Asymmetric Catalysis

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# The Enantioselective, Brønsted Acid Catalyzed, Vinylogous Mannich Reaction**

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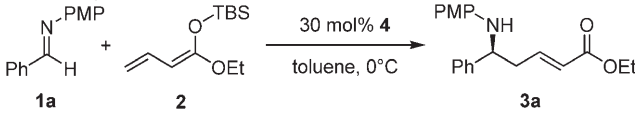
*Dedicated to Professor Peter Welzel*

Asymmetric Mannich reactions are among the most fundamental carbon–carbon bond forming reactions in organic chemistry, and the reaction products are versatile intermediates in the synthesis of chiral, enantiomerically enriched amines.[1] Vinylogous Mannich reactions of α,β-unsaturated carbonyl compounds, furnishing highly functionalized δ-amino α,β-unsaturated carbonyl compounds, have established themselves in natural product synthesis.[2] However, only very few catalytic, enantioselective versions have been devised, and these are limited to very special substrate patterns. Building on the results of Martin,[3] Hoveyda, Snapper, and Carswell developed silver-catalyzed, vinylogous Mannich reactions of 2-silyloxy furans, leading to highly enantiomerically enriched butenolides.[4] Chen and co-workers recently reported the first direct asymmetric vinylogous Mannich reaction of α,α-dicyanoalkenes and *tert*-butyloxycarbonyl (Boc)-protected imines with a bifunctional thiourea catalyst, leading to the corresponding products in high yields, excellent enantioselectivities, and complete γ-regioselectivity.[5] Jørgensen and Niess catalyzed the same reaction successfully under phase-transfer conditions with a chiral pyrrolidinium salt in up to 95% *ee*.[6]

Herein we report the first catalytic, enantioselective, vinylogous Mukaiyama–Mannich reactions of acyclic silyl dienolates and imines to furnish highly valuable δ-amino α,β-unsaturated carboxylic esters in high yields, complete regioselectivity and good to very good enantioselectivities. We employed a 2,2′-dihydroxy-1,1′-binaphthyl (binol)-based phosphoric acid as chiral catalyst of the same type which the groups of Akiyama and Terada introduced independently into asymmetric catalysis.[7] Such chiral Brønsted acids have proven to be exceptional chiral catalysts for a broad range of highly enantioselective imine addition reactions which involve chiral contact ion pairs generated in situ.[8–13] In this context, Akiyama and co-workers have already developed highly enantioselective normal Mannich reactions of silylketene acetals with Brønsted acid of this type.[7a,b]

As a model reaction, we chose the reaction of imine **1a** and TBS-substituted dienolate **2**,[14] which led to the vinylogous Mannich product **3a**, and investigated various phosphoric acids **4a–f** (each 30 mol%) in toluene at 0°C (Table 1 and Scheme 1). Phosphoric acids with bulky 3,3′-substituents in the binol backbone led to promising levels of enantioselectivity, with the 3,3′-bismesityl derivative **4e** being the most enantioselective chiral catalyst, and thus it was selected for further optimization studies (Table 1, entry 5). Coordinating solvents, such as THF and 1,4-dioxane, exhibited a positive effect on the enantioselectivity of the reaction and Mannich product **3a** was now obtained with e.r. 91:9 (Table 2, entries 3 and 4). Reaction times, however, remained long under these conditions and product yields were only moderate. On the other hand, alcohols as solvent increased the reaction rate to such an extent that reactions were complete within 1–2 h at 0°C or room temperature, respectively, with only 5 mol% of catalyst (Table 2, entries 5 and 6). The decrease in enantioselectivity which was initially observed was compensated

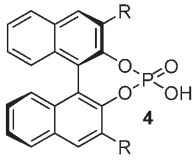
***Table 1:*** Optimization of chiral Brønsted acid **4**.[a]




**1a** **2** **3a**

| Entry | 4 | *t* [h] | e.r.[b] | Yield [%][c] |
|---|---|---|---|---|
| 1 | **4a** | 20 | 59:41 | 97 |
| 2 | **4b** | 52 | 53:47 | 70 |
| 3 | **4c** | 52 | 53:47 | 92 |
| 4 | **4d** | 120 | 81:19 | 77 |
| 5 | **4e** | 68 | 85:15 | 52 |
| 6 | **4f** | 92 | 70:30 | 40 |

[a] Reaction conditions: **1a** (1 equiv), **2** (3 equiv), **4** (30 mol%), 0°C, 0.16 M in toluene, PMP = *para*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl. [b] Determined by HPLC on chiral stationary phases (see the Supporting Information). [c] Yield of isolated product.




**4**

**4a:** R = H
**4b:** = 4-*t*BuC$_6$H$_4$
**4c:** = 3,5-(CH$_3$)$_2$C$_6$H$_3$
**4d:** = 9-anthracenyl
**4e:** = 2,4,6-(CH$_3$)$_3$C$_6$H$_2$
**4f:** = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$

***Scheme 1.*** 3,3′-Substituted phosphoric acids **4a–f** based on binol that were investigated.

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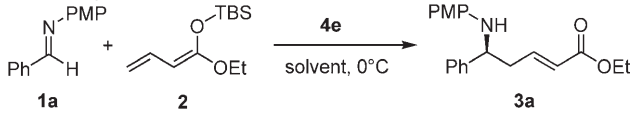
***Table 2:*** Optimization of reaction conditions.[a]




1a 2 3a

| Entry | Solvent | 4e [mol%] | t [h][b] | e.r.[c] | Yield [%][d] |
|---|---|---|---|---|---|
| 1 | toluene | 30 | 68 | 85:15 | 52 |
| 2 | $CH_2Cl_2$ | 30 | 68 | 75:25 | 56 |
| 3 | THF | 30 | 68 | 91:9 | 65 |
| 4 | 1,4-dioxane[e] | 30 | 68 | 91:9 | 68 |
| 5 | *n*BuOH | 5 | 1 | 72:28 | 91 |
| 6 | *t*BuOH[e] | 5 | 1 | 84:16 | 75 |
| 7 | *t*BuOH/1,4-dioxane 5:1 | 5 | 2 | 90:10 | 81 |
| 8 | THF/*t*BuOH/2-Me-2-BuOH 1:1:1[f] | 5 | 8 | 94:6 | 87 |

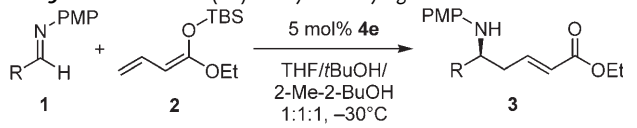
[a] Reaction conditions: **1a** (1 equiv), **2** (3 equiv), **4e** (5–30 mol%), 0.16 M. [b] Entries 1–4 were stopped after 68 h, entries 5–8 proceeded to >99% conversion (HPLC). [c] Determined by HPLC on chiral stationary phases (see the Supporting Information). [d] Yield of isolated product. [e] RT. [f] −30°C, $H_2O$ (1.0 equiv).

through the use of a solvent mixture of *t*BuOH/1,4-dioxane (5:1) (Table 2, entry 7). Optimal results were eventually obtained in a solvent mixture containing equal amounts of THF, *t*BuOH, and 2-Me-2-BuOH with 1 equiv of water, which allowed the reaction to proceed quantitatively within 8 h at −30°C with only 5 mol% of catalyst. Under these conditions, the vinylogous Mannich product **3a** was obtained in 87% yield, complete γ-regioselectivity, and an enantiomeric ratio of 94:6 (Table 2, entry 8).

The optimized procedure is broadly applicable to reactions with aromatic and heteroaromatic aldimines, which were converted into the corresponding vinylogous Mannich products **3a–o** in good to very good enantioselectivities (up to e.r. 96:4), and typically high yields (Table 3). The products contained exclusively *E* double bonds, and accordingly no cyclization to the corresponding 5,6-dihydro-2-pyridones was observed. Electron-rich aldimines required longer reaction times and afforded lower yields than electron-poor aldimines (see Table 3, entries 5 and 7). *Para*-substituted aldimines showed higher enantioselectivities than *ortho*- and *meta*-substituted aldimines. Also, an aliphatic, nonenolizable aldimine, such as pivalimine, afforded the corresponding vinylogous Mannich product **3o** in good yield and enantioselectivity (Table 3,entry 14).

To demonstrate the practicality of the process, the reaction of imine **1c** was performed with just 1.2 equiv of the silyl dienolate **2** and 5 mol% of phosphoric acid **4e** on a gram scale under otherwise identical conditions. Vinylogous Mannich product **3c** was obtained in 92% yield and e.r. 95:5 after 12 h at −30°C (Scheme 2). The reaction may also be performed as a three-component Mannich reaction with aldehyde, amine, and silyl dienolate as starting materials, as was demonstrated for the same reaction (Scheme 2). Mannich product **3c** was isolated in 93% yield and e.r. 96:4; thus, even slightly better results were obtained than with the preformed imine.

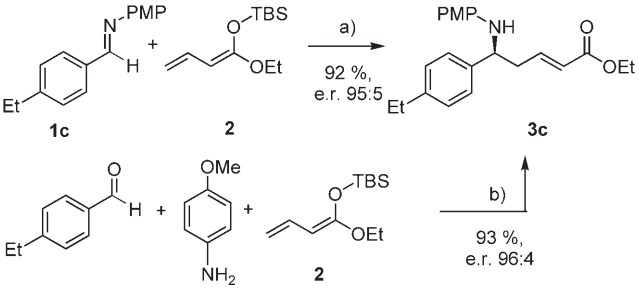
***Table 3:*** Brønsted acid (**4e**)-catalyzed vinylogous Mannich reactions.[a]




1 2 3

| Entry | R | 3 | t [h][b] | e.r.[c] | Yield [%][d] |
|---|---|---|---|---|---|
| 1 | Ph | **3a** | 8 | 94:6 | 87 |
| 2 | 4-$MeC_6H_4$ | **3b** | 4 | 95:5 | 89 |
| 3 | 4-$EtC_6H_4$ | **3c** | 3 | 96:4 | 88 |
| 4 | 4-$PentC_6H_4$ | **3d** | 6 | 95:5 | 92 |
| 5 | 4-$MeOC_6H_4$ | **3e** | 72 | 91:9 | 66 |
| 6 | 4-$FC_6H_4$ | **3f** | 5 | 91:9 | 93 |
| 7 | 4-$CNC_6H_4$ | **3g** | 1 | 91:9 | 94 |
| 8 | 3-$ClC_6H_4$ | **3h** | 2 | 91:9 | 94 |
| 9 | 3-$MeC_6H_4$ | **3i** | 6 | 90:10 | 90 |
| 10 | 2-Me-Ph | **3k** | 9 | 90:10 | 87 |
| 11 | 2-naphthyl | **3l** | 8 | 92:8 | 90 |
| 12 | 3-thiophenyl | **3m** | 6 | 92:8 | 92 |
| 13 | 3-furyl | **3n** | 7 | 95:5 | 88 |
| 14 | *t*Bu | **3o** | 48 | 91:9 | 83 |

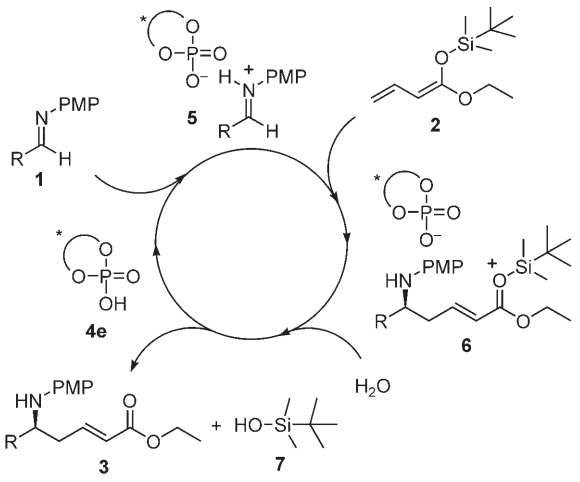
[a] Reaction conditions: **1** (1 equiv), **2** (3 equiv), **4e** (5 mol%), −30°C, 0.16 M in THF/*t*BuOH/2-Me-2-BuOH (1:1:1), $H_2O$ (1.0 equiv), TBS = *tert*-butyldimethysilyl. [b] Conversion >99% (HPLC). [c] Determined by HPLC on chiral stationary phases (see the Supporting Information). [d] Yield of isolated product.




***Scheme 2.*** a) **1c** (1.15 g, 1.0 equiv), **2** (1.30 g, 1.2 equiv), **4e** (5 mol%), −30°C, 12 h, 30 mL THF/*t*BuOH/2-Me-2-BuOH (1:1:1), $H_2O$ (1.0 equiv). b) Aldehyde (1.0 equiv), amine (1.0 equiv), **2** (3.0 equiv), **4e** (5 mol%), −30°C, 3 h, 6 mL THF/*t*BuOH/2-Me-2-BuOH (1:1:1), $H_2O$ (1.0 equiv), PMP = *para*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl.

Our optimized reaction conditions are distinctly different from the procedure which Akiyama et al. developed for the normal Mannich reaction. In particular, the use of the 2-hydroxyphenyl group as imine substituent had proven to be essential for obtaining high enantioselectivities in the normal Mannich reaction, which was rationalized through a double coordination of the phosphoric acid to the imine.[7a,b] In the vinylogous Mannich reaction reported herein, however, such an imine afforded the product with no enantioselectivity under our conditions.[15] We assume that in the first step of the catalytic cycle a chiral contact ion pair **5** is formed through monocoordination of phosphoric acid **4e** to imine **1** (Scheme 3). Subsequently, silyl dienolate **2** adds to contact ion pair **5** in the carbon–carbon bond-forming process and generates contact ion pair **6** which is converted into product **3** and silanol **7** through the aqueous solvent, whereupon chiral




***Scheme 3.*** Proposed catalytic cycle.

phosphoric acid **4e** is regenerated. To shed some light on this issue, we followed the synthesis of vinylogous Mannich product **3a** (R = Ph) by mass spectrometry. Through ESI(+)-MS/MS, contact ion pair **6a** was clearly detected and also structurally characterized.[16] In addition, using online NMR experiments, the quantitative formation of silanol **7** was observed in the same reaction.

In conclusion, we have described the first catalytic, enantioselective, vinylogous Mannich reaction of acyclic silyl dienolates, furnishing valuable δ-amino α,β-unsaturated carboxylic esters in high yields, complete regioselectivity and good to very good enantioselectivities. Although an excess of nucleophile has been typically employed for the purpose of increasing the reaction rate, almost identical results have been obtained with a nearly stoichiometric ratio of reactants and longer reaction times. The process is further facilitated by the discovery that it may be executed successfully as a three-component Mannich reaction, which avoids the need to synthesize the imine in a separate step.[18]

## *Experimental Section*

General procedure: Aldimine **1c** (96 mg, 0.40 mmol, 1.0 equiv) and catalyst **4e** (12 mg, 0.02 mmol, 5 mol%) were dissolved in 2.5 mL of a solvent mixture (THF/*t*BuOH/2-Me-2-BuOH 1:1:1 and 1.0 equiv $H_2O$) and cooled to −30 °C. After 1 min silyl dienolate **2** (274 mg, 1.20 mmol, 3.0 equiv) was added in one portion, whereupon the reaction mixture was stirred for 3 h at −30 °C. The solvents were removed in vacuo and the crude product was purified by flash chromatography ($SiO_2$, diethyl ether/petroleum ether 1:5) to afford 124 mg (88%, e.r. 96:4) of (2*E*, 5*S*)-**3c**. The enantiomeric ratio was determined by HPLC on a chiral stationary phase (see the Supporting Information).[17]

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[1] Reviews: a) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; b) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; c) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; d) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797.

[2] Reviews: a) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929; b) S. K. Bur, S. F. Martin, *Tetrahedron* **2001**, *57*, 3221; c) S. F. Martin, *Acc. Chem. Res.* **2002**, *35*, 895; d) for a conceptually different approach towards vinylogous Mannich products, see M. Lautens, E. Tayama, D. Nguyen, *Org. Lett.* **2004**, *6*, 345.

[3] S. F. Martin, O. D. Lopez, *Tetrahedron Lett.* **1999**, *40*, 8949.

[4] E. L. Carswell, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2006**, *118*, 7388; *Angew. Chem. Int. Ed.* **2006**, *45*, 7230.

[5] T.-Y. Liu, H.-L. Cui, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 1878.

[6] B. Niess, K. A. Jørgensen, *Chem. Commun.* **2007**, 1620.

[7] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756; c) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; d) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360; see also: e) Q-X Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu, L.-Z. Gong, *J. Am. Chem. Soc.* **2007**, *129*, 3790.

[8] Reviews: a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; b) S. J. Connon, *Angew. Chem.* **2006**, *118*, 4013; *Angew. Chem. Int. Ed.* **2006**, *45*, 3909; c) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744, and references therein.

[9] Reduction of imines with Hantzsch esters: see, for example, a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; b) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84; d) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; e) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074; f) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830; g) M. Rueping, A. P. Antonchick, *Angew. Chem.* **2007**, *119*, 4646; *Angew. Chem. Int. Ed.* **2007**, *46*, 4562.

[10] Aza Diels–Alder reactions with imines: see, for example, a) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; b) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070; c) T. Akiyama, Y. Tamura, J. Itoh, H. Morita, K. Fuchibe, *Synlett* **2006**, 141.

[11] Friedel–Crafts reactions with imines: see, for example, a) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804; b) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292; c) G. B. Rowland, E. B. Rowland, Y. Liang, J. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 2609; d) G. Li, G. B. Rowland, E. B. Rowland, J. C. Antilla, *Org. Lett.* **2007**, *9*, 4065.

[12] For a selection of further applications with imines see: a) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254; b) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; c) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802; d) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086; e) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903; f) M. J. Wanner, R. N. S. van der Haas, K. R. de Cuba, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2007**, *119*, 7629: *Angew. Chem. Int. Ed.* **2007**, 46, 7485.

[13] For a selection of other applications, see: a) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299; *Angew. Chem. Int. Ed.* **2006**, *45*,

  

4193; b) M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem.* **2007**, *119*, 2143; *Angew. Chem. Int. Ed.* **2007**, *46*, 2097; c) E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 12084; d) X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 1135; *Angew. Chem. Int. Ed.* **2008**, *47*, 1119; e) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, *120*, 603; *Angew. Chem. Int. Ed.* **2008**, *47*, 593.

[14] S. E. Denmark, G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800.

[15] Imines with different nitrogen substituents afforded the following e.r.: 2-$HOC_6H_4$ 50:50, 2-$MeOC_6H_4$ 66:34, Ph 95:5, 4-$MeC_6H_4$ 94:6.

[16] Contact ion pair **6a** ($m/z = 1024$) cleanly fragments during collision experiments in the ion trap into product **3a** ($m/z = 326$) and the silyl ester of phosphoric acid **4e** ($m/z = 699$).

[17] The absolute configuration of the products was assigned by conversion of the related ethyl (2*E*,5*S*)-5-phenylamino-5-(4-chlorophenyl)-2-pentenoate (e.r. 92:8) into the saturated acid followed by comparison of the rotation value with reported data (see the Supporting Information).

[18] Note added in proof: Akiyama et al. reported on a phosphoric acid catalyzed, vinylogous Mannich reaction of 2-silyloxyfurans: T. Akiyama, Y. Honma, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2008**, *350*, 399.

  