VIP Organocatalysis

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N-Phosphinyl Phosphoramide—A Chiral Brønsted Acid Motif for the Direct Asymmetric N,O-Acetalization of Aldehydes**

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The advent of 1,1′-binaphthalene-2,2′-diol (BINOL) phosphates as powerful Brønsted acid catalysts heralded a new era in asymmetric organocatalysis.[1] The recognition of the bifunctional mode of activation of these catalysts in reactions of imines with nucleophiles inspired organic chemists to design a variety of new asymmetric transformations.[2] At the same time, significant effort has also been devoted to the construction of other Brønsted acid motifs such as thioureas,[3] dicarboxylic acids,[4] and disulfonic acids.[5] A remarkable innovation in this area occurred when Yamamoto et al. introduced *N*-triflyl phosphoramides for the activation of less reactive substrates such as ketones, silyl enol ethers, and aldehydes.[6–8] Our recent discovery of chiral disulfonimides and their use as Lewis acid precatalysts for the activation of aldehydes, has revealed yet another potentially important class of chiral acid catalysts.[9] In research on BINOL-derived phosphoric acids little effort has been made towards the design of new analogues with alternative functionalities, except for certain modifications of their backbone[10] and the above-mentioned derivatization. As theoretical studies confirm that these catalysts simultaneously activate electrophiles by protonation and nucleophiles through interaction with the basic P=O group,[11] we are interested in exploring derivatives with alternative acidic and basic sites to further expand the utility of this fascinating type of organocatalyst.[12] Here we introduce *N*-phosphinyl phosphoramides as a new motif for organocatalysis (Figure 1).

We hypothesized that the additional basic P=O functionality of an *N*-phosphinyl phosphoramide could stabilize different transition-state geometries in the bifunctional activation of two reacting substrates. Additionally, by bringing in two new substituents, these catalysts could be easily modified and fine-tuned for a particular reaction. We now show that this new class of Brønsted acids can indeed be used in the first highly enantioselective direct N,O-acetalization of aldehydes.

Cyclic N,O-acetals are a frequently encountered structural motif in natural products and in pharmaceuticals.[13–14]

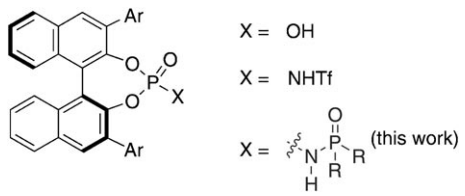
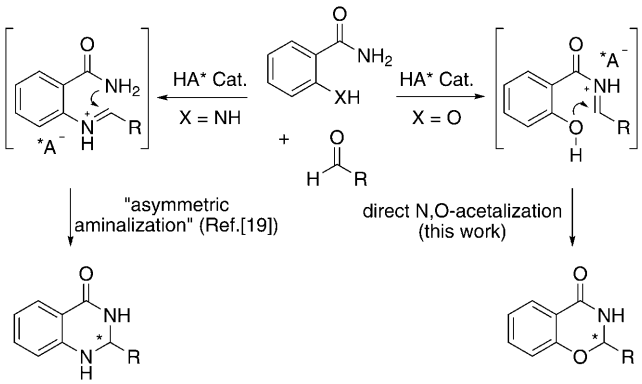


Figure 1. *N*-Phosphinyl phosphoramide as a new motif for asymmetric Brønsted acid catalysis.

The importance of the stereochemistry of the acetal carbon in N,O-acetal-containing drugs is illustrated by the different bioactivities of their enantiomers.[14a,15] In 2005, Antilla et al. reported the first catalytic asymmetric method for the synthesis of chiral aminals by the addition of sulfonamides to imines, using a VAPOL (vaulted biphenanthrol)-derived phosphoric acid.[16] They also extended this strategy to the preparation of chiral N,O-acetals by the BINOL phosphoric acid catalyzed enantioselective addition of alcohols to *N*-benzoyl imines.[17] However, this methodology is limited to acyclic N,O-acetals and to the use of preformed imines as electrophiles. As part of our long-standing interest in the development of asymmetric acetalization reactions,[18] we reported the direct enantioselective synthesis of cyclic aminals from aldehydes through a sequence consisting of imine formation and intramolecular amidation (Scheme 1).[19] However, analogous N,O-acetalizations have been entirely unknown, which is unsatisfying since cyclic N,O-acetals, especially benzoxazinones, have recently gained importance because of their pharmaceutical applications.[20] For example, chlorothenoxazine is well appreciated for its analgesic activity.[21] So far only achiral acids or amines have been used in the preparation of benzoxazinones from substituted



Scheme 1. Catalytic asymmetric N,N- and N,O-acetalizations.

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salicylamides and aldehydes.[22,23] Indeed, we found this transformation to be extremely challenging when we tested a variety of established chiral Brønsted acid catalysts. Consequently, we embarked on the development of a new chiral catalyst for the asymmetric synthesis of benzoxazinones from aldehydes.

In our initial studies we exposed a mixture of 2-hydroxy-4-methylbenzamide (**1a**) and isovaleraldehyde (**2a**) to a catalytic amount of (*S*)-TRIP[24] (**4**) (10 mol%) at 50°C (Figure 2). A slow but efficient reaction occurred and the benzoxazinone[25] derivative **3a** was obtained with a promising e.r. of 78:22 (Table 1, entry 1). The more acidic *N*-triflyl phosphoramide catalyst **5** resulted in reduced enantioselectivity (Table 1, entry 2). As various other phosphoric acids also failed to give an improvement,[26] we began focusing on the development of the novel bisphosphorylimide catalyst **6**, which was easily accessible from (*S*)-TRIP chloride (TRIP-Cl) and diphenyl phosphoramidate using NaH as the base.[26,27] Use of catalyst **6** provided product **3a** with an improved enantioselectivity of 85:15 e.r. (Table 1, entry 3). To further rigidify the chiral pocket provided by the catalyst, we explored the possiblity of replacing the phenoxide moiety in **6** with other groups. In the event, several chiral *N*-phosphinyl phosphoramides (**7a–f**) were synthesized from the corresponding diaryl phosphinamide and TRIP-Cl and were tested in the model reaction. Gratifyingly, catalyst **7a** considerably improved the enantioselectivity but at the expense of the reaction rate (Table 1, entry 4). Interestingly, the arene substituents present in the phosphinyl moiety exerted a striking influence on the reaction outcome.

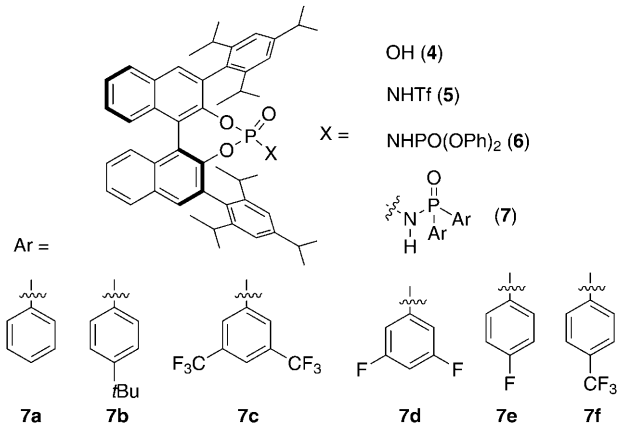
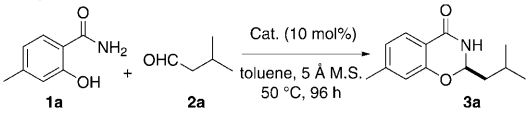


Figure 2. Catalysts tested.

While catalysts **7a** (Ar = Ph) and **7b** (Ar = 4-*t*BuC$_6$H$_4$) gave similar results, aryl groups containing electron-withdrawing substituents at the *meta* positions provided higher reaction rates but gave significantly lower enantioselectivities (Table 1, entries 6 and 7). Gratifyingly, we found that catalyst **7e** with a *para*-fluorophenyl group, significantly improved the enantioselectivity, although the yield was only moderate (Table 1, entry 8). A further improvement in both the reaction rate and the enantioselectivity was observed with catalyst **7f** (Ar = 4-CF$_3$C$_6$H$_4$; Table 1, entry 9), which provided the product **3a** with an e.r. of 95:5 and was selected for exploration of the substrate scope. The yield of the reaction could be further improved to 90% by using an excess of aldehyde (Table 1, entry 10).

With the optimized conditions in hand, we tested a variety of aldehydes in the reaction with amide **1a** (Table 2). The N,O-acetalization catalyzed by *N*-phosphinyl phosphoramide **7f** proved to be quite general. Aliphatic α-unbranched and α-branched aldehydes were converted into benzoxazinones **3** with high yields and enantioselectivities (Table 2, entries 1–5). The linear aliphatic aldehyde **2g** afforded still good but slightly lower enantioselectivity (Table 2, entries 6 and 7), while benzaldehyde gave rather moderate enantioselectivity (entry 8). We further investigated the applicability of this

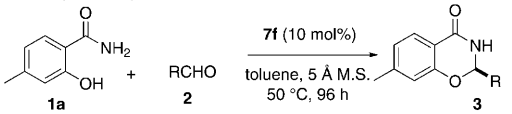
Table 1: Optimization of reaction conditions.

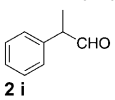
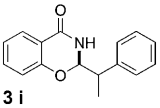


Entry[a]	Catalyst	Yield [%][b]	e.r.[c]
1	**4**	66	78.0:22.0
2	**5**	74	57.0:43.0
3	**6**	80	85.0:15.0
4	**7a**	52	93.5:6.5
5	**7b**	50	94.0:6.0
6	**7c**	75	60.0:40.0
7	**7d**	73	87.5:12.5
8	**7e**	64	94.5:5.5
9	**7f**	73	95.0:5.0
10[d]	**7f**	90	95.0:5.0

[a] Unless otherwise specified, reactions were performed on 0.1 mmol scale (0.05 M solution), 5 Å M.S. (50 mg). [b] Yield of isolated product. [c] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [d] Reaction carried out with 8 equivalents of **2a**.

Table 2: Aldehyde scope.



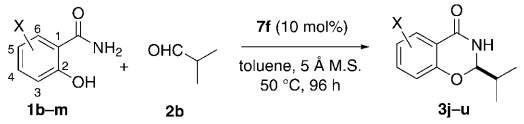
Entry[a]	RCHO	Product	Yield [%][b]	e.r.[c]
1	*i*BuCHO (**2a**)	**3a**	90	95.0:5.0
2	*t*BuCH$_2$CHO (**2b**)	**3b**	94	94.5:5.5
3	*i*PrCHO (**2c**)	**3c**	90	96.0:4.0
4	(Et)$_2$CHCHO (**2d**)	**3d**	81	98.0:2.0
5	CyCHO (**2e**)	**3e**	95	96.0:4.0
6	PhCH$_2$CHO (**2f**)	**3f**	83	91.5:8.5
7	*n*PrCHO (**2g**)	**3g**	97	92.0:8.0
8	PhCHO (**2h**)	**3h**	50	75.5:24.5
9[d]	 **2i**	 **3i**	69	*syn*: 98.5:1.5 *anti*: 86.5:13.5

[a] The reactions were performed with 0.1 mmol of **1a** and 0.8 mmol of **2**, 5 Å M.S. (50 mg). [b] Yield of isolated product. [c] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [d] 2-Hydroxybenzamide (**1b**) was used. Cy = cyclohexyl.

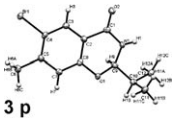
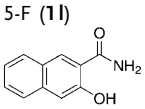
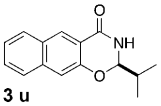
catalyst system to the diastereoselective N,O-acetalization of 2-phenyl propionaldehyde. The reaction delivered product **3i** in good yield with 1:1 d.r. (Table 2, entry 9). The *syn* product was obtained with an excellent e.r. of 98.5:1.5 and the *anti* isomer with 86.5:13.5 e.r.[28]

The generality of the reaction was also investigated with several substituted 2-hydroxybenzamides (Table 3). The electronic properties of the arene substituents showed little influence on the enantioselectivity and all, electron-rich,

Table 3: 2-Hydroxybenzamide scope.



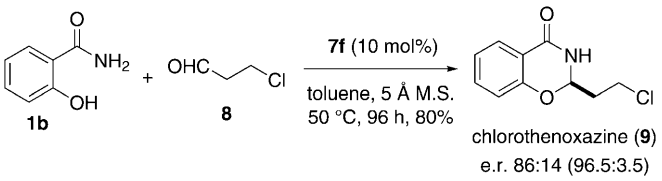
1b–m **2b** **3j–u**

Entry[a]	X	Product	Yield [%][c]	e.r.[d]
1	H (**1b**)	**3j**	89	95.0:5.0
2[b]	3-Me (**1c**)	**3k**	96	96.0:4.0
3	5-Me (**1d**)	**3l**	97	96.0:4.0
4	6-Me (**1e**)	**3m**	97	94.0:6.0
5	4-OMe (**1f**)	**3n**	98	95.5:4.5
6	5-OMe (**1g**)	**3o**	95	94.5:5.5
7	4-Me, 5-Br (**1h**)	 **3p**	91	96.0:4.0
8[b]	5-Me, 3-Br(**1i**)	**3q**	84	95.0:5.0
9	4-Me, 3,5-Cl (**1j**)	**3r**	78	95.5:4.5
10	5-Cl (**1k**)	**3s**	88	95.0:5.0
11	5-F (**1l**)	**3t**	89	95.0:5.0
12	 **1m**	 **3u**	95	93.5:6.5

[a] The reactions were performed with 0.1 mmol of **1** and 0.8 mmol of **2b**, 5 Å M.S. (50 mg). [b] The reaction was carried out at 60°C. [c] Yield of isolated product. [d] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase.

electron-neutral, and electron-poor benzamides furnished the corresponding products in similarly high yields and enantioselectivites. While substrate **1j**, substituted with two chlorine atoms, gave slightly lower yield, the enantioselectivity remained excellent (Table 3, entry 9). Furthermore, 3-hydroxynaphthamide (**1m**) gave the corresponding product **3u** with similarly high enantioselectivity (Table 3, entry 12). The absolute configuration of N,O-acetal **3p** was determined to be *R* by single-crystal X-ray analysis.[28] The absolute configuration of all other products was assigned by analogy.

We were also able to demonstrate the utility of our methodology in the synthesis of the analgesic pharmaceutical chlorothenoxazine (**9**, Scheme 2). The enantiomers of this drug have been separated before by chromatography on a chiral stationary phase, but the biological properties of the individual enantiomers have not yet been determined.[29] Using standard conditions, we obtained the product in good yield with reasonable enantioselectivity (e.r. 86:14).[30] Importantly, highly enantiomerically enriched product **9** could be obtained after a single recrystallization from methanol.



1b **8**

Scheme 2. Synthesis of chlorothenoxazine

Mechanistically, we believe the reaction to proceed via an *N*-benzoylimine, generated from the aldehyde and 2-hydroxybenzamide. Protonation of the imine with catalyst **7f** delivers a chiral ion pair, in which the chiral counteranion dictates the approach of the phenol nucleophile towards the *re* enantioface of the imine as shown in Figure 3. In accordance with our design, we propose that the Brønsted basic phosphinyl oxygen (^{2}P=O) activates the nucleophile in the transition state.

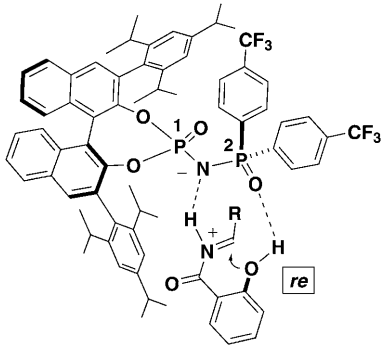
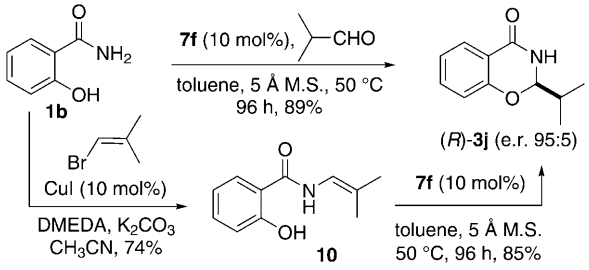


Figure 3. Stereochemical model.

To obtain further evidence for the intermediacy of a benzoylimine, we prepared enamide **10** as a latent imine surrogate by means of Cu-catalyzed N-alkenylation and subjected it to the acetalization reaction conditions (Scheme 3). This reaction afforded the corresponding product with the same enantioselectivity as in the two-component reaction suggesting the imine as a common intermediate.



1b **10**

Scheme 3. Synthesis and cyclization of enamide **10**. DMEDA = *N*,*N*'-dimethylethylenediamine.

In conclusion, we have designed chiral *N*-phosphinyl phosphoramides as a new motif for asymmetric Brønsted acid catalysis. The *N*-phosphinyl phosphoramide **7f** was identified

as the first highly effective and enantioselective catalyst for the direct synthesis of cyclic N,O-acetals from aldehydes and hydroxy amides. The additional functional group and substituents of the *N*-phosphinyl phosphoramide allow expeditious fine-tuning of the chiral Brønsted acid catalyst. The potentially broad utility of this motif will be further explored in our laboratories.

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Keywords: Brønsted acid catalysis · cyclic N,O-acetals · organocatalysis · *N*-phosphinyl phosphoramides

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[30] The low e.r. in the reaction may be a consequence of the generation of trace amount of HCl from the decomposition of β-chloropropionaldehyde.

