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Chiral Brønsted Acid Catalyzed Enantioselective Hydrophosphonylation of Imines: Asymmetric Synthesis of α-Amino Phosphonates

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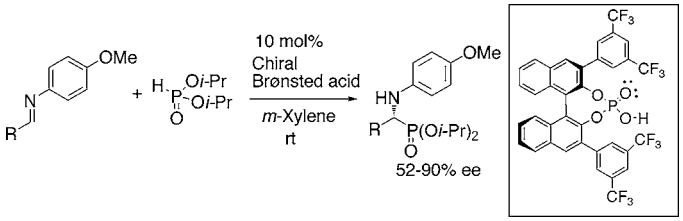
ABSTRACT



A cyclic phosphoric acid derivative, derived from (*R*)-BINOL, was used as a chiral Brønsted acid (10 mol %) in hydrophosphonylation of aldimines with diisopropyl phosphite at room temperature. α-Amino phosphonates were obtained with good to high enantioselectivities.

The development of novel chiral catalysts for asymmetric synthesis continues to be one of the most challenging topics in modern synthetic organic chemistry because it provides the most efficient way to approach the synthesis of enantiopure compounds. Although a significant number of metal-oriented chiral catalysts have been developed so far,[1] metal-free chiral organocatalysts have recently emerged as a novel chiral catalyst family.[2] In contrast to metal-oriented chiral catalysts, which are generated in situ from metal complexes and chiral ligands, organocatalysts exhibit catalytic activity by themselves and are generally stable in air and easily stored. Although a number of chiral organocatalysts have been reported, strong chiral Brønsted acids have been less explored until quite recently.[3] It is expected that chiral Brønsted acid catalysts would electrophilically activate carbon−oxygen or carbon−nitrogen double bonds and chiral induction would be realized. We have recently synthesized a novel chiral Brønsted acid **1**, derived from (*R*)-BINOL and demonstrated its catalytic activity in the Mannich-type reaction.[4,5]

α-Amino phosphonic acids and phosphonate esters have attracted attention[6] not only because they are biologically attractive peptide mimics of α-amino acids but also because they exhibit intriguing biological activities such as enzyme

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inhibitors.[7] Lewis acid or Brønsted acid catalyzed hydrophosphonylation of imines with dialkyl phosphite provides a useful method for access to the α-amino phosphonic acid derivatives.[8] Diastereoselective addition of phosphite derivatives to chiral imines,[9] chiral Lewis acid-catalyzed enantioselective addition of phosphites to imines,[10] and other methods[11] have been successfuly achieved for the preparation of optically active α-amino phosphonates.[12,13] We wish to report herein hydrophosphonylation of imines catalyzed by a chiral Brønsted acid **1** (Figure 1).

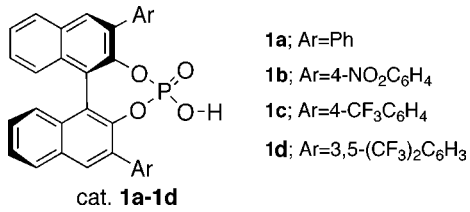
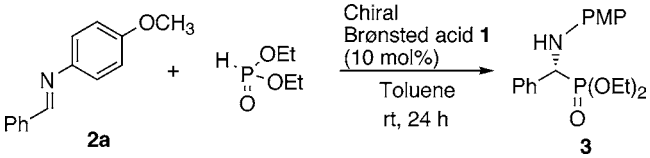


Figure 1.

At the outset, we studied the hydrophosphonylation reaction of diethyl phosphite with *N*-benzylidene *p*-anisidine (**2a**) in the presence of the phosphoric acid derivative **1** (10 mol %) in toluene at room temperature. α-Amino phosphonate **3** was obtained in good yield and the effect of the 3,3′-substituents on **1** is shown in Table 1. A phosphoric acid **1b** (Ar = 4-$NO_2C_6H_4$), which exhibited the highest enantioselectivity in the Mannich-type reaction,[4] turned out to be less effecitve. Among the Brønsted acids examined, **1d** (Ar = 3,5-$(CF_3)_2C_6H_3$) exhibited the highest enantioselectivity and reactivity (entry 4).

Table 1. Effect of 3,3′-Substituents of Phosphoric Acid 1[a]

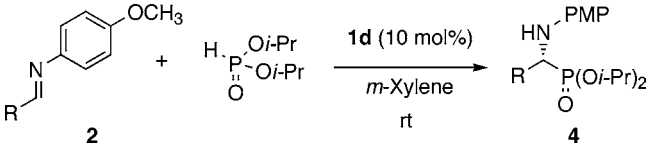


entry	acid	yield (%)	ee (%)
1	**1a**	70	23
2	**1b**	90	23
3	**1c**	69	35
4	**1d**	99	43

[a] 2.0 equiv of diethyl phosphite was employed.

The absolute stereochemistry of diethyl phosphonate **3** was determined to be *R* by deprotection of the *p*-$MeOC_6H_4$ moiety of **3** by means of CAN, and comparison of its optical rotation with the literature data.[14] The absolute stereochemistries of other phosphonates were speculated to be *R* by analogy. The results of the hydrophosphonylation of diisopropyl phosphite[15] with imines **2** by means of phosphoric acid **1d** (10 mol %) in *m*-xylene[16] at room temperature[17] is shown in Table 2. The α-amino phosphonates **4** were

Table 2. Results of the Phosphonylation[a]



entry	R	time (h)	yield (%)	ee (%)
1	C_6H_5	24	84	52
2	*o*-$CH_3C_6H_4$	46	76	69
3	*o*-$NO_2C_6H_4$	24	72	77
4	$C_6H_5CH{=}CH$	101	92	84
5	*p*-$CH_3C_6H_4CH{=}CH$	170	88	86
6	*p*-$ClC_6H_4CH{=}CH$	145	97	83
7	*o*-$CH_3C_6H_4CH{=}CH$	171	80	82
8	*o*-$ClC_6H_4CH{=}CH$	70	82	87
8	*o*-$NO_2C_6H_4CH{=}CH$	49	92	88
10	*o*-$CF_3C_6H_4CH{=}CH$	46	86	90
11	1-naphthyl-CH=CH	168	76	81

[a] 2.0 equiv of diisopropyl phosphite was employed.

obtained in high yields with good to high enantioselectivities. In particular, aldimines derived from cinnamaldehyde derivatives exhibited high enantioselectivities (entries 3−8).

To elucidate the reason high enantioselectivity was observed with **1d**, we have studied the effect of phosphorus

(5) Subsequently, similar phosphoric acid catalyzed reactions were reported; see: (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804−11805.

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(11) (a) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem.* **2000**, *65*, 6121−6131. (b) Déjugnat, C.; Etemad-Moghadam, G.; Rico-Lattes, I. *Chem. Commun.* **2003**, 1858−1859.

(12) For a review on asymmetric synthesis of organophosphorus compounds, see: Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279−1332.

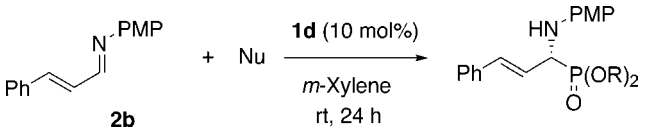
(13) For a recent example of hydrophosphonylation reaction catalyzed by a chiral thiourea, see ref 10e.

(14) Deprotection of *N*-*p*-methoxyphenyl group of **3** by means of CAN gave free amine in 57% yield: $[\alpha]^{25}_D$ +11.5 (*c* 1.9, $CHCl_3$) [lit.[9d] (*R*)-form: $[\alpha]^{20}_D$ +17.2 (*c* 1.0, $CHCl_3$)].

(15) The diisopropyl esters gave better results than the corresponding diethyl esters in terms of enantioselectivity, vide infra.

(16) The reaction in *m*-xylene showed slighly higher enantioselectivity than that in toluene.

Table 3. Effect of Nucleophile

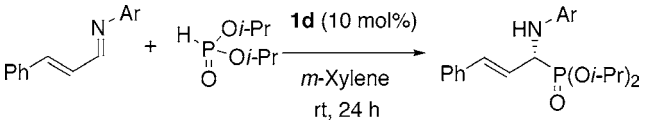


entry	Nu	yield (%)	ee (%)
1	$HPO(O\text{-}i\text{-}Pr)_2$	92	84
2	$HPO(OEt)_2$	70	73
3	$P(O\text{-}i\text{-}Pr)_3$	23	3

nucleophiles (Table 3). Among the dialkyl phosphites examined, diisopropyl phosphite gave the highest enantioselectivity. It is noted that use of trialkyl phosphite as a nucleophile deteriorated both reactivity and enantioselectivity (entry 3). Based on the results, the OH moiety of the dialkyl phosphite is suggested to play an important role in determining the high enantioselectivity.

Screening of the *N*-substituent on the imines showed that the presence of an *o*-hydroxy moiety decreased the enantioselectivity (Table 4). This result contrasts with the case of

Table 4. Effect of *N*-Substituent



entry	Ar	time (h)	yield (%)	ee (%)
1	$4\text{-}MeOC_6H_4$	187	58	87
2	C_6H_5	69	74	88
3	$2\text{-}HOC_6H_4$	87	33	39

Mannich-type reactions we studied,[4] wherein the presence of *o*-hydroxy moiety was essential for the high chiral induction.

We would like to propose the following nine-membered transition state (Figure 2), wherein phosphate **1d** plays 2 roles: (1) the phosphoric acid hydrogen activates the imine as a Brønsted acid and (2) phosphoryl oxygen activates the

(17) The reaction at 0 °C took much longer time for completion without beneficial effect on enantioselectivity.

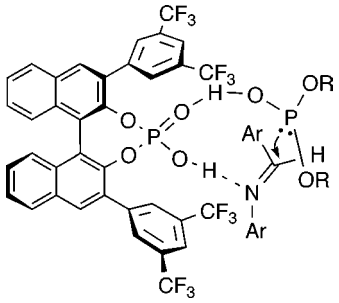


Figure 2. Plausible reaction mechanism.

nucleophile by coordinating with the hydrogen of the phosphite[18]as a Brønsted base, thereby promoting *re* facial attack to the imine and increasing the enantioselectivity by proximity effect. We would like to propose that phosphoric acid **1d** works as a bifunctional chiral Brønsted acid[19] bearing both Brønsted acidic and Brønsted basic sites.

In summary, the hydrophosphonylation of imines with diisopropyl phosphite has been found to be catalyzed by a chiral Brønsted acid, derived from (*R*)-BINOL. The process affords α-amino phosphonates in good to high enantioselectivity. Aldimines, in particular, derived from cinnamaldehyde derivatives exhibit high enantioselectivity. Further applications of this phosphoric acid catalysts to other asymmetric reactions are in progress in this laboratory.

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Supporting Information Available: Experimental procedures, spectra data, characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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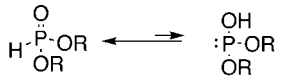
(18) It is known that phosphonate−phosphite tautomerism exists with the phosphite form as the active nucleophilic form and the phosphonate tautomer as the almost exclusive favored but nonnucleophilic form.[10d]



Phosphonate form (unreactive) ⟷ Phosphite form (reactive)

(19) For bifunctional Lewis acids, see: Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989−1999.