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Organocatalytic Asymmetric Synthesis of Chiral Dioxazinanes and Dioxazepanes with *In Situ* generated Nitrones via Tandem Reaction Pathway using a Cooperative Cation Binding Catalyst

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ABSTRACT: Heterocyclic skeletons play major roles in pharmaceuticals and biological processes. Cycloaddition reactions are most suitable synthetic tools to efficiently construct chemically diverse sets of heterocycles with great structural complexity owing to the simultaneous or sequential formation of two or more bonds often with a high degree of selectivity. Herein, we report an unprecedented formal cycloaddition of *N*-Boc-*N*-hydroxy-amido sulfones as the nitrone precursors with terminal-hydroxy-α,β-unsaturated carbonyls in the presence of Song's chiral oligoEG as a cation binding catalyst and KF as a base to afford a wide range of highly enantio- and diastereo-enriched six-membered dioxazinane and seven-membered dioxazepane heterocycles. In this process, nitrones as well as terminal-hydroxy-α,β-unsaturated carbonyls serve as "amphiphilic" building units and the reaction proceeded through a sequence of tandem pathway, oxa-Mannich/oxa-Michael/tautomerization/protonation. The cation-binding catalysis in a densely confined chiral space *in situ* formed by the incorporation of potassium salt, is the key of this successful catalysis. This strategy opens a new pathway for the asymmetric synthesis of diverse heterocyclic skeletons of great complexity.

INTRODUCTION

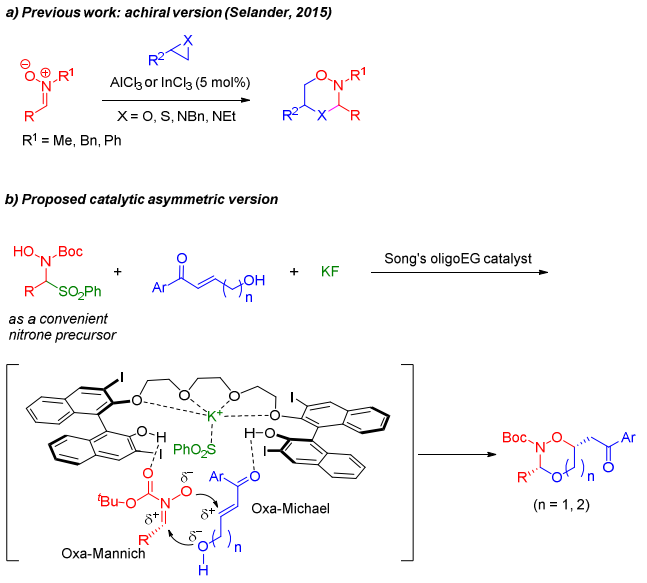
Heterocyclic skeletons play major roles in pharmaceuticals and biological processes.[1] More than 90% of new drugs contain heterocycles as the core structures, and a significant amount of new scientific insight, discovery, and application taking place at the interface of chemistry and biology is crossed by heterocyclic compounds.[2] Therefore, the construction of heterocyclic compounds with noble skeletons has been a pivotal point in organic methodology development for decades, which can open new advances in diverse research areas. A number of methodologies have been developed for the synthesis of different heterocycles with different ring sizes.[1] In particular, cycloaddition reactions are most suitable synthetic tools to efficiently produce chemically diverse sets of heterocycles with great structural complexity owing to the simultaneous or sequential formation of two or more bonds often with a high degree of selectivity.[3] As a result, developing cycloaddition-based synthetic methods for the efficient construction of heterocyclic compounds is becoming a very attractive strategy in modern organic synthesis. In particular, cycloaddition reactions involving nitrones as 1,3-dipoles allow the incorporation of two heteroatoms into the skeletons in a single step,[4] and thus nitrones have been used as highly versatile reagents for the preparation of heterocyclic compounds via [3 + 2],[5] [3 + 3],[6,7] [4 + 3],[8] [2 + 2 + 3],[9] and [5 + 2][10] cycloaddition reactions with diverse dipolarophiles.

Quite recently, Selander and coworkers successfully used nitrones to construct quite noble heterocyclic skeletons. The formal [3 + 3] cycloaddition of nitrones with the activated dipolarophiles such as oxiranes and aziridines using Lewis acid catalyst furnished 1,4,2-dioxazinanes and 1,2,4-oxadiazinanes, respectively (Scheme 1a).[11] Various dioxazine and oxadiazine frameworks are found in the skeletons of the Sarcodonin class of natural products, exhibiting a wide spectrum of biological activity such as anti-HIV, antioxidant, and anti-cancer activity.[12] Thus, developing a general synthetic method to access each stereoisomers possessing these heterocyclic skeletons is highly desirable. However, according to the reported protocol,[11] the products can be obtained only as a mixture of stereoisomers. Further drawback of this method is the requirement of unpractical *N*-substituents (e. g., *N*-CH_3, *N*-benzyl, *N*-Ph), which are not trivial to remove, preventing further modification on the nitrogen atom.

Recently, we reported a new type of easily accessible 1,1′-bi-2-naphthol (BINOL)-based organocatalysts bearing phenols and polyether units for asymmetric cation-binding catalysis.[13] The ether oxygens act as a Lewis base to coordinate metal ions such as K^+, thus generating a soluble chiral anion in a confined chiral space. Moreover, the terminal phenol groups are capable of simultaneously

activating the electrophile by hydrogen bonding interaction, resulting in a well-organized transition state leading excellent stereoinduction. This new type of cooperative cation-binding

Scheme 1. Transformations of Nitrones to Dioxazinanes or Dioxazepanes



catalytic system has been successfully applied to desilylative kinetic resolution of silyl-protected racemic alcohols,[13b] asymmetric Strecker reaction using potassium cyanide,[13c] and kinetic resolution of β-sulfonyl ketones through enantioselective β-elimination.[13e] Quite recently, we reported that the same catalyst can act as an extremely efficient bifunctional Brønsted acid-base catalyst, enabling a ppm-level loading organocatalytic enantioselective silylation of simple alcohols.[13d] The structural simplicity and vast application potential of the catalyst stimulated us to explore more challenging catalytic asymmetric reactions for the synthesis of heterocycles containing noble new scaffolds.

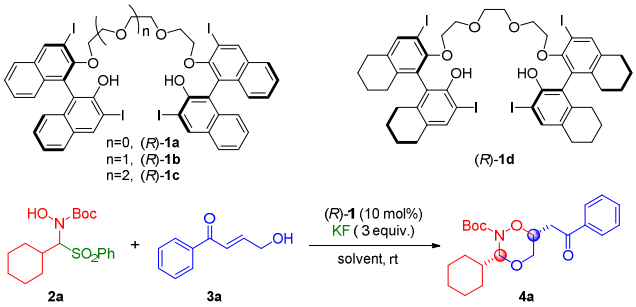
We envisioned that the bifunctionality of nitrones and terminal-hydroxy-α,β-unsaturated ketones would enable them to undergo catalytic cycloaddition reactions, affording chiral 1,4,2-dioxazinane and 1,4,2-dioxazepane heterocycles via oxa-Mannich/oxa-Michael tandem reactions. In this reaction, potassium fluoride upon the activation by the chiral cation-binding catalyst would enable to generate the corresponding nitrone substrate *in situ* from *N*-hydroxy α-amido sulfones. Moreover, other amphiphilic building unit, terminal-hydroxy α,β-unsaturated ketones would be also activated by hydrogen bonding interaction with catalyst. Subsequently, catalyst would bring both activated reacting partners together in proximity, producing the desired product with an asymmetric induction (Scheme 1b). Notably, terminal-hydroxy-α,β-unsaturated carbonyls, also containing donor–acceptor sites successfully served as amphiphilic reagents for the asymmetric synthesis of chiral tetrahydrofurans[14a] and chiral 1,3-oxazolidines[14b] using cinchona-based bifunctional catalysts.

Herein, we report the first asymmetric synthesis of highly enantio- and diastereo-enriched 1,4,2-dioxazinane and 1,4,2-dioxazepane heterocycles via organocatalytic Mannich/Michael tandem reactions of nitrones generated *in situ* from *N*-hydroxy α-amido sulfones with terminal-hydroxy α,β-unsaturated ketones using a cation-binding catalyst.

RESULTS AND DISCUSSION

To prove our assumption, *N*-hydroxy cyclohexyl α-amido sulfone (**2a**) as the corresponding nitrone precursor[15] with (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**3a**) were chosen as the model substrates. In the presence of catalyst **1** (10 mol%) and KF (3 equiv.) as a base, the effect of catalyst structure ((*R*)-**1a–d**) on the reaction outcome was first investigated in toluene (entries 1–4). The reactions proceeded smoothly as per our expectations, affording the desired product **4a**. Based on our knowledge of the catalytic performance of chiral oligoEGs **1**,[13] ether chain length (entries 1–3) as well as the acidity of phenolic protons (entry 2 vs. entry 4) are critical for the catalytic performance in this reaction. Consistently, catalyst **1b** was found to be optimum in terms of yield (91% yield) and stereoselectivity (93% ee, dr >20:1) (entry 2). In further experiments,

Table 1. Initial Catalyst and Solvent Screening for Asymmetric Cycloaddition[a]

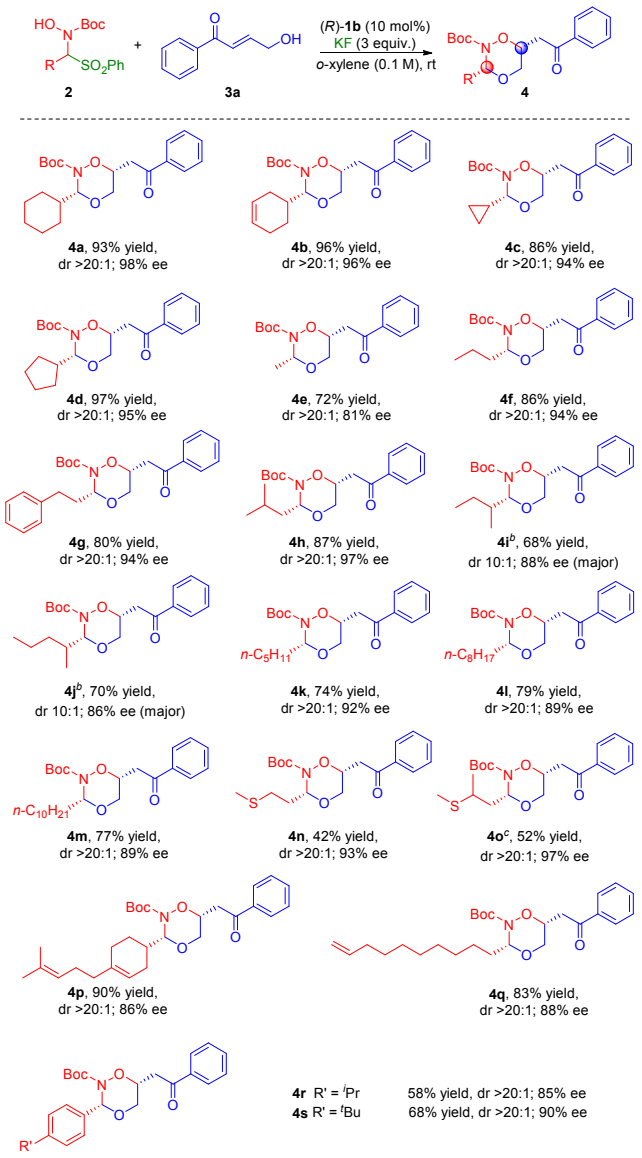


Entry	Catalyst	Solvent (0.1 M)	Yield (%)[b]	ee (%)[c]	dr[d]
1	(*R*)-**1a**	toluene	80	29	>20:1
2	(*R*)-**1b**	toluene	91	93	>20:1
3	(*R*)-**1c**	toluene	87	69	>20:1
4	(*R*)-**1d**	toluene	89	71	>20:1
5	(*R*)-**1b**	CH_2Cl_2	78	55	>20:1
6	(*R*)-**1b**	THF	69	92	>20:1
7	(*R*)-**1b**	1,4-dioxane	37	53	>20:1
8	(*R*)-**1b**	ethyl acetate	85	98	>20:1
9	(*R*)-**1b**	mesitylene	92	98	>20:1
10	**(*R*)-1b**	**o-xylene**	**93**	**98**	**>20:1**

[a]Reactions were performed with **2a** (0.1 mmol), **3a** (1.3 equiv.), KF (3 equiv.), and (*R*)-**1** (10 mol%) in the solvent indicated at 25 °C for 24 h. [b]The yield was determined after chromatographic purification. [c]% ee was determined by HPLC analysis using a chiral stationary phase. [d]The diastereomeric ratio (dr) was determined by ^{1}H NMR and found to be >20:1.

different solvents were examined (entries 5–10). When nonpolar solvents such as *o*-xylene and mesitylene were used, excellent yields and enantioselectivities were obtained. Interestingly, ethyl acetate, a polar solvent, was also shown to be an excellent solvent (entry 8). However, other polar solvents such as THF, and 1,4-dioxane proved to be worse in terms of yields and asymmetric induction (entries 6–7).

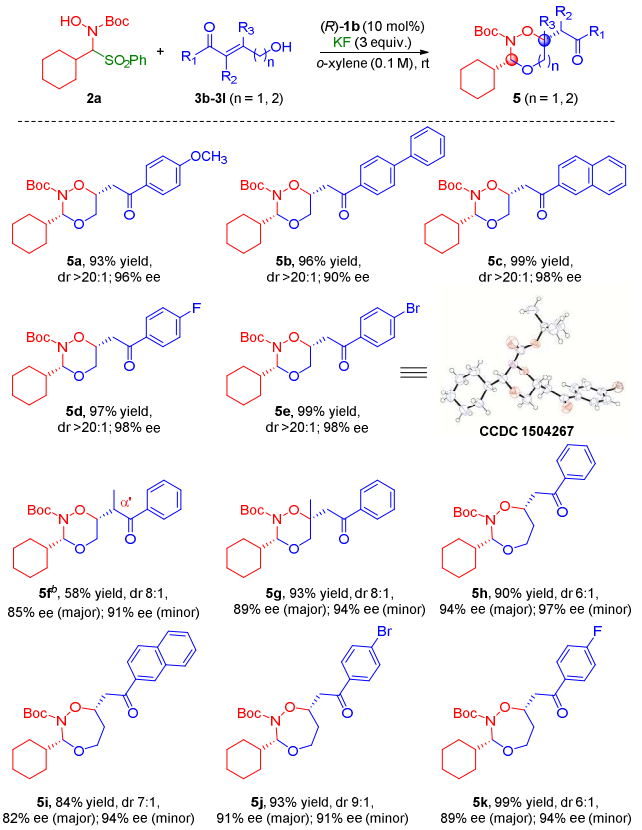
Table 2. Substrate Scope of the Cycloaddition Reaction of Amido Sulfone 2 with 3a[a]



[a]Reactions were performed with **2** (0.1 mmol), **3a** (1.3 equiv.), KF (0.3 mmol) and (*R*)-**1b** (10 mol%) in *o*-xylene (1.0 mL) at 25 °C for 24 h. The yield was determined after chromatographic purification, and the % *ee* was determined by HPLC analysis using a chiral stationary phase. Diastereomeric ratio (dr) was determined by ^{1}H NMR. [b]ca. 1.5:1 of *R*/*S* (or *S*/*R*) mixture at α-position of the side chain of **4i** and **4j**, see the supporting information for details. [c]1:1 of *R*/*S* (or *S*/*R*) mixture at β-position of the side chain of **4o**, see the supporting information for details.

With the optimal conditions (Table 1, entry 10) in hand, the generality of our protocol was evaluated with *N*-hydroxy α-amido sulfones **2** as the nitrone precursors. As shown in Table 2, a variety of linear, branched, and cyclic aliphatic *N*-hydroxy Boc-α-amido sulfones **2** were successfully reacted with **3a** in the presence of KF (3 equiv.) and catalyst (*R*)-**1b** (10 mol%) in *o*-xylene, affording diverse 3,6-disubstituted 1,4,2-dioxazinanes **4a–4q** in high stereoselectivities (up to 98% ee and 20:1 dr for *syn*-diastereomer). Moreover, aromatic *N*-hydroxy Boc-α-amido sulfones (**2r** and **2s**) also furnished the Mannich product **4r** and **4s**, respectively, in high stereoselectivity (up to 90% ee and 20:1 dr for *syn*-diastereomer).

Table 3. Substrate Scope of the Cycloaddition Reaction of Amido Sulfone 2a with 3[a]

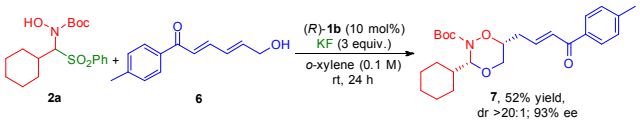


[a]Reactions were performed with **2a** (0.1 mmol), **3** (1.3 equiv.), KF (0.3 mmol) and (*R*)-**1b** (10 mol%) in *o*-xylene (1.0 mL) at 25 °C for 24 h. The yield was determined after chromatographic purification and the % *ee* was determined by HPLC analysis using a chiral stationary phase. Diastereomeric ratio (dr) was determined by ^{1}H NMR. [b]ca. 2:1 of *R*/*S* (or *S*/*R*) mixture at α'-position of the side chain of **5f**, see the supporting information for details.

Various γ- and δ-hydroxy-α,β-unsaturated ketones **3** were investigated for the substrate scope of this reaction. As shown in Table 3, the reaction with a series of γ-hydroxy-α,β-unsaturated ketones **3b–3h** bearing electron rich as well as electron deficient aromatic ring underwent smoothly with *N*-α-amido sulfone **2a** to furnish the desired products **5a–5g** with excellent diastereo- (up to >20:1 dr) and enantioselectivity (up to 98% ee). Notably, β-substituted α,β-unsaturated ketone, **3h**, also smoothly

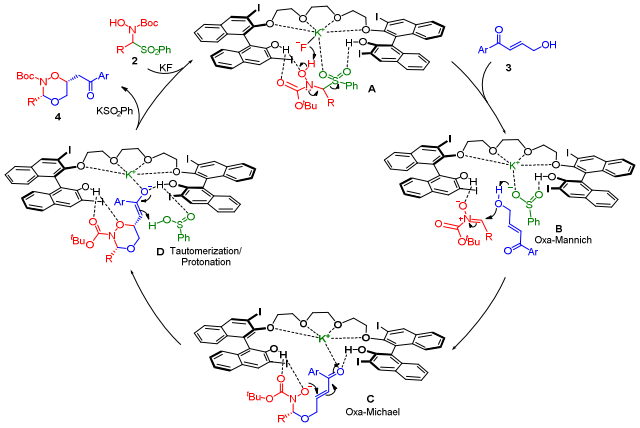
converted to the corresponding 1,4,2-dioxazinanes **5g**, having a quaternary stereogenic center. The relative and absolute configurations were determined as (*3R,6R*) by single crystal X-ray crystallographic analysis of the compound **5e**[16] and by analogy the same configuration was assigned to all the compounds. In addition, the reaction scope was further explored for the synthesis of seven-membered 1,4,2-dioxazepanes by using *δ*-hydroxy-*α,β*-unsaturated ketones. Delightfully, all (*E*)-5-hydroxy-1-arylpent-2-en-1-ones (**3i**–**3l**) subjected to this reaction afforded the seven-membered 1,4,2-dioxazepanes **5h**–**5k** in high yield and steroselctivities (82-97% ee, 6:1 – 9:1 dr). To the best of our knowledge, this is the first example of the synthesis of seven-membered 1,2,4-oxazepane heterocycles.

Scheme 2. Chiral 1,4,2-Oxazinane 7 from Terminal-Hydroxy Dienones



Finally, terminal-hydroxy dienones were also examined for this reaction. Interestingly, (2*E*,4*E*)-6-hydroxy-1-(*p*-tolyl)hexa-2,4-dien-1-one **6** reacted with **2a** via Mannich/vinylogous Michael cascade reaction, producing only 6-membered 1,4,2-dioxazinane product **7** with excellent diastereo- and enantioselectivity (93% ee and >20:1 dr) (Scheme 2).

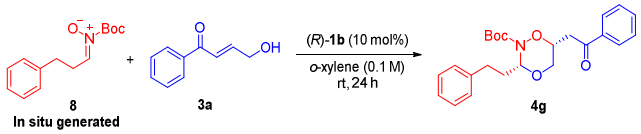
Scheme 3. Plausible Catalytic Cycle



Based on the product formation under the tandem pathway, a plausible mechanism is outlined as shown in Scheme 3. Initial simultaneous activation of potassium fluoride and *α*-amido sulfone **2** by the catalyst **1b** (complex **A**) and subsequent interaction of **3** with complex **A** formed an adduct **B**, in which both the activated reacting partners immediately participated in oxa-Mannich reaction to generate the intermediate **C**. Next, the intermediate **C** was readily converted to the intermediate **D** through an oxa-Michael reaction. The intermediate **D** finally furnished the desired chiral product **4** via tautomerization/protonation. As shown in the proposed mechanism, the cation (K^+)-binding to the catalyst is critical to induce high reactivity and high enantioselectivity by the formation of the chiral cage.

To support the proposed reaction mechanism, the reaction of nitrone **8** was performed with **3a** in the presence of potassium benzene sulfinate **9a**, resembling the reaction conditions with *N*-hydroxy Boc-protected amido sulfone **2a** and **3a** in the presence of KF (condition a in Scheme 4). As shown from the results of Scheme 4, moderate chemical yield and excellent stereoselectivity (91% ee and >20:1 dr) were obtained. However, in the absence of potassium sulfinate (condition b in Scheme 4), the reaction proceeded very sluggishly, affording trace amount of product. According to the above experimental results, as we proposed, efficient incorporation of potassium sulfinate as a cocatalyst or additive is critical to induce high reactivity and high enantioselectivity by the formation of the chiral cage. The complexation of potassium sulfinate with the catalyst was also seen very clearly in the measurements of ^{13}C spin-lattice relaxation (T_1)[17] and ESI-HRMS (positive ion mode, calculated for $C_{46}H_{34}I_4KO_6^+$: 1228.8166; Found: 1228.8157) (see the Supporting Information).

Scheme 4. Critical Effects of Potassium Sulfinate for the Catalysis



CONCLUSIONS

In summary, we have described the formal cycloaddition of *N*-Boc-*N*-hydroxy-amido sulfones as the nitrone precursors with terminal-hydroxy-*α,β*-unsaturated carbonyls, in the presence of a Song's chiral oligoEG as a cation binding catalyst and KF as a base to access diverse highly enantio- and diastereo-enriched 1,4,2-dioxazinane and dioxazepane heterocycles with potentially interesting biological activity. In this process, terminal-hydroxy-*α,β*-unsaturated carbonyls as well as nitrones serve as "amphiphilic" building units and a sequence of tandem pathway, oxa-Mannich/oxa-Michael/tautomerization/protonation, leads to the final products. The cation-binding catalysis in a densely confined chiral space *in situ* formed by the incorporation of potassium salt, is the key of this successful catalysis. We believe that our cation-binding catalysis strategy would open a new pathway for the asymmetric synthesis of diverse heterocyclic skeletons of great complexity.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization data for all the products. 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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Table of Contents