Organic LETTERS

Letter

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An Efficient One-Pot Approach to the Construction of Chiral Nitrogen-Containing Heterocycles under Mild Conditions

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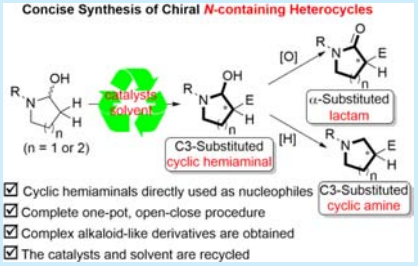
Supporting Information

ABSTRACT: A new, general, and practical procedure for the highly enantioselective synthesis of functionalized nitrogen-containing heterocycles has been developed. The simple cyclic hemiaminals were directly catalyzed for the first time as nucleophiles in an enamine-based asymmetric conjugate addition reaction. The practical approach recycles the catalyst and solvent which make it possible for large-scale and diversity-oriented chemical production.

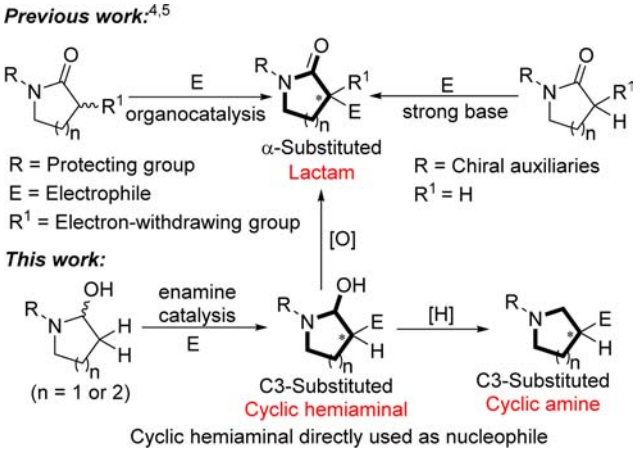


Chiral nitrogen-containing heterocycles, such as cyclic hemiaminal, lactam, and cyclic amine, are the ubiquitous substructures in numerous natural products and biologically active compounds.[1,2] Especially, lactams also serve as important building blocks toward the corresponding acyclic amino acids, such as γ-aminobutyric acids (GABAs), which are used in the regulation of neurological disorders such as Parkinson's disease and epilepsy.[3]

Consequently, significant efforts have been directed towards the development of facile access to these intriguing scaffolds. However, the asymmetric modification, starting from simple cyclic hemiaminal, lactam, or cyclic amine, is still viewed as a challenging task. Previously, the asymmetric organocatalytic approach has offered straightforward access to chiral α-substituted lactams; however, most cases are limited to the lactams containing an electron-withdrawing group at the α-position (Scheme 1, top, left).[4] In sharp contrast to the lactams containing a strongly electron-withdrawing group, the asymmetric functionalization of α-nonsubstituted lactams represents a challenging problem due to the higher pK_a value of the corresponding α-protons. Procedures for the asymmetric functionalization of α-nonsubstituted lactams can be found; however, they all rely on the use of chiral auxiliaries attached to the lactam nitrogen atom, and together with a strong base, such as LDA or *n*-BuLi, which can generate amide enolates from lactams to carry out nucleophilic additions at the α-position of lactams (Scheme 1, top, right).[5] Therefore, despite extensive efforts, the rapid and efficient synthesis of target nitrogen-containing heterocycles is still a challenging task in the field of synthetic organic chemistry.

Additionally, it is not hard to find that the C3-substituted cyclic hemiaminals could be used as versatile synthetic intermediates for the construction of nitrogen-containing heterocycles (Scheme 1, bottom). In a continuation of our

Scheme 1. Structures of Representative Chiral Nitrogen-Containing Heterocycles and Strategy for Their Synthetic Modification



ongoing interest and efforts in the chemistry of lactols,[6] we questioned whether this concept could be shifted to cyclic hemiaminals. At this point, however, the direct use of cyclic hemiaminals as nucleophiles is still one of the untested areas of enamine catalysis;[7] this may be ascribed to two significant challenges: (1) mechanistically validated *N*-Michael addition should be avoided[8] and (2) suitable conditions should be identified that would not deactivate the amine catalyst (Scheme 2).[9] We report herein the first case, which directly applies the simple cyclic hemiaminals as nucleophiles in aminocatalytic reactions providing facile access to C3-functionalized cyclic

Received: June 19, 2015
Published: July 22, 2015

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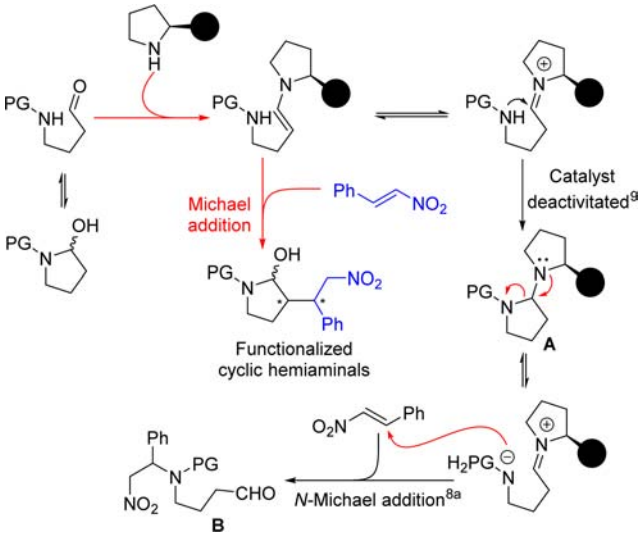
DOI: 10.1021/acs.orglett.5b01772
Org. Lett. 2015, 17, 3794−3797

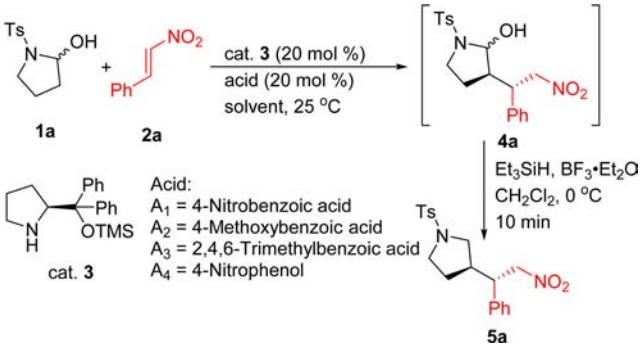
Scheme 2. Hypothesis and Challenges of Simple Cyclic Hemiaminals Directly Used As Nucleophiles



hemiaminals.[10,11] In line with these considerations, our initial experiments were carried out for the direct C3-functionalization of the cyclic hemiaminal **1a** with *β*-nitrostyrene **2a** under the best conditions from our previous work.[6] Unexpectedly, the reaction gave no desired product after 48 h with the commercially available catalyst **3** and toluene as the solvent (Table 1, entry 1). Consistent with the work of Chen and co-workers,[9] the intermediate **A** could deactivate the catalyst (Scheme 2, **A**), and water may be helpful for catalyst turnover. Indeed, in the presence of water (10% v/v), **4a** was formed after 24 h, and however, it is not stable enough for analysis. For a clean HPLC separation, we then subjected the crude **4a** to the reduction with $Et_3SiH/BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 0 °C for only 10 min, yielding C3-substituted cyclic amine **5a** in 84% yield with 94% enantiomeric excess (ee) and 10:1 diastereoselectivity (dr) in a one-pot procedure (Table 1, entry 2). Moreover, to our delight, the relative byproduct (Scheme 2, **B**), which is from the hypothesized N-Michael reaction, is not observed. Apparently, a homogeneous condition, when a mixture of CH_3CN/H_2O (10% v/v) was used as the solvent, works much more efficiently (Table 1, entry 3). With these promising results, several other solvent systems were tried (Table 1, entries 4–6); the mixture of THF/H_2O showed excellent results providing **5a** with an excellent yield and stereoselectivity (Table 1, entry 4). However, considering both the efficiency and economy of the reaction system, $EtOH/H_2O$ is used as the final solvent system (Table 1, entry 6). Similar good results were obtained with other acidic additives (Table 1, entries 7–9). A subsequent screening of alcohols such as MeOH, *i*-PrOH, and *t*-BuOH was conducted, but no improvements in results were noticed.[12]

Having established the optimal reaction conditions (Table 1, entry 6), the scope and generality of this new asymmetric conjugate addition reaction, with respect to both electrophiles and nucleophiles, were investigated, the simple cyclic hemiaminal **1** was treated with *β*-nitrostyrene **2** in the presence of **3** (20 mol %) and *p*-NO_2PhCOOH (20 mol %) in a mixture of $EtOH/H_2O$ (10% v/v) at 25 °C. As shown in Scheme 3, various electron-rich, electron-neutral, or electron-deficient nitroolefins with different substitution patterns in different positions of the aromatic ring reacted smoothly with cyclic hemiaminal **1** affording the final Michael adducts with good to excellent yields (71–91%) and enantioselectivities (97–99%),

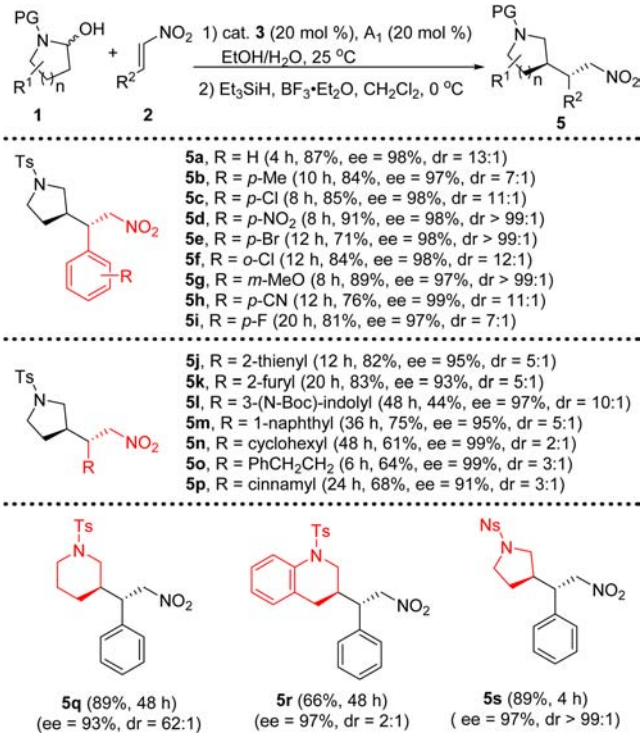
Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	time[b] (h)	yield[c] (%)	dr[d] (%)	ee (%)
1	toluene	48	–	–	–
2	$toluene/H_2O$	24	84	10:1	94
3	CH_3CN/H_2O	8	80	14:1	98
4	THF/H_2O	18	89	16:1	99
5	$acetone/H_2O$	8	73	11:1	98
6	$EtOH/H_2O$	4	87	13:1	98
7[e]	$EtOH/H_2O$	4	80	13:1	98
8[e]	$EtOH/H_2O$	5	82	9:1	98
9[e]	$EtOH/H_2O$	24	88	11:1	99

[a]See the Supporting Information for more details. [b]For the first step. [c]Yield of the isolated major diastereomer of **5a**. [d]Determined by Chiral HPLC analysis. [e]Acid A_2, A_3, and A_4 were used as acidic additives for entries 7, 8, and 9, respectively. THF = tetrahydrofuran. TMS = trimethylsilyl.

Scheme 3. Scope of the Reaction[a]



[a]See the Supporting Information for experimental details. Diastereomeric ratios were determined by Chiral HPLC analysis. Yields are of the isolated major diastereomer.

DOI: 10.1021/acs.orglett.5b01772
Org. Lett. 2015, 17, 3794–3797

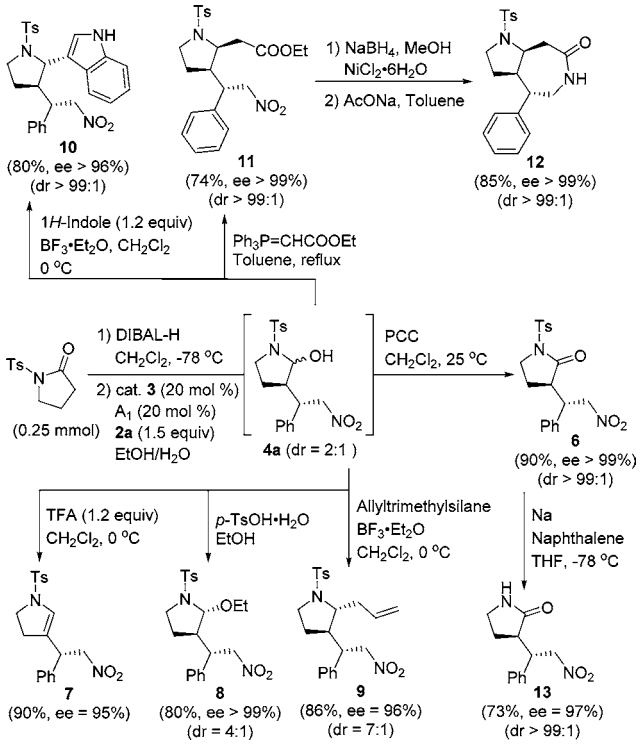
as well as diastereoselectivities (7:1 → 99:1) (**5a**−**5i**). Heteroaromatic nitroolefins **2j** and **2k** were also viable substrates, furnishing the corresponding products **5j** and **5k** in excellent yields and enantioselectivities. In addition, similar good results were attained for the nitroalkenes substituted with N-Boc protected indol or an even bulkier naphthyl group (**5l** and **5m**). Particularly noteworthy is the excellent enantioselectivity and good yield observed in the case of the less reactive alkyl nitroolefins, albeit diastereoselectivities were low for both cases (**5n** and **5o**). Remarkably, the reactions also proceeded efficiently with the α,β-unsaturated nitroolefin **2p** to afford the corresponding product **5p** in 68% yield and 91% ee. Surprisingly, the cyclic hemiaminal **1q** containing a six-membered ring gave an even higher diastereoselectivity (**5q**); however, combination with one more phenyl ring generated product **5r** with much lower diastereoselectivity albeit in good yield and excellent enantioselectivity. It should be noted that 2-nitrobenzenesulfonyl (Ns) could also be used as the protecting group yielding **5s** with excellent stereoselectivity and high yield.

It should be noted that the conjugate addition generated products as a white precipitate, except for **5n** and **5o**, in the reaction process under the optimized conditions. Accordingly, we envisioned a recycling of the organocatalyst to have a more practical and eco-friendly methodology. Consistent with this hypothesis, a 0.3 mmol scale reaction of **1a** and **2a** (0.36 mmol, 1.2 equiv) was investigated as a model, and the final product was isolated by simple centrifugation.[12] The catalyst and the excess **2a** remained in the filtrate. Then, **1a** (0.3 mmol) and **2a** (0.36 mmol) were added to the solution for the next cycle of the conjugate addition. This procedure was repeated several times with excellent results obtained, and there was only a marginal loss of reactivity or stereoselectivity after four cycles. Notably, to our knowledge, this is the first example of recycling of the unsupported catalyst, diphenylprolinol silyl ether **3**, in an enamine-based asymmetric Michael reaction.[13] As the catalyst was readily recycled and the reaction was scalable, this method should be suitable for diversity-oriented chemical production.

To highlight the potential of this novel approach, a complete open−close procedure,[9] starting from simple lactam to α-substituted lactam **6** in one pot, was carried out on a larger scale, which proceeded smoothly with maintained efficiency and enantioselectivity as well as diastereoselectivity (Scheme 4). With the crucial intermediate **4a**, subsequent subjection to acid catalysis afforded several highly functionalized heterocyclic derivatives **7**, **8**, and **9** with good yield and excellent stereoselectivity. It is clear that, in our desired Michael adduct, a nitrogen-containing heterocycle originally occurred, which is strongly distinguished from the normal enamine-based Michael reaction.[14] According to this salient feature, a range of valuable skeletons **10**, **11**, and **12**, containing multiple rings or a polycyclic alkaloid-like molecule, were synthesized in good to excellent yields via ordinary conditions. Furthermore, removal of the *N*-tosyl group was successfully achieved using Na/Naphthalene at −78 °C delivering the target molecule **13** in 73% yield.

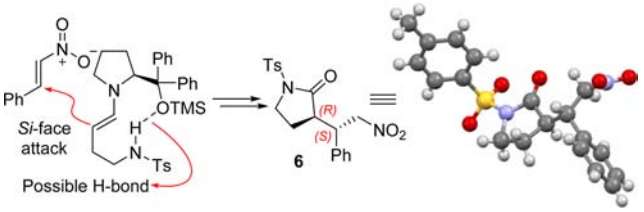
The absolute configuration of the product was estimated by single-crystal X-ray analysis of compound **6** as shown in Scheme 5.[15] According to the excellent stereoselectivity of the products, we proposed a model that a plausible intermolecular H-bond and together with the steric hindrance of the aryl and silyl substituents of the catalyst **3** dominate the stereoselectivity and catalytic activity on the *si*-face of enamine.[14]

Scheme 4. Synthetic Transformations[a]



[a]See the Supporting Information for experimental details. Diastereomeric ratios were determined by Chiral HPLC analysis. Yields are of the isolated major diastereomer. TFA = trifluoroacetic acid. *p*-TsOH·H_2O = *p*-toluenesulfonic acid. Ts = *p*-methylbenzenesulfonyl. DIBAL-H = diisobutylaluminum hydride.

Scheme 5. Possible Transition State and the X-ray Crystal Structure of 6



In summary, we have developed a highly efficient organocatalytic strategy for the construction of chiral nitrogen-containing heterocycles. Starting from simple cyclic hemiaminals, α-substituted lactams, C3-substituted cyclic amines, and even more complex heterocycles were obtained in high yield with excellent stereoselectivity (up to 99% ee, >99:1 dr). One-pot, mild reaction conditions were used, and the catalyst and solvent were recyclable. Additionally, the synthetic potential of this strategy was highlighted by the efficient synthesis of complex heterocycles possessing two or three stereogenic centers, which otherwise are difficult to access from traditional conjugate additions of aliphatic aldehydes with β-nitrostyrenes. Further synthetic application of this transformation and mechanistic studies are underway in our laboratory.

DOI: 10.1021/acs.orglett.5b01772
Org. Lett. 2015, 17, 3794−3797

■ ASSOCIATED CONTENT

Supporting Information

Detailed optimization, experimental procedures, spectroscopic data for all new compounds, and X-ray data (cif) for **6**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01772.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank two reviewers for their constructive and pertinent comments. This work was supported by the NSFC-Shandong Joint Fund for Marine Science Research Centers (No. U1406402), National Nature Science Foundation of China (Nos. 21302156, 81473337, 81274184), and Ocean University of China (OUC).

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(15) CCDC 1403667 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DOI: 10.1021/acs.orglett.5b01772
Org. Lett. 2015, 17, 3794−3797