Asymmetric Catalysis

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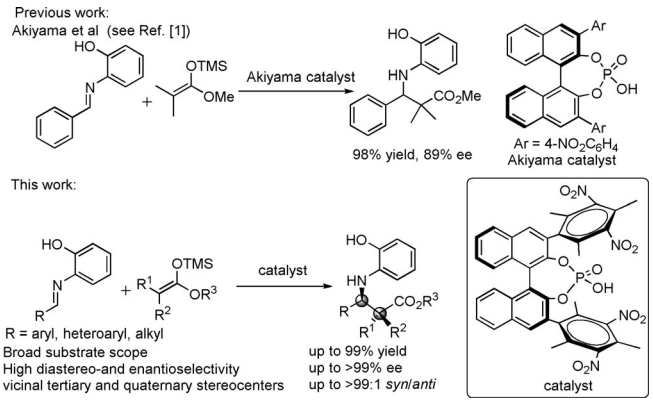
A Powerful Chiral Phosphoric Acid Catalyst for Enantioselective Mukaiyama–Mannich Reactions

Fengtao Zhou and Hisashi Yamamoto**

Abstract: *A new BINOL-derived chiral phosphoric acid bearing 2,4,6-trimethyl-3,5-dinitrophenyl substituents at the 3,3′-positions was developed. The utility of this chiral phosphoric acid is demonstrated by a highly enantioselective (ee up to >99%) and diastereoselective (syn/anti up to >99:1) asymmetric Mukaiyama–Mannich reaction of imines with a wide range of ketene silyl acetals. Moreover, this method was successfully applied to the construction of vicinal tertiary and quaternary stereogenic centers with excellent diastereo- and enantioselectivity. Significantly, BINOL-derived N-triflyl phosphoramide constitutes a complementary catalyst system that allows the title reaction to be applied to more challenging imines without an N-(2-hydroxyphenyl) moiety.*

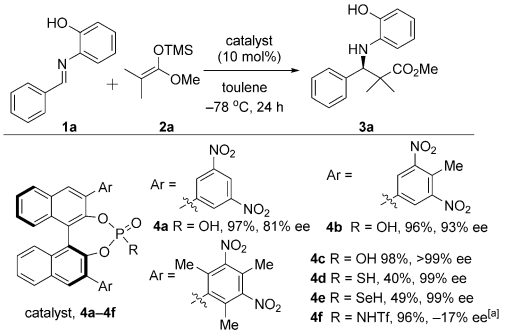
BINOL-derived chiral phosphoric acids, demonstrated independently by Akiyama[1] and Terada[2] in 2004 to serve as powerful Brønsted acid catalysts for enantioselective Mukaiyama–Mannich reactions, have emerged as versatile catalysts for the enantioselective formation of carbon–carbon and carbon–heteroatom bonds.[3,4] Chiral phosphoric acids are recognized to be one of the ideal catalysts for the activation of basic substrates, including imines and ketimines, through hydrogen bonding or ion pairing in a bifunctional fashion.[3] Asymmetric Mukaiyama–Mannich reaction of ketene silyl acetals with aldimines using a chiral phosphoric acid catalyst is thus a direct method for the enantioselective preparation of β-amino acid derivatives.[5,6] Although several phosphoric acid catalysts have recently been developed for asymmetric Mukaiyama–Mannich reactions,[7] the selectivity of the reactions is not always exclusive and the development of more reactive and highly selective chiral Brønsted acid catalysts is highly desirable.

The nitro group is known to be one of the strongest electron-withdrawing groups, and can serve as a substituent on Brønsted acids to enhance their acidity; for example, introduction of 4-nitrophenyl groups into the 3,3′-positions of BINOL-derived phosphoric acid improved both the yield and enantioselectivity of various Mukaiyama–Mannich reactions.[1] Herein, we report a general highly diastereo- and enantioselective Mukaiyama–Mannich reaction catalyzed by a new BINOL-derived chiral phosphoric acid bearing 2,4,6-trimethyl-3,5-dinitrophenyl substituents at the 3,3′-position (Scheme 1).



Scheme 1. Asymmetric Mukaiyama–Mannich reactions catalyzed by chiral phosphoric acids.

We began our study with the reaction of imine **1a** with ketene silyl acetal **2a** and tested various phosphoric acids (**4a**–**4f**), and the results are shown in Scheme 2. Catalyst **4a** led to a smooth Mukaiyama–Mannich reaction to give **3a** in excellent yield (97%) within 24 h in toluene at −78 °C. However, the enantioselectivity (81% *ee*) was moderate, as was that of catalyst reported by Akiyama in 2004 (89% *ee*).[1] We envisaged replacement of the hydrogen atom in the *para* position of the 3,5-dinitrophenyl ring with an alkyl group, which would force the nitro group out of the plane of the



Scheme 2. Optimization of the Mukaiyama–Mannich reaction with various phosphoric acids. Unless otherwise specified, all reactions were performed at −78 °C for 24 h under nitrogen with **1a** (0.1 mmol, 1.0 equiv), **2a** (0.3 mmol, 3.0 equiv), catalyst **4** (0.01 mmol, 10 mol%) in toluene (1 mL). Product *ee* values were determined by HPLC on a chiral stationary phase. [a] for 6 h.

[*] Dr. F. Zhou, Prof. Dr. H. Yamamoto
Molecular Catalyst Research Center, Chubu University
1200 Matsumoto-cho, Kasugai, Aichi 487-8501 (Japan)
E-mail: fengtaozhou@163.com
hyamamoto@isc.chubu.ac.jp

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phenyl ring so that the oxygen atoms of the nitro groups would be located near the domain of the phosphoric acids, to improve the enantioselectivity of the reaction. In fact, the catalyst **4b**, which bears a methyl group at the *para* position of the 3,5-dinitrophenyl ring, gave the product **3a** with slightly higher enantioselectivity (93% *ee*). Next, catalyst **4c**, which bears 2,4,6-trimethyl-3,5-dinitrophenyl substituents at the 3,3′-positions of BINOL-derived phosphoric acid delivered the product **3a** in high yield and with amazingly high enantioselectivity (98% yield and >99% *ee*, respectively). Steric and electronic effects may explain the origin of the high enantioselectivity from the three methyl groups. First, the acidities of four benzoic acids[8] were compared: 2,4,6-trimethylbenzoic acid ($pK_a = 3.45$), 4-nitrobenzoic acid ($pK_a = 3.40$), 3,5-dinitrobenzoic acid ($pK_a = 2.80$), and 2,4,6-trimethyl-3,5-dinitrobenzoic acid ($pK_a = 2.27$). The electron-withdrawing effect of the 2,4,6-trimethyl-3,5-dinitrophenyl substituents may thus increase the acidity of the phosphoric acid. Furthermore, with these three methyl groups, the two nitro groups are perpendicular to the phenyl ring of the 2,4,6-trimethyl-3,5-dinitrophenyl substituents. The oxygen atoms of the nitro groups are thus aligned towards the phosphoric acid moiety of the catalyst. We further tested the catalysts **4d** and **4e**, which were obtained by replacing the hydroxy group of **4c** with SH and SeH, respectively. However, both catalysts gave a lower yield than **4c**. The reaction proceeded very well when catalyzed by the more acidic *N*-triflyl phosphoramide **4f** at −78 °C for 6 h, but delivered the product with much lower enantioselectivity (−17% *ee*). The reaction is believed to proceed through a dual-activation pathway via the formation of a cyclic transition state between the phosphoric acid and the aldimine.[7b] The presence of a 2-hydroxyphenyl moiety on the aldimine is essential to achieve a high level of enantioselectivity, and the absence of a 2-hydroxyphenyl group on the aldimine resulted in lower yield and enantioselectivity (52% yield and 80% *ee*, respectively).[9]

However, in the case of more acidic but bulkier *N*-triflyl phosphoramides, free rotation of the triflyl group may prevent the formation of the cyclic transition state. A Mukaiyama–Mannich reaction catalyzed by *N*-triflyl phosphoramides might proceed through a different pathway (Figure 1). For example, catalyst **4g** was a very efficient catalyst for both 2-(benzylideneamino)phenol **1a** and *N*-Benzylideneaniline **5a**, affording the corresponding products with high enatioslelectivity (92% *ee* and 94% *ee*, respectively; Scheme 3). This result indicates that Mannich reactions

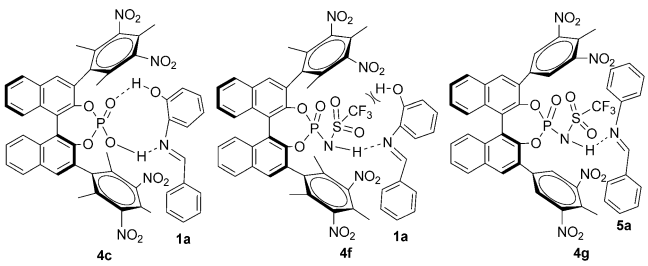
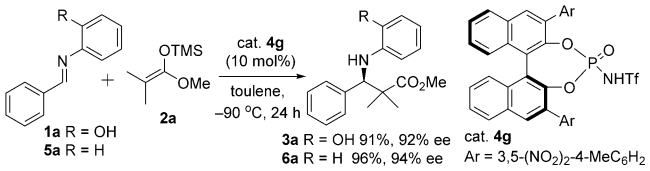


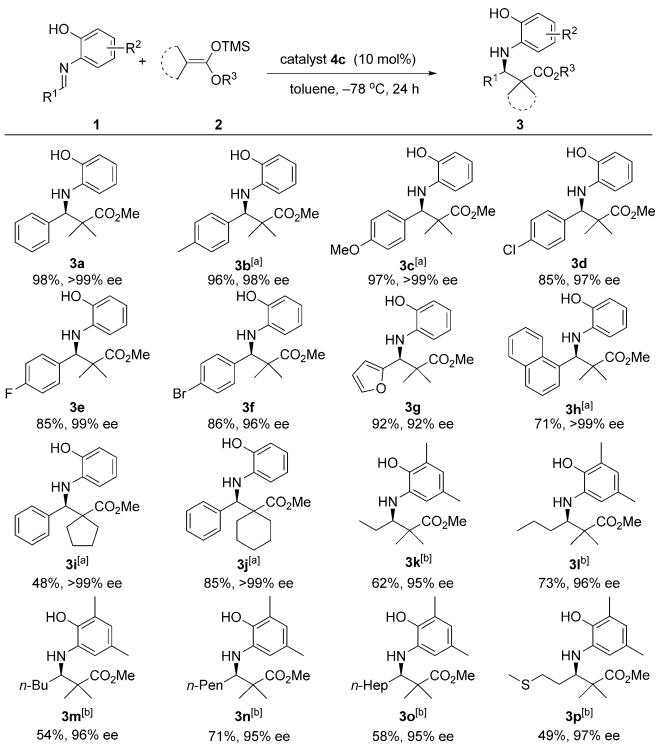
Figure 1. Proposed transition states of the reactions of aldimines with catalysts **4c**, **4f**, and **4g**.



Scheme 3. Enantioselective Mukaiyama–Mannich reactions catalyzed by *N*-trifly phosphoramide **4g**. Unless otherwise specified, all reactions were performed at −78 °C for 24 h under nitrogen with **1** (0.1 mmol, 1.0 equiv), **2a** (0.3 mmol, 3.0 equiv), catalyst **4g** (0.01 mmol, 10 mol%) in toluene (1 mL). Product *ee* values were determined by HPLC on a chiral stationary phase.

catalyzed by *N*-triflyl phosphoramides don't require the presence of a 2-hydroxyphenyl moiety on the aldimine to achieve high enantioselectivity.

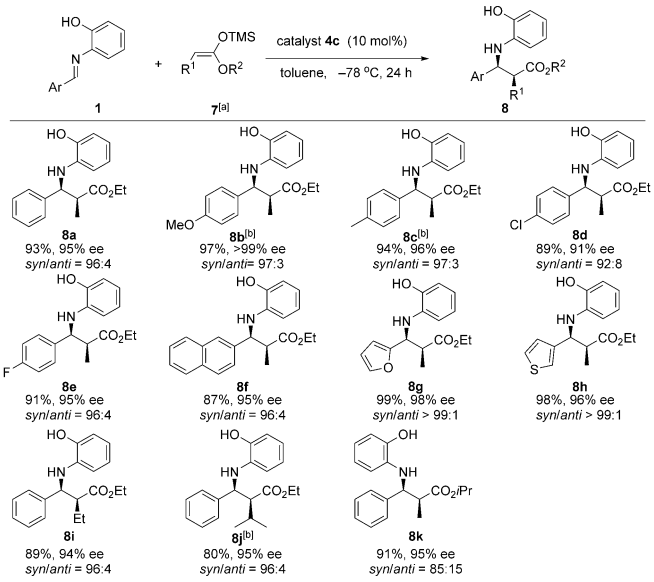
With the optimized reaction conditions in hand, the Mukaiyama–Mannich reaction catalyzed by phosphoric acid **4c** was extended to a series of imines and the ketene silyl acetal **2a**, and the results are shown in Scheme 4. Not only aldimines derived from aromatic aldehydes bearing either an electron-withdrawing group, such as F, Cl, Br, or an electron-



Scheme 4. Scope of the enantioselective Mukaiyama–Mannich reaction catalyzed by phosphoric acid **4c**. Unless otherwise specified, all reactions were performed at −78 °C for 24 h under nitrogen with **1** (0.1 mmol, 1.0 equiv), **2** (0.3 mmol, 3.0 equiv) and catalyst **4c** (0.01 mmol, 10 mol%) in toluene (1 mL). Product *ee* values were determined by HPLC on a chiral stationary phase. [a] −40 °C for 48 h. [b] The imine was prepared from the corresponding aldehyde (0.3 mmol, 1.5 equiv) and 6-amino-2,4-xylenol (0.2 mmol, 1.0 equiv) in situ in the presence of 4 Å MS. The reactions were carried out at −50 °C for 24 h.

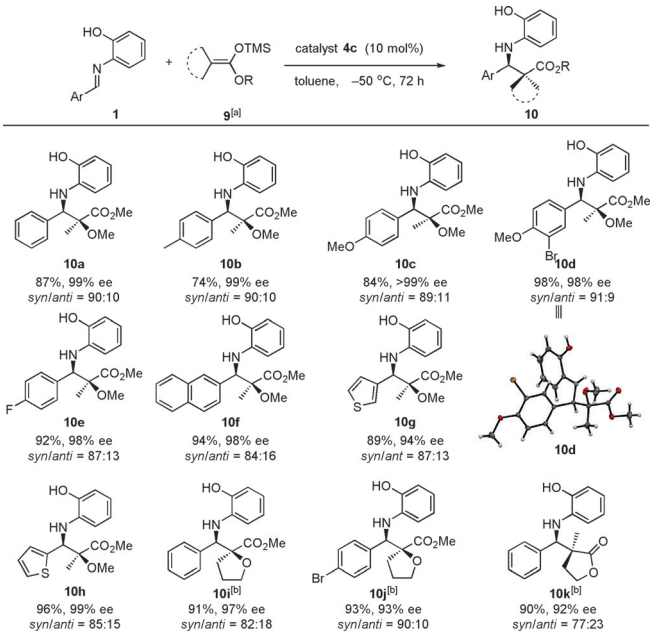
donating group such as OMe and Me, but also aldimines derived from heterocyclic or bulky aromatic aldehydes proceeded smoothly, giving the corresponding products **3a**–**3h** in good to high yields and with excellent enantioselectivity (92 to >99% *ee*). Furthermore, ketene silyl acetals **2b** and **2c**, which bear a cyclohexyl or cyclopentyl group, also afforded the products **3i** and **3j** in good yields and with excellent enantioselectivity (>99% *ee*). Significantly, imines derived from aliphatic aldehydes are very challenging substrates for the asymmetric Mukaiyama–Mannich reaction.[5,6d] To our delight, imines prepared from aliphatic aldehydes underwent successful asymmetric Mukaiyama–Mannich reaction to give the corresponding products in good yields and with excellent enantioselectivity.

Next, we tested monosubstituted ketene silyl acetals to achieve high diastereoselectivity and the results are shown in Scheme 5. The reaction of ketene silyl acetal **7a** ($E/Z = 9:1$) derived from ethyl propionate proceeded smoothly and the corresponding product **8a** was obtained in 95% *ee* and 96:4 (*syn*/*anti*). Aromatic aldimines bearing electron-donating or electron-withdrawing substituents gave the corresponding adducts **8b**–**8e** with good diastereoselectivity (*syn*/*anti* up to 97:3) and high enantioselectivity (91 to >99% *ee*). Furthermore, aldimines bearing a bulky aromatic ring or a heterocyclic ring were also tolerated and delivered the products **8f**–**8h** in good yields with excellent diastereoselectivity (*syn*/*anti* up to >99:1) and high enantioselectivity (up to 98% *ee*). Additionally, ketene silyl acetals derived from other esters were also suitable substrates and delivered the corresponding adducts **8i**–**8k** with high diastereoselectivity and excellent enantioselectivity.



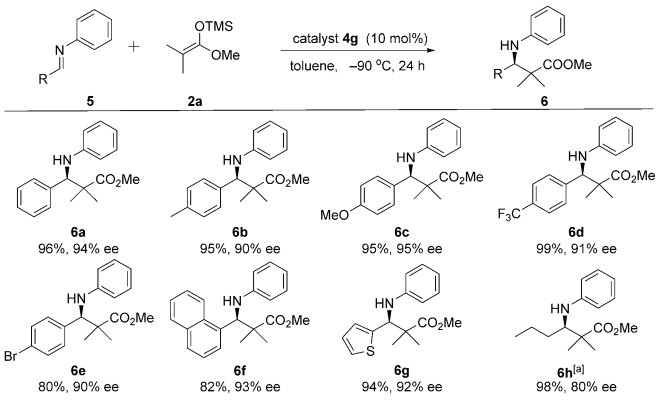
Scheme 5. Diastereoselective and enantioselective Mukaiyama–Mannich reactions. Unless otherwise specified, all reactions were performed at −78 °C for 24 h under nitrogen with **1** (0.1 mmol, 1.0 equiv), **7** (0.3 mmol, 3.0 equiv), catalyst **4c** (0.01 mmol, 10 mol%) in toluene (1 mL). Product *ee* values were determined by HPLC on a chiral stationary phase. The diasteroselectivit6 ratios were determined by ^{1}H NMR spectroscopy. [a] **7a**: R^1 = Me, R^2 = Et, E/Z = 90:10; **7b**: R^1 = Et, R^2 = Et, E/Z = 90:10; **7c**: R^1 = *i*Pr, R^2 = Et, E/Z = 91:9; **7d**: R^1 = Me, R^2 = *i*Pr, E/Z = 98:2; [b] −40 °C for 48 h.

Encouraged by these results, we expanded the substrate scope to more challenging ketene silyl acetals bearing two different substituents on the vinyl carbon, and the results are shown in Scheme 6. A ketene silyl acetal derived from methyl 2-methoxypropanoate furnished the product **10a**, which bears vicinal tertiary and quaternary stereogenic centers, in good yields and with excellent enantioselectivity. Aldimines bearing both electron-donating and electron-withdrawing group gave the adducts **10b**–**10d** with good diastereoselectivity (up to 91:9) and high enantioselectivity (up to >99% *ee*) The absolute configuration of the major isomer of **10d** was determined to be (2*S*, 3*R*) by X-ray analysis.[10] Aldimines derived from heterocyclic aldehydes were also suitable substrates, giving the adducts **10f** and **10h** with good enantioselectivity and diastereoselectivity. Furthermore, the ketene silyl acetals **9b** and **9c**, derived from 2-tetrahydrofuroic acid methyl ester and 2-methylbutanolide, were also applied to this process and delivered the products **10i**–**10k** in excellent enantioselectivity (up to 97% *ee*) and moderate to good diastereoselectivity (*syn*/*anti* up to 90:10).



Scheme 6. Construction of vicinal tertiary and quaternary stereogenic centers. Unless otherwise specified, all reactions were performed at −50 °C for 72 h under nitrogen with **1** (0.1 mmol, 1.0 equiv), **9** (0.3 mmol, 3.0 equiv), catalyst **4c** (0.01 mmol, 10 mol%) in toluene (1 mL). Product *ee* values were determined by HPLC on a chiral stationary phase. The diasteroselectivity ratios were determined by ^{1}H NMR spectroscopy. [a] **9a**: (1,2-dimethoxyprop-1-enyloxy)trimethylsilane, E/Z = 91:9; [b] −78 °C for 48 h.

However, the Mukaiyama–Mannich reaction catalyzed by chiral phosphoric acid required a 2-hydroxyphenyl moiety on the aldimine to achieve a high level of enantioselectivity. A



Scheme 7. Enantioselective Mukaiyama–Mannich reactions catalyzed by *N*-Tf phosphoramide. Unless otherwise specified, all reactions were performed at −90 °C for 24 h under nitrogen with **5** (0.1 mmol, 1.0 equiv), **2a** (0.3 mmol, 3.0 equiv), catalyst **4g** (0.01 mmol, 10 mol%) in toluene (1 mL). Product *ee* values were determined by HPLC on a chiral stationary phase. [a] The imine was prepared from butyraldehyde (0.3 mmol, 1.5 equiv) and aniline (0.2 mmol, 1.0 equiv) in situ in the presence of 4 Å MS. The reactions were carried out at −78 °C for 12 h.

more acidic *N*-triflyl phosphoramide **4g** presents a complementary strategy to this type of chemistry. The substrate scope of this catalyst system was investigated and the results are shown in Scheme 7. A wide range of aldimines gave products **6a–6e** in good yields and with excellent enantioselectivity. Additionally, the reaction of imines bearing a heterocyclic ring and or aliphatic substituent proceeded smoothly and the corresponding products **6f–6h** were obtained in high yields and with good enantioselectivity.

In summary, we have developed a new BINOL-derived chiral phosphoric acid bearing 2,4,6-trimethyl-3,5-dinitrophenyl substituents at the 3,3′-positions for highly enantioselective Mukaiyama–Mannich reactions. In the presence of this organocatalyst, both aromatic and aliphatic imines were well tolerated and delivered the corresponding β-amino-acid derivatives in good yields with high diastereo- and enantioselectivity. Furthermore, this method was successfully applied to more challenging ketene silyl acetals bearing two different substituents on the vinyl carbon, leading to adducts containing vicinal tertiary and quaternary stereogenic centers with excellent enantioselectivity and moderate to good diastereoselectivity in one step. Significantly, the long-standing problem of enantioselective Mukaiyama–Mannich reactions catalyzed by chiral phosphoric acids requiring a 2-hydroxyphenyl moiety on the aldimine was solved by taking advantage of a *N*-triflyl phosphoramide catalyst. The corresponding products were obtained in good yields and with high enantioselectivity. Intensive investigations into the application of this new class of chiral phosphoric acids are underway in our laboratory.

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Keywords: asymmetric catalysis · Brønsted acids · chiral phosphoric acids · Mukaiyama–Mannich reactions · quaternary stereogenic centers

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[9] Catalyst **4c** catalyzed the reaction of the aldimine *N*-Benzylideneaniline **5a** with **2a**, giving adduct **6a** in 52% yield and 80% *ee* at −90 °C after 48 h.

[10] The relative and absolute stereochemistry of the major isomer of **10d** was determined to be (2*S*, 3*R*) by X-ray crystallography (see the Supporting Information) and those of the others were surmised by analogy.

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