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Asymmetric Organocatalyzed Reaction Sequence To Synthesize Chiral Bridged and Spiro-Bridged Benzofused Aminals via Divergent Pathways

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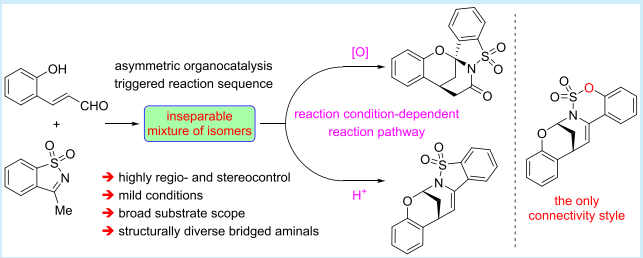
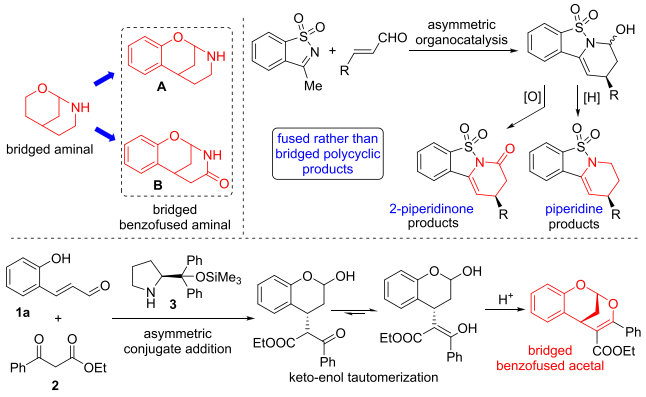
Supporting Information

ABSTRACT: A highly efficient asymmetric organocatalysis-triggered reaction sequence is developed. 2-Hydroxy cinnamaldehydes and cyclic *N*-sulfonyl ketimines were both used as multisite substrates (more than two reactive sites) to access structurally diverse chiral bridged and spiro-bridged benzofused aminal derivatives, where an inseparable equilibrating mixture of isomers can be regioselectively converted into bridged benzofused aminals with different ring connectivities via divergent pathways. Several stereoselective transformations of the resulted bridged aminals are presented.



The efficient construction of molecules of medicinal interest is an important area of drug discovery and has thus attracted considerable attention from both synthetic and medicinal chemists. The bridged aminal skeleton,[1] especially its benzofused form,[2] can be found in numerous natural and synthetic products, many of which have been reported to exhibit intriguing biological activities (Scheme 1, top left); however, despite their medicinal interest, to the best of our knowledge all of the reported methodologies focused on only their racemic synthesis,[3] and the development of methodologies for the catalytic asymmetric construction of a chiral bridged benzofused aminal skeleton has not been reported to date, which thus remains an important but challenging task in asymmetric synthesis.

Scheme 1. Different Bridged Aminal Scaffolds and Our Previous Work



The cyclic *N*-sulfonyl ketimines, which can be easily prepared from the commercially available saccharin, have been well studied and applied in a variety of asymmetric organocatalytic transformations as bifunctional substrates to construct fused rather than bridged polycyclic compounds,[4] and during the sequential reaction processes, the base-catalyzed or spontaneous imine-enamine tautomerization generated the key nitrogen nucleophile for the intramolecular cyclization, leading to fused cyclic hemiaminal intermediates, followed by reduction and oxidation, respectively, to give the corresponding piperidine and 2-piperidinone scaffolds, which are the key component of the bridged benzofused aminals **A** and **B** (Scheme 1, top right).

On the basis of structural analysis, both the benzofused aminals **A** and **B** have in common a 2,4-disubstituted chromane moiety in their bridged ring system. We recently found that 2-hydroxy cinnamaldehydes have the unique advantage of installing the 2,4-disubstituted chromane moiety in a bridged ring system through a conjugate addition-triggered reaction sequence (Scheme 1, bottom),[5] where the acid-promoted keto−enol tautomerization provides the required oxygen nucleophile in the oxocarbenium-ion-induced acetal formation process.

The control or switching of chemical equilibrium toward diverse product formation has been a versatile tool for

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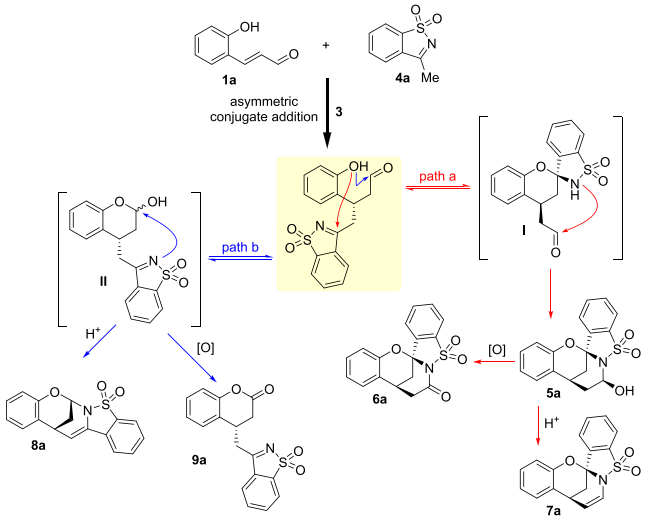
synthetic chemists.[6] As shown in Scheme 2, we proposed that the diphenylprolinol-silyl-ether-**3**-catalyzed conjugate addition

Scheme 2. Design of Synthetic Strategies

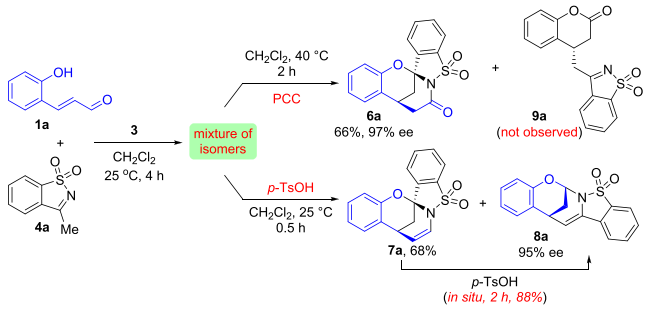


of cyclic *N*-sulfonyl ketimine **4a** to 2-hydroxy cinnamaldehyde **1a** by asymmetric iminium catalysis would regioselectively deliver two multifunctional intermediates **I** and **II**, which are at the very least in equilibrium in the reaction mixture that might introduce two competitive reaction pathways, path a and path b, leading to structurally diverse heterocyclic compounds. In path a, the ketimine with a sulfonyl group is expected to be attacked first by the phenolic hydroxyl group to give the spirocyclic four-substituted chroman-2-amine intermediate **I**, followed by an intramolecular cyclization reaction delivering hemiaminal product **5a**, which could be converted into either the spiro-bridged benzofused aminal **6a** under oxidative reaction conditions or the spiro-bridged benzofused aminal **7a** through the acid-promoted dehydration. Whereas, in path b, the formation of the four-substituted chroman-2-ol intermediate **II** would be accomplished by the attack of the phenolic hydroxyl group on the aldehyde group, and the acid-promoted oxocarbenium ion-formation-induced cyclization procedure would form the bridged polycyclic structure **8a**. Meanwhile, the oxidation of hemiacetal intermediate **II** would enable the formation of the four-substituted chroman-2-one product **9a**. Accordingly, the key issue we hoped to address in this study was the chemo- and regioselectivity of this asymmetric organocatalyzed reaction sequence to furnish the structurally diversified chiral bridged and spiro-bridged benzofused aminal products.

In our continuing effort on the construction of fused polycyclic acetal[7] and aminal[8] compounds, herein we report a highly regio- and stereoselective reaction sequence triggered by the asymmetric organocatalytic conjugate addition of cyclic *N*-sulfonyl ketimines to 2-hydroxy cinnamaldehydes, thus providing structurally diversified bridged and spiro-bridged benzofused aminal products.[9] Although both cyclic *N*-sulfonyl ketimines[4] and 2-hydroxy cinnamaldehydes[10] are very useful synthons in asymmetric organocatalytic transformations, to the best of our knowledge, they have been used for the first time as multisite substrates (more than two reactive sites),[11] which showed unique advantages in the construction of chiral bridged benzofused polycyclic ring system.

We initially attempted the reaction of cyclic *N*-sulfonyl ketimine **4a** with 2-hydroxy cinnamaldehyde **1a** in the presence of aminocatalyst **3** and in the absence of any additive (Scheme 3). To our surprise, the reaction proceeded smoothly in

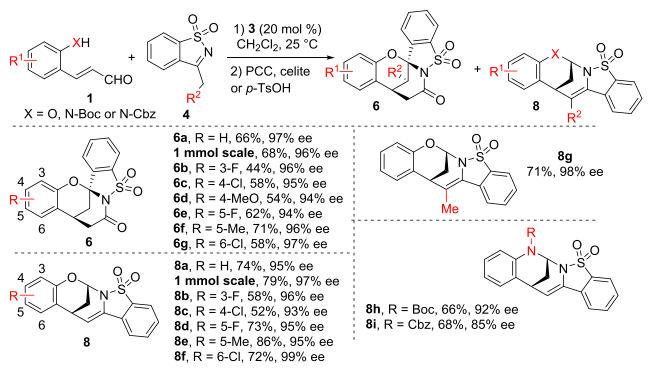
Scheme 3. Divergent Reaction Pathways for the Reaction Sequence of 1a and 4a



CH_2Cl_2 solvent at 25 °C but afforded an inseparable equilibrating mixture of isomers, which could possibly be the result of the above-mentioned two competitive reaction pathways. Unexpectedly, we found that the oxidation of this reaction mixture with pyridinium chlorochromate (PCC) in a one-pot procedure provided the spiro-bridged benzofused aminal **6a** bearing a quaternary stereogenic center as the sole product in good yield with excellent enantioselectivity as a single diastereomer, and no isolable oxidation product **9a** was obtained. On the contrary, the dehydration of this mixture in CH_2Cl_2 solvent at 25 °C catalyzed by the *p*-toluenesulfonic acid (*p*-TsOH) resulted in two separable regioisomeric products, the spiro-bridged aminal **7a** and the bridged polycyclic aminal **8a**. Interestingly, **7a** was found to be less stable under such acidic conditions at 25 °C with increasing reaction time and was gradually converted into **8a** with excellent regio- and stereocontrol.[12]

Next, we investigated the substrate scope with respect to 2-hydroxy cinnamaldehydes for constructing the spiro-bridged aminal **6** and the bridged polycyclic aminal **8** by reaction with cyclic *N*-sulfonyl ketimine **4a** via the conjugate addition−oxidation sequence and the conjugate addition−dehydration sequence, respectively. As shown in Scheme 4 (Cbz = carboxybenzyl; Boc = *tert*-butoxycarbonyl), the 2-hydroxy cinnamaldehydes having substituents at different positions of the phenyl ring, regardless of their electronic properties,

Scheme 4. Substrate Scope of the Reaction of 1 and 4 To Construct Spiro-Bridged Aminals 6 and Bridged Benzofused Aminals 8



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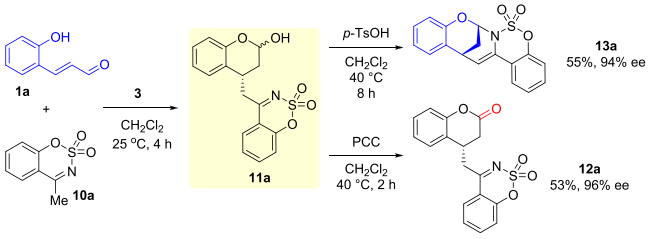
performed well in the designed two-step reaction sequence in one pot, giving the corresponding spiro-bridged benzofused aminal products **6a−g** and bridged benzofused aminal products **8a−f**, respectively, in moderate to good yield with high stereoselectivities. Notably, product **8g** with a methyl substituent could also be obtained with high levels of stereocontrol. To our delight, *N*-Boc- and *N*-Cbz-protected 2-amino cinnamaldehyde are also suitable substrates, giving bridged benzofused *N*,*N*-acetal products **8h** and **8i** in good yield, albeit a slightly lower enantioselectivity was detected for **8i**. Furthermore, reactions on a 1 mmol scale gave compounds **6a** and **8a** with similar results as the reactions carried out on a 0.1 mmol scale.

However, during the evaluation of the substrate scope of the cyclic *N*-sulfonyl ketimines, we found that the steric hindrance effect arising from the ring size of the cyclic *N*-sulfonyl ketimines has critical effects on the reactivity of these substrates (Scheme 5) because the reaction of the six-membered cyclic *N*-sulfonyl ketimine **10a** with 2-hydroxy cinnamaldehyde **1a** gave only the four-substituted chroman-2-ol intermediate **11a**, the structure of which was unequivocally identified by nuclear magnetic resonance (NMR) spectroscopy, whereas the product derived from competitive path a (see Scheme 2) was not detected under the same catalytic conditions as those above. Subsequently, the obtained hemiacetal product **11a** can be readily oxidized in one pot, resulting in four-substituted chromane-2-one **12a**. Delightfully, the bridged benzofused aminal **13a** could be efficiently accessed by a one-pot acid-catalyzed enamine-oxonium cyclization procedure.

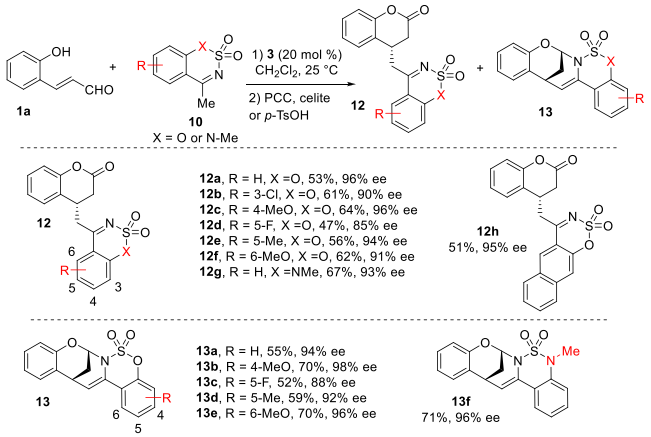
Scheme 5. Different Behaviors of Six-Membered Cyclic *N*-Sulfonyl Ketimine 10a



The substrate scope for the asymmetric conjugate-addition-triggered reaction sequence of the six-membered cyclic *N*-sulfonyl ketimines **10** to 2-hydroxy cinnamaldehyde **1a** was then investigated, and the results are summarized in Scheme 6. When the R substituents on the aromatic rings of the six-membered cyclic *N*-sulfonyl ketimines **10** were varied, regardless of the positions and the electronic nature, good yields and high stereoselectivities were achieved for four-substituted chromane-2-one products **12a−f** and the bridged benzofused aminals **13a−e**, respectively. When the phenyl ring was replaced by a naphthalene group, similar good results were obtained for product **12h**. Notably, by changing the phenolic oxygen atom in six-membered cyclic *N*-sulfonyl ketimine to a nitrogen atom, the two sequential processes preceded smoothly, leading to the desired products four-substituted chromane-2-one product **12g** and the bridged benzofused aminal **13f**, respectively, in good yield with high stereoselectivities.

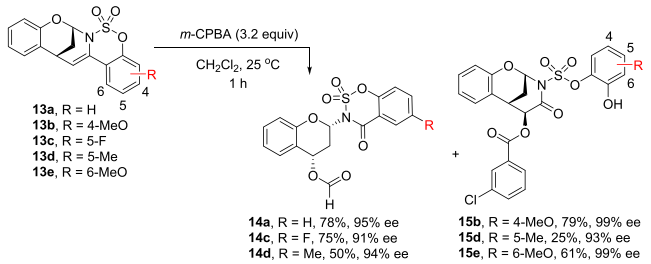
To investigate the synthetic utility of these bridged benzofused aminals, we focused our attention on the

Scheme 6. Substrate Scope of the Reaction of 1a and 10 To Construct Four-Substituted Chromane-2-ones 12 and Bridged Benzofused Aminals 13



modification of the enamine moiety in the structure of **13** (Scheme 7; for a proposed mechanism, see Scheme S1).[13] By treatment with *m*-chloroperbenzoic acid (*m*-CPBA), the enamine moiety in **13a** could undergo an epoxidation reaction, followed by oxirane cleavage and double Baeyer−Villiger oxidation, leading to 4-chromanol derivative **14a**.[14] It is observed that the electronic effects of the substituents on the aromatic ring of *N*-sulfonyl ketimine play a critical role in this cascade transformation. An electron-withdrawing group, such as the fluorine atom, on the benzene ring could effectively take part in the reaction, providing **14c** as the only product, whereas upon introducing a methyl group instead of fluorine atom, the normal aminal product **14d** accompanied by the unexpected bridged aminal **15d** was obtained in a 2:1 ratio (based on the isolated yield). Because of the electron-donating effect of the methyl group, we proposed that there should be a Dakin-type rearrangement after the epoxidation step to yield the substituted phenol product. As expected, the stronger electron-donating effect of the methoxy group on the ortho and para positions resulted in the formation of the bridged aminals **15b** and **15e**, respectively, as the sole products in 79 and 61% yield.

Scheme 7. Synthetic Transformations of 13 via Oxidative Cleavage



As illustrated in Scheme 8, the hydrogenation of **8a** in the presence of Pd/C as the catalyst resulted in the formation of bridged aminal **16** with excellent diastereoselectivity. Additionally, the four-substituted chromane-2-one product **9a** could be readily obtained after the in situ hydrolysis of **6a** under acidic conditions (33% HBr in AcOH at reflux), which could not be accessed through the oxidation of the reaction mixture resulting from the conjugate addition of **1a** and **4a**.

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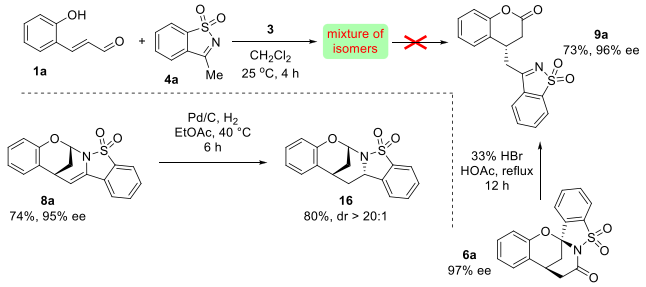
Scheme 8. Preparation of Four-Substituted Chromane-2-one 9a and Bridged Aminal 16



The structures and stereochemistries of **6a** (CCDC 1915200), **8a** (CCDC 1913911), **14d** (CCDC 1913912), and TBS-protected **17** (CCDC 1918877) were unambiguously determined by single-crystal X-ray analysis (Figure 1; the H atoms are omitted for clarity; TBS = *tert*-butyldimethylsilyl; DMAP = 4-dimethylaminopyridine). All other compound structures were assigned by analogy assuming a uniform reaction pathway. The relative stereochemistry of the novel chiral center in product **16** was confirmed by nuclear Overhauser effect (NOE) experiments (see the Supporting Information).

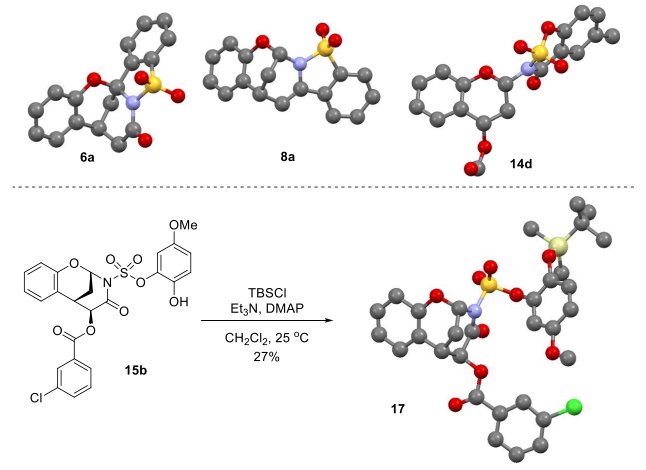


Figure 1. X-ray structures of compounds **6a**, **8a**, **14d**, and **17**.

In summary, we have developed an asymmetric organocatalysis triggered reaction sequence of cyclic *N*-sulfonyl ketimines to 2-hydroxy cinnamaldehydes, which provides an efficient protocol for the enantioselective synthesis of structurally diverse chiral bridged and spiro-bridged benzo-fused aminal derivatives with high levels of regio- and stereocontrol. It should be noted that the first conjugate addition step of the developed reaction sequence afforded an inseparable equilibrating mixture of isomers, which could be converted into bridged aminal products with different ring connectivities through divergent pathways. Additionally, the steric hindrance effect arising from the ring size of the cyclic *N*-sulfonyl ketimines has critical effects on the regioselectivity of the sequential process because the cyclic *N*-sulfonyl ketimines with different ring sizes provided different types of heterocyclic products. Furthermore, several chemical transformations were conducted to extend the structural complexity and diversity of both the bridged and spiro-bridged aminals. The medicinal evaluation of the obtained aminal products is now underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01874.

Detailed optimization, complete experimental procedures, spectroscopic data for all new compounds, X-ray data, and proposed reaction mechanism for the formation of compounds **14** and **15** (PDF)

Accession Codes

CCDC 1913911−1913912, 1915200, and 1918877 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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