excellent enantioselectivities (97% to >99% ee) and high diastereoselectivities (93:7−99:1 dr). We presented the first highly enantioselective Michael addition of α-substituted *β*-ketoesters to nitroolefins catalyzed by **VI** and, in particular, the first organocatalytic Henry reaction of common ketones used as acceptors with excellent results. We hope that this strategy of developing a practical and efficient tandem Michael−Henry reaction can spark more efforts into the designing of such organocatalytic reactions. This approach constitutes our future direction aimed at expanding the scope and applications of these powerful tandem processes.

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Supporting Information Available: Experimental procedures, characterization, spectra, chiral HPLC conditions, and X-ray crystallographic data (CIF file of **3f**: CCDC 670273). This material is available free of charge via the Internet at http://pubs.acs.org.

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