ORGANIC LETTERS

2011
Vol. 13, No. 8
2054–2057

Chiral Magnesium BINOL Phosphate-Catalyzed Phosphination of Imines: Access to Enantioenriched α-Amino Phosphine Oxides

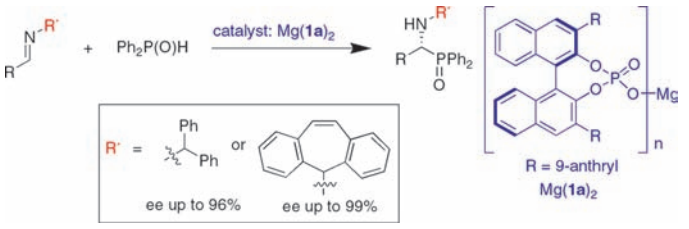
Gajendrasingh K. Ingle,[†] Yuxue Liang,[†] Michael G. Mormino,[†] Guilong Li,[‡] Frank R. Fronczek,[§] and Jon C. Antilla*,[†]

Department of Chemistry, University of South Florida, 4202 East Fowler Avenue, Tampa, Florida 33620, United States, School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou, 510275, China, and Department of Chemistry X-ray Laboratory, Louisiana State University, Baton Rouge, Louisiana 70803, United States

jantilla@usf.edu

Received February 19, 2011

ABSTRACT



A new method to synthesize chiral α-amino phosphine oxides is reported. The reaction combines *N*-substituted imines and diphenylphosphine oxide and is catalyzed by a chiral magnesium phosphate salt. A wide variety of aliphatic and aromatic aldimines substituted by electron-neutral benzhydryl or dibenzocycloheptene groups were excellent substrates for the addition reaction. The dibenzocycloheptene protected imines afforded improved enantioselectivity in the resulting products. Substituted diphenylphosphine oxide nucleophiles also showed good reactivity.

Chiral phosphorus containing compounds such as α-amino phosphonic acids and their derivatives have attracted considerable attention due to their promising biological properties.[1] They have found applications as antibacterials,[2] antiviral agents,[3] and enzyme inhibitors.[4] The absolute configuration of phosphonyl compounds strongly influences their biological properties;[5] therefore

[†] University of South Florida.
[‡] Sun Yat-Sen University.
[§] Louisiana State University.

(1) For reviews on biological activity of α-amino phosphonic acids and their derivatives, see: (a) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193–215. (b) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868–3965.

(2) (a) Atherton, F. R.; Hassall, R. W.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29–40. (b) Huber, J. W.; Gilmore, W. F.; Robertson, L. W. *J. Med. Chem.* **1975**, *18*, 106–108. (c) Pratt, R. F. *Science* **1989**, *246*, 917–919.

(3) Huang, J.; Chen, R. *Heteroat. Chem.* **2000**, *11*, 480–492.

(4) (a) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652–1661. (b) Bird, J.; De Mello, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. *J. Med. Chem.* **1994**, *37*, 158–169. (c) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4622–4628.

(5) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Charles, A. F.; Rogers, W. L.; Smith, S. A.; Deforrest, J. M.; Oehl, R. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1995**, *38*, 4557–4569.

(6) For review, see: (a) Merino, P.; Marqués-López, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195–1208. (b) Ordóñez, M.; Rojas-cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17–49.

(7) For organocatalytic hydrophosphonylation, see: (a) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583–2585. For recent work on hydrophosphonylation, see:(c) Nakamura, S.; Nakashima, H.; Yamamura, A.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1209–1212. (d) Cheng, X.; Goddard, R.; Buth, G.; List., B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079–5081. (e) Zhao, D.; Wang, Y.; Mao, L.; Wang, R. *Chem.—Eur. J.* **2009**, *15*, 10983–10987. For hydrophosphoynlation of ketimines, see:(f) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, *131*, 18240–18241. For a theoretical study on the chiral phosphoric acid catalyzed hydrophosphonylation, see:(g) Yamanaka, M.; Hirata, T. *J. Org. Chem.* **2009**, *74*, 3266–3271. (h) Akiyama, T.; Morita, H.; Bachu, P.; Mori, K.; Yamanaka, M.; Hirata, T. *Tetrahedron* **2009**, *65*, 4950–4956.

10.1021/ol200456y
Published on Web 03/17/2011

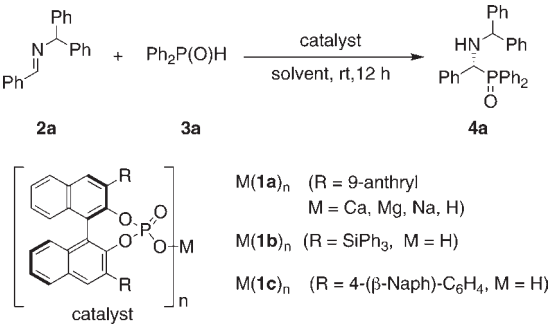
numerous methods for the enantioselective synthesis of chiral α-amino phosphoric acids by hydrophosphonylation of imines (aza-Pudovik reaction) are reported.[6,7] However, other α-amino phosphorus derivatives such as α-amino phosphine oxides have had much less attention for their biological properties due to the lack of a direct enantioselective synthetic route.

Recently, organocatalyzed hydrophosphination using secondary phosphines[8] has also been demonstrated. Additionally, in 2007, Melchiorre[9] and Córdova[10] reported enantioselective organocatalytic hydrophosphination of α,β-unsaturated aldehydes with diphenylphosphine using a chiral secondary amine catalyst to provide enantioenriched aldehydes with β-phosphine substitution. However, very few examples exist with phosphine oxides as the nuclophile. In 1999, Shibasaki reported the first catalytic asymmetric addition of diphenylphosphine oxide to cyclic imines, catalyzed by a heterobimetallic lanthanoid complex.[11] The corresponding chiral amino phosphine oxide products were obtained in good yield and enantioselectivity, but the substrate scope of this reaction was limited to cyclic imines. In 2009, a chiral guanidinium salt-catalyzed phospha-Mannich reaction of *N*-tosyl imines with di-1-naphthyl phosphine oxide was reported.[12] The α-amino phosphine oxide products were obtained in high yield and high ee. However, only a single example of a diphenyl phosphine oxide as a nucleophile was reported, and with moderate ee. Lastly the addition of dialkyl phosphine oxides to *N*-acyl pyrroles was reported recently, obtaining products with excellent yield and enantioselectivity.[13]

The use of chiral phosphoric acids to activate imine substrates for nuclophilic addition is well studied.[14] Recently, Ishihara and co-workers reported that purification of chiral phosphoric acids by silica gel chromatography can result in mixtures of the free acid and the alkali or alkaline earth metals, as their phosphate salts.[15] These phosphate salts were found to be active catalysts for new transformations.[16]

Herein we report a highly enantioselective addition of diphenylphosphine oxide to *N*-substituted imines catalyzed by chiral BINOL magnesium phosphate.[17] During the screening process we soon realized an electron-neutral, unactivated protecting group provided considerable enhancement in the yield and enantioselectivity, similar to that observed by Wulff and co-workers in an aziridination reaction.[18]

Table 1. Catalytic Reaction Condition Optimization for the Enantioselective Addition of Diphenylphosphine Oxide to *N*-Benzhydryl Imine



entry[a]	catalyst (mol %)[b]	solvent	yield (%)[c]	ee (%)[d]
1	H(**1b**) Purified on silica gel (10)	toluene	68	0
2	H(**1c**) Purified on silica gel (10)	toluene	61	38
3	H(**1a**) Purified on silica gel (10)	toluene	72	82
4	H(**1a**) Purified on silica gel (10)	CH_3CN	97	91
5	Na(**1a**) (10)	CH_3CN	56	55
6	$Ca(\mathbf{1a})_2$ (5)	CH_3CN	96	91
7	$Mg(\mathbf{1a})_2$ (5)	CH_3CN	95	93
8	$Mg(\mathbf{1a})_2$ (2.5)	CH_3CN	92	80
9	H(**1a**) washed with HCl (10)	CH_3CN	87	80

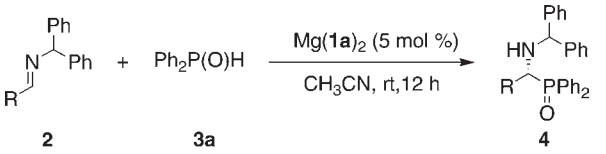
[a] General conditions: 1.2 equiv of imine and 1.0 equiv of diphenylphosphine oxide. [b] See Supporting Information for details on the synthesis of the catalysts and for the optimization table. [c] Isolated yields. [d] Ee determined by chiral HPLC analysis.

We began by examining the catalytic asymmetric addition of diphenylphosphine oxide **3a** to benzhydryl imine **2a** as a model reaction (Table 1). During optimization we found that acetonitrile and 'H(**1a**) purified on silica gel' were found to be the best solvent and catalyst for this reaction (entry 4). In the wake of the new results published by Ishihara,[15] we screened alkali, and alkaline earth metal phosphate salts. Na(**1a**) allowed for only a 55% ee (entry 5), while $Ca(\mathbf{1a})_2$ resulted in a 91% ee (entry 6). $Mg(\mathbf{1a})_2$ was found to be the best catalyst, providing 93% asymmetric induction (entry 7). However, lowering the catalyst loading of $Mg(\mathbf{1a})_2$ to 2.5 mol % resulted in a decrease in ee (entry 8). It was interesting to note that 'H(**1a**) washed with hydrochloric acid' achieved only a 80% ee for the resulting product (entry 9).

A series of substitued imines were then investigated for the asymmetric hydrophosphination reaction in the

(8) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mazzanti, A.; Sambri, L.; Melchiorre, P. *Chem. Commun.* **2007**, 722–724.
(9) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4504–4506.
(10) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4507–4510.
(11) Yamakoshi, K.; Harwood, S. J.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 2565–2568.
(12) Fu, X.; Loh, W.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H.; Wang, J.; Tan, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 7387–7390.
(13) Zhao, D.; Mao, L.; Wang, Y.; Yang, D.; Zhang, Q.; Wang, R. *Org. Lett.* **2010**, *12*, 1880–1882.
(14) For reviews on chiral phosphoric acid, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (c) Terada, M. *Chem. Commum.* **2008**, 4097–4112.
(15) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823–3826.
(16) (a) Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1135–1138. (b) Drouet, F.; Lalli, C.; Liu, H.; Masson, G.; Zhu, J. *Org. Lett.* **2011**, *13*, 94–97. For reports on metal and Brønsted acid catalysis, see:(c) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350–9365.
(17) Lv, J.; Li, X.; Zhong, L.; Luo, S.; Cheng, J.-P. *Org. Lett.* **2010**, *12*, 1096–1099.
(18) Zhang, Y.; Lu, Z.; Desai, A.; Wulff, W. D. *Org. Lett.* **2008**, *10*, 5429–5432.

Table 2. Catalytic Asymmetric Addition of Diphenylphosphine Oxide to *N*-Benzhydryl Imines

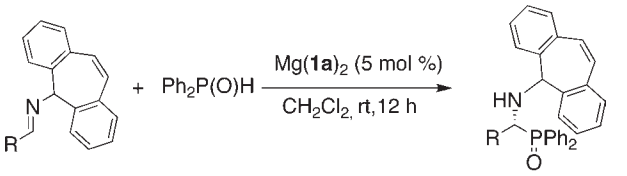


2 3a 4

entry[a]	R	product	yield (%)[b]	ee (%)[c]
1	Ph (**2a**)	**4a**	95	93
2	4-MeOC$_6$H$_4$ (**2b**)	**4b**	95	90[d]
3	2-MeC$_6$H$_4$ (**2c**)	**4c**	96	89
4	3-MeC$_6$H$_4$ (**2d**)	**4d**	95	92
5	4-FC$_6$H$_4$ (**2e**)	**4e**	95	90
6	4-BrC$_6$H$_4$ (**2f**)	**4f**	97	92
7	4-NO$_2$C$_6$H$_4$ (**2g**)	**4g**	97	95
8	1-Naph (**2h**)	**4h**	95	96
9	2-Furyl (**2i**)	**4i**	93	91
10	*c*-C$_6$H$_{11}$ (**2j**)	**4j**	96	91
11[e]	isopropyl	**4k**	92	86
12[e]	*n*-Propyl	**4l**	88	62
13[e]	*n*-Butyl	**4m**	65	52
14[e]	Ph-(CH$_2$CH$_2$)	**4n**	73	48

[a] General conditions: 1.2 equiv of imine and 1.0 equiv of the phopshine oxide with 5 mol % Mg(**1a**)$_2$. [b] Isolated yields. [c] Ee determined by chiral HPLC analysis. [d] Using the optimized conditions, with Ca(**1a**)$_2$ as the catalyst, a 96% yield and 81% ee of **4** could be obtained. [e] Imine was generated *in situ* (see Supporting Information).

Table 3. Catalytic Asymmetric Addition of Diphenylphosphine Oxide to Imines **5**



5 3a 6

entry[a]	R	product	yield (%)[b]	ee (%)[c]
1	Ph (**5a**)	**6a**	90	99[d]
2	4-MeOC$_6$H$_4$ (**5b**)	**6b**	92	92
3	2-MeC$_6$H$_4$ (**5c**)	**6c**	92	96
4	4-FC$_6$H$_4$ (**5d**)	**6d**	95	16
5	2-Furyl (**5e**)	**6e**	98	87
6[e,f]	isopropyl	**6f**	72	85
7[d]	*n*-Propyl	**6g**	73	80
8[d]	*n*-Butyl	**6h**	84	74
9[d]	Ph-(CH$_2$CH$_2$)	**6i**	86	93

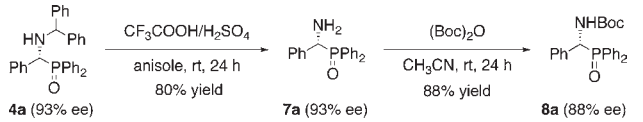
[a] General conditions: 2.0 equiv of imine and 1.0 equiv of the phosphine oxide with 5 mol % Mg(**1a**)$_2$. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Using the optimized conditions, with Ca(**1a**)$_2$ as the catalyst, a 95% yield and 90% ee of **6** were obtained, and with 'H(**1a**) washed with HCl', a 90% yield and 79% ee of **6** were found. [e] Imine was generated in situ. [f] (*S*)-H(**1a**) was used to synthesize Mg(**1a**)$_2$.

presence of catalyst Mg(**1a**)$_2$ under the optimized reaction conditions (Table 2). To our delight, all the imines underwent addition of diphenylphosphine oxide to afford α-amino phosphine oxide products in excellent yield and enantioselectivity. Electron-donating substituents in the *para*- (entry 2), *ortho*- (entry 3), and *meta*- (entry 4) positions were all shown to be excellent substrates for the phospha-Mannich reaction. Likewise, the use of electron-withdrawing substituents (entries 5−7) in the *para*-position also provided for high yields and excellent asymmetric induction. A sterically hindered 1-napthyl substituted imine was also an excellent substrate, allowing the preparation of **4h** in 95% yield with 96% ee (entry 8). A heteroaromatic (2-furyl) substitution also proved to be a good substrate with a high yield and ee for product **4i** being observed (entry 9). We also examined the aliphatic substrate scope; cyclohexyl and isopropyl imines gave good yields and enantioselectivities (entries 10 and 11). However, it was found that *n*-propyl, *n*-butyl, and 3-phenyl propyl substituted imines afforded moderate yields and enantioselectivities when chosen as a substrate for the reaction (entries 12−14).

Next we chose to investigate the imine protecting group on the nucleophilic addition. We began this study by preparing **5a** from benzaldehyde and 5*H*-dibenzo[*a*,*d*]cyclohepten-5-amine.[19] Optimization of the reaction conditions revealed the best selectivity when 2 equiv of imine **5a** were treated with 1 equiv of diphenylphosphine oxide in CH_2Cl_2 at room temperature (Table 3). In order to determine the utility of the new protecting group, we synthesized four new imines (Table 3, **5b**−**e**). We opted to synthesize the imines which had induced a relatively lower enantioselectivity with the benzhydryl protecting group in our previous study (see Table 2). When we subjected **5a** to the optimized reaction conditions, we found a 90% yield and 99% ee for the resulting product **6a**. For the benzhydryl protecting group, product **4a** was obtained with a 96% yield and 93% asymmetric induction. For imine **5b**, a 92% ee was obtained for product **6b**, while in the case of the benzhydryl protected imine a 90% ee was observed in product **4b**. Imines **5c** and **5d** both underwent diphenylphosphine oxide addition with excellent yield and enantioselectivity. For the products **6c** and **6d**, an increased asymmetric induction was observed when compared to the benzhydryl protected counterpart **4c** and **4e** respectively. However, for the heteroaromatic (2-furyl) imine, the product **6e** was obtained in lower enantiomeric excess (87%) than product **4i** (91%). In the case of aliphatic aldimines, imines derived from isobutyl aldehydes gave comparable results in terms of yield and enantioselectivity (**4k** and **6f**). The products **6g**, **6h** showed better asymmetric induction than products **4l**, **4m**. The dibenzocycloheptene protecting group was critical for asymmetric induction in **6i**; the product was obtained in 93% ee, while product **4n** gave only a 48% ee. Overall 5*H*-dibenzo[*a*,*d*]cyclohepten-5-amine derived imines gave better asymmetric inductions in the resulting products than benhydryl imines, while

(19) Hjelmencrantz, A.; Friberg, A.; Berg, U. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1293–1300.

Scheme 1. Deprotection of **4a** and Determination of Absolute Configuration



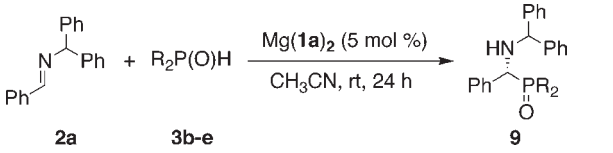
yields for both protecting groups were comparable. We hypothesized that the dibenzocycloheptene protected imines could have enhanced CH$-\pi$[20] and $\pi-\pi$[21] stacking interactions with catalyst Mg(**1a**)$_2$ in the transition state, which lead to a better asymmetric induction in the resulting products.

We have also shown that the benzhydryl group can be removed with good yield to provide the α-amino phosphine oxide **7a**, with preserved enantioselectivity (Scheme 1). Protection of the amine with a Boc group allowed for product **8a**, which was used to deterimine the absolute stereochemistry of the chiral phosphine oxide through X-ray crystallographic analysis (see Supporting Information).

The reactivity of various aliphatic/aromatic phosphine oxides[22] was evaluated for a hydrophosphination reaction (Table 4). To our satification, aromatic phosphine oxides bearing either an electron-withdrawing (entries 1 and 2) or electron-donating substituent (entries 3 and 4) underwent nucleophilic addition to *N*-benzhydryl imine affording products in good yield and excellent enantioselectivity. However, aliphatic phosphine oxides such as benzyl, di-*tert*-butyl, and diethyl phosphine oxide as well as sterically demanding aromatic phosphine oxide (2,6-dimethyl phosphine oxide) did not undergo a phospha-Mannich reaction under optimized conditions.

In summary, we have developed a new method where diphenylphosphine oxides can be added to imines with excellent yields and enantioselectivities catalyzed by a chiral phosphate salt. This method provides a simple and direct access to chiral α-amino phosphine oxides. In this study, we have examined the addition of diphenylphosphine oxide to two different *N*-substituted imines. The imines synthesized from 5*H*-dibenzo[*a*,*d*]cyclohepten-5-amine provided better enantioselectivity than those derived from benzhydryl imines, while both imines gave comparable yields. Also, the substituted diphenylphosphine oxides were excellent nucleophiles obtaining chiral α-amino phosphine oxides in good yield and enantioselectivity.

Table 4. Catalytic Asymmetric Addition of Aromatic Phosphine Oxides (**3b**−**e**) to *N*-Benzhydryl Imine



entry[a]	R	product	yield (%)[b]	ee (%)[c]
1	4-ClC_6H_4 (**3b**)	**9b**	93	84[d]
2	4-FC_6H_4 (**3c**)	**9c**	88	84
3	4-MeOC_6H_4 (**3d**)	**9d**	79	87
4	4-MeC_6H_4 (**3e**)	**9e**	63	89

[a] General conditions: 1.2 equiv of imine and 1.0 equiv of oxide **3b**−**e** with 5 mol % Mg(**1a**)$_2$. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] With CH_2Cl_2 as a the solvent, a 78% yield and 80% ee of **9b** were obtained, while using Ca(**1a**)$_2$ as the catalyst resulted in a 77% yield and 79% ee of **9b**.

Acknowledgment. We thank the National Institutes of Health (NIH GM-082935) and the National Science Foundation (NSF-0847108) for financial support.

Supporting Information Available. Characterization, chiral HPLC conditions, experimental preparation, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) For a review, see: Nishio, M. *Tetrahedron* **2005**, *61*, 6923–6950.
(21) (a) Janiak, C. *J. Chem. Soc., Dalton Trans.* **2000**, 3885–3896. (b) Roesky, H. W.; Andruh, M. *Coord. Chem. Rev.* **2003**, *236*, 91–119.
(22) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 10521–10523.