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Asymmetric synthesis of dimethyl-1,2-bis-(diphenylphosphino)-1,2-ethanedicarboxylate by means of a chiral palladium template promoted hydrophosphination reaction☆

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Abstract—An optically pure C_2-symmetrical diphosphine ligand containing two ester functional groups at the two chiral carbon stereogenic centres was prepared efficiently from the asymmetric hydrophosphination reaction between diphenylphosphine and dimethyl acetylenedicarboxylate in the presence of an organopalladium(II) complex derived from (*S*)-*N*,*N*-dimethyl-1-(1-naphthyl)ethylamine.

Enantiomerically pure diphosphines containing selected functionalities have long been considered as powerful auxiliaries for metal based homogenous asymmetric catalysis.[1] These chiral ligands have also been used extensively in asymmetric organic synthesis,[2] biochemistry[3] and chemotherapy.[4] We have recently reported a new class of chiral phosphine-supported gold(I) anticancer complexes.[5] These activities and selectivities can be controlled efficiently by selected functionalities and their stereochemistry within a particular chiral phosphine supporter. Despite their important roles in many aspects of science, the synthesis of these reactive and potentially unstable chiral ligands remains a major challenge. We have previously reported the asymmetric synthesis of a series of functionalized phosphanorbornenes.[6] Herein we present the preparation of a di-ester-substituted diphosphine via a simple chiral palladium template promoted hydrophosphination reaction.

As illustrated in Scheme 1, the addition reaction between diphenylphosphine and dimethyl acetylenedicarboxylate proceeded smoothly at −78 °C in the presence of the chiral palladium template (*S*)-**1** and a trace amount of NEt_3 in CH_2Cl_2. The reaction was monitored by ^{31}P NMR spectroscopy and was found to be complete in 2 h to give a 6:1 mixture of diastereomers (*S*,*RR*)-**2** and (*S*,*SS*)-**2** in a quantitative yield. The 121 MHz ^{31}P NMR spectrum of each diastereomer in $CDCl_3$ exhibited a pair of doublets. For the major isomer (*S*,*RR*)-**2**, the doublet resonances occurred at δ 36.1 and 55.3 (J_{PP} 39 Hz). For the minor isomer (*S*,*SS*)-**2**, the doublets were observed at δ 36.6 and 57.2 (J_{PP} 37 Hz). The cationic diastereomers could not be separated efficiently by chromatography or fractional crystallization. The diastereomeric mixture was then treated with concd HCl to remove the naphthylamine auxiliary resulting in the dichloro complexes (*RR*)-**3** and (*SS*)-**3**. Repeated crystallization of the enantiomeric mixture from dichloromethane and diethyl ether gave the optically pure major isomer (*RR*)-**3**[†] as pale yellow prisms (40%), $[\alpha]_{435}$ +110 (*c* 0.3, CH_2Cl_2). The ^{31}P NMR spectrum of (*RR*)-**3** in $CDCl_3$ exhibited a sharp singlet at δ 58.0.

☆ Electronic Supplementary Information (ESI) available: ^{31}P NMR of crude product containing both complexes (*S*,*RR*)-**2** and (*S*,*SS*)-**2** along with ^{1}H and ^{31}P NMR of complex (*RR*)-**3**.

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[†] *Selected physical and spectroscopic data* for (*R*,*R*)-**3**·CH_2Cl_2: mp 231–232 °C; $[\alpha]_{435}$ +110 (*c* 0.3, CH_2Cl_2). Anal. Calcd for $C_{31}H_{30}Cl_4O_4P_2Pd$: C, 47.9; H, 3.9. Found C, 47.7; H, 3.8. ^{31}P NMR ($CDCl_3$) δ 58.0 (s); ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 6H, C*H*$_3$), 4.23 (d, 2H, J_{PH} = 6.2 Hz, C*H*), 7.52–7.93 (m, 20H, aromatics).
For (*R*,*R*)-**4**: $[\alpha]_D$ −109 (*c* 0.6, $CHCl_3$). ^{31}P NMR ($CDCl_3$) δ −6.1 (s); ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 6H, C*H*$_3$), 4.19 (d, 2H, J_{PH} = 5.9 Hz, C*H*), 7.26–7.69 (m, 20H, aromatics).

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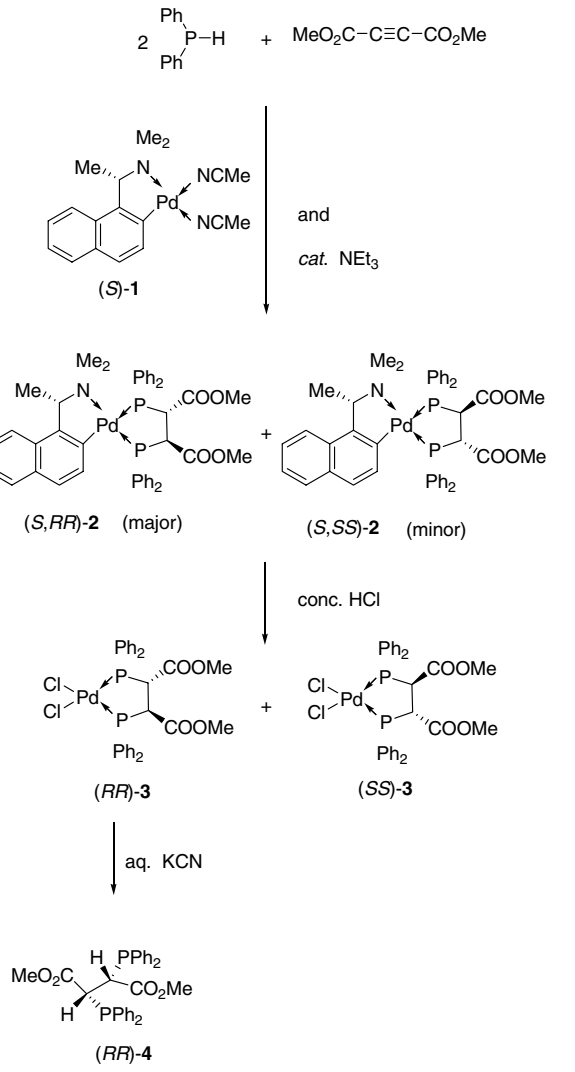


Scheme 1.

The molecular structure and the absolute stereochemistry of (*RR*)-**3** were determined by X-ray crystallography[‡] (Fig. 1). The five-membered chelate ring has the asymmetric skew conformation of λ helicity with both ester substituents on the asymmetric carbon centres of *R* absolute configuration occupying equatorial sites.

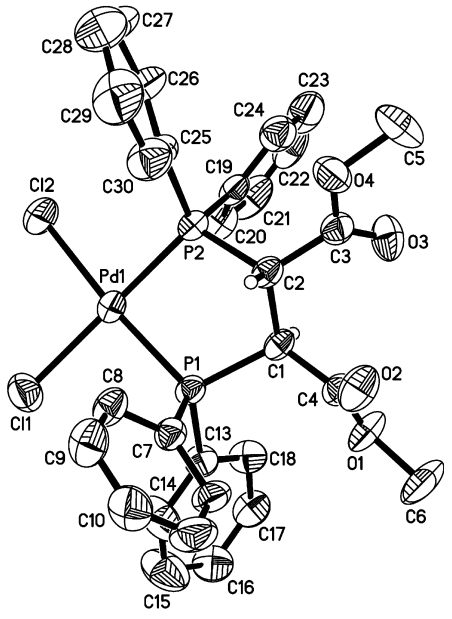
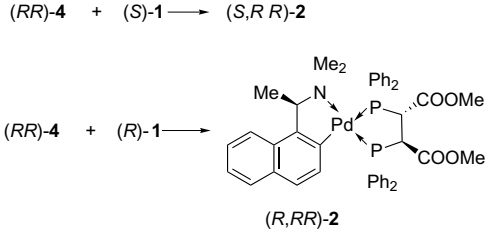


Figure 1.

Treatment of a CH_2Cl_2 solution of (*R*,*R*)-**3** with aqueous potassium cyanide liberated the optically pure diphosphine (*R*,*R*)-**4**[†] as a white solid in a quantitative yield, $[\alpha]_D$ −109 (*c* 0.6, $CHCl_3$). The ^{31}P NMR spectrum of the free diphosphine in $CDCl_3$ exhibited a sharp singlet at δ −6.1. As illustrated in Scheme 2, the optical purity of (*R*,*R*)-**4** was confirmed by the quantitative repreparation of (*S*,*RR*)-**2** from the liberated ligand and (*S*)-**1**; the 202 MHz ^{31}P NMR spectrum ($CDCl_3$) of the crude product exhibited only a pair of doublet signals at δ 36.1 and 55.3 (J_{PP} 39 Hz). These signals are identical to those recorded for the major diastereomer (*S*,*RR*)-**2** generated directly from the asymmetric hydrophosphination reaction. As a further test of the optical purity of the liberated ligand and to confirm the identity of the minor product generated in the addition reaction, (*R*,*R*)-**4** was recoordinated to the equally accessible (*R*)-**1**. The ^{31}P NMR spectrum of the crude recomplexation product in $CDCl_3$ exhibited only a pair of doublets at δ 36.6 and 57.2 (J_{PP} 37 Hz). These signals were identical with those observed for the minor product generated from the hydrophosphination reaction. Hence, it could be confirmed that diastereomer (*S*,*SS*)-**2** was indeed the minor



Scheme 2.

[‡] *Crystal data for* (*R*,*R*)-**3**·CH_2Cl_2: $C_{31}H_{30}Cl_4O_4P_2Pd$; *FW* = 776.69; light yellow prisms; space group *P*1, *a* = 8.9387(3), *b* = 9.6553(3), *c* = 10.4811(4) Å, *V* = 843.89(5) Å^3, *Dc* = 1.582 Mg m^{-3} for *Z* = 1; λ(Mo-Kα) = 0.71073 Å; Bruker Kappa Apex II CCD diffractometer (298 K); A total of 10051 unique data were collected in the range $4 \leqslant 2\theta \leqslant 69°$ of which 6939 were refined [$I > 2\sigma(I)$]. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques giving *R* and *R*w values of 0.0478 and 0.0955, respectively. The absolute configuration of the complex was determined unambiguously using the Flack parameter [final value $\chi = -0.05(3)$]. All non-hydrogen atoms were refined anisotropically while all hydrogen atoms were introduced at a fixed distance from carbon atoms and were assigned fixed thermal parameters. CCDC 612065. An ORTEP plot of complex (*R*,*R*)-**3** with numbering scheme was given in Figure 1. Hydrogen atoms except the two on the chiral centres and a CH_2Cl_2solvent molecule have been omitted for clarity. Selected interatomic distances (Å) and angles (°) are as follows: Pd(1)–P(2) 2.228(2), Pd(1)–P(1) 2.239(2), Pd(1)–Cl(2) 2.346(2), Pd(1)–Cl(1) 2.353(2), P(2)–Pd(1)–P(1) 87.44(6), P(2)–Pd(1)–Cl(2) 88.14(7), P(1)–Pd(1)–Cl(2) 174.43(8), P(2)–Pd(1)–Cl(1) 174.11(7), P(1)–Pd(1)–Cl(1) 90.97(7), Cl(2)–Pd(1)–Cl(1) 93.77(7).

product of the asymmetric synthesis and the liberated diphosphine (*R*,*R*)-**4** is optically pure.

In conclusion, the hydrophosphination described is very efficient and the diester-substituted diphosphine can be prepared in a large quantity without the involvement of the tedious and inefficient resolution steps. We are currently preparing a range of functionalized diphosphines in their enantiomerically pure forms using a similar synthetic scheme.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.025.

References and notes

1. (a) *Asymmetric Catalysis*; Bosnich, B., Ed.; Martinus Nijhoff: Boston, MA, 1986; (b) Kagan, H. B.; Sasaki, M. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley-Interscience: New York, 1990; Vol. I, Chapter 3; (c) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857–871.
2. (a) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Org. Chem.* **1999**, *64*, 2994–2995; (b) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375–1411; (c) Leung, P. H.; He, G.; Lang, H.; Liu, A.; Loh, S. K.; Selvaratnam, S.; Mok, K. F.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2000**, *56*, 7–15; (d) Hockless, D. C. R.; Gugger, P. A.; Leung, P. H.; Mayadunne, R. C.; Pabel, M.; Wild, S. B. *Tetrahedron* **1997**, *53*, 4083–4094; (e) Leung, P. H.; Liu, A.; Mok, K. F. *Tetrahedron: Asymmetry* **1999**, *10*, 1309–1314.
3. Berners-Price, S. J.; Roman, R. E.; Salder, P. J. *J. Inorg. Biochem.* **1987**, *31*, 197–209.
4. Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375–1411.
5. Leung, P. H.; Chan, S. H.; Song, Y. C. US Patent 0,114,695 A1, 2003.
6. Leung, P. H. *Acc. Chem. Res.* **2004**, *37*, 169–177, and references cited therein.