A simple route to a novel enantiomerically pure P-chiral phosphine ligand containing a tertiary amide functional group

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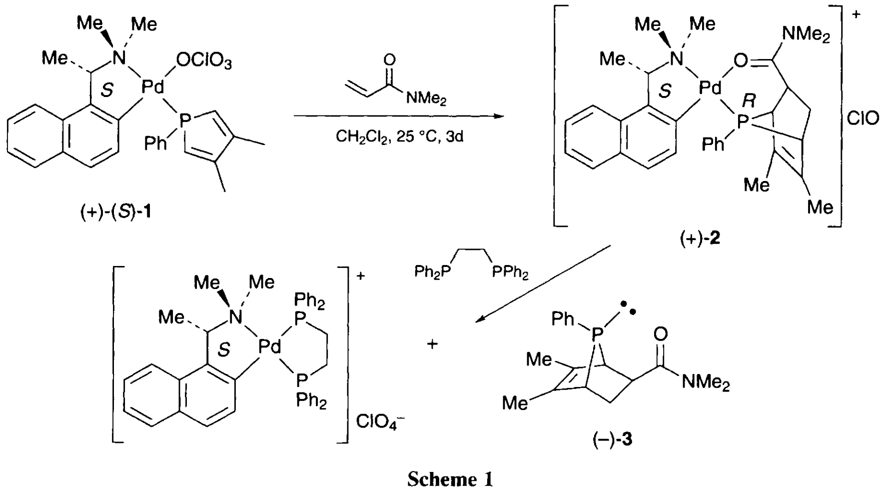
A new palladium(II) complex containing an amido-substituted P-chiral phosphine ligand is prepared efficiently by the asymmetric Diels–Alder reaction between *N*,*N*-dimethylacrylamide and 1-phenyl-3,4-dimethylphosphole; the chelating properties of the functionalised ligand and the absolute configurations of the four newly generated stereocentres are determined by single-crystal X-ray analysis, and the optically active phosphine ligand displaced from the palladium template with 1,2-bis(diphenylphosphino)ethane.

Currently, there is an intensive search for chiral phosphine bearing chirotopic functional groups that are capable of providing secondary interactions with the reacting substrates in homogeneous asymmetric catalysis.[1,2] It has been demonstrated that in many instances the incorporation of amides, amines, esters and hydroxy groups into the appropriate phosphine auxiliaries can dramatically improve both the stereoselectivity and the reactivity of these stereochemically demanding processes.[3] These functionalised phosphine ligands, interestingly, invariably rely upon carbon chirality and are prepared from their corresponding chirons. Surprisingly, however, there have been no reports on the application of analogous functionalised P-chiral phosphines in asymmetric catalysis. Such molecules should be potentially powerful auxiliaries, since their P-chiral donors, and hence the primary chirality inducers, are coordinated directly onto the catalytic metal centres, while a secondary control is operated simultaneously by the selected functionalities. It should be noted that, apart from a few unsubstituted P-chiral diphosphines which can be prepared efficiently by asymmetric synthesis,[4] substituted phosphines with phosphorus stereogenic centres are generally obtained by optical resolution.[5] Presumably, the difficulties associated with these procedures have hampered the advancement of this attractive approach. Here we describe a simple and efficient asymmetric synthesis of a P-chiral phosphine ligand containing an amide function.

The highly reactive perchlorato complex, (+)-(*S*)-**1**, was prepared *in situ* by treating the corresponding chloro species with silver perchlorate in CH_2Cl_2.[6] Upon coordination, the cyclic diene, 1-phenyl-3,4-dimethylphosphole (DMPP) is activated and is capable of reacting with dienophiles.[7] Thus, treatment of (+)-(*S*)-**1** with excess *N*,*N*-dimethylacrylamide in CH_2Cl_2 at room temperature for 3 days gave the corresponding [4 + 2] cycloaddition product, (+)-**2** in essentially quantitative yield (Scheme 1). Prior to purification, the ^{31}P NMR spectrum of the crude product in $CDCl_3$ exhibited a sharp singlet at δ 109.2. No other ^{31}P resonance signals could be detected in the 202 MHz NMR spectra, thus indicating that only a single diastereoisomer is formed in the Diels–Alder reaction. The compound was subsequently crystallized as highly stable colourless needles from chloroform–light petroleum in 85% isolated yield, mp 216–217 °C (decomp.), $[\alpha]_D$ + 193.8 (*c* 0.2, CH_2Cl_2).† Attempts to accelerate the cycloaddition process by using higher reaction temperatures, however, gave lower yields of the desired complex along with the formation of several unidentified impurities. Furthermore, no reaction was observed when the perchlorato complex was replaced by its chloro analogue. The complex behaves as a typical 1 : 1 electrolyte, both in acetone and in CH_2Cl_2.

The solid-state molecular structure and the absolute stereochemistry of (+)-**2** have been determined by single-crystal X-ray analysis.‡ This study reveals that the reaction of (+)-(*S*)-**1** with *N*,*N*-dimethylacrylamide has resulted in the cleavage of the Pd–$OClO_3$ bond in (+)-(*S*)-**1**, and that the amido substituted phosphine ligand created coordinates to palladium as a bidentate chelate *via* the bridgehead phosphorus atom and the oxygen atom of the amide group in a slightly distorted square planar geometry [the angles at palladium are in the ranges 90.9(2)–95.8(1) and 172.2(2)–177.0(2)°] (Fig. 1). The geo-



Scheme 1

metry of the coordinated naphthylamine ligand is essentially identical to that observed in (+)-(*S*)-**1**, with Pd–N aand Pd–C distances of 1.979(5) and 2.133(3) Å respectively [*cf.* mean values of 1.979 and 2.141 Å respectively for the two independent molecules in (+)-(*S*)-**1**] with a retention of an axial geometry for the methyl group at the (*S*) chiral centre [C(11)]. The puckering of the PdC_3N ring results in the naphthyl ring being folded by *ca.* 23° out of the coordination plane. The Pd–O and Pd–P distances to the chelating phosphine ligand [2.119(4) and 2.216(1) Å] are noticeably shorter than those to the oxygen and phosphorus atoms in (+)-(*S*)-**1** (2.203 and 2.247 Å); the corresponding O–Pd–P angles are 92.7(1) and 91.0(1)° respectively. The geometry of the chelating phosphine is essentially the same as that observed in a related racemic ruthenium(II) complex reported by Vac and coworkers.[7]

In light of the observed *exo* structure, we conclude that amide ligation precedes the Diels–Alder [4 + 2] cycloaddition and the consequent formation of an (*R*)stereocentre at phosphorus, together with three new carbon stereocentres [at C(23), C(26) and C(27)]. From a mechanistic standpoint, the five-membered orthometallated naphthylamine chelate in (+)-(*S*)-**1** provides an ideal, but rare template for both the activation and the stereochemical control of the Diels–Alder [4 + 2] cycloaddition process between DMPP and *N*,*N*-dimethylacrylamide. The cyclic diene, which contains a typical 'soft' phosphorus donor, is expected to coordinate strongly to Pd^{II}. Indeed, it has been well documented that this ortho-metallated chelate directs the binding of all monodentate phosphorus donor atoms regiospecifically to the palladium site which is located *trans* to the σ-donating nitrogen.[8] On the other hand, the direct activation of the 'hard' amide function by the soft metal ion in the transition state between (+)-(*S*)-**1** and (+)-**2** is intriguing. The kinetically labile perchlorate ligand in (+)-(*S*)-**1** offers a readily available site for the reacting *N*,*N*-dimethylacrylamide so that the dienophile and DMPP can be coordinated simultaneously on the chiral template during the course of the cycloaddition reaction. Treatment of (+)-**2** with 1,2-bis(diphenylphosphino)ethane in dichloromethane liberated the optically active amido-substituted phosphine ligand (−)-**3** as a colourless oil with $[\alpha]_D - 1.9$ (*c* 0.6, CH_2Cl_2). The ^{31}P NMR spectrum of the free ligand in $CDCl_3$ exhibited a sharp singlet at δ 98.0. This low field signal confirms that the *exo–syn* stereochemical relationship is retained.[7] Owing to the configurational instability of the uncoordinated bridgehead phosphorus stereogenic centre,[9] the liberated ligand cannot be stored for longer than *ca.* 30 min, and was therefore re-complexed immediately to selected metal ions. These optically active ligand complexes are stable, and the chiral phosphine can be readily re-released by further treatment with 1,2-bis(diphenylphosphino)ethane. Investigations on the catalytic properties of these metal complexes are currently in progress.

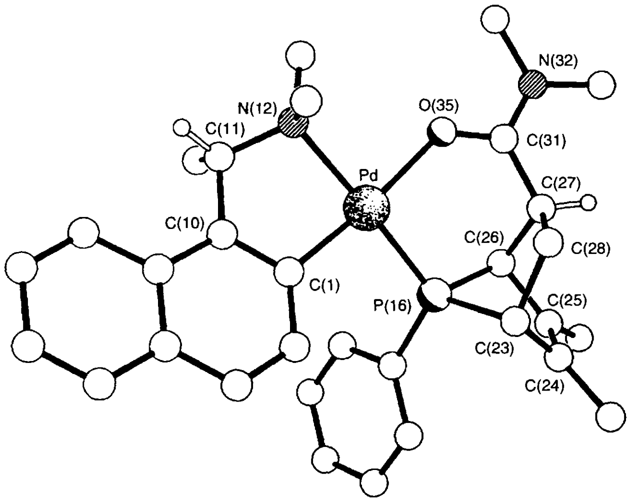


Fig. 1 The molecular structure of the cation in (+)-**2**, showing the four new chiral centres formed in the Diels–Alder [4 + 2] cycloaddition reaction

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Footnotes

† ^{1}H NMR [300.00 MHz, $CDCl_3$]: δ 1.66 (s, 3H), 1.90 (d, 3H, 6.6 Hz), 1.93 (s, 3H), 2.38 (m, 1H), 2.66 (d, 3H, 1.2 Hz), 2.88 (d, 3H, 3.3 Hz), 2.93 (m, 1H), 3.09 (t, 1H, 1.9 Hz), 3.20 (s, 3H), 3.30 (m, 1H), 3.37 (s, 3H), 3.57 (t, 1H, 1.9 Hz), 4.30 (qnt, 1H, 6.0 Hz), 6.67–7.60 (m, 11H).

‡ *Crystal data* for (+)-**2**: $C_{31}H_{38}ClN_2O_5PPd$, M = 691.5, monoclinic, space group $P2_1$, a = 7.512(1), b = 17.559(2), c = 12.346(1) Å, β = 103.87(1)°, U = 1581.0(2) Å^3, Z = 2, D_c = 1.45 g cm^{-3}, μ(Mo-Kα) = 0.76 mm^{-1}, $F(000)$ = 712. A clear plate of dimensions 0.53 × 0.40 × 0.12 mm was used. 2878 Independent reflections were measured on a Siemens P4/PC diffractometer with Mo-Kα radiation (graphite monochromator) using ω-scans. The structure was solved by the heavy-atom method and all the major occupancy non-hydrogen atoms (the ClO_4 anion is disordered) were refined anisotropically using full-matrix least-squares based on F^2 to give R_1 = 0.030, wR_2 = 0.079 for 2720 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 50°$] and 374 parameters. The absolute configuration was determined unambiguously by use of the Flack parameter [x^+ = −0.08(8), x^- = +1.09(8)]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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