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COMMUNICATION

Synthesis of chiral supramolecular bisphosphinite palladacycles through hydrogen transfer-promoted self-assembly process

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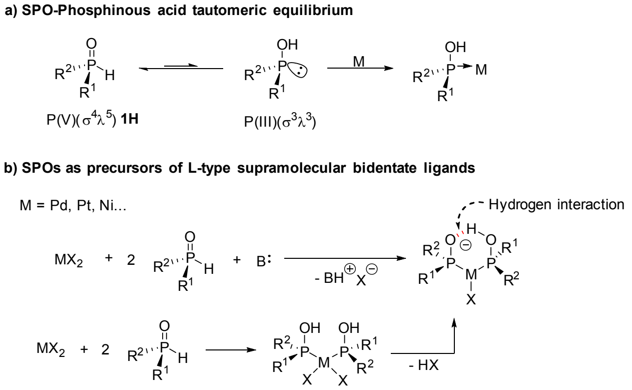
***P*-Chiral secondary phosphine oxides react with $Pd_2(dba)_3$ in acidic medium to provide chiral supramolecular bisphosphinite palladacycles through H-transfer-based self-assembly process prior to a SPO-promoted oxidative addition of an acid to a Pd(0) centre. The one-pot methodology allows variations of the X-type ligand at will. Eight complexes have been characterised by X-ray diffraction.**

Supramolecular chemistry has witnessed unbridled growth spurred on by a host of applications in a variety of areas including self-assembly phenomena.[1] A broad spectrum of research in coordination appears under this key word since supramolecular interactions are nowadays used to self-assemble ligands so as to tune the coordination spheres of metal catalysts. For instance, there is scope for the building of appealing libraries of supramolecular bidentate ligands through non-covalent interactions between two monodentate ligands such as hydrogen bonding, coordinating bonding, ionic bonding and so on.[2] In this respect, secondary phosphine oxides (SPOs) have become a notorious appealing preligand class owing to their potential for the construction of self-assembled bidentate ligands via hydrogen interaction. In concrete terms, the pentavalent tetracoordinated phosphorous form P(V)($\sigma^4\lambda^5$) is usually in favourable tautomeric equilibrium with the trivalent triccordinated phosphorous form, namely the phosphinous acid (PA) P(III)($\sigma^3\lambda^3$). This equilibrium is shifted towards the trivalent phosphorous tautomer in the presence of a late transition metal via coordination through unshared electron pair of the phosphorous atom (Scheme 1a).[3] Although seldom exhibited, two *cis*-coordinated PAs arising from enantiopure SPOs may lead to a chiral six-membered hydrogen bonded monoanionic diphosphorous chelate structure[4] resulting from the deprotonation of one of the PAs by either an added base[5] or the anionic X-type ligand dissociated from the metal (Scheme 1b).[6]



Scheme 1 Coordination of PAs to soft transition-metal centre.

As bidendate ligands prove to be of crucial importance to steer the selectivity outcome of a transition-catalysed reaction, it is thus not surprising that such PA-based supramolecular chelate structures are extensively used in homogenous catalysis[7] with the *avant la lettre* examples disclosed by Van Leeuwen as the backdrop.[8] Achieving variations of the chelate structure sounds rather straightforward as evidenced by the large available portfolio of metal(II) complexes displaying relevant and subtle alterations of bite and cone angles by changing R^1 and R^2. In contrast, accessing complexes in which the anionic X-type ligand is different from chloride or acetate may be a strenuous task since it heavily depends on the used starting metal(II) source (Scheme 1b). To date, this challenge necessarily implies either the presynthesis of a non-commercial metal(II) starting source or subsequent additional synthetic steps from wisely chosen home-prepared PA-based metallacycles such as the silver salt-promoted substitution of the chloride ligand of $[Pd\{(\mathbf{1})_2H\}]_2(\mu\text{-}Cl)_2$ when more original palladacycles are desired.[3] Given the influence of this ligand type on the course of Pd-catalysed reactions,[9] developing a one-pot method that allows a direct access to any

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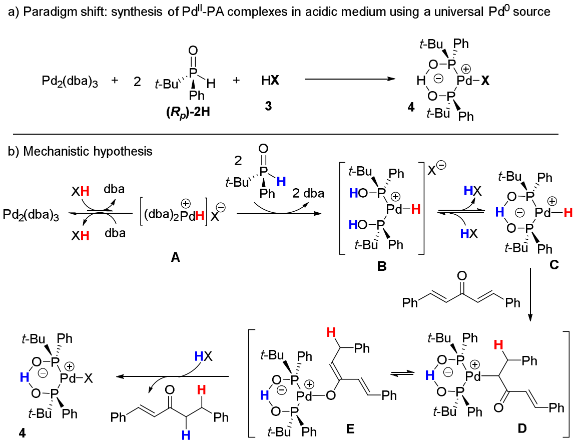
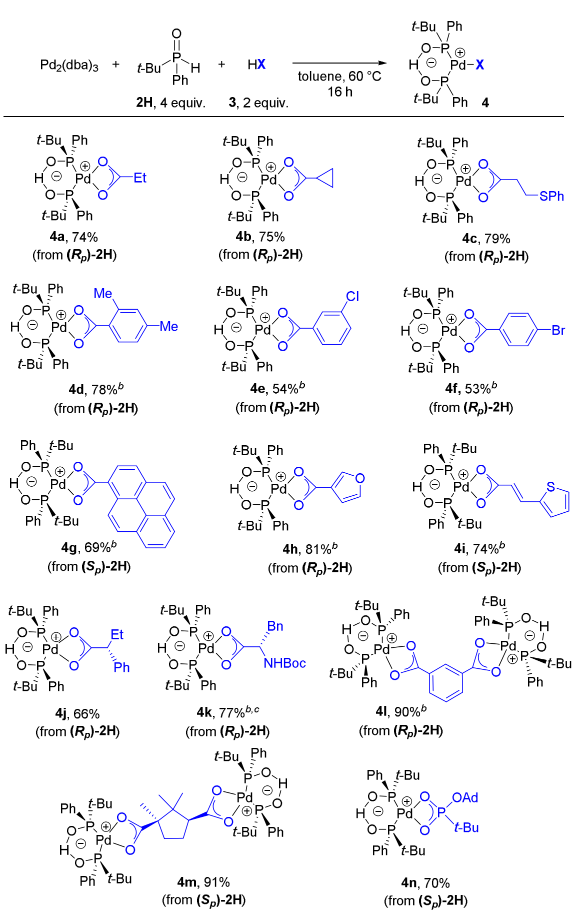
supramolecular bisphosphinite palladacycles appears highly desirable but represents a real *tour de force*.

Our solution to tackle this salient issue relies on a paradigm shift, namely operating in acidic conditions rather than basic or neutral conditions (See Scheme 2a versus Scheme 1b) with hydrogen transfer concept as Ariadne's thread. Let us consider the commercially available Pd$_2$(dba)$_3$ as a universal source for such complexes[10] (Scheme 2b). One could imagine that the treatment of Pd$_2$(dba)$_3$ by an acid HX would lead to the complex **A** resulting from an oxidative addition step.[11] Coordination of two PAs **(R_p)-2H** to the metal(II) centre would then be needed to thwart the unfavourable equilibrium associated with such a chemical event and would therefore provide the complex **B**. The counter-ion-promoted deprotonation of one of the two PAs would thereafter allow the formation of the supramolecular bisphosphinite hydrido-palladacycle **C**. Insertion of one of the two double bonds of dba into the H-Pd bond would then afford the organopalladium species **D** in supramolecular ligand-promoted equilibrium with the palladium enolate **E** via an oxa-π-allylpalladium.[12] The ionic character of the O-Pd bond would eventually favour the heterolytic fission through acidolysis so as to provide the expected complex **4**. If successful, this entirely self-assembly approach would surely represent a pinnacle in the field since it would potentially open up access to a new illusory contour library.



Scheme 2 Proposed strategy.

Table 1 Scope of the process.^{a}



^{a}Reaction conditions: Pd$_2$(dba)$_3$ (0.1 mmol), **2H** (0.4 mmol), **3** (0.2 mmol), toluene (5 mL), 60 °C, 16 h; Yields of the isolated complexes are reported. ^{b}Structurally characterised by X-ray diffraction analysis. ^{c}Slightly contaminated with a side-complex formed during the purification step.

Gratifyingly, treating Pd$_2$(dba)$_3$ by propionic or cyclopropyl-carboxylic acid at 60 °C in the presence of the easily prepared enantioenriched (*Rp*)-*t*-butyl(phenyl)phosphine oxide **1**[13] and toluene as solvent led to complexes **4a** and **4b** respectively in good yields. ^{31}P {1H} NMR analysis in CDCl$_3$ of the crude mixture revealed a single resonance at δ 95.5 and 95.6 ppm respectively, suggesting the presence of a single diastereomer. Interestingly, our hydrogen-transfer based transformation proceeded smoothly when a phenylthio group-containing carboxylic acid compound was involved, and this despite well-known ligand properties (see **4c**). Aromatic carboxylic acid substrates were also subjected to suffer this Pd(0)-mediated self-assembly process (see **4d**-**f**). It should be stressed that our supposable string of chemical events left intact the C-Cl and C-Br bonds, highlighting the high selectivity of the method towards the carboxylic acid moiety. The method was also compatible with polyfused aromatic as well as heteroaromatic caroboxylic acid compounds (see **4g** and **4h**-**i** respectively). What is worthy of note is that **4i**, in which the chemical integrity of the double bond is preserved, could be isolated in 74% yield, although (*E*)-3-(2-thienyl)acrylic acid could also play the role of H-acceptor. Under the same conditions, using (2*R*)-phenylbutyric acid or *N*-Boc-L-phenylalanine led to **4j** and **4k** respectively for which both L-type and X-type ligands are chiral. It should be stressed that **4j** showed a promising activity in the asymmetric isomerisation reaction of allylic alcohols (see ESI). When the reaction was conducted with dicarboxylic acids, dinuclear supramolecular architectures were obtained in excellent yield. Whereas the use of isophtalic acid allowed the formation of the symmetrical supramolecular structure **4l**, the use of (+)-camphoric acid resulted in the formation of the chiral unsymmetrical edifice **4m** possessing six stereogenic centres. Lastly, our developed self-assembly approach is not restricted

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to carboxylic acids as it could be extended to alkyl H-phosphonate (see **4n**). This could pave the way for the synthesis of self-assembled hybrid catalysts comprised of a metal catalyst and an organocatalyst masked as X-type ligand of the metal.

Eight complexes were structurally characterised by single-crystal X-ray diffraction analysis. X-ray crystallography confirmed that our hypothetical chemical sequence took place with retention of configuration at the phosphorous atom in spite of the required temperature (60 °C) and acidic reaction conditions. Noteworthy is the fact that they display a [LL'Pd(k^2-OOCR)]-like general formula where LL' is a σ-donor supramolecular bidentate L-type ligand. As a rule, the four-membered M–O–C–O chelate is prone to overcome an opening as a result of an incoming ligand.[14] These κ^2-OOCR palladium structures are often suspected as key intermediates in catalytic reactions,[15] sometimes detected in solution[16] or gas phase[17] but seldom structurally characterised owing to their propensity to form oligomeric carboxylate-bridged structures.[14] To the best of our knowledge, only a very small number, with R limited to a methyl or trifluoromethyl group, has been fully characterised.[6b,18] Even rarer still are the structurally characterised dinuclear complexes {(LL')$_2$Pd$_2$[k^2-(OOC)$_2$R]}. The Fig. 1 provides a unique example in this regard.

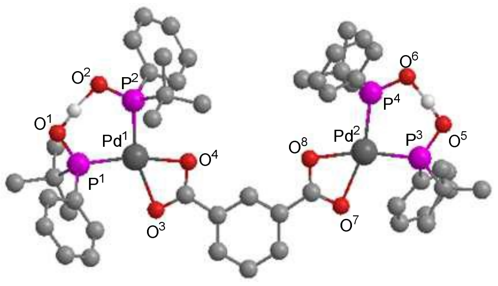
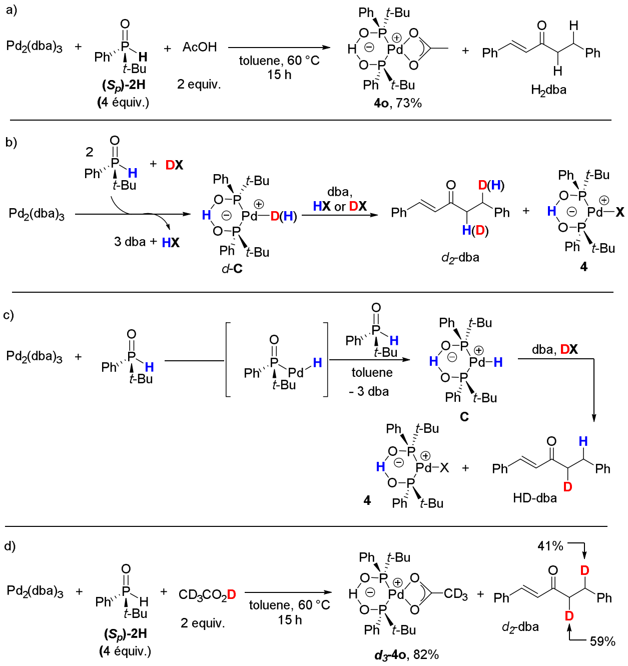


Fig. 1 Ball and stick plot of the crystal structure of **4l** with most hydrogens omitted for clarity. Selected bond lengths (Å) and angles (°) Pd1–P1 2.240(13), Pd1–P2 2.229(12), Pd1–O3 2.247(3), Pd1–O4 2.111(3), Pd2–P3 2.225(13), Pd2–P4 2.235(12), Pd2–O7 2.220(3), Pd2–O8 2.165(4), P1–O1 1.557(3), P2–O2 1.527(4), P3–O5 1.551(3), P4–O6 1.529(4), O3–C21 1.258(5), O4–C21 1.271(5), O7–C28 1.273(5), O8–C28 1.290(5), P2–Pd1–P1 90.94(5), O4–Pd1–O3 60.29(12), P3– Pd2–P4 91.32(5), O8–Pd2–O7 60.46(12).

The crystallographic data of **4l** and other structurally characterised complexes show that the metal centres are located in a distorted square-planar structure with bite angles of 91.1° and 60.4° on average for PA based- and benzoate bidentate ligands respectively. The C-O bond length average of carboxylate moieties (1.273 Å) is approximately intermediate between those of single (1.43 Å) and double C-O bonds (1.22 Å) and thus in accordance with a partial double bond character. The short distance between the oxygen atoms O^1 – O^2 and O^5 – O^6 (2.405 Å on average) and the absence of ν_{OH} in the 3000 – 3500 cm^{-1} region indicate a strong and symmetrical O – H – O bonding.[4,19] In addition, the P-O bond lengths (in the range of 1.527 – 1.557 Å) are significantly longer than typical P=O lengths (in the range of 1.48 – 1.50 Å).[20] These observations are in line with the presence of H bonds assisted by a negative charge[21] spread out between the two oxygen atoms of the supramolecular six-membered diphosphorous chelate structure. In any case, the Pd-O bond lengths are significantly shorter than those reported for the Pd(K^2-acetato)[(**1**)$_2$H] analogous (R^1 = R^2 = adamantyl or diadamantyl) while the Pd-P distances are longer,[6b,18a] presumably due to the less pronounced π-acceptor character of PAs involved in the latter.

Having in mind all the structural features of such architectures, we lastly investigated the mechanism. As our mechanistic rationale was based on a Pd-mediated H-transfer to dba ligands of the starting metal source, we first sought to highlight the production of H$_2$dba concomitantly with the formation of our supramolecular complexes. As hypothesised, the treatment of Pd$_2$(dba)$_3$ by acetic acid in the presence of **(*Sp*)-2H** afforded both the complex **4p** in 73% yield and the expected monoreduced adduct H$_2$dba (Scheme 3a) under the same conditions as those previously utilised.



Scheme 3 Mechanistic investigation.

We then assumed that this key step would be preceded by the formation of the 14-electron species **C** resulting from the oxidative addition of an acid HX to Pd(0) followed by *cis*-coordination of two **(*Sp*)-2H**. If true, performing the same reaction with deuterium labelled acid DX instead of HX would led to the formation of d_2-dba with equal deuterium incorporation rate at the α and β position of the ketone (Scheme 3b). Indeed, once ***d*-C** is formed by consumption of a molecule of DX, a molecule of HX should be released and could therefore compete with the former. Alternatively, **C** might also result from the oxidative addition of **(*Sp*)-2H** to Pd(0) and subsequent coordination of an additional **(*Sp*)-2H** to metal centre similarly to what Tanaka *et al* reported for the Pd(0)-catalysed hydrophosphinylation of alkynes in the presence of

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symmetrical diphenylphosphine oxide.[22] This option would consequently afford HD-dba as co-product of **4** in which deuterium would be exclusively located at the α position of the ketone (Scheme 3c). The reaction of Pd$_2$(dba)$_3$ with d_6-acetic acid yielded $\boldsymbol{d^3}$**-4p** and d_2-dba with deuterium incorporation rates of 41% and 59% at the α and β position of the ketone respectively (Scheme 4d). This clearly supports the mechanistic pathway involving an oxidative addition of the acid to the metal. The unequal distribution can be rationalised by a KIE[23] which should be more significant for the oxidative addition step than for the acidolysis step, the former being presumably the rate determining step owing to the associated unfavourable equilibrium.[11]

To conclude, we developed a self-assembling method allowing the production of supramolecular chiral bisphosphinite palladacycles for which a κ^2-fashion coordinated X-type ligand seemed to be modifiable at will. For the first time, the proposed approach was based on the use of a universal Pd(0) source. Our mechanistic study suggested that phosphinous acids as ligands are prone to stabilise intermediates resulting from the oxidative addition of an acid to a Pd(0) metal centre. Eight complexes were structurally characterised by X-ray diffraction analysis including unusual chiral dinuclear species. Crystallographic data showed that the coordination of phosphinous acids to Pd(II) took place with retention of configuration at the *P* atom despite the used temperature and the acidic reaction medium.

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