Synthesis of $\alpha,\alpha'$-trans-Oxepanes through an Organocatalytic Oxa-conjugate Addition Reaction

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Supporting Information

ABSTRACT: Oxepanes are found in a wide range of natural products; however, they are challenging synthetic targets due to enthalpic and entropic barriers. Organocatalytic oxa-conjugate addition reactions promoted by the $\text{gem}$-disubstituted (Thorpe−Ingold) effect stereoselectively provided $\alpha,\alpha'$-trans-oxepanes. In addition, the potential of an organocatalytic tandem oxa-conjugate addition/$\alpha$-oxidation was demonstrated in a rapid generation of molecular complexity. These organocatalytic oxa-conjugate addition reactions would provide powerful tools for the synthesis of natural products that contain highly functionalized oxepanes.

Architecturally complex 7-membered cyclic ethers (oxepanes) are found in a wide range of structurally or biologically interesting natural products (Figure 1). Relative to tetrahydrofurans and tetrahydropyrans, oxepanes are challenging synthetic targets due to enthalpic and entropic barriers.

Given the continued interest and challenges these molecules present as potential synthetic targets, the number of methods available for the construction of oxepanes has steadily increased. Despite progress toward this goal, currently available methods for the synthesis of oxepanes possess several limitations. For example, with the notable exception of ring-closing metathesis (RCM), catalytic methods remain scarce. In addition, the stereoselective synthesis of $\alpha,\alpha'$-trans-oxepanes remains a challenging task since they are thermodynamically less favorable than the corresponding $\text{cis}$ isomers. Further limitations include the challenges associated with preparation of chiral substrates with preinstalled stereocenters, limited substrate scope, and competitive formation of smaller size rings according to Baldwin’s rules. Therefore, despite the advances of the past decade, there still exists a great need for synthetic approaches toward $\alpha,\alpha'$-trans-oxepanes that address these limitations.

During the last century, considerable progress has been made in the conjugate addition of carbon nucleophiles to a diverse set of acceptors for $\text{C}−\text{C}$ bond formation. However, there has been far less interest in the analogous conjugate addition of alcohols to $\alpha,\beta$-unsaturated carbonyl compounds (oxa-conjugate addition reaction) and its application to the stereoselective synthesis of acyclic and cyclic ethers. This is especially true with respect to the synthesis of medium-sized cyclic ethers. This can be attributed to the low reactivity of oxygen nucleophiles, the reversibility of the reaction, and the lack of control in the stereoselectivity. To date, there have been only a few reports on the synthesis of medium-sized cyclic ethers through an intramolecular oxa-conjugate addition reaction. As an example, Martin and co-workers reported the synthesis of an oxepane through the oxa-conjugate addition reaction of a...
hydroxy ester. However, the reaction suffered from competing tetrahydropryan formation, required an internal (Z)-double bond to achieve good yields, and had a narrow substrate scope. Despite the scarcity of successful examples, however, the oxa-conjugate addition reaction has the potential to be a highly straightforward and efficient method for the synthesis of medium-sized cyclic ethers. Herein, we describe our investigation of the organocatalytic oxa-conjugate addition reaction promoted by the gem-disubstituent (Thorpe−Ingold) effect in the stereoselective synthesis of α,α′-trans-oxepanes.

To test the feasibility of the oxa-conjugate addition reaction for the stereoselective synthesis of oxepanes, we prepared α,β-unsaturated aldehyde 5 and subjected it to the conditions shown in Scheme 1. Our initial attempts at the oxa-conjugate addition reaction, under a variety of reaction conditions (pyrrolidine, (R)-6, (S)-6, DBU, Et₃N, KO′Bu, NaH, or Tf₂NH), failed to provide the desired oxepane 7. We attributed the unsuccessful results to the low reactivity of the oxygen nucleophile, entropic factors, and/or transannular and torsional strain.

To overcome these obstacles, we envisioned the introduction of a structural element that would promote conformational preorganization of α,β-unsaturated aldehydes for an intramolecular oxa-conjugate addition reaction. We hypothesized that a 1,3-dithiane group installed on α,β-unsaturated aldehydes could satisfy these requirements on the basis of the gem-disubstituent effect (Thorpe−Ingold effect). The gem-disubstituent effect has been shown to have a profound effect on the formation of medium-sized rings. Among the functional groups used to elicit the gem-disubstituent effect, the 1,3-dithiane group is one of the most effective. The 1,3-dithiane group is an acyl anion equivalent with impressive reactivity which allows umpolung-based strategies and serves as a latent functional group for a carbonyl, hydroxy, or olefinic group or hydrogen atoms.

To explore the feasibility of the oxa-conjugate addition reaction promoted by the gem-disubstituent effect in the synthesis of oxepanes, we prepared the α,β-unsaturated aldehyde 11 with a 1,3-dithiane group by coupling dithiane 8 with alkyl iodide 9 followed by MnO₂ oxidation (Scheme 2). Aldehyde 11 was then subjected to a secondary amine-catalyzed oxa-conjugate addition reaction. We anticipated that the gem-disubstituent effect as well as the iminium activation would help overcome the ring strain and accelerate the cyclization step.

After an extensive search for reaction conditions, treatment of 11 with (R)-6 (20 mol %) and BzOH provided the α,α′-trans-oxepane 12 as the major diastereomer in good stereoselectivity (α,α′-trans:α,α′-cis = 7:1), but in low yield (19%). Encouraged by this initial success in the stereoselective synthesis of α,α′-trans-oxepane 12, we decided to test the hypothesis that the position of 1,3-dithiane group might affect the reactivity and stereoselectivity. We prepared α,β-unsaturated aldehyde 15a with the 1,3-dithiane group at the C₄ position by coupling 13 with (S)-glycidyl benzyl ether ((S)-1a) followed by MnO₂ oxidation (Scheme 3). We were delighted to find that the organocatalytic oxa-conjugate addition reaction of 15a in the presence of (R)-6 (20 mol %) and BzOH followed by NaBH₄ reduction successfully provided the desired α,α′-trans-oxepane 18a through the more favorable iminium intermediate 16B (dr = 8:1, 67% for two steps).
Surprisingly, when the reaction was run for a prolonged period, the stereoselectivity was reduced to provide a 1:1 mixture of 17a and the corresponding α,α′-cis-oxepane, suggesting that the organocatalytic oxa-conjugate addition reaction was reversible. Probing the reaction further, 15a was treated with (R)-6 and BzOH and monitored for the formation and ratio of α,α′-trans- and α,α′-cis-oxepanes at different time points using NMR. We observed that the α,α′-trans-oxepane 17a was initially formed as the major diastereomer. However, after 24 h, the reaction provided a 1:1 mixture of 17a and the corresponding α,α′-cis-oxepane. This data suggests that the formation of the α,α′-trans-oxepane 17a through the organocatalytic oxa-conjugate addition is a kinetically controlled process.

To investigate the substrate scope and stereoselectivity of the reaction, α,β-unsaturated aldehydes 15b–e with a variety of substituents at the C2 position were prepared25 and subjected to the standard reaction conditions (Table 1). We were pleased to find that the organocatalytic oxa-conjugate addition reaction of 15b–e in the presence of (R)-6 provided α,α′-trans-oxepanes 17b–e in good-to-excellent stereoselectivities (dr = 6:20:1).

Recently, the organocatalytic tandem reaction, which carries out at least two reactions under the same reaction conditions, has drawn a considerable amount of attention.26 It avoids time-consuming, costly protecting-group manipulations as well as the isolation of reaction intermediates. In this way, molecular complexity is achieved quickly and often accompanied by high levels of stereoselectivity. Building on the aforementioned work, we attempted an organocatalytic tandem oxa-conjugate addition/α-oxidation (Scheme 4).27 The organocatalytic tandem oxa-conjugate addition/α-oxidation of 15a in the presence of (R)-6 and PhNO followed by NaNBH₄ reduction afforded 20 (62% for two steps) as a single diastereomer.28 The organocatalytic tandem reaction would provide a powerful tool for the rapid synthesis of natural products since these α-functionalized medium-sized cyclic ethers are abundant in natural products.

In summary, we have established an efficient method for the stereoselective synthesis of oxepanes based on the organocatalytic oxa-conjugate addition reaction promoted by the gem-disubstituent effect. It is noteworthy that the organocatalytic oxa-conjugate addition reaction of α,β-unsaturated aldehydes allows for the formation of α,α′-trans-oxepanes, which has proven challenging in other approaches. We have also demonstrated the potential of the organocatalytic tandem oxa-conjugate addition/α-oxidation in a rapid generation of molecular complexity. We plan to extend this organocatalytic oxa-conjugate addition reaction to the stereoselective synthesis of biologically important natural products.

### Table 1. Substrate Scope of the Organocatalytic Oxa-Conjugate Addition Reaction

| entry | R         | yield (%) | dr  |
|-------|-----------|-----------|-----|
| a     | CH₂OBn    | 67        | 8:1 |
| b     | Et        | 87        | 6:1 |
| c     | Ph        | 56        | 6:1 |
| d     | C((CH₃)₂CH₂)OBn | 82  | 17:1 |
| e     | CH₂((R)-OPMB)OBn | 64  | 20:1 |

*Combined yield of the isolated α,α′-trans- and α,α′-cis-oxepane alcohols after NaNBH₄-reduction of the corresponding oxepane aldehydes. The diastereomeric ratio (α,α′-trans/α,α′-cis) was determined by integration of relevant ¹H NMR spectroscopic signals of the crude oxepane aldehydes.

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