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Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid Derived from TADDOL

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Abstract: A novel cyclic dialkyl phosphate was synthesized starting from (+)-diethyl tartrate. Its catalytic activity as a chiral Brønsted acid has been examined in the Mannich-type reaction of a ketene silyl acetal with aldimines as a model reaction. The corresponding β-amino acid esters were obtained with high enantioselectivity.

Keywords: asymmetric synthesis; Brønsted acid; Mannich-type reaction; organic catalysis; TADDOL

The development of novel chiral catalysts continues to be an important goal of synthetic organic chemistry.[1] Recently, small organic compounds have been recognized as efficient chiral catalysts for a number of synthetic reactions.[2] As part of our ongoing program directed towards the development of carbon-carbon bond forming reactions catalyzed by Brønsted acids,[3] we focused on strong chiral Brønsted acids as the electrophilic activator of carbon-nitrogen double bond.[4] We designed the novel chiral phosphate (**1**) as a bifunctional Brønsted acid, starting from (*R*)-BINOL, and have demonstrated its catalytic activity in the enantioselective Mannich-type reaction of ketene silyl acetal with an aldimine.[5,6] Although Lewis acid catalysts[7] and organocatalysts such as L-proline[8] have been employed for enantioselective Mannich-type and Mannich reactions, chiral strong Brønsted acids had not been reported as a chiral catalyst for this reaction. We next paid attention to chiral Brønsted acids based on the TADDOL scaffold (**2**) because the TADDOL scaffold is expected to have different electronic and steric impacts in comparison with the BINOL scaffold. In this communication, we report the preparation of novel chiral phosphate **2** starting from (+)-diethyl tartrate and its catalytic activity in the Mannich-type reaction.

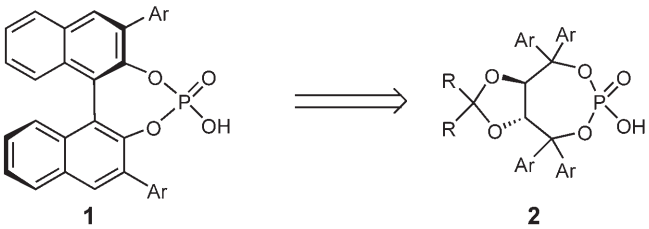
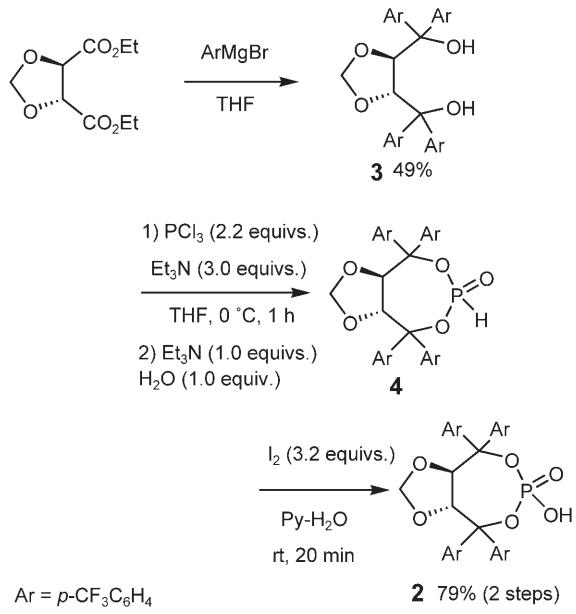


Figure 1. Plausible transition state.

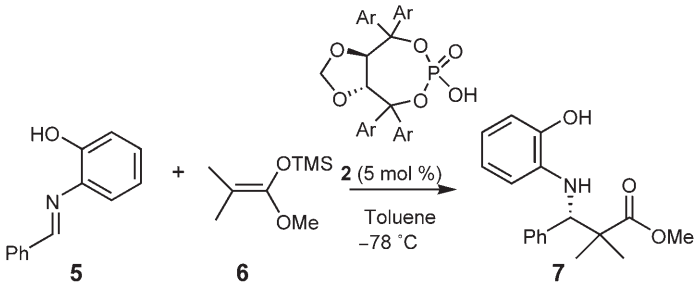
The catalysts were prepared starting from methylidene-protected (+)-diethyl tartrate through Grignard addition followed by phosphorylation (Scheme 1). Direct transformation of TADDOL derivative **3** to cyclic phosphate **2** by use of $POCl_3$, which was effective for the preparation of chiral phosphate **1** bearing the BINOL scaffold,[5] was unsuccessful. Therefore, an alternative synthetic route was devised by treatment of **3** with PCl_3 and subsequent oxidation of dialkyl phosphite **4**[9] by I_2, affording dialkyl phosphate **2** in good yields.

At the outset, the Mannich-type reaction of an aldimine **5** with ketene silyl acetal **6** was examined by use of 5 mol% of Brønsted acid **2** and the results are shown in Table 1. When **2a** (Ar = Ph) was employed in toluene



Scheme 1. Preparation of chiral catalysts; yields are given for Ar = *p*-$CF_3C_6H_4$.

Table 1. Effect of the Brønsted acid.[a]



Entry	Ar	Acid	Time [h]	Yield [%]	ee [%]
1	Ph	**2a**	24	0	–
2	p-$C_6H_5C_6H_4$	**2b**	66	47	31
3	p-FC_6H_4	**2c**	26	63	34
4	p-$CF_3C_6H_4$	**2d**	21	97	73

[a] 1.5 equivs. of ketene silyl acetal **6** and 5 mol % of Brønsted acid **2** were employed.

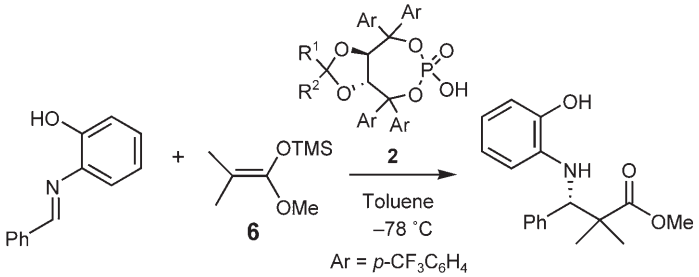
at $-78\,^{\circ}C$, no reaction took place and imine **5** was recovered (entry 1). Introduction of substituents on the aromatic rings had beneficial effects. When **2b** (Ar = p-$C_6H_5C_6H_4$) was employed, β-amino ester **7** was obtained in 47% yield with 31% ee (entry 2). Use of **2d** (R = p-$CF_3C_6H_4$) improved both chemical yield and enantioselectivity (73% ee) (entry 4). The stereochemistry of **7** was determined by comparison of the optical rotation and retention time of the products by HPLC analysis.[5,7c]

Next, effect of the acetal moiety was examined by use of **2** (Ar = p-$CF_3C_6H_4$) and the results are shown in Table 2. It is noted that introduction of an alkyl or aryl moiety on the methylene carbon decreased the enantioselectivity (entries 2–4). Variation of the aryl and acetal groups revealed that **2d** was optimal for this purpose.

We further screened the *N*-substituents of imine and the results are shown in Table 3. As expected, 4-methoxyphenyl group deteriorated the enantioselectivity (entry 1). Introduction of methyl group on the phenyl ring improved the enantioselectivity[10] and 2-hydroxy-4-methylphenyl group showed the highest enantioselectivity (entry 4).

The results of the Mannich-type reaction of various aldimines with **6** catalyzed by **2d** (5 mol %) are shown in Table 4. A range of aldimines derived from aromatic aldehydes gave β-amino esters in high yields with good to excellent enantioselectivities. Aldimines derived from *p*-fluorobenzaldehyde and *p*-methylbenzaldehyde, in particular, gave β-amino esters **9** in 92% ee (entries 3 and 5). Although 10 mol % of the Brønsted acid **1**, based on the BINOL scaffold, was required,[5] the present

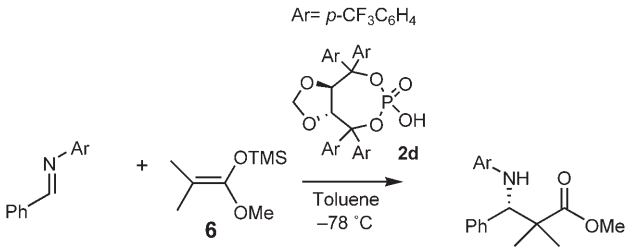
Table 2. Effect of the acetal moiety.[a]

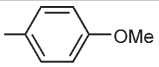
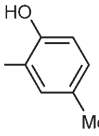
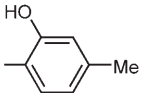


Entry	R^1, R^2	Time [h]	Yield [%]	ee [%]
1	H, H	21	97	73
2	Me, Me	21	62	56
3	H, Ph	48	82	65
4	H, 1-naphthyl	38	48	68

[a] 1.5 equivs. of ketene silyl acetal **6** and 5 mol % of Brønsted acid **2** were employed.

Table 3. Effect of *N*-substituent.



Entry	Ar	Time [h]	Yield [%]	ee [%]
1		38	65	19
2		21	97	73
3		22	83	76
4		30	quant	89

[a] 1.5 equivs. of ketene silyl acetal **6** and 5 mol % of Brønsted acid **2d** were employed.

Mannich-type reaction was catalyzed by lower loadings (5 mol %) to afford β-amino esters in high yields.

Based on the above results, we surmise that the Mannich-type reaction took place *via* a 9-membered transition state, wherein the phosphate hydrogen activated the imine and the phosphoryl oxygen interacted with the hydrogen of the imine's OH group by hydrogen bonding (Figure 2).[11] The nucleophile attacked the *Re*-face preferentially. Thus, **2** functioned as a bifunctional Brønsted acid bearing a Brønsted basic site.

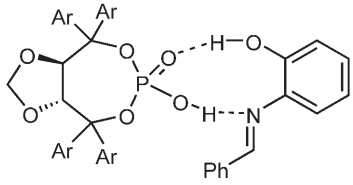


Figure 2.

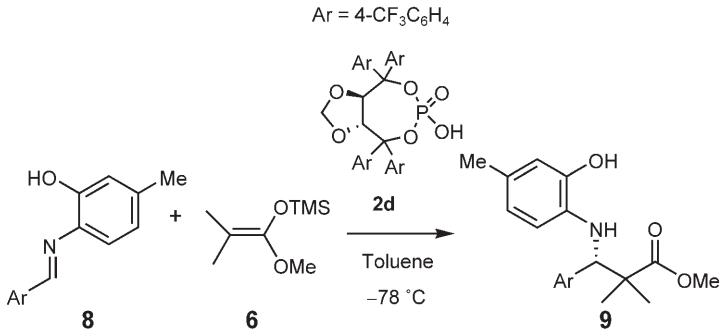
In summary, we have synthesized a novel chiral Brønsted acid based on the TADDOL scaffold. In comparison to the Brønsted acid based on the BINOL scaffold, the Mannich-type reaction was catalyzed at lower loading (5 mol %) to give β-amino esters in higher enantioselectivities (up to 92% ee). The present Brønsted acid will add a new entry into the organocatalyst family and its application to other asymmetric reactions is now in progress in our laboratory.

Experimental Section

Typical Procedure for the Mannich-Type Reactions (Table 4, Entry 1)

To a solution of *N*-benzylidene-2-hydroxy-4-methylaniline (**8**; Ar = C_6H_5) (31.7 mg, 0.150 mmol) and phosphate **2d** (5.8 mg, 0.0075 mmol) in toluene (1 mL) was added dropwise a solution of ketene silyl acetal **6** (45 μL, 0.225 mmol) for 3 min at

Table 4. Results of the Mannich-type reactions catalyzed by **2d**.[a]



Entry	Ar	Time [h]	Yield [%]	Ee [%]
1	Ph	30	100	89
2	4-ClC_6H_4	51	81	85
3	4-FC_6H_4	48	95	92
4	4-$MeOC_6H_4$	51	85	89
5	4-$CH_3C_6H_4$	48	96	92

[a] 1.5 equiv of ketene silyl acetal **6** and 5 mol% of Brønsted acid **2d** were employed.

−78 °C. After being stirred for 30 h at that temperature, the mixture was quenched by successive addition of saturated $NaHCO_3$ (5 mL), saturated KF solution (3 mL), and MeOH/THF (3 mL) at −78 °C and was kept stirring for further 30 min at room temperature. The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The remaining solid was purified by TLC (SiO_2, hexane:ethyl acetate = 5:1 v:v) to give β-amino ester **9** (Ar = C_6H_5); yield: 46.9 mg (0.150 mmol, 100%). The enantiomeric excess was determined to be 89% on a Daicel Chiralpak AD-H column.

Acknowledgements

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