Synthesis of a New Chiral Cyclic *o*-Hydroxynaphthylphosphonodiamide and its Application as Ligand Catalyst in Asymmetric Silylcyanation of Aromatic Aldehydes

Ke He, Zhenghong Zhou,* Lixin Wang, Kangying Li, Guofeng Zhao, Qilin Zhou, Chuchi Tang

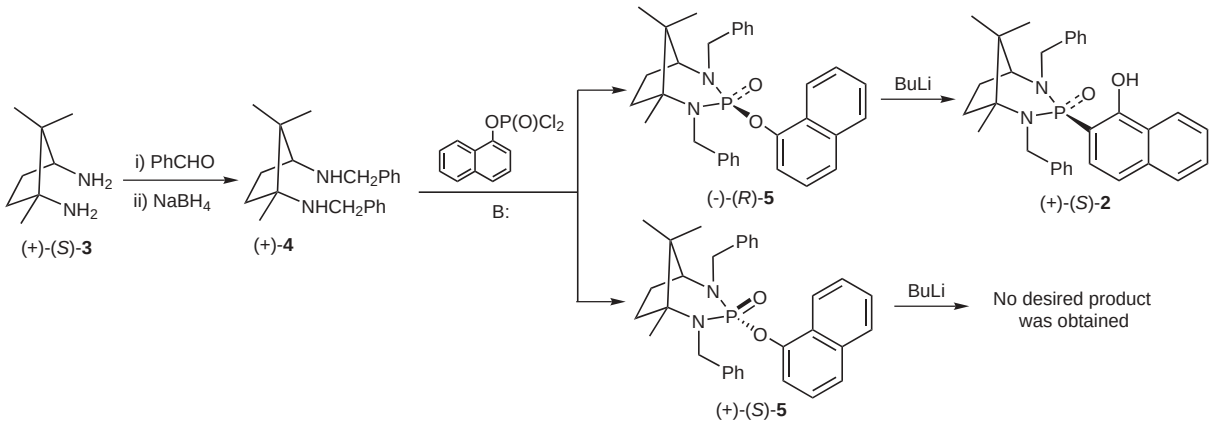
State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China
Fax +86(22)23503438; E-mail: z.h.zhou@nankai.edu.cn

Received 24 March 2004

Abstract: A new chiral cyclic *o*-hydroxynaphthylphosphonodiamide (+)-**2** was synthesized starting from (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine. The absolute configuration of phosphorus atom was determined as *S* by X-ray diffraction analysis. Excellent enantioselectivity (up to 98.3% ee) was achieved in asymmetric silylcyanation of aromatic aldehydes using a chiral titanium complex prepared in situ from Ti(O*i*-Pr)$_4$ and (+)-**2** as the catalyst.

Key words: chiral phosphonodiamide, asymmetric silylcyanation, catalysis, enantioselectivity, aromatic aldehyde

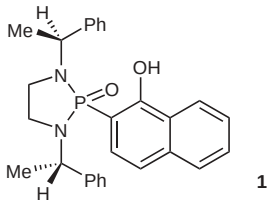
Optically active cyanohydrins are important intermediates in organic synthesis for the synthesis of a variety of valuable classes of chiral compounds, such as α-amino acids, α-hydroxyl carboxylic acids, β-amino alcohols, vicinal diols, α-hydroxyketones, etc. Many efficient approaches have been reported for obtaining them by biochemical and chemical methods.[1] In the latter, the most important one was the asymmetric silylcyanation of aldehydes with trimethylsilylcyanide catalyzed by a Lewis acid, such as Ti(O*i*-Pr)$_4$, $TiCl_4$, $AlCl_3$, $SmCl_3$, etc. in the presence of a chiral ligand. In this reaction, a wide range of chiral ligands have been elaborated, such as Schiff bases,[2] diols,[3] diamides,[4] phosphorus compounds,[5] etc. As shown in literature, most of the effective chiral ligands have a free hydroxyl group or an amino group bearing at least a N-H bond which is favorable to coordinate conveniently with the metal atom in Lewis acid. Thus the moiety of the coordinated metal atom should work as a Lewis acid center (LA). Moreover, if a phosphoryl group (P=O) is existed at an appropriate position in the ligand molecule, the unshared electron pair on oxygen atom should act as a Lewis base (LB). In the catalyst, it contains both a Lewis acid center and a Lewis base center, namely, LALB catalyst. It is a new type of chiral bifunctional catalyst.[5b] Based on these findings, recently, a new cyclic *o*-hydroxynaphthylphosphonodiamide (**1**) was synthesized starting from (–)-α-phenylethylamine and employed in the asymmetric silylcyanation of aromatic aldehydes in the presence of Ti(O*i*-Pr)$_4$ by our research group. The corresponding cyanohydrins were obtained in high chemical yields with good to excellent enantiomeric excesses up to 90%.[6] In order to further improve the enantioselectivity of this type of cyclophosphonodiamides, in this paper, we will report the synthesis of a new cyclic *o*-hydroxynaphthylphosphonodiamide (**2**) containing a phosphorus stereocenter starting from (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine (**3**) and its application in asymmetric silylcyanation of aromatic aldehydes (Figure 1, Scheme 1).



(+)-(*S*)-**3** (+)-**4** (-)-(*R*)-**5** (+)-(*S*)-**2** (+)-(*S*)-**5**

Scheme 1

SYNLETT 2004, No. 9, pp 1521–1524
Advanced online publication: 29.06.2004
DOI: 10.1055/s-2004-829075; Art ID: U08304ST



1

Figure 1

Dibenzylation of (+)-**3**[2i] derived from D-camphor led to *N*,*N*′-dibenzyl-1,2,2-trimethylcyclopentane-1,3-diamine (**4**). The cyclization of the latter with *O*-1-naphthyl phosphorodichloridate afforded *O*-naphthyl phosphorodiamidate (**5**). A pair of diastereomers of **5** was obtained via column chromatography. A subsequent P-O to P-C rearrangement upon treatment of (–)-**5** with *n*-BuLi resulted in the formation of cyclic (+)-*o*-hydroxynaphthylphosphonodiamide (**2**). The corresponding rearrangement product of (+)-**5** was not obtained under the same conditions. The absolute configuration of the phosphorus atom in (+)-**5** was determined as *S* via *X*-diffraction analysis.[7] Thus the absolute configuration of the phosphorus atom in (–)-**5** should be *R*. At the same time, crystallographic study shown that the absolute configuration of the phosphorus atom in (+)-**2** was *S*.[8] Therefore, the rearrangement from (–)-**5** to (+)-**2** proceeded with total retention of configuration at the phosphorus atom.

The catalytic effect of the titanium complex formed in situ from (+)-(*S*)-**2** and Ti(O*i*-Pr)$_4$ in asymmetric silylcyanation of aromatic aldehydes was investigated. The experimental results were listed in Table 1.

Usually, the silylcyanation reaction was best conducted in methylene chloride. We firstly examined the influence of the amount of ligand used on the enantioselectivity of the reaction. It was found that a variation of decrease in yield and enantiomeric excesses value was observed depending on the substrate employed with the reducing of the amount of (+)-(*S*)-**2** from 40 mol% to 20 mol%. As to the substrate *o*-methoxybenzaldehyde whose ee value was 98% and 97%, respectively, only a very slight change in yield and enantioslectivity was observed (entries 6 and 7). While for some substrates, such as *p*-methoxybenzaldehyde, *m*-methoxybenzaldehyde and α-naphthyl aldehyde, this change led to an obvious decrease in enantioselectivity (entries 12 and 13, 14 and 15, 18 and 19). Further reducing the amount of (+)-(*S*)-**2** to 10 mol% resulted in remarkable decrease both in yield and enantioselectivity (entry 8). These results showed that the change from the ligand **1** to (+)-(*S*)-**2** led to a significant improvement in the enantioselectivity. Under the same condition, the use of 40 mol% of ligand **1** led to only 90% ee for the substrate *o*-methoxybenzaldehyde. Although a slight high ligand loading (20–40 mol%) was required for the silylcyanation. However, it is gratifying that ligand (+)-(*S*)-**2** was very stable and could be readily recovered and reused without loss of its catalytic activity and asymmetric induction ability. It was found that a 4:1 molar ratio of ligand to Ti(O*i*-Pr)$_4$ resulted in better enantioselectivity, whereas the use of one equivalent of ligand (+)-(*S*)-**2** per Ti(O*i*-Pr)$_4$ led to higher chemical yield (entries 1, 5 and entries 6, 9). Buono reported that the introduction of *i*-PrOH as an additive has a dramatic influence on the enantioselectivity in asymmetric silylcyanation.[5d] However, only a little increase in selectivity was observed in our research (entries 1, 4 and entries 6, 11). The reaction temperature was also found to be an essential factor to the reaction. The reaction at 20 °C generally led to better results than that carried out at 0 °C. An increase in reaction temperature resulted in a detrimental effect to the reaction due to the instability of the adduct silyl ether. The nature of the substrate aromatic aldehyde has a dramatic influence on the catalytic effect. Generally, the enantioselectivity of aldehyde substituted with electron donating group (methyl and methoxy) on the benzene ring was better than that of electron withdrawing group (chloro and nitro) substituted one. Moreover, the enantioselectivity was also affected by the position of the substituent on the benzene ring. When methoxy substituted benaldehyde was employed as the substrate, it was found that the enantioselectivity falls in the order: *o*>*m*>*p* (entries 6, 14 and 12). This finding indicates that not only the electrical effect but also the position of the subtituent (or steric effect) had a decisive role on the enantioselectivity of the reaction.

In conclusion, a new chiral cyclic *o*-hydroxynaphthylphosphonodiamide (+)-**2** was synthesized and the absolute configuration of phosphorus atom was determined by the X-ray diffraction analysis. Excellent results (up to 98.3% ee) were achieved in the asymmetric silylcyanation of aromatic aldehydes using (+)-**2** as the ligand catalyst in the presence of Ti(O*i*-Pr)$_4$.[10] Investigations on further extending the range of substrates and application of this compound for other asymmetric reaction are continuing in our laboratory.

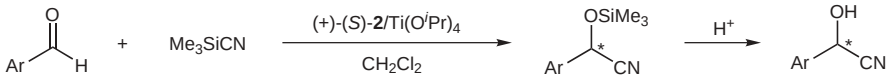
Acknowledgment

We are grateful to the National Natural Science Foundation of China (No. 20272025) and the Ph. D. Programs of Ministry of Education of China for generous financial support for our programs.

References

(1) (a) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147. (b) Schmidt, M.; Herve, S.; Klempier, N.; Griengl, H. *Tetrahedron* **1996**, *52*, 7833. (c) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555. (d) Mori, A.; Nitta, H.; Kudo, M.; Inous, S. *Tetrahedron Lett.* **1991**, *32*, 4333.

Table 1 Asymmetric Silylcyanation of Aromatic Aldehydes Catalyzed by (+)-(*S*)-**2**/Ti(O*i*-Pr)$_4$



Entry	Ar	(+)-(*S*)-**2** (mol%)	Ti(O*i*-Pr)$_4$ (mol%)	*i*-PrOH (mol%)	Reaction temp. (° C)	Yield[a] (%)	$[\alpha]_D$ (*c* 1, $CHCl_3$)	Ee[c] (%)
1	Ph	40	10	20	20	84	+23.8	53 (54.2)[b]
2	Ph	20	5	10	20	74	+19.6	44
3	Ph	40	10	20	0	90	+15.1	34
4	Ph	40	10	/	20	90	+12.5	28
5	Ph	40	40	20	20	96	+22.2	47
6	2-MeOC$_6$H$_4$	40	10	20	20	87	+26.8	98 (98.3)[b]
7	2-MeOC$_6$H$_4$	20	5	10	20	78	+26.4	97
8	2-MeOC$_6$H$_4$	10	2.5	5	20	69	+14.4	53
9	2-MeOC$_6$H$_4$	40	40	20	20	91	+24.5	90
10	2-MeOC$_6$H$_4$	40	10	20	0	78	+25.0	92
11	2-MeOC$_6$H$_4$	40	10	/	20	86	+24.8	91
12	4-MeOC$_6$H$_4$	40	10	20	20	64	+25.5	54
13	4-MeOC$_6$H$_4$	20	5	10	20	50	+15.4	32
14	3-MeOC$_6$H$_4$	40	10	20	20	78	+34.6	84
15	3-MeOC$_6$H$_4$	20	5	10	20	73	+10.6	26
16	2-MeC$_6$H$_4$	40	10	20	20	75	+32.5	78
17	2-MeC$_6$H$_4$	20	5	10	20	74	+30.5	72 (70.0)[b]
18	α-Naphthyl	40	10	20	20	66	+55.0	84
19	α-Naphthyl	20	5	10	20	55	+37.3	57
20	4-MeC$_6$H$_4$	40	10	20	20	81	+40.0	78
21	4-ClC$_6$H$_4$	40	10	20	20	71	+22.5	55
22	4-NO$_2$C$_6$H$_4$	40	10	20	20	73	+5.5	35

[a] Isolated yield.
[b] Determined by HPLC analysis of silyl ether on a chiralcel OD column.
[c] Determined by comparison of specific rotation values: Ar = Ph, $[\alpha]_D^{20}$ +45 (*c* 1, $CHCl_3$) in ref.[1a]; Ar = 2-MeOC$_6$H$_4$, $[\alpha]_D^{20}$ –21.0 (*c* 1.25, $CHCl_3$) with 77% ee in ref.[1a]; Ar = 4-MeOC$_6$H$_4$, $[\alpha]_D^{20}$ +45.5 (*c* 1, $CHCl_3$) with 95% ee in ref.[1a]; Ar = 3-MeOC$_6$H$_4$, $[\alpha]_D^{20}$ –40.8 (*c* 1.25, $CHCl_3$) with 99% ee in ref.[1a]; Ar = 2-MeC$_6$H$_4$, $[\alpha]_D^{20}$ +21.3 (*c* 1.03, $CHCl_3$) with 61% ee in ref.[9]; Ar = α-Naphthyl, $[\alpha]_D^{20}$ +48.0 (*c* 1.325, $CHCl_3$) with 73% ee in ref.[9]; Ar = 4-MeC$_6$H$_4$, $[\alpha]_D^{20}$ +47.4 (*c* 1.822, $CHCl_3$) with 92% ee in ref.[9]; Ar = 4-ClC$_6$H$_4$, $[\alpha]_D^{20}$ +27.2 (*c* 1.487, $CHCl_3$) with 66% ee in ref.[9]; Ar = 4-NO$_2$C$_6$H$_4$, $[\alpha]_D^{20}$ +4.6 (*c* 1.417, $CHCl_3$) with 29% ee in ref.[9]

(2) (a) Feng, X. M.; Gong, L. Z.; Hu, W. H.; Li, M.; Mi, A. Q.; Jiang, Y. Z. *Chem. J. Chin. Univ.* **1998**, *19*, 1416. (b) Jiang, Y. Z.; Zhou, X. G.; Hu, W. H.; Li, M.; Mi, A. Q. *Tetrahedron: Asymmetry* **1995**, *6*, 2915. (c) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385. (d) Belokon, T.; Flego, M.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1293. (e) Tararov, V.; Hibbs, D. E.; Hursthouse, M. B.; Ikonnikov, N. S.; North, M.; Orizu, C.; Belokon, T. *Chem. Commun.* **1998**, 387. (f) Belokon, T.; Caveda-Cepas, S.; Green, B.; Ikonikov, N. S.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M. *J. Am. Chem. Soc.* **1999**, *121*, 3968. (g) Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett.* **2000**, *40*, 7457. (h) Jiang, Y. Z.; Zhou, X. G.; Hu, W. H.; Li, Z.; Mi, A. Q. *Tetrahedron: Asymmetry* **1995**, *6*, 405. (i) Yang, Z. H.; Wang, L. X.; Zhou, Z. H.; Zhou, Q. L.; Tang, C. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1579. (j) Zhou, X. G.; Huang, J. S.; Ko, P. H.; Cheung, K. K.; Che, Z. M. *J. Chem. Soc., Dalton Trans.* **1999**, 3303.

(3) (a) Mori, M.; Imma, H.; Nakai, T. *Tetrahedron Lett*. **1997**, *38*, 6229. (b) Qian, C.; Zhu, C.; Huang, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2131. (c) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Chem. Commun*. **1990**, 1364. (d) Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589.

(4) Hwang, C. D.; Hwang, D. R.; Uang, B. J. *J. Org. Chem.* **1998**, *63*, 6762.

(5) (a) Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 2405. (b) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641. (c) Hamashida, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805. (d) Brunel, J. M.; Legrand, O.; Buono, G. *Tetrahedron: Asymmetry* **1999**, *10*, 1979. (e) Zhou, Z. H.; Yang, Z. H.; Liu, J. B.; Tang, C. C. *Acta Sci. Natur. Univ. Nankai* **2002**, *35*, 6. (f) Yang, W. B.; Fang, J. M. *J. Org. Chem.* **1998**, *63*, 1356.

(6) (a) Yang, Z. H.; Zhou, Z. H.; Wang, L. X.; Li, K. Y.; Zhou, Q. L.; Tang, C. C. *Synth. Commun.* **2002**, *32*, 2751. (b) Yang, Z. H.; Zhou, Z. H.; He, K.; Wang, L. X.; Zhao, G. F.; Zhou, Q. L.; Tang, C. C. *Tetrahedron: Asymmetry* **2003**, *14*, 3937.

(7) He, K.; Zhou, Z. H.; Zhao, G. F.; Wang, H. G.; Tang, C. C. *Chem. J. Chin. Univ.* **2003**, *24(11)*, 1997.

(8) He, K.; Zhou, Z. H.; Zhao, G. F.; Tang, C. C. *Main Group Metal Chem.* **2004**, *27*, in press.

(9) Matthews, B. R.; Jackson, W. R.; Jayatilake, G. S.; Wilshire, C.; Jacobs, H. A. *Aust. J. Chem.* **1988**, *41*, 1697.

(10) **General procedure for the asymmetric silylcyanation of aromatic aldehydes:**
To a solution of (+)-(*S*)-**2** (0.275 g, 0.54 mmol) in 5 mL of methylene chloride was added Ti(OPr-*i*)$_4$ (37.2 μL, 0.13 mmol) under a nitrogen atmosphere at 20 °C and resulting mixture was stirred for 1 h at the same temperature. Then *iso*-propanol (15.6 μL, 0.26 mmol), 2 mL of methylene chloride, benzaldehyde (0.142 g, 1.34 mmol) and trimethylsilyl cyanide (200 μL, 16 mmol) were added to it and the whole stirred for 24 h at the same temperature. After determination of the enantiomeric excess value of the cyanohydrin trimethylsilylether by chiral HPLC, the mixture was poured into a mixture of 1 N HCl (30 mL) and ethyl acetate (40 mL) and stirred vigorously for 6 h. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with brine and dried over anhydrous magnesium sulfate. After removal of solvent the residue was purified by thin layer chromatography on silica gel to afford 150 mg (84% yield) of the corresponding cyanohydrin. $[\alpha]_D^{20}$ +23.8 (c 1, $CHCl_3$), ^{1}H NMR (δ, $CHCl_3$): 3.51 (s, 1H, OH), 5.48 (d, 1H, CH), 7.43–7.49 (m, 5H, 5 H_{arom}).
Spectroscopic data for all prepared compounds are available from the authors.