Enantioselective Allylic Alkylation Catalyzed by Novel C_2-Symmetric Bisphosphinites

by **Yaşar Gök*** and **Halil Zeki Gök**

Department of Chemistry, Faculty of Arts and Sciences, Osmaniye Korkut Ata University, TR-80000 Osmaniye (phone: +90-328-8271000/2541; fax: +90-328-8250097; e-mail: yasargok@osmaniye.edu.tr)

In this article, we present our results concerning new C_2-symmetric bisphosphinites with a (1*R*,2*R*)-1,2-bis([1,1′:3′,1″-terphenyl]-5′-yl)ethane backbone. For the given chirality of the backbone, derivatives with aromatic and aliphatic substituents at the donor P-atoms were synthesized with moderate yields in a straightforward manner. These compounds were evaluated in the Pd^0-catalyzed enantioselective allylic alkylations (up to 67% ee).

Introduction. – Designing an appropriate ligand is one of the challenges in the field of asymmetric transition-metal catalysis [1]. Given the complexity of most catalytic processes, a rational design of a chiral ligand is seldom straightforward. Therefore, the development of new ligands is often the result of a knowledge-based intuition or of serendipity. A chiral ligand has to fulfill suitable electronic and steric requirements for a wide variety of catalytic reactions for excellent enantioselective inductions [2].

Phosphorus compounds play an important role in several fields of synthesis, especially as ligands in transition metal catalysis. Starting from 1968, tens of thousands of phosphorus compounds have been developed and evaluated as ligands in several enantioselective transformations [3]. Among the P-based ligands, phosphines and phosphinites attracted increased interest due to their wide range of steric and electronic properties [4]. Phosphinites are easier to synthesize and also provide different chemical, electronic, and structural properties as compared with phosphines [3]. The metal–P bonds of phosphinites are often stronger than related in phosphines due to the presence of the electron-withdrawing P–OR group [5].

As part of our ongoing interest in the development of enantioselective catalysts [6], we synthesized new C_2-symmetric bisphosphinites with a (1*R*,2*R*)-1,2-bis([1,1′:3′,1″-terphenyl]-5′-yl)ethane backbone (*Fig.*). A C_2-symmetry axis minimizes the number of possible diastereoisomeric transition states [7]. Due to the elimination of less-selective

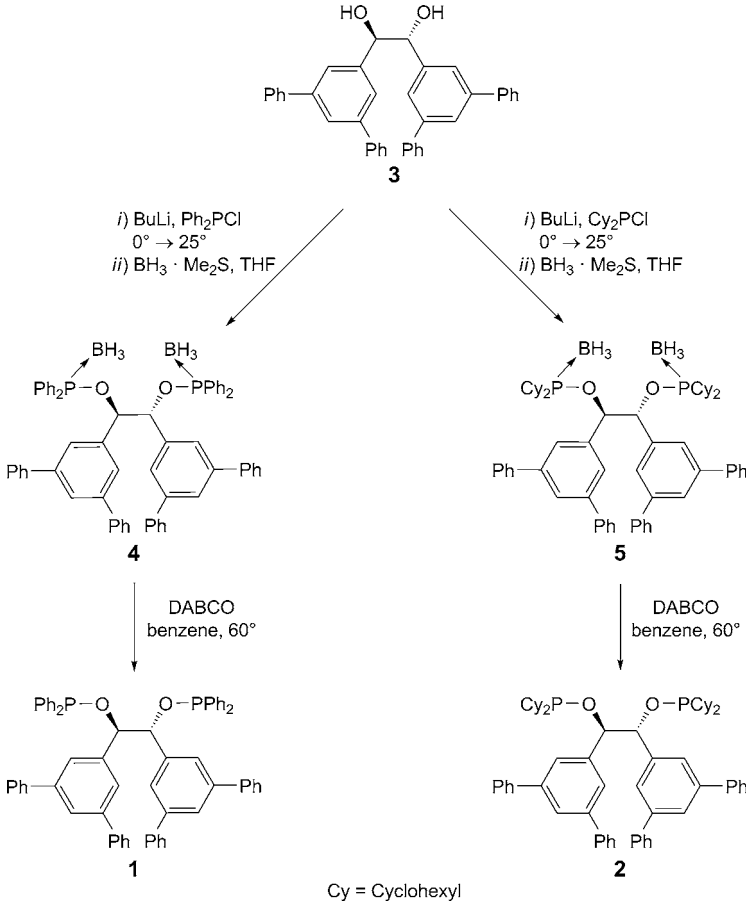
1 **2**

Figure. *Bisphosphinite ligands*

reaction pathways, the enantioselectivity can be very high. For the given sense of chirality of the backbone, Ph and cyclohexyl substituents at the P donor groups were synthesized with moderate yields in a straightforward manner. These compounds were evaluated in Pd^0-catalyzed enantioselective allylic alkylations.

Results and Discussion. – The synthetic route towards enantiomerically pure C_2-symmetric bisphosphinites **1** and **2** started with (1*R*,2*R*)-1,2-bis([1,1′:3′,1″-terphenyl]-5′-yl)ethane-1,2-diol (**3**), which was earlier described by our group (*Scheme*) [8]. In general, bisphosphinite ligands are synthesized very efficiently in one step by reacting the corresponding enantiomerically pure diol with 2 equiv. of the desired chlorophosphine in the presence of a base. According to this general procedure, chiral diol **3** was treated with Ph_2PCl and chloro(dicyclohexyl)phosphine (Cy_2PCl) to obtain the corresponding bisphosphinite ligands. Unfortunately, from both reactions, oxidation products instead of the desired bisphosphinites were obtained and confirmed by ^{31}P-

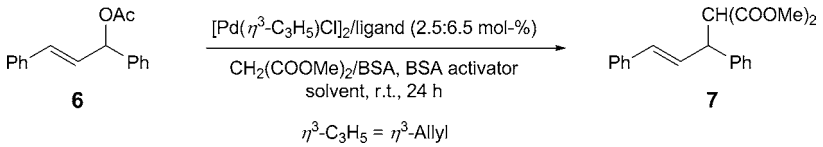
Scheme. *Synthesis of Bisphosphinite Ligands* **1** *and* **2**



NMR spectrum. To overcome this problem, temporary protection with BH_3 was required, which allowed isolation, purification, and storage of the adduct for a longer time [6d][9]. Bisphosphinite–borane **4** and **5** were easily derived from the diol **3**. When diol **3** was treated with Ph_2PCl (3.5 equiv.) or Cy_2PCl (3.5 equiv.) in the presence of BuLi and subsequently protected *in situ* with $BH_3 \cdot Me_2S$, bisphosphinite-boranes **4** and **5** were obtained in moderate yields. The last step of our synthetic route, *i.e.*, deprotection, could be accomplished by treatment with 1,4-diazabicyclo[2.2.2]octane (DABCO; 4.5 equiv.) in benzene at 60°.

We investigated the Pd^0-catalyzed enantioselective allylic alkylation in the presence of the newly synthesized bisphosphinite ligands **1** and **2** (*Table*). The transition metal-catalyzed allylic alkylation reaction, which has become part of modern organic synthesis, is one of the most versatile and flexible methods for the enantioselective formation of C–C and C–heteroatom bonds [10]. We focused our attention on the allylic substitution of racemic (2*E*)-1,3-diphenylallyl acetate (**6**) with dimethyl malonate (DMM), which served as test reaction to determine the efficiency of the newly synthesized enantioselective catalysts (*Table*) [6a][11]. The nucleophile was generated from DMM (3 equiv.) in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA; 3 equiv.) and BSA activator AcOLi (0.1 mol-%). The best result was obtained with ligand **1** (*Table*, *Entry 1*). When we decreased the amount of the ligand **1** (0.025 equiv.), a slightly lower enantioselectivity was observed, accompanied by a decrease in yield (*Table*, *Entry 2*). We observed also a pronounced BSA activator effect (*Table*, *Entry 3*). When AcOK was used, no reaction occurred (*Table*, *Entry 3*). To our disappointment, we found no conversion at all when we used THF as solvent

Table. *Pd^0-Catalyzed Enantioselective Allylic Alkylation of* **6** *with Dimethyl Malonate in the Presence of Bisphosphinite Ligands* **1** *and* **2**



6 **7**

η^3-C_3H_5 = η^3-Allyl

Entry	Ligand	BSA Activator	Solvent	Yield [%][a])	ee [%][b])[c])
1	**1**	AcOLi	CH_2Cl_2	25	67 (*R*)
2[d])	**1**	AcOLi	CH_2Cl_2	15	64 (*R*)
3	**1**	AcOK	CH_2Cl_2	n.d.[e])	–
4	**1**	AcOLi	THF	n.d.[e])	–
5	**1**	AcOK	THF	n.d.[e])	–
6	**2**	AcOLi	CH_2Cl_2	35	18 (*S*)
7[d])	**2**	AcOLi	CH_2Cl_2	40	17 (*S*)
8	**2**	AcOK	CH_2Cl_2	n.d.[e])	–
9	**2**	AcOLi	THF	10	18 (*S*)
10	**2**	AcOK	THF	n.d.[e])	–

[a]) Yield of isolated product. [b]) Determined by HPLC analysis with a chiral stationary phase (*Chiralcel OD-H*). [c]) The absolute configuration was assigned by the sign of the optical rotation. [d]) 2.5 mmol-% of ligand was used. [e]) n.d., Not determined.

(*Table*, *Entries 4* and *5*). When we performed the reaction with ligand **2**, we observed moderate yield and poor enantioselectivity (*Table*, *Entry 6*). The enantioselectivity and the yield were slightly changed when 0.025 equiv. of the ligand **2** was used (*Table*, *Entry 7*). In the presence of AcOK, no reaction occured (*Table*, *Entry 8*). Switching to THF as solvent resulted in a sharp decrease of the yield; however, the enantioselectivity was roughly the same (*Table*, *Entry 9*). We determined no conversion when AcOK was used as BSA activator (*Table*, *Entry 10*).

In conclusion, we have synthesized new C_2-symmetric bisphosphinites with (1*R*,2*R*)-1,2-bis([1,1′:3′,1″-terphenyl]-5′-yl)ethylene backbone. For the given sense of chirality of the backbone, bearing Ph-substituted P-atoms, *i.e.*, **1**, and cyclohexyl-substituted P-atoms **2** were synthesized with moderate yields in a straightforward manner. Their effectiveness was illustrated in Pd^0-catalyzed enantioselective allylic alkylations. The best catalytic results were obtained in the presence of Ph-substituted bisphosphinite ligand **1** (up to 67% ee). Making the ligand electron-rich led to lower enantioselectivity, as shown in the case of cyclohexyl-substituted bisphosphinite ligand **2**. It is noteworthy that opposite enantiomers were obtained when the electronic properties of the P-atoms were changed.

Y. G. and *H. Z. G.* wish to thank the *Scientific & Technological Research Council of Turkey* (*TUBITAK*) (Project No: TBAG-112T017).

Experimental Part

General. All reactions were carried out under Ar in dry solvents under anh. conditions, unless stated otherwise. All reagents were purchased and used without further purification, unless noted otherwise. Anal. TLC: *Macherey–Nagel SIL G-25 UV$_{254}$* plates. Flash chromatography (FC): *ROCC* silica gel (SiO_2; 0.040 – 0.063 mm). Anal. chiral HPLC: *VWR Hitachi* series, with DAD detection. M.p.: *Thermo Scientific 9200* melting-point apparatus. Optical rotations: *Krüss P3000* series polarimeter. IR Spectra: *PerkinElmer Spectrum 65* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance 400* spectrometer; δ in ppm rel. to Me_4Si; ^{31}P-NMR chemical shifts rel. to an external standard of 85% H_3PO_4; J in Hz. ^{13}C-NMR spectra were recorded using the attached-proton test. ESI-MS: *Agilent LC/MSD* and *Bruker Daltonics MALDI-TOF* mass spectrometer; in m/z.

*(1*R,*2*R*)-1,2-Di(1,1′:3′,1″-terphenyl-5′-yl)ethane-1,2-diyl Bis[diphenyl(phosphinite)]–borane (1:2)* (**4**). To a soln. of *(1*R,*2*R*)-1,2-bis([1,1′:3′,1″-terphenyl]-5′-yl)ethane-1,3-diol* (**3**; 25 mg, 0.048 mmol) in dry THF was added BuLi (0.240 ml, 0.386 mmol) at 0°, and the mixture was stirred for 1 h at r.t. Ph_2PCl (0.035 ml, 0.168 mmol) was added dropwise to the resulting mixture. After stirring for 3 h, $BH_3 \cdot Me_2S$ (0.06 ml, 0.578 mmol) was carefully added, and stirring was continued for 2 h. Evaporation *in vacuo* and purification by FC (SiO_2; hexane/AcOEt 85:15) afforded **4** (20 mg, 45%). White foam. M.p. 156 – 157°. $[\alpha]_D^{20} = +20$ ($c = 1.0$, $CHCl_3$). IR: 3537, 3057, 3032, 2924, 2854, 2377, 1595, 1576, 1497, 1435, 1029, 758, 696. ^{1}H-NMR (400 MHz, DMSO): 0.7 – 1.0 (br. *m*, 2 BH_3); 5.9 – 6.01 (*m*, 2 H); 7.23 – 7.24 (*m*, 4 H); 7.3 – 7.5 (*m*, 34 H); 7.57 – 7.67 (*m*, 8 H). ^{13}C-NMR (100 MHz, DMSO): 82.45 (*d*, $J = 6.5$); 124.95 (*d*, $J = 46$); 127.2 (*d*, $J = 67$); 128.5 (*d*, $J = 10.6$); 128.73 (*t*, $J = 6.5$); 130.2 (*d*, $J = 11$); 130.6 (*d*, $J = 11$); 131 (*d*, $J = 11$); 131.2 (*d*, $J = 18$); 132 (*d*, $J = 33$); 137.8, 139.7, 140.2. ^{31}P-NMR (162 MHz, DMSO): 106.62. MALDI-TOF-MS: 938.84 ($[M + H + Na]^+$), 981.81 ($[M - 2\,H + 3\,Na]^+$). Anal. calc. for $C_{62}H_{54}B_2O_2P_2$ (914.66): C 81.41, H 5.95, found: C 81.20, H 6.00.

*(1*R,*2*R*)-1,2-Di(1,1′:3′,1″-terphenyl-5′-yl)ethane-1,2-diyl Bis[dicyclohexyl(phosphinite)]–borane (1:2)* (**5**). To a soln. of **3** (25 mg, 0.048 mmol) in dry THF was added BuLi (0.240 ml, 0.386 mmol) at 0°, and the mixture was stirred for 1 h at r.t. Then, Cy_2PCl (0.039 ml, 0.168 mmol) was added dropwise. After stirring for 3 h, $BH_3 \cdot Me_2S$ (0.06 ml, 0.578 mmol) was added carefully to the mixture, and stirring was continued for 2 h. Evaporation *in vacuo* and purification by FC (SiO_2; hexane/AcOEt 85:15)

afforded in **5** (28 mg, 62%). White foam. M.p. 114–115°. $[\alpha]_D^{20} = +8$ ($c = 1.07$, $CHCl_3$). IR: 3365, 3055, 2931, 2855, 2382, 2358, 1624, 1452, 1443, 1182, 1171, 1124, 1098, 1059, 1047, 1003, 914, 897, 883, 760, 611. ^{1}H-NMR (400 MHz, DMSO): 1.2–1.35 (br. *m*, 20 H); 1.69–1.75 (*m*, 8 H); 1.8–1.9 (*m*, 22 H); 5.35–5.36 (*m*, 2 H); 7.35–7.4 (*m*, 4 H); 7.41–7.45 (*m*, 8 H); 7.54–7.55 (*m*, 4 H); 7.59–7.64 (*m*, 8 H); 7.77–7.79 (*m*, 2 H). ^{13}C-NMR (100 MHz, DMSO): 24.7 (*d*, $J = 2.76$); 25.6 (*d*, $J = 1.8$); 25.9 (*d*, $J = 1.2$); 26.3 (*d*, $J = 4$); 26.4 (*d*, $J = 6.6$); 34.5 (*d*, $J = 38.5$); 86.4 (*d*, $J = 2.3$); 123.5, 126.2 (*d*, $J = 4$); 127.3, 127.6, 128.8, 140.7, 141.3, (*d*, $J = 10.8$); 142.5. ^{31}P-NMR (162 MHz, DMSO): 119.26. ESI-MS: 956.2 ($[M + NH_4]^+$), 957.2 ($[M + NH_4 + H]^+$). Anal. calc. for $C_{62}H_{78}B_2O_2P_2$ (938.85): C 79.32, H 8.37, found: C 79.71, H 8.45.

*(1*R,2R*)-1,2-Di(1,1′:3′,1″-terphenyl-5′-yl)ethane-1,2-diyl Bis[diphenyl(phosphinite)]* (**1**). A mixture of **4** (60 mg, 0.066 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO; 34 mg, 0.29 mmol) in dry benzene (3 ml) was heated to 60° for 12 h under Ar. Evaporation *in vacuo* and purification by FC (dry Al_2O_3; dry CH_2Cl_2) gave **1**.

*(1*R,2R*)-1,2-Di(1,1′:3′,1″-terphenyl-5′-yl)ethane-1,2-diyl Bis[dicyclohexyl(phosphinite)]* (**2**). A mixture of **5** (70 mg, 0.074 mmol) and DABCO (349 mg, 0.34 mmol) in dry benzene (3 ml) was heated to 60° for 12 h under Ar. Evaporation *in vacuo* and purification by FC (dry Al_2O_3; dry CH_2Cl_2) gave **2**.

Pd^0-Catalyzed Enantioselective Allylic Alkylation: General Procedure. Ligand **1** (0.05 mmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol) were dissolved in degassed CH_2Cl_2 under Ar using *Schlenk* techniques. The mixture was stirred for 1 h at 50° and cooled to r.t. Then, *(2*E*)-1,3-diphenylprop-2-enyl acetate* (**6**; 1 mmol) in CH_2Cl_2 was added, and the mixture was stirred at r.t. for 30 min. Finally, a soln. of *N*,*O*-bis(trimethylsilyl)acetamide (BSA; 3 mmol), AcOLi (0.1 mmol), and dimethyl malonate (DMM; 3 mmol) was added to the mixture. The mixture was stirred for 16 h at r.t. Next, Et_2O was added, and the mixture was washed with a sat. NH_4Cl soln., dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by FC (SiO_2; hexane/AcOEt 90:10) to afford the target compound.

All adducts were fully characterized by comparison of their spectral data with those reported in the literature. The absolute configurations were assigned *via* correlation of their optical rotation with literature values [12]. The enantiomeric excess (ee) was determined by chiral HPLC analysis: *Chiralcel OD-H* column (250 × 4.6 mm, particle size, 10 μm); solvent, hexane/^{i}PrOH 99:1, flow rate, 1 ml/min; *T*, 35°, t_R 25.60 and 27.26 min for (−)-(*R*)-7 and (+)-(*S*)-**7**, resp.

REFERENCES

[1] I. Ojima, 'Catalytic Asymmetric Synthesis', 2nd edn., Wiley–VCH, New York, 2000; M. Beller, C. Bolm, 'Transition Metals for Organic Synthesis', Wiley–VCH, Weinheim, 2004, Vol. 2.

[2] K. Inoguchi, S. Sakuraba, K. Achiwa, *Synlett* **1992**, 169.

[3] A. Börner, 'Phosphorus Ligands in Asymmetric Catalysis', Wiley–VCH, Weinheim, 2008.

[4] D. Elma, F. Durap, M. Aydemir, A. Baysal, N. Meric, B. Ak, Y. Turgut, B. Gümgüm, *J. Organomet. Chem.* **2013**, *729*, 46; D. Hobus, J. Hasenjager, B. Driessen-Holscher, A. Baro, K. V. Axenov, S. Laschat, W. Frey, *Inorg. Chim. Acta* **2011**, *374*, 94; H. Park, R. Kumareswaran, T. V. RajanBabu, *Tetrahedron* **2005**, *61*, 6352; M. Diéguez, O. Pàmies, C. Claver, *Chem. Rev.* **2004**, *104*, 3189; B. M. Trost, W. Tang, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 14785.

[5] P. W. Galka, H.-B. Kraatz, *J. Organomet. Chem.* **2003**, *674*, 24.

[6] a) Y. Gök, T. Noël, J. Van der Eycken, *Tetrahedron: Asymmetry* **2010**, *21*, 2275; b) Y. Gök, T. Noël, J. Van der Eycken, *Tetrahedron: Asymmetry* **2010**, *21*, 2768; c) T. Noël, Y. Gök, J. Van der Eycken, *Tetrahedron: Asymmetry* **2010**, *21*, 540; d) E. Vervecken, M. Van Overschelde, T. Noël, Y. Gök, S. A. Rodríguez, S. Cogen, J. Van der Eycken, *Tetrahedron: Asymmetry* **2010**, *21*, 2321; e) Y. Gök, J. Van der Eycken, *Helv. Chim. Acta* **2012**, *95*, 831.

[7] J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581.

[8] Y. Gök, L. Kekeç, *Tetrahedron Lett.* **2014**, *55*, 2727.

[9] I. J. S. Fairlamb, S. Grant, A. C. Whitwood, J. Whitthall, A. S. Batsanov, J. C. Collings, *J. Organomet. Chem.* **2005**, *690*, 4462; D. Bradley, G. Williams, H. Lombard, M. Van Niekerk, P. P. Coetzee, *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2799.

[10] Z. Lu, S. Ma, *Angew. Chem., Int. Ed.* **2008**, *47*, 258; T. Rovis, in 'New Frontiers in Asymmetric Catalysis', Eds. K. Mikami, M. Lautens, Wiley–VCH, Weinheim, 2007, p. 276; B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; B. M. Trost, C. Lee, 'Catalytic Asymmetric Synthesis', Ed. I. Ojima, Wiley–VCH, Weinheim, 2000; A. Pfaltz, M. Lautens, 'Comprehensive Asymmetric Catalysis', Eds. E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer Verlag, Berlin, 1999, Vol. II, pp. 833; B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; J. Tsuji, 'Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis', Wiley, Chichester, 2000; S. A. Godleski, 'Comprehensive Organic Synthesis', Eds. B. M. Trost, I. Fleming, M. F. Semmelhack, Pergamon Press, Oxford, 1990.

[11] D. S. Clyne, Y. C. Mermet-Bouvier, N. Nomura, T. V. RajanBabu, *J. Org. Chem.* **1999**, *64*, 7601; R. K. Sharma, M. Nethaji, A. G. Samuelson, *Tetrahedron: Asymmetry* **2008**, *19*, 655.

[12] Y. Tanaka, T. Mino, K. Akita, M. Sakamoto, T. Fujita, *J. Org. Chem.* **2004**, *69*, 6679; Š. Vyskočil, M. Smrčina, V. Hanuš, M. Polášek, P. Kočovský, *J. Org. Chem.* **1998**, *63*, 7738; B. Wiese, G. Helmchen, *Tetrahedron Lett.* **1998**, 39, 5727; D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael, M. R. Gagné, *J. Am. Chem. Soc.* **2000**, *122*, 7905.

Received July 02, 2014