Asymmetric Catalysis

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Enantio- and Diastereoselective Assembly of Tetrahydrofuran and Tetrahydropyran Skeletons with All-Carbon-Substituted Quaternary Stereocenters**

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Tetrahydrofuran (THF) and tetrahydropyran (THP) as well as their analogues in higher oxidation states are important structural units found in natural products and bioactive unnatural molecules.[1] Among them, many have all-carbon-substituted quaternary stereocenters in the 3-/4-(THF) and 3-/5-(THP) positions, such as the highly neurotrophic compounds jiadifenin and tricholomalide A, the anticancer compound maoecrystal V, and the antibiotic dihydrobotrydial (Figure 1).[2] Efficient construction of all-carbon-substituted quaternary stereocenters is a well-known challenge in organic

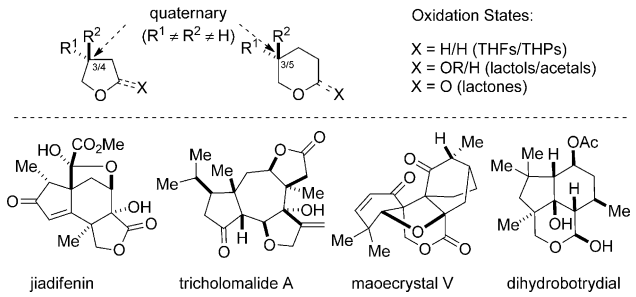
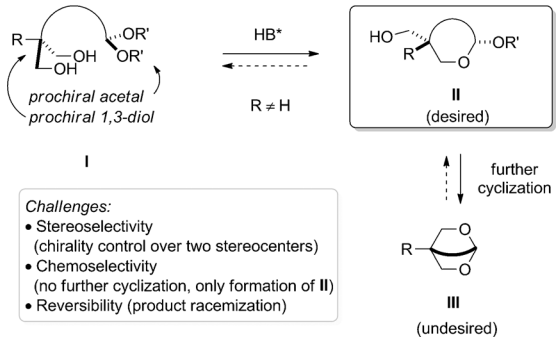


Figure 1. Key THF/THP subunits bearing a quaternary stereocenter and selected natural products containing these units.

synthesis.[3] Particularly challenging are the above-mentioned skeletons where the stereocenters are relatively remote to the more controllable positions adjacent to the oxygen atoms. Traditional general and efficient strategies to address such challenges are scarce and typically require multiple steps.[4] A general, straightforward, and step-economical approach is in high demand.

Catalytic enantioselective desymmetrization of *meso* 1,3-diols has been recently intensively explored.[5–6] However, the majority of these desymmetrization reactions are based on monoacylation, typically with an in situ generated chiral acylation reagent.[5] Other reaction types for 1,3-diol desymmetrization are noteworthy but scarce.[6] Inspired by the recent success of chiral Brønsted acid catalyzed desymmetrization reactions developed by our group and others,[7–9] as



Scheme 1. Reaction design.

well as chiral acetal formation reactions reported by the List and Nagorny groups,[10] we hypothesized that a prochiral 1,3-diol tethered to an acetal (e.g., **I**, Scheme 1) may undergo intramolecular mono-transacetalization to form cyclic acetal **II** stereoselectively with chiral acid catalysis. The enantioenriched cyclic acetal **II** is in an intermediate redox state that can be readily reduced to substituted THFs/THPs or oxidized to lactones. However, this seemingly straightforward process may encounter several challenges: 1) The proper choice of a chiral catalyst with suitable acidity is important not only to promote the first desired cyclization, but also to prevent the subsequent undesired cyclization to form symmetric bicycle **III**; 2) The expected chirality control over two stereocenters imposes additional difficulty; 3) Potential reversibility of the process may cause product racemization. Nevertheless, the desired process represents a new reaction type for 1,3-diol desymmetrization, in which two stereocenters (including a remote quaternary one) are simultaneously generated.

We began to test our hypothesis with dimethyl acetal **1a** [Eq. (1)]. Initial evaluation of chiral phosphoric acid catalysts indicated that the desired reaction could proceed cleanly to form the desired cyclic acetal **2a**. After expending considerable effort to optimize the reaction conditions (see the Supporting Information for details), we found that (*S*)-**A** could catalyze the reaction (at 0 °C in the presence of 4 Å molecular sieves) with excellent enantio- and diastereoselectivity (94 % *ee*, 12:1 d.r.). The reaction of **1a′**, which bears a diethyl acetal moiety, did not proceed as expected even with an extended reaction time. These results are in contrast to the previously reported transacetalization reaction with diethyl acetals.[10a,b]

Next, we studied the reaction scope (Table 1). A range of dimethyl acetals can participate in the desymmetrization reaction, efficiently establishing two stereocenters with good to excellent enantio- and diastereoselectivity. Different functional groups (e.g., ethers and aryl halides) and heterocycles

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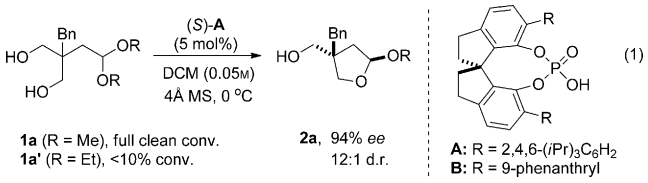
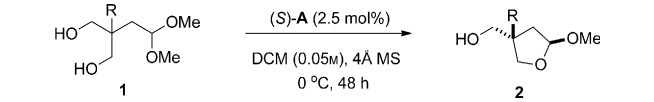
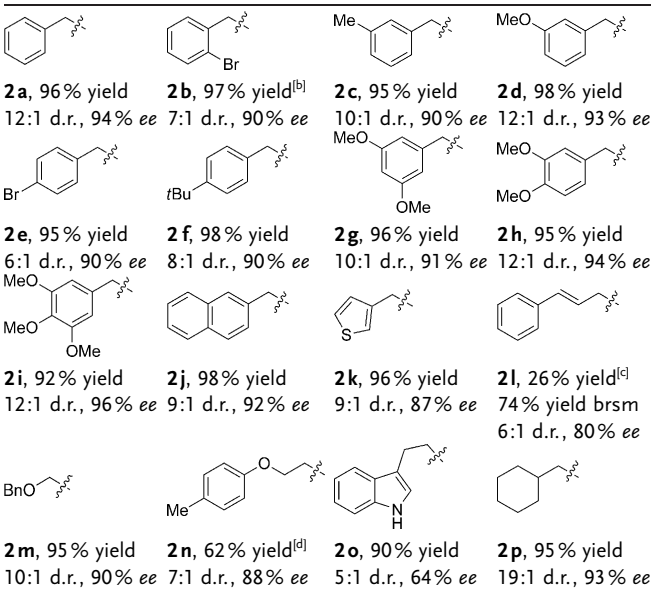


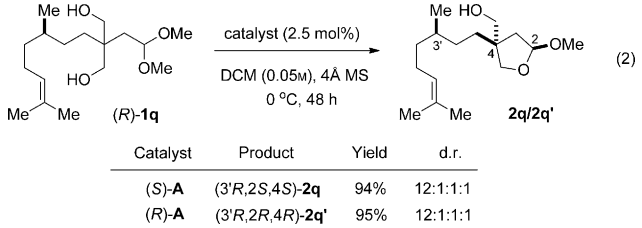
Table 1: Synthesis of five-membered cyclic acetals. The stuctures shown refer to the R groups.[a]





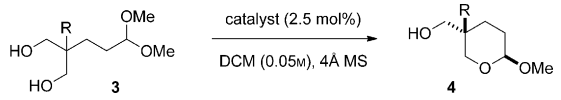
[a] The reactions were typically conducted on a 0.25 mmol scale, except for **2d** (0.10 mmol) and **2i** (0.75 mmol); yield of isolated products are provided. The d.r. values were determined by ^{1}H NMR or HPLC analysis, and the *ee* values were determined by HPLC. [b] Reaction conducted at RT for 72 h. [c] Reaction conducted at 55 °C for 24 h. The conversion was 35%, and the yield based on recovered starting material was 74%. [d] Reaction conducted for 72 h, with the starting material making up the remainder of the mass balance.

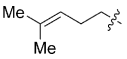
(e.g., thiophene and indole) are amenable to the mild conditions. An enantiopure acetal (*R*)-**1q** with an existing stereocenter was also examined [Eq. (2)]. With (*R*)- or (*S*)-**A** catalyst, the corresponding cyclic acetal **2q** or **2q′** could be obtained with excellent efficiency and stereoselectivity. The stereochemistry of these two products indicated that an existing remote stereocenter in the substrate has little influence on the central configuration of the key transition state, which is mainly dictated by the catalyst.



Catalyst	Product	Yield	d.r.
(*S*)-**A**	(3′*R*,2*S*,4*S*)-**2q**	94%	12:1:1:1
(*R*)-**A**	(3′*R*,2*R*,4*R*)-**2q′**	95%	12:1:1:1

Table 2: Synthesis of six-membered cyclic acetals.[a]



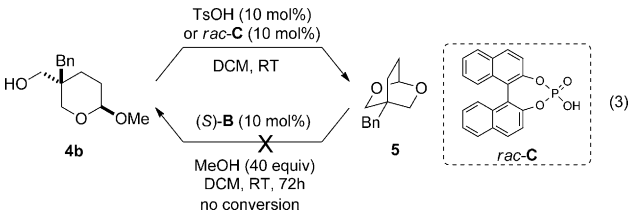
Entry	R		Catalyst (*T*, *t*)	Product/observation
1		(**3a**)	(*S*)-**A** (RT, 36 h)	<10% conversion
2			(*S*)-**B** (0 °C, 48 h)	**4a**, 90% yield, 4:1 d.r. 94% *ee* (major)
3	Bn	(**3b**)	(*S*)-**B** (0 °C, 48 h)	**4b**, 95% yield, 3:1 d.r. 93% *ee* (major)

[a] The reactions were conducted on a 0.25 mmol scale for **3a** and 1.0 mmol scale for **3b**.

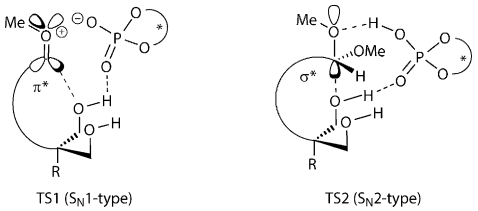
We were also interested in extending the above protocol to the synthesis of six-membered-ring acetals (THP). Substrate **3a** with an extended linker was examined. Unfortunately, under the previously optimized conditions, the reaction of **3a** did not proceed as expected (<10% conversion, Table 2, entry 1). Nevertheless, we were delighted to identify (*S*)-**B** [structure shown in Equation (1)] as the catalyst of choice to promote the formation of the desired six-membered-ring acetal **4a** in high yield with excellent enantioselectivity (Table 2, entry 2). Benzyl-substituted acetal **3b** is also a suitable substrate (Table 2, entry 3). The dramatic difference in the performance of catalysts **A** and **B** clearly demonstrates that the cyclization reaction is sensitive to subtle variations in the catalyst structure. A catalyst with suitable acidity and a chiral environment is critically important to both the stereoselectivity and the chemical efficiency of the reaction.

It is noteworthy that almost no side products were formed with the above standard protocols. However, during the synthesis of racemic products using the less bulky acid *rac*-**C** [Eq. (3)], sometimes we could observe bicyclic acetal byproducts of type **III** (Scheme 1). Therefore, in order to gain insight into the reaction mechanism, we carried out some control experiments [Eq. (3)]. We confirmed that acetal **4b** can cyclize to form **5** with a catalytic amount of either *p*-TsOH or *rac*-**C**. However, acetal **5** is not susceptible to ring-opening by methanol in the presence of acid **B**. These results rule out the possibility of involving the bicyclic intermediates of type **III** and their reversible ring-opening under the standard conditions.

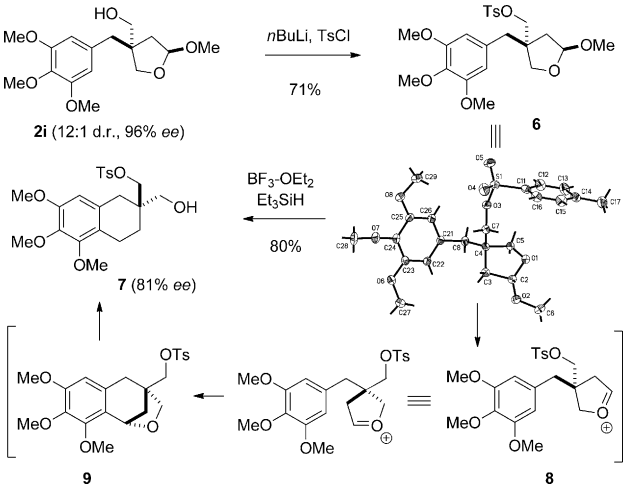
On the basis of our experimental results, we propose two transition states (**TS1** and **TS2**) to rationalize the possible reaction mechanisms corresponding to the S_N1 and S_N2 pathways, respectively. In the S_N1 scenario, an oxocarbenium intermediate is initially formed, and its ion-pairing interaction with the chiral phosphate provides a chiral environment for



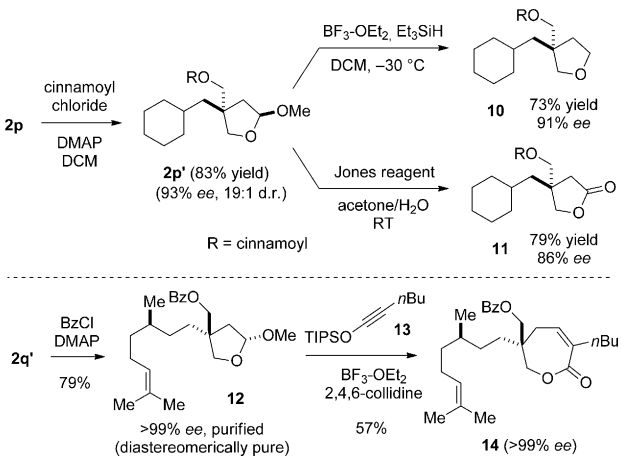
subsequent discrimination of the *meso* 1,3-diol unit. The hydroxy group selectively activated by hydrogen bonding with the phosphoryl oxygen then approaches the π* orbital of the oxocarbenium unit. In contrast, in the S_N2 pathway, one of the methoxy groups is activated by hydrogen bonding, lowering the σ*(C–O) orbital level for subsequent backside attack of the selectively activated hydroxy group.[11] In an in situ ^{1}H NMR experiment we observed two distinct methoxy signals when the substrate and the catalyst were mixed. However, this observation is consistent with both mechanisms. More complicated activation modes are also possible due to the presence of multiple hydrogen-bonding sites.



The highly functionalized cyclic acetals produced by our desymmetrization process can be transformed into other useful chiral molecules. Tosylation of acetal **2i** afforded **6**, whose absolute configuration was confirmed by X-ray crystallography (Scheme 2). Treatment of **6** with BF_3–OEt_2 and Et_3SiH gave tetrahydronaphthalene **7** which is decorated with an all-carbon-substituted quaternary stereocenter in the 2-position. The reaction presumably involves Friedel–Crafts acylation of oxocarbenium **8** followed by reduction of the bicyclic intermediate **9**. As shown in Scheme 3, after protection of the free hydroxy group, the acetal **2p** in an intermediate redox state can also be reduced to tetrahydrofuran **10** or oxidized to lactone **11**. Moreover, with our ring-expansion protocol,[12] the five-membered cyclic acetal **2q′** could be expanded to the seven-membered lactone **14** with an all-carbon-substituted quaternary stereocenter in the δ-position to a carbonyl group.[13] It is noteworthy that installation of



Scheme 2. Determination of the absolute configuration of **6** and synthesis of 1,2,3,4-tetrahydronaphthalenes bearing an all-carbon-substituted quaternary stereocenter at C-2.



Scheme 3. Useful transformations of the desymmetrization products.

these remote all-carbon-substituted quaternary stereocenters are not straightforward by other strategies. It is worth mentioning that *ee* loss was observed in the formation of **7** and **10**–**11**, which is because, among the four product isomers of our desymmetrization reaction, in the major enantiomer of the minor diastereomer the quaternary stereocenter has the opposite absolute configuration to the analogous position in the major enantiomer of the major diastereomer. Therefore, subsequent derivatizations involving removal of the acetal stereocenter should give products with *ee* values also influenced by the starting d.r. values.[14]

In summary, we have developed a new asymmetric desymmetrization reaction for the assembly of tetrahydrofuran and tetrahydropyran skeletons with simultaneous generation of two stereocenters (tertiary and all-carbon-substituted quaternary) with high efficiency and stereoselectivity. It also represents a new reaction type (acetalization) for the catalytic asymmetric desymmetrization of *meso* 1,3-diols. The choice of a suitable chiral acid catalyst is the key to the success of this process, and subtle variations in catalyst acidity and chirality results in dramatic changes in both chemo- and stereoselectivity. The cyclic acetal products can be readily transformed into other useful chiral building blocks bearing remote all-carbon-substituted quaternary stereocenters that are not straightforward to access by other methods.

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[14] Additional slight loss of *ee* in the formation of lactone **11** might be due to the strongly acidic conditions, which may cause side reactions, such as those in Scheme 1 and Equation (3).

