Communication

Chiral Phosphoric Acid-Catalyzed Enantioselective and Diastereoselective Spiroketalizations

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Chiral Phosphoric Acid-Catalyzed Enantioselective and Diastereoselective Spiroketalizations.

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Spiroketals, stereoselective synthesis, chiral phosphoric acid

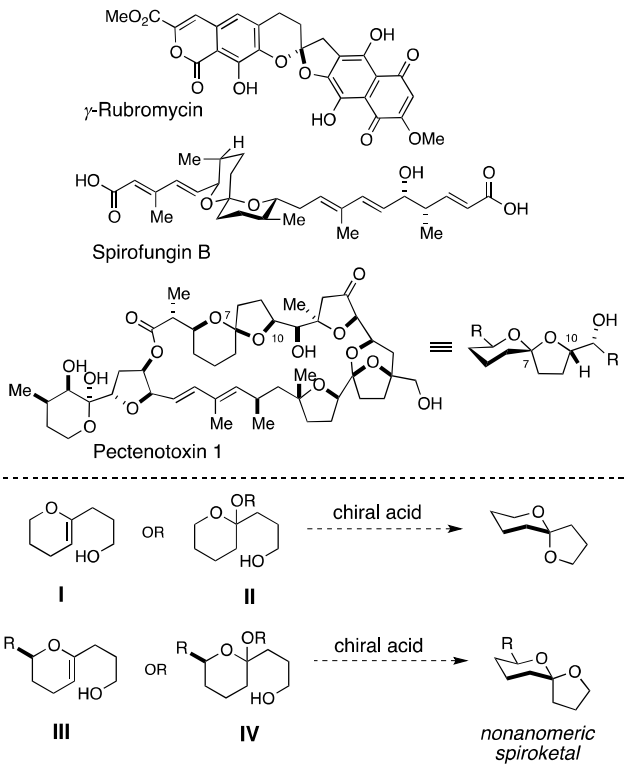
ABSTRACT: Catalytic enantioselective and diastereoselective spiroketalizations with BINOL-derived chiral phosphoric acids are reported. The chiral catalyst can override the inherent preference for the formation of thermodynamic spiroketals, and highly selective formation of non-thermodynamic spiroketals 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 the natural product being synthesized.[2] In some instances, the spiroketal stereochemistry is established under thermodynamic control utilizing the 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 the cases when the conformational and stereoelectronic factors prevent the formation of the desired configuration under the 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] there are only few general methods available. Typically, these methods rely on the 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 been previously 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, represent the first examples of successful chiral catalyst-controlled enantioselective or diastereoselective spiroketalization reported to date.[17]

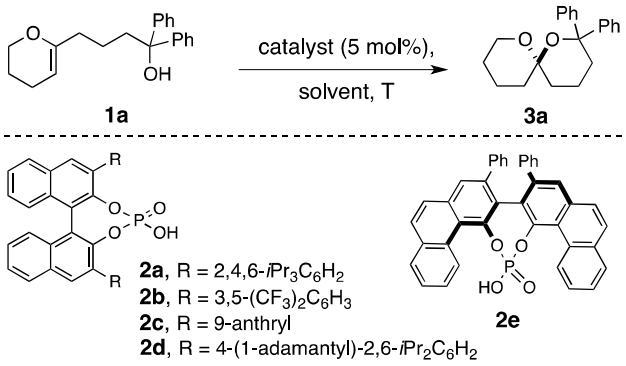
While it is known that the substrates similar to **I**–**IV** could undergo an acid-catalyzed spiroketalizations, it is likely that the conditions required for the cyclization of **II** and **IV** would result in substantial epimerization of the resultant spiroketals. In contrast, studies by Deslongchamps and coworkers indicate that kinetic spiroketalization of cyclic enol ethers such as **I** or **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**.

Figure 1. Natural products containing synthetically challenging spiroketals.



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

Table 1. Optimization of the conditions for the enantioselective spiroketalization[a]

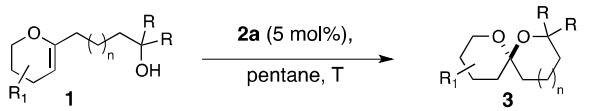


entry	catalyst	solvent	T, °C	time,[b] h	ee
1	(*S*)-**2a**	CH_3CN	rt	0.5	7
2	(*S*)-**2a**	THF	rt	12[c]	10
3	(*S*)-**2a**	EtOAc	rt	12[c]	16
4	(*S*)-**2a**	PhH	rt	1	24
5	(*S*)-**2a**	Toluene	rt	1	25
6	(*S*)-**2a**	CCl_4	rt	1	40
7	(*S*)-**2a**	Hexanes	rt	0.5	63
8	(*S*)-**2a**	Cyclohexane	rt	0.5	60
9	(*S*)-**2a**	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 the purification by the column chromatography. Unless specified otherwise, reactions were performed on 0.1 mmol scale (0.02 M solution). [b]Time required for the reactions to reach completion. [c]Incomplete conversion.

Based on 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 14-15), the addition of 4 Å MS together with lowering the temperature resulted in improvement of the ee (entries 16-17). Although the role of 4 Å MS is yet to be clarified, it is likely that the molecular sieves are important for the suppression of the racemic pathways proceeding through the formation of anomeric hemiketals.

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

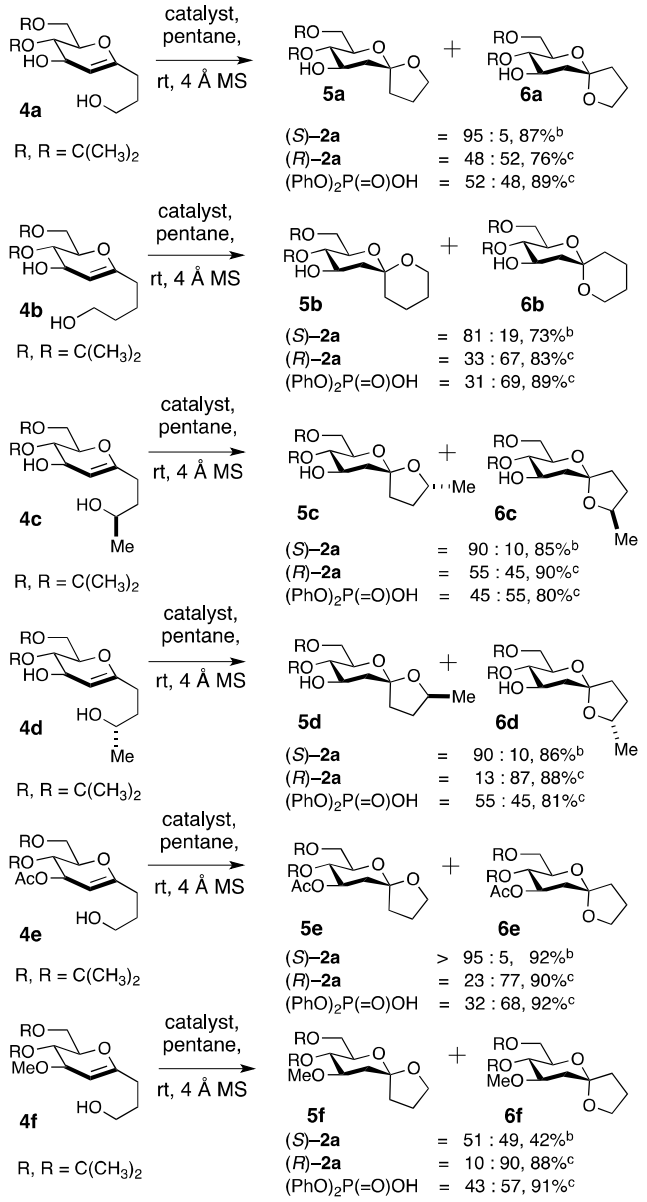
[a]Reactions were performed on 0.1–0.05 mmol scale (0.02 M solution). (*R*)-**2a** catalyst has been used. [b]Reactions were conducted with (*S*)-**2a** catalyst.

The scope of the enantioselective spiroketalization was evaluated next (Table 2).[12,13] Substrates **1b–1g** were synthesized and subjected to the optimized spiroketalization conditions. While the introduction of *p*-MeS- substituents at 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 with significantly shorter reaction times (24 h, 0 °C). The backbone of the cyclic enol ether may tolerate substituents, as exemplified by entry 7. The spiroketalization of **1g** thus led to spiroketal **3g** in good yield and enantioselectivity (89%, 90% ee).

While we have demonstrated that **2a** could catalyze highly stereoselective spiroketalizations of achiral precursors, in the-

ory, the chirality of the substrate may completely override the course of cyclization dictated by the catalyst. Consequently, the possibility of utilizing **2a** for the diastereoselective spiroketalization was investigated next (Scheme 1).

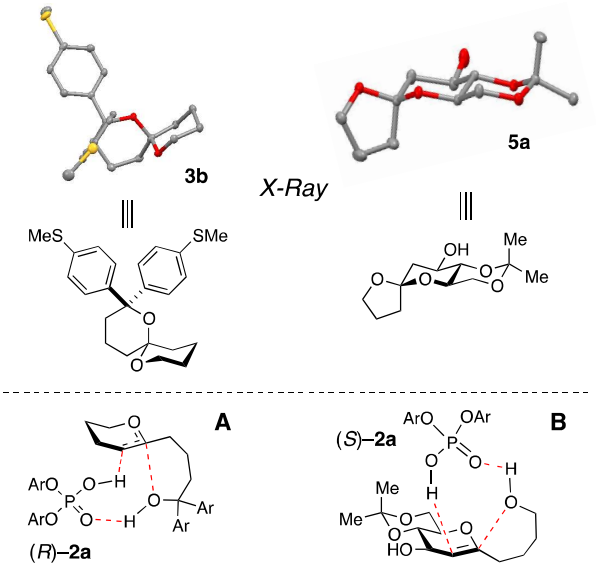
Scheme 1. Substrate scope of the diastereoselective spiroketalization[a]



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

D-glycal derivatives **4a**–**4f** were synthesized[11] and treated with (*S*)–**2a**, (*R*)–**2a**, as well as with $(PhO)_2PO_2H$ to provide spiroketals **5** and **6**. The treatment of **4a** with (*S*)-**2a** (5 mol%) resulted in a highly diastereoselective cyclization, leading to non-thermodynamic spiroketal **5a** (95:5 dr).[12] Remarkably, the exposure of **4a** to (*R*)-**2a** as well as to $(PhO)_2PO_2H$ provided ~1:1 mixtures of non-thermodynamic and thermodynamic spiroketals **5a** and **6a**. Longer exposure of **4a** to $(PhO)_2P(=O)OH$ (4 h) resulted in complete isomerization of **5a** into **6a**. Treatment of the homolog of **4a**, glucal derivative **4b**, with chiral (*S*)-**2a** also resulted in selective formation of the non-thermodynamic [6.6] spiroketal **5b** (dr = 81:19). Similarly, the treatment of **4b** with (*R*)-**2a** or $(PhO)_2PO_2H$ (10 mol%) provided ~1:2 mixture of the non-thermodynamic and thermodynamic spiroketals. These reactions do 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 non-thermodynamic spiroacetals **5c** and **5d** in good yields and selectivities (dr = 90:10). While the substrates **4a**-**4d** had a free C3 hydroxyl group that may participate in hydrogen bonding with the catalyst, the presence of free hydroxyl is not essential. Accordingly, the acetylated derivative of **4a**, compound **4e**, may be effectively cyclized to form a non-thermodynamic spiroketal **5e** with excellent selectivity (dr >95:5).[14] However, spiroketalization of the methylated derivative **4f** with (*S*)-**2a** was non-selective, resulting in ~1:1 mixture of the non-thermodynamic and thermodynamic spiroketals. At the same time, the exposure of **4f** to (*R*)-**2a** resulted in the predominant formation of thermodynamic spiroketal **6f** (dr = 10:90) while the treatment with $(PhO)_2PO_2H$ provided ~1:1.3 mixture of isomers. Although it is not clear why the (*S*)-**2a**-catalyzed cyclization of **4f** proceeds with the lower stereoselectivity compared to the corresponding reactions of **4a** or **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 approximately 6 times slower than the isomerization of **5a** to thermodynamic spiroketal **6a**.[15]

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



The absolute configuration of chiral spiroketal **3b** as well as the relative configuration of the non-thermodynamic spiroketal **5a** were confirmed by X-ray crystallography (Figure 2). In both cases, the stereochemistry of the spiroketal stereocenter may be correlated with the stereochemistry of the 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 the oxocarbenium ions, we believe that a mechanism involving concerted protonation and C–O bond formation is very likely in non-polar solvents

such as pentane.[16] Correspondingly, we propose that chiral phosphoric acids act as bi-functional catalysts that promote the reaction through the intermediacy of the transition states similar to **A** and **B** (*cf.* Figure 2).

In summary, this communication describes the chiral catalyst-controlled enantioselective and diastereoselective spiroketalizations leading to non-thermodynamic spiroketals. BINOL-derived chiral phosphoric acids have served as effective catalysts for the highly selective cyclizations of various achiral and chiral cyclic enol ethers. Our method allows controlling the facial selectivity of addition to *D*-glucal derivatives **4a-4e**, and further studies of this transformation and similar processes are currently underway.[17]

Supporting Information Available.
Experimental procedures, ^{1}H and ^{13}C NMR spectra, and X-ray data for **3b** and **5a** are available free of charge via the Internet at http://pubs.acs.org.

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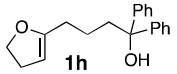
11) The synthetic procedures for the preparation of **1a–1g** and **4a–4f** are provided in the supporting information.

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

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



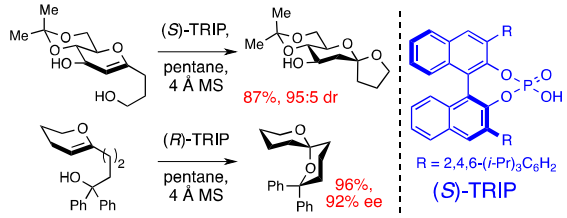
1h

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

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

16) For the examples of "preassociation" mechanism, in which the nucleophiles are proposed to stabilize the development of oxocarbenium ions in the transition state, refer to the following: (a) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238-8248. (b) Wurst, J. M.; Liu, G.; Tan, D. S. *J. Am. Chem. Soc.* **2011**, *133*, 7916-7925.

17) A related report focused on asymmetric spiroketalization catalyzed by confined Brønsted acids was disclosed during the preparation of this manuscript: Coric, I.; List, B. *Nature* **2012**, *483*, 315-319.


Me
Me
O
O
HO
HO
(S)-TRIP,
pentane,
4 Å MS
87%, 95:5 dr
(R)-TRIP
pentane,
4 Å MS
96%,
92% ee
Ph
Ph
R = 2,4,6-(i-Pr)3C6H2
(S)-TRIP

TOC