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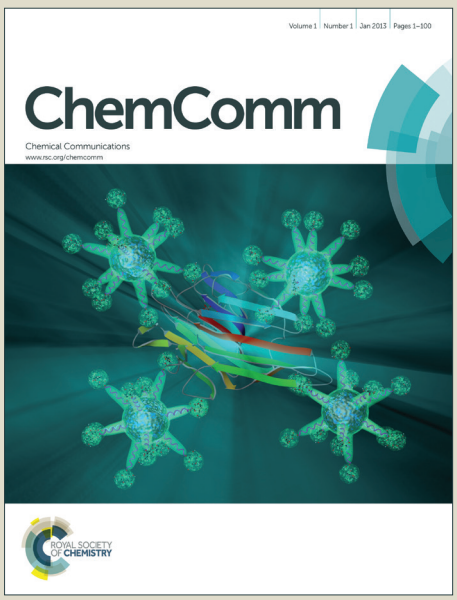

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ARTICLE TYPE

One-Pot Enantioselective Construction of Indoloquinolizidine Derivatives Bearing Five Contiguous Stereocenters Using Aliphatic Aldehydes, Nitroethylenes, and Tryptamine†

Yu Tan,[a] Han-Lin Luan,[a] Hua Lin,[a] Xing-Wen Sun,*[a] Xiao-Di Yang,[a] Han-Qing Dong,[b,c] and Guo-Qiang Lin*[a,b]

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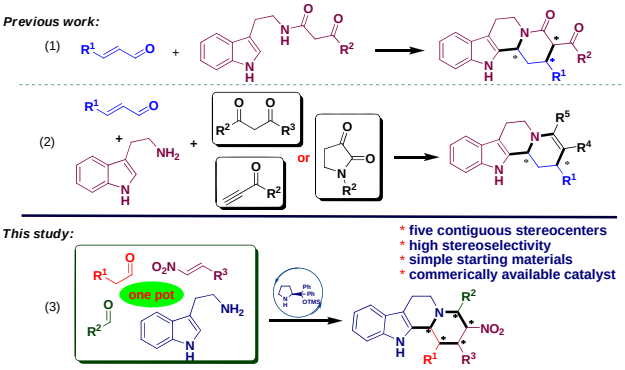
An organocatalytic cascade reaction was established for the construction of indoloquinolizidine derivatives bearing five contiguous stereocenters from readily available aliphatic aldehydes, nitroethylenes, and tryptamine. This one-pot process gave 30-55% overall yields with excellent d.r. (>20:1 in all cases) and ee (91-98%). Additionally, quaternary stereogenic carbon center-containing indoloquinolizidines were prepared through NBS-mediated cyclization of one of the intermediates.

The indoloquinolizidine skeleton is often embedded in indole alkaloids, such as reserpine, hirsutine, yohimbine, and cotynantheol, exhibiting a wide range of biological activities.[1] However, the natural sources for these therapeutically potential compounds are quite limited due to the difficulty in re-engineering them through biosynthesis. From a synthetic and medicinal chemistry viewpoint, the design and synthesis of natural product-like libraries provides an attractive approach for biological screening. Owing to their high efficiency, operational convenience, and functional group tolerance, asymmetric organocatalytic cascade reactions have provided diverse, enantiopure natural and natural-like products in an ecologically, environmentally, and economically benign manner in the past decade.[2] Recently, several powerful organocatalytic one-pot methodologies have been developed for the synthesis of enantiopure indoloquinolizidines using α,β-unsaturated aldehydes with 1,3-dicarbonyl compounds, 1,2-dicarbonyl compounds or alkyl propiolates, and tryptamine.[3] Nevertheless, these methods are confined to a restricted variety of substrates, affording no more than three chiral centers ((1) and (2) of Scheme 1). Therefore, new strategies for the synthesis of complex and diverse indoloquinolizidine derivatives from readily available starting materials with high level of efficiency and selectivity are still in great demand.

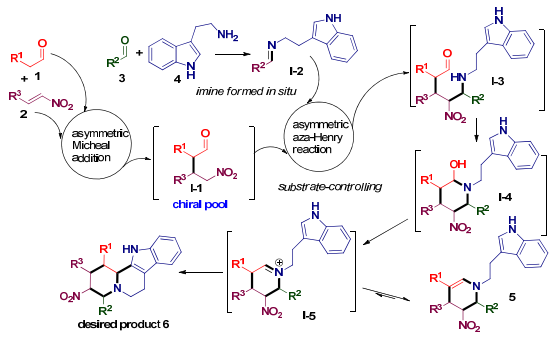
Very recently, our group reported a Michael/aza-Henry/hemiaminalization reaction sequence which involved in situ generated aliphatic imines and other readily available starting materials catalyzed by commercially available diarylprolinol silyl ether, the so-called Jørgensen[4]-Hayashi[5c] catalyst, under mild conditions to construct enantiopure tetrahydropyridines with good yields and excellent stereoselectivities.[6b,7] As a continuation of our ongoing effort in developing new organocatalytic one-pot reactions for the construction of functional-oriented frameworks,[6] we herein disclose an organocatalytic cascade sequence for the preparation of indoloquinolizidines containing five adjacent stereocenters from readily available aliphatic aldehydes, nitroethylenes, and tryptamine (bottom of Scheme 1).



Scheme 1 Strategies for the construction of indo loquinolizidinederivatives from simple starting materials.

Our initially proposed cascade reaction design is shown in Scheme 2. We envisaged that the whole sequence would begin with an asymmetric Michael addition[5] between aliphatic aldehyde **1** and nitrostyrene **2** to generate **I-1**, which then serve as a chiral pool in the following steps. Upon in situ formation of imine **I-2** from aliphatic aldehyde **3** and tryptamine **4**, a substrate-controlled asymmetric aza-Henry (nitro-Mannich)[8] reaction could occur between **I-1** and **I-2** to produce **I-3**, which could take place hemiaminalization to afford intermediate I-4 and then undergo elimination to the cyclic iminium intermediate **I-5**. This intermediate could either isomerise to tetrahydropyridine **5** or go through Pictet-Spengler (P-S) reaction[9] to provide the desired product **6**. Although this new Michael/aza-Henry/hemiaminalization/dehydration/P-S cascade sequence seems to be straightforward and rational, it is confronted with several challenges. First, the in situ formed imine **I-2** might decompose rapidly or undergo side reactions such as Aldol or Mannich reaction under the catalytic conditions. Second, the P-S reaction usually requires acidic conditions while the aza-Henry reaction has to be performed under basic conditions. Third, there

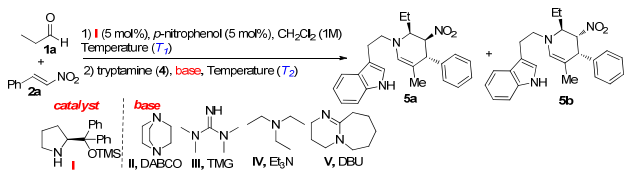
is a predictable competition between aldehyde **1** and **3**. In addition to the above challenges, the five newly-created stereocenters in the desired products may have issues related to both thermodynamic and kinetic equilibrium.[3g,7a]



Scheme 2 The initially proposed cascade reaction sequence.

In view of the above analyses, our model reaction was carried out using propanal **1a** and nitrostyrene **2a**as starting materials, diphenylprolinol silyl ether **I** as catalyst and p-nitrophenol as additive in CH_2Cl_2. After nitrostyrene **2a** in the first step was consumed, tryptamine, base and 4 Å molecular sieves were added to the mixture. When DABCO was applied as the base, no desired product was observed. Instead, the side product **5** was obtained as a mixture of **5a** and **5b** in the ratio of 16:1 (Table 1, entry 1).[10a, 10c] This suggested that the P-S reaction did not occur under the current conditions. Since the P-S cyclization usually takes place under acidic conditions, we decided to turn our attention to the exploration of different bases to optimize the Michael/aza-Henry/hemiaminalization/dehydration sequence.

Table 1 Optimization of Michael/aza-Henry/hemiaminalization /dehydration sequences.[a]

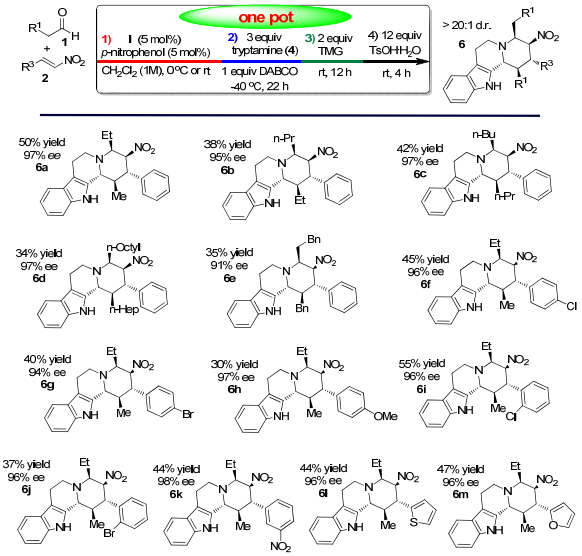


Entry	Base	T_2 (°C)	Yield (5a)(%)[b]	5a: 5b[c]	ee (5a)[d] (%)
1	II	25	57	16 : 1	94
2	III	25	39	18 : 1	94
3	IV	25	45	16 : 1	94
4	V	25	42	> 20 :1	94
5	II	0	12	1 : 4.6	94
6[e]	II	0	66	> 20 :1	94
7[e]	II	-20	70	> 20 :1	95
8[e]	II	-40	80	> 20 :1	95
9[e]	II	-60	38	> 20 :1	95
10[e,f]	**II**	**-40**	**75**	**> 20 :1**	**97**
11[e,g]	II	-40	46	> 20 :1	97

[a] The reaction was performed using **1a** (0.75 mmol), **2a** (0.25 mmol, 1M), *p*-nitrophenol (5 mol%), **I** (5 mol%) at rt (T_1). After **2a** was consumed, **4** (0.75 mmol), base (0.25 mmol, 1 equiv.), and 4 Å molecular sieves (MS) (50 mg) were added to stir for 22 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] CH_2Cl_2 (4 mL) and TMG (0.5 mmol) were added to stir for another 12 h at rt. [f] The T_1 was 0 °C. [g] The T_1 was -20 °C.

Several organic bases, TMG, Et_3N, DBU (entries 2-4) and inorganic bases (K_3PO_4, K_2CO_3) were tested, but none of them gave better yields. Different chiral catalysts were also investigated and the ee values of **5a** were 94% in all cases (see supporting information). To our surprise, upon lowering the temperature (T_2) to 0 °C, the reaction favoured the production of **5b** (entry 5). Moreover, we found that **5b** could isomerise to **5a** under basic conditions. Based on this inspiring result, we added 2 equivalent of TMG as base to accelerate the transformation from **5b** to **5a**. To our delight, upon treatment with excess base, the ratio of **5a**:**5b** was increased to >20:1 (entry 6). After carefully screening of temperature (T_2), -40 °C was found to be the optimal temperature (entries 7-9) (for more details, see supporting information). With these results in hand, the reaction temperature (T_1) of the Michael addition step was screened. When the Michael addition was performed at 0 °C the ee was increased to 97% without significant impact on yield or diastereoselectivity (entry 10). However, when the T_1 was lowered to -20 °C, the yield decreased considerably (entry 11).

With these promising results, we examined a series of acids such as CF_3SO_3H, $BF_3{\cdot}Et_2O$ and $TsOH{\cdot}H_2O$ for the P-S reaction step. To our delight, **6a**[10c, 11] was obtained in good yield (50%), with excellent diastereoselectivity (>20:1 d.r.) and enantioselectivity (97% ee) using 12 equivalent of $TsOH{\cdot}H_2O$ as acid and propanal **1a**, nitrostyrene **2a**, and tryptamine **4a** as starting materials. This example constitutes, by far, the most convenient organocatalytic cascade protocol for the asymmetric construction of poly-substituted indoloquinolizidine derivates *via* five linear steps in one pot (Scheme 3).

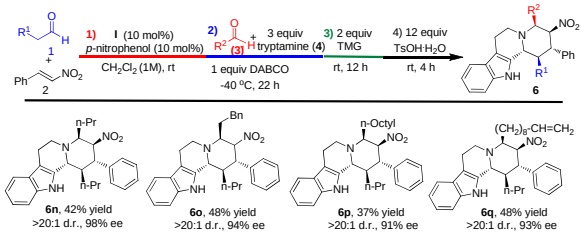


Scheme 3 One-pot synthesis of indoloquinolizidine. The reaction was performed using **1** (0.75 mmol), **2** (0.25 mmol, 1M), *p*-nitrophenol (5 mol%), **I** (5 mol%) at 0 °C (**1** = propanal) or rt. After compound **2** was consumed, tryptamine **4** (0.75 mmol), DABCO (0.25 mmol) and 4 Å MS (50 mg) were added to stir for 22 h. Then CH_2Cl_2 (4 mL) and TMG (0.5 mmol) were added to stir for additional 12 h at rt. Finally, $TsOH{\cdot}H_2O$ (3 mmol) was added and stirring was kept for 4 h at rt.

After the optimal reaction conditions were identified, we next examined the reaction scope and generality with respect to alkyl aldehydes and β-substituted nitroethylenes. Gratifyingly, this

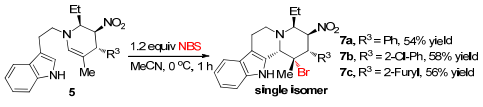
method was quite amenable to linear alkyl aldehydes (**6a-d** in Scheme 3). For phenylethyl aldehyde, the desired product could be obtained in 35% yield, with >20:1 d.r. and 91% ee (**6e**). Moreover, β-aryl-nitroethylenes with the phenyl ring bearing an electron-donating or electron-withdrawing group were all well tolerated (**6f**–**k**). Although product **6h** with an electron-donating aryl substituent was furnished in relatively low yield (30%), the d.r. remained >20:1 and the ee 97%. In addition, substitutions at the *o*, *m*, and *p*- positions of the phenyl ring in the nitroalkenes were acceptable for this cascade reaction, and the desired products were obtained in 37%–55% yields and with excellent diastereo- and enantioselectivities (**6i**–**k**). β-Heteroaryl nitroethylenes, like 2-thienyl or 2-furyl nitroethylene, also proved to be good substrates, affording the desired indoloquinolizidine products in good yields with excellent d.r. and ee (products **6l**–**m**).

With the encouraging results above in hand, we next sought to employ different aliphatic aldehydes in the second step to generate imines in suit for the cascade sequence. We were pleased to find out that decreasing the loading of aldehyde **1** from 3.0 to 1.2 equiv successfully avoided its interference with the subsequent imine formation, and the desired products were obtained in 37~48% yields with excellent chemoselectivities and stereoselectivities in all cases (Scheme 4, **6n**–**q**). It is worth pointing out that a long-chain alkyl aldehyde with terminal olefin also exhibited good performance in this cascade reaction (**6q**).



Scheme 4 One-pot synthesis of indoloquinolizidine: scope with respect to two different alkyl aldehydes. The reaction was performed using **1** (0.3 mmol), **2** (0.25 mmol, 1M), *p*-nitrophenol (10 mol%), **I** (10 mol%) at rt. After **2** was consumed, **3** (0.75 mmol), **4** (0.75 mmol), DABCO (0.25 mmol) and 4 Å MS (50 mg) were added to stir for 22 h. Then CH_2Cl_2 (4 mL) and TMG (0.5 mmol) were added to stir for additional 12 h at rt. Finally, $TsOH{\cdot}H_2O$ (3 mmol) was added and stirring was kept for 4 h at rt.

Also noteworthy is that tetrahydropyridines **5** could act as a versatile building block in the diversity-oriented synthesis of indoloquinolizidine analogues using abundant enamine chemistry.[12] For example, when tetrahydropyridines **5** were treated with 1.2 equivalents of bromosuccinimide (NBS) in MeCN at 0 °C, the desired products **7** were obtained in 54%–58% yield as a single isomer. The absolute configuration of the bromide-containing indoloquinolizidine **7a** with a quaternary stereogenic center was unambiguously determined by X-ray crystallography.[10b, 11]



Scheme 5 Synthesis of quaternary stereogenic center-containing indoloquinolizidine derivatives.

In summary, an organocatalytic cascade one-pot reaction sequence has been developed for the construction of indoloquinolizidines using aliphatic aldehydes, nitroethylenes, tryptamine as starting materials and commercially available diphenylprolinol silyl ether as catalyst. This cascade strategy proceeded through Michael addition, aza-Henry reaction, hemiaminalization, dehydration, and P-S reaction to provide highly substituted enantioenriched indoloquinolizidines bearing five contiguous stereocenters in 30%–55% (>79% for each step) yield and with excellent d.r (>20:1) and ee (91%–98%). To the best of our knowledge, this is also a unique example of aza-Henry reaction making use of tryptamine. Furthermore, quaternary carbon-containing indoloquinolizidines could be prepared through the bromocyclization of the intermediate **5**. Ongoing studies are focused on the development of additional cyclization protocols using other electrophiles based on enamine chemistry with respect to the diversity synthesis-oriented of indoloquinolizidine analogues.

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Notes and references

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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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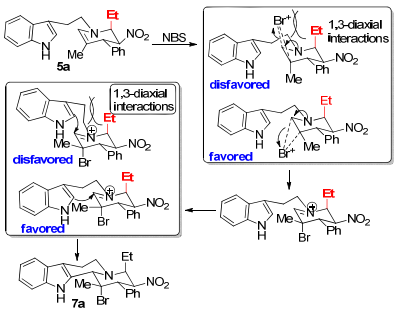
10 (a) The absolute configuration of **5a** and **6** was determined based on the previous results in reference 6b and X-ray crystallography of **6c**, CCDC 969090. (b) **7a**, CCDC 969089. (c) Please see supporting information for details.

11 Explanations of compound **7a**'s stereochemistry.



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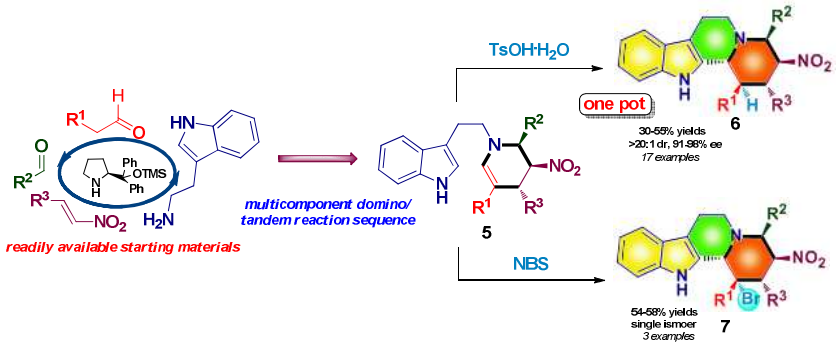
Graphical Abstract

One-Pot Enantioselective Construction of Indoloquinolizidine Derivatives Bearing Five Contiguous Stereocenters Using Aliphatic Aldehydes, Nitroethylenes, and Tryptamine †

Yu Tan,[a] Han-Lin Luan,[a] Hua Lin,[a] Xing-Wen Sun,*[a] Xiao-Di Yang,[a] Han-Qing Dong,[b,c] and Guo-Qiang Lin*[a,b]



Indoloquinolizidine Derivatives: An organocatalytic cascade reaction was established for the construction of indoloquinolizidine derivatives bearing five contiguous stereocenters from readily available aliphatic aldehydes, nitroethylenes, and tryptamine. This one-pot process gave 30-55% overall yields with excellent d.r. (>20:1 in all cases) and ee (91-98%). Additionally, quaternary stereogenic carbon center-containing indoloquinolizidines were prepared through NBS-mediated cyclization of one of the intermediates.