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TETRAHEDRON: *ASYMMETRY*

Molecular recognition in the palladium complex promoted asymmetric synthesis of a keto-ester heterofunctionalized P-chiral phosphine

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Abstract

A chiral organopalladium complex promoted asymmetric Diels–Alder reaction between 1-phenyl-3,4-dimethyl-phosphole and methyl-*trans*-4-oxo-2-pentenoate gives the corresponding keto-carboxylate heterofunctionalized P-chiral phosphine ligand in which the keto group is stereoselectively located in the *exo* position of the phosphanorbornene skeleton. © 1998 Elsevier Science Ltd. All rights reserved.

Enantiomerically pure phosphines containing stereogenic phosphorus centres are often used as ligands for homogeneous asymmetric catalysis.[1] Furthermore, it has been well established that the introduction of selected functional groups into this class of phosphines can improve dramatically the efficiency of the existing chiral ligands.[2] In view of their critical importance in synthetic chemistry, it is surprising to note that synthetic approaches to these chiral ligands are relatively undeveloped. To date, most functionalized phosphines containing resolved stereogenic phosphorus centres were obtained from tedious multi-step syntheses or by resolution. Recently, several examples of the asymmetric synthesis of mono-functionalized P-chiral phosphines have been reported.[3] Nevertheless, no asymmetric syntheses of such chiral ligands containing hetero-functional groups have been hitherto reported. Here we describe a simple approach to a P-chiral phosphine containing one ketone and one ester functional group. The approach involves a chiral palladium complex promoted asymmetric Diels–Alder reaction between the cyclic diene 1-phenyl-3,4-dimethyl-phosphole (DMPP) and methyl-*trans*-4-oxo-2-pentenoate.

The highly reactive perchlorato complex (S_c)-**1** was generated in situ by treating the corresponding chloro species with silver perchlorate in CH_2Cl_2.[4] Upon coordination, DMPP is activated toward the Diels–Alder reaction. Accordingly, several mono-functionalized phosphines have been prepared by treating (S_c)-**1** with different dieneophiles.[3] In these earlier asymmetric syntheses, it was observed that the weak Pd–$OClO_3$ bond in (S_c)-**1** was invariably displaced by the reacting dienophile so that the cyclic

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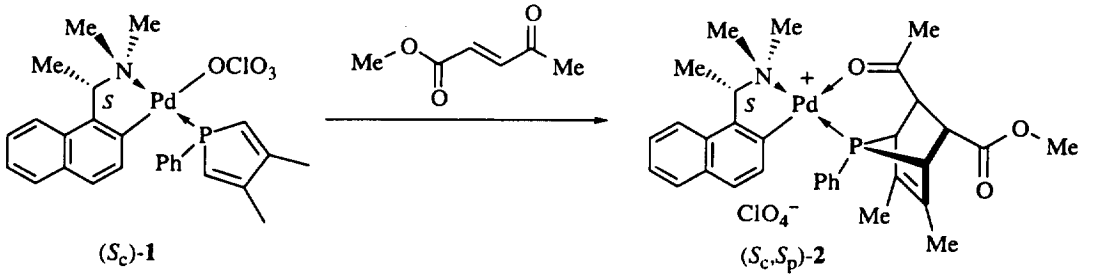
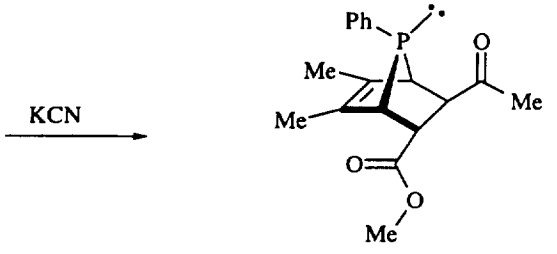
diene and the dienophile were coordinated simultaneously on the chiral palladium template during the course of cycloaddition reaction to give the corresponding *exo*-cycloadduct stereoselectively. In contrast to the simple dienophiles, methyl-*trans*-4-oxo-2-pentenoate used in the present study contains both keto and ester functionalities. The oxygen atoms of both functional groups are known to be appropriate donor atoms toward palladium(II)[5] and hence they may compete for the coordination site in the chiral template. Thus, although it has been reported that the naphthylamine auxiliary in (S_c)-**1** can control the formation of chiral phosphorus centre stereospecifically,[6] two distinct diastereomers may still be produced arising from the *exo*/*endo* dispositions of the two non-equivalent functional groups. Interestingly, it was found that the treatment of (S_c)-**1** with the excess methyl-*trans*-4-oxo-2-pentenoate in 1,2-dichloroethane at room temperature gave predominantly one product (Scheme 1). The reaction was monitored by ^{31}P NMR spectroscopy and found to be complete in 3 days with 80% of (S_c)-**1** being converted to (S_c,S_p)-**2**. Prior to crystallization, the 202 MHz ^{31}P NMR spectrum of the crude product in $CDCl_3$ exhibited a distinct sharp singlet at δ 114.5 together with several as yet unidentified minor signals in the higher field region. The cationic complex was crystallized from chloroform–diethyl ether as pale yellow platy rhombs in 40% isolated yield, mp 181–183°C (decomp), $[\alpha]_D$ 126.9 (c=0.9, CH_2Cl_2). Interestingly, although (S_c,S_p)-**2** is stable in the solid state, it decomposes slowly when dissolved in most common organic solvents. The inefficiency in the isolation of (S_c,S_p)-**2** by the recrystallization process may indeed be due to its instability in solution.





The solid state molecular structure and the absolute stereochemistry of (S_c,S_p)-**2** have been determined by single-crystal X-ray analysis. This study established that the hetero-functionalized phosphine ligand created in the Diels–Alder reaction coordinates to palladium as a bidentate ligand via the bridgehead phosphorus atom and the oxygen atom of the keto group (Fig. 1).[7] The absolute configurations of the five new chiral centres at P, C(22), C(25), C(26) and C(27) are *S*, *S*, *R*, *R* and *R*, respectively. (S_c,S_p)-**2** crystallizes with two crystallographically independent molecules in the asymmetric unit. Both molecules have identical absolute configurations and very similar conformations. The geometries at the two independent palladium centres are essentially the same and do not differ significantly from that observed in the related keto-substituted P-chiral phosphine.[8] Clearly, while the naphthylamine auxiliary

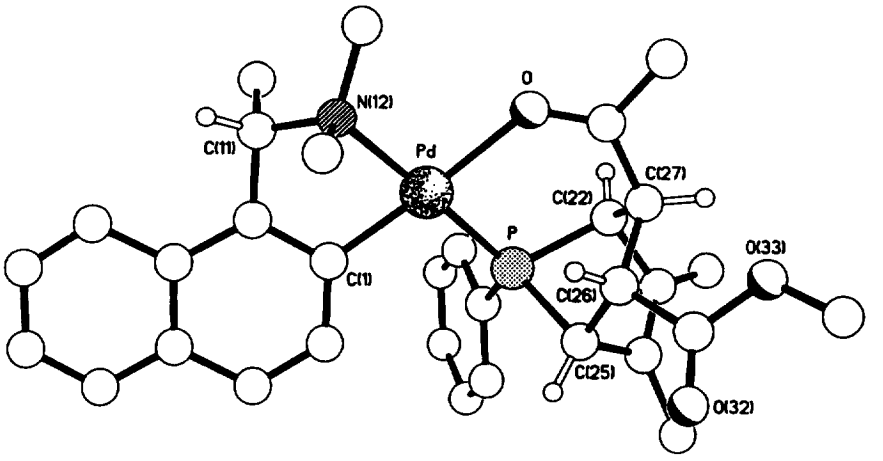
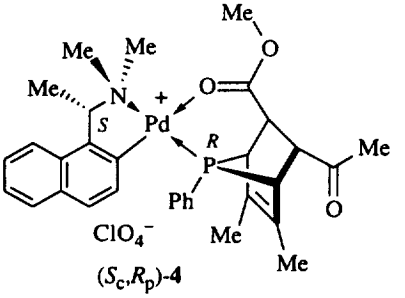


Fig. 1. Molecular structure and absolute stereochemistry of complex (S_c,S_p)-**2**

is controlling the absolute stereochemistry of the entire Diels–Alder reaction, the organopalladium reaction centre also recognizes the difference between the oxygen atoms of the keto and ester functional groups. Evidently the chiral metal template favours the formation of (S_c,S_p)-**2** and discriminates against the ester bonded diastereomer (S_c,R_p)-**4**. It is noteworthy that the development of transition metal complexes with such a high degree of C=O selectivity may significantly influence the design of catalysts in homogenous asymmetric catalysis.[9]



Treatment of a CH_2Cl_2 solution of (S_c,S_p)-**2** with aqueous potassium cyanide liberated the naphthylamine auxiliary and (R_p)-**3**. The auxiliary was removed by extraction with dilute sulfuric acid and the enantiomerically pure phosphine was obtained quantitatively as an air-sensitive white solid, $[\alpha]_D$ −15.8 (c=1.2, $CHCl_3$), ^{31}P NMR ($CDCl_3$) δ 104.8 (s). The low field ^{31}P resonance indicates that the *exo–syn* stereochemistry is retained.[3] Investigations into the origins of this functional group selectivity in the Diels–Alder reaction are currently in progress.

Acknowledgements

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7. Crystal data for (S_c,S_p)-**2**: $[C_{32}H_{37}NO_3PPd][ClO_4]\cdot CHCl_3$, M=839.98, monoclinic, $P2_1$ (no 4), a=10.750(2), b=11.418(2), c=30.514(6) Å, β=97.84(1)°, V=3711(1) Å^3, Z=4 (there are two crystallographically independent molecules in the asymmetric unit), D_c=1.503 g cm^{-3}, μ(Mo-K_α)=8.77 cm^{-1}, F(000)=1712, T=293 K; a very pale yellow platy rhomb, 0.60×0.42×0.16 mm, Siemens P4/PC diffractometer, ω-scans, 6881 independent reflections. The structure was solved by direct methods and all the major occupancy non-hydrogen atoms were refined anisotropically using full-matrix least-squares based on F^2 to give R_1=0.078, wR_2=0.189 for 4564 independent observed absorption corrected reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq 50°$] and 867 parameters. The absolute chirality was determined by internal reference to the known naphthylamine centre and by use of the Flack parameter [x=−0.05(20)].
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