Palladium-complex-promoted Asymmetric Diels–Alder Reaction: Stereoselective Synthesis of a New Sulfinyl-substituted Phosphine Ligand containing Three Carbon, One Phosphorus and One Sulfur Stereogenic Centres

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Palladium(II) complexes derived from the optically active forms of *N,N*-dimethyl-1-(1-naphthyl)ethylamine are efficient promoters for the asymmetric Diels–Alder reaction between 1-phenyl-3,4-dimethylphosphole and divinyl sulfoxide; the absolute configurations of the five newly generated chiral centres in this cycloaddition reaction were determined by a crystal structural analysis of a product complex.

Enantiomerically pure phosphine ligands are arguably the most powerful chiral auxiliaries in many aspects of asymmetric catalysis.[1] To date, chelating phosphines with chirality residing in the carbon skeletons are readily prepared from their corresponding chirons.[2] The synthetic approaches employed, however, are rarely applicable in the preparation of P-chiral ligands which are of significant importance in chemistry, biology and industry.[3] In fact, most of the enantiomerically pure P-chiral phosphines in the literature were obtained *via* optical resolutions although several excellent examples on the enantioselective synthesis of such compounds have been reported recently.[4] Recently, we have reported a chiral palladium complex promoted synthesis of a rigid P-chiral diphosphine ligand in its enantiomerically pure forms.[5] We now delineate the asymmetric synthesis and structure of the first palladium complex containing a sulfinyl-substituted phosphine ligand in which three carbon, one phosphorus and one sulfur stereocentres have been generated enantioselectively in a single step.

Treatment of the cyclic diene 1-phenyl-3,4-dimethylphosphole (DMPP) with the bis(acetonitrile) complex[6] (−)-(*R*)-1 in CH$_2$Cl$_2$ for 1 h gave (−)-2 regiospecifically[7] in quantitative yield, mp 152–153 °C, [α]$_D$ −240.0 (*c* = 0.6, CH$_2$Cl$_2$).† Upon complexation to palladium(II), DMPP is activated and thus capable of reacting with dienophiles to give the corresponding [4 + 2] cycloaddition products.[8] The Diels–Alder reaction between the coordinated diene in (−)-2 and divinyl sulfoxide was achieved by heating the reaction mixture at 75 °C for 8 d in 1,2-dichloroethane (Scheme 1). Under these conditions, however, the cycloaddition was complicated by a competing carbon–chlorine bond cleavage process in which a chloro ligand was abstracted from 1,2-dichloroethane by palladium during the course of heating. Thus, silica gel column chromatography of the crude product afforded the unexpected chloro complex (−)-3 in 20% yield. The pale-yellow complex crystallised from

benzene–diethyl ether as a C$_6$H$_6$ solvate, mp 171–172 °C, [α]$_D$ −80.0 (*c* = 0.5, C$_6$H$_6$). Attempts to use non-chlorinated solvents for the cycloaddition reaction were unsuccessful. The molecular structure and the absolute stereochemistry of (−)-3 were determined by X-ray crystallographic analysis.‡ Fig. 1 shows the ORTEP drawing of the complex. It revealed that the sulfinyl-substituted ligand coordinates to palladium as a monodentate *via* phosphorus. The sulfinyl function is attached to the *exo* position at C(20) of the rigid bicyclic ring with the Ph–P group orientated in the *syn* orientation.[8] The absolute configurations at the P, S, C(15), C(18) and C(20) stereocentres are *S, R, S, S* and *R*, respectively. The vinyl-sulfoxide group is not coordinated to palladium.

It has been well documented that the cleavage of carbon–halogen bonds can be promoted by phosphine metal complexes under similar reaction conditions.[9] This competitive process, however, is believed to deter the desired Diels–Alder reaction and thus accounts for the low yield of (−)-3. In order to confirm this, we have prepared the chloro complex (−)-5 from the corresponding dimeric species (−)-4[6,7] and DMPP: mp 139–142 °C, [α]$_D$ −334.9 (*c* = 1.0, CH$_2$Cl$_2$). The chloro ligand
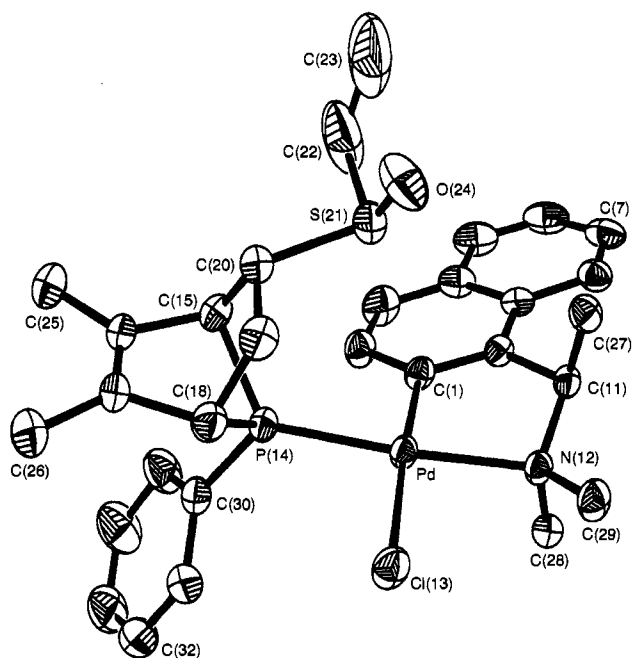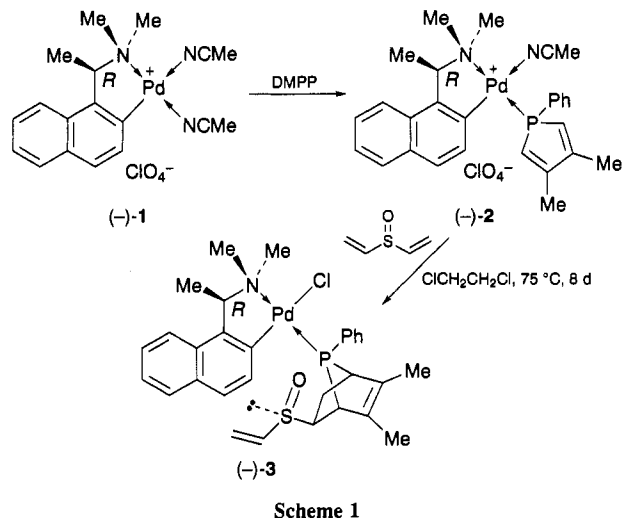

Scheme 1

Fig. 1 ORTEP drawing of (−)-3 with thermal ellipsoid plot (50% probability for non-hydrogen atoms with hydrogen atoms and the C$_6$H$_6$ solvate molecule omitted for clairty). Selected bond lengths (Å) and angles (°): Pd–C(1), 2.006(5); Pd–N(12), 2.147(4); Pd–Cl(13), 2.405(1); Pd–P(14), 2.223(1); P(14)–C(15), 1.866(7); P(14)–C(18), 1.848(6); C(16)–C(17), 1.304(8); C(19)–C(20), 1.566(7); C(20)–S(21), 1.830(4); S(21)–C(22), 1.698(10); S(21)–O(24), 1.469(5); C(22)–C(23), 1.329(22); C(15)–P(14)–C(18), 80.8(3); C(16)–C(15)–C(20), 103.9(5); C(17)–C(18)–C(19), 108.6(5); C(15)–C(16)–C(17), 112.0(5); C(15)–C(20)–C(19), 105.7(4); S(21)–C(22)–C(23), 114.3(8).

Scheme 2
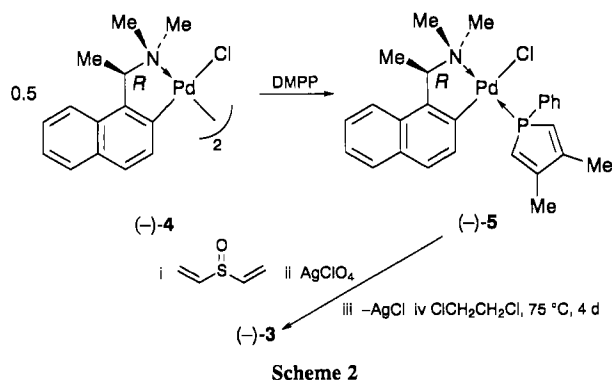
in (−)-**5** occupied the second readily available coordination site on the palladium(II) template. It was found that the neutral complex indeed failed to undergo the [4 + 2] cycloaddition under the reaction conditions described above. On removing the chloro ligand with silver perchlorate, however, (−)-**3** was obtained in similar yields (Scheme 2). Our experiments clearly indicate that the cycloaddition reaction between DMPP and divinyl sulfoxide, and hence the stereoselectivity in the product formation,[10] require the formation of a reaction intermediate in which both precursors are held by palladium in proper orientation. This is in agreement with the reported observation that the generation of the thermodynamically unstable *exo–syn* isomer in similar Diels–Alder reactions involving DMPP required the dienes and dienophiles to be coordinated simultaneously on the catalyst during the course of cycloaddition reaction.[8,11] We therefore believe that the bifunctional ligand, once formed, chelates to the two available sites of the palladium catalyst *via* the sulfinyl group and the phosphorus donor atom. Subsequently, the sulfinyl group breaks away from any metal linkage, succumbing to the competing chloride abstraction process to give (−)-**3**. In the ongoing investigation of the chelating properties of this new class of sulfinyl-substituted ligands, the studies by our group on the two model ligands, (±)-[2-(methylsulfinyl)ethyl]diphenyl]arsine and phosphine provide us with useful handles.[12] When treated with (−)-**1**, these ligands coordinated to palladium exclusively *via* E–O donor atoms (where E = P or As). In the presence of excess chloride ion or under unfavourable steric constraints, they coordinate to the metal ion solely *via* a M–E bond.

Of the two methodologies described here, we found that it was more convenient practically to prepare (−)-**3** from (−)-**5** as illustrated in Scheme 2. The approach requires a shorter reaction time (compared with Scheme 1) which may be due to the absence of the coordinating MeCN ligand. Furthermore, the chloro complex (−)-**5** is very stable and, unlike (−)-**2**, it is readily isolated by simple crystallisations. Nevertheless, in both approaches, the organopalladium unit controls the generation of the five chiral centres stereoselectively. In addition, (+)-**3** has been prepared in similar yield using the equally accessible (+)-**1** and (+)-**4** as promoters. Further investigation on the chemical and physical properties of the optically active sulfinyl-substituted phosphine ligand is currently in progress.

Footnotes

† All the isolated new complexes were analysed satisfactorily. Their spectroscopic data are available from the authors upon request.

‡ *Crystal data* for (−)-**3**: $C_{36}H_{41}ClNOPPdS$, $M_W = 708.6$, trigonal, space group $P3_1$; $a = 15.868(2)$ Å, $c = 11.831(2)$ Å, $V = 2580.0(13)$ Å^3, $Z = 3$, $D_c = 1.368$ g cm^{-3}, $\mu = 7.53$ cm^{-1}. The reflections were obtained by an automated random search routine at room temperature on a Siemens R3m/V four-circle diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). A total of 9502 reflections were collected and 5569 observed reflections [$F > 3\sigma(F)$] were used in the refinement. Semi-empirical absorption corrections were applied. The structure was solved by direct methods. All non-hydrogen atoms were located from Fourier difference maps and were refined anisotropically. Solution and refinement based on space groups $P3_1$ and $P3_2$ were tried. However, the latter space group led to an S configuration at C(11) of the aminoethylnaphthalene ligand which contradicted the chirality of the starting material used. Hence space group $P3_1$ was chosen. The function minimised during full-matrix least squares refinement was $\Sigma w \mid F_0 - F_c \mid^2$ where $w^{-1} = \sigma^2(F) + 0.0004F^2$ giving $R = 0.034$, $R_w = 0.036$ and $S = 1.00$. All calculations were performed on a Digital Equipment Corp. MicroVax II computer using the Siemens SHELXTL PLUS package. Atomic coordinates, bond lengths and angles, and thermal parameters for (−)-**3** have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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