Pergamon

Tetrahedron Letters 40 (1999) 2565–2568

TETRAHEDRON LETTERS

Catalytic Asymmetric Addition of Diphenylphosphine Oxide to Cyclic Imines

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Received 26 December 1998; accepted 22 January 1999

Abstract

The catalytic asymmetric addition of diphenylphosphine oxide to cyclic imines is reported for the first time. The addition, catalyzed by a heterobimetallic lanthanoid complex, gives the corresponding amino phosphine oxide products in good to excellent yields and up to 93% ee. The preliminary result of the application of one of these products as a chiral ligand is also described.

Keywords: diphenylphosphine oxide; asymmetric addition; cyclic imines; heterobimetallic catalysis; borane reduction.

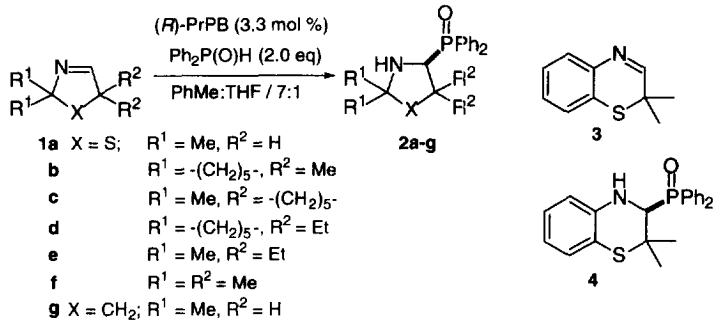
Interest in α-aminophosphorus compounds, in particular α-aminophosphonic acids and their analogs, has greatly increased over the years [1,2]. Applications of these acyclic compounds are very diverse with their uses ranging from herbicides [3] to enzyme inhibitors [4]. More recently however, cyclic α-amino phosphonates have proven to be important and promising applications have been published [5,6]. The high biological activity of these phosphorus-containing compounds together with their use in the development of new chiral ligands, has hugely increased the need for their syntheses in enantiomerically pure forms.

We have recently reported a highly efficient route to α-amino phosphonates by the catalytic enantioselective addition of dimethylphosphite to acyclic [7,8] and cyclic imines [9,10], using heterobimetallic LPB and YbPB complexes, respectively. To further demonstrate the practical usefulness of these reactions we initially investigated the syntheses of novel asymmetric α-amino phosphine oxides and α-amino phosphines as potentially important biologically active precursors and also as possible chiral ligands. We considered that the syntheses of cyclic amino phosphine oxides would provide both promising medicinal candidates and also more efficient chiral ligands than their acyclic counterparts. However, direct conversion of the phosphonate into the corresponding phosphine oxide (by addition of PhMgBr) failed, as deprotonation of the amine hydrogen caused the elimination of the phosphite group, thus regenerating the imine. Consequently, we considered that the asymmetric introduction of phosphine oxide should be developed, and started to investigate the feasibility of the catalytic asymmetric addition of diphenylphosphine oxides to cyclic imines.

We now wish to report the first catalytic asymmetric addition of diphenylphosphine oxide to

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00203-8

cyclic imines to afford α-amino phosphine oxides in 75-93% ee and in 50-98% yield. Furthermore, a preliminary application of product **2g** as a chiral ligand is also described.



Several important reasons for developing an efficient method for the addition of diphenylphosphine oxide in an asymmetric manner should be considered. Since the deprotonated phosphine oxide will be coordinated to the center metal, the optimum size of the reaction space in the catalyst should be different for diphenylphosphine oxide and dimethylphosphite. This size difference, which can be altered by changing the lanthanoid metal, could give rise to differing reactivities of the catalyst species. Also, because diphenylphosphine oxide should be deprotonated by the heterobimetallic catalyst, the pKa difference between phosphine oxide and phosphite could alter the degree of asymmetric induction. Therefore, the Brönsted basisity of the catalyst should be optimized by changing the alkali metal [11,12].

We prepared thiazoline **1a** [13] and used it to optimize our hydrophosphination reaction, as it has already been shown to be an excellent substrate for the asymmetric addition of dimethyl phosphite. Firstly, we examined the effect of rare earth metals in the LnPB complex upon the hydrophosphination reaction. Several lanthanoid metals were screened and all gave excellent results (88-91% ee), however, the use of Pr proved to be the best. The choice of alkali metal for the PrMB complex proved to be important, with K giving a better result (89% ee) than either Li (78% ee) or Na (87% ee). Interestingly, the introduction of potassium using KHMDS gave a better yield (98%) than when KO'Bu was used (90%), although ees were the same. Next we investigated the effect of catalyst amount (3.3-20 mol %) and phosphine oxide addition (1.0-5.0 eq), and again all results were excellent (89-92% ee), but 3.3 mol% of PrPB and 2.0 equivalents of phosphine oxide were optimum. Finally, solvent effects were examined and we observed that this reaction gives excellent yields and ees (82-91% ee) with a variety of solvents, however, a 7:1 ratio of toluene:THF gave the best result. The optimized result for this substrate, 98% yield and 91% ee, was extremely encouraging as it was better than the reported hydrophosphonylation of the same imine [9].

Once the reaction conditions had been optimized, thiazolines **1b-f**, benzothiazine **3** [13], and pyrroline **1g** [14] were synthesized to investigate the scope of the reaction. Addition of diphenylphosphine oxide gave the thiazolidinylphospine oxides **2b-f** in 81-93% ee and in 50-

98% yield, pyrrolidinylphosphine oxide **2g** in 75% ee and in 63% yield, and thiazinylphosphine oxide **4** in 82% ee and in 72% yield. Importantly, recrystallization using CH_2Cl_2/hexane gave both phosphine oxide products **2a** and **2f** in 99% ee and approximately 80% yield.

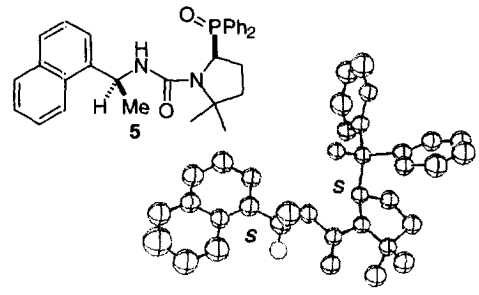
Treatment of pyrrolidinylphosphine oxide **2g** with *S*-1-(1-napthyl)ethyl isocyanate gave the corresponding urea **5** in good yield (70%). Recrystallization (by slow evaporation of a THF solution) allowed us to unequivocally determine the absolute configuration of this urea as *S* by X-ray crystallography (R value = 7%). This is the same absolute configuration as the sulfur-containing hydrophosphonylation products, and although we have so far been unable to assign the absolute configuration of the thiazolidinylphospine oxides, we believe that they will also have the same stereochemistry.

Table 1. Preparation of phosphine oxide products

Imine	Product	yield (%)	ee (%)
1a	**2a**	98	91 [a]
1b	**2b**	98	93 [a]
1c	**2c**	95	92 [a]
1d	**2d**	98	81 [a]
1e	**2e**	76	82 [a]
1f	**2f**	50	92 [a]
1g	**2g**	63	75 [b]
3	**4**	72	82 [a]

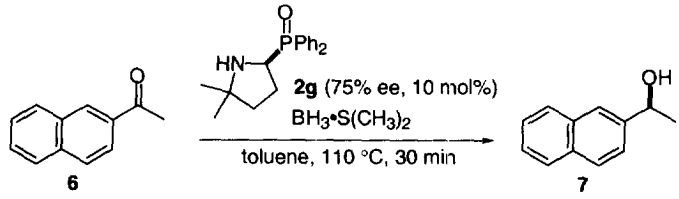
[a] 50 °C, 50 h. [b] Room temperature, 96 h.

X-ray structure of urea **5**



We have developed a highly efficient catalytic asymmetric addition of diphenylphosphine oxide to cyclic imines to give the amino phosphine oxides **2a-g** and **4** in good to excellent ees and good to excellent yields. To the best of our knowledge this is the first reported example of its kind [15].

Applications of the amino phosphine oxide products currently being investigated include the examination of their biological activities and also their usefulness as chiral ligands. Preliminary results show that pyrrolidinylphosphine oxide **2g** (75% ee) catalyzes the reduction of ketone **6**, in the presence of $BH_3 \bullet S(CH_3)_2$, to give the corresponding alcohol **7** in good yield (56%) and moderate ee (21%) [16,17].



Further applications of the amino phosphine oxide products are currently being investigated.

General Procedure : $Pr(O^iPr)_3$ [18] (448 μL of a 0.2 M solution in THF, 0.09 mmol), KHMDS (476 μL of a 0.57 M solution in toluene, 0.27 mmol) and H_2O (90 μL of a 1.0 M solution in THF, 0.09 mmol) were added sequentially to a stirred solution of pre-dried (*R*)-BINOL (77 mg, 0.27 mmol), in THF (2.5 mL) under argon. The solution was stirred for 1 hour at room temperature, then the solvent was evaporated under reduced pressure, and toluene:THF / 7:1 (3.6 mL) was added. The pale yellow solution was stirred for 1 hour at room temperature to give the (*R*)-PrPB catalyst solution (0.025 M).

To the above freshly prepared (*R*)-PrPB solution (3.6 mL of a 0.025 M solution, 0.09 mmol) under argon, was added thiazoline **1a** (857 mg, 2.7 mmol), and the mixture was stirred for 10 mins at room temperature. Diphenylphosphine oxide (1.09 g, 5.91 mmol) was added and the suspension was stirred at 50 °C for 50 hours. The reaction mixture was quenched by addition of sat. NH_4Cl solution and then neutralized with sat. $NaHCO_3$ solution. The aqueous layer was extracted several times with EtOAc, and the combined organic layers were washed with sat brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a yellow oil, which solidified on standing. Purification of the crude material by flash column chromatograpthy (EtOAc:hexane / 1:1 as eluent) afforded the thiazolidinylphosphine oxide **2a** as a white powder in 98% yield. The enantiomeric excess was determined to be 93% by chiral HPLC analysis (Daicel CHIRALPAK AS, ^iPrOH/Hex = 1/9, flow rate: 1.0 mL/min, retention time = 10 min and 15 min).

Acknowledgments:

CREST and JSPS are thanked for their financial support. Prof. Nakamura and Dr. Isobe, at The University of Tokyo, are thanked for their kind assistance with X-ray crystallography.

References and Notes

[1] Sardarian, A. R.; Kaboudin, B. *Tetrahedron Lett.* **1997**, *38*, 2543-2546.
[2] Takahashi, H.; Yoshioka, M.; Imai, N.; Onimura, K.; Kobayashi, S. *Synthesis* **1994**, 763-764.
[3] Franz, J. E. *Chem. Abstr.* **1972**, *77*, 165079k.
[4] Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193-215.
[5] Boduszek, B.; Oleksyszyn, J.; Kam, C-M.; Selzler, J.; Smith, R. E.; Powers, J. C. *J. Med. Chem.* **1994**, *37*, 3969-3976.
[6] Powers, J. C.; Boduszek, B.; Oleksyszyn, J. PCT Int. Appl. WO 95 29691. **1995**.; *Chem. Abstr.* **1996**, *124*, 203102m.
[7] Sasai, H.; Arai, A.; Tahara, M.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656-6657 and references cited therein.
[8] By using the catalytic asymmetric hydrophosphonylation method with LPB, several α-amino phosphonic acids are commercially available from Hokko Chemical Industry Co., Ltd. and Aldrich.
[9] Gröger, H.; Saida, Y.; Arai, S.; Martens, J.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9291-9292.
[10] Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089-3103.
[11] Shibasaki, M.; Sasai, H.; Arai, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236-1256.
[12] Shibasaki, M.; Iida, T.; Yamada, Y. M. A. *J. Synth. Org. Chem. Japan* **1998**, *56*, 344-356.
[13] Gröger, H.; Tehranfar, D.; Martens, J. *Heteroatom Chem.* **1997**, *8*, 207-215.
[14] Bonnett, R.; Clark, V. M.; Giddey, A.; Todd, S. A. *J. Chem Soc.* **1959**, 2087-2093.
[15] A diastereoselective reaction was recently reported: Gaumont, A.-C.; Simon, A.; Denis, J.-M. *Tetrahedron Lett.* **1998**, *39*, 985-988.
[16] Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1986-2012.
[17] Gamble, M. P.; Smith, A. R. C.; Wills, M. *J. Org. Chem.* **1998**, *63*, 6068-6071.
[18] Purchased from Kojundo Chemical Laboratory Co., Ltd. Fax: +81-492-84-1351.