

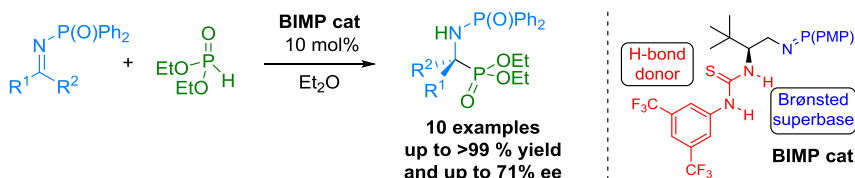
Bifunctional Iminophosphorane Catalyzed Enantioselective Ketimine Phospha-Mannich Reaction

Gerard P. Robertson^a
Alistair J. M. Farley^a
Darren J. Dixon^{*a}

^a The Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, U.K.

darren.dixon@chem.ox.ac.uk

Dedicated to Professor Steven V. Ley on the occasion of his 70th 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

α -Aminophosphonic acid derivatives are α -amino acid analogues that have found widespread use as biologically relevant peptide mimics¹ and have shown a range of biological activities such as anti-bacterial,^{2a,b} anti-HIV^{2c,d} and protease inhibition.^{2e,f} As important biological building blocks, their absolute configuration is significant and accordingly new improved methods for their enantioselective synthesis is desirable.³

A direct approach to access such compounds is through the 1,2-addition of phosphite pro-nucleophiles to imine electrophiles.⁴ These reactions can be catalyzed by Brønsted bases and chiral Brønsted bases can be used to impart asymmetry into the products.⁵ 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.⁶ 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. In contrast, the corresponding reaction of ketimines has been much less studied due to their substantially reduced electrophilicity and the difficulties associated with poor catalyst-enabled substrate activation and enantioface

discrimination;⁷ a problem that necessitates the use of metal ion catalysts, stoichiometric additives or the use of activated ketimine electrophiles. For example, Shibasaki *et al.* reported the highly enantioselective *N*-thiophosphinoyl ketimine phospha-Mannich reaction under copper(I) catalysis,^{8a} whereas Nakamura used substoichiometric quantities of commercially available cinchona alkaloids in the presence of super stoichiometric quantities of Na₂CO₃ for the enantioselective addition of diethyl phosphite to *N*-mesitylene sulfonyl-protected ketimines.^{8b} Very recently, Chimni *et al.* and Reddy *et al.* described the catalytic enantioselective phospha-Mannich reaction of reactive isatin-derived ketimines catalyzed by bifunctional cinchona-derived thiourea and squaramide catalysts respectively.^{8c,d}

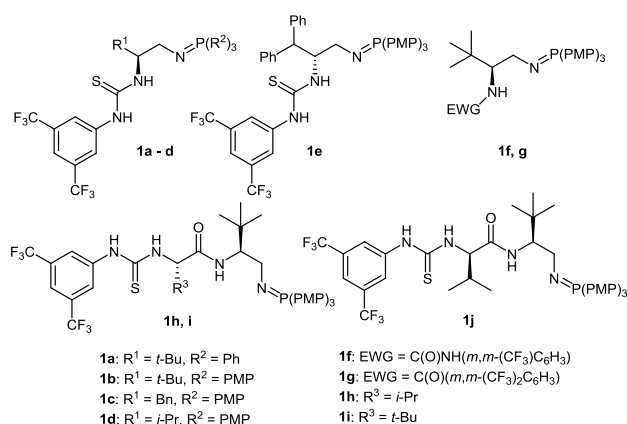
Table 1 Proof of concept and optimization studies in the ketimine phospha-Mannich reaction^a

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

^aReactions performed using 0.20 mmol of **3**, 2.0 eq of **2a** and 10 mol% catalyst. ^bIsolated yield. ^cDetermined by HPLC analysis on a chiral stationary phase. ^dEnantiomer (*R*)-**4a** obtained.

In an attempt to overcome the reactivity problem of certain classes of electrophiles and pro-nucleophiles, we recently developed a new class of bifunctional superbases organocatalysts incorporating for the first time the triarylaminophosphorane moiety as the Brønsted base and with it achieved the first general enantioselective organocatalytic ketimine nitro-Mannich reaction.^{9,10} The juxtaposition of both the organosuperbase 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 phospho-Mannich reaction of unactivated *N*-DPP ketimines.

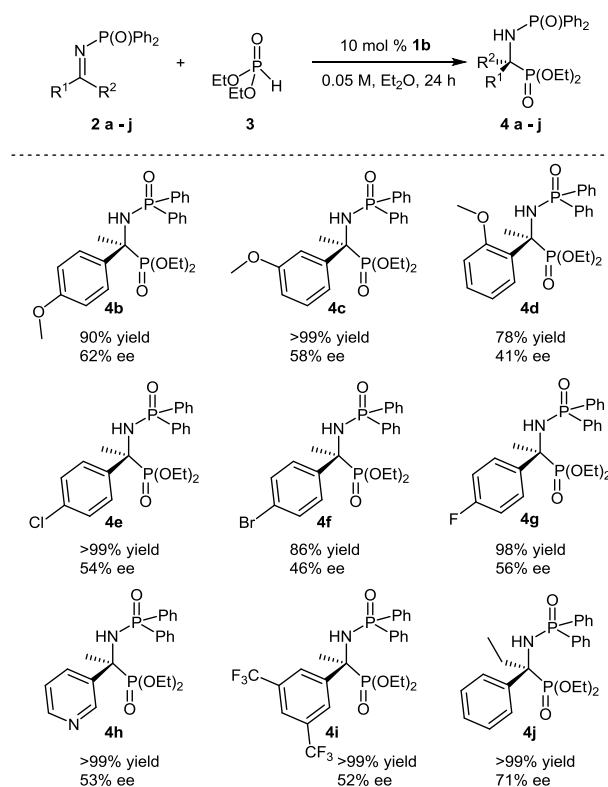
Figure 1 1st and 2nd generation BIMP catalysts



We chose the 1,2-addition of diethyl phosphite **3a** to the unactivated *N*-DPP-protected ketimine of acetophenone **2a** as our model system. Promising reactivity was initially established using 10 mol % of our previously reported 1st generation *tert*-leucine derived BIMP catalyst **1a** derived from triphenylphosphine (Table 1, entry 1). After just 24 hours at rt, 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 1st generation BIMP organocatalysts led to no improvement in the level of enantiocontrol, (Table 1, entries 6 and 7) and accordingly alternative 2nd generation BIMP organocatalyst designs were considered. Introducing an additional amino acid residue¹¹ between the iminophosphorane moiety and Schreiner-type thiourea¹² 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 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 2.¹³

Table 2 Scope of the BIMP catalyzed phospho-Mannich reaction^a



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 41–62% ee). Furthermore, a 3-pyridyl substrate performed well (>99% yield, 53% ee) and pleasingly the reaction was also applicable to the ethyl homologue 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).

In summary we have developed an organocatalytic ketimine phospho-Mannich reaction of phosphite pro-nucleophiles 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.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at xx

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

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- (13) **Representative procedure for the enantioselective ketimine phospho-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) was added diethyl phosphite **3** (26 µL, 0.20 mmol, 1.0 equiv) at rt. Stirring was maintained for 24 h whereupon the reaction mixture was purified by flash column chromatography [petroleum ether to petroleum ether/EtOAc 1:2, EtOAc then EtOAc: MeOH 9:1] to afford the phospho-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 colourless solid. ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.03 (t, J = 7.0 Hz, 3 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.82 (d, J_{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); ³¹P NMR (CDCl₃, 162 MHz) δ (ppm): 20.1 (J_{PP} = 29.3 Hz), 24.8 (J_{PP} = 29.3 Hz); HRMS (ESI+) calcd. for C₂₄H₂₉NNaO₄P₂ 480.1464, found 480.1454. See Supporting Information for full characterization data.