Acetals

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The Catalytic Asymmetric Acetalization**

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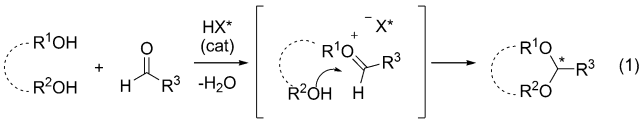
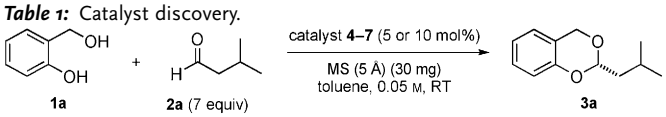
The Brønsted acid catalyzed acetalization of aldehydes with alcohols is one of the most common transformations in organic synthesis and yet catalytic asymmetric versions, until today, have been entirely unknown [Eq. (1)].[1] The advent of



asymmetric Brønsted acid catalysis has recently enabled the enantioselective generation of chiral N,N-, N,O-, and N,S-acetals, either from imines or directly from aldehydes.[2,3] The success of these reactions is based on the well-established ability of chiral phosphoric acids to direct the enantioselective addition of nucleophiles to imines.[3] However, the corresponding enantioselective additions to oxocarbenium ion intermediates, which are required for obtaining O,O-acetals, are much less developed.[4] Although acetals are among the most common stereocenters in organic molecules,[5] there are only few examples of their catalytic asymmetric synthesis.[6,7] We have recently reported that chiral Brønsted acids catalyze intramolecular asymmetric transacetalizations and spiroacetalizations generating chiral acetals with high enantioselectivity.[8,9] However, although our laboratory has pursued the direct asymmetric acetalization of aldehydes with alcohols for many years now, and has investigated numerous chiral Brønsted acid catalysts, unfortunately, very little success towards this goal has been encountered. Here we report that a new member of our recently developed class of chiral confined Brønsted acids finally enables this elusive transformation with excellent selectivity and scope.

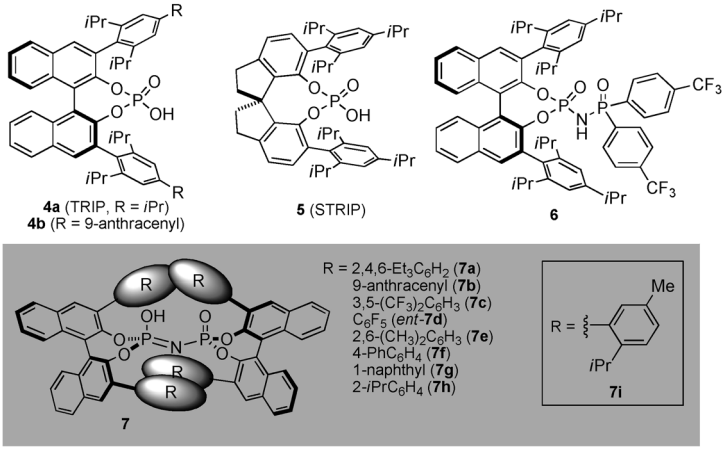
The summary of our investigations towards asymmetric acetalization with diol **1a** and aldehyde **2a** is given in Table 1. A catalytic amount of TRIP (**4a**; Scheme 1), one of the most successful phosphoric acid catalysts,[10,3f] catalyzes the reaction at room temperature giving cyclic acetal **3a** with an e.r. (enantiomeric ratio) of 66.5:33.5 and 66% conversion after 7 days (Table 1, entry 1). The recently developed spirocyclic

Table 1: Catalyst discovery.



Entry	Catalyst (mol%)	t[a]	Conv. [%]	e.r.
1	**4a** (10)	7 d	66	66.5:33.5
2	**5** (10)	7 d	19	79:21
3	**4b** (10)	7 d	50	52.5: 47.5
4	**6** (10)	7 d	31	51.5:48.5
5	**7a** (10)	7 d	66	79:21
6	**7b** (10)	7 d	<5	–
7	**7c** (10)	2 h	>99	71:29
8	**7d** (10)	2 h	>99	41.5:58.5
9	**7e** (10)	7 d	91	81:19
10	**7f** (10)	3 h	>99	84.5:15.5
11	**7g** (10)	20 h	>99	90:10
12	**7g** (5)	22 h	>99	90.5:9.5
13	**7h** (5)	4 d	>99	93.5:6.5
14	**7i** (5)	48 h	>99	95:5
15[b]	**7i** (5)	48 h	>99	95.5:4.5

[a] d = day. [b] 2 equiv of **2a**, 10 mg of molecular sieves, 0.1 M concentration.



Scheme 1. Catalysts **4**–**7**.

analogue STRIP (**5**), which proved to be superior to TRIP on several occasions, gave a slightly improved e.r. of 79:21, but displayed lower reactivity (Table 1, entry 2).[8b] Catalysts **4b** and **6**, which provided excellent results for the related N,N- and N,O-acetalizations of aldehydes,[2e,f] did not give any improvement (Table 1, entries 3 and 4). This striking failure of some of the most successful phosphoric acid catalysts illustrates the general difficulty of dealing with oxocarbenium ion intermediates in Brønsted acid catalysis.

Recently, our group has developed a new generation of stronger Brønsted acids, based on a C_2-symmetric imidodi-

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phosphate anion.[9a,11,12] The architecture of these catalysts enables the construction of chiral confined Brønsted acids with extremely sterically demanding chiral environments. We hypothesized that in such a surrounding, a putative oxocarbenium ion intermediate could be geometrically restrained. This would result in a reduction of transition-state diversity, leading to an increased enantioselectivity. However, testing our previously reported confined acids **7a**,**b** for the acetalization reaction did not result in an improvement of the enantioselectivity and reactivity (Table 1, entries 5 and 6).

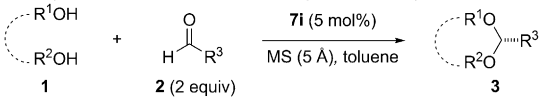
We reasoned that the chiral environment created by imidodiphosphoric acids **7a**,**b** might be either too sterically demanding or of inappropriate geometrical shape to efficiently support the transition state of the acetalization. However, our design of the imidodiphosphoric acids enables the construction of very diverse chiral environments. Owing to the presence of four substituents R, the steric demand of the active site remains very high even with less sterically demanding substituents. In comparison, with phosphoric acids that possess only two substituents, these are often required to be very bulky, limiting the choice of the substituent and consequently the geometrical variability of the chiral environment.

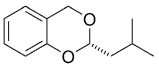
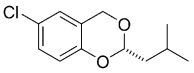
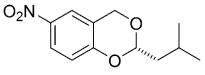
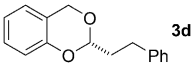
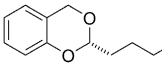
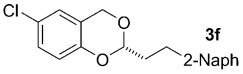
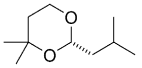
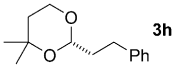
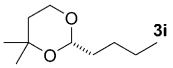
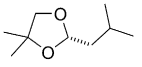
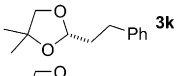
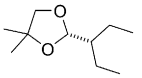
We tested several imidodiphosphoric acid catalysts **7c**–**i** with a variety of substituents R. Catalysts **7c** and **7d** with electron-withdrawing 3,5-$(CF_3)_2C_6H_3$ and C_6F_5 substituents were especially active, giving full conversion in two hours, although with low enantioselectivity (Table 1, entries 7 and 8). Catalysts **7e**–**g** with various substitution patterns all gave improved enantioselectivity and reactivity compared to catalysts **4a**,**b**, **5**, **6**, and **7a**,**b** (Table 1, entries 9–11**)**. The striking differences in the reactivity and selectivity between catalysts **7a**,**b** and **7e**, compared to catalysts **7f**,**g** emphasize the structural versatility of the active sites available with our confined acids. For example, while catalyst **7f** with *p*-biphenyl substituents provided full conversion in 3 h, catalyst **7b** was almost completely inactive. Presumably, the four 9-anthracenyl substituents in **7b** completely block access of the substrates to the active site. To our delight, confined imidodiphosphoric acid **7g** with the unsymmetrical 1-naphthyl substituent gave a promising enantiomeric ratio of 90:10 and allowed for lower catalyst loading (Table 1, entries 11 and 12).[12] Focusing on nonsymmetric substituents R, we next tested the *o*-isopropylphenyl-substituted catalyst **7h**, which further improved the enantioselectivity (Table 1, entry 13). Based on modeling studies, we expected that an extra substituent in the 4- or 5-position on the 2-*i*Pr-phenyl group might provide a more rigid catalyst structure by increasing the steric interaction between different substituents. Gratifyingly, catalyst **7i**, which was prepared from the natural product thymol, enabled a highly enantioselective reaction giving acetal **3a** with an enantiomeric ratio of 95.5:4.5 (Table 1, entries 14 and 15).

Having established satisfactory conditions, we set out to explore the generality of the reaction (Table 2). Placing chloro or nitro substituents on the aromatic ring of the diol does not significantly affect the enantioselectivity, although with the nitro-substituted diol the reactivity was significantly lower (Table 2, entries 2 and 3). Different aldehydes afforded still good but slightly lower enantioselectivities (Table 2, entries 4–6). We next investigated the applicability of this catalytic system to other classes of diols. Gratifyingly, with a simple aliphatic 1,3-diol (3-methylbutane-1,3-diol, **1b**), the enantioselectivity was even higher and enantiomeric ratios between 95.5:4.5 and 97.5:2.5 could be obtained (Table 2, entries 7–9). Encouraged by these results we next tackled the acetalization with a 1,2-diol to access five-membered acetals. Acetalization of isovaleraldehyde with 2-methylpropane-1,2-diol (**1c**) proceeded with exceptional enantioselectivity giving product **3j** with an e.r. of 99.8:0.2 at 0 °C (Table 2, entry 10). Linear and α-branched aldehydes could be employed with equal success in the reaction (Table 2, entries 11 and 12), although lower reactivity was observed with the branched aldehyde.

Although our asymmetric acetalization reaction could be performed with aliphatic aldehydes very efficiently, aromatic aldehydes present an additional challenge as these are more sensitive towards acid-catalyzed racemization under the reaction conditions. Gratifyingly, catalyst **7i** enabled the asymmetric acetalization of benzaldehyde with 1,2-diol **1c** giving the five-membered acetal **3m** in 89% yield with an e.r. of 95.5:4.5 (Table 3, entry 1). Encouraged by this result, we

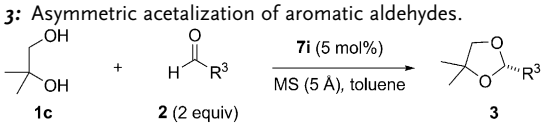
Table 2: Asymmetric acetalization of aliphatic aldehydes.

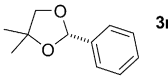
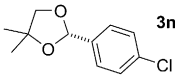
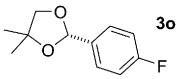
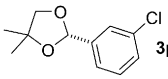
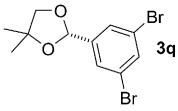
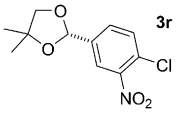
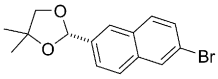


Entry	*T*, *t*[a]	Product	Yield [%]	e.r.
1	RT, 2 d	 **3a**	86	96:4
2	RT, 4 d	 **3b**	82	95:5
3	50 °C, 10 d	 **3c**	93	94.5:5.5
4	RT, 4 d	 **3d**	83	94.5:5.5
5	RT, 4 d	 **3e**	75	93.5:6.5
6	RT, 4 d	 **3f**	86	91.5:8.5
7	50 °C, 6 d	 **3g**	83	96.5:3.5
8	RT, 2 d	 **3h**	93	95.5:4.5
9	RT, 2 d	 **3i**	86	97.5:2.5
10	0 °C, 22 h	 **3j**	72	99.8:0.2
11	RT, 3 d	 **3k**	72	99:1
12	RT, 10 d	 **3l**	82	99.5:0.5

[a] d = day.

Table 3: Asymmetric acetalization of aromatic aldehydes.



Entry	*T*, *t*[a]	Product	Yield [%]	e.r.
1	RT, 2 d	 **3m**	89	95.5:4.5
2	RT, 62 h	 **3n**	79	98:2
3	RT, 42 h	 **3o**	74	96:4
4a	RT, 5 d	 **3p**	65	98.5:1.5
4b	50 °C, 4 d		85	95:5
5	50 °C, 6 d	 **3q**	83	99.5:0.5
6	60 °C, 7 d	 **3r**	79	97.5:2.5
7	RT, 52 h	 **3s**	77	96.5:3.5

[a] d = day.

next tested a variety of aromatic aldehydes. Acetals **3n–p** with substituents in either *p*- or *m*-positions on the phenyl ring could be obtained with excellent enantioselectivity (Table 3, entries 2–4). With disubstituted benzaldehydes **3q,r** equally excellent enantiomeric ratios of 99.5:0.5 and 97.5:2.5 were obtained, even at slightly elevated reaction temperatures (Table 3, entries 5 and 6). Likewise, the asymmetric acetalization of 6-bromo-2-naphthaldehyde proceeded with a high enantiomeric ratio of 96.5:3.5 (Table 3, entry 7). The absolute configurations of acetals **3f** and **3s** were determined to be *S* by single-crystal X-ray analysis (Figure 1). The configurations of other products were assigned by analogy.

A proposed mechanism for our asymmetric acetalization is shown in Scheme 2. Initially, the reversible addition of the primary alcohol moiety of the diol to the aldehyde leads to the

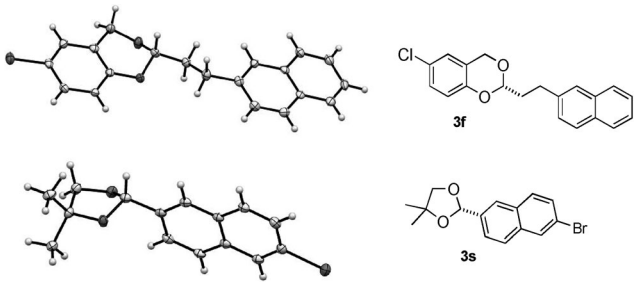
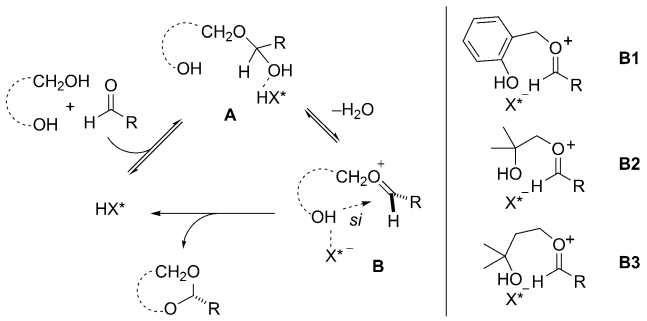


Figure 1. Crystal structures of acetals **3f** and **3s** (ellipsoids at the 50% probability level).[14]



Scheme 2. Plausible mechanism.

formation of hemiacetal intermediate **A**. Protonation of its OH moiety by the catalyst results in the expulsion of a water molecule and formation of the crucial oxocarbenium ion intermediate **B**. The chiral imidodiphosphate counteranion provides a chiral environment for the oxocarbenium cation,[13] and functions as a base that directs the nucleophilic attack of the second alcohol moiety to the *si* face of the oxocarbenium ion furnishing the *S*-configured cyclic acetal.

Based on initial mechanistic studies we believe that alternative pathways proceeding through tertiary-alcohol- and phenol-derived oxocarbenium ions are less probable. We have prepared racemic methyl acetal derivatives of the proposed hemiacetal intermediates **A** (OMe instead of OH), as alternative precursors for oxocarbenium ions **B1** and **B2**. When treated with catalyst **7i** these gave enantioselectivities that are very similar to those obtained in the direct acetalization reactions. In contrast, the acetal precursors for the tertiary-alcohol- and phenol-derived oxocarbenium ions gave different results (see the Supporting Information for details).

In summary, we have developed the first catalytic asymmetric acetalization of aldehydes. We demonstrate that imidodiphosphoric acids are an excellent platform for the construction of Brønsted acids with structurally versatile confined chiral microenvironments. A novel Brønsted acid, **7i**, readily available from natural thymol, drastically outperforms known catalysts and delivered acetals with excellent enantioselectivity. Several practical applications of our methodology, for example in kinetic resolutions, can be envisioned. Also, selective substitution reactions at the acetal stereogenic center with preservation of enantiopurity are appealing. Further exploration of the asymmetric acetalization and confined chiral Brønsted acid catalysts is in progress in our laboratories.

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Keywords: acetalization · acetals · asymmetric catalysis · confined Brønsted acids · organocatalysis

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[14] CCDC 915231 (**3 f**) and 915232 (**3 s**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Communications

Acetals

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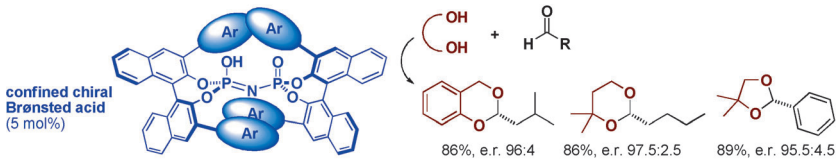
The Catalytic Asymmetric Acetalization



In straitened circumstances: In an asymmetric version of the acid-catalyzed acetalization of aldehydes, a novel member of the chiral confined Brønsted acid family significantly outperformed previously established catalysts, providing cyclic acetals with excellent enantioselectivity (see scheme; Ar = 2-*i*Pr-5-MeC_6H_3).