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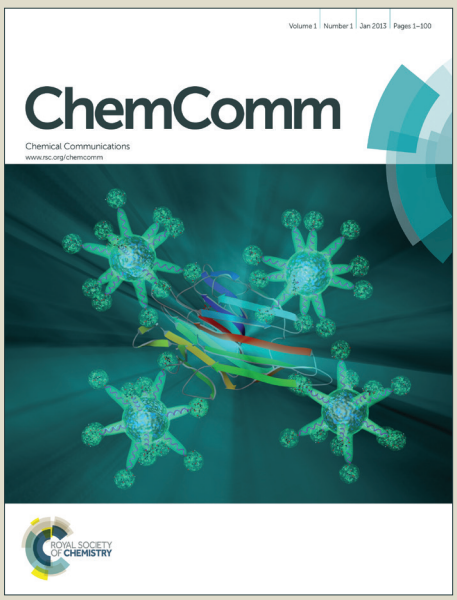

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ARTICLE TYPE

Highly Efficient Asymmetric Synthesis of Quaternary Stereocenter-Containing Indolizidine and Quinolizidine Alkaloids Using Aldehydes, Nitroalkenes, and Unactivated Cyclic Ketimines†

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A highly efficient approach for the construction of indolizidines and quinolizidines bearing a bridged quaternary stereocenter has been established in a one-pot fashion using aldehydes, nitroalkenes, and cyclic ketimines with excellent enantioselectivities and in high yields. Moreover, this method could be applied to the synthesis of indolizidine in gram scale.

Indolizidine and quinolizidine scaffolds, regarded as privileged structures occurred in many bioactive natural products, pharmaceuticals, and drugs, have drawn an intriguing attention from industrial and academic community for a long time (Figure 1).[1,2,3]

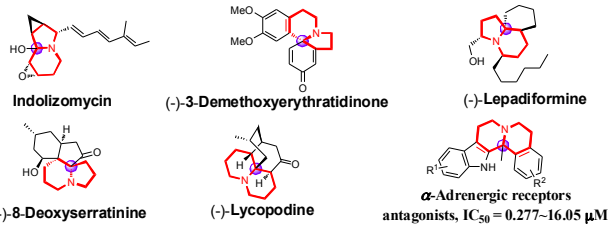
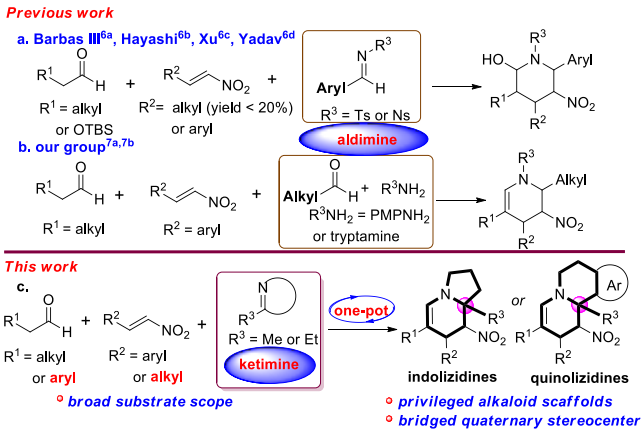


Fig. 1 Representative indolizidines and quinolizidines bearing a bridged quaternary carbon stereocenter.

Great efforts[2,3] have been made toward the highly efficient construction of natural indolizidines and quinolizidines as well as their derivatives for medicinal-related studies. However, among these powerful achievements, efficient and enantioselective assembly of indolizidine and quinolizidine skeletons containing bridged quaternary stereocenter still remains to be challenging.[3] Substituent installed at the bridged carbon atom can not only affect the molecule architecture, but also may alter the compound's relevant pharmacological properties, for example, the magic methyl effect.[4] Therefore, new catalytic asymmetric synthetic strategies to construct these privileged frameworks from readily available starting materials are extremely appealing and in high demand.

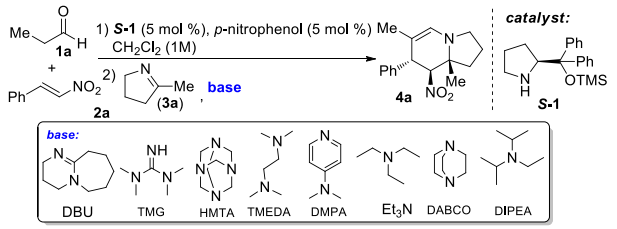
Asymmetric one-pot organocatalytic cascade reactions have been successfully applied to produce large libraries of diverse and enantioenriched privileged motifs with indisputable advantages in terms of availability of starting materials, atom economy, and step economy.[5] As a powerful tool, asymmetric Michael-*aza*-Henry(nitro-Mannich)-hemiaminalization cascade reactions involving aldehydes, nitroethylenes and aldimines have been employed independently to forge piperidine derivatives by Barbas III[6a], Hayashi[6b], Xu[6c], and Yadav[6d] (Scheme 1a). Recently, our group demonstrated that in-situ formed alkyl imines could also undergo this one-pot process to generate tetrahydropyridines and indoloquinolizidine derivatives (Scheme 1b).[7a,7b] Following this success, we wondered if the Michael adducts of aldehydes and nitroalkenes could serve as a chiral pool to react with ketimines in aza-Henry reaction. In this case, indolizidine and quinolizidine frameworks could be produced after the subsequent hemiaminalization. Despite substantial advancement in asymmetric Michael-aza-Henry-hemiaminalization cascade reactions, there are still challenges in this area. In contrast to aldimines, ketimines have been barely explored in asymmetric aza-Henry reaction,[8a] particularly the unactivated ketimines.[8b,8c] Moreover, less reactive *β*-alkyl-substituted nitroolefins have also been rarely studied. The only example with *β*-alkyl-nitroethylenes was reported by Barbas III and co-workers utilizing *β*-*n*-heptyl-nitroethylene to yield the desired piperidine in only 18% yield.[6a] In addition, there have been no report to employ the enolizable aldehyde bearing an aromatic substitution in *α*-position as a substrate. Herein, we disclosed a robust and highly efficient methodology for the preparation of a wide array of chiral indolizidine and quinolizidine scaffolds containing a bridged quaternary stereocenter using a broad spectrum of unactivated cyclic ketimines, aldehydes and nitroalkenes (Scheme 1c).



Scheme 1 Asymmetric Michael-aza-Henry-hemiaminalization cascade reaction sequence.

Initially, propanal **1a**, *β*-phenyl-nitrostyrene **2a**, and commercial available cyclic ketimine **3a** were examined as model substrates. Based on our previous work, propanal **1a** reacted with nitrostyrene **2a** using 5 mol % of Jørgensen[9]–Hayashi[10] catalyst ***S*-1** and 5 mol % of *p*-nitrophenol[9d] as additive in CH_2Cl_2 at room temperature (Table 1). When nitrostyrene **2a** was consumed after 30 min, 1.5 equiv of ketimine **3a** was added to the mixture. In spite of no extra base, the desired product **4a** was obtained after 3 h at room temperature in 9% yield, >20:1 dr and 95% ee (Table 1, entry 1), presumably the weak basicity of imine itself accounted for this result. Actually, base plays a significant role in aza-Henry reaction, having a great impact on both yield and diastereoselectivity.[7a,8] Therefore, various organic bases were screened. Strong bases like DBU and TMG were found to be ineffective for this cascade reaction and gave product **4a** in low yield (entries 2-3). On the other hand, bases with moderate basicity proved to be efficient in this cascade reaction. Among HMTA, TMEDA, DMAP, Et_3N, DABCO and DIPEA, DIPEA showed the best yield. The employment of 1 equiv of DIPEA as base gave the desired product in 85% yield, >20:1 dr and 95% ee (entries 4-9). The reaction with 0.5 equiv of DIPEA led to dramatic drop of yield while high stereoselectivity was retained (entry 10). When the reaction was carried out at 0 °C, the ee was increased to 98%, along with 91% isolated yield and >20:1 dr. This procedure was considered to be our optimal conditions for this cascade reaction (entry 11).

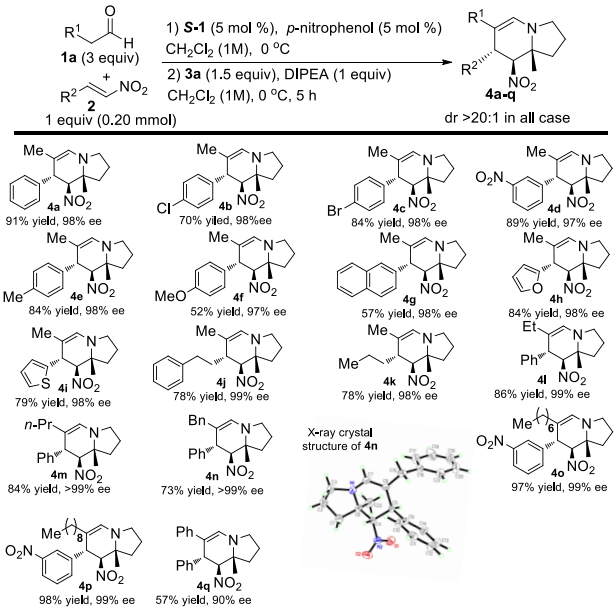
Table 1 Optimization of cascade sequence. [a]



Entry	Base	Yield (%)[b]	dr[c]	ee (%)[d]
1	none	9	> 20 : 1	95
2	DBU	18	> 20 : 1	95
3	TMG	29	> 20 : 1	95
4	HMTA	50	> 20 : 1	95
5	TMEDA	64	> 20 : 1	95
6	DMAP	66	> 20 : 1	95
7	Et_3N	72	> 20 : 1	95
8	DABCO	77	> 20 : 1	95
9	DIPEA	85	> 20 : 1	95
10[e]	DIPEA	46	> 20 :1	95
11[f]	DIPEA	91	> 20 :1	98

[a] Unless otherwise noted, the reaction was performed using **1a** (0.60 mmol), **2a** (0.20 mmol, 1M, 1 equiv), *p*-nitrophenol (5 mol %), ***S*-1** (5 mol %) at rt. After **2a** was consumed, **3a** (0.30 mmol) and base (0.20 mmol) were added and the reaction mixture was stirred for another 3 hours. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] 0.5 equiv (0.1 mmol) of DIPEA. [f] The reaction was performed at 0 °C (5 h + 5 h).

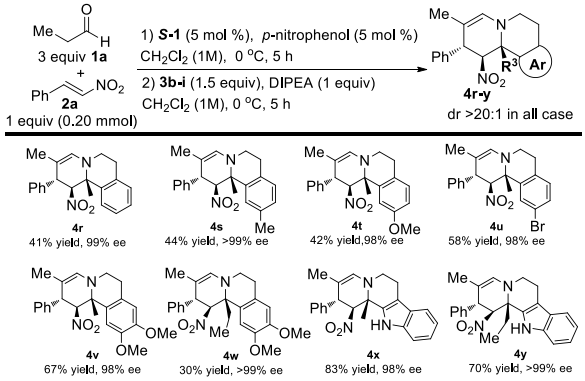
With the optimized conditions in hand, the substrate scope and generality of this one-pot sequences were investigated (Scheme 2). Gratifyingly, a variety of nitroethylenes with different functional groups were tolerant to this cascade reaction and provided the indolizidines in good to excellent yields (52-91%) with excellent ee (97-99%) and >20:1 dr (**4a-k**). It's worthy to mention that the less reactive *β*-alkyl-nitroalkenes could also proceed efficiently to yield the corresponding products in 78% yield and excellent enantioselectivities (**4j-k**). The allowance of *β*-alkyl-nitroethylenes for this cascade reaction could provide potential building blocks or intermediates toward the asymmetric synthesis of natural bioactive alkaloids such as emetamine, protoemetinol and their analogs.[2n,11] Additionally, aldehydes with different substitutions gave the corresponding indolizidine products in good to nearly quantitative yields (57-98%) and with excellent ee (90->99%), >20:1 dr (**4l-q**). Noteworthy, phenylacetaldehyde, an enolizable aldehyde, also presented good performance (**4q**). To the best of our knowledge, this is the first example using *α*-aromatic substituted aldehyde as substrate in this cascade sequence. The absolute configuration of **4** was determined based on the previous stereochemistry outcome of aldimine substrates[7a,7b] and X-ray crystal analysis of compound **4n**.[12]



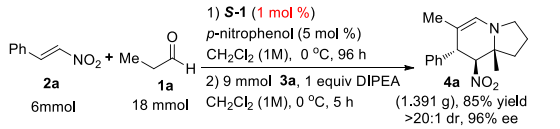
Scheme 2 One-pot synthesis of indolizidines.

Next, we extended this strategy to synthesize quinolizidines using six-membered ketimines. A variety of benzo- and indoloquinolizidines were obtained successfully with excellent ee (98->99%), >20:1 dr and in moderate to excellent yields (30-83%) (**4r-y**) (Scheme 3). Notably, ethyl-ketimine substrates (R^3 = Et) also proved to be compatible for this cascade reaction, giving acceptable yields and excellent stereoselectivities (**4w**, **4y**).

To further illustrate the efficiency and practicality of this novel one-pot cascade reaction, a gram scale synthesis of indolizidine **4a** was achieved in 85% yield with 96% ee and >20:1 dr. In this case, a lower loading of catalyst ***S*-1** (1 mol %) was applied for the reaction with **1a**, **2a** and **3a** as substrates (Scheme 4). This result demonstrated a promising blueprint for the applicability of this cascade sequence.



Scheme 3 One-pot synthesis of quinolizidines.



Scheme 4 Gram-scale one-pot stereoselective synthesis of indolizidine **4a**.

In summary, we have developed an efficient, enantioselective one-pot cascade approach for the construction of a diverse range of indolizidine and quinolizidine alkaloids containing a bridged quaternary stereocenter and an enamine functional group using commercially available catalyst. A series of readily available aldehydes, nitroethylenes and cyclic ketimines proved to be well tolerated and the desired products were obtained in high yields and with excellent stereoselectivities, even in gram-scale. Further investigations of asymmetric organocatalytic cascade reactions and their applications in natural product synthesis are under way in our group.

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† Electronic supplementary information (ESI) available: Complete experimental, procedures, product characterization, and two crystallographic (cif). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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