Organic LETTERS

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Dual-Organocatalyst-Promoted Asymmetric Cascade Reaction: Highly Efficient Construction of Enantiopure Fully Substituted Tetrahydro-1,2-oxazines

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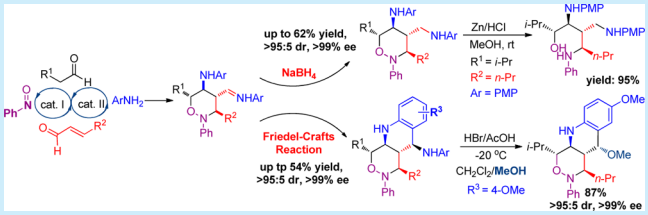
Supporting Information

ABSTRACT: A four-component asymmetric α-aminoxylation/*aza*-Michael/Mannich cascade reaction for the construction of fully substituted chiral tetrahydro-1,2-oxazine derivatives was accomplished in high yields with excellent enantio- and diastereoselectivities under mild conditions. The 1,2-oxazine derivative could be transformed to the corresponding multifunctional chiral amino alcohol by N−O cleavage and fused-tricyclic 4-amino-substituted tetrahydroquinolines in good yields with excellent stereoselectivities followed by a Friedel−Crafts reaction. Also a 4-alkoxy-substituted tetrahydroquinoline was achieved by C-4 inversion of a 4-amino-substituted tetrahydroquinoline.

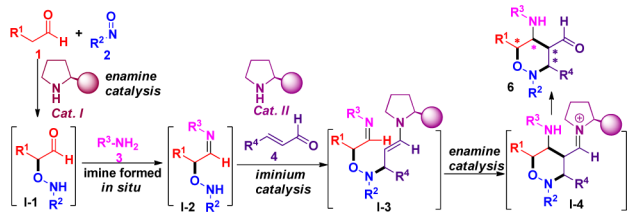


The desire for the ideal synthesis of complex natural products has stimulated the emergence of organocatalytic cascade reactions, which strive to emulate nature in the construction of intricate molecules. In the pursuit of atom economy, they avoid costly, time-consuming protection−deprotection processes and the isolation of intermediates. Particularly, they trap unstable intermediates to generate useful enantiopure building blocks with excellent stereoselectivities, thereby facilitating the efficient synthesis of natural products.[1] Chiral secondary amine catalysts, which either activate aldyhydes by enamine formation or iminium-ion formation, are considered as ideal organocatalysts[2] and successfully used in cascade reactions for the construction of complicated usually multistereocenter-containing structures from simple starting materials.[3]

1,2-Oxazines are valuable chiral building blocks[4] frequently found in various biologically active compounds.[5] They possess remarkable synthetic utilities, often manipulated via a reductive N−O bond cleavage that forms highly functionalized 1,4-amino alcohols seen in a number of bioactive natural products. Recently, there has been great progress in the synthesis of 1,2-oxazines, particularly in the field of chiral tetrahydro-1,2-oxazines.[6] Nevertheless, to the best of our knowledge, there are no methods presented for the synthesis of chiral fully substituted tetrahydro-1,2-oxazines to date.

Previously, we reported the successful preparation of chiral dihydro-1,2-oxazine using alkyl aldehyde, nitrosobenzene, and α,β-unsaturated aldehyde.[7] We envisioned that, with the primary amine, the aldehyde intermediate **I-1**[8] would be converted to imine in situ, which would subsequently undergo an *aza*-Michael addition[9]/Mannich[10] cascade reaction to provide a fully substituted tetrahydro-1,2-oxazine with four newly formed stereocenters in the presence of a chiral secondary amine catalyst (Scheme 1). However, besides

Scheme 1. Proposed Organocatalytic Cascade Reaction for the Synthesis of Optically Tetrahydro-1,2-oxazines



stereoselectivity issues, five chemoselectivity issues were found to be challenging: (1) α-Aminoxylation intermediate **I-1** may oligomerize[11] or may react with excess aldehyde **1** in the presence of a secondary imine catalyst via an aldol reaction; (2) imine intermediate **I-2** may react with excess aldehyde **1** via a Mannich reaction catalyzed by a secondary amine; (3) an undesired Michael reaction between aldehyde **1** and α,β-unsaturated aldehyde **4** may compete with the *aza*-Michael addition step; (4) α,β-unsaturated aldehyde **4** and amine **3** may be transformed to the corresponding imine in situ, bridling the entry of α,β-unsaturated aldehyde **4** into the desired reaction cycle; (5) a side intramolecular aldol reaction may also intefere with the final intramolecular Mannich reaction. Herein, we report our efforts to meet these challenges and demonstrate the accessibility of enantioenriched fully substituted tetrahydro-1,2-oxazines by dual-organocatalytic asymmetric cascade reactions in moderate yields with high enantio- and diastereoselectivities.

The preliminary experiments were initiated by adding 4-methoxyaniline to the mixture of **1a** and **2a** with L-proline as the catalyst when the first α-aminoxylation reaction was

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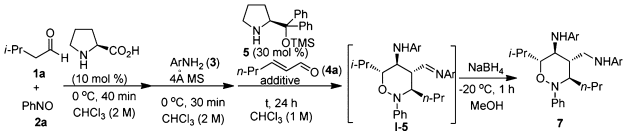
completed,[12] followed by the addition of (*E*)-hex-2-enal **4a** and prolinol derivative **5**. Unfortunately, there was only a trace of the desired product found in the complex reaction mixture (Table 1, entry 1). Lowering the reaction temperature to −20 °C, a suitable temperature for the intramolecular Mannich reaction,[13] gave a negative result (Table 1, entries 2, 3). Inspection of the loading ratio of the starting materials revealed that an excessive loading of 4-methoxyaniline was the key to reaching higher chemoselectivity (Table 1, entry 4). Reduction of the desired imine intermediate **I-5** in situ was completed with a 42% yield, with over 95:5 dr and 99% ee. When the additive was examined, AcOH was found to give a better yield (50%) (Table 1, entries 5, 6). However, aniline and 4-choroaniline gave worse results (Table 1, entries 7, 8). Not surprisingly, a reduced loading of catalyst **5** afforded a lower yield (Table 1, entry 9). To our delight, the best yield was ultimately achieved in the absence of 4 Å MS as a 62% yield, without compromising stereoselectivities (Table 1, entry 10). Thus, the optimal reaction conditions were finally established.

Table 1. Optimization of the Reaction Conditions[a]

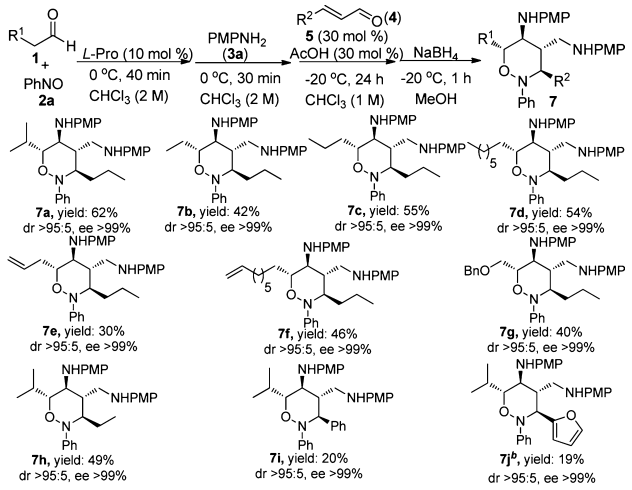


entry	Ar	additive	t (°C)	yield[b]	dr[c]	ee (%)[d]
1	PMP	none	20	trace	nd	nd
2	PMP	none	0	trace	nd	nd
3	PMP	none	−20	trace	nd	nd
4[e]	PMP	none	−20	42%	>95:5	>99
5[e]	PMP	NaOAc (0.5 equiv)	−20	41%	>95:5	>99
6[e]	PMP	AcOH (0.3 equiv)	−20	50%	>95:5	>99
7[e]	Ph	AcOH (0.3 equiv)	−20	42%	>95:5	>99
8[e]	4-Cl-Ph	AcOH (0.3 equiv)	−20	44%	>95:5	>99
9[e,f]	PMP	AcOH (0.2 equiv)	−20	30%	>95:5	>99
10[e,g]	**PMP**	**AcOH (0.3 equiv)**	**−20**	**62%**	**>95:5**	**>99**

[a]The reaction was performed using nitrosobenzene **2a** (0.25 mmol, 1 M, 1 equiv), aldehyde **1a** (3 equiv), amine **3** (1 equiv), α,β-unsaturated aldehyde **4a** (2 equiv), 4 Å MS, catalyst L-proline, and **5** in $CHCl_3$. See Supporting Information for details. [b]Isolated yield of product **6a**. [c]Determined by ^{1}H NMR of the crude product. [d]For the determination of ee, see Supporting Information. [e]The ratio of **1a**:**2a**:**3**:**4a** = 3:1:5:3. [f]Catalyst **5** (20 mol %) was used, and the reaction time was 2 d. [g]Without 4 Å MS.

With the optimal reaction conditions identified (Table 1, entry 10), the scope of this cascade reaction was investigated. A variety of aldehydes for the first α-aminoxylation were examined, with butyraldehyde and pentanal giving moderate yields, 42% and 55% respectively (Scheme 2, **7b**, **7c**). A long chain aliphatic aldehyde, such as nonanal, also proved to be a good substrate, providing the desired 1,2-oxazine product in good yield (Scheme 2, **7d**). Terminal olifinic aldehyde, pent-4-enal, and dec-9-enal afforded 30% and 46% yields, respectively (Scheme 2, **7e**, **7f**). Linear aliphatic aldehydes bearing a functional group, such as −OBn, could also be employed as a substrate in the domino reaction (Scheme 2, **7g**). In addition, this method could accommodate various aliphatic α,β-unsaturated aldehydes as well (Scheme 2, **7h**). Aromatic α,β-unsaturated aldehydes could also be applied in this reaction system, though (*E*)-cinnamaldehyde and (*E*)-3-(furan-2-yl)-acrylaldehyde offered lower yields, 20% and 19% respectively (Scheme 2, **7i**, **7j**). It should be mentioned that, in all these cases, over 95:5 dr and 99% ee were obtained. The absolute configuration of the tetrahydro-1,2-oxazine products was identified unambiguously through X-ray crystallographic analysis of imide derivative **8a** derived from the corresponding adduct **7a** (see Supporting Information for details).[14]

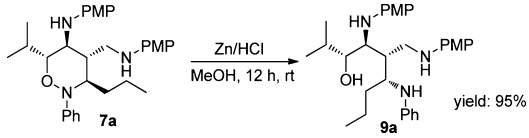
Scheme 2. Synthesis of Chiral Tetrahydro-1,2-oxazine[a]



[a]The reaction was performed using nitrosobenzene **2a** (0.25 mmol, 1 M), aldehyde **1** (0.75 mmol), amine **3a** (1.25 mmol), α,β-unsaturated aldehyde **4** (0.75 mmol), AcOH (30 mol %), catalyst L-proline (10 mmol %), and **5** (30 mmol %) in $CHCl_3$. See Supporting Information for details. [b]The reaction time was 2 d.

With optically pure 1,2-oxazines in hand, the synthetic utility of the cascade products was next examined. The 1,2-oxazine product **7a** can be hydrogenolyzed to the corresponding valuable amino alcohol derivative **9a** in 95% yield by N−O bond hydrogenolysis in the Zn/HCl system. Given the prevalent occurrence of the chiral amino alcohol moiety in nature, they are potential chiral building blocks used for the preparation of conformationally restricted peptides and biologically active nonproteinogenic analogues. Thus, our present route provides an easy access to a potentially diverse set of such compounds (Scheme 3).

Scheme 3. N−O Cleavage



Furthermore, the imine intermediate **I-5** could be subjected to an intramolecular Friedel−Crafts reaction in situ in the presence of a Lewis or Brønsted acid. This one-pot multicomponent cascade reaction might furnish the corresponding multisubstituted 4-amino-substituted tetrahydroquinoline derivative **10** with five newly formed stereocenters. The tetrahydroquinoline ring moiety is a ubiquitous structural motif presented in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[15] In particular, 4-amino-substituted tetrahydroquinoline compounds, such as martinellic acid and martinelline, have become synthetic targets of many research groups, possessing potent

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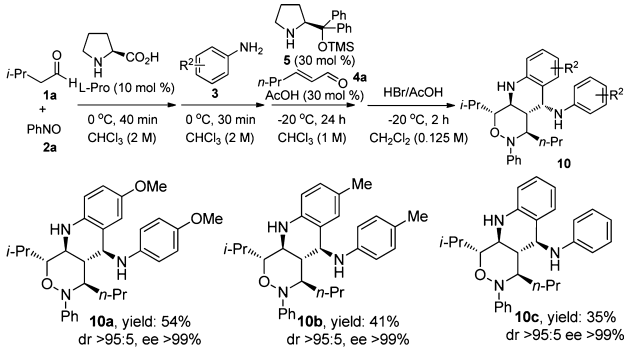
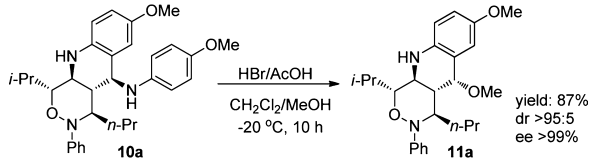
antagonist activities toward bradykinin (BK) B1 and B2 receptors.[16] Screening of the acids, such as HBr, HCl, AcOH, and BF_3·OEt, proved that HBr (AcOH solution) was the suitable Brønsted acid for this transformation. Based on the optimal conditions, this one-pot cascade reaction provided the corresponding 4-amino-substituted 1,2,3,4-tetrahydroquinoline derivatives **10** in 35−54% yields, with over 95:5 dr and 99% ee (Scheme 4).

Scheme 4. One-Pot Synthesis of 4-Amino-Substituted Tetrahydroquinoline Derivative



Also, 4-amino-substituted tetrahydroquinoline derivative **10a** could be transformed to its corresponding 4-alkoxy-substituted tetrahydroquinoline derivative **11a** through an "S_N2-like substitution" process in the presence of HBr (AcOH solution) at −20 °C with high stereoselectivity (Scheme 5).[17] The configuration of tetrahydroquinoline derivative **10** and **11a** was assigned by NOSY (see Supporting Information for details).

Scheme 5. C4 Functionalization of Tetrahydroquinoline Derivative



In summary, an efficient access to enantiopure fully substituted chiral tetrahydro-1,2-oxazine derivatives was developed via a dual-organocatalyst promoted four-component asymmetric *α*-aminoxylation/*aza*-Michael/Mannich cascade reaction under mild conditions. This method allows the synthesis of fully substituted tetrahydro-1,2-oxazine derivatives in good yields (up to 62%), with excellent enantio- (ee >99% in all cases) and diastereoselectivities (dr >95:5 in all cases). The 1,2-oxazine derivative can be transformed to the corresponding multifunctional chiral amino alcohol by N−O cleavage. Furthermore, to build on this strategy, an *α*-aminoxylation/*aza*-Michael/Mannich/Friedel−Crafts cascade reaction was successfully developed, affording fused tricyclic 4-amino-substituted tetrahydroquinolines in good yields with excellent stereoselectivities. Also a 4-alkoxy-substituted tetrahydroquinoline was achieved by C-4 inversion of a 4-amino-substituted tetrahydroquinoline. We are currently investigating the catalytic mechanism of the cascade reaction and the application of this methodology to asymmetric syntheses of some natural and natural-like compounds and will report the results in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data; copies of ^{1}H and ^{13}CNMR spectra; and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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