Communication

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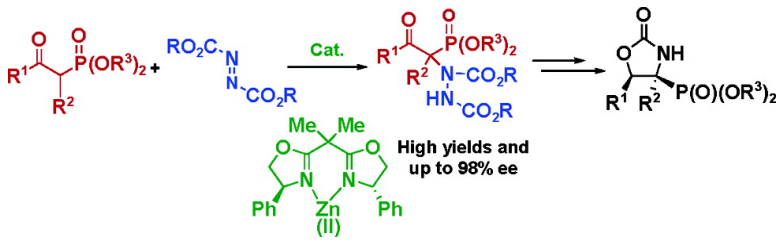

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An Easy Approach to Optically Active α-Amino Phosphonic Acid Derivatives by Chiral Zn(II)-Catalyzed Enantioselective Amination of Phosphonates

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Optically active α-amino phosphonic acids[1] have found widespread use as analogues of α-amino acids, where the tetrahedral phosphonic acid functionality replaces the planar and less bulky carboxylic acid. α-Amino phosphonic acids have been employed as single units, as well as incorporated into peptides where the phosphonamide moiety is able to mimic the tetrahedral transition states of enzyme-mediated peptide bond hydrolysis. These structural features cause a unique enzyme response which led to the discovery of new antibacterial agents[2] and inhibitors of protease,[3,4] including HIV-protease.

The stereoselective formation of optically active α-amino phosphonic acid derivatives[5] is an important task for organic chemists due to the interesting and important biological properties of these compounds. On the basis of the type of bond-forming reaction, several different approaches toward α-amino phosphonic acids are conceivable (Scheme 1, paths a−d). One direct approach involves the nucleophilic addition of a phosphite to an imine (path a, C−P bond formation).[6] Path b (C−C bond formation) employs the anionic phosphonic analogue of glycine, which adds to an electrophilic carbon center.[7] Conversely, the addition of nucleophiles[8] to cationic phosphonoglycine equivalents has also been applied for the asymmetric synthesis of α-amino phosphonic acids (path c, C−C bond formation). Another attractive solution is provided by the electrophilic amination of a formally α-phosphonate carbanion (path d, C−N bond formation).[9]

Following path d in Scheme 1 for the formation of optically active α-amino phosphonic acids, a variety of asymmetric reactions have been developed utilizing the chiral auxiliary principle.[9] However, according to the best of our knowledge, no direct catalytic enantioselective formation of C−N bonds has been developed for the preparation of optically active α-amino phosphonic acid derivatives. In this communication, we present the catalytic enantioselective direct amination[10] of *β*-keto phosphonates catalyzed by chiral zinc(II) complexes giving optically active α-amino phosphonic acid derivatives in good yields and very high enantioselectivities.[11]

Several different chiral bisoxazoline−metal(II) complexes can catalyze the catalytic enantioselective α-amination of (1-methyl-2-oxo-2-phenylethyl)phosphonic acid diethyl ester **1a** with diethyl and dibenzyl azodicarboxylates **2a**,**b** (eq 1) (see Supporting Information). Table 1 shows the results of the use of a catalyst formed by a combination of chiral bisoxazoline ligands and $Zn(OTf)_2$. The chiral ligand (*S*)-**4c** gave the best results compared with those of (*R*,*R*)-**4b** and (*S*)-**4a** (Table 1, entries 1−3). For catalyst $Zn(OTf)_2$−(*S*)-**4c**, the aminated product **3a** was obtained in high yield and with up to 92% ee using **2a** as the aminating reagent in various solvents at room temperature (entries 3−5). It should be noted that increasing the reaction temperature to 40 °C led to higher conversion, and the high enantiomeric excess of the product was still maintained (entry 6). Compound **2b** is also a suitable aminating reagent (entry 7), as high yield and enantiomeric excess of **3b** were obtained. Furthermore, the use of a base such as Et_3N or other additives, such as HFIP[12] (entry 8), did not have any influence on the outcome of the amination reaction.

Scheme 1. Different Approaches to α-Amino Phosphonic Acids Based on the Type of Bond Formed

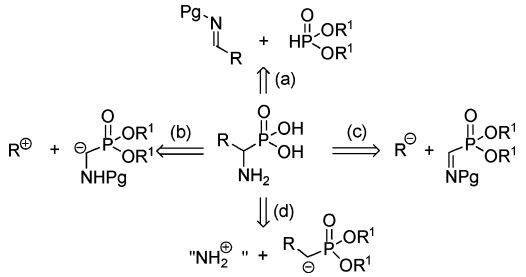
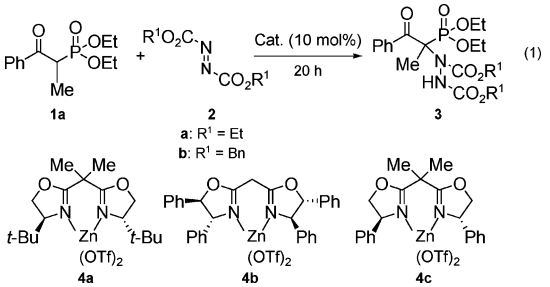


Table 1. Catalytic Enantioselective α-Amination of (1-Methyl-2-oxo-2-phenylethyl)phosphonic Acid Diethyl Ester **1a** with Azodicarboxylates **2a**,**b** under Various Conditions



entry	catalyst	azodicarboxylate	solvent	*T* (°C)	conv.[a] (%)	ee[b] (%)
1	**4a**	**2a**	CH_2Cl_2	rt	20	12
2	**4b**	**2a**	CH_2Cl_2	rt	30	−26
3	**4c**	**2a**	CH_2Cl_2	rt	80	92
4	**4c**	**2a**	Et_2O	rt	90	82
5	**4c**	**2a**	$Cl(CH_2)_2Cl$	rt	88	91
6	**4c**	**2a**	CH_2Cl_2	40	96	89
7	**4c**	**2b**	CH_2Cl_2	rt	90	92
8[c]	**4c**	**2b**	CH_2Cl_2	rt	90	92

[a] Determined by ^1H NMR. [b] Enantiomeric excess determined by chiral stationary phase HPLC. [c] HFIP (1 equiv added).

The enantioselective α-amination reaction was shown to be a general reaction for both acyclic and cyclic *β*-keto phosphonates using dibenzyl azodicarboxylate **2b** as the nitrogen source and $Zn(OTf)_2$−(*S*)-**4c** as the catalyst (eq 2), as shown in Table 2.

Acyclic *β*-keto phosphonates bearing alkyl, benzyl, naphthyl, or phenyl substituents as R^1 (**1a**−**d**) all reacted smoothly with dibenzyl

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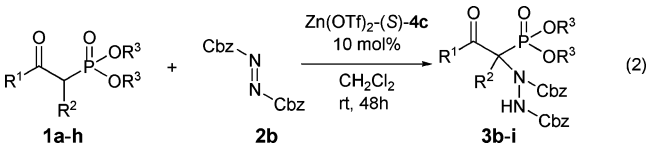
Table 2. Catalytic Enantioselective α-Amination of Acyclic and Cyclic β-Keto Phosphonate Esters **1a**−**h** with **2b** in the Presence of 10 mol % $Zn(OTf)_2$−(*S*)-**4c**



(2)

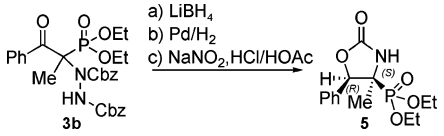
1a-h **2b** **3b-i**

	β-Keto Phosphonate				
entry	R^1	R^2	R^3	yield[a] (%)	ee[b] (%)
1	Ph	Me	Et (**1a**)	85 − **3b**	92
2	2-Np	Me	Et (**1b**)	93 − **3c**	92
3	Bn	Me	Et (**1c**)	60 − **3d**	95
4	Me	Me	Et (**1d**)	75 − **3e**	85
5	Ph	Allyl	Et (**1e**)	85 − **3f**	98[c,d]
6	Ph	Me	Me (**1f**)	97 − **3g**	94
7		$(CH_2)_3$	Et (**1g**)	98 − **3h**	95
8		$(CH_2)_4$	Et (**1h**)	98 − **3i**	94

[a] Isolated yield. [b] Enantiomeric excess determined by chiral stationary phase HPLC. [c] Enantiomeric excess determined after forming oxazolidinone (see Supporting Information). [d] At 140 h reaction time.

azodicarboxylate **2b** to give the corresponding α-aminated adducts **3b**−**e** in good isolated yields and with high enantiomeric excesses (Table 2, entries 1−4). The reaction of the α-allyl−β-keto phosphonate ester **1e** with **2b** also afforded the corresponding optically active aminated adduct **3f** in 85% yield and with excellent enantioselectivity (98% ee) (entry 5). Changing the ester functionality from ethyl phosphonate (**1a**) to methyl phosphonate (**1f**) improved the yield and enantioselectivity slightly (entry 6). The catalytic enantioselective amination of the cyclic β-keto phosphonates **1g**,**h** proceeded also in high yields and in a highly enantioselective manner as 95 and 94% ee was obtained for the two different ring sizes (entries 7 and 8).

Scheme 2. Formation of Oxazolidinone **5**



To make the catalytic enantioselective Lewis acid-catalyzed α-amination reaction of β-keto phosphonates more useful, further transformations of the α-aminated product were achieved (Scheme 2). Reduction of the β-keto functionality in **3b** proceeded in a high diastereoselective manner using $LiBH_4$ giving the *N*-amino oxazolidinone. Further deprotection and N−N bond cleavage afforded the oxazolidinyl−phosphonic acid derivative, (4-methyl-2-oxo-5-phenyloxazolidin-4-yl)phosphonic acid diethyl ester **5**, in 60% overall yield and with a diastereomeric ratio of >10:1. The absolute configuration of **5** was determined by X-ray analysis (see Supporting Information). The formation of the optically active **5** represents a new alternative procedure to the Ru−BINAP procedure developed by Noyori et al.[13]

The stereochemical outcome of the reaction catalyzed by $Zn(OTf)_2$−(*S*)-**4c** can be accounted for by a tetrahedral intermediate in which it is assumed that it is the enolate form of β-keto phosphonate which coordinates to the Lewis acid.[14] In this intermediate, a six-membered chairlike transition state is formed leaving the *Re* face of the α-carbon atom of the β-keto phosphonate accessible for the amination reagent, leading to the observed stereochemical outcome of the reaction. See Supporting Information for the proposed intermediate.

In summary, we have developed a highly enantioselective amination reaction of β-keto phosphonates with commercially available azodicarboxylates catalyzed by a combination of chiral bisoxazoline ligands and $Zn(OTf)_2$. After deprotection, the corresponding optically active α-amino−β-hydroxy phosphonic acid derivatives were obtained.

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Supporting Information Available: Complete experimental procedures and characterization of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Kafarski, P.; Lejczak, B. *Phosphorous, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. (b) *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons, 2000. (c) Palacios, F.; Alanso, C.; Sanros, J. *Chem. Rev.* **2005**, *105*, 899 (this is a review dealing with β-amino phosphonates).

(2) (a) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29. (b) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234. (c) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassal, C. H.; Homes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56.

(3) (a) Ginnousis, P. P.; Bartleet, P. A. *J. Med. Chem.* **1987**, *30*, 1603. (b) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652.

(4) (a) Peyman, A.; Budt, K.-H.; Spanig, J.; Stowasser, B.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 4549. (b) Peyman, A.; Stahl, W.; Wagner, K.; Ruppert, D.; Budt, K.-H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2601. (c) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625. (d) Haebich, D.; Hansen, J.; Paessens, A. Eur. Pat. Appl. EP 472077, 1992, Bayer A. G.; *Chem. Abstr.* **1992**, *117*, 27161z. (e) Powers, J. C.; Boduszek, B.; Oleksyszyn, J. PCT Int. Appl. WO 95 29691, 1995, Georgia Technol. Research Corp.; *Chem. Abstr.* **1996**, *124*, 203102m.

(5) Gröger, H.; Hammer, B. *Chem.*−*Eur. J.* **2000**, *6*, 943.

(6) (a) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (b) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656. (c) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (d) Schlemminger, I.; Saida, Y.; Gröger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818. (e) Gröger, H.; Saida, Y.; Arai, S.; Martens, J.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9291. (f) Davis, F. A.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 7249 and references therein.

(7) (a) Baldwin, I. C.; Williams, M. J.; Beckett, P. P. *Tetrahedron*: *Asymmetry* **1995**, *6*, 679. (b) Sawamura, M.; Ito, J. *Tetrahedron Lett.* **1989**, *30*, 2247. (c) Togni, A.; Pastor, S. D. *Tetrahedron Lett.* **1989**, *30*, 1071.

(8) Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558.

(9) (a) Hanessian, S.; Bennani, Y. L. *Synthesis* **1994**, 1272. (b) Denmark, S. E.; Chatani, N.; Pansare, S. V. *Tetrahedron* **1992**, *48*, 2191. (c) Pagliarin, R.; Papeo, G.; Sello, G.; Sisti, M. *Tetrahedron* **1996**, *52*, 13783. (d) Jommi, G.; Miglierini, G.; Pagliarin, R.; Sello, G.; Sisti, M. *Tetrahedron* **1992**, *48*, 7275.

(10) Reviews: (a) Greck, C.; Droillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, *7*, 1377. (b) Erlik, E. *Tetrahedron* **2004**, *60*, 8747. For chiral Lewis acid-catalyzed reactions, see: (c) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420. (d) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367. (e) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595.

(11) For catalytic halogenation and Mannich reactions of β-keto phosphonates, see: (a) Bernardi, L.; Jørgensen, K. A. *Chem. Commun* **2005**, 1324. (b) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimazu, T.; Umebayashi, N.; Tamura, T.; Sesamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447. (c) Kjærsgaard, A.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 804.

(12) For example, where HFIP was used in catalytic asymmetric reactions, see: (a) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Wills, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

(13) Kitamura, M.; Tokunaga, M.; Pham, T.; Lubell, W. D.; Noyori, R. *Tetrahedron Lett.* **1995**, *36*, 5769.

(14) For an investigation of Lewis acid−bisoxazoline intermediates, see: Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem.*−*Eur. J.* **2002**, *8*, 1888.

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