JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Bifunctional Iminophosphorane Organocatalysts for Enantioselective Synthesis: Application to the Ketimine Nitro-Mannich Reaction

Marta G. Núñez, Alistair J. M. Farley, and Darren J. Dixon*

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

Supporting Information

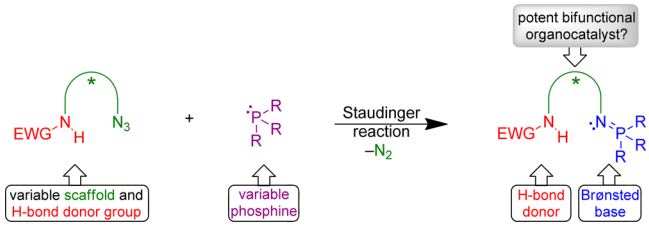
ABSTRACT: The design, synthesis, and development of a new class of modular, strongly basic, and tunable bifunctional Brønsted base/H-bond-donor organocatalysts are reported. These catalysts incorporate a triarylimino-phosphorane as the Brønsted basic moiety and are readily synthesized via a last step Staudinger reaction of a chiral organoazide and a triarylphosphine. Their application to the first general enantioselective organocatalytic nitro-Mannich reaction of nitromethane to unactivated ketone-derived imines allows the enantioselective construction of β-nitroamines possessing a fully substituted carbon atom. The reaction is amenable to multigram scale-up, and the products are useful for the synthesis of enantiopure 1,2-diamine and α-amino acid derivatives.

The addition of a carbon- or heteroatom-centered acid to an electron-deficient carbon−carbon (C═C) or carbon−heteroatom (C═X) double bond is a reaction of fundamental importance in organic synthesis. Such reactions offer perfect atom economy, are often energetically favorable, and can generate products that are chiral.[1] Brønsted basic reagents can be employed to catalyze the addition by generating the ion-paired conjugate base as the key nucleophilic entity, and asymmetry in the Brønsted base can relay through to the product via energetically discriminated transition states.[2] To this end, a plethora of chiral single-enantiomer Brønsted bases have been developed for a wide range of enantioselective addition reactions. These range from relatively weak chiral tertiary amines to organic superbases[3] such as amidines,[4] guanidines,[5] phosphazenes,[6] and cyclopropenimines.[7]

Within the past decade, one particular class of base that has received considerable attention is that of the bifunctional Brønsted base/H-bond donor organocatalyst.[8] These catalysts typically possess both a tertiary amine group and a hydrogen-bond donor group appropriately positioned on a chiral scaffold. Additional organization of the transition structure through stabilization of developing negative charge by the H-bond donor can result in increased reaction rates and/or enantioselectivity relative to H-bond donor free analogues.[9] Although this class continues to demonstrate synthetic utility, it is not without its limitations; reaction times are often long even with the most reactive reagent combinations, and arguably the range of pro-nucleophiles and electrophiles amenable to asymmetric union is relatively narrow. This low catalytic activity often stems from the relatively weak Brønsted basicity of the tertiary amine moiety, providing insufficient activation of the pro-nucleophile. To address some of these limitations, we proposed to develop a new class of bifunctional organocatalysts that possessed a much stronger and tunable Brønsted basic group. Our hope was that through the synergistic effects of the stronger Brønsted base and the H-bond donor, good reactivity and selectivity in new and challenging enantioselective organocatalytic addition reactions would be obtained. Herein we report our findings.

From the outset, we wanted a design that relied on a clean and efficient last step generation of the Brønsted basic moiety of the catalyst; this would greatly simplify their synthesis and handling. To this end we considered the Staudinger reaction[10] of a triarylphosphine and an enantiopure organoazide possessing an effective H-bond donor group (Scheme 1). Our hope was that

Scheme 1. Concept and Design of a New Class of Bifunctional Iminophosphorane (BIMP) Organocatalysts



the strong nucleophilicity of the triarylphosphine would create a strongly Brønsted basic iminophosphorane moiety through favorable loss of dinitrogen gas.[11] As many triarylphosphine reagents are readily available, this simple design could allow the synthesis of a range of bifunctional catalysts with electronic and/or steric variations at the iminophosphorane moiety. Further variations to the chiral scaffold and the H-bond donor group would add favorably to the diversity of catalysts accessible through this design.

The premise of our catalyst design was the enhanced Brønsted basicity of the triaryliminophosphorane functionality relative to the weak tertiary amine group. Interestingly, whereas the basicities of triaminoiminophosphoranes are reported—such as P_1-^{t}Bu with a pK_{BH+} (MeCN) of 26.98 (Figure 1)—the Brønsted basicities of triaryliminophosphoranes are not. Accordingly, to quantify the basicity of triaryliminophosphoranes, pK_{BH+} measurements were carried out on a model triphenylphosphine-derived iminophosphorane, **1a** (derived from cyclohexyl azide; see Supporting Information). Indeed its pK_{BH+} (MeCN) of 22.7 was determined to be 4 orders of magnitude greater than

Received: September 3, 2013
Published: October 9, 2013

   dx.doi.org/10.1021/ja409121s | J. Am. Chem. Soc. 2013, 135, 16348−16351

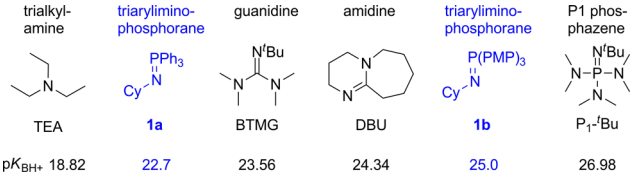
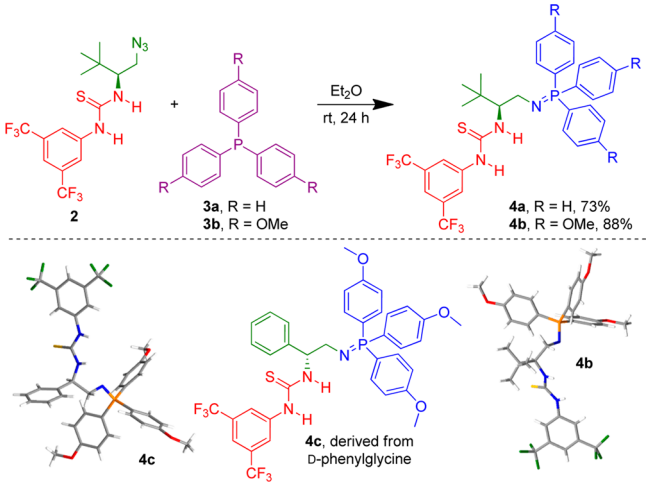


Figure 1. pK_{BH+} (MeCN) measurements of a tertiary amine and some common organic superbases and two triaryliminophosphorane superbases **1a** and **1b**. PMP = *para*-methoxyphenyl.

that of triethylamine and comparable to that of guanidines and other organic superbases, thus validating our design concept.[3,12] Importantly, tris(4-methoxyphenyl)phosphine-derived iminophosphorane **1b** was found to be a further hundred-fold more basic (pK_{BH+} (MeCN) of 25.0), thus demonstrating that the basicity of the triaryliminophosphorane moiety can be readily modified by varying the electronics of the triarylphosphine component.

L-*tert*-Leucine-derived azide **2** was then prepared on a gram scale (see Supporting Information) and reacted separately with equimolar quantities of both triphenylphosphine and tris(4-methoxyphenyl)phosphine in anhydrous diethyl ether (Scheme 2). In both cases after stirring for 24 h bifunctional

Scheme 2. Synthesis of Two Representative BIMPs and Single-Crystal X-ray Structures of 4b and 4c (P, orange; N, blue; S, yellow; O, red; F, green; H, white)

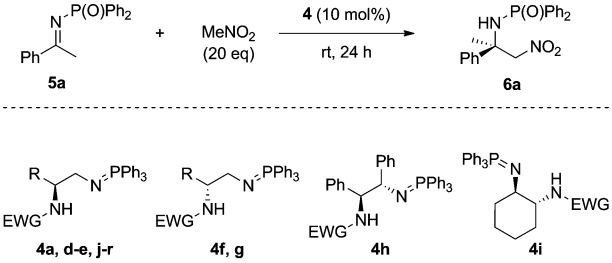


iminophosphoranes **4a** and **4b** were isolated as bench-stable solids by precipitation and filtration.[13] In the case of tris(4-methoxyphenyl)phosphine-derived catalyst **4b**, crystals of suitable quality for single-crystal X-ray diffraction were obtained (Scheme 2), allowing the unambiguous determination of its solid-state structure. Furthermore, in the enantiomeric series, the single-crystal X-ray structure of D-phenylglycine-derived iminophosphorane **4c** was also obtained.

To demonstrate the synthetic potential of this new class of bifunctional organocatalysts, we selected the challenging enantioselective organocatalytic nitro-Mannich (or aza-Henry) reaction of nitromethane with unactivated ketone-derived imines (ketimines). Unlike the many variations of the well-developed organocatalytic enantioselective nitro-Mannich reaction of aldehyde-derived imines (aldimines),[14] the corresponding ketimine variant has no reported general solution.[15] We believed that the strong Brønsted basicity of the triaryliminophosphorane and the appropriate positioning of an effective H-bond donor group over a suitable chiral scaffold could provide both the potency and control required.[16]

To expedite screening, a library of BIMP catalysts (**4a**, **4d**–**i**) was made *in situ* from the corresponding catalytically inactive azides and triphenylphosphine by simply stirring equimolar amounts in diethyl ether at rt for 24 h (see Supporting Information). This library was assessed for performance in the reaction of nitromethane with acetophenone-derived *N*-diphenylphosphinoyl (DPP) ketimine **5a** (Table 1).[17] Pleasingly,

Table 1. Proof of Concept and Optimization Studies in the Nitro-Mannich Reaction of Nitromethane with *N*-Diphenylphosphinoyl Ketimine 5a[a]



4a: R = ^{t}Bu, EWG = C(S)NH(3,5-$(CF_3)_2C_6H_3$)
4d: R = Bn, EWG = C(S)NH(3,5-$(CF_3)_2C_6H_3$)
4e: R = ^{i}Pr, EWG = C(S)NH(3,5-$(CF_3)_2C_6H_3$)
4f: R = Ph, EWG = C(S)NH(3,5-$(CF_3)_2C_6H_3$)
4g: R = Ph_2CH, EWG = C(S)NH(3,5-$(CF_3)_2C_6H_3$)
4h: EWG = C(S)NH(3,5-$(CF_3)_2C_6H_3$)
4i: EWG = C(S)NH(3,5-$(CF_3)_2C_6H_3$)
4j: R = ^{t}Bu, EWG = C(O)NH(3,5-$(CF_3)_2C_6H_3$)
4k: R = ^{t}Bu, EWG = C(S)NH(4-$CF_3C_6H_4$)
4l: R = ^{t}Bu, EWG = C(S)NH(4-$NO_2C_6H_4$)
4m: R = ^{t}Bu, EWG = C(S)NH(4-$MeOC_6H_4$)
4n: R = ^{t}Bu, EWG = C(S)NH(4-MeC_6H_4)
4o: R = ^{t}Bu, EWG = C(S)NHPh
4p: R = ^{t}Bu, EWG = C(O)(3,5-$(CF_3)_2C_6H_3$)
4q: R = ^{t}Bu, EWG = Ts
4r: R = ^{t}Bu, EWG = Boc

entry	catalyst	conversion,[b] ee[c] (%)	entry	catalyst	conversion,[b] ee[c] (%)
1	**4a**	98, *85*	9	**4k**	98, *79*
2	**4d**	93, *78*	10	**4l**	98, *84*
3	**4e**	94, *77*	11	**4m**	98, *70*
4	**4f**	95, *77*[d]	12	**4n**	99, *68*
5	**4g**	93, *70*[d]	13	**4o**	98, *73*
6	**4h**	48, *34*[d]	14	**4p**	98, *11*
7	**4i**	98, *20*[d]	15	**4q**	92, *0*
8	**4j**	97, *79*	16	**4r**	99, *0*

[a]Reactions performed using 0.2 mmol of ketimine **5a** in 0.2 mL of $MeNO_2$ at rt. [b]Conversion was determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]Enantiomeric excess (ee) was determined by HPLC analysis on a chiral stationary phase. [d]Enantiomer (*S*)-**6a** was obtained.

using neat nitromethane (20 equiv) and 10 mol % catalyst, all BIMPs demonstrated excellent reactivity in the formation of addition product **6a**; conversion after 24 h was near full with all but catalyst **4h**. Furthermore, enantioselectivities were good except with catalysts **4h** and **4i** (Table 1, entries 6, 7). L-*tert*-Leucine-derived catalyst **4a** outperformed the other catalysts in terms of enantioselectivity (85% ee at rt, Table 1, entry 1) and was therefore selected as the scaffold of choice for the remainder of the optimization studies.

BIMPs **4j**–**r** possessing a range of H-bond donor groups including thiourea, urea, amide, sulfonamide, and carbamate were investigated for performance. In all cases good conversion to addition product **6a** was observed after 24 h at rt (Table 1, entries 8–16). Pleasingly both urea and thioureas with electron-donating or electron-withdrawing substituents (**4a**, **4j**–**o**) attached to the aromatic ring imparted high levels of enantioselectivity in the reaction (Table 1, entries 1, 8–13). However, electron-deficient aryl amide **4p** afforded the product

dx.doi.org/10.1021/ja409121s | J. Am. Chem. Soc. 2013, 135, 16348–16351

with poor enantiocontrol (Table 1, entry 14), and both sulfonamide **4q** and carbamate **4r** yielded the product in racemic form (Table 1, entries 15, 16). From these results, it was clear that the H-bond donor group was playing a key role in controlling the stereochemical outcome of the reaction and that the Schreiner-type 3,5-bis(trifluoromethyl)phenyl thiourea moiety of catalyst **4a** was optimal.[18]

With the best scaffold and H-bond donor group identified, we turned our attention to the Brønsted base moiety and studied how the reaction rate varied as a function of the electronics of the triarylphosphine component. Catalyst **4a** (R = H) and its analogues **4b** (R = MeO) and **4s** (R = Cl) were used in the reaction of ketimine **5a** with nitromethane, and conversion to addition product **6a** was measured by ^{1}H NMR analysis (Figure 2). The reaction rate was indeed governed by the aryl

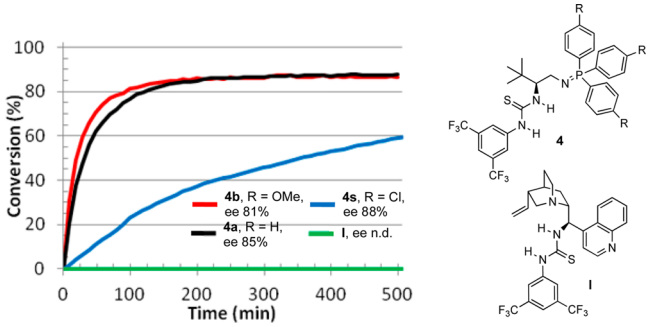


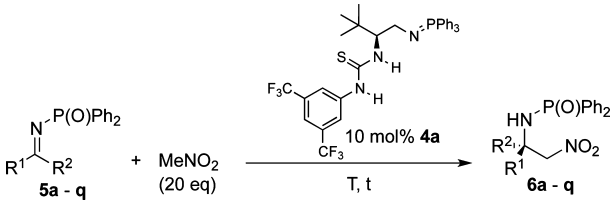
Figure 2. Comparison of reaction rates with BIMP catalysts **4a**, **4b**, and **4s** and cinchonine-derived bifunctional organocatalyst **I**.

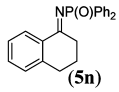
substituents of the iminophosphorane moiety. The reaction with catalyst **4s** was slower than that with **4a** or **4b**, in line with a more electron-deficient triarylphosphine generating a weaker base. As a direct comparison, when cinchonine-derived bifunctional organocatalyst **I** was used as the catalyst in the same ^{1}H NMR kinetic experiment, *no product was detected even after a prolonged* reaction *time of 32 h*. The above experiments clearly demonstrate that the enhanced basicity of iminophosphoranes compared to tertiary amines is responsible for the increase in catalytic activity.

Although catalyst **4b** was marginally superior to **4a** in terms of reaction rate, **4a** was more enantioselective and was therefore chosen as the catalyst to investigate the substrate scope in the nitro-Mannich addition of nitromethane to ketimines. To maximize enantioselectivity, reactions were performed in chilled (0 or −15 °C) nitromethane. Good to excellent enantioselectivities were obtained with aromatic ketone-derived imines bearing either electron-withdrawing or electron-donating substitutents (up to 95% yield, up to 95% ee; Table 2, entries 1−12). Phenyl ethyl ketone-derived imine **5m** also afforded the product with high enantioselectivity, as did the tetralone-derived imine substrate **5n** albeit in lower yield in the latter case (Table 2, entries 13, 14). Heteroaromatic ketimines **5o** and **5p** gave the desired products in near quantitative yields and with good enantioselectivities (Table 2, entries 15, 16). Pleasingly, the reaction was also applicable to aliphatic ketimine **5q** (Table 2, entry 17).[19]

The performance of our new BIMP catalysts for enantioselective catalysis on a preparative scale was investigated next. To minimize reaction time, the most active catalyst, **4b**, was selected for this purpose. Using 1 mol % **4b**, 10 g of ketimine **5a** was reacted with 10 equiv of nitromethane at rt over 21 h to afford the

Table 2. Scope of Asymmetric Nitro-Mannich Reaction of Ketimines[a]



Entry	R^1	R^2	T/°C	t/h	Yield (%)	ee (%)[b]
1	C_6H_5 (**5a**)	Me	−15	96	86	95
2	4-MeC_6H_4 (**5b**)	Me	0	48	93	89
3	4-MeOC_6H_4 (**5c**)	Me	0	48	95	91
4	3-MeOC_6H_4 (**5d**)	Me	0	48	88	91
5	2-MeOC_6H_4 (**5e**)	Me	0	48	62	93
6	4-PhC_6H_4 (**5f**)	Me	0	24	92	90
7	4-$NO_2C_6H_4$ (**5g**)	Me	−15	48	92	86
8	2-FC_6H_4 (**5h**)	Me	−15	96	89	94
9	4-ClC_6H_4 (**5i**)	Me	0	20	90	90
10	4-BrC_6H_4 (**5j**)	Me	0	48	84	90
11	3,4-$Cl_2C_6H_3$ (**5k**)	Me	0	20	92	87
12	3,5-$(CF_3)_2C_6H_3$ (**5l**)	Me	−15	96	95	90
13	C_6H_5 (**5m**)	Et	0	48	95	92
14	 (**5n**)		−15	96	40*	92
15	2-furyl (**5o**)	Me	0	48	97	84
16	3-pyridyl (**5p**)	Me	0	48	97	82
17	cyclohexyl (**5q**)	Me	0	48	71	78

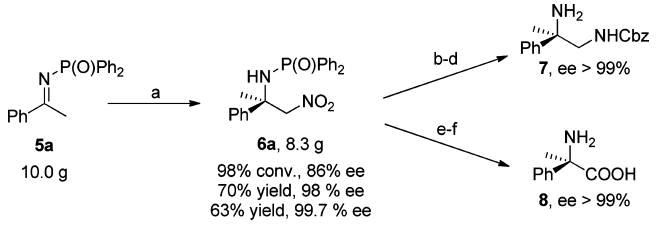
[a]Reactions were carried out on 0.2 mmol of **5** at the indicated temperature. [b]Enantiomeric excess (ee) was determined by HPLC analysis on a chiral stationary phase. *Conversion was 50%.

crude product in 98% conversion and 86% ee. After recrystallization, 8.3 g of addition product **6a** (70% yield) was obtained in 98% ee, and a further recrystallization afforded **6a** in >99% ee. In a short demonstration of synthetic utility this enantiopure β-nitroamine was converted to the corresponding 1,2-diamine derivative **7**[20] via a nickel boride-mediated reduction of the nitro group followed by Cbz protection and then DPP removal. Furthermore, **6a** was transformed into fully substituted α-amino acid **8**[21] by a two-step sequence involving a Nef oxidation followed by DPP removal (Scheme 3).

In summary, we have designed and developed a new and effective class of modular bifunctional iminophosphorane superbase organocatalysts and have applied it to the first metal-free catalytic enantioselective addition of nitromethane to unreactive ketone-derived imines, a reaction where existing tertiary amine organocatalysts are impotent. The synthesis of the catalysts from catalytically inactive and readily synthesized azide precursors and triarylphosphines allows for rapid catalyst screening and optimization. The nitro-Mannich reaction of ketimines can be performed on a multigram scale and allows ready access to synthetically relevant, nitrogen-containing chiral building blocks possessing a fully substituted carbon atom. Work to uncover the full capabilities of this new catalyst design is ongoing, and the results will be disclosed in due course.

dx.doi.org/10.1021/ja409121s | J. Am. Chem. Soc. 2013, 135, 16348−16351

Scheme 3. Preparative-Scale Synthesis of 6a and Derivatization into Enantiopure Diamine 7 and Quaternary α-Amino Acid 8[a]



[a]Reagents and conditions: (a) 1 mol % **4b** (231 mg), 17 mL of $MeNO_2$ (10 equiv), 21 °C, 21 h, recrystallization (propan-2-ol), 70%; (b) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 84%; (c) CbzCl, Na_2CO_3, H_2O/dioxane, 90%; (d) HCl, MeOH, 73%; (e) $KMnO_4$, KOH, KH_2PO_4, ^{t}BuOH; (f) HCl, MeOH, 57% over 2 steps.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

Darren.dixon@chem.ox.ac.uk

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the EPSRC (Leadership Fellowship to D.J.D., Postdoctoral Fellowship to M.G.N., and Studentship to A.J.M.F.), the EC (IEF to M.G.N. [PIEF-GA-2009-254637]), and AstraZeneca (Studentship to A.J.M.F.). We also thank Alison Hawkins for X-ray structure determination and the Oxford Chemical Crystallography Service for use of the instrumentation. X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code **966013-966014**.

■ REFERENCES

(1) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991.

(2) (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.

(3) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Wiley: New York, 2009.

(4) (a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (b) Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880. (c) Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076.

(5) (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (c) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245. (d) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (e) Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 7299. (f) Sohtome, Y.; Tanaka, S.; Takada, K.; Yamaguchi, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 9254. (g) Misaki, T.; Jin, N.; Kawano, K.; Sugimura, T. *Chem. Lett.* **2012**, *41*, 1675. For reviews see: (h) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737. (i) Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, *4*, 488. (j) Leow, D.; Tan, C.-H. *Synlett* **2010**, 1589. (k) Ishikawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 1555. (l) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210.

(6) (a) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (b) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 19370. (c) Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 4685.

(7) (a) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552. (b) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799.

(8) Seminal work: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Li, H. M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (d) Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603. (e) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (f) Ye, J. X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (g) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (h) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (i) Andrés, J. M.; Manzano, R.; Pedrosa, R. *Chem.—Eur. J.* **2008**, *14*, 5116. For reviews see: (j) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (k) Connon, S. J. *Chem. Commun.* **2008**, 2499. (l) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229.

(9) (a) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151. Review: (b) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Olçüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042.

(10) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. Review: (b) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353. (c) Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley: New York, 1993.

(11) Iminophosphoranes as Lewis bases: Steiner, A.; Zacchini, S.; Richards, P. I. *Coord. Chem. Rev.* **2002**, *227*, 193.

(12) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.

(13) Further tests demonstrated that the catalysts showed remarkable stability to water; partitioning (±)-**4c** between CH_2Cl_2 and water for 2 min, then drying with $MgSO_4$ and treatment with excess PS-BEMP afforded essentially pure catalyst in 94% yield.

(14) (a) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151. (b) Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401. (c) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887.

(15) (a) García Ruano, J. L.; Topp, M.; López-Cantarero, J.; Alemán, J.; Remuiñán, M. J.; Belén Cid, M. *Org. Lett.* **2005**, *7*, 4407. (b) Pahadi, N. K.; Ube, H.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 8700. (c) Tan, C.; Liu, X.; Wang, L.; Wang, J.; Feng, X. *Org. Lett.* **2008**, *10*, 5305. (d) Wang, L. W.; Tan, C.; Liu, X. H.; Feng, X. M. *Synlett* **2008**, 2075. (e) Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 11773.

(16) Triethylamine is ineffective in promoting the reaction; see ref 15b.

(17) Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, 1205.

(18) Seminal work: Wittkopp, A.; Schreiner, P. R. *Chem.—Eur. J.* **2003**, *9*, 407. For reviews see: Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

(19) Currently the reaction is limited to nitromethane; analogous reactions with nitroethane were slow and proceeded with poor diastereo- and enantioselectivity.

(20) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

(21) Viso, A.; Fernández de la Pradilla, R.; Tortosa, M.; García, A.; Flores, A. *Chem. Rev.* **2011**, *111*, PR1.