Asymmetric Catalysis

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Organocatalytic Enantioselective Synthesis of 1,4-Dioxanes and Other Oxa-Heterocycles by Oxetane Desymmetrization

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Abstract: *A new asymmetric synthesis of chiral 1,4-dioxanes and other oxa-heterocycles has been developed by means of organocatalytic enantioselective desymmetrization of oxetanes. This mild process proceeds with exceedingly high efficiency and enantioselectivity to establish the quaternary stereocenters. This method complements the existing, yet limited, strategies for the synthesis of these oxa-heterocycles.*

Chiral 1,4-dioxane scaffolds occur in a wide range of natural products and pharmaceutical agents.[1] For example, the compounds **I**, **II**, and **III** exhibit impressive antiviral, anticancer, and cardiotonic activities, respectively (Figure 1). Moreover, they proved important in organic synthesis. The 1,4-dioxane unit serves as a useful chiral backbone in the ligand **IV**.[2] Despite their proven versatility, efficient asymmetric assembly of chiral 1,4-dioxanes has remained underdeveloped, and currently relies largely on the traditional strategies employing chiral starting materials.[1–3] Asymmetric catalysis has not been well exploited to date,[4] particularly for general 1,4-dioxanes (functionalized but not restricted to certain bicyclic frameworks). Herein we report the first approach of this type and it is enabled by efficient intramolecular desymmetrization of oxetanes.

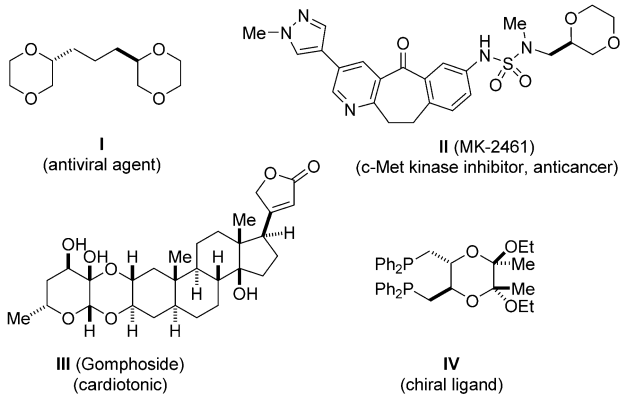

Figure 1. Useful chiral 1,4-dioxane-containing molecules.

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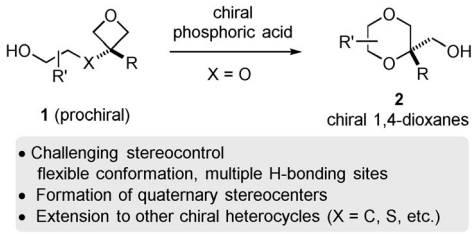
In addition to their applications in drug discovery,[5] oxetanes have recently attracted increasing attention regarding their asymmetric transformations into a variety of chiral building blocks.[6–10] Inspired by these pioneering studies, we envisioned that, upon suitable activation by a chiral phosphoric acid catalyst,[11] oxetanes (**1**) bearing an ethylene glycol tether at the 3-position would result in stereocontrolled ring-opening to form chiral 1,4-dioxanes (**2**; X = O, Scheme 1).

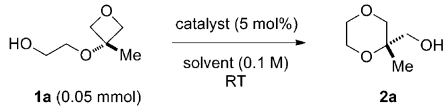


Scheme 1. Design of chiral 1,4-dioxane synthesis.

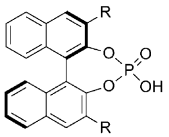
Quaternary stereocenters can be generated provided that the oxetane substrates are 3,3-disubstituted.[12] However, the stereocontrol and catalyst turnover might be challenging because of the presence of multiple hydrogen-bonding sites. Furthermore, additional difficulty may arise from orientation of the flexible side chain to achieve a stereocontrolled transition state. Nevertheless, herein we describe not only the realization of this highly enantioselective process, but also its extension to the synthesis of other chiral oxa-heterocycles (e.g., X = C, S, etc.; Scheme 1), whose asymmetric syntheses are in high demand but limited.

We started with the oxetane **1a** as the model substrate (Table 1). With the representative BINOL-derived chiral phosphoric acid **A1** (TRIP) as a catalyst, the intramolecular reaction proceeded smoothly at room temperature in toluene to form the desired 1,4-dioxane **2a**, albeit with moderate efficiency and enantioselectivity (entry 1). Further screening of other phosphoric catalysts indicated that the catalyst chiral backbones and 3,3′-substituents have dramatic influence on the reaction outcome (entries 2–8). For example, the spiroindane-derived acid **B1** exhibits almost no catalytic activity, presumably because of relatively low acidity and a sterically hindered chiral pocket. While most other catalysts can promote the reaction with good efficiency, only the catalyst **B4** gave excellent enantioselectivity (entry 8).[13] The reaction shows negligible solvent effects on the enantioselectivity, but a decreased rate was observed in Et_2O and MeCN (entries 12 and 13), presumably because of competitive binding of the solvents to the catalyst. Among them, DCE proved best with

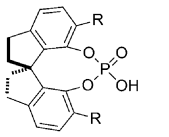
Table 1: Reaction optimization.



1a (0.05 mmol) **2a**



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

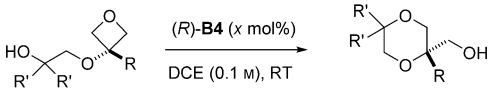


(*R*)-**B1**: R = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
(*R*)-**B2**: R = 9-anthryl
(*R*)-**B3**: R = 9-phenanthryl
(*R*)-**B4**: R = 1-pyrenyl

Entry	Catalyst	Solvent	*t* [h]	Conv. [%][a]	*ee* [%][b]
1	**A1**	toluene	24	33	−28
2	**A2**	toluene	12	100	−47
3	**A3**	toluene	24	100	−71
4	**A4**	toluene	12	100	−42
5	**B1**	toluene	24	< 10	–
6	**B2**	toluene	24	90	59
7	**B3**	toluene	24	85	43
8	**B4**	toluene	12	100	96
9	**B4**	benzene	12	100	97
10	**B4**	DCM	12	100	98
11	**B4**	DCE	2	100	98
12	**B4**	Et_2O	12	78	96
13	**B4**	MeCN	12	79	96
14[c]	**B4**	DCE	2	100	97
15[d]	**B4**	DCE	2	100	98
16[e]	**B4**	DCE	12	100	98
17[f]	**B4**	DCE	24	100	97

[a] Determined by ^{1}H NMR analysis with CH_2Br_2 as an internal standard. [b] Determined by chiral-phase HPLC analysis of the corresponding benzoate derivative of **2a**. [c] Run with 0.5 M concentration. [d] Run with 0.05 M concentration. [e] Run with 2 mol% of catalyst. [f] Run with 1 mol% of catalyst. DCE = 1,2-dichloroethane, DCM = dichloromethane.

Table 2: Scope for chiral 1,4-dioxane synthesis.



1 (0.5 mmol) **2**

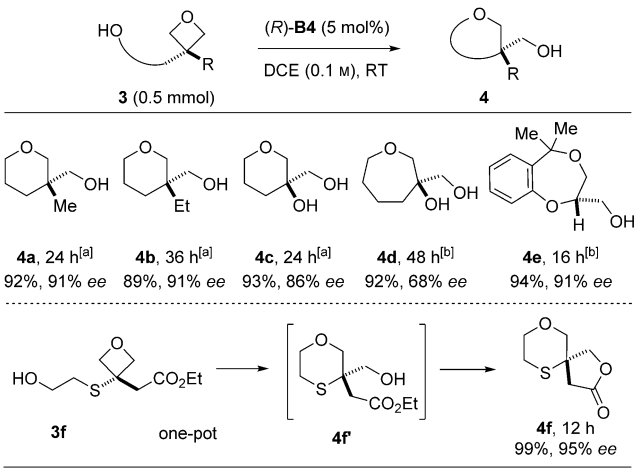
Entry	R	R′	*x*	*t* [h]	**2**	Yield [%][a]	*ee* [%]
1	Me	H	2	12	**2a**	93	98
2	*n*Bu	H	2	24	**2b**	95	95
3	*i*Pr	H	3	36	**2c**	95	92
4		H	3	12	**2d**	92	99
5[b]	CF_3	H	10	60	**2e**	92	98
6	$BnO(CH_2)_3$	H	5	12	**2f**	89	99
7	$TBSO(CH_2)_3$	H	5	12	**2g**	97	99
8	$HO(CH_2)_4$	H	5	12	**2h**	99	97
9	vinyl	H	5	8	**2i**	93	96
10		H	5	12	**2j**	91	96
11	allyl	H	3	12	**2k**	91	98
12		H	5	36	**2l**	89	98
13[c]	Ph	H	5	30	**2m**	98	92
14		H	5	24	**2n**	98	93
15[d]	Me	Me	5	12	**2o**	92	94
16[d]	Me	allyl	5	36	**2p**	91	91

[a] Yield of isolated product. [b] Run at 60 °C. [c] Run with 0.2 M concentration. [d] Run in toluene solvent (0.02 M). TBS = *tert*-butyldimethylsilyl.

regard to reaction rate, yield, and enantioselectivity (entry 11). The reaction concentration has a very limited impact on the outcome (entries 14 and 15). Further decreasing the catalyst loading to 1–2 mol% resulted in essentially no erosion in yield and enantioselectivity, although a longer time is needed (entries 16 and 17). All these results indicated that this catalytic system is very robust.

We next examined the substrate scope of the reaction (Table 2). A wide range of oxetanes (**1**) with different substituents smoothly participated in the desymmetrization process to afford the desired 1,4-dioxanes **2**, bearing quaternary stereocenters, with uniformly excellent efficiency and enantioselectivity. Alkyl groups, including primary and secondary ones, and aryl groups are all suitable substituents. However, the trifluoromethyl (CF_3) group significantly retards the reaction, and almost no conversion was observed at room temperature. The electron-withdrawing CF_3 group might inductively reduce the Lewis basicity of the oxetane, thus weakening its hydrogen-bonding ability. Nevertheless, with slight modification of the reaction conditions (10 mol% of **B4**, 60 °C), the desired product **2e** was successfully obtained in high yield and excellent enantiomeric excess (entry 5). The mild reaction conditions can tolerate an array of functional groups, such as ethers, silyl-protected alcohols, alkenes, alkynes, and free alcohols. We also evaluated the effect of external acid and base additives. In the presence of one equivalent of a carboxylic acid (e.g., AcOH, BzOH), the reaction of **1a** proceeded with comparable efficiency. However, the addition of a base (e.g., $PhNH_2$, $BnNH_2$, pyridine) shut down the reactivity (see the Supporting Information for details). Heterocycles, such as thiophene, can be incorporated into the product (**2n**) with excellent efficiency (entry 14). Notably, when two competing internal alcohol nucleophiles are present (entry 8), the reaction exhibits excellent chemoselectivity and exclusively forms the six-membered dioxane product (**2h** vs. seven-membered oxepane). Moreover, increased steric hindrance in close proximity to the internal alcohol functionality does not affect the reaction efficiency and enantioselectivity (R′ = Me or allyl; entries 15 and 16), again highlighting the robustness of this process.

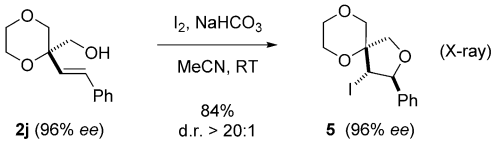
Our intramolecular oxetane desymmetrization process is not limited to the synthesis of enantioenriched 1,4-dioxanes. With slight modification of the side chain, the protocol can be extended to the synthesis of other oxa-heterocycles. For example, the tetrahydropyrans **4a–c** can be efficiently obtained with high enantioselectivity (Scheme 2). It is worth noting that the efficient synthesis of these tetrahydropyrans bearing quaternary stereocenters has not been so straightforward previously.[14] Therefore, our approach provides an excellent complement to the existing strategies. Furthermore, the seven-membered oxepane **4d** can also be synthesized in high yield, albeit with moderate enantioselectivity. The



Scheme 2. Synthesis of other oxa-heterocycles. Yield is that of the isolated product. [a] Run in toluene (0.02 M). [b] Run with 10 mol% of catalyst at 60 °C. [c] Run in toluene (0.1 M).

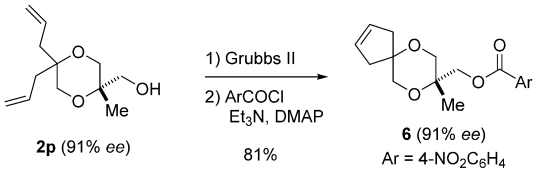
increased difficulty in stereocontrol might be due to the more flexible seven-membered ring transition state. Nevertheless, the benzofused 1,4-dioxepane **4e** was generated with excellent enantioselectivity. Finally, incorporation of a sulfur atom in the side chain (**3f**) results in smooth formation of spirocyclic 1,4-oxathiane **4f**. Notably, the initial ring-opening product **4f'** undergoes spontaneous lactonization under the standard reaction conditions. It is noteworthy that these oxa-heterocycles are all useful scaffolds and such a unified general strategy to access all these chiral heterocycles was not available previously.[15,16]

To further demonstrate the utility of our process, we carried out some derivatizations of the products. For example, iodoetherification of **2j** proceeded with high efficiency and diastereoselectivity to form the spirocycle **5**, which bears both 1,4-dioxane and tetrahydrofuran rings [Eq. (1)]. Its absolute

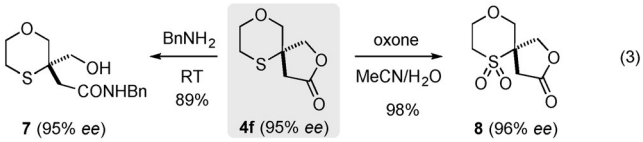


(1)

stereochemistry was confirmed by X-ray crystallography. The diallyl-substituted 1,4-dioxane **2p** could undergo smooth ring-closing metathesis and subsequent esterification to form the spirocycle **6** [Eq. (2); DMAP = 4-(*N*,*N*-dimethylamino)pyridine]. Finally, the 1,4-oxathiane **4f** could undergo mild transamidation and oxidation to efficiently form amide **7** and sulfone **8**, respectively [Eq. (3)]. Notably, in all these transformations no erosion in enantiopurity was observed.



(2)



(3)

We propose the transition-state TS to provide insight into the mechanism (Figure 2). The chiral phosphoric acid catalyst might play a bifunctional role. The primary interaction is the hydrogen bond between the acid proton and oxetane. Despite

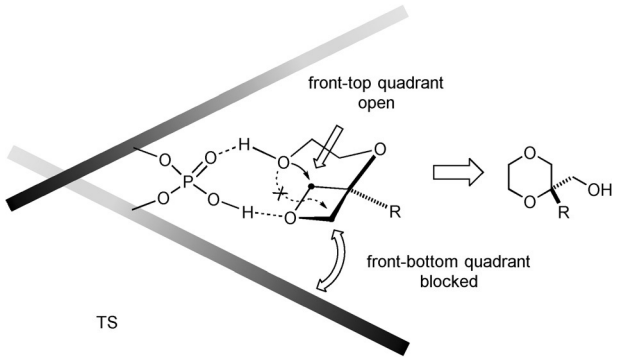


Figure 2. Proposed transition state.

the presence of an ether moiety in the side chain, the preference for oxetane activation is attributed to the higher Lewis basicity of oxetane (vs. normal ether).[17] This preference is not only important for smooth product formation, but also crucial to successful catalyst turnover in view of the presence of multiple hydrogen bonding sites in the 1,4-dioxane product. In the meanwhile, the phosphoryl oxygen atom serves as a basic site to interact with the hydroxy group by hydrogen bonding, which not only increases the oxygen nucleophilicity, but also restricts the flexible side chain to a chair-like conformation. In this transition state, the internal nucleophile approaches the more open front-top quadrant, since the front-bottom quadrant is blocked by the bulky pyrenyl group in the catalyst.[18] These rationalizations are consistent with the product stereochemistry.

In conclusion, we have developed a new catalytic asymmetric approach for the synthesis of chiral 1,4-dioxanes, an important scaffold of broad utility, but lacking a general and efficient protocol for its synthesis. It is also the first demonstration of organocatalytic oxetane desymmetrization by an alcohol nucleophile. With a suitable choice of the chiral phosphoric acid catalyst, a range of variously substituted 1,4-dioxanes bearing quaternary stereocenters were synthesized with excellent efficiency and enantioselectivity. The method also demonstrated broad functional-group compatibility. The catalyst turnover, which allows low catalyst loading, is remarkable in view of the presence of multiple hydrogen-bonding sites in both substrate and product. This versatile and robust process can also be extended to the synthesis of other useful chiral oxa-heterocycles, thereby providing an attractive complement to the existing strategies. The highly enantio-

enriched products obtained from our process can serve as precursors to other useful chiral molecules. Mechanistically, the acid catalyst might play a bifunctional role to guide a highly ordered cyclic transition state to ensure excellent stereocontrol.

Acknowledgments

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