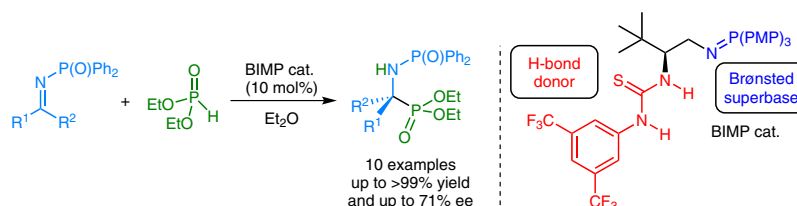


# Bifunctional Iminophosphorane Catalyzed Enantioselective Ketimine Phospha-Mannich Reaction

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Dedicated to Professor Steven V. Ley on the occasion of his 70<sup>th</sup>  
birthday



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**Abstract** The enantioselective phospha-Mannich reaction of diethyl phosphite to unactivated *N*-DPP-protected ketimines catalyzed by a bifunctional iminophosphorane (BIMP) superbase organocatalyst is described. The reaction is applicable to ketimines bearing electron-rich and electron-poor aryl substituents and occurs with excellent yields and moderate enantioselectivities under mild reaction conditions.

**Key words** asymmetric catalysis, bifunctional organocatalysis, phospha-Mannich, ketimine, superbase

$\alpha$ -Aminophosphonic acid derivatives are  $\alpha$ -amino acid analogues that have found widespread use as biologically relevant peptide mimics<sup>1</sup> and have shown a range of biological activities such as antibacterial,<sup>2a,b</sup> anti-HIV<sup>2c,d</sup> and protease inhibition.<sup>2e,f</sup> As important biological building blocks, their absolute configuration is significant and accordingly new improved methods for their enantioselective synthesis is desirable.<sup>3</sup>

A direct approach to access such compounds is through the 1,2-addition of phosphite pro-nucleophiles to imine electrophiles.<sup>4</sup> These reactions can be catalyzed by Brønsted bases and chiral Brønsted bases can be used to impart enantioselectivity.<sup>5</sup> To date, much attention has focussed on asymmetric phospha-Mannich reactions to imine electrophiles derived from aldehydes (aldimines) and highly enantioselective examples using both metal-rich and metal-free catalyst systems have been reported.<sup>6</sup> In the latter case the emphasis has been largely placed on the development of methodologies using bifunctional single enantiomer tertiary amine Brønsted base/H-bond donor organocatalysts.<sup>5</sup> In contrast, the corresponding reaction of ketimines has been much less studied due to their substantially reduced electrophilicity and the difficulties associated with poor cata-

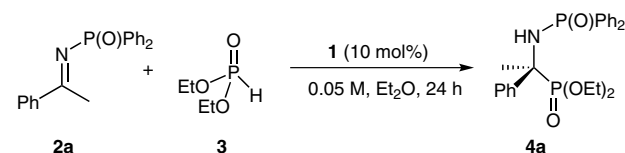
lyst-enabled substrate activation and enantioface discrimination;<sup>7</sup> a problem that necessitates the use of metal ion catalysts, stoichiometric additives or the use of activated ketimine electrophiles. For example, Shibasaki and co-workers reported the highly enantioselective *N*-thiophosphinoyl ketimine phospha-Mannich reaction under copper(I) catalysis,<sup>8a</sup> whereas Nakamura et al. used catalytic quantities of commercially available cinchona alkaloids in the presence of super stoichiometric quantities of Na<sub>2</sub>CO<sub>3</sub>, for the enantioselective addition of diethyl phosphite to *N*-mesitylene sulfonyl protected ketimines.<sup>8b</sup> Very recently, Chimni and co-workers and Reddy and co-workers described the catalytic enantioselective phospha-Mannich reaction of reactive isatin-derived ketimines catalyzed by bifunctional cinchona-derived thiourea and squaramide catalysts, respectively.<sup>8c,d</sup>

In an attempt to overcome the reactivity problem of certain classes of electrophiles and pro-nucleophiles, we recently developed a new class of bifunctional superbase organocatalysts incorporating for the first time the triaryliminophosphorane moiety as the Brønsted base and with it achieved the first general enantioselective organocatalytic ketimine nitro-Mannich reaction.<sup>9</sup> The juxtaposition of both the organosuperbase<sup>10</sup> and an appropriate hydrogen bond donor group over a chiral scaffold was critical for successful enantioselective catalysis (high reactivity and enantiocontrol). As a part of this program into the development of novel asymmetric methodologies for challenging electrophiles, we wish to report the first organocatalytic enantioselective phospha-Mannich reaction of unactivated *N*-DPP ketimines.

We chose the 1,2-addition of diethyl phosphite **3** to the unactivated *N*-DPP-protected ketimine derived from acetophenone **2a** as our model system for testing the performance of our bifunctional iminophosphorane (BIMP) catalysts (Table 1 and Figure 1). Promising reactivity was initial-

ly established using 10 mol% of our previously reported first-generation *tert*-leucine derived BIMP catalyst **1a** with triphenylphosphine (Table 1, entry 1). After just 24 hours at room temperature, 74% yield of product **4a** was afforded with an encouraging ee of 56%. However, switching to the analogous but more basic catalyst **1b** derived from tris(*p*-methoxyphenyl)phosphine gave rise to a significant boost in reactivity and a slight boost in enantiocontrol; adduct **4a** was afforded in quantitative yield and with 58% ee (Table 1, entry 2). The analogous L-phenylalanine or L-valine-derived catalysts, **1c** and **1d** respectively, resulted in a drop in enantioselectivity in both cases (Table 1, entries 3 and 4). Employing catalyst **1e**, possessing the diphenylmethyl group as part of its chiral scaffold, resulted in a drop in the enantioselectivity to 23% ee (Table 1, entry 5). Simple modification of the thiourea hydrogen bond donor group of the first-generation BIMP organocatalysts led to no improvement in the level of enantiocontrol (Table 1, entries 6 and 7), and accordingly alternative second-generation BIMP organocatalyst designs were considered. Introducing an additional amino acid residue<sup>11</sup> between the iminophosphorane moiety and Schreiner-type thiourea<sup>12</sup> allowed diastereomers **1h** and **1j** to be synthesized and compared in the reaction. Interestingly neither catalyst outperformed **1b**, but taken together showed that the valine residue in both catalysts was dominating enantioselectivity (Table 1, entries 8 and 10). Building on these observations catalyst **1i** was tested in

**Table 1** Proof of Concept and Optimization Studies in the Ketimine Phospha-Mannich Reaction<sup>a</sup>



Entry	Catalyst	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>1a</b>	74	56
2	<b>1b</b>	99	58
3	<b>1c</b>	60	45
4	<b>1d</b>	85	47
5	<b>1e</b>	>99	23 <sup>d</sup>
6	<b>1f</b>	>99	51
7	<b>1g</b>	84	8
8	<b>1h</b>	>99	55
9	<b>1i</b>	70	42
10	<b>1j</b>	41	17 <sup>d</sup>

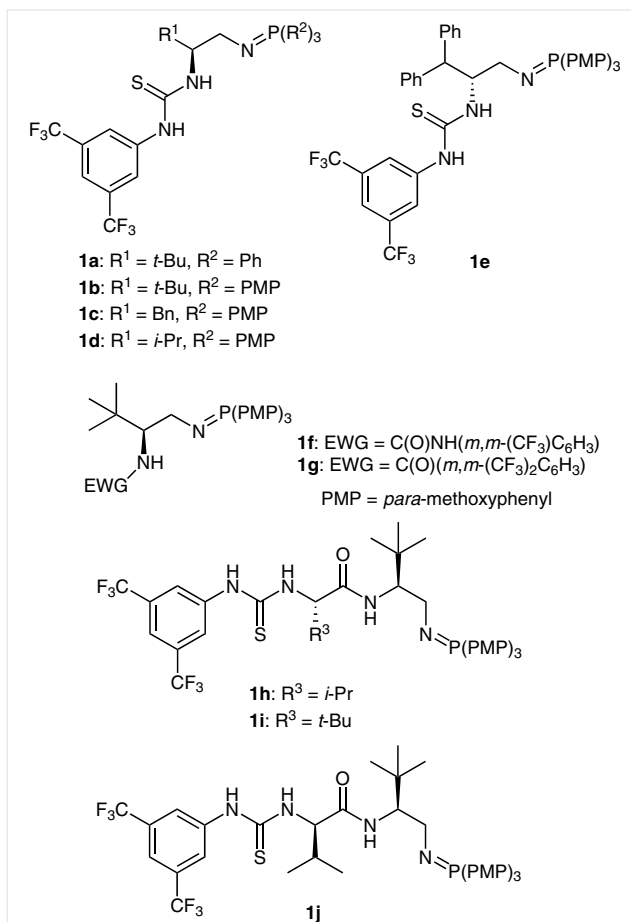
<sup>a</sup> Reactions were performed using **3** (0.20 mmol), **2a** (2.0 equiv) and catalyst (10 mol%).

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by HPLC analysis on a chiral stationary phase.

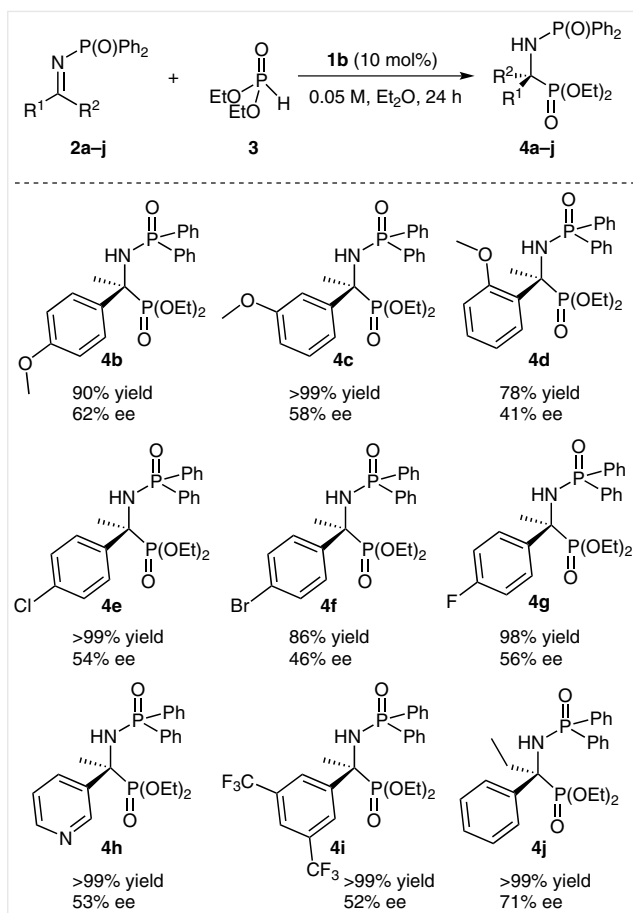
<sup>d</sup> Enantiomer (*R*)-**4a** was obtained.

the reaction in the hope that an additional boost in selectivity would be witnessed, but disappointingly enantioselectivity was reduced to 42% ee (Table 1, entry 9). Having identified the best catalyst as **1b**, a brief re-optimization of the reaction conditions, with respect to solvent, concentration and temperature, was carried out but no augmentation of the enantioselectivity was observed and the optimal conditions remained the same as for Table 1, entry 2.<sup>13</sup>



**Figure 1** First- and second-generation BIMP catalysts

With optimized conditions in hand, we next investigated the substrate scope and found good tolerance over a range of electron-rich and electron-deficient aromatic ketimines: yields were typically >99% and enantioselectivities ranged from 41 to 62% ee (Scheme 1). Furthermore, a 3-pyridyl substrate performed well (>99% yield, 53% ee) and pleasingly the reaction was also applicable to the ethyl homologue of **2a** which afforded product **4j** in 71% ee and in quantitative yield. Absolute configuration of **4a** was established as *S* by comparison of the specific rotation of a derivative with that of a literature compound (see Supporting Information).



**Scheme 1** Scope of the BIMP-catalyzed phospho-Mannich reaction<sup>a</sup>

In summary we have developed an organocatalytic ketimine phospho-Mannich reaction of diethyl phosphite to unactivated *N*-DPP ketimines with excellent yields and moderate enantioselectivities. Further work focussing on the development of novel asymmetric methodologies for challenging electrophiles is ongoing in our group and the results will be disclosed in due course.

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## Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1560530>.

## References and Notes

- (a) Hiratake, J.; Oda, J. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211. (b) *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P.; Hudson, H. R., Eds.; John Wiley & Sons: New York, **2000**.
- (a) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassal, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature (London)* **1978**, *272*, 56. (b) Atherton, F. R.; Hassal, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29. (c) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625. (d) Alonso, E.; Solis, A.; del Pozo, C. *Synlett* **2000**, 698. (e) Hirschmann, R.; Smith, A. B. III.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234. (f) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4622.
- (a) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29. (b) Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17. (c) Albrecht, L.; Albrecht, A.; Krawczyk, H.; Jørgensen, K. A. *Chem. Eur. J.* **2010**, *16*, 28. (d) Bera, K.; Nambhothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234. (e) Kolodiazhnyi, O. I.; Kukhar, V. P.; Kolodiazhna, A. O. *Tetrahedron: Asymmetry* **2014**, *25*, 865. (f) Faisca Phillips, A. M. *Mini-Rev. Org. Chem.* **2014**, *11*, 164. (g) Dziegielewski, M.; Pieta, J.; Kaminska, E.; Albrecht, L. *Eur. J. Org. Chem.* **2015**, 677.
- (a) Merino, P.; Marqués-López, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195. (b) Angelini, T.; Bonollo, S.; Lanari, D.; Pizzo, F.; Vaccaro, L. *Org. Biomol. Chem.* **2013**, *11*, 5042.
- For reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, **2005**. (c) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584. (d) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. (e) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (f) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632. For reviews on Brønsted base/H-bond donor bifunctional organocatalysts, see: (g) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (h) Connon, S. J. *Chem. Commun.* **2008**, 2499. (i) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229. (j) Quintavella, A.; Cerisoli, L.; Montroni, E. *Current Organocatalysis* **2014**, *1*, 107.
- For selected examples using metals, see: (a) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (b) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 10521. (c) Huang, M.; Li, C.; Huang, J.; Duan, W.-L.; Xu, S. *Chem. Commun.* **2012**, 48, 11148. For selected examples using organocatalysts, see: (d) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. J. *Org. Chem.* **2006**, *71*, 6269. (e) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (f) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (g) Nakamura, S.; Nakashima, H.; Sugimoto, H.; Sano, H.; Hattori, M.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2008**, *14*, 2145. (h) Fu, X.; Loh, W.-T.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H.; Wang, J.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2009**, *48*, 7387.
- (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (b) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.
- (a) Yin, L.; Bao, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2013**, *135*, 10338. (b) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, *131*, 18240. (c) Kumar, A.; Sharma, V.; Kaur, J.; Kumar, V.; Mahajan, S.; Kumar, N.; Chimni, S. S. *Tetrahedron* **2014**, *70*, 7044. (d) George, J.; Sridhar, B.; Reddy, B. V. S. *Org. Biomol. Chem.* **2014**, *12*, 1595.

- (9) (a) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348. (b) Goldys, A. M.; Núñez, M. G.; Dixon, D. J. *Org. Lett.* **2014**, *16*, 6294. (c) Goldys, A. M.; Dixon, D. J. *Macromolecules* **2014**, *47*, 1277.
- (10) (a) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Wiley: New York, **2009**. For a review on chiral organosuperbases, see: (b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737. (c) Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, *4*, 488. (d) Leow, D.; Tan, C.-H. *Synlett* **2010**, 1589. (e) Ishikawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 1555. (f) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210. (g) Selig, P. *Synthesis* **2013**, *45*, 703. (h) Krawczyk, H.; Dziegielewska, M.; Deredas, D.; Albrecht, A.; Albrecht, Ł. *Chem. Eur. J.* **2015**, *21*, 10268. For recent selected examples, see: (i) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (j) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (k) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (l) Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 7299. (m) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210. (n) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552. (o) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306. (p) İşik, M.; Unver, M. Y.; Tanyeli, C. *J. Org. Chem.* **2015**, *80*, 828. (q) Gao, X.; Han, J.; Wang, L. *Org. Lett.* **2015**, *17*, 4596.
- (11) Zhu, Q. A.; Lu, Y. X. *Angew. Chem. Int. Ed.* **2010**, *49*, 7753.
- (12) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.
- (13) **Representative Procedure for the Enantioselective Ketimine Phospha-Mannich Reaction:** To a solution of ketimine **2a** (128 mg, 0.40 mmol, 2.0 equiv) and catalyst **1b** (15 mg, 0.020 mmol, 0.10 equiv in 4.0 mL of diethyl ether) was added diethyl phosphite **3** (26  $\mu$ L, 0.20 mmol, 1.0 equiv) at rt. Stirring was maintained for 24 h whereupon the crude reaction mixture was purified directly by flash column chromatography [petroleum ether to petroleum ether–EtOAc (1:2), EtOAc then EtOAc–MeOH (9:1)] to afford the phospha-Mannich addition product **4a**. **Diethyl {(1S)-1-[(Diphenylphosphoryl)amino]-1-phenylethyl}phosphonate (4a):** The title compound **4a** was isolated in 99% yield (91 mg) and 58% ee as a colorless solid.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.03 (t,  $J$  = 7.0 Hz, 3 H), 1.25 (t,  $J$  = 7.0 Hz, 3 H), 1.82 (d,  $J_{\text{PH}}$  = 17.0 Hz, 3 H), 3.53 (ddq,  $J$  = 10.0, 7.0, 7.0 Hz, 1 H), 3.81 (ddq,  $J$  = 10.0, 7.0, 7.0 Hz, 1 H), 4.03–4.20 (m, 3 H), 7.18–7.30 (m, 5 H), 7.31–7.47 (m, 4 H), 7.51 (dd,  $J$  = 7.5, 1.5 Hz, 2 H), 7.55–7.64 (m, 2 H), 7.82–7.91 (m, 2 H).  $^{31}\text{P NMR}$  (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 20.1 ( $J_{\text{PP}}$  = 29.3 Hz), 24.8 ( $J_{\text{PP}}$  = 29.3 Hz). HRMS: (ESI $^+$ ):  $m/z$  calcd for  $\text{C}_{24}\text{H}_{29}\text{NNaO}_4\text{P}_2$ : 480.1464; found: 480.1454. See Supporting Information for full characterization data.