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Catalytic Enantioselective Synthesis of 1,4-Benzodioxepines

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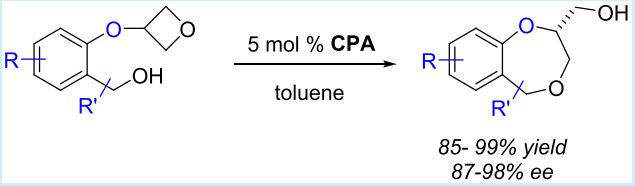
Supporting Information

ABSTRACT: An efficient organocatalytic enantioselective synthesis of chiral 1,4-benzodioxepines is described. By proper incorporation of an intramolecular oxetane desymmetrization process, a range of benzylic alcohols bearing an internal oxetane reacted in the presence of a suitable chiral phosphoric acid catalyst to form chiral 1,4-benzodioxepines with high enantioselectivity. This process provides a new catalytic asymmetric example of direct synthesis of seven-membered heterocycles with good stereocontrol.

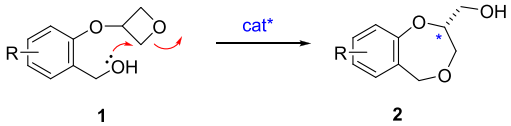


1,4-Benzodioxepines are useful substructures of a range of natural products and biologically important molecules.[1] As a result, strategies for the assembly of such motifs are highly desirable, particularly in the context of asymmetric synthesis. While various approaches have been known for the synthesis of these benzene-fused seven-membered heterocycles, essentially all of them are racemic or achiral.[2] It is worth noting that there have been very few catalytic asymmetric strategies to directly assemble such cyclic structures and concomitantly establish a stereogenic center.

Seven-membered ring formation with simultaneous stereocontrol is not a trivial task.[3,4] Compared with a six-membered ring, seven-membered ring formation experiences both unfavorable kinetics and thermodynamics. Moreover, the ring-closing transition state is much less ordered than that of six-membered ring, which is particularly detrimental to the effective stereocontrol. Therefore, it is a challenge to develop a catalytic asymmetric approach for such a cyclization event.

In continuation of our interests in asymmetric opening reactions of strained rings,[5] we envisioned that benzyl alcohol **1** bearing an *ortho*-tethered oxetane moiety may undergo an intramolecular ring-opening reaction, which could directly deliver 1,4-benzodioxepine **2** (Scheme 1).[6,7] It was also expected to induce chirality in this desymmetrization process with a chiral catalyst, though it could be challenging. It is worth noting that the incorporation of an oxygen atom between the arene and oxetane makes these substrates easily accessible and thus renders this process a highly expedient approach for the synthesis of chiral 1,4-benzodioxepine and their analogues.

Scheme 1. Reaction Design



We began our study with **1a** as the model substrate. Chiral phosphoric acids were employed as catalysts for this process in view of their demonstrated success for the oxetane desymmetrization.[5,8] However, in the presence of 10 mol % of **A1**, almost no conversion of **1a** was observed in toluene for 48 h (Table 1, entry 1). It indicated that the barrier of this reaction is relatively high, which further corroborates the elusive transition state when compared with 5- and 6-membered ring formation. Next, a higher reaction temperature was evaluated. Fortunately, at 80 °C, the reaction successfully afforded the desired product **2a**, albeit with moderate conversion and very low enantioselectivity (entry 2). Further screening of various chiral phosphoric acids with different chiral backbones and 3,3′-substituents indicated that the SPINOL-based catalyst **B1** showed higher enantioselectivity but lower catalytic activity (entry 6). In contrast, catalyst **B4** showed much higher catalytic activity while maintaining reasonably good stereocontrol. Thus, **B4** was used for further optimization. Indeed, with **B4**, the same transformation could go to completion at room temperature with only 5 mol % of catalyst (entry 10). As mentioned above, the stereodetermining transition state for 7-membered ring formation might be loose and not well-ordered. To further restrict the freedom of this transition state, we employed tertiary alcohol **1b**. To our surprise, the same conditions resulted in immediate increase of the enantioselectivity to 90% ee (entry 11). This dramatic change in the outcome might be attributed to the Thorpe−Ingold effect.[9] Next, other parameters, such as solvents, concentration, and temperature, were optimized. Other

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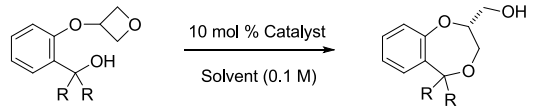
Table 1. Optimization of Reaction Conditions[a]

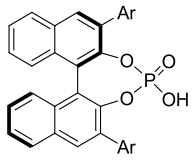


1a: R = H
1b: R = Me

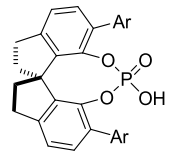
2a: R = H
2b: R = Me

entry	1	cat.	solvent	T (°C)	t (h)	conv[b] (%)	ee[c] (%)
1	**1a**	**A1**	toluene	rt	48	trace	
2	**1a**	**A1**	toluene	80	36	72	13
3	**1a**	**A2**	toluene	80	24	100	10
4	**1a**	**A3**	toluene	80	24	100	8
5	**1a**	**A4**	toluene	80	24	100	26
6	**1a**	**B1**	toluene	80	36	45	69
7	**1a**	**B2**	toluene	80	12	100	51
8	**1a**	**B3**	toluene	80	12	100	44
9	**1a**	**B4**	toluene	80	6	100	62
10[d]	**1a**	**B4**	toluene	rt	24	100	69
11[d]	**1b**	**B4**	toluene	rt	24	100	90
12[d]	**1b**	**B4**	CH_2Cl_2	rt	24	98	82
13[d]	**1b**	**B4**	Et_2O	rt	24	16	83
14[d]	**1b**	**B4**	THF	rt	24	<5	
15[d]	**1b**	**B4**	MeCN	rt	24	16	74
16[d]	**1b**	**B4**	toluene	0	48	74	91
17[d,e]	**1b**	**B4**	toluene	rt	36	100	92

[a]Unless noted otherwise, reactions were performed with oxetane **1a** or **1b** (0.05 mmol), catalyst (10 mol %), and solvent (0.5 mL). [b]Determined by ^{1}H NMR analysis with CH_2Br_2 as an internal standard. The converted material is fully transformed to the desired product. [c]Determined by HPLC analysis. [d]5 mol % **B4** was used. [e]c = 0.05 M.



(*R*)-**A1**: Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
(*R*)-**A2**: Ar = 9-anthryl
(*R*)-**A3**: Ar = 9-phenanthryl
(*R*)-**A4**: Ar = 1-pyrenyl

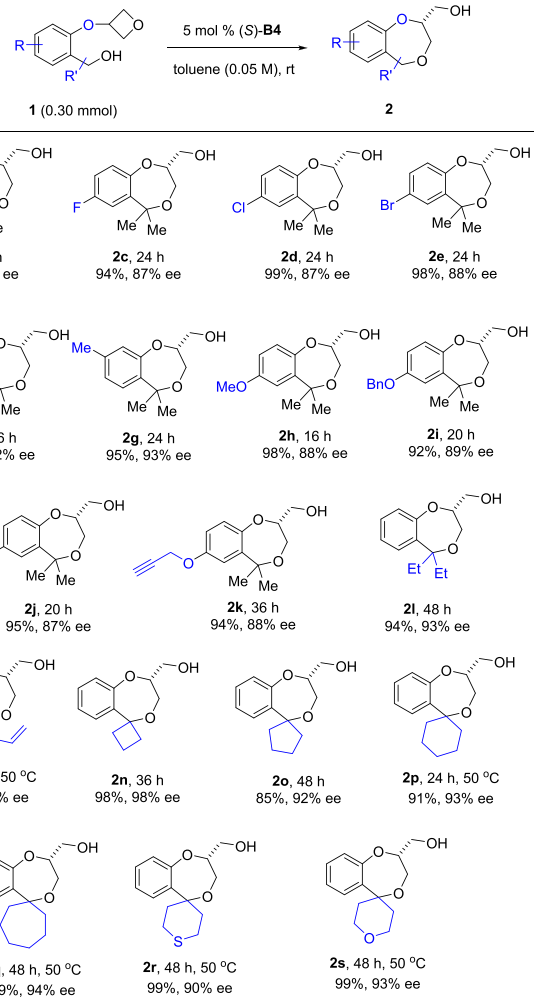


(*S*)-**B1**: Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
(*S*)-**B2**: Ar = 9-anthryl
(*S*)-**B3**: Ar = 9-phenanthryl
(*S*)-**B4**: Ar = 1-pyrenyl

solvents did not improve the outcome (entries 12−15). Decreasing the temperature to 0 °C slightly improved the enantioselectivity but compromised the reaction efficiency (entry 16). However, at a low concentration (0.05 M), both excellent efficiency and high enantioselectivity could be achieved (entry 17). Notably, substrates **1** could be easily prepared in two steps, including nucleophilic substitution of the commercially available *p*-tosylate of oxetan-3-ol with a phenol bearing an *o*-carbonyl substituent followed by nucleophilic addition of the carbonyl group. These steps were straightforward and high yielding.

With the optimized conditions in hand, we next explored the substrate scope of the intramolecular oxetane desymmetrization reaction (Scheme 2). A range of substrates **1b−k** with different electron-withdrawing and -donating substituents on the aromatic ring all proceeded smoothly to form the desired 1,4-benzodioxepines **2b−k** with excellent efficiency and high enantioselectivities (87−93% ee). The electronic property and position of substituents showed minor influence on the reaction outcomes. Various functional groups, such as halogens, ethers, alkenes, and alkynes, are well-tolerated in

Scheme 2. Reaction Scope



[a]Isolated yield.

this mild reaction. Oxetanes **1l−s** tethered with different benzylic tertiary alcohols were all suitable substrates, furnishing the corresponding products with good to excellent efficiency and enantioselectivities (90−98% ee). Generally, the increased steric hindrance of the alcohol unit could lead to increased enantioselectivity but decreased reactivity. Notably, the use of cyclic alcohols provided easy access to the construction of spiro heterocycles (**2n−s**). The absolute configuration of enantiopure **2e** was confirmed to be *R* by single-crystal X-ray crystallography (Figure 1), and those of other products were assigned by analogy based on the transition-state model.

The substrate scope was further investigated for the synthesis of other heterocycles. Sulfur-tethered oxetane **1b-S**

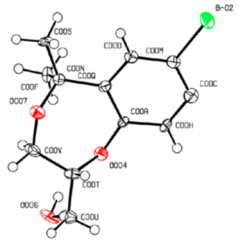


Figure 1. X-ray crystal structure of **2e**.

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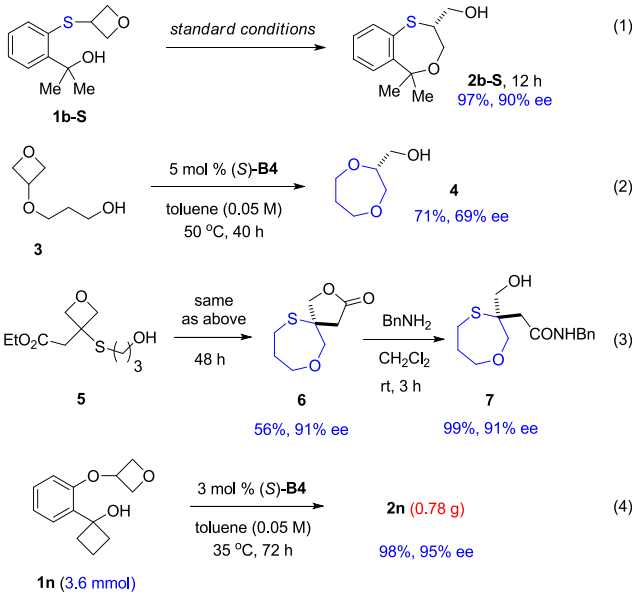
also worked well, providing the desired 1,4-oxathiepine **2b-S** in 97% yield with 90% ee (eq 1). In addition to benzene-fused

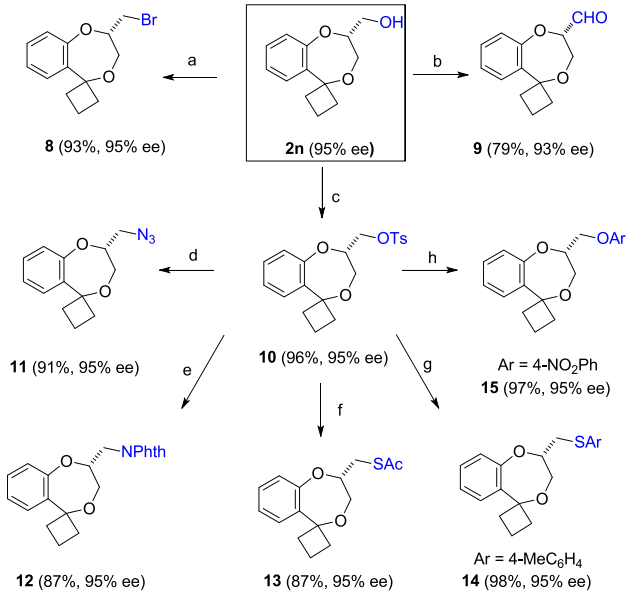


substrates, we also investigated those without a benzene ring. For example, oxetane **3** provided the desired 1,4-dioxepine **4** with good efficiency but moderate enantioselectivity (69% ee, eq 2). The diminished enantioselectivity might be due to the more flexible aliphatic side chain and, thus, the less organized ring-closing transition state. Interestingly, oxetane **5** underwent a ring-opening/lactonization cascade reaction to afford the corresponding spiro-heterocycle **6** with moderate efficiency and high enantioselectivity (91% ee). Subsequent ring-opening with benzylamine took places smoothly to give 1,4-oxathiepane **7** in quantitative yield (eq 3). This result indicated that the construction of a quaternary stereocenter in this process is feasible. Finally, to demonstrate the robustness of this protocol, a scale-up synthesis of **2n** was carried out. In the presence of 3 mol % of (*S*)-**B4**, the reaction of **1n** on 3.6 mmol scale proceeded smoothly at 35 °C to afford the desired product **2n** without obvious erosion in yield or enantioselectivity (98%, 95% ee, eq 4).

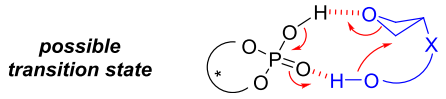
The 1,4-benzodioxepine products formed in our reaction could serve as precursors for the synthesis of other useful chiral molecules. For example, bromination of **2n** with triphenylphosphine and carbon tetrabromide afforded the corresponding bromide **8**. After oxidation by Dess−Martin periodinane, aldehyde **9** could be formed with high efficiency. Tosylation of **2n** followed by S_N2 substitution reactions with various nucleophiles readily delivered the desired compounds **11**−**15** with good to excellent efficiency. In all of these transformations, the high enantiopurity essentially remained intact (Scheme 3).

A simplified transition-state model is depicted to rationalize the possible interactions involved in this catalytic reaction. We believe that the chiral phosphoric acid serves as a bifunctional catalyst. The acid functionality provides the primary activation of the oxetane unit by hydrogen bonding. In the meanwhile, the phosphoryl oxygen provides a secondary hydrogen bonding with the nucleophile hydroxyl group, which increases its nucleophilicity. With these two interactions, the transition state is relatively rigid, which explains the observed good asymmetric induction.

Scheme 3. Product Transformations[a]



[a]Conditions: (a) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt; (b) DMP, CH_2Cl_2, rt; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt; (d) NaN_3, DMSO, 80 °C; (e) potassium phthalimide, DMF, 80 °C; (f) AcSK, DMF, rt; (g) 4-MePhSH, Cs_2CO_3, DMF, 80 °C; (h) 4-$NO_2C_6H_4OH$, K_2CO_3, DMF, 80 °C.



In conclusion, we have developed an efficient catalytic enantioselective synthesis of chiral 1,4-benzodioxepines, which are important structures lacking efficient asymmetric access. In particular, catalytic asymmetric synthesis of such seven-membered ring structures involves a poorly ordered transition state, making stereocontrol illusive. The present reaction was able to overcome this challenge by incorporating an intramolecular oxetane desymmetrization on properly designed substrates. With the suitable chiral phosphoric acid catalyst, this process proceeded efficiently to form a wide range of chiral 1,4-benzodioxepines with high enantioselectivity. This catalytic process features mild reaction conditions and good functional group compatibility. It is also expected to extend to the synthesis of other chiral heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04244.

Experimental details, copies of ^1H and ^{13}C spectra of new compounds, and HPLC chromatograms (PDF)

Accession Codes

CCDC 1967687 contains 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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