Communication

Chiral Phosphoric Acid Catalyzed Highly Enantioselective Desymmetrization of 2-Substituted and 2,2-Disubstituted 1,3-Diols via Oxidative Cleavage of Benzylidene Acetals

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Chiral Phosphoric Acid Catalyzed Highly Enantioselective Desymmetrization of 2-Substituted and 2,2-Disubstituted 1,3-Diols via Oxidative Cleavage of Benzylidene Acetals

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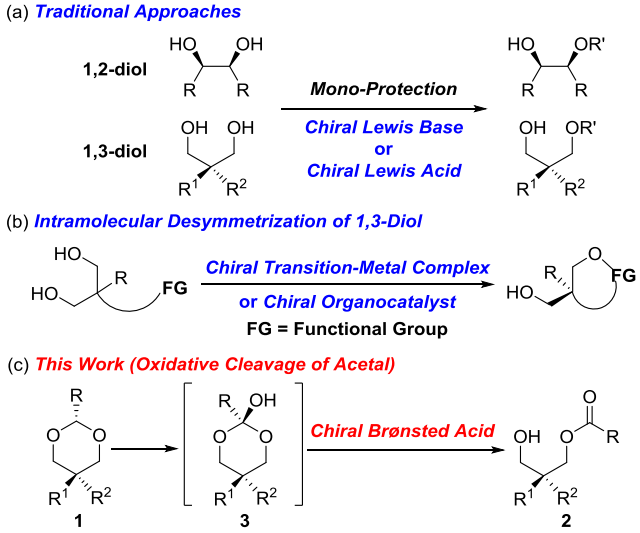
Supporting Information Placeholder

ABSTRACT: A highly enantioselective catalytic protocol for the desymmetrization of a wide variety of 2-substituted and 2,2-disubstituted 1,3-diols is reported. This reaction proceeds through the formation of an "ortho ester" intermediate via oxidation of 1,3-diol benzylidene acetal by dimethyldioxirane (DMDO) and the subsequent proton transfer catalyzed by chiral phosphoric acid (CPA). The mechanism and origins of enantioselectivity of this reaction are identified using DFT calculations. The oxidation by DMDO is rate-determining, and the phosphoric acid significantly accelerates the proton transfer; the attractive interactions between the benzylidene part of the substrate and the 2,4,6-triisopropyl group of CPA are the key to high enantioselectivity.

Enantioselective desymmetrization of *meso* or prochiral compounds is one of the most powerful strategies in asymmetric catalysis.[1] In particular, the desymmetrization of diols has captured much attention for providing access to important chiral alcohols, as well as a wide variety of valuable building blocks.[2] Over the past decades, many chiral Lewis bases and Lewis acids have been demonstrated successfully for desymmetrization of diols (Scheme 1a).[2] However, the successful substrates are mostly limited to *meso*-1,2-diols that are secondary alcohols.[2,3] Desymmetrization of 2-substituted 1,3-diol remains a formidable challenge because of the long distance of pro-stereogenic center with hydroxyl group[4] and the strong nucleophilicity of primary alcohols.[2,5-8] Recently, intramolecular desymmetrizations of 1,3-diols were realized using chiral transition-metal catalysts or organocatalysts (Scheme 1b).[9] Although these approaches have been shown to give chiral cyclic compounds efficiently, a pre-installed functional group in the substrate is required.[9]

For the enantioselective desymmetrization of simple 2-substituted 1,3-diols, only a few direct approaches have been reported.[5-8] Harada and co-workers described asymmetric ring-opening of 1,3-dioxane using chiral boron Lewis acid with excellent selectivity.[6] Trost and co-workers elegantly demonstrated highly enantioselective acylation of 2-aryl-1,3-diols and later 2-alkyl-1,3-diols with chiral dinuclear zinc catalyst.[7] More recently, Kang and co-workers have used chiral copper oxazoline complexes for desymmetrization of 2-substituted 1,2,3-triols and 2,2-disubstituted 1,3-diols with excellent enantioselectivity.[8] Nevertheless, the development of new strategies to achieve highly enantioselective desymmetrization of 2-substituted and 2,2-disubstituted 1,3-diols under mild reaction conditions is still highly demanded.

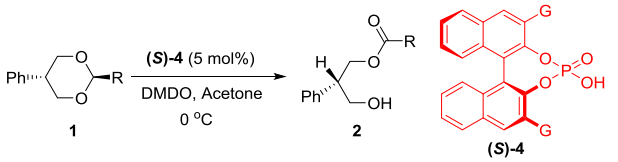
SCHEME 1. Strategies for Catalytic Enantioselective Desymmetrization of Diols



Benzylidene acetals are widely used in protection of diols in organic synthesis and can be selectively oxidized.[10] Recently, dimethyldioxirane (DMDO) was reported as a good oxidant for selective oxidation of benzylidene acetal **1** to ester **2** via the proposed intermediate **3** (Scheme 1c).[11] We noted that a proton transfer process was involved from intermediate **3** to the final product, and we postulated that this key H-transfer could present new opportunities for asymmetric catalysis by chiral phosphoric acids, which are demonstrated to be excellent chiral proton transfer catalysts.[12-15] Herein, we describe the development of this new method for highly enantioselective desymmetrization of 2-substituted and 2,2-disubstituted 1,3-diols. The mechanism and origins of enantioselectivity of this reaction are also revealed by density functional theory (DFT) calculations.

We first studied the reaction of 2-phenyl-1,3-propadiol benzylidene acetal with DMDO[16,17] in the presence of chiral Brønsted acid (*S*)-**4a** (TRIP)[18] (Table 1). We were excited to find that (*S*)-TRIP delivered product (*S*)-**2a**[19] with 65% *ee* in 66% yield (entry 1). Further catalyst screening left TRIP remaining as the optimal catalyst (entries 2-5). All the yields are moderate to low, because significant amount of 2-phenyl-1,3-propadiol supposedly from decomposition of substrate **1a** was observed. At this point, we surmised that the electronic and steric characters of the acetal may be crucial to the oxidation step and may also affect enantioselectivity. Thus, we investigated other substrates with different electronic and steric effects. To our delight, substrate **1b** with *p*-methoxyphenyl (PMP) gave the desired product (*S*)-**2b**[19] in 99% yield and 95% *ee* (entry 6).

TABLE 1. Reaction Optimization[a]



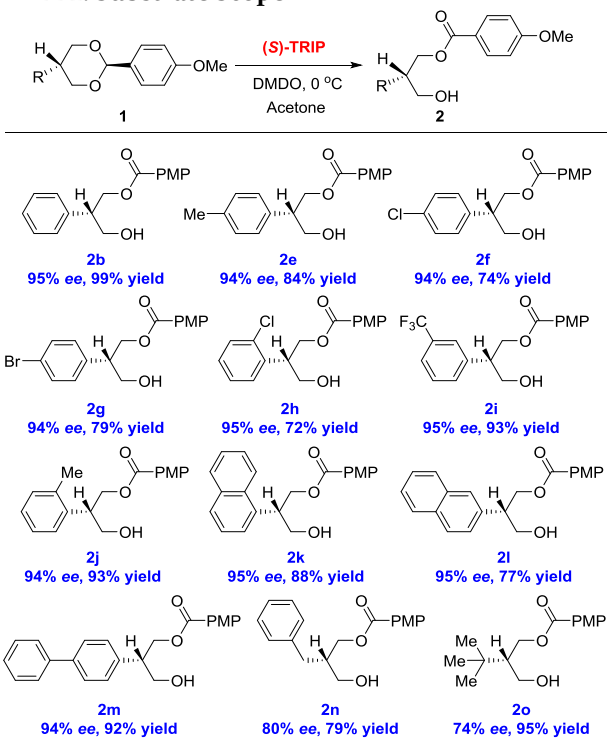
entry	catalyst, G	substrate (R)	yield (%)[b]	*ee* (%)[c]
1	(*S*)-**4a**, 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$	**1a** (Ph)	**2a**:66	65
2	(*S*)-**4b**, 1-naphthyl	**1a** (Ph)	**2a**:68	59
3	(*S*)-**4c**, 9-anthryl	**1a** (Ph)	**2a**:40	39
4	(*S*)-**4d**, 3,5-(CF$_3$)$_2$C$_6$H$_3$	**1a** (Ph)	**2a**:38	27
5	(*S*)-**4e**, SiPh$_3$	**1a** (Ph)	**2a**:25	35
6	**(*S*)-4a, 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$**	**1b (4-MeO-Ph)**	**2b:99**	**95**
7	(*S*)-**4a**, 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$	**1c** (4-Cl-Ph)	**2c**:56	65
8	(*S*)-**4a**, 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$	**1d** (1-naphthyl)	**2d**:39[d]	90

[a] Conditions: **1** (0.1 mmol), cat. (5 mol%), and DMDO (0.3 mmol) at 0 °C. [b] Isolated yield. [c] Enantiomeric excess determined by chiral HPLC analysis. [d] Low conversion.

With the optimal conditions in hand, we next turned our attentions to the substrate scope. In most cases, the desired product **2** was obtained with good yield and excellent *ee*. As shown in Table 2, a wide range of substrates with electron-donating and electron-withdrawing groups at *ortho*-, *meta*-, and *para*-positions of the phenyl ring were found to be suitable in this reaction (**2b**-**2j** and **2m**). The nature of the aromatic ring does not have a significant effect on enantioselectivity. The reactions with 1-naphthyl and 2-naphthyl substituents also led to products (**2k** and **2l**) with high *ee*. In addition, alkyl substituents, such as benzyl and *tert*-butyl groups, were also tolerated in the reaction, giving the products (**2n** and **2o**) with a bit lower *ee*.[20]

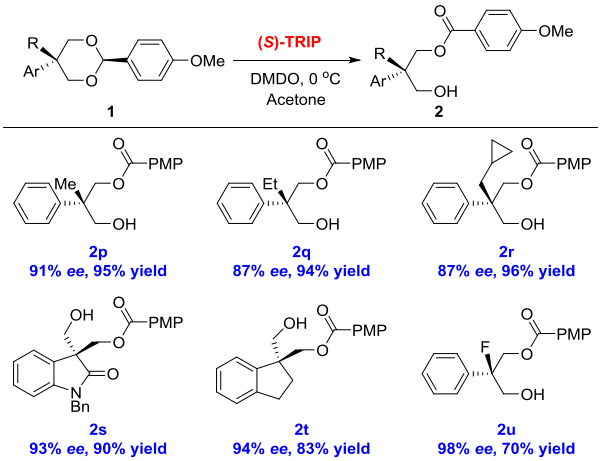
Catalytic construction of chiral quaternary stereogenic center is one of the most challenging areas in modern organic synthesis.[21] Therefore, a broad range of substrates from 2,2-disubstituted 1,3-diols were examined (Table 3). Gratifyingly, desired products (**2p**-**2u**) with a chiral quaternary stereocenter were obtained with good yield and excellent enantioselectivity. For example, product (*S*)-**2p**[19] containing a chiral all-carbon quaternary center was obtained with 91% *ee* in 95% yield. Particularly, oxindole based product (**2s**) was generated in 93% *ee*, which provides opportunity for further transformations to indoline alkaloids.[22] Product **2u** with a fluoro-substituted chiral quaternary center was obtained in excellent *ee* as well.[23]

TABLE 2. Substrate Scope[a]



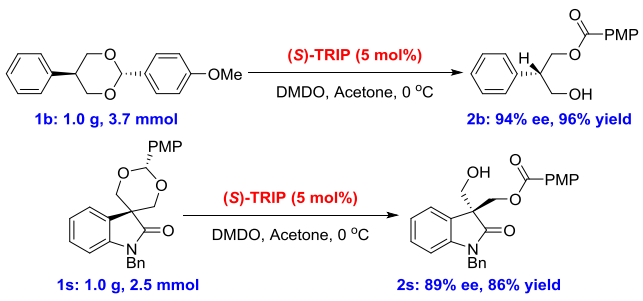
[a] Conditions: **1** (0.1 mmol), cat. (5 mol%), and DMDO (0.3 mmol) at 0 °C. Isolated yield. Enantiomeric excess determined by chiral HPLC analysis.

TABLE 3. Substrate Scope[a]



[a] Conditions: **1** (0.1 mmol), cat. (5 mol%), and DMDO (0.3 mmol) at 0 °C. Isolated yield. Enantiomeric excess determined by chiral HPLC analysis.

SCHEME 2. Gram-Scale Reactions

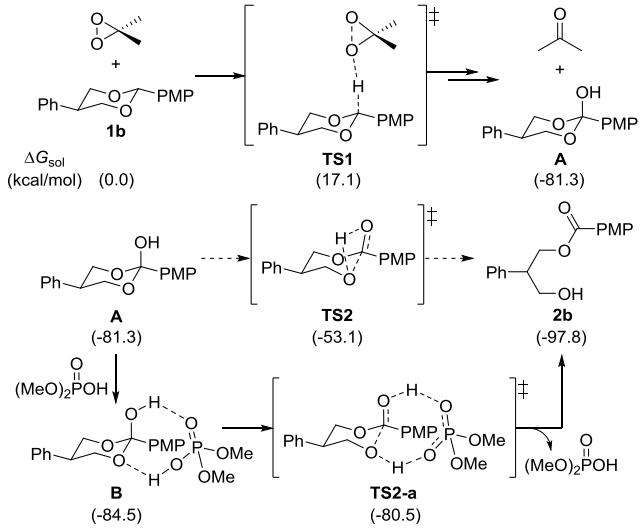


To test the practicality of this new method, gram-scale reactions were carried out (Scheme 2). Enantioselective

desymmetrization of 1.0 g of **1b** and **1s** afforded desired products **2b** and **2s** without notable erosion of either yield or enantioselectivity, demonstrating that the current method is suitable to prepare chiral building blocks in organic synthesis.

To better understand the mechanism and origins of enantioselectivity of this reaction, density functional theory (DFT) calculations were performed on the reaction of acetal **1b** and DMDO including dimethyl phosphate (Scheme 3) or chiral phosphoric acid (Figure 1).[24] As shown in Scheme 3, the dioxirane oxidation of the tertiary C-H bond of acetal **1b** via a diradical transition state **TS1** requires an activation free energy of 17.1 kcal/mol. The formed radical pair is highly unstable and rebounds without barrier[25] to form acetone and an "ortho ester" intermediate **A**. This oxidation process is exergonic by 81.3 kcal/mol. The formation of final product **2b** through an intramolecular [1,3]-proton shift process via **TS2** is difficult, requiring an activation free energy of 28.2 kcal/mol.[26] However, in the presence of dimethyl phosphate as catalyst, the proton transfer process via **TS2-a** is very facile with a barrier of only 4.0 kcal/mol. This is in agreement with previous discovery that the phosphoric acid is an excellent proton shuttle.[13,27] Therefore, the oxidation of acetal by DMDO is the rate-determining step for this reaction, and the overall free energy barrier is 17.1 kcal/mol, accounting for the low reaction temperature of 0 °C.

SCHEME 3. DFT-Computed Free Energies for the Reaction between Acetal 1b and DMDO in the Presence of Dimethyl Phosphate



To explore the origins of enantioselectivity, we studied biphenol-derived chiral phosphoric acid (the model of (*S*)-**4a**)[28] catalyzed proton transfer transition states **TS2-a-R** and **TS2-a-S**, which led to products (*R*)-**2b** and (*S*)-**2b**, respectively. The computed free energy of **TS2-a-S** is 2.0 kcal/mol lower than that of **TS2-a-R** (Figure 1). This energy difference corresponds to a 40:1 ratio of (*S*)-**2b** to (*R*)-**2b** at 0 °C, in good agreement with the 95% *ee* obtained experimentally. There are no obvious steric clashes in these two diastereomeric transition states. The main difference is the orientation of *p*-methoxyphenyl (PMP) group of the substrate relative to the 2,4,6-triisopropylphenyl group of the catalyst. As shown in the blue frame in Figure 1, two aryl groups are far way in **TS2-a-R**, while they forms a T-shaped configuration[29] in **TS2-a-S**, indicating attractive aryl-aryl interactions.[30] Further calculations show a 1.4 kcal/mol advance for the orientation of two aryl groups in **TS2-a-S**. This is the major contribution to the 2.0 kcal/mol preference for the formation of (*S*)-**2b**. Since the attractive interactions between the PMP part of the substrate and the 2,4,6-triisopropyl group of the catalyst are the key to high enantioselectivity, we predicted that the replacement of the PMP group by the methyl group in the substrate would significantly lower the enantioselectivity (from 40:1 to 3.6:1 for the *S*/*R* ratio at 0 °C by DFT calculations, see the SI). This was later validated by the experimental *S*/*R* ratio of 1.3:1 for the reaction of *trans*-2-methyl-5-phenyl-1,3-dioxane with DMDO in the presence of chiral phosphoric acid (*S*)-**4a**.

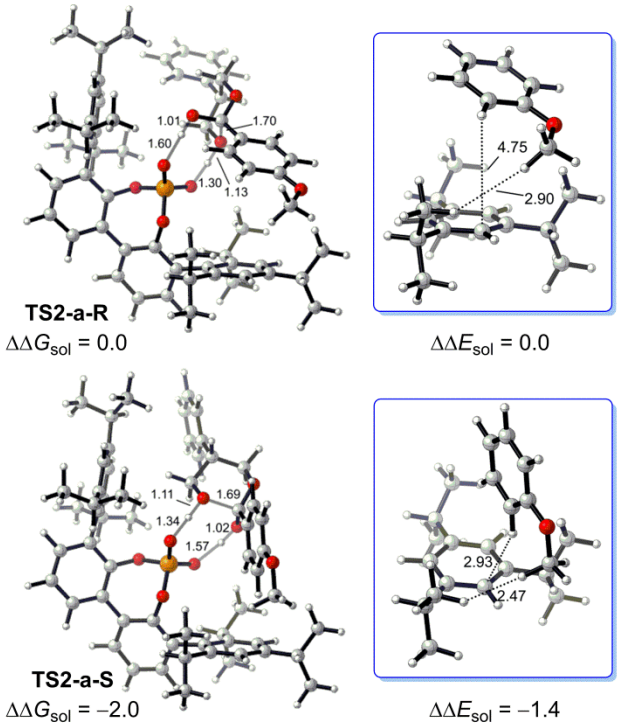


Figure 1. DFT-optimized chiral phosphoric acid catalyzed proton transfer transition states **TS2-a-R** and **TS2-a-S** (carbon, gray; hydrogen, white; oxygen, red; phosphorus, orange; distances are given in angstroms) and DFT-computed relative energies (in kcal/mol).

In summary, we have developed a novel protocol for highly enantioselective desymmetrization of 2-substituted and 2,2-disubstituted 1,3-diols via oxidative cleavage of benzylidene acetals in the presence of chiral phosphoric acid. DFT calculations show that the oxidation of acetal by DMDO is rate-determining, and the attractive aryl-aryl interactions between substrate and catalyst are the key to high enantioselectivity. Extensions of the strategy to other systems are currently underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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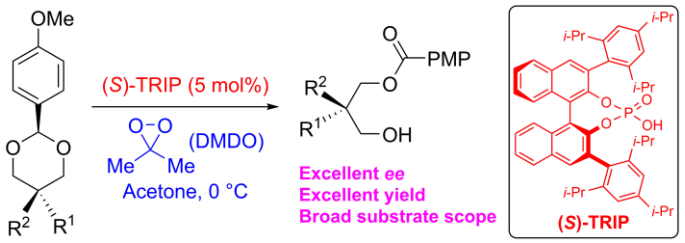
TOC


OMe
(S)-TRIP (5 mol%)
(DMDO)
Me Me
Acetone, 0 °C
PMP
OH
Excellent ee
Excellent yield
Broad substrate scope
i-Pr
(S)-TRIP