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Alexandre Vasseur, Romain Membrat, Davide Palpacelli, Michel Giorgi, Didier Nuel, et al.. Synthesis of chiral supramolecular bisphosphinite palladacycles through hydrogen transfer-promoted self-assembly process. *Chemical Communications*, 2018, 54 (72), pp.10132 - 10135. 10.1039/c8cc06283h . hal-01870774

HAL Id: hal-01870774

<https://hal.science/hal-01870774>

Submitted on 6 Apr 2019

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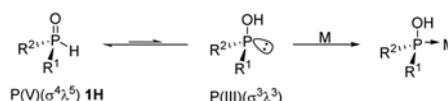
Synthesis of chiral supramolecular bisphosphinite palladacycles through hydrogen transfer-promoted self-assembly process†

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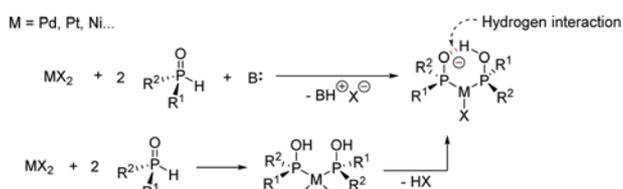
P-Chiral secondary phosphine oxides react with Pd₂(dba)₃ in an acidic medium to provide chiral supramolecular bisphosphinite palladacycles through a H-transfer-based self-assembly process prior to SPO-promoted oxidative addition of an acid to a Pd(0) centre. The one-pot methodology allows variations of the X-type ligand as desired. Eight complexes have been characterised by X-ray diffraction.

Supramolecular chemistry has witnessed huge growth due to a host of applications in a variety of areas including self-assembly phenomena.¹ A broad spectrum of research in coordination has been conducted since supramolecular interactions are nowadays used to self-assemble ligands to tune the coordination spheres of metal catalysts. For instance, there is scope for the synthesis of supramolecular bidentate ligands through non-covalent interactions such as hydrogen bonding, coordinate bonding, and ionic bonding between two monodentate ligands.² In this respect, secondary phosphine oxides (SPOs) have become an 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)(σ⁴λ⁵) is usually in favourable tautomeric equilibrium with the trivalent tricoordinated phosphorous form, namely, phosphinous acid (PA) P(III)(σ³λ³). This equilibrium is shifted towards the trivalent phosphorous tautomer in the presence of a late transition metal *via* coordination through the 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

a) SPO-Phosphinous acid tautomeric equilibrium



b) SPOs as precursors of L-type supramolecular bidentate ligands



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

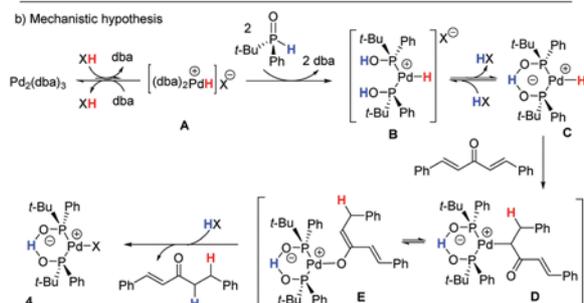
deprotonation of one of the PAs by either an added base⁵ or the anionic X-type ligand dissociated from the metal (Scheme 1b).⁶

As bidentate ligands are 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 catalysis⁷ with *avant la lettre* examples disclosed by Van Leeuwen as the backdrop.⁸ Achieving variations of the chelate structure seems rather straightforward as evidenced by the extensive available metal(II) complexes displaying relevant and subtle alterations of bite and cone angles by changing R¹ and R². In contrast, accessing complexes in which the anionic X-type ligand is different from chloride or acetate may be a challenging task since it heavily depends on the used starting metal(II) source (Scheme 1b). To date, this challenge necessitates either the presynthesis of a non-commercial metal(II) starting source or subsequent additional synthetic steps from appropriately chosen home-prepared PA-based metallacycles such as the silver salt-promoted substitution of the chloride ligand of [Pd{(1)₂H}]₂(μ-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 direct access to any supramolecular bisphosphinite palladacycles appears highly desirable but is a huge challenge.

a) Paradigm shift: synthesis of Pd^{II}-PA complexes in acidic medium using a universal Pd⁰ source



b) Mechanistic hypothesis

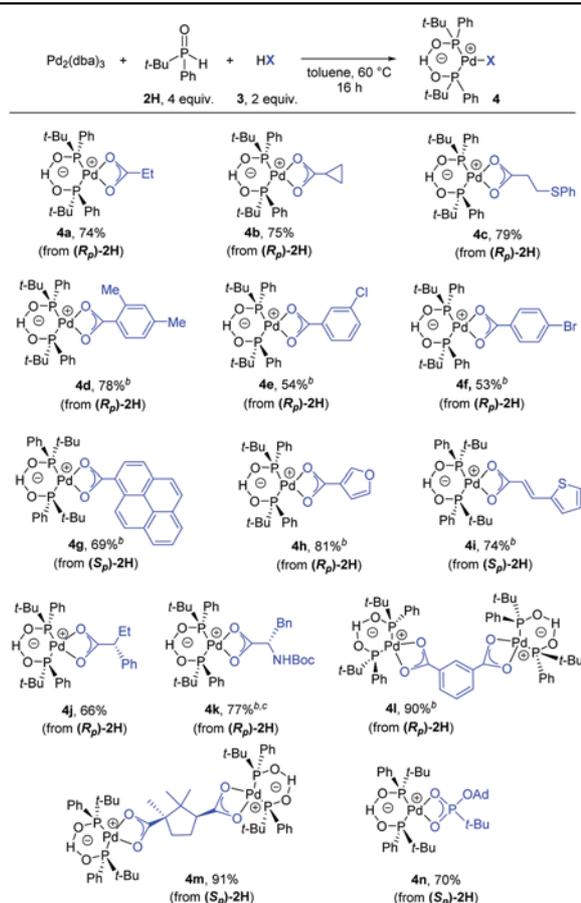


Scheme 2 Proposed strategy.

Our solution to tackle this salient issue relies on a paradigm shift, namely, operating in acidic conditions rather than basic or neutral conditions (Scheme 2a *versus* Scheme 1b) with the hydrogen transfer concept as Ariadne's thread. Let us consider commercially available Pd₂(dba)₃ as a universal source for such complexes¹⁰ (Scheme 2b). One can assume that the treatment of Pd₂(dba)₃ with 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 avoid 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* oxa- π -allylpalladium.¹² The ionic character of the O–Pd bond would eventually favour heterolytic fission through acidolysis to provide the expected complex **4**. If successful, this entirely self-assembled approach would surely represent a significant advancement in the field since it would potentially grant access to a new illusory contour library.

Fortunately, treating Pd₂(dba)₃ with propionic or cyclopropanecarboxylic acid at 60 °C in the presence of the easily prepared enantioenriched (*R_p*)-*t*-butyl(phenyl)phosphine oxide (**R_p**)-**2H**¹³ and toluene as the solvent led to complexes **4a** and **4b**, respectively, in good yields (Table 1). ³¹P{¹H} NMR analysis in CDCl₃ of the crude mixture revealed a single resonance at δ 95.5 and 95.6 ppm, 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 despite well-known ligand properties (please see **4c**). Aromatic carboxylic acid substrates were also subjected to this Pd(0)-mediated self-assembly process (see **4d–f**). It should be stressed that our chemical reactions left the C–Cl and C–Br bonds intact, highlighting the high selectivity of the method towards the carboxylic acid moiety. The method was also compatible with polyfused aromatic as well as heteroaromatic

Table 1 Scope of the process^a



^a Reaction conditions: Pd₂(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.

carboxylic acid compounds (**4g** and **4h–i**, respectively). It is worthy of note 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 a H-acceptor. Under the same conditions, using (*2R*)-phenylbutyric acid or *N*-Boc-*L*-phenylalanine led to **4j** and **4k**, respectively, for which both *L*-type and *X*-type ligands were chiral. It should be stressed that **4j** showed promising activity in the asymmetric isomerisation reaction of allylic alcohols (ESI[†]). When the reaction was conducted with dicarboxylic acids, dinuclear supramolecular architectures were obtained in excellent yields. Also, the use of isophthalic acid allowed the formation of the symmetrical supramolecular structure **4l**; the use of (+)-camphoric acid resulted in the formation of the chiral unsymmetrical structure **4m**, possessing six stereogenic centres. Lastly, our developed self-assembly approach was not restricted to carboxylic acids as it could be extended to alkyl H-phosphonate (please see **4n**). This can pave the way for the synthesis of self-assembled hybrid catalysts comprising a metal catalyst and an organocatalyst masked as an *X*-type ligand of the metal.

Eight complexes were structurally characterised by single-crystal X-ray diffraction analysis. X-ray crystallography confirmed

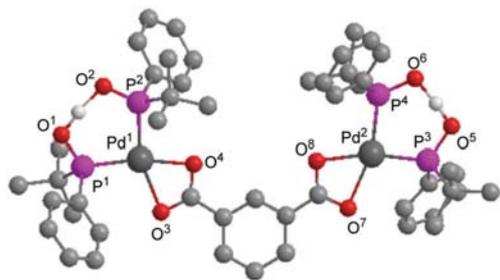
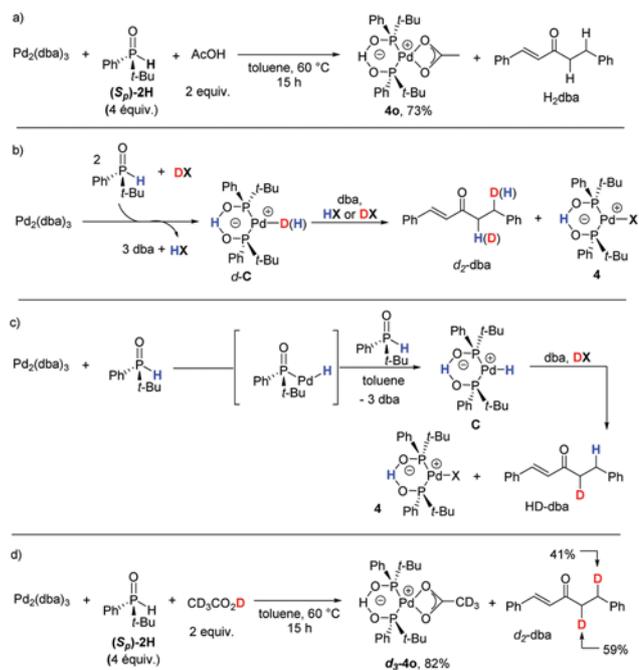


Fig. 1 Ball and stick plot of the crystal structure of **4I** with most hydrogens omitted for clarity. Selected bond lengths (Å) and angles (°) Pd1–P1 2.240(13), Pd1–P2 2.229(12), Pd1–O3 2.247(3), Pd1–O4 2.111(3), Pd2–P3 2.225(13), Pd2–P4 2.235(12), Pd2–O7 2.220(3), Pd2–O8 2.165(4), P1–O1 1.557(3), P2–O2 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).

that our hypothetical chemical sequence occurred with retention of configuration at the phosphorous atom despite the required temperature (60 °C) and acidic reaction conditions. Also, they displayed 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 overcoming an opening as a result of an incoming ligand.¹⁴ These κ^2 -OOCR palladium structures are often suspected as key intermediates in catalytic reactions¹⁵ and are sometimes detected in solution¹⁶ or gas phase¹⁷ but are 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 are the structurally characterised dinuclear complexes $\{(LL')_2Pd_2[k^2-(OOC)_2R]\}$. Fig. 1 provides a unique example in this regard.

The crystallographic data of **4I** 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 average C–O bond length of carboxylate moieties (1.273 Å) is approximately between those of C–O single (1.43 Å) and double bonds (1.22 Å) and is thus in accordance with partial double bond character. The short distance between the oxygen atoms O¹–O² and O⁵–O⁶ (2.405 Å on average) and the absence of ν_{OH} in the 3000–3500 cm^{-1} region indicate 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 agreement with the presence of H bonds assisted by a negative charge²¹ 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 $Pd(k^2\text{-acetato})[(1)_2H]$ analogous complex ($R^1 = R^2 = \text{adamantyl}$ or diadamantyl), whereas the Pd–P distances are longer,^{6b,18a} presumably due to the less pronounced π -acceptor character of PAs involved in the latter.

Considering all the structural features of such architectures, we lastly investigated the mechanism. As our mechanistic



Scheme 3 Mechanistic investigation.

rationale was based on Pd-mediated H-transfer to dba ligands of the starting metal source, we first sought to highlight the production of H₂dba concomitantly with the formation of our supramolecular complexes. As hypothesised, the treatment of Pd₂(dba)₃ with acetic acid in the presence of (*Sp*)-2H afforded both the complex **4o** in 73% yield and the expected mono-reduced adduct H₂dba (Scheme 3a) under the same conditions as those previously utilised.

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 the *cis*-coordination of two (*Sp*)-2H. If true, performing the same reaction with deuterium-labelled acid DX instead of HX would lead to the formation of *d*₂-dba with equal deuterium incorporation rates at the α and β positions of the ketone (Scheme 3b). Indeed, once *d*-C is formed by the consumption of a molecule of DX, a molecule of HX should be released and can 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 the metal centre, which is similar to that reported by Tanaka *et al.* for the Pd(0)-catalysed hydrophosphinylation of alkynes in the presence of symmetrical diphenylphosphine oxide.²² This option would consequently afford HD-dba as a co-product of **4**, in which deuterium would be exclusively located at the α position of the ketone (Scheme 3c). The reaction of Pd₂(dba)₃ with *d*₆-acetic acid yielded *d*³-**4o** and *d*₂-dba with deuterium incorporation rates of 59% and 41% at the α and β positions of the ketone, respectively (Scheme 3d). This clearly supported the mechanistic pathway involving oxidative addition of the acid to the metal. The unequal distribution can be rationalised by 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 -coordinated X-type ligand seemed to be modifiable as desired. 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 stabilising 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) occurred with the retention of configuration at the P atom despite the used temperature and the acidic reaction medium.

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