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Caleb Medena, Corinne Aubert, Etienne Derat, Louis Fensterbank, Geoffrey Gontard, et al.. Helical Bisphosphinites in Asymmetric Tsuji-Trost Alkylation: a Remarkable P:Pd Ratio Effect. *Chem-CatChem*, 2021, 13 (21), pp.4543-4548. 10.1002/cctc.202101072 . hal-03420672

HAL Id: hal-03420672

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Helical bisphosphinite in asymmetric Tsuji-Trost allylation: a remarkable P/Pd ratio effect

--Manuscript Draft--

Manuscript Number:	
Article Type:	Full Paper
Corresponding Author:	Marion Barbazanges Sorbonne Universite Paris, FRANCE
Corresponding Author E-Mail:	marion.barbazanges@sorbonne-universite.fr
Order of Authors (with Contributor Roles):	Marion Barbazanges Caleb Medena Corinne Aubert Etienne Derat Louis Fensterbank Geoffrey Gontard Omar Khaled Cyril Ollivier Nicolas Vanthuynne Marc Petit
Keywords:	helicene * phosphinite * homogeneous catalysis * chirality * Tsuji-Trost allylation
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Abstract:	This article discloses a study on a chiral bis-phosphorylated-helical ligand in the palladium-catalyzed Tsuji-Trost allylation. The use of 2,15-bisphosphinite[6]helicenes allowed to evidence a remarkable ligand effect, in which the (R) and (S) isomeric products can be selectively formed as a direct function of the amount of ligand

	introduced. Study of the organometallic species involved through ³¹ P NMR analysis of a model complex and X-Ray diffraction analysis together with DFT calculations shed light on this phenomenon.
Author Comments:	<p>Dear Editor,</p> <p>This cover letter attends the submission of the article entitled "Helical bisphosphinite in asymmetric Tsuji-Trost allylation: a remarkable P/Pd ratio effect". It discloses a comprehensive study on a chiral bis-phosphorylated helical ligand in palladium-catalyzed Tsuji-Trost allylation. We found that, unlike the other carbohelicenes evaluated in the literature, the use of 2,15-bisphosphinite[6]helicenes led to a remarkable ligand effect. Indeed, the (R) and (S) isomeric products can be formed selectively as a direct function of the amount of ligand introduced. The study of the organometallic species involved through ³¹P NMR analysis of a model complex and X-Ray diffraction analysis as well as DFT calculations on reactive intermediates shed light on this phenomenon. Moreover, these results highlight the critical importance of screening the ligand-to-metal ratio when evaluating new ligands.</p> <p>We therefore this article is of great interest to those working in the field of helicene chemistry, but also to the wider ChemCatChem community.</p>
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Helical bisphosphinite in asymmetric Tsuji-Trost allylation: a remarkable P/Pd ratio effect.

Caleb Medena,^[a] Corinne Aubert,^[a] Etienne Derat,^[a] Louis Fensterbank,^[a] Geoffrey Gontard,^[a] Omar Khaled,^[a] Cyril Ollivier,^[a] Nicolas Vanthuyne,^[b] Marc Petit,^[a] Marion Barbazanges*^[a]

Dedication ((optional))

[a] C. Medena, Dr. C. Aubert, Dr. E. Derat, Pr. L. Fensterbank, G. Gontard, O. Khaled, Dr. C. Ollivier, Dr. M. Petit, and Dr. M. Barbazanges Sorbonne Université, Faculté des Sciences et Ingénierie, CNRS, Institut Parisien de Chimie Moléculaire (UMR CNRS 8232), 4 place Jussieu, 75252 Paris Cedex 05 (France).

E-mail: marion.barbazanges@sorbonne-universite.fr

[b] Dr. N. Vanthuyne, Aix Marseille Univ
CNRS, Centrale Marseille, iSm2,
Marseille (France)

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Abstract: This article discloses a study on a chiral bisphosphorylated-helical ligand in the palladium-catalyzed Tsuji-Trost allylation. The use of 2,15-bisphosphinite[6]helicenes allowed to evidence a remarkable ligand effect, in which the (*R*) and (*S*) isomeric products can be selectively formed as a direct function of the amount of ligand introduced. Study of the organometallic species involved through ³¹P NMR analysis of a model complex and X-Ray diffraction analysis together with DFT calculations shed light on this phenomenon.

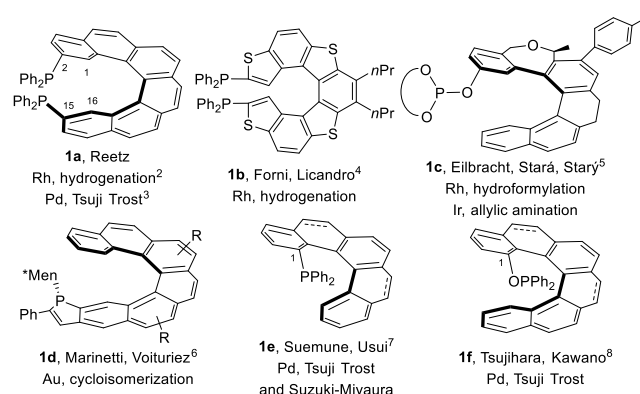
Introduction

Helicenes are organic aromatic compounds formed of several *ortho*-fused rings which naturally adopt a helical configuration and possess high chiroptical properties. They have already found broad applications in optics, electronics and biology as well as in organic and supramolecular chemistry.[1] Nevertheless, application of these scaffolds as chiral ligands in organometallic catalysis still remains a challenge to tackle and only a few examples are disclosed in the literature.

The first use of a chiral helical ligand in asymmetric organometallic catalysis was reported by Reetz and co-workers in 1997 who designed a chiral 2,15-bis(diphenylphosphino) [6]helicene bisphosphane **1a** (Figure 1).[2] By using this chiral ligand in rhodium-catalyzed itaconic acid ester hydrogenation reaction, enantiomeric excesses (*ee*'s) were nonetheless limited (39%). When used in 2000 in palladium catalyzed Tsuji-Trost allylation, higher *ee*'s of 84-88% were obtained.[3] To improve these first *ee*'s and to enlarge the catalytic scope, the research groups focused on helicene structural modification. If the synthesis of Forni's and Licandro's tetrathiaheterohelicene bisphosphane **1b** led to similar *ee*'s in hydrogenations,[4] Eilbracht, Starý and Stará disclosed the synthesis and the use of phosphite-substituted [6]pseudohelicenes such as **1c**, possessing both helical and central chirality.[5] This ligand, substituted in position 2, led to allylic amination product in high *ee* (up to 94% *ee*). In 2014, Marinetti, Voituriez and co-workers moved a step forward in helicene-driven enantioselective

organometallic catalysis by synthesizing helical phosphindoles **1d**, embedding the phosphorus atom in the helical ring.[6] The corresponding cationic gold(I) complex was successfully used in enantioselective 1,6-enyne cycloisomerization (up to 86% *ee*'s) as well as allene-ene hydroxycyclization (up to 92% *ee*'s). In 2016, Suemune, Usui and co-workers described the use of a 1-phosphane-[5]-helicene **1e** as chiral ligand. By substituting the helicene in the position 1, the reaction site is set as close as possible from the chiral helical cavity. Hence, they performed highly enantioselective palladium-catalyzed Tsuji-Trost allylation as well as Suzuki-Miyaura cross-coupling.[7] Noteworthy, the crystallized [Pd]helicene complex discloses a Pd-arene π -stacking interaction, blocking the conformation and thus rationalizing the high selectivity observed. Shortly after, Tsujihara, Kawano and co-workers reported the use of a 1-phosphinite-[6]-helicene **1f**, disclosing a similar reactivity in Tsuji-Trost allylation (Figure 1).[8]

Figure 1. Helical phosphorus ligands in organometallic catalysis.

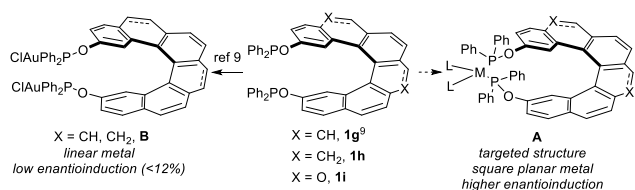


We reported in 2019 the synthesis of chiral 2,15-bisphosphinite [6]helicene **1g** (Scheme 1) and its use in gold-cycloisomerization reactions of 1,6-enynes. While the catalytic activity proved to be satisfying as cycloisomerization occurred, low *ee*'s up to 6% were obtained. No significant improvement was observed in a methoxycyclization reaction as the product was isolated in 12%

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ee in the best conditions. We linked these very low enantiomeric excesses to the linear coordination of gold(I) together with the absence of aurophilic interaction in the involved catalyst.[9] We thus envisaged to move from linear gold(I) to a square planar complex, in order to maximise the steric hindrance around the metal and thus optimize the enantioinduction. Moreover, in order to increase the flexibility of the helicene and to tune the electronics of the template, we completed the study by synthesizing non-rearomatized helix **1h** as well as an oxygenated analog **1i** (Scheme 1).

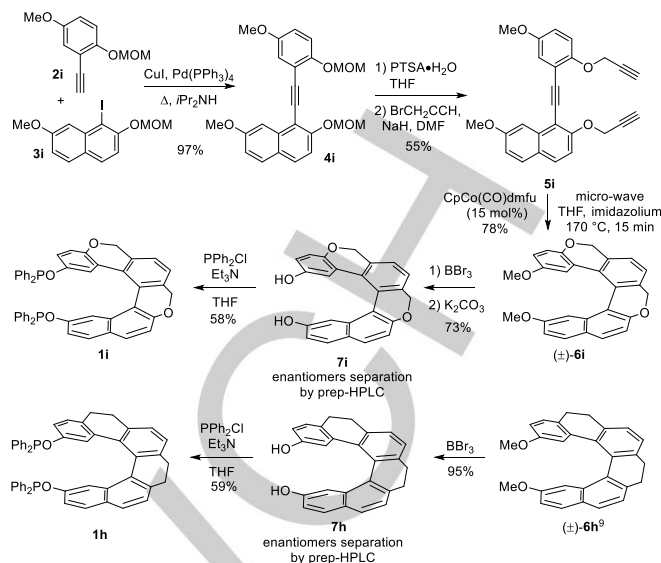
Scheme 1. Synthetic strategy



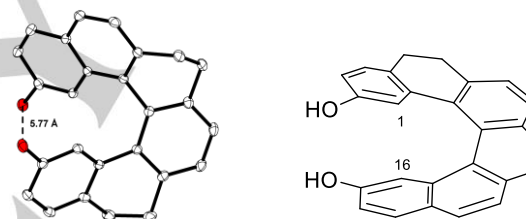
Results and Discussion

Ligand synthesis

If formation of saturated bismethoxyhelicene **6h** (Scheme 2) directly arose from literature procedures,[9],[10] heterohelicene **6i** was synthesized by a Sonogashira cross-coupling between alkyne **2i** and iodide **3i**. Cleavage of both methoxymethyl (MOM) protecting groups in **4i** revealed to be tricky as the free phenol function tends to cyclize and yield the corresponding benzofuran. Therefore a one-pot deprotection/alkylation sequence was required to get to the corresponding propargylic ether **5i**. Cobalt-catalyzed [2+2+2] cycloaddition led then efficiently to the desired helix **6i**. Whereas methoxy cleavage in **6h** by treatment with BBr₃ led to saturated helix **7h** as expected, partial cleavage of the benzylic ethers in **7i** was observed and acyclic adducts were isolated.[11] Gratifyingly, subsequent treatment under basic conditions (K₂CO₃, acetone, reflux) led to the heterohelix of interest **7i**. We developed preparative chiral HPLC methods that led to excellent separation of both enantiomers of helix **7h** and **7i** (*ee*>99%, see supporting information).[12] Subsequent phosphorylation was achieved by treatment with PPh₂Cl in the presence of triethylamine as the base (Scheme 2).

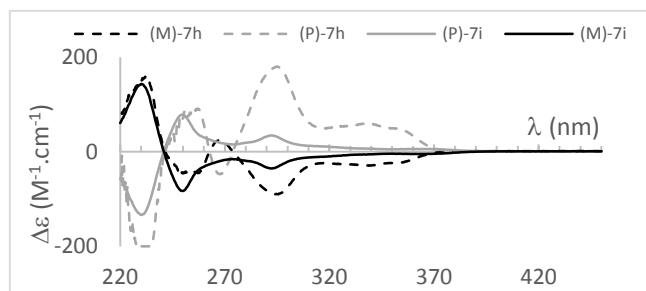
Scheme 2. Synthesis of bisphosphinites **1h** et **1i** (dmfu: dimethylfumarate)

Saturated helix **7h** was crystallized through slow CD₂Cl₂ evaporation (Figure 2). X-ray analysis revealed that it has an inner pitch elevation (C1...C16 distance) of 3.065(5) Å and an oxygen-oxygen distance of 5.777(4) Å. The terminal inner helix torsion angles show an unequal opening at 3.3(6)° and 26.5(5)°. The interplanar angle of the two terminal rings is 56.4(3)°.

Figure 2. X-ray of (±)-**7h** with thermal ellipsoids at 30% probability. Hydrogen atoms and solvent omitted for clarity

Optical activities of the helix **7h** and **7i** were measured by circular dichroism spectroscopy. Tetrahydrohelicene **7h** and oxahelicene **7i** exhibited a similar optical rotation of $[\alpha]_D = +1010$ (c 0.05 mg/mL, CHCl₃) [−1005 (c 0.05 mg/mL, CHCl₃)] and +900 (c 0.05 mg/mL, CHCl₃) [−990 (c 0.05 mg/mL, CHCl₃)], respectively, for the (*P*) enantiomer [(*M*) enantiomer]. CD spectrum of tetrahydrohelicene (*P*)-**7h** disclosed a broad negative band around (−)228 nm, a small positive band at (+)251 nm and an intense one at (+)295 nm, accompanied with a shoulder at (+)350 nm (Figure 3, dotted line). CD spectrum of (*P*)-**7i** is very similar to tetrahydrohelicene one, with a broad negative band at (−)230 nm and two positives bands at (+)250 nm and (+)292 nm, although the band at (+)292 nm is attenuated (Figure 3, plain line).

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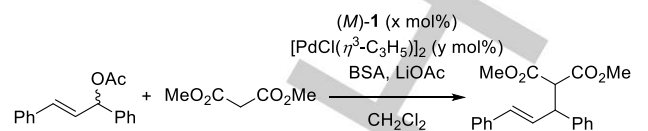
Figure 3. Helixols **7h** and **7i** electronic circular dichroism spectra in CH₂Cl₂**Chiral HELIXOL derivatives in Tsuji-Trost reaction**

These ligands were then evaluated in enantioselective catalysis. We selected palladium(II) to fit in a square planar complex, and Tsuji-Trost allylation[13],[14] as the catalytic reaction for the sake of comparison with the previously reported results where carbohelicenes were used as ligands. These previously published results are reported in Table 1, entries 1-4.

First evaluation and optimization of the reaction conditions were conducted with fully aromatized bisphosphinite (*M*)-**1g**. When no ligand is introduced, no conversion of the starting material was observed (entry 5).[15] Surprisingly, when 2,15-bisphosphinite [6]helicene (*M*)-**1g** is introduced in classical conditions, in a phosphorus atom : palladium atom ratio (P:Pd) of 2:1, non-reproducible results were obtained as both enantiomers were obtained in turn, albeit in very low enantiomeric excesses ranging from 25% (*S*) to 16% (*R*) (entry 6).

We thus played around the phosphorus/palladium ratio and doubled the amount of ligand introduced. In this case, the selectivity is recovered as the (*S*) enantiomer is obtained in a reproducible fashion with an excess of 49% (entry 7). We then tested the reaction using this time an increasing amount of palladium (entries 8 to 12). Surprisingly, under all these conditions was observed an inversion of selectivity. Indeed, the use of 4% mol (P:Pd = 1.2:1, entry 8) then 5% mol (P:Pd = 1:1, entry 9) of the palladium complex leads to the predominant formation of the (*R*) enantiomer in 41% and 50% ee, respectively. The enantiomeric excess peaks at 62% when we use 8% mol (P:Pd = 0.6:1, entry 11) of the palladium complex.

The influence of temperature was then evaluated. When the reaction was carried out at 0°C, no conversion was observed (entry 13). At reflux, the desired product was obtained with 52% enantiomeric excess, ie a slight decrease in the latter (entry 14). We then assessed the influence of the helical skeleton. When oxahelicene (*M*)-**1i** was used under optimized conditions, the (*R*) allylation isomer was isolated in a similar 60% ee (entry 15). Switching to the saturated carbohelicenes derivative (*M*)-**1h** led to a slight improvement and the (*R*) product was obtained in 66% ee (entry 16).

Table 1. Asymmetric Tsuji-Trost allylation in the presence of chiral helical phosphinites (*M*)-**1**.

	L*	x	y	introduced P:Pd ratio	T	Yield	ee ^[a]
1 ³	1a	0.5	0.25	2:1	rt	60-64% ^[b]	84-88% (<i>S</i>)
2 ³	1a	1	0.25	4:1	rt	100% ^[b]	82-86% (<i>S</i>)
3 ⁷	1e	1	0.5	1:1	rt	99% ^[c]	71-94% (<i>S</i>)
4 ⁸	1f	10	2.5	2:1	0 °C	96%	84-90% (<i>S</i>)
5	1g	0	2.5	0:1	rt	0%	-
6	1g	5	2.5	2:1	rt	90-95%	25% (<i>S</i>) to 16% (<i>R</i>)
7	1g	10	2.5	4:1	rt	89%	49% (<i>S</i>)
8	1g	5	4	1.2:1	rt	52%	41% (<i>R</i>)
9	1g	5	5	1:1	rt	89%	50% (<i>R</i>)
10	1g	5	6	0.8:1	rt	89%	60% (<i>R</i>)
11	1g	5	8	0.6:1	rt	88%	62% (<i>R</i>)
12	1g	5	10	0.5:1	rt	69%	60% (<i>R</i>)
13	1g	5	8	0.6:1	0°C	0%	-
14	1g	5	8	0.6:1	40°C	93%	52% (<i>R</i>)
15	1i	5	8	0.6:1	rt	62%	60% (<i>R</i>)
16	1h	5	8	0.6:1	rt	63%	66% (<i>R</i>)

[a] All results were homogenized for the use of (*M*)-ligand, for the sake of clarity, see reference 15. HPLC conditions: Chiralpak AD-H, hexanes/isopropanol 90:10, 1 ml/min, λ = 254 nm; [b] conversion; [c] Cs₂CO₃ was used as the base

It should be noted that the P:Pd ratio does not commonly influence the observed ee in Tsuji-Trost allylation, nor in the case of helical ligands as reported by Reetz and co-workers.[16] This ratio is often not even taken into account while studying new catalytic conditions, as two equivalents of "binding group" (here phosphorus atom) per palladium atom are required to generate a reactive palladium species. However, we can find in the literature a few reports featuring the crucial influence of the ligand-to-metal ratio by using specific ligands such as chiral phosphine oxazoline **L1** and **L3** or phosphorus-nitrogen-nitrogen ligand **L2** (Figure

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4).^[17] Impressive improvements in the selectivity (from racemates to nearly optically pure products) with sometimes reversal of the selectivity are reported by modulating the ligand-to-palladium ratio and the authors generally evoked a change of the ligand coordination mode.^[18]

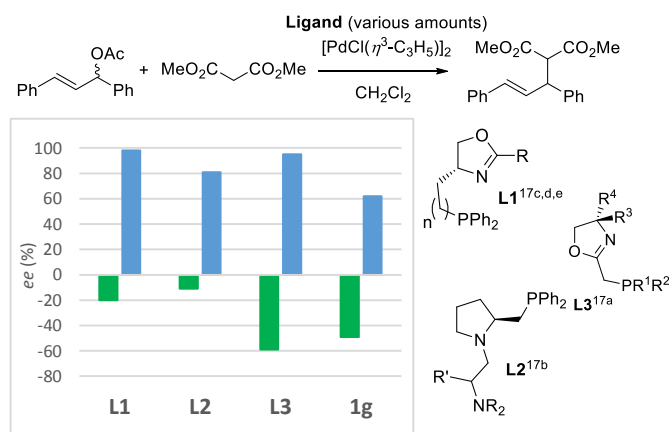


Figure 4. Ligands with crucial ligand-to-metal ratio effect in Tsuji-Trost allylation^[17]

Metallic species study

In order to clarify the evolution of the enantioselectivity we observed, we carried out ³¹P NMR monitoring (CD₂Cl₂, 162 MHz, rt) of the metallic species in solution, by using a model palladium complex, (MeCN)₂PdCl₂, and successive additions of bisphosphinite ligand (*M*-**1g**). Figure 5 represents together the spectrum of the starting bisphosphinite ligand (*M*-**1g**) (Spectrum **S1**, $\delta = 108.1$ ppm) as well as the monitoring of the reaction by successive additions of ligand on palladium.

First, we added 0.25 equivalent of ligand (*M*-**1g**) i.e. a ratio of phosphinite functions/palladium atom = P:Pd = 0.5:1. This ratio corresponds to that of the catalytic species which leads to the (*R*) isomer with a 60% enantiomeric excess when [Pd(η^3 -C₃H₅)Cl]₂ was used as a source of palladium (Table 1, entry 12). After 1 h at rt, full consumption of the ligand was observed to give species **I** whose chemical shift is $\delta = 103.3$ ppm in ³¹P NMR (spectrum **S2**). Another 0.25 equivalent of ligand was then added to the NMR tube, for a total of 0.5 equiv and a P:Pd ratio of 1:1. This ratio corresponds to that of the catalytic species which leads to isomer (*R*) with an excess of 50% (Table 1, entry 9). After 1 h stirring, species **I** at 103.3 ppm is still present and we observed the appearance of a second species **II** at $\delta = 117.8$ ppm (spectrum **S3**). We then performed another addition of 0.5 equivalent of ligand, i.e. a total of 1 equiv and a P:Pd ratio = 2:1. This ratio corresponds to that of the catalytic identity which leads in turn to the (*S*) and the (*R*) isomer with low enantiomeric excesses (Table 1, entry 6). After 1 h, we noted the total disappearance of the first species **I** and the unique presence of species **II** (spectrum **S4**). This second species revealed highly sensitive to air as it quickly decomposed to the secondary phosphine oxide ($\delta = 77.9$ ppm) with concomitant helicol **7g** formation. Finally, one additional equivalent of ligand **1g** was added to species **II** to reach the 4:1 P:Pd ratio corresponding to that of the catalytic species yielding the (*S*)-enantiomer in 49% ee (Table 1, entry 7). Appearance of a third species was observed. This new species is dissymmetric as the two phosphinites groups splitted in two singlets at $\delta = 113.9$

(1P), 107.1 (1P) (Spectrum **S5**). Unfortunately, it also revealed highly unstable as it quickly decomposed in the NMR tube.

This experiment suggests that there can be at least three different catalytic species in solution according to the amount of ligand.

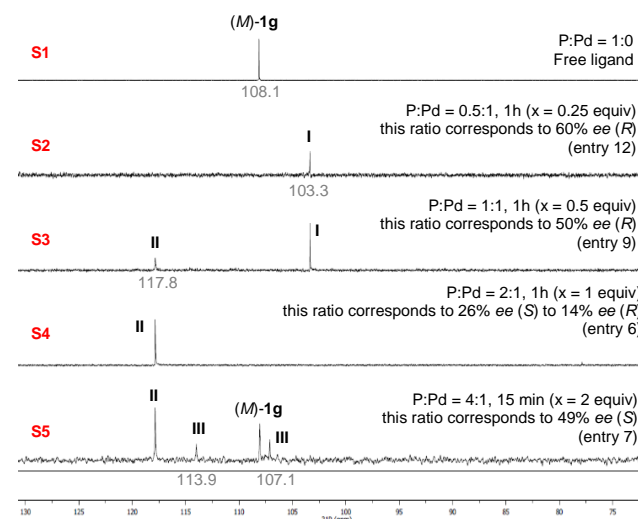


Figure 5. ³¹P NMR monitoring of the metallic species in model PdCl₂(MeCN)₂ system

DFT calculations shed light on a possible structure for the 1 : 1 P : Pd species **I**. Indeed, similarly to what was observed by Usui, Suemune and co-workers for the 5-phosphane helical ligand (X-ray crystallography),^[7] Species **I** may rely on a palladium-arene stacking (Calculated Pd-arene distance = 2.806 Å and 3.108 Å, Figure 6). Transposed to the real catalyst [(η^3 -C₃H₅)PdCl]₂, the allyl environment would be strongly asymmetric that can explain the 60% ee observed (Figure 6).

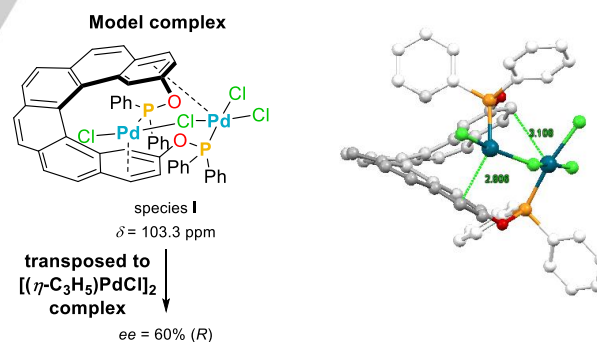


Figure 6: suggested structure for model species (*M*)-**I** (Pd- π C = 2.806 Å and 3.108 Å) (DFT).

To elucidate the stereoselectivity observed with this P:Pd ratio, DFT calculations preceded by DFTB (namely with xtb) conformational search were performed for geometry optimization of (π -allyl)palladium intermediates ((*M*)-**I-syn,syn**, (*M*)-**I-anti,anti** and (*M*)-**I-syn,anti**), the (*syn,syn*), (*syn,anti*) and (*anti,anti*) characterizing the approach and the conformation of the allyl part.^[19] Figure 7 shows their calculated relative energies of formation, with (*M*)-**I-syn,anti** being the most stable based on these calculations. Indeed, the (*M*)-**I-syn,syn** (*endo* approach of the allyl partner) and (*M*)-**I-anti,anti** (*exo* approach) intermediates suffer from steric repulsion between the helicene backbone and the allylic groups, leading to allylic chain isomerization. Assuming

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that nucleophilic attack on the allyl complex takes place at the C1 allylic carbon atom due to the larger *trans* effect of phosphorus,[20] (*M*)-**I-syn,anti** affords the product with (*R*) configuration. This is clearly reflected in the longer Pd-C1 bond (2.44 Å and 2.46 Å for Pd··C1 vs 2.21 Å and 2.20 Å for Pd··C3) and the higher computed Hirschfeld-charge of the C1 position (0.02e⁻ at C1 vs 0.001e⁻ at C3).

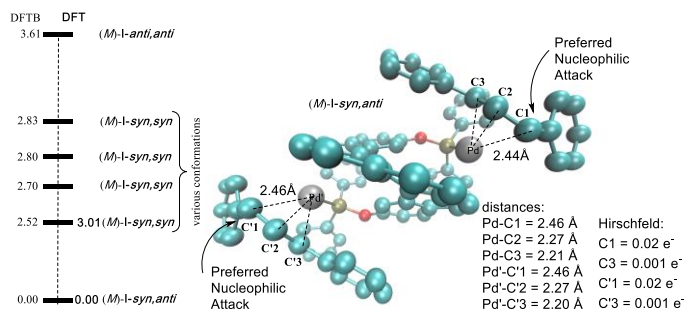


Figure 7: Calculated energies of formation (DFT) of the (π -allyl)palladium intermediates with (*M*)-1 (P : Pd = 1 : 1) and structure of the more stable one (*M*)-**I-syn,anti**.

More information arose from crystallization of **S3** mixture by slow evaporation of deuterated dichloromethane (Figure 8). X-ray diffraction disclosed a 2:1 P:Pd complex, that ratio matches species **II**. This species is a dimeric bimetallic species. The average P---P distance is 8.44(4) Å, and both helices disclose a rather short, average 3.06(15) Å, inner pitch elevation (C1---C16). The interplanar angles of the two terminal rings are 55.2(4)^o and 53.2(4)^o. Both palladiums adopt a planar square geometry with P-Pd-P angles of 99.9(1)^o and 100.4(1)^o.

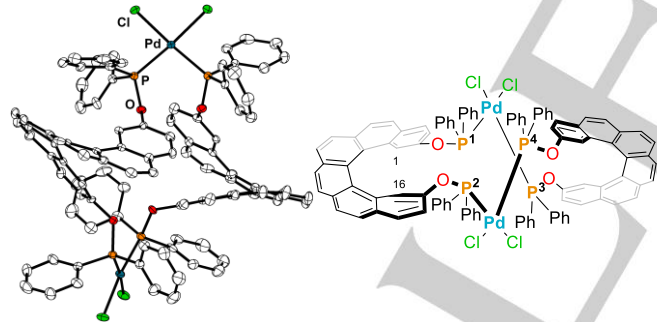


Figure 8: X-ray of model species of a 2:1 P:Pd complex, matching (*P,P*)-**II** ratio, with thermal ellipsoids at 30% probability. Hydrogen atoms and solvent omitted for clarity.

This bimetallic complex revealed nearly no steric hindrance at either of the chlorine atom. This finding would easily explain the non-reproducible and very low *ee* obtained when a P:Pd = 2:1 ratio is used in catalysis (Table 1, entry 6). DFT calculations of the real reactive intermediates confirmed this finding as both C1 and C3 carbons have similar charges (Hirschfeld charges) and similar Pd-C distances in all conformers, whatever the *endo* or *exo* approach of the allyl partner, or its *syn-anti* conformational switch (the most stable intermediate (*M*)-**I-syn,syn** is represented in Figure 9) (see SI for details on the other intermediates).^[19] Such an energy profile should in theory lead to racemic products.

However, due to experimental uncertainties, a slight defect or excess of ligand tips the balance one way or the other.

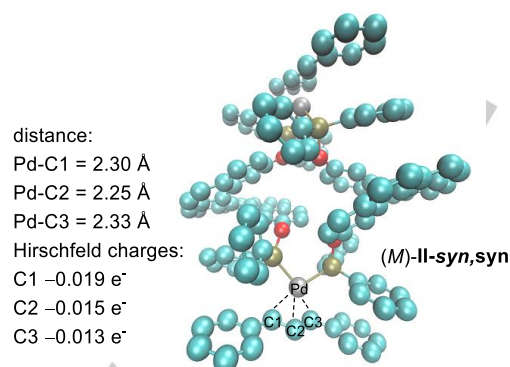


Figure 9: Calculated structure (DFT) for (*M*)-**II-syn,syn**, the most stable (π -allyl)palladium reaction intermediate with (*M*)-1 (P : Pd = 2 : 1).

Finally, the 4:1 P:Pd species **III** was investigated. In the presence of 2 equivalents of ligand per palladium atom, we can suggest the mono-ligandation of the bisphosphinite, with two unequivalent phosphinite moieties per ligand. Such a species would be structurally similar to the one probably formed in Tsujihara's and Kawano's report with monodentate phosphinite **1f** (P:Pd = 2:1) and would explain the formation of the same (*S*) enantiomer they obtained albeit with erosion of the stereoselectivity, as the phosphinite function is anchored in position 2, so further than in Tsujihara's and Kawano's report (1-phosphinite[6]helicene, 89% *ee* (*S*)).^[8] Once again, DFT calculations confirmed the enantioselection with a preferred attack on C1 leading to (*S*) enantiomer. Interestingly, we found a sandwich conformer lying just above the most stable one (*M*)-**III-syn,syn**, in which π -stacking between the allylic moiety and the phosphinite makes the electrophilic carbons inaccessible (Figure 10).

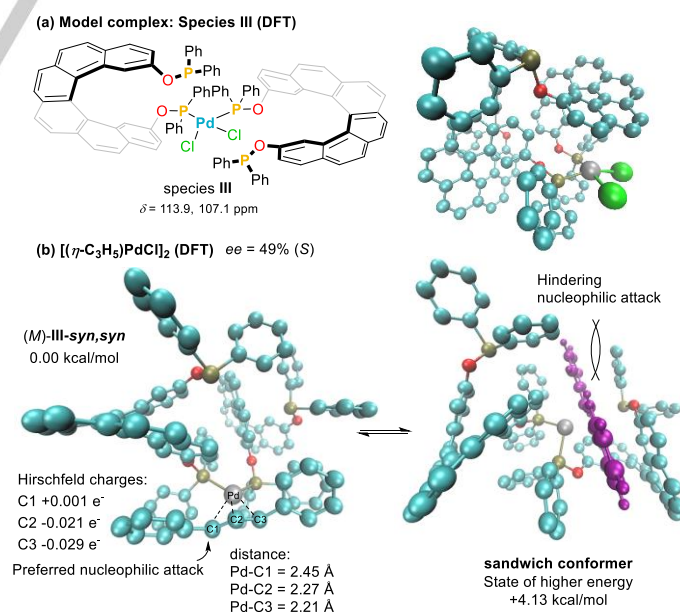


Figure 10: (a) Suggested structure for model species (*M*)-**III** (DFT); (b) Calculated structure (DFT) of the most stable (π -allyl)palladium intermediate (*M*)-**III-syn,syn** (P : Pd = 4 : 1) (left) and of the one of higher energy (right)

Conclusion

The study of chiral 2,15-bisphosphinite[6]helicene as a ligand in asymmetric palladium-catalyzed Tsuji-Trost allylic alkylation led to remarkable results in term of switch of stereoselectivity. Unlike the related results disclosed with 1-phosphinite[6]helicene, 1-phosphane[5]helicene or 2,15-bisphosphine[6]helicene, the ligand-to-metal ratio revealed critical with this peculiar ligand. Indeed, we have shown that this ratio had a dramatical effect on the stereoselectivity when using chiral 2,15-bisphosphinites [6]helicene ligand. In fact, we showed that the (*R*) and (*S*) isomers can be selectively formed as a direct function of the amount of ligand introduced by moving from 4:1 to 1:1 phosphore-to-palladium ratio. Thanks to ³¹P NMR study on a model palladium complex, X-ray analysis of a 2:1 P:Pd adduct and DFT calculations, we suggested three different organometallic structures in 1:1, 2:1 and 4:1 P:Pd ratios. DFT calculations on these complexes matched the enantioselectivity observed in reaction conditions. This study enlightens the key importance of ligand-to-metal ratio screening while evaluating new ligands. Studies are undergoing in our laboratory to crystallizing the two other organometallic species to confirm their structures.

Experimental Section

To a mixture of [Pd(η^3 -C₃H₅)Cl]₂, phosphinite ligand, and LiOAc (1.8 mg, 0.027 mmol, 10 mol%) in CH₂Cl₂ (0.5 mL) was added a solution of 1,3-diphenyl-2-propenyl acetate (52.3 mg, 0.20 mmol, 1 equiv) in CH₂Cl₂ (1.5 mL) at room temperature under Ar atmosphere. After 30 min, dimethyl malonate (70 μ L, 0.60 mmol, 3.0 equiv) and *N,O*-bis(trimethylsilyl)acetamide (BSA) (154 μ L, 0.60 mmol, 3.0 equiv) were successively added at rt. After 24 h, the reaction mixture was diluted quenched with water. The separated aqueous layer was extracted with CH₂Cl₂, and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (PE/EtOAc 95/5) afforded the desired product as a white solid.

Acknowledgements

This work was supported by the CNRS, Sorbonne Université, IUF and Agence Nationale de la Recherche (ANR-13-JS07-0013-HELICATS). We warmly thank Siham El Aani, Corentin Fagnan, Tiffany Gosse, Delphine Haddad, Soizic Queric and Shiwen Zheng who worked on starting material synthesis.

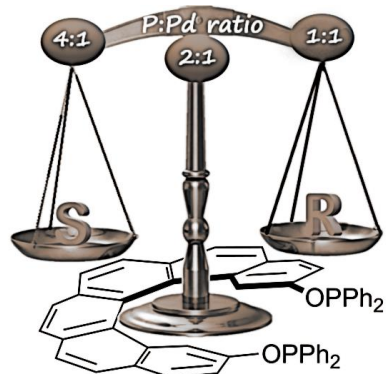
Keywords: helicene • phosphinite • homogeneous catalysis • chirality • Tsuji-Trost allylation

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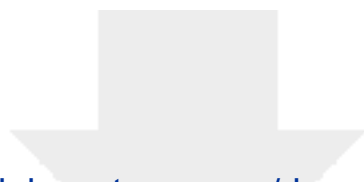
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A remarkable effect of the ligand to metal ratio in the palladium-catalyzed Tsuji-Trost allylation is revealed here. By changing the amount of chiral bisphosphinite[6]helicene ligand in the catalytic system, (*R*) and (*S*) isomeric products were selectively obtained. ³¹P NMR, X-ray and DFT calculation were used to shed light on this reaction.

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