Enantioselective construction of lactone[2,3-*b*]piperidine skeletons *via* organocatalytic tandem reactions†

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A highly enantioselective construction of δ- and γ-lactone[2,3-*b*]piperidine skeletons was accomplished by tandem aza-Diels–Alder reaction–hemiacetal formation–oxidation from *N*-Tos-1-aza-1,3-butadienes and aliphatic dialdehydes.

The lactone[2,3-*b*]piperidine structures are key units in some biologically important natural products. For example, the dimeric indole alkaloid haplophytine (Fig. 1), isolated from the leaves of *Haplophyton cimicidum*, and its biosynthetic precursor aspidophytine, contain a γ-lactone[2,3-*b*]piperidine motif. Their total synthesis has triggered considerable attention owing to the appealing complex structures.[1] Zoanthamines, a family of marine alkaloids isolated from the zoanthid *Zoanthus*, possess a δ-lactone[2,3-*b*]piperidine structure, and have an array of important biological activities.[2] In addition, lycojapodine A, a novel alkaloid recently obtained from *Lycopodium japonicum* with an unprecedented tetracyclic ring system, exhibit significant inhibitory activities on acetylcholinesterase and HIV-1.[3] The lactone[2,3-*b*]piperidines are also interesting intermediates in organic synthesis.[4] However, currently there are few reports concerning the facile catalytic asymmetric synthesis of lactone[2,3-*b*]piperidine skeletons.

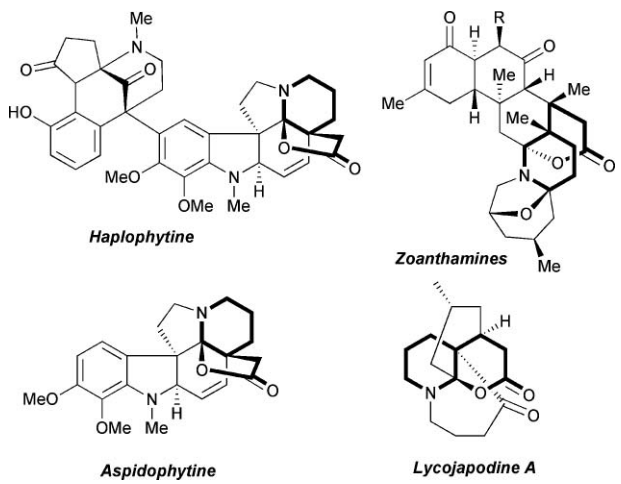
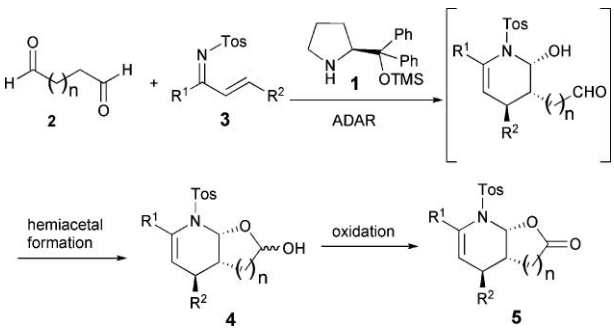


Fig. 1 Natural products containing lactone[2,3-*b*]piperidine structures.

Recently we have developed the asymmetric inverse electron demand aza-Diels–Alder reaction (ADAR) of *N*-sulfonyl-1-aza-1,3-butadienes and aldehydes or α,β-unsaturated aldehydes by the catalysis of chiral secondary amines, providing efficient protocols to access highly enantioenriched piperidine derivatives.[5] We envisaged that a bicyclic compound bearing adjacent aminal–hemiacetal structures would be generated from *N*-Tos-1-aza-1,3-butadienes and an aliphatic dialdehyde,[6] *via* a tandem ADAR–intramolecular cyclisation process.[7] Thus, the desired chiral lactone[2,3-*b*]piperidine skeletons could be obtained by a subsequent oxidation reaction (Scheme 1).



Scheme 1 Tandem aza-Diels–Alder reaction-hemiacetal formation-oxidation reaction to access lactone[2,3-*b*]piperidine skeletons.

Based on these considerations, we initially investigated the reaction of aqueous glutaraldehyde **2a** (50% in water) and *N*-Tos-1-aza-1,3-butadiene **3a** in MeCN at room temperature catalysed by a chiral α,α-diphenylprolinol *O*-TMS ether **1** (Scheme 1, 10 mol%) and benzoic acid (10 mol%).[8] Upon the complete consumption of diene **3a**, the bicyclic hemiacetal **4a** was isolated in 90% yield as a diastereomeric mixture, which was further oxidised with 2-iodoxybenzoic acid (IBX)[9,10] to afford **5a** in excellent stereocontrol (Table 1, entry 1, dr > 99 : 1, >99% ee). Similar results were obtained in other solvents such as MeOH, toluene and DCM (entries 2–4). However, very sluggish reactivity was observed in THF and the product **4a** was isolated in low yield (entry 5). High yield and outstanding enantioselectivity were also attained using acetic acid as the additive (entry 6).

Having established the optimal reaction conditions, the substrate scope of this reaction was investigated. The hemiacetal intermediates **4** were directed converted to the corresponding lactone[2,3-*b*]piperidine derivatives **5** by IBX oxidation. The results are summarised in Table 2. For the reactions of glutaraldehyde **2a**, a few *N*-Tos-1-aza-1,3-butadienes bearing an ester group at the 4-position were successfully applied, and the δ-lactone products **5a–5e** were smoothly obtained in excellent enantioselectivities with fair isolated yields *via* a two-step procedure (Table 2,

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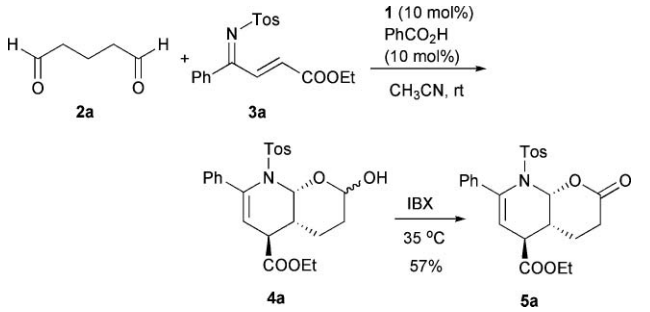
† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products. See DOI: 10.1039/b922053d

Table 1 Screening studies on tandem ADAR–hemiacetal formation–oxidation reaction[a]

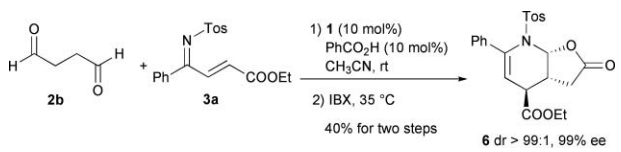


Entry	Solvent	Time/h	Yield [b](%)	ee [c](%)
1	MeCN	2	90	99
2	MeOH	5	83	99
3	Toluene	2	81	99
4	DCM	2	81	99
5	THF	96	30	99
6[d]	MeCN	2	89	99

[a] Unless noted otherwise, the reaction was conducted with catalyst **1** (0.01 mmol), **2a** (0.2 mmol), **3a** (0.1 mmol) and PhCOOH (0.01 mmol) in solvent (1.0 mL) at rt. [b] Isolated yield for **4a**. [c] Determined by chiral HPLC analysis of **5a**, dr > 99 : 1. [d] CH_3COOH was used.

entries 1–5). Nevertheless, when *N*-Tos-1-aza-1,3-butadienes with an ester substituent at the 2-position were used, much lower reactivity was observed in MeCN. Fortunately, the reaction could be greatly accelerated by using DCM as the solvent and more benzoic acid (100 mol%) was required. The yields were acceptable and the stereoselectivities were also remarkable (entries 6–8). Moreover, two *N*-Tos-1-aza-1,3-butadienes without activating substituents were tested. Although the cycloaddition reaction turned out to be more sluggish, good conversions could be ensured by extending the reaction time, especially for an alkyl-substituted substrate. The enantioselectivities were still satisfactory (entries 9 and 10).

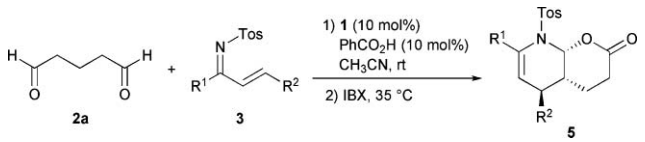
On the other hand, succinaldehyde **2b** was employed with *N*-Tos-1-aza-1,3-butadiene **3a** for the synthesis of γ-lactone[2,3-*b*]piperidine derivative. As illustrated in Scheme 2, the expected target compound **6** was similarly afforded, also in excellent stereoselectivity.



Scheme 2 Synthesis of γ-lactone[2,3-*b*]piperidine skeleton.

In conclusion, we have developed a tandem inverse electron demand aza-Diels–Alder reaction–intramolecular hemiacetal formation–oxidation reaction to construct δ- and γ-lactone[2,3-*b*]piperidine skeletons. This tandem process exhibited good efficiency and excellent stereocontrol under environmentally friendly and mild reaction conditions, utilising readily available *N*-Tos-1-aza-1,3-butadienes and aliphatic dialdehydes as the starting materials. These enantiomerically pure heterocycles might find

Table 2 Synthesis of δ-lactone[2,3-*b*]piperidine derivatives[a]



Entry	R^1	R^2	Time/h	Yield [b](%)	ee [c](%)
1	Ph	COOEt	2	**5a**, 51	99
2	*p*-ClC_6H_4	COOEt	5	**5b**, 53	99
3	*p*-BrC_6H_4	COOEt	5	**5c**, 54	99
4	*p*-$MeOC_6H_4$	COOEt	8	**5d**, 46	99
5	2-Thienyl	COOEt	5	**5e**, 51	97
6[d]	COOEt	Ph	22	**5f**, 50	99
7[d]	COOEt	*p*-BrC_6H_4	24	**5g**, 45	98
8[d]	COOEt	*p*-$MeOC_6H_4$	26	**5h**, 42	99
9	Ph	*p*-BrC_6H_4	36	**5i**, 47	98
10	Ph	Me	230	**5j**, 45	90

[a] Unless noted otherwise, the reaction was conducted with **2a** (0.2 mmol), **3** (0.1 mmol), catalyst **1** (0.01 mmol) and PhCOOH (0.01 mmol) in MeCN (1.0 mL) at rt. [b] Isolated yield for two steps. [c] Determined by chiral HPLC analysis, dr > 99 : 1. The absolute configuration of the products was proposed based on the similarity as what was previously reported, see ref. 5a. [d] 100 mol% of PhCOOH was used in DCM.

applications in the synthesis of compounds with medicinal importance.

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