J|A|C|S
COMMUNICATIONS

Published on Web 04/12/2007

A Vaulted Biaryl Phosphoric Acid-Catalyzed Reduction of α-Imino Esters: The Highly Enantioselective Preparation of α-Amino Esters

Guilong Li, Yuxue Liang, and Jon C. Antilla*

Department of Chemistry, University of South Florida, 4202 East Fowler Avenue CHE205A, Tampa, Florida 33620

Received January 23, 2007; E-mail: jantilla@cas.usf.edu

Chiral amino acids are some of the most important small molecules found in biological systems. Natural and unnatural α-amino acids are also highly utilized in academia and in the pharmaceutical, biotech, and chemical industries. Therefore, the discovery of general methodology that can produce chiral α-amino acid derivatives in high yield and with useful levels of enantioselectivity is of considerable importance.[1]

Relatively straightforward *catalytic asymmetric* approaches to chiral α-amino acid derivatives include the Strecker reaction,[2] the alkylation of glycine derivatives,[3] and the alkylation of α-imino esters.[4] Perhaps the most straightforward and desirable means to produce chiral amino acid derivatives is the direct reduction of α-enamides[5] or α-imino esters.[6] α-Imino ester reductions are attractive routes to amino acids as they are readily produced from ketones and are available with numerous substitution patterns.

A recently emerging direction for organocatalysis has resulted from the initial discoveries by Akiyama[7a] and Terada[7b] that chiral phosphoric acid catalysts can provide excellent enantioselectivities in a number of new transformations.[8] An important later development in chiral phosphoric acid catalysis has been the enantioselective reduction of unsymmetric ketimines.[9] These reductions, first reported in a general study by Rueping,[9a] and then subsequently by List,[9b] show that imines derived from a wide variety of ketones could be reduced with excellent enantioselectivity. MacMillan reported, soon thereafter, that a general one-pot asymmetric reductive amination starting directly from the ketone, a reaction long sought by organic chemists, was possible with this chemistry.[9c] While these publications are excellent, they only contain a limited amount of *cyclic* α-imino ester substrates. It became apparent to us that a general, highly enantioselective, organocatalytic reduction of *acyclic* α-imino esters was not previously reported. We wish to communicate our results, which show that acyclic α-imino esters can be reduced to provide α-amino esters in high yield and with excellent enantioselectivity using a chiral VAPOL[10] derived phosphoric acid catalyst.

Due to the previous success we have found using phosphoric acid catalysts prepared from the bisphenols VAPOL[11] and VANOL (Figure 1), we chose to begin an evaluation of their potential ability in the asymmetric reduction of imines derived from α-keto esters.

Our initial experiments proved successful as **PA-1e** catalyzed the Hantzsch ester reduction of **2a** to give moderate enantioselectivities of the corresponding α-amino ester **3a** in chloroform and in dichloromethane (Table 1, entries 1 and 2). Coordinating solvents such as THF and 1,4-dioxane gave considerably reduced yields (entries 3 and 4). However, the reaction provided quantitative conversion and excellent enantiomeric excess (96%) in nonpolar and noncoordinating solvents such as benzene and toluene (entries 5 and 6). Methyl ester substitution (entry 7) gave a slight improvement in enantiomeric excess, but the resulting α-amino ester proved difficult to separate from the Hantzsch ester byproduct so subsequent chemistry was evaluated with ethyl ester substitution.

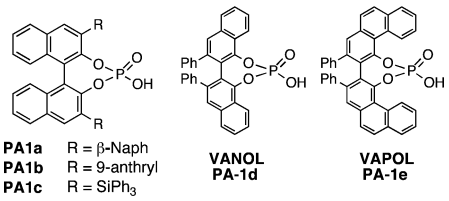
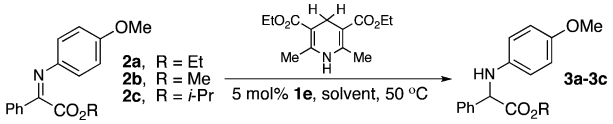


Figure 1. Chiral phosphoric acids.

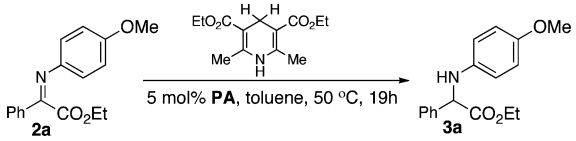
Table 1. The Effect of Solvent on the Catalytic Asymmetric Reduction of Imino Esters with Catalyst **1e**



entry	substrate	solvent	time, h	yield, %[a]	ee
1	**2a**	$CHCl_3$	20	73	47
2	**2a**	CH_2Cl_2	20	78	55
3	**2a**	THF	24	<1	ND
4	**2a**	1,4-dioxane	20	<5	ND
5	**2a**	benzene	20	99	96
6	**2a**	**toluene**	**19**	**99 (93)**[b]	**96**
7	**2b**	toluene	21	99	**98**
8	**2c**	toluene	88	16	5

[a] Determined by ^{1}H NMR. [b] Isolated yield.

Table 2. The Effect of Phosphoric Acid Catalyst on Imino Ester Reduction



entry	catalyst	yield, %[a]	ee
1	**1a**	29	27
2	**1b**	77	80
3	**1c**	6	1
4	**1d**	<5	17
5	**1e**	**99 (93)**[b]	**96**

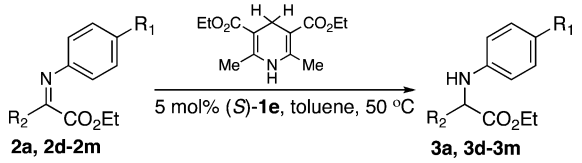
[a] Determined by ^{1}H NMR. [b] Isolated yield.

Isopropyl ester substitution (entry 8) gave a much lower yield and a very low enantioselectivity (5%), presumably due to steric hindrance.

An evaluation of a variety of chiral phosphoric acids in the reduction of α-imino esters confirmed to us that **1e** was a superior catalyst (Table 2). Catalyst **1a** (entry 1), while somewhat bulky, did not provide good reactivity (29% NMR yield) or enantioselectivity (27%). Catalyst **1b** (entry 2), a much more hindered acid, provided the amino ester in a moderate ee, while **1c** (entry 3), the catalyst used by MacMillan[9c] for the successful asymmetric reductive amination of ketones, was virtually inactive using the

10.1021/ja070519w CCC: $37.00

Table 3. VAPOL Phosphoric Acid-Catalyzed Asymmetric Reduction of α-Imino Esters



entry	R_1	R_2	time, h	yield, %[a]	ee
1	OMe	Ph	19	93	96(*R*)[d]
2	OMe	4-MeC_6H_4	22	98	96
3	OMe	4-MeOC_6H_4	22	96	94
4	OMe	4-ClC_6H_4	18	95	98
5	OMe	4-BrC_6H_4	18	93	98
6	OMe	4-$CF_3C_6H_4$	21	98	96
7	OMe	3,5-FC_6H_3	18	95	98
8	H	Ph	18	94	95
9[b]	OMe	Me	21	88	99(*S*)[d]
10[b]	OMe	$(CH_2)_5CH_3$	18	90	96
11[b]	OMe	CH_2CH_2Ph	19	85[c]	98

[a] Isolated yields. [b] Imino esters were formed in situ from the corresponding keto ester and *p*-anisidine in the presence of 4 Å molecular sieves (reductive amination). Entries 9 and 10 were run at room temperature. [c] Yield was determined after LAH reduction to the corresponding alcohol (see Supporting Information). [d] The absolute stereochemistry of **3a** and **3k** was determined after deprotection by comparison with literature rotation data for the known amino acid esters (see Supporting Information).

described conditions. It is interesting that, while our previously reported imine amidation chemistry[11] was particularly sensitive to the purification methods for **1e**, the above chemistry shows no deleterious effects even with batches of catalyst that have given less than ideal results with the methodology in ref 11.

In an effort to establish generality, we initiated a study where we varied the α-imino ester substrate (Table 3). Aryl substitution on the imine carbon (R_2) showed no deleterious effects when *para*-electron-donating groups were used (entries 2 and 3). Likewise, the use of *para*-electron-withdrawing groups on the arene ring gave a substrate that could be reduced with excellent yield and selectivity (entries 4−6). A *meta*-substituted (3,5-FC_6H_3) arene was also a suitable substrate for this reaction (entry 7).

When the imine nitrogen was substituted with a phenyl group (R_1 = H, entry 8), the chemistry was virtually identical to the *p*-methoxyphenyl-substituted case (entry 1). We were pleased to find that in our initial evaluation the use of primary alkyl-substituted ketimines is suitable for reductions, providing high yield and enantiomeric excess in three cases (entries 9−11). It should be noted that in these three examples the imines were not preformed but generated in situ in the presence of molecular sieves, before the asymmetric reduction (reductive amination). In the last case (entry 11), the resulting α-amino ester could not be separated cleanly from the Hantzsch ester byproduct, so subsequent LAH reduction was necessary to provide an isolated yield (85% over two steps). We determined the absolute stereochemistry of products **3a** and **3k** via CAN deprotection of the PMP group and comparison with the absolute rotation and ee of the respective known amino acid ester.[12]

During the discovery of this chemistry, we have found that, in general, the use of in situ generated α-imino esters gave lower overall yields (10−20%) but identical ee's. However, in the three cases utilizing alkyl-substituted α-imino esters, we found good yield. These investigations provide clear evidence that this methodology can be adapted to a general one-pot procedure, albeit with some potential loss in yield.

In conclusion, we have developed chemistry whereby the C═N group of α-imino esters can be reduced with excellent yield and enantioselectivity utilizing hindered chiral phosphoric acids.

Acknowledgment. We thank the University of South Florida for generous start-up funds and a New Researcher Award. J.C.A. also thanks the Petroleum Research Fund for additional funding (PRF 45899-G1). The authors also thank Emily B. Rowland for catalyst preparation.

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

References

(1) (a) *Synthesis of Optically Active Amino Acids*; Williams, R. M., Ed.; Pergamon Press: Oxford, 1989. (b) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290.

(2) For reviews of the catalytic asymmetric Strecker reaction, see: (a) Groger, H. *Chem. Rev.* **2003**, *103*, 2795. (b) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764. (c) Vachel, P.; Jacobsen, E. N. *Comp. Asymmetric Catal., Suppl.* **2004**, *1*, 117.

(3) For reviews in this area, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518.

(4) (a) Johannsen, M. *Chem. Commun.* **1999**, 2233. (b) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114.

(5) (a) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (b) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (c) Burk, M. J.; Bienewald, F. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol. 2.

(6) (a) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer: Heidelberg, 1999. (b) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994. (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (d) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 6360.

(7) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.

(8) For recent review articles on the use of chiral Brønsted acids as catalysts, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (c) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (f) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909.

(9) (a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (d) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (e) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832. (f) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.

(10) Note: for details on the current commercial availability of VAPOL, VANOL, and their phosphoric acids, see the Supporting Information. For their synthesis, see: Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-Y.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.

(11) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696.

(12) See Supporting Information for requisite details.

JA070519W