Preparation of β-Amino Esters by a Chiral Brønsted Acid Catalyzed Mannich-Type Reaction

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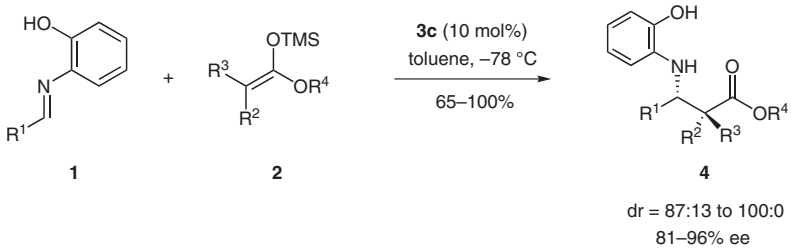
Abstract: Mannich-type reactions of ketene silyl acetals with aldimines proceeded smoothly under the influence of 10 mol% of a cyclic chiral phosphate derivative derived from (*R*)-BINOL as a chiral Brønsted acid catalyst to furnish β-amino esters with excellent enantioselectivities.

Key words: chiral Brønsted acid, asymmetric synthesis, catalyst, Mannich-type reaction, β-amino esters



Scheme 1 Preparation of β-amino esters

Introduction

Chiral β-amino acids and their esters are useful intermediates for the preparation of biologically important nitrogen-containing compounds. There are a number of methods for the preparation of β-amino esters in enantiomerically enriched form. Mannich-type reactions of silyl enolates with aldimines provide a useful method for the preparation of β-amino carbonyl compounds.[1,2] Several chiral Lewis acids have been developed as catalysts for Mannich-type reactions, with Cu, Zr, Ag, Pd, and others as the central metal.[3]

Recently, chiral organocatalysts have emerged as novel asymmetric catalysts.[4] The salient features of organocatalysts are that they are (1) highly stabile toward water and oxygen, (2) easy to handle, and (3) metal-free and environmentally benign. L-Proline derivatives,[5] chiral thioureas,[6] and cinchona alkaloids[7] have been reported to promote Mannich and Mannich-type reactions as organocatalysts.[8]

In 2004, our research group first demonstrated that enantiopure phosphoric acids, derived from (*R*)-BINOL, are highly effective as a chiral Brønsted acid catalyst for Mannich-type reactions.[9] The phosphoric acid catalyst was further applied by us[10] and others[11] to numerous kinds of asymmetric reactions, such as nucleophilic addition to aldimines, cycloaddition reactions, reductions, the Nazarov reaction, and so on[12] in addition to the Mannich and Mannich-type reactions.[13]

The synthetic procedure outlined in Scheme 1 constitutes the treatment of ketene silyl acetals **2** with aldimines **1** in the presence of 10 mol% of phosphoric acid **3c** to give the corresponding β-amino esters **4** with high diastereoselectivity and high to excellent enantioselectivity.

Scope and Limitations

Chiral phosphoric acids (Figure 1) were extensively examined for the reaction of a ketene silyl acetal, derived from methyl 2-methylpropanoate with an aldimine derived from benzaldehyde. Although the parent phosphoric acid **3a** gave the corresponding β-amino ester **4a** as a racemate, the use of **3b**, bearing phenyl groups on the 3,3′-positions improved the enantioselectivity to 27% ee. The highest enantioselectivity was observed using phosphoric acid **3c** bearing 4-nitrophenyl groups at the 3,3′-positions.

The results for the phosphoric acid **3c** catalyzed Mannich-type reaction are shown in Table 1. 1-Ethoxy-1-(trimethylsiloxy)prop-1-ene, a ketene silyl acetal derived from ethyl propanoate, proved to be an excellent nucleophile. The corresponding α-methyl-β-amino esters **4** were ob-

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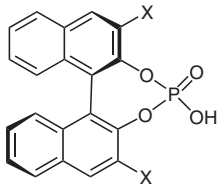
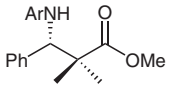
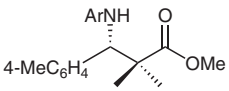
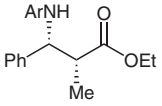
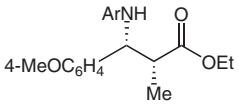
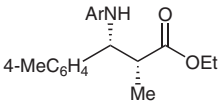
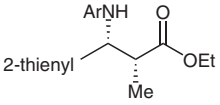
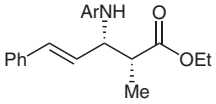
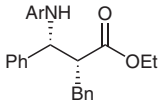
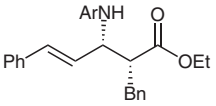
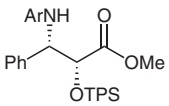


3a X = H
3b X = Ph
3c X = 4-$O_2NC_6H_4$

Figure 1 Chiral Brønsted acids

tained with good to high diastereoselectivity in favor of the *syn* isomer and the enantioselectivity of the *syn* isomer reached 96% ee. Not only aldimines derived from aromatic aldehydes but also those derived from heteroaromatic aldehydes and α,β-unsaturated aldehydes exhibited high to excellent enantioselectivity.

Table 1 Chiral Phosphoric Acid **3c** Catalyzed Enantioselective Mannich-Type Reactions

Product[a] **4**		Yield[b] (%)	Ratio *syn*/*anti*	ee (%)
4a		100	–	89
4b		100	–	89
4c		100	87:13	96
4d		100	92:8	88
4e		100	94:6	81
4f		81	94:6	88
4g		91	95:5	90
4h		100	93:7	91
4i		65	95:5	90
4j		79	100:0	91

[a] Ar = 2-hydroxyphenyl.
[b] Yield of isolated product.

1-Methoxy-1-(trimethylsiloxy)-2-(triphenylsiloxy)ethene, a ketene silyl acetal derived from methyl 2-(triphenylsiloxy)acetate, also exhibited excellent diastereoselectivity and high enantioselectivity in the formation of **4j**.

Although aldimines derived from aromatic aldehydes and α,β-unsaturated aldehydes proved to be excellent substrates for the phosphoric acid catalyzed Mannich-type reactions, aldimines derived from aliphatic aldehydes did not give the corresponding β-amino esters.

The use of aldimines derived from 2-aminophenol is essential for attaining excellent enantioselectivity. The 2-hydroxyphenyl group on nitrogen showed remarkably superior enantioselectivity in comparison with the 4-hydroxy group. It is clear that hydrogen bonding of the 2-hydroxyphenyl group on the *N*-aryl group plays an important role in combination with phosphoric acid activation.[9b]

In summary, the phosphoric acid **3c**, derived from (*R*)-BINOL, is an effective catalyst for the Mannich-type reaction; the corresponding β-amino esters **4** were obtained with high to excellent enantioselectivity.

All reactions were carried out under N_2 in oven-dried glassware with magnetic stirring. Toluene was distilled over CaH_2 and stored over MS 4Å. (*R*)-3,3′-Bis(4-nitrophenyl)-1,1′-binaphthyl-2,2′-diyl phosphate (**3c**) is commercially available from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).[14] All products have been previously synthesized in the literature and characterized.[9b]

Methyl (*S*)-3-[(2-Hydroxyphenyl)amino]-2,2-dimethyl-3-phenylpropanoate (4a); Typical Procedure[3d]

To a soln of *N*-benzylidene-2-hydroxyaniline (1.06 g, 5.38 mmol) and phosphoric acid **3c** (328.2 mg, 0.56 mmol) in toluene (20 mL) at –78 °C was added dropwise a soln of 1-methoxy-2-methyl-1-(trimethylsiloxy)prop-1-ene (1.43 g, 8.22 mmol) in toluene (12 mL) over 32 min. The mixture was stirred at this temperature for 22 h and then the mixture was quenched, at –78 °C, by the addition of sat. $NaHCO_3$. After filtration through Celite, the filtrate was extracted with EtOAc. The combined organic layers were concentrated and the crude mixture was treated with THF (40 mL) and 10% HCl (10 mL) at 0 °C for 20 min. The mixture was extracted with EtOAc and the combined organic layers were successively washed with 10% HCl, brine, dried (anhyd Na_2SO_4), and concentrated to dryness. The remaining solid was purified by column chromatography (silica gel, hexane–EtOAc, 5:1) to give β-amino ester **4a** (1.61 g, 100%); R_f = 0.4 (hexane–EtOAc, 3:1); 89% ee [HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH, 5:1, flow rate: 0.5 mL/min, UV = 244 nm): t_R = 11.1 (minor isomer, 3*R*), 16.3 min (major isomer, 3*S*)].

$[\alpha]_D^{25}$ +0.2 (*c* 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 5 H), 6.69 (dd, *J* = 7.7, 1.5 Hz, 1 H), 6.61 (ddd, *J* = 7.7, 7.7, 1.5 Hz, 1 H), 6.53 (ddd, *J* = 7.7, 7.7, 1.5 Hz, 1 H), 6.38 (dd, *J* = 7.7, 1.5 Hz, 1 H), 5.80 (br s, 1 H), 4.55 (br s, 1 H), 4.55 (s, 1 H), 3.69 (s, 3 H), 1.24 (s, 3 H), 1.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7, 144.3, 139.0, 135.5, 128.3, 127.9, 127.41, 121.0, 117.9, 114.4, 113.9, 64.6, 52.2, 47.4, 24.4, 20.0.

Ethyl (2*R*,3*R*)-3-[(2-Hydroxyphenyl)amino]-2-methyl-3-phenylpropanoate (4c); Typical Procedure[9b]

To a soln of *N*-benzylidene-2-hydroxyaniline (32.0 mg, 0.162 mmol) and phosphoric acid **3c** (9.5 mg, 0.0161 mmol) in toluene (1

mL) at –78 °C was added dropwise a soln of 1-ethoxy-1-(trimethylsiloxy)prop-1-ene (*E*/*Z*, 87:13; 50 μL, 0.246 mmol) over 3 min. The mixture was stirred at this temperature for 17 h and then quenched by the addition of sat. $NaHCO_3$ and sat. KF soln at –78 °C. After filtration through Celite, the filtrate was extracted with EtOAc. The combined organic layers were washed successively with 10% HCl and brine, dried (anhyd Na_2SO_4), and concentrated to dryness. The crude solid was purified by TLC (silica gel, hexane–EtOAc 3:1) to give β-amino ester **4c** (45.6 mg, 100%); R_f = 0.2 (hexane–EtOAc, 3:1); ratio *syn*/*anti* 87:13; 96% ee [HPLC (Daicel Chiralpak AS-H, hexane–*i*-PrOH, 30:1, flow rate: 0.55 mL/min, UV = 244 nm): t_R = 48.3 (major isomer, 2*R*,3*R*), 56.7 min (minor isomer, 2*S*,3*S*)].

IR ($CHCl_3$): 3603, 3342, 3028, 2986, 1724, 1611, 1514, 1497, 1454, 1267, 1202, 1184 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 6.76–6.53 (m, 3 H), 6.42 (dd, *J* = 7.9, 1.5 Hz, 1 H, *syn*), 6.33 (dd, *J* = 7.8, 1.5 Hz, 1 H, *anti*), 6.00 (br s, 1 H, *anti*), 5.46 (br s, 1 H, *syn*), 4.76 (br s, 1 H, *syn*), 4.72 (d, *J* = 4.8 Hz, 1 H, *syn*), 4.34 (br s, 1 H, *anti*), 4.33 (d, *J* = 8.8 Hz, 1 H, *anti*), 4.17 (q, *J* = 7.1 Hz, 2 H, *anti*), 4.06 (q, *J* = 7.1 Hz, 2 H, *syn*), 2.96 (dq, *J* = 4.8 Hz, 7.1 Hz, 1 H, *syn*), 2.89 (dq, *J* = 8.8 Hz, 7.1 Hz, 1 H, *anti*), 1.24 (t, *J* = 7.1 Hz, 3 H, *anti*), 1.21 (d, *J* = 7.1 Hz, 3 H, *syn*), 1.14 (t, *J* = 7.1 Hz, 3 H, *syn*), 1.09 (d, *J* = 7.1 Hz, 3 H, *anti*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1 (*anti*), 174.6 (*syn*), 145.8 (*anti*), 143.9 (*syn*), 140.8 (*syn*), 135.8 (*syn*), 134.8 (*anti*), 128.5, 128.4, 128.1, 127.5, 127.3, 127.0, 126.9, 121.1 (*syn*), 120.6 (*anti*), 119.6 (*anti*), 117.7 (*syn*), 116.1 (*anti*), 114.6 (*anti*), 114.3 (*anti*), 113.4 (*syn*), 62.1 (*anti*), 61.0 (*anti*), 60.9 (*syn*), 60.0 (*syn*), 46.8 (*anti*), 46.4 (*anti*), 15.3 (*anti*), 14.1 (*anti*), 13.9 (*syn*), 12.0 (*syn*).

MS (DI): *m*/*z* (%) = 299 (M^+, 6), 198 (100), 135 (7), 120 (14), 117 (9), 115 (6), 105 (10), 91 (24), 77 (17), 65 (14).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.37; H, 7.29; N, 4.56.

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