# Asymmetric synthesis of keto-substituted *P*-chiral phosphines by means of an unusual *exo*/*endo*-stereochemically controlled Diels–Alder reaction

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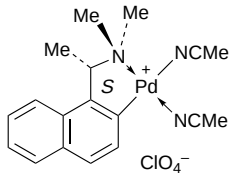
**An asymmetric Diels–Alder reaction between 1-phenyl-3,4-dimethylphosphole and ethyl vinyl ketone promoted by a chiral organopalladium complex gives the corresponding keto-substituted phosphine ligands in which the keto group can be stereospecifically located in the *endo*- or *exo*-positions of the phosphanorbornene skeleton.**

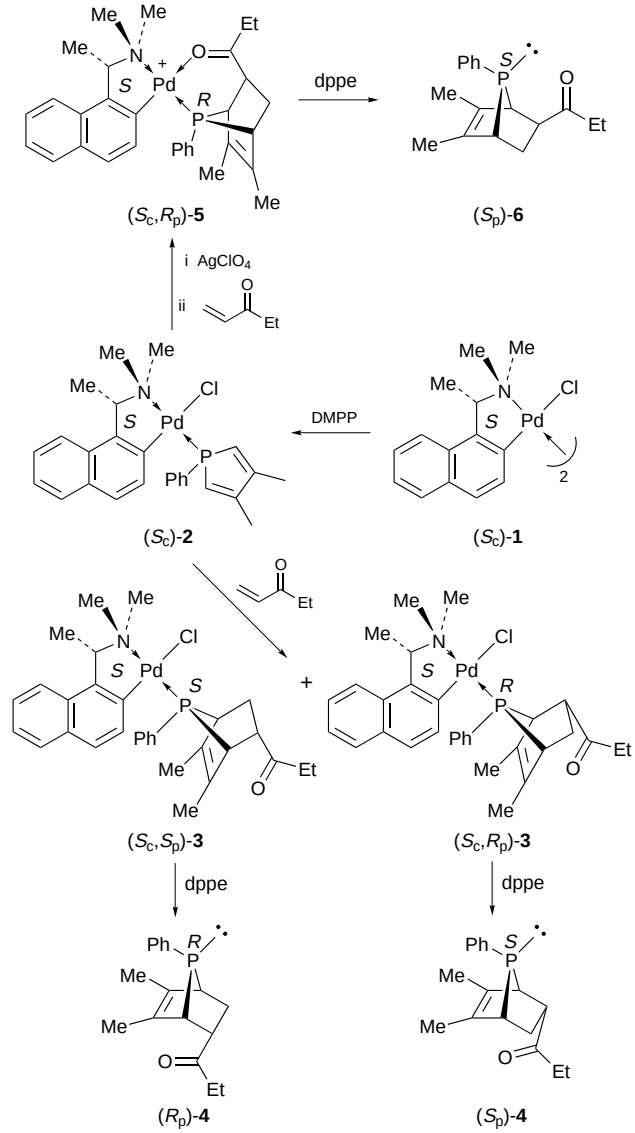
Asymmetric Diels–Alder reactions undoubtedly provide one of the most efficient and elegant methods for the synthesis of chiral 6-membered rings.[1] Since its discovery in 1928, this methodology has been used frequently in the synthesis of important chiral natural products such as antibiotics and prostaglandins. Using this method for carbon–carbon bond formation, we herein report the first asymmetric synthesis of keto-substituted *P*-chiral phosphines. Although ketophosphines are relatively common and their distinct chemistry as well as their synthetic applications are well established,[2] the number of such optically active P–O ligands is surprisingly low.[3] Certainly, no enantiomerically pure ketophosphines containing resolved tertiary phosphorus stereocentres have been reported hitherto.

Uncoordinated 1-phenyl-3,4-dimethylphosphole (DMPP) shows no reaction with ethyl vinyl ketone. The coordination of



($S_c$)-**7**

the phosphine ligand to the chiral reaction template ($S_c$)-**1**,[4] however, activates the cyclic diene towards [4 + 2] cycloaddition reactions (Scheme 1). Hence, treatment of the neutral complex ($S_c$)-**2** with ethyl vinyl ketone in $CH_2Cl_2$ at room temperature for 6 d gave a 1 : 2.5 diastereomeric mixture of the two *endo*-cycloaddition products, ($S_c$,$R_p$)-**3** and ($S_c$,$S_p$)-**3**, in quantitative yield. Prior to crystallization, the 202 MHz $^{31}$P NMR spectrum of the crude product in $CDCl_3$ exhibited two sharp singlets at $\delta_P$ 125.5 (major) and 126.6 (minor). The major isomer was subsequently crystallized from $CH_2Cl_2$–$Et_2O$ as pale yellow needles (70%), mp 135–136 °C, $[\alpha]_D$ +31.8 (*c* 1, $CH_2Cl_2$). An X-ray structural analysis revealed that this major isomer is ($S_c$,$S_p$)-**3** and the absolute configurations of the four new chiral centres at P, C(22), C(25) and C(27) are *S*, *R*, *S* and *R*, respectively (Fig. 1).‡ Treatment of ($S_c$,$S_p$)-**3** with 1,2-bis(diphenylphosphino)ethane (dppe) in $CH_2Cl_2$ liberated the optically pure ketophosphine, ($R_p$)-**4**, from the chiral metal template as an air-sensitive colourless oil in 85% yield, $[\alpha]_D$ −30.0 (*c* 1, $CHCl_3$), $\delta_P$ 109.0 (s). Stereospecific displacement of the ketophosphine was confirmed by the quantitative re-preparation of ($S_c$,$S_p$)-**3** from liberated ($R_p$)-**4** and ($S_c$)-**1**: the 202 MHz $^{31}$P NMR spectrum of the crude product indicated the diastereomer ($S_cS_p$)-**3** only. In a further test of optical purity, the diastereomer ($R_c$,$S_p$)-**3** was prepared from ($R_p$)-**4** and the equally accessible ($R_c$)-**1**: only one sharp singlet was observed at $\delta_P$ 126.6. Partially resolved ($S_p$)-**4** was liberated similarly from ($S_c$,$R_p$)-**3** by treatment with dppe. The free ligand was purified by re-coordination to ($R_c$)-**1** forming the highly crystalline complex ($R_c$,$R_p$)-**3** from which pure ($S_p$)-**4** was liberated. It is noteworthy that the intermolecular cycloaddition process could be completed in 16 h by heating the reaction mixture at 70 °C in 1,2-dichloroethane. Under these more vigorous reaction conditions, however, the product formation became non-selective and a 1 : 1 mixture of the two diastereomeric complexes was obtained.



**Scheme 1**

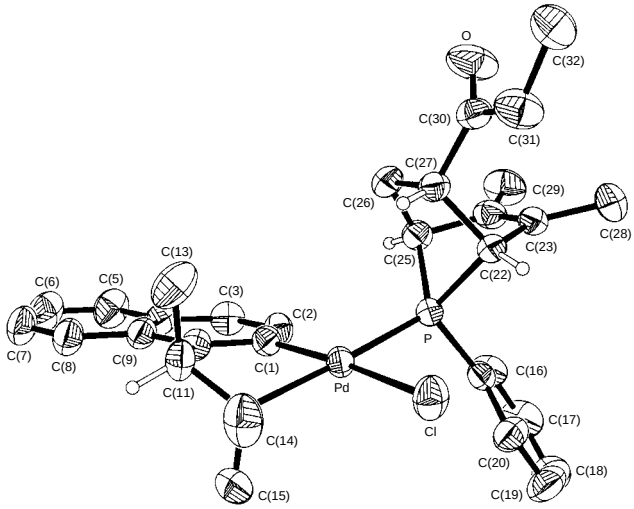



**Fig. 1** Molecular structure and absolute stereochemistry of complex ($S_c$,$S_p$)-**3**. Selected bond lengths (Å) and angles (°); Pd–P 2.241(0), Pd–Cl 2.411(1), Pd–C(1) 2.014(2), Pd–N(12) 2.151(1), P–C(22) 1.860(2), P–C(25) 1.858(2), O–C(30) 1.201(2), C(22)–C(27) 1.582(2), C(27)–C(30) 1.530(2), C(23)–C(24) 1.336(3); C(1)–Pd–N(12) 80.7(1), C(22)–P–C(25) 81.0(1), P–C(22)–C(27) 98.8(1), C(22)–C(27)–C(30) 110.3(1), C(27)–C(30)–O 121.3(2).

Interestingly, the removal of the chloro ligand in ($S_c$)-**2** clearly decelerates the cycloaddition process. Thus, when a $CH_2Cl_2$ solution of ($S_c$)-**2** was stirred with a stoichiometric quantity of $AgClO_4$, filtered, and then treated directly with ethyl vinyl ketone at room temperature, the corresponding cycloaddition reaction required 9 d for completion. Furthermore, the $^{31}P$ NMR spectrum of a $CDCl_3$ solution of the crude product obtained from this slow reaction indicated that both ($S_c$,$R_p$)-**3** and ($S_c$,$S_p$)-**3** were not formed. The spectrum included only a singlet at $\delta_P$ 107.3. This new product was crystallized from $CH_2Cl_2$–$Et_2O$ as yellow prisms (85%), mp 197–198 °C, $[\alpha]_D$ + 232.7 (*c* 1, $CH_2Cl_2$). An X-ray structural analysis confirmed that it is ($S_c$,$R_p$)-**5** and the absolute configurations of its four chiral centres at P, C(22), C(25) and C(27) are *R*, *S*, *R* and *R*, respectively (Fig. 2).‡ It is noted that, interestingly, the C=O bond distance [1.218(6) Å] in this cationic complex is longer than its counterpart [1.201(2) Å] in ($S_c$,$S_p$)-**3**. The lengthening

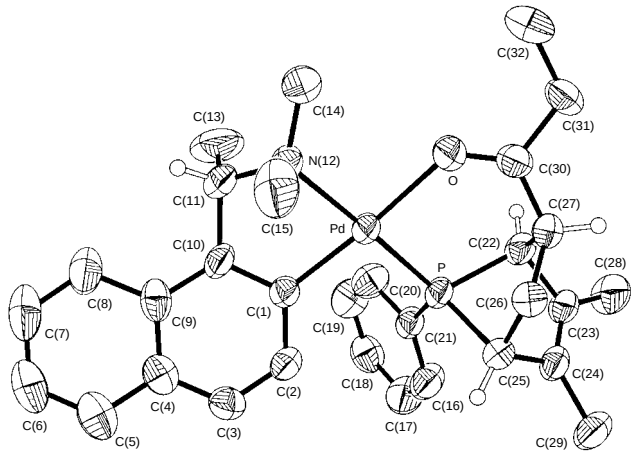



**Fig. 2** Molecular structure and absolute stereochemistry of the cation in ($S_c$,$R_p$)-**5**. Selected bond lengths (Å) and angles (°); Pd–P 2.226(1), Pd–O 2.156(4), Pd–C(1) 1.980(5), Pd–N(12) 2.134(4), P–C(22) 1.840(5), P–C(25) 1.853(5), O–C(30) 1.218(6), C(22)–C(27) 1.571(8), C(27)–C(30) 1.503(7), C(23)–C(24) 1.312(9); P–Pd–O 91.2(1), P–Pd–C(1) 95.7(1), P–Pd–N(12) 177.0(2), O–Pd–C(1) 172.4(2), O–Pd–N(12) 91.0(2), C(1)–Pd–N(12) 82.3(2), Pd–P–C(22) 112.1(2), Pd–P–C(25) 115.6(2), C(22)–P–C(25) 81.4(2), P–C(22)–C(27) 100.2(3), C(22)–C(27)–C(30) 109.1(4), C(27)–C(30)–O 123.1(5), C(30)–O–Pd 128.9(4).

of the C=O bond in the *O*-bonded complex is perhaps an indication of the weakening of the double bond character *via* coordination. Treatment of ($S_c$,$R_p$)-**5** with dppe liberated the optically pure ($S_p$)-**6** from the chiral metal template as an air-sensitive colourless oil in 73% yield, $[\alpha]_D$ −17.2 (*c* 1, $CH_2Cl_2$), $\delta_P$ 94.5 (s). The optical purity of ($S_p$)-**6** was confirmed by the quantitative re-preparation of ($S_c$,$R_p$)-**5** from the liberated ligand and ($S_c$)-**7**:[5] the 202 MHz $^{31}P$ NMR spectrum of the crude product indicated diastereomer ($S_c$,$R_p$)-**5** only. Consistent with this, the diastereomeric complex ($R_c$,$R_p$)-**5**, prepared from ($S_p$)-**6** and ($R_c$)-**7**, showed a sharp singlet at a clearly different $^{31}P$ chemical shift, *i.e.* at $\delta_P$ 110.0.

From a mechanistic standpoint, the transition state involved in the formation of ($S_c$,$R_p$)-**5** requires both the diene and the dienophile to be coordinated simultaneously on the cationic palladium template during the course of the intramolecular cycloaddition reaction. Such an intramolecular mechanism, however, is not involved in the synthesis of *endo*-diastereomers **3** which are clearly produced by an intermolecular cycloaddition reaction. Furthermore, we believe that the coordinated DMPP is electronically activated by the neutral palladium template throughout the intermolecular *endo*-cycloaddition process. Owing to the electron deficiency in the cationic transition state of the *exo*-cycloaddition reaction, the coordinated DMPP is less activated and hence a longer reaction time is required for the intramolecular process. Indeed, such a low activation prohibits the potential competing intermolecular cycloaddition reaction and hence the *exo*-cycloadduct is formed exclusively. Furthermore, as the diene and the dienophile of the *exo*-cycloaddition reaction are coordinated on the chiral template, their stereochemical orientations in the transition state are being controlled simultaneously by the naphthylamine auxilliary. Accordingly the slower *exo*-cycloaddition shows a much higher degree of stereoselectivity than the corresponding faster *endo*-process.

## Footnotes and References

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‡ *Crystal data* for ($S_c$,$S_p$)-**3**: $[C_{31}H_{37}ClNOPPd]\cdot Et_2O$, $M$ = 686.56, orthorhombic, space group $P2_12_12_1$, $a$ = 11.8359(2), $b$ = 14.0404(2), $c$ = 20.7878(3) Å, $V$ = 3454.53(9) Å$^3$, $Z$ = 4, $D_c$ = 1.320 g cm$^{-3}$, $\mu$(Mo-Kα) = 6.91 cm$^{-1}$, $F(000)$ = 1432. A colourless block with dimensions 0.50 × 0.38 × 0.28 mm was used for diffraction studies, 8315 ($R$ = 0.0152) independent reflections were measured on a Siemens SMART CCD diffractometer with Mo-Kα radiation using $\omega$-scans. All the non-hydrogen atoms were refined anisotropically. Full-matrix least-squares refinement based on $F^2$ with absorption corrected data gave $R_1$ = 0.0198, $wR_2$ = 0.0483 for 7844 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leqslant 58.20°$] and 379 parameters.

*Crystal data* for ($S_c$,$R_p$)-**5**: $[C_{31}H_{37}NOPPd][ClO_4]$, $M$ = 676.4, monoclinic, space group $P2_1$, $a$ = 7.625(1), $b$ = 16.814(2), $c$ = 12.400(1) Å, $\beta$ = 104.82(1)°, $V$ = 1536.9(3) Å$^3$, $Z$ = 2, $D_c$ = 1.46 g cm$^{-3}$, $\mu$(Mo-Kα) = 7.82 cm$^{-1}$, $F(000)$ = 696. A pale yellow prism of dimensions 0.53 × 0.38 × 0.15 mm was used. 3639 independent reflections were measured on a Siemens P4/PC diffractometer with Mo-Kα radiation using $\omega$-scans. All the non-hydrogen atoms were refined anisotropically. In the full-matrix least-squares refinement on $F^2$ the model converged at $R_1$ = 0.035, $wR_2$ = 0.088 for 3351 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leqslant 55°$] and 349 parameters. CCDC 182/597.

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