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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Chiral Phosphoric Acid-Catalyzed Enantioselective and Diastereoselective Spiroketalizations

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Supporting Information

ABSTRACT: Catalytic enantioselective and diastereoselective spiroketalizations with BINOL-derived chiral phosphoric acids are reported. The chiral catalyst can override the inherent preference for the formation of thermodynamic spiroketals, and highly selective formation of nonthermodynamic spiroketals could be achieved under the reaction conditions.

The spiroketal moiety is an important structural motif that is observed in a variety of natural products and, in certain cases, may be imperative for small-molecule interactions with a biological target.[1] Although spiroketalizations are now considered routine, most of the modern approaches rely on ad hoc solutions that are governed by the unique structural features of natural product being synthesized.[2] In some instances, the spiroketal stereochemistry is established under thermodynamic control utilizing equilibrating conditions during the cyclization. Often, this is sufficient for achieving the desired natural product architecture, as the majority of the natural spiroketals are thermodynamic. However, a stereoselective synthesis of this functionality becomes significantly more challenging in cases where the conformational and stereoelectronic factors prevent the formation of the desired configuration under equilibrating conditions or when the spiroketal moiety is the only source of stereoisomerism in the natural product (Figure 1).[3] While having flexibility in the syntheses of stereodefined spiroketals would be beneficial to many areas of organic chemistry, including target-[1−3] and diversity-oriented syntheses,[4] only a few general methods are available. Typically, these methods rely on substrate-[5] or auxiliary-directed stereoinduction to form the spiroketal stereocenter.[6] Accordingly, a direct chiral-catalyst-based approach might significantly simplify the construction of stereodefined spiroketals and would be complementary to the other strategies.

Being interested in expanding the scope of chiral-catalyst-controlled additions to oxocarbenium ions, our group investigated the possibility of utilizing chiral catalysts for the stereoselective synthesis of spiroketals. We surmised that the treatment of **I**−**IV** with chiral Brønsted acids, such as chiral phosphoric acids (CPAs), might be used for enantioselective or diastereoselective spiroketalizations (Figure 1).[7,8] CPAs have previously been employed to catalyze the formation of chiral *N*,*N*-,[9a−c,e] *N*,*O*-,[9d] *N*,*S*-,[9h] and simple *O*,*O*-acetals.[9f,g] This study, along with the contemporaneous report by the List group,[17] represent the first examples of successful chiral-catalyst-controlled enantioselective and diastereoselective spiroketalizations reported to date.

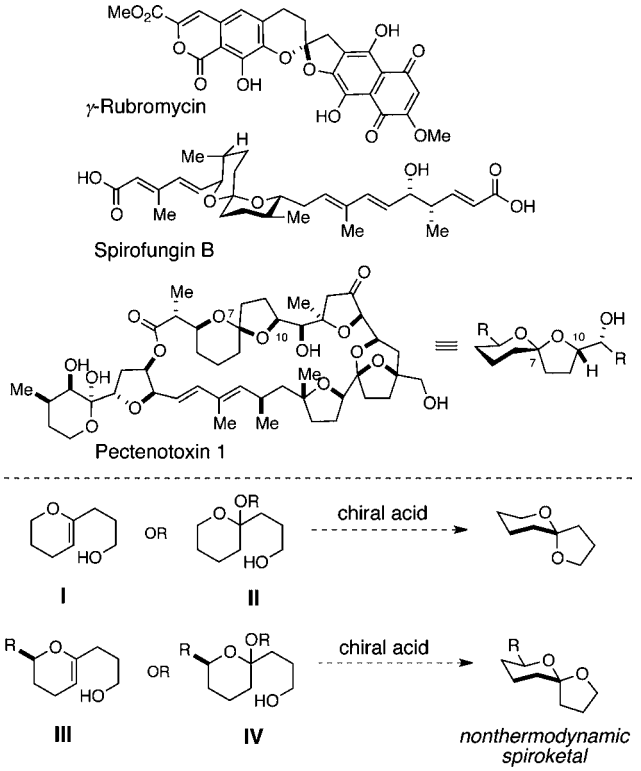


Figure 1. Natural products containing synthetically challenging spiroketals.

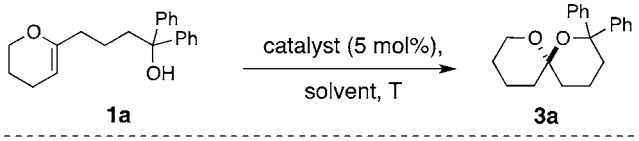
While it is known that substrates similar to **I**−**IV** can undergo acid-catalyzed spiroketalizations, it is likely that the conditions required for the cyclization of **II** and **IV** would result in substantial epimerization of the resultant spiroketals. In contrast, studies by Deslongchamps and co-workers indicate that kinetic spiroketalization of cyclic enol ethers such as **I** and **III** might be accomplished by weak acids without epimerization.[10] Therefore, we decided to investigate the possibility of CPA-catalyzed enantioselective and diastereoselective spiroketalizations of cyclic enol ethers similar to **I** and **III**.

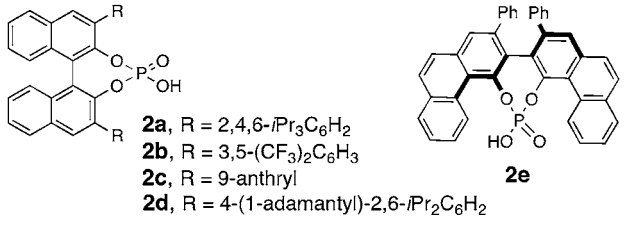
First, the spiroketalization of enol ether **1a** was investigated (Table 1).[11] Both chiral and achiral phosphoric acids were effective catalysts in promoting the spiroketalization of **1a** to **3a**.

Received: March 20, 2012
Published: April 30, 2012

dx.doi.org/10.1021/ja302704m | J. Am. Chem. Soc. 2012, 134, 8074−8077

Table 1. Optimization of the Conditions for the Enantioselective Spiroketalization[a]





entry	catalyst	solvent	*T*, °C	time,[b] h	ee
1	(*S*)-**2a**	CH_3CN	rt	0.5	7
2	(*S*)-**2a**	THF	rt	12[c]	10
3	(*S*)-**2a**	EtOAc	rt	12[c]	16
4	(*S*)-**2a**	PhH	rt	1	21
5	(*S*)-**2a**	toluene	rt	1	25
6	(*S*)-**2a**	CCl_4	rt	1	24
7	(*S*)-**2a**	hexanes	rt	0.5	63
8	(*S*)-**2a**	cyclohexane	rt	0.5	60
9	(*S*)-**2a**	pentane	rt	0.5	69
10	(*R*)-**2b**	pentane	rt	0.5	−16
11	(*S*)-**2c**	pentane	rt	1	1
12	(*R*)-**2d**	pentane	rt	1	−43
13	(*R*)-**2e**	pentane	0	4	23
14	(*S*)-**2a**	pentane	0	4	73
15	(*S*)-**2a**	pentane	−35	40	66
16	(*S*)-**2a**	pentane, 4 Å MS	0	14	84
17	**(*S*)-2a**	**pentane, 4 Å MS**	**-35**	**40**	**92**

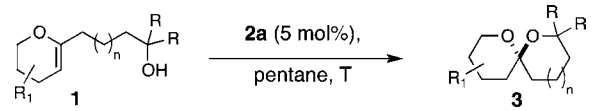
[a]Phosphoric acids were washed with 6 M HCl after purification by column chromatography. Unless specified otherwise, the reactions were performed on a 0.1 mmol scale (0.02 M solution). [b]Time required for the reactions to reach completion. [c]Incomplete conversion.

Initially, this compound was treated with (*S*)-TRIP catalyst **2a** (5 mol %) in different solvents (entries 1−9). While the reactions in relatively polar solvents (entries 1−5) resulted in low levels of stereocontrol, spiroketalizations conducted in hydrocarbon solvents (entries 7−9) proceeded with higher enantioselectivities and shorter reaction times.

On the basis of these studies, pentane was selected as the solvent of choice, and the optimization of the catalyst was conducted next (entries 10−13). All of the evaluated catalysts **2b**−**2e** catalyzed the formation of enantioenriched **3a**. However, the originally selected catalyst **2a** provided significantly higher levels of stereocontrol, and it was therefore selected for further studies. Although lowering the reaction temperature did not significantly affect the enantioselectivity of the spirocyclization (entries 14 and 15), the addition of 4 Å molecular sieves (MS) along with lowering the temperature resulted in an improvement of the ee (entries 16 and 17). Although the role of 4 Å MS is yet to be clarified, it is likely that molecular sieves are important for the suppression of racemic pathways proceeding through the formation of anomeric hemiketals.

The scope of the enantioselective spiroketalization was evaluated next (Table 2).[12,13] Substrates **1b**−**g** were synthesized and subjected to the optimized spiroketalization

Table 2. Substrate Scope of the Enantioselective Spiroketalization[a]



entry	precursor	product	T, °C	time, h	yield, %	ee, %
1	**1a**	**3a**	−35	40	96[b]	92
2	**1b** R = 4-(MeS)Ph	**3b**	−30	22	81	93
3	**1c**	**3c**	−35	40	82	75
4	**1d**	**3d**	−35	48	96[b]	94
5	**1e**	**3e**	0	24	93	96
6	**1f**	**3f**	0	24	88	74
7	**1g**	**3g**	0	24	89	90

[a]Reactions were performed on a 0.1−0.05 mmol scale (0.02 M solution) using (*R*)-**2a** as the catalyst. [b](*S*)-**2a** was used as the catalyst.

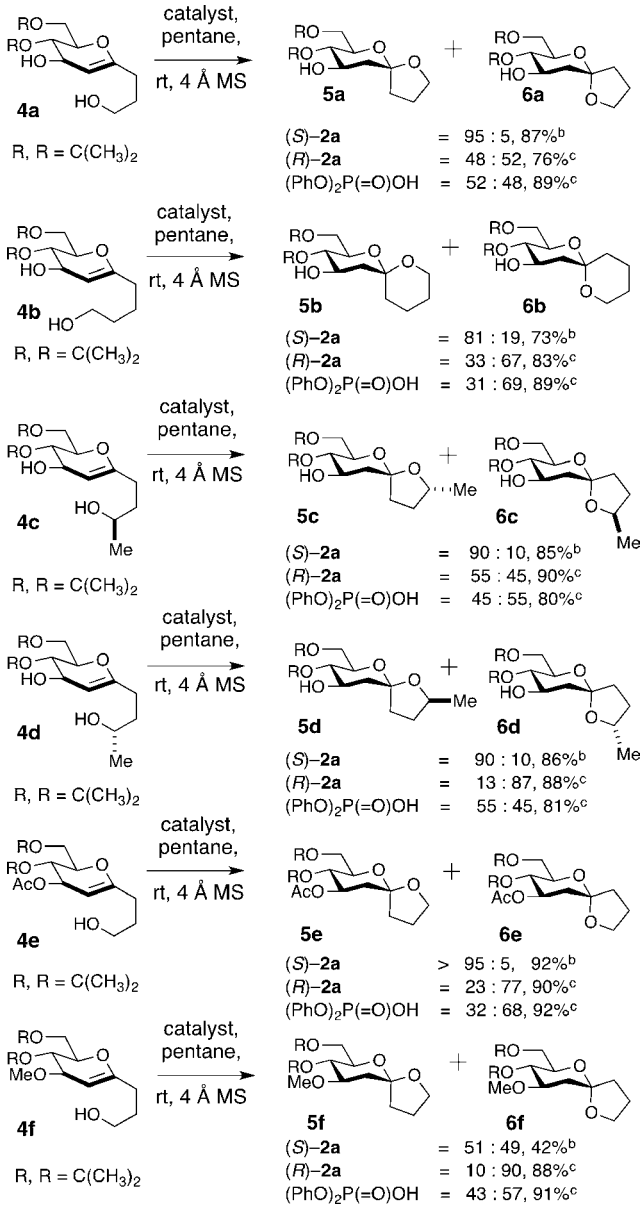
conditions. While the introduction of *p*-MeS substituents on the aromatic rings (entry 2) and extension of the tether length (entry 4) did not affect the reaction yield and selectivity, the cyclization of **1c** containing less-rigid Bn groups (entry 3) resulted in decreased conversion and ee. Although the preparation of enantioenriched **3e** and **3f** might be complicated by epimerization, the spiroketalization reactions of **1e** and **1f** (entries 5 and 6) proceeded with good to excellent levels of enantioselectivity and significantly shorter reaction times (24 h, 0 °C). The backbone of the cyclic enol ether may tolerate substituents, as exemplified by **1g** (entry 7), which gave spiroketal **3g** in good yield (89%) and enantioselectivity (90% ee).

While we have demonstrated that **2a** was able to catalyze highly stereoselective spiroketalizations of achiral precursors, in theory, the chirality of the substrate may completely override the course of cyclization dictated by the catalyst. Consequently, the possibility of utilizing **2a** for diastereoselective spiroketalizations was investigated next (Scheme 1).

D-Glycal derivatives **4a**−**f** were synthesized[11] and treated with (*S*)-**2a** and (*R*)-**2a** as well as with $(PhO)_2PO_2H$ to provide spiroketals **5** and **6**. The treatment of **4a** with (*S*)-**2a** (5 mol %)

dx.doi.org/10.1021/ja302704m | J. Am. Chem. Soc. 2012, 134, 8074−8077

Scheme 1. Substrate Scope of the Diastereoselective Spiroketalization[a]



[a]The reactions with (*S*)-**2a** or (*R*)-**2a** (5 mol %) were performed for 14 h, and those with $(PhO)_2PO_2H$ (10 mol %) were performed for 2 h. Longer exposure to $(PhO)_2PO_2H$ (10 mol %) resulted in complete equilibration to the thermodynamic spiroketal. [b]Yield of nonthermodynamic spiroketal **5**. [c]Combined yield of **5** and **6**.

resulted in a highly diastereoselective cyclization, leading to nonthermodynamic spiroketal **5a** (95:5 dr).[12] Remarkably, exposure of **4a** to (*R*)-**2a** or $(PhO)_2PO_2H$ provided a ∼1:1 mixture of nonthermodynamic and thermodynamic spiroketals **5a** and **6a**. Longer exposure of **4a** to $(PhO)_2PO_2H$ (4 h) resulted in complete isomerization of **5a** into **6a**. Treatment of glucal derivative **4b** (the homologue of **4a**) with chiral (*S*)-**2a** also resulted in selective formation of the nonthermodynamic [6,6] spiroketal **5b** (dr = 81:19). Similarly, treatment of **4b** with (*R*)-**2a** or $(PhO)_2PO_2H$ (10 mol %) provided a ∼1:2 mixture of the nonthermodynamic and thermodynamic spiroketals. These reactions did not appear to be sensitive to the substitution of the tethered alcohol. Thus, diastereomeric glycals **4c** and **4d** were cyclized with (*S*)-**2a** to provide nonthermodynamic spiroacetals **5c** and **5d** in good yields and selectivities (dr = 90:10). While substrates **4a**–**d** had a free C3 hydroxyl group that may participate in hydrogen bonding with the catalyst, the presence of the free hydroxyl was not essential. Accordingly, the acetylated derivative of **4a**, compound **4e**, was effectively cyclized to form the nonthermodynamic spiroketal **5e** with excellent selectivity (dr > 95:5).[14] However, spiroketalization of the methylated derivative **4f** with (*S*)-**2a** was nonselective, resulting in a ∼1:1 mixture of the nonthermodynamic and thermodynamic spiroketals. At the same time, exposure of **4f** to (*R*)-**2a** resulted in the predominant formation of thermodynamic spiroketal **6f** (dr = 10:90), while treatment with $(PhO)_2PO_2H$ provided a ∼1:1.3 mixture of isomers. Although it is not clear why the (*S*)-**2a**-catalyzed cyclization of **4f** proceeds with the lower stereoselectivity than the corresponding reactions of **4a** and **4e**, the drop in dr cannot be attributed to the higher susceptibility of **5f** to epimerization. Thus, $(PhO)_2PO_2H$-catalyzed epimerization of **5f** to **6f** is ∼6 times slower than the isomerization of **5a** to thermodynamic spiroketal **6a**.[15]

The absolute configuration of chiral spiroketal **3b** and the relative configuration of the nonthermodynamic spiroketal **5a** were confirmed by X-ray crystallography (Figure 2). In both

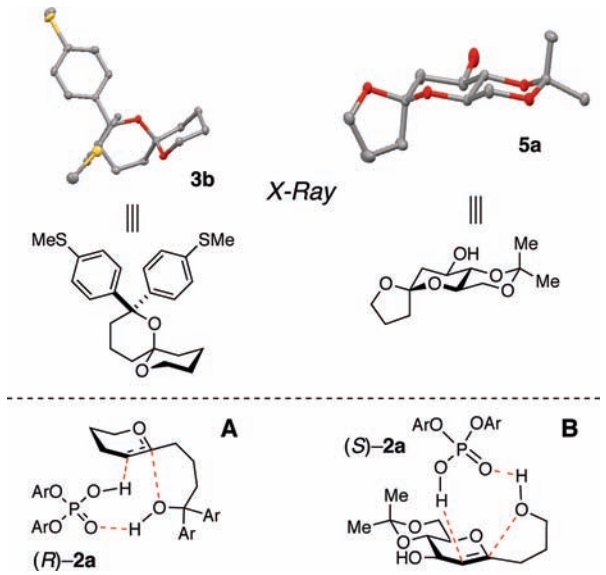


Figure 2. Plausible transition-state assemblies for the enantioselective and diastereoselective CPA-catalyzed spiroketalizations.

cases, the stereochemistry of the spiroketal stereocenter could be correlated with the stereochemistry of catalyst **2a** [e.g., (*R*)-**2a** promotes the reaction from the *Re* face of **1b** while (*S*)-**2a** provides the *Si* face addition product **5a**). Although spiroketalizations of cyclic enol ethers are proposed to proceed through the intermediacy of oxocarbenium ions, we believe that a mechanism involving concerted protonation and C–O bond formation is very likely to occur in nonpolar solvents such as pentane.[16] Correspondingly, we propose that CPAs act as bifunctional catalysts that promote the reaction through the intermediacy of transition states similar to **A** and **B** (Figure 2).

In summary, this communication has described chiral-catalyst-controlled enantioselective and diastereoselective spiroketalizations leading to nonthermodynamic spiroketals. BINOL-derived chiral phosphoric acids can serve as effective

dx.doi.org/10.1021/ja302704m | *J. Am. Chem. Soc.* 2012, 134, 8074–8077

catalysts for highly selective cyclizations of various achiral and chiral cyclic enol ethers. Our method allows control of the facial selectivity of addition to D-glucal derivatives **4a−e**, and further studies of this transformation and similar processes are currently underway.[17]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H and ^{13}C NMR spectra, and X-ray data for **3b** and **5a** (CIF). 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 interest.

■ ACKNOWLEDGMENTS

P.N. acknowledges the University of Michigan and Robert A. Gregg for financial support. We thank Prof. Adam Matzger, Dr. Saikat Roy, Dr. Jeff Kampf, and Kira Landenberger for their help with the X-ray crystallographic analysis of **3b** and **5a**. We acknowledge funding from NSF Grant CHE-0840456 for X-ray instrumentation.

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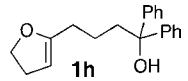
(11) The synthetic procedures for the preparation of **1a−g** and **4a−f** are provided in the Supporting Information.

(12) Substrates **3a−g** and **5a−f** may undergo isomerization during purification by column chromatography. However, the addition of triethylamine (1−2% v/v) to the eluent almost completely suppressed the epimerization.

(13) A significant background spiroketalization rate complicated the preparation and purification of **1h** and precluded unambiguous evaluation of this and related substrates.



1h

(14) Cyclization of a triisopropylsilyl-containing derivative proceeded at significantly lower rate and gave only trace quantities of the spiroketal product.

(15) The exposure of pure **5a** to $(PhO)_2PO_2H$ (10 mol %) in pentane for 2 h provided a **5a**:**6a** ratio of ∼1.6:1. The reaction of pure **5f** under the identical conditions resulted in a **5f**:**6f** ratio of ∼10:1.

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(17) A related report focused on asymmetric spiroketalization catalyzed by confined Brønsted acids was disclosed during the preparation of this manuscript. See: Coric, I.; List, B. *Nature* **2012**, *483*, 315.