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Chirality control in 2,2′-biphosphole ligand leading to enantiopure Pd complex†

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Asymmetric alkylation of the 3,4-dimethyl-5-phenyl-2,2′-biphospholyl anion with the (2*R*, 4*R*)-(−)-pentaneditosylate leads to a new chirally flexible 2,2′-biphosphole ligand as a mixture of three diasteroisomers. By complexation with Pd(II), a chirality control occurs to afford enantiopure Pd complex.

Considerable efforts have been devoted to the development of new chiral ligands owing to the growing importance of transition metal catalysed asymmetric synthesis.[1] Among these chiral ligands, diphosphanes have played a dominant role, in particular chirally rigid atropoisomeric ligands (*e.g.* BINAP, DuPHOS).[1] Recently, a new approach has emerged where conformationnally flexible diphosphanes (*e.g.* BIPHEP) are used in asymmetric activation process.[2] The dynamic chirality control takes place in inert metal coordination sphere by using a chiral controller. We have recently reported the use of the chirally flexible BIPHOS ligand in asymmetric catalysis owing to the combination of a crystallisation induced spontaneous resolution of this diphosphane and its kinetic stabilisation by coordination with $PdCl_2$.[3] This chiral flexible ligand exists in solution as an equilibrium of six stereoisomers (Fig. 1) because

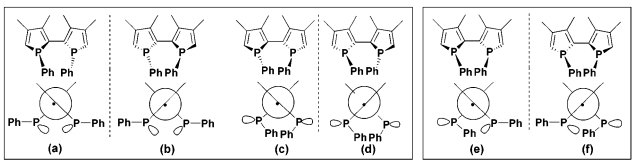
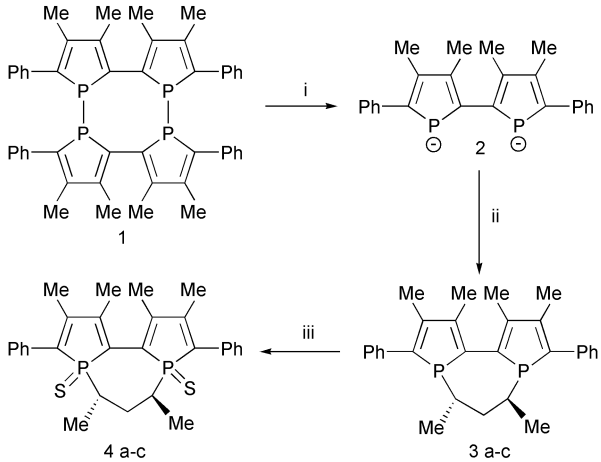


Fig. 1 The different stereoisomers of BIPHOS that possess two chiral centers and one chiral axis; each stereoisomer is also represented in a Newman projection along the axis of the C–C linking the phosphole rings.

of the configurational instability of the axial chirality generated by the 2,2′-biphosphole framework and of the central chiralities of the phosphorus atoms.[4] In order to generalise the use of 2,2′-biphosphole type ligands in asymmetric catalysis, it's necessary to control the chirality of this ligand. This can be achieved in two steps : first by introducing a chiral controller on the 2,2′-biphosphole framework such as a chiral chain to connect the two phosphorus atoms and secondly by complexation to select the best configuration to accommodate the metal centre. In order to prepare this new type of 2,2′-biphosphole ligand, we have investigated the asymmetric alkylation of the 3,4-dimethyl-5-phenyl-2,2′-biphospholyl anion **2** with the enantiomerically pure (2*R*,4*R*)-(−)-pentaneditosylate.†

The 2,2′-biphospholyl anion **2**[5] was obtained from the phosphole tetramer **1** after cleavage of the two phosphorus–phosphorus bonds by naphthalene sodium in THF (Scheme 1). **2** reacted with the enantiomerically pure ditosylate to afford the 2,2′-biphosphole compound **3** in 65% yield as a mixture of three diastereoisomers **3a** (δp 18), **3b** (δp 31 (d), δp 27(d), J_{PP} 42) and **3c** (δp 16) in the ratio 80 : 15 : 5. These diastereoisomers have



Scheme 1 Reagents and conditions : i, Na-naphthalene, THF, 25 °C; ii, (−)-(*R*,*R*)-TsOCH(CH_3)–CH2–CH(CH_3)OTs, THF, 25 °C; iii, S_8, CH_2Cl_2, 25 °C.

been converted into their more air-stable disulfides derivatives **4** (Scheme 1), a process that occurs with retention of configuration at phosphorus.[6] Disulfides **4**, obtained as a mixture of **4a–c** could be separated by column chromatography and characterised by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy and mass spectroscopy. The molecular structures of **4a** and **4c** have been established by X-ray diffraction studies[7] (Fig. 2 and 3). For both

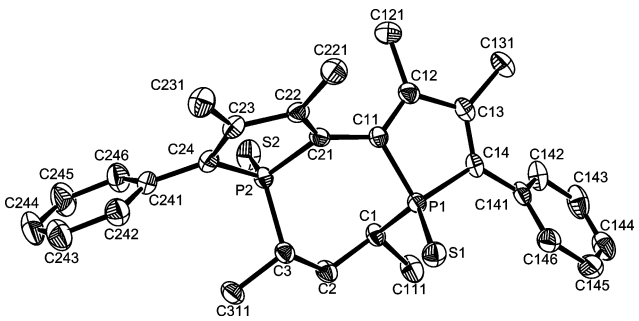


Fig. 2 Molecular view of **4a** with atom labelling scheme. Ellipsoids at 50%.

compounds all structural parameters, distances and angles, are in good agreement with reported structures.[4,8] The molecular structure of the major diastereoisomer **4a** shows that the (*S*,*S*) phosphorus stereochemistry is associated with the (*R*) axial chirality of the 2,2′-biphosphole framework as shown by the P(1)–C(11)–C(21)–P(2) torsion angle of −55.4(2)°. For the diastereoisomer **4c**, the (*R*,*R*) central chirality is associated with the (*S*) axial chirality as shown by the P(1)–C(11)–C(21)–P(2) torsion angle of 84.3(3)°[mean value]. The large difference observed with the torsion angle in **4a** is certainly related to the strain introduced by the chiral bridge in the *S*[*R*p,*R*p] configuration.[9] Concerning compound **4b**, its absolute configuration could not be established. However, the two phosphorus

† Electronic supplementary information (ESI) available: selected spectroscopic NMR data. See http://www.rsc.org/suppdata/cc/b3/b301613g/

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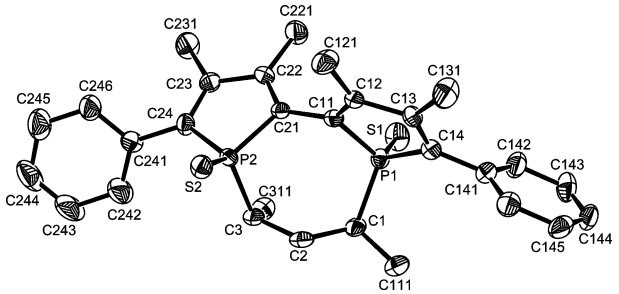
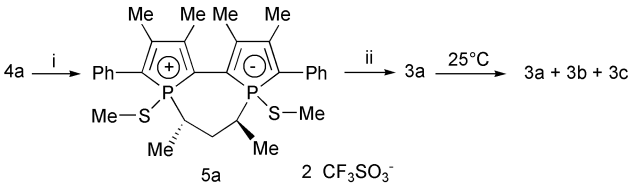


Fig. 3 Molecular view of **4c** with atom labelling scheme. Ellipsoids at 50%.

resonances observed at δp = 67.3 and δp = 63.3 are consistent with two diastereotopic phosphorus having opposite phosphorus configurations (*R*,*S*). According to these results, the chiral controller have induced (1) a good carbon-to-phosphorus induction as the original (*R*,*R*) chirality of the enantiomerically pure ditosylate induces the preferred (*S*,*S*) stereochemistry of the phosphorus atoms, (2) a partial chirality control of the 2,2′-biphosphole framework as three diastereoisomers are obtained among the six expected. The substitution of the two phenyl groups by a short chain prevents the formations of (a) and (b) forms and favour the (c), (d), (e) (or (f)) configurations (Figure 1). Among these three forms, the best candidate for chelating a metal appears to be the isomer (e) (or (f)).

To confirm the stereolability of the 2,2′-biphosphole **3a**, we have carried out the desulfurization of compounds **4a** and **4c** using a stereospecific method.[10] Compound **4a** reacted with methyltrifluoromethane sulfonate to give compound **5a** in quantitative yield. Then at −70 °C, the reduction of **5a** led to the quantitative formation of **3a** but an isomerization proceeded at −30 °C giving a mixture of **3a–c** at room temperature in the ratio 80 : 15 : 5 (Scheme 2). A similar reaction conducted on **4c**



Scheme 2 Reagents and conditions : i, CF_3SO_3Me, CH_2Cl_2, 25 °C; ii, t-BuSLi, CH_2Cl_2/Et_2O, −70 °C.

gave the same mixture at room temperature. These results confirm that 2,2′-biphosphole **3** exists in solution at room temperature as an equilibrium mixture of three diastereoisomers.

However, in presence of a transition metal, this equilibrium shifts to one preferentially configuration. Treatment of **3a–c** with 1 equiv. of $[PdCl_2(CH_3CN)_2]$ led to complete consumption of the ligand to afford [$PdCl_2$(2,2′-biphosphole)] **6** (90%) and an unidentified product (10%).[11] The X-ray structure of **6**[12] (Fig. 4) indicates that only the predicted [*R*p,*S*p] configuration of 2,2-biphosphole is complexed to the metal centre. The axial chirality of the 2,2-biphosphole framework disappeared upon complexation. Indeed, owing to the strain induced by chelation on the metal, the P(1)–C(11)–C(21)–P2 torsion angle, −8.2(2)°, is drastically reduced from the values observed in **4a** and **4c** . The two rings P(1) C(11) C(12) C(13) C(14) P(2) C(21) C(22) C(23) C(24) might be considered as planar with the largest deviation being −0.261(2) Å at C(14).

In summary, we have developed a new simple access to enantiopure 2,2′-biphosphole complex based on a two step chirality control process. Applications in asymmetric catalysis are currently underway.

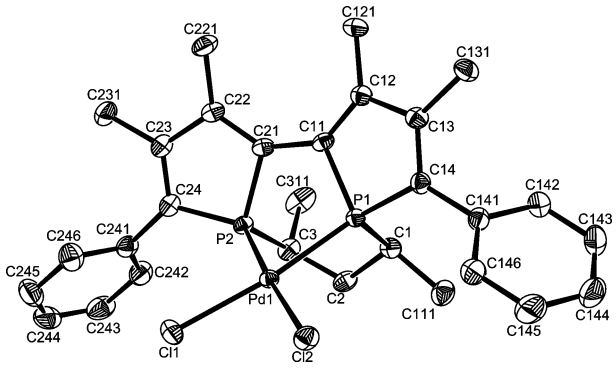


Fig. 4 Molecular view of complex **6** with atom labelling scheme. Ellipsoids at 50%. Selected bond lengths (Å) and bond angles(°): Pd–P(1) 2.2735(6); Pd–P(2) 2.2479(6); Pd–Cl(1) 2.3381(7); Pd–Cl(2) 2.3515(6); P(1)–Pd–P(2) 78.02(2); P(1)–Pd–Cl(1) 169.31(2); P(2)–Pd–Cl(1) 91.29(2); P(2)–Pd–Cl(2) 176.14(3); Cl(1)–Pd–Cl(2) 92.53(2).

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7 *Crystal data*. *R*[Sp,Sp,*S*c,*S*c]-(+)**4a**: $C_{29}H_{32}P_2S_2$, M = 506.61, orthorhombic, *a* = 6.568(1), *b* = 12.240(2), *c* = 33.217(7) Å, *U* = 2670.4(8) Å^3, *T* = 180 K, space group $P2_12_12_1$ (no 19), *Z* = 4, μ(Mo–Kα) = 1.26 mm^{-1}, 20164 reflections measured, 5457 unique (R_{int} = 0.048) which were used in all calculations. The final *R* and *wR*(F2) were 0.0327 and 0.0733 respectively (all data), Flack's parameter = 0.00(6). CCDC 203934. Crystal data. *S*[*R*p,*R*p,*S*c,*S*c]-(+)**4c**: $C_{29}H_{32}P_2S_2$, M = 506.61, monoclinic, *a* = 12.225(1), *b* = 16.667(1), *c* = 13.365(1) Å, β = 90.08(1)°, *U* = 2723.0(4) Å^3, *T* = 180 K, space group $P2_1$ (no 4), *Z* = 4, μ(Mo–Kα) = 1.236 mm^{-1}, 20784 reflections measured, 10919 unique (R_{int} = 0.045) which were used in all calculations. The final *R* and *wR*(F^2) were 0.0410 and 0.0862 respectively (all data), Flack's parameter = 0.07(6) ; the crystal is twinned (twin law: 1 0 0 0–1 0 0 0–1) and emulates orthorhombic. CCDC 203935. See http://www.rsc.org/suppdata/cc/b3/b301613g/ for crystallographic data in .cif or other electronic format.

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9 To define absolute configuration, axial chirality is given first and central chiralities are between square brackets.

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11 According to ^{31}P NMR, this unidentified product is a palladium complex with four diastereotopic phosphorus having opposite phosphorus configurations [*R*p,*S*p) (δp 53.2 (d), δp 51.2(d), J_{PP} 3.25 ; δp 52.9(s), δp 50.9(s)).

12 *Crystal data*. [*R*p,*S*p,*S*c,*S*c]-(+)**6**: $C_{29}H_{32}Cl_2P_2Pd,CH_2Cl_2$, M = 704.71, monoclinic, *a* = 9.1318(7), *b* = 12.1101(11), *c* = 14.1276(10) Å, β = 104.042(8)°, *U* = 1515.6(2) Å^3, *T* = 180 K, space group $P2_1$ (no 4), *Z* = 2, μ(Mo–Kα) = 1.09 mm^{-1}, 15118 reflections measured, 5886 unique (R_{int} = 0.046) which were used in all calculations. The final *R* and *wR*(F^2) were 0.0255 and 0.0512 respectively(all data), Flack's parameter = 0.00(2). CCDC 203936.