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**[2+1] Cycloaddition Affording
Methylene- and
Vinylidenecyclopropane
Derivatives: A Journey around
the Reactivity of Metal-
Phosphinito-Phosphinous Acid**

Complexes

Hervé Clavier*^[a] and Gérard Buono^[a]

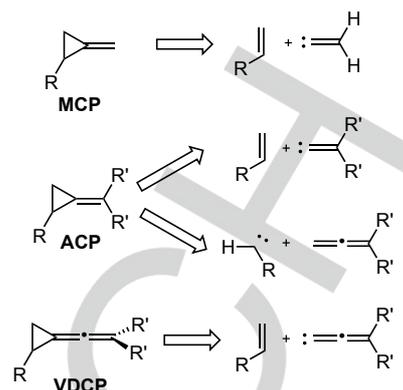
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Abstract: Metal-phosphinito-phosphinous acid complexes are interesting catalysts exhibiting unique reactivities. In this account, we intend to provide a clear overview of palladium- and platinum- phosphinito-phosphinous acid complexes preparation starting from secondary phosphine oxides, and their applications in catalysis. They have been mainly used to develop [2+1] cycloadditions affording methylenecyclopropane derivatives using norbornenes and various alkynes as partners. As a function of the catalyst, the reaction conditions, or the nature of the reagents, different synthetic transformations have been observed: [2+1] cycloadditions giving rise to either alkylidenecyclopropanes or vinylidenecyclopropanes, tandem [2+1]/[3+2] cycloadditions... The mechanisms of these reactions have been studied to rationalize the different reactivities observed.

1. Introduction

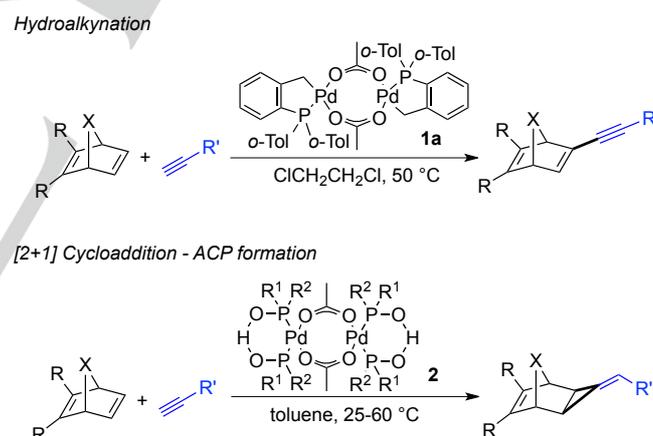
Highly strained small molecules, such as cyclopropane derivatives, have always received a particular attention from the synthetic chemists community. Not only because their preparation represents a synthetic challenge but also as versatile synthons that can be used in a myriad of organic transformations. As subgroups of the class of cyclopropanes, methylenecyclopropane (MCP), alkylidenecyclopropane (ACP) and vinylidenecyclopropane (VDCP) derivatives have witnessed an ever-increasing number of applications in organic synthesis, in particular in late transition metal catalysis.^{1,2} Such interest was made possible thanks to the development of straightforward and efficient methodologies of preparation. Among the various strategies to prepare MCP derivatives, those based on [2+1] cycloadditions as key step are extremely powerful. The addition of carbenes to allenes or alkylidenecarbenes to alkenes represents the easiest routes for the synthesis of MCPs and ACPs, as highlighted by the numerous applications developed since 60's (Scheme 1).³ VDCPs are generally synthesized by the *in-situ* formation of a vinylidenecarbene intermediate - from diazoallenes or by the treatment of halogenoalkynes, halogenoallenes or polyhalogenocyclopropanes with a strong base - and its addition to alkenes.

Over the past decade, a significant part of our work has been dedicated to the investigation of the coordination chemistry of secondary phosphine oxides (SPOs)⁴ with transition metals⁵ and the use of the resulting complexes in new synthetic transformations. In the course for new applications in catalysis for phosphinito-phosphinous acid-containing palladium(II) complexes **2**, they have been tested for the hydroalkynylation of norbornadiene derivatives with alkyl- and aryl-substituted alkynes. Our group has thus reported that the Herrmann-Beller phosphapalladacycle **1a** was a very powerful catalyst for this



Scheme 1. [2+1] cycloaddition-based methodologies for the preparation of MCPs, ACPs and VDCPs.

reaction (Scheme 2).⁶ While surprisingly, with the same reactants, catalyst **2** led to the formation of alkylidenecyclopropane-containing products through a formal [2+1] cycloaddition (Scheme 2).⁷ From these pioneering results, we further investigated the reactivity of phosphinito-phosphinous acid-containing palladium complexes and platinum-based analogues, and discovered several new transformations leading to s methylenecyclopropane derivatives as products but also as intermediates in the formation of more elaborate molecules.



Scheme 2. Hydroalkynylation versus [2+1] cycloaddition: chemodivergent palladium-promoted transformations

This Account describes our group's contribution toward the preparation of alkylidene- and vinylidenecyclopropanes by [2+1] cycloaddition using metal-phosphinito-phosphinous acid-promoted catalyses and the associated reactivities of these useful synthons.

2. ACPs formation using palladium-phosphinito-phosphinous acid complexes

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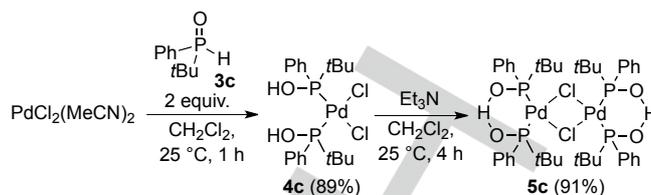
Hervé Clavier graduated from the Ecole Nationale Supérieure de Chimie de Rennes and received his M.Sc. in organic chemistry from the Université de Rennes where he completed his Ph.D. in 2005 under the supervision of Drs Jean-Claude Guillemin and Marc Mauduit. He then joined the research group of Prof. Steven Nolan as a post-doctoral fellow and followed him to the ICIQ in Tarragona. Early 2009, he moved to the School of Chemistry at the University of St Andrews to continue working with Prof. Nolan as a senior researcher. In October 2009, he was appointed Chargé de Recherche (CNRS) at Aix Marseille Université and obtained his habilitation in 2015. His scientific interests include coordination chemistry, transition metal catalysis and the development of new synthetic methodologies.



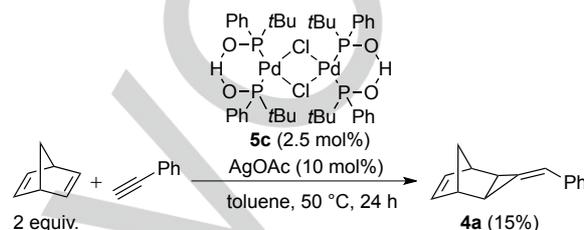
Gérard Buono is Emeritus professor of Ecole Centrale Marseille. He received a "Doctorat es Sciences Physiques" at the University Aix-Marseille in 1977 on the dynamic stereochemistry of pentacoordinate phosphorus. He became Professor of Organic Chemistry in 1987 at the University of Aix-Marseille and in 2003 at the Ecole Centrale Marseille. He headed the UMR CNRS "Synthesis Catalysis Chirality" (2000-2004) and the team "Chirosciences" (2008-2012) of the iSm2 UMR 7313. His research fields include asymmetric synthesis and catalysis, the design of chiral P-stereogenic organophosphorus compounds and their applications in catalysis as ligands and lipase inhibitors. He has published over 170 research papers and book chapters as well as 10 patents. He supervised or co-supervised 40 PhD theses.



Palladium-based complexes bearing a phosphinito-phosphinous acid ligand were originally prepared by Dixon and Rattray from secondary phosphine oxides and PdCl_2K_2 .⁸ Early 2000's, the group of Li improved the synthetic procedure of complexes **5** using $\text{PdCl}_2(\text{cod})$ as palladium source and a subsequent treatment with triethylamine.⁹ Latter, Dai and Leung¹⁰ reported that upon treatment of $\text{PdCl}_2(\text{MeCN})_2$ with *tert*-butyl(phenyl)phosphine oxide **3c**, complex **4c** bearing two phosphinous acids was almost quantitatively formed (Scheme 3).¹¹ In presence of triethylamine, **4c** was converted into the chloro-bridged palladium dimer **5c** bearing phosphinito-phosphinous acid ligands. Unfortunately, **5c** was found inefficient to catalyze [2+1] cycloadditions between norbornene derivatives and alkynes.⁷ This lack of activity was attributed to the chlorine atoms which bind strongly palladium centers and prevent the release of a reaction site. However, by combining **5c** to 4 equivalents of silver acetate, it was possible to isolate ACP **4a** with 15% yield after 24 h of reaction at 50 °C (Scheme 4). These results prompted us to develop new palladium-phosphinito-phosphinous acid complexes bearing acetate ligands.⁷ The treatment of $\text{Pd}(\text{OAc})_2$ with 2 equiv. of secondary

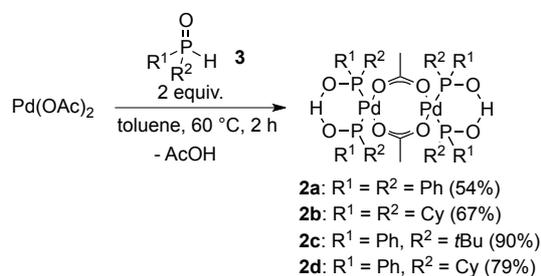


Scheme 3. Preparation of μ -chloro-bridged palladium dimer **5c** bearing phosphinito-phosphinous acid ligands.



Scheme 4. [2+1] cycloaddition mediated by μ -chloro-bridged palladium dimer **5c**

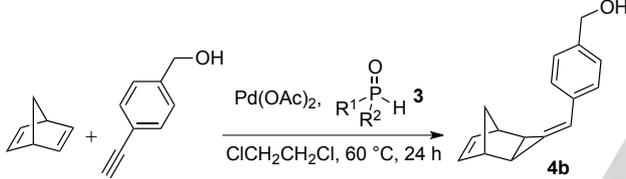
phosphine oxides (SPO) **3** at 60 °C for 2 h led to the coordination of two phosphinous acids while the released acetate trapped one proton from the phosphinous acid proton hence triggering the formation of the phosphinito-phosphinous acid ligand (Scheme 5). Dimeric μ -aceto-bridged species **2** were isolated in moderate to good yields according to the phosphorus substituents. Unfortunately, once isolated some of these complexes, for example **2a** and **2b** with phenyl and cyclohexyl P-substituents respectively, showed a low solubility in most organic solvents and did not allowed complete characterizations. Moreover, the catalytic activity of these well-defined complexes were found to be quite low. For example with **2c**, only 17% of **4a** was isolated after 24 h of reaction at 50 °C.⁷ Further studies demonstrated that addition of acetic acid in catalytic amounts enhanced the activity displayed by complexes **2**. Instead of adding acid to the reaction media, the AcOH released upon *in-situ* generation of the catalysts from $\text{Pd}(\text{OAc})_2$ can advantageously used for this purpose.



Scheme 5. Synthesis of μ -aceto-bridged palladium species bearing phosphinito-phosphinous acid ligands.

A thorough comparison between various SPO **3** highlighted the influence of the substituents on the phosphorus atom (Table 1).¹² Whereas with SPO preligands **3a** and **3c** moderate activities were observed (entries 1 and 4), a better yield was reached with PhBnP(O)H **3e** (entry 7). However the best results were obtained with cyclohexyl substituted SPOs **3b** and **3d** (entries 2 and 5). With these SPOs, it was even possible to carry out the reaction at room temperature and isolate ACP **4b** in good yield (entries 3 and 6). The catalytic system with PhCyP(O)H **3d** performed better in toluene. This SPO is generally the most efficient for this [2+1] cycloaddition and other reactivities which will be presented therein. Importantly, the [2+1] cycloaddition between norbornene derivatives and alkynes can be achieved only in presence of SPO preligands; no reaction occurred with triphenylphosphine, bidentate phosphorus-based ligands or phosphinic acid. Only ethyl phenylphosphinate **3f** allowed the formation of ACP but in low yield and along with many by-products (entry 8).

Table 1. SPO screening for the palladium-promoted [2+1] cycloaddition.^[a]

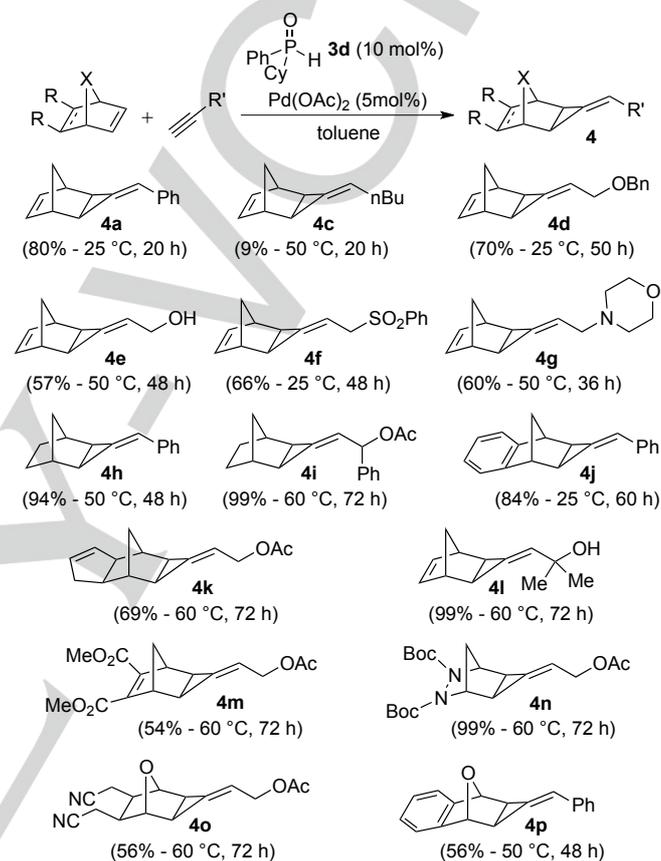


Entry	SPO 3	Yield (%)
1	3a , R ¹ = R ² = Ph	15
2	3b , R ¹ = R ² = Cy	91
3 ^[b]	3b , R ¹ = R ² = Cy	78
4	3c , R ¹ = Ph, R ² = <i>t</i> Bu	33
5	3d , R ¹ = Ph, R ² = Cy	88
6 ^[c]	3d , R ¹ = Ph, R ² = Cy	65
7	3e , R ¹ = Ph, R ² = Bn	50
8	3f , R ¹ = Ph, R ² = OEt	5

[a] Reaction conditions: Pd(OAc)₂ (5 mol%), SPO (12.5 mol%), norbornadiene (1 mmol), alkyne (0.5 mmol), ClCH₂CH₂Cl (2.5 mL), 60 °C, 24 h. [b] Reaction performed at 20 °C. [c] Reaction carried out at 20 °C in toluene.

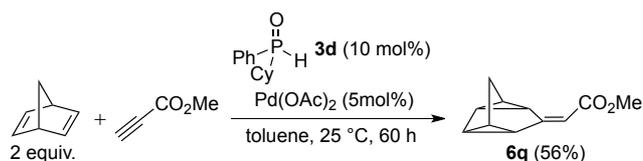
Using the catalytic system Pd(OAc)₂ and PhCyP(O)H **3d**, the scope of the [2+1] cycloaddition was found particularly broad.^{7,13} As depicted in Scheme 6, various alkylidencyclopropanes could be prepared in moderate to quantitative yields. There is a good tolerance to various functional groups such as ethers, alcohols, sulfones, amines, nitriles, etc. Secondary propargyl

acetates or tertiary propargyl alcohols were also good alkyne partners (ACPs **4i** and **4l**). In addition of norbornadiene, many bicyclo[2.2.1]heptene compounds could be used: norbornene, benzonorbornadiene, dicyclopentadiene, bicyclic hydrazines and oxo-bridged [2.2.1] bicycles. However, the [2+1] cycloaddition could not be achieved with less reactive bicyclo[2.2.2]oct-7-ene derivatives.



Scheme 6. Selected scope of the [2+1] cycloaddition between norbornene derivatives and alkynes.

With electron-deficient alkynes such as methyl propiolate, the expected ACP **4** was observed in the crude reaction mixture as well as a by-product.⁷ After silica gel chromatography, only the by-product was isolated in 56% and identified as the rearranged product **6q** resulting from a valence isomerization process (Scheme 7).¹⁴



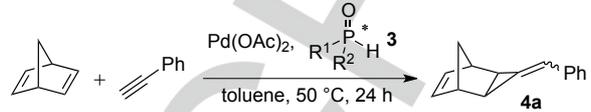
Scheme 7. [2+1] cycloaddition with methylpropiolate as partner.

Since the carbon-carbon double bond configuration of [2+1] cycloadducts **4** can be either *E* or *Z*, they exhibit a peculiar chirality called geometrical enantiomeric isomerism (*cis-trans* enantiomerism or *Z-E* enantiomerism).¹⁵ Taking advantage of the SPO stereogenic center – when the two substituents R^1 and R^2 of the phosphorus atom are different – we were wondering if we could achieve the [2+1] cycloaddition in an enantioselective fashion. Several enantiopure SPOs were prepared according to the methodologies we developed¹⁶ and tested in catalysis using norbornadiene and phenylacetylene as benchmark substrates (Table 2).^{7,17} Despite moderate yields, phenyl *tert*-butyl substituted SPO **3c** gave a promising asymmetric induction of 59% ee (entries 1 and 2). As expected, enantiopure SPO **3d** performed better but led to a low ee (22%, entry 3). With other SPOs, almost no chiral induction was observed (entries 4-6). The absolute configuration of enantiopure (+)-**4a** was determined by vibrational circular dichroism (VCD) and assigned to the *E* isomer.

A closer examination of both the catalytic system and reaction conditions allowed the improvement of enantiomeric excesses.¹⁷ First, phosphinous acid-containing palladium complex **5c** was found to be a more competent when it was associated to silver acetate. Especially since we discovered that the addition of chiral carboxylic acid boosted the enantiomeric induction (Table 3, entries 1 and 2). (*S*)-(+)-Mandelic acid gave the best results but no matched-mismatched effect was clearly demonstrated. Better ees were also reached when the reaction was performed in diethylether at 40 °C. The exemplification to other substrates showed that despite low yields in cycloadducts **4**, high optical purities could be achieved (Table 3). For product **4r**, the

inversion of the ratio between the norbornadiene derivative and the alkyne even led to up to 95% ee (entry 5).

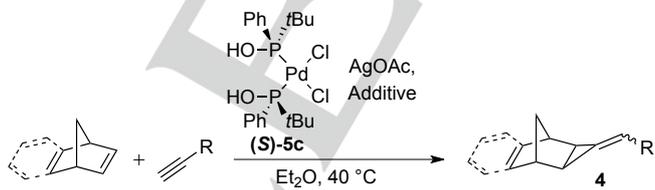
Table 2. SPO screening for the enantioselective formation of cycloadduct **4a**.^[a]

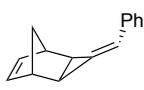


Entry	SPO 3	Yield (%)	ee (%) ^[b]
1	(<i>S</i>)-(-)- 3c , $R^1 = \text{Ph}$, $R^2 = t\text{Bu}$	40	58 (-)
2	(<i>R</i>)-(+)- 3c , $R^1 = \text{Ph}$, $R^2 = t\text{Bu}$	42	59 (+)
3 ^[c]	(-)- 3d , $R^1 = \text{Ph}$, $R^2 = \text{Cy}$	80	22 (-)
4	(-)- 3g , $R^1 = \text{Ph}$, $R^2 = \text{Me}$	47	0
5	(-)- 3h , $R^1 = \text{Ph}$, $R^2 = n\text{Bu}$	64	4 (-)
6	(-)- 3i , $R^1 = \text{Ph}$, $R^2 = 2\text{-biphenyl}$	21	0

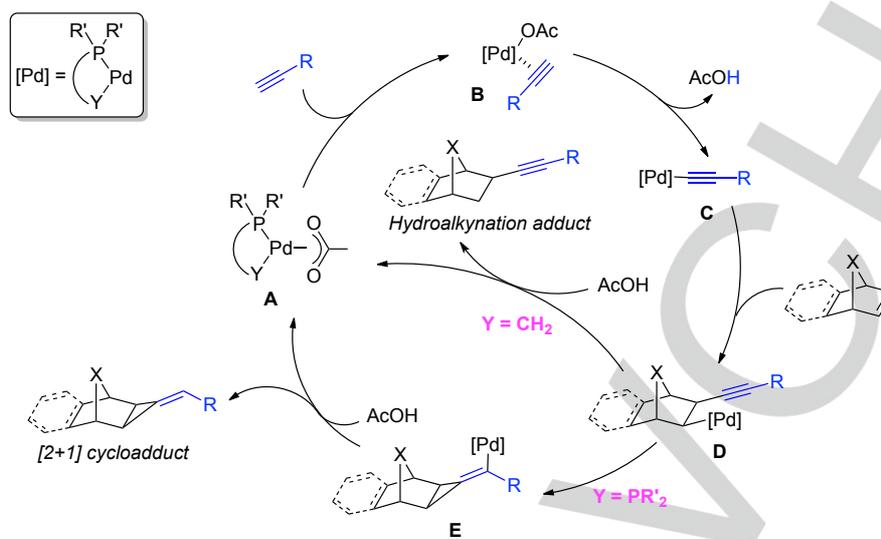
[a] Reaction conditions: Pd(OAc)₂ (5 mol%), SPO **3** (10 mol%), norbornadiene (1 mmol), phenylacetylene (0.5 mmol), toluene (5 mL), 60 °C, 24 h. [b] ee values were determined by chiral HPLC. [c] Reaction carried out at 25 °C for 20 h.

Table 3. Selected examples of enantioselective [2+1] cycloadditions between norbornene derivatives and alkynes.^[a]



Entry	Additive	Time (h)	Product	Yield (%)	ee (%) ^[b]
1	none	24		72	58
2	(<i>S</i>)-(+)-Mandelic acid	24	(-)-(<i>Z</i>)- 4a	65	70
3	(<i>S</i>)-(+)-Mandelic acid	48	(+)- 4j	26	67
4	(<i>S</i>)-(+)-Mandelic acid	48		28	80
5 ^[c]	(<i>S</i>)-(+)-Mandelic acid	64	(-)- 4r	21	95
6	(<i>S</i>)-(+)-Mandelic acid	63	(+)- 4s	25	72

[a] Reaction conditions: (**S**)-**5c** (5 mol%), AgOAc (10 mol%), norbornadiene derivative (2 mmol), alkyne (1 mmol), Et₂O (5 mL). [b] ee values were determined by chiral HPLC. [c] Reaction carried out with norbornadiene (1 mmol) and alkyne (2 mmol).



Scheme 8. Proposed mechanism for Pd-catalysed hydroalkynylation and [2+1] cycloaddition reactions.

We were intrigued by the mechanism of the [2+1] cycloaddition, especially since the use of a phosphapalladacycle, such as the Herrmann-Beller catalyst **1a**, led a chemodivergent reaction with the formation of hydroalkynylation products.⁶ Additional experimental results using acids or bases as additives showed that acidolyses are key steps in both catalytic cycles. Hydroalkynylation is not influenced by the presence of acid but completely quenched in presence of base, whereas the [2+1] cycloaddition is favored by the addition of acid but indifferent to the presence of base.¹² Mass spectrometry experiments, in particular collision-activated reactions (CAR) / collision-induced dissociation (CID) allowed to gain insight into the reaction of alkynes with the catalyst and highlighted the formation of palladium-acetylide species.¹⁸ Then, a computational study was performed to rationalize the difference of reactivities between both catalytic systems (phosphapalladacycle vs. phosphinito-phosphinous acid palladium).¹² The mechanisms depicted in Scheme 8 are based on density functional theory calculations and take into account experimental observations. For reader's convenience, palladium catalysts have been drawn on their monomeric form. Both reactions start with the η^2 -coordination of the alkyne to catalyst **A** to afford species **B** which evolve to η^1 -coordination, so called palladium acetylide **C**, with release of acetic acid. The insertion of the activated carbon-carbon double bond of the norbornene derivative into the Pd-carbon bond by a *syn*-carbometallation give the key intermediate **D**. At this stage, with the Herrmann-Beller catalyst **1a** ($Y = \text{CH}_2$), the acidolysis step is fast and lead to the hydroalkynylation product. However, with phosphinito-phosphinous acid palladium complexes **2** ($Y = \text{PR}'_2$), the carbon-carbon triple bond inserts into the palladium-carbon bond to form a vinyl-palladium species **E** which after acidolysis afford the [2+1] cycloadduct. To explain that the second insertion occurs only with catalysts **2**, it was supposed that in the phosphinito-phosphinous acid ligand the two

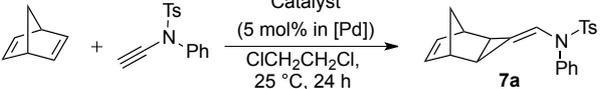
phosphorus atoms are non-equivalent but interchangeable. As a result, the complex can adapt its geometry to favor the second insertion.

3. Phosphapalladacycle-Mediated Synthesis of ACPs

As aminomethylenecyclopropanes **7** are known to possess interesting biological activities,¹⁹ we studied the possibility to prepare them by [2+1] cycloaddition using ynamides as partners.²⁰ The reaction conditions and mainly the nature of the palladium-based catalyst were investigated using norbornadiene and *N*-phenyl-*N*-tosylynamide (Table 4). Whereas with combination of SPO **3c** with $\text{Pd}(\text{OAc})_2$ gave no reaction, the use of the often more competent $\text{PhCyP}(\text{O})\text{H}$ **3d** allowed to isolate the expected cycloadduct **7a** with 44% after 24 h of reaction at 25 °C (entries 1 and 2). Surprisingly, with the Herrmann-Beller catalyst **1a**, the same ACP **7a** was isolated and in a higher yield (66%, entry 3). This ability of phosphapalladacycles to promote the [2+1] cycloaddition with ynamides – and not the hydroalkynylation – was tested with other catalysts **1b** and **1c** which gave ACP **7a** in moderate yields (entries 4 and 5). Of note, with the more electron-rich phosphapalladacycle **1c**, the valence isomerized compound **8a** was obtained as a by-product (entry 5). The scope of the phosphapalladacycle-mediated [2+1] cycloaddition was then explored with various ynamides and a range of norbornadiene and norbornene derivatives (Scheme 9). Overall, moderate to good yields were obtained in short reaction times. The catalyst system showed a good tolerance to various ynamides, 7-substituted norbornadienes, benzonorbornadiene, norbornene, bicyclic hydrazines or oxa-bridged [2.2.1] bicycles. Due the *E/Z* geometry of the formed carbon-carbon double bond,

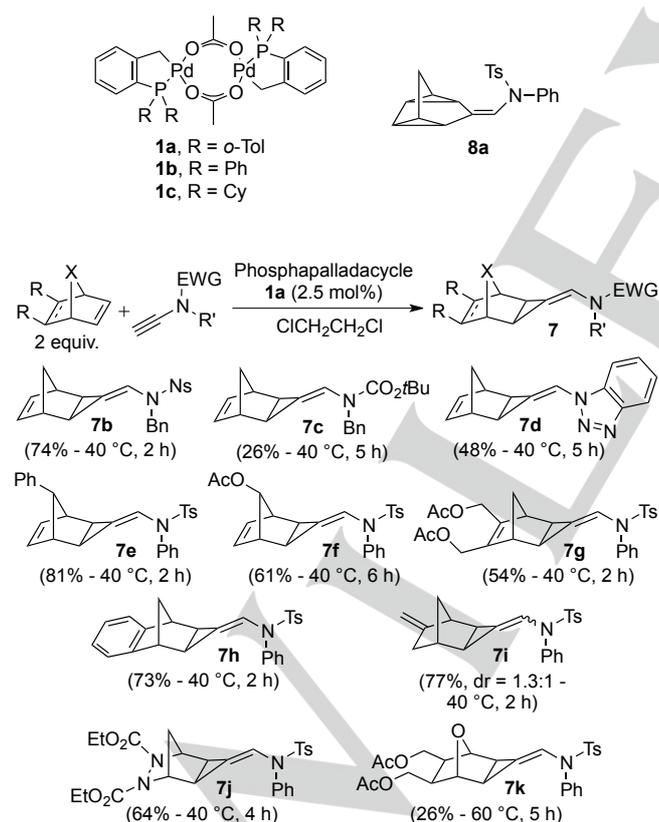
compound **7i** was obtained as mixture of two diastereomers but with a low diastereoselectivity.

Table 4. Pd-mediated [2+1] cycloaddition of norbornadiene with ynamide.^[a]



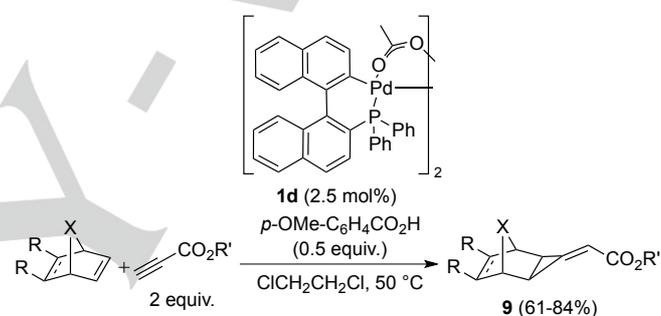
Entry	Catalyst	Yield (%)
1	Pd(OAc) ₂ /PhfBuP(O)H 3c	0
2	Pd(OAc) ₂ /PhCyP(O)H 3d	44
3	Phosphapalladacycle 1a	66
4	Phosphapalladacycle 1b	44
5	Phosphapalladacycle 1c	48 ^[b]

[a] Reaction conditions: [Pd] (5 mol%), SPO **3** (10 mol%), norbornadiene (1 mmol), ynamide (0.5 mmol), ClCH₂CH₂Cl (3 mL), 25 °C, 24 h. [b] 18% of **8a** was also isolated.



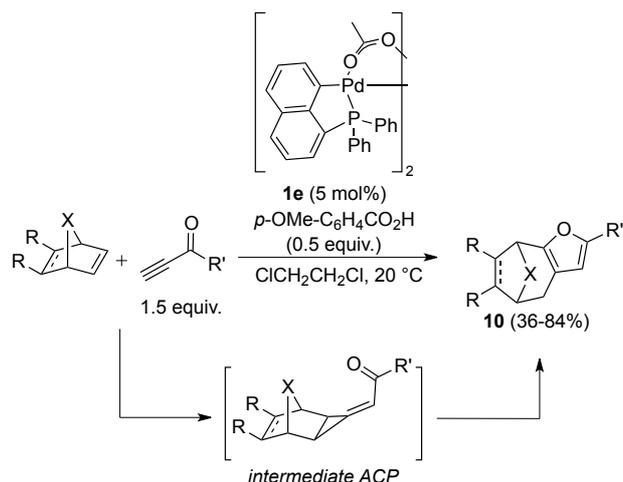
Scheme 9. Selected scope of the [2+1] cycloaddition between norbornene derivatives and ynamides.

To explain the formation ACPs **7** instead of hydroalkylation products, we believed that the strong polarization of the carbon-carbon triple bond of ynamide induced by the nitrogen atom favored the second insertion into the carbon-palladium bond over the acidolysis (step from **D** to **E**, Scheme 8). This hypothesis was corroborated by the work of Ding and Hou, who reported the [2+1] cycloaddition of norbornadiene derivatives with various propiolates (Scheme 10).²¹ In this reaction, **1a** was found to be a good catalyst (43% yield) but after an optimization of the catalyst's structure, the binaphthyl-containing complex **1d** exhibited higher efficiency (64%). A further study of the reaction conditions showed that the addition of a substoichiometric amount of acid, such as *p*-methoxybenzoic acid, enhanced the catalytic activity. The scope of this reaction was found particularly broad and good yields were generally obtained (Scheme 10). Importantly, with norbornadiene, polycyclic structures equivalent to **6q** (Scheme 7) and resulting from an isomerization process were obtained.



Scheme 10. Phosphapalladacycle-catalyzed [2+1] cycloaddition with propiolate derivatives.

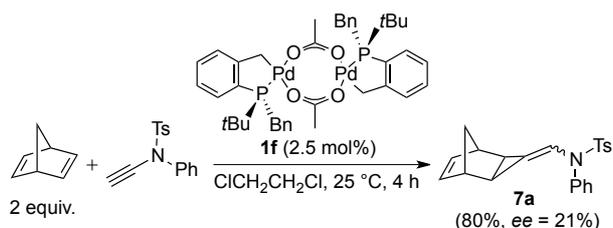
The group of Hou investigated also ynones as partners in [2+1] cycloaddition.²² In this case, no ACP could be isolated since [2+1] cycloadducts rearranged rapidly into polysubstituted furan derivatives **10** (Scheme 11). In this reaction, the biphenyl-based



Scheme 11. [2+1] cycloaddition with ynones followed by a rearrangement.

phosphapalladacycle **1e** displayed a higher catalytic activity than the Herrmann-Beller complex **1a** (64% vs. 34% at 50 °C). This transformation occurred under mild reaction conditions and its scope was found broad.

Our group having synthesized the enantiopure phosphapalladacycle **1f**,²³ we decided to evaluate it in asymmetric [2+1] cycloaddition with ynamide and norbornadiene (Scheme 12).²⁰ **1f** displayed a good activity since the expected ACP **7a** was obtained with a good yield of 80%. However, the chiral induction was found relatively modest (21% ee).

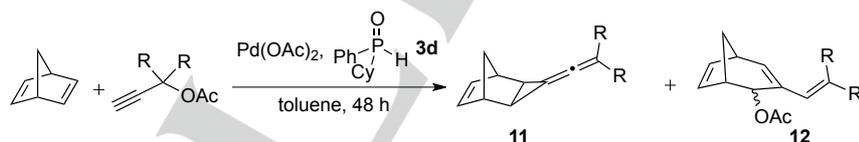


Scheme 12. Enantioselective [2+1] cycloaddition with ynamides.

4. Palladium-Phosphinito-Phosphinous Acid Catalyzed Formation of VDCPs

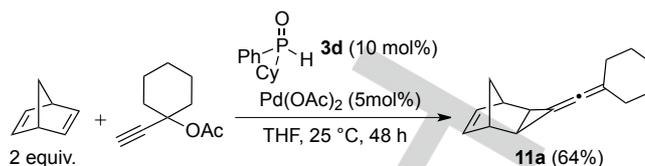
During the scope exploration of the [2+1] cycloaddition mediated by the Pd(OAc)₂/SPO **3d** catalytic system, tertiary propargyl acetates were tested as partners.⁷ To our great surprise, the expected ACPs **4** were not obtained, but vinylidenecyclopropanes resulting from the release of acetic acid were isolated in low to good yield (64% for VDCP **11a**, Scheme 13).

Table 5. Influence of the reaction conditions on the [2+1] cycloadditions affording VDCPs **11**.^[a]



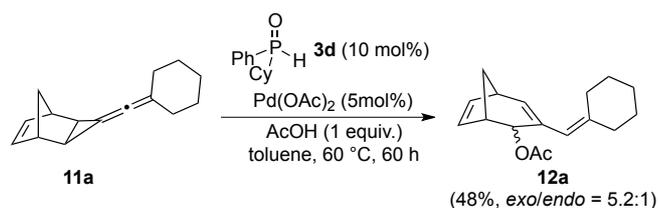
Entry	T (°C)	Product 11	Yield (%)	Product 12	Yield (%)	<i>exo/endo</i> ^[b]
1	25		22		33	9:1
2	60	11a	18	12a	68	9:1
3	25		8		32	9:1
4	60	11b	<5	12b	60	9:1

[a] Reaction conditions: Pd(OAc)₂ (5 mol%), SPO **3d** (10 mol%), norbornadiene (2 mmol), tertiary propargylacetate (1 mmol), toluene (5 mL), 48 h. [b] determined by ¹H NMR.



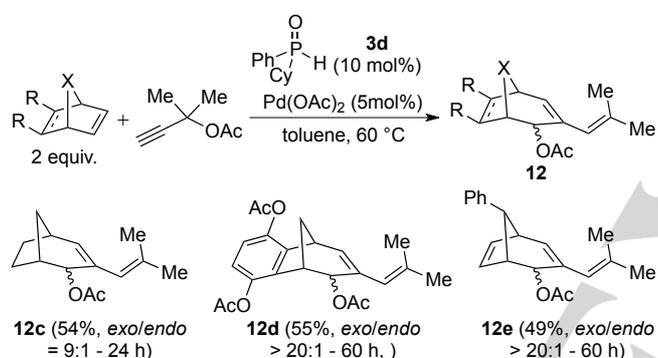
Scheme 13. Formation of vinylidenecyclopropane by [2+1] cycloaddition.

In order to improve the yields of VDCPs **11**, the reaction conditions were further investigated (Table 5).²⁴ When the [2+1] cycloaddition was performed at room temperature in toluene instead of THF, only small quantities of **11a** were isolated (22%, entry 1). This can be explained by the formation of a by-product which was identified as a bicyclo[3.2.1]octadiene **12a**. This new product was obtained as a 9:1 mixture of diastereomers corresponding to an *exo* or *endo* stereochemistry of the acetoxy group; the *exo* being the major diastereomer. Increasing the reaction temperature to 60 °C led to decrease the yield in VDCP **11a** but improved significantly those of **12a** without changing the *exo/endo* diastereoselectivity (entry 2). The same trend was observed with another tertiary propargyl acetate which gave at 60 °C almost only the bicyclo[3.2.1]octadiene **12b** in 60% yield and with a 9:1 diastereomeric ratio (entries 3 and 4). These observations suggested that VDCPs **11** are intermediates in the formation of compounds **12**. This was confirmed by the treatment of **11a** with 1 equivalent of acetic acid in presence of the palladium-phosphinito-phosphinous acid ligand (Scheme 14). After 60 h, **12a** resulting from the cleavage of cyclopropane distal bond and incorporation of AcOH was isolated in 48% yield but with a lower diastereoselectivity (5.2:1).



Scheme 14. Pd-catalyzed ring-expansion of vinylidenecyclopropane.

This unusual tandem [2+1]/ring-expansion sequence was applied to several norbornene derivatives (Scheme 15). Compared to other products **12**, bicyclo[3.2.1]octadienes **12d** and **12e** were obtained from benzonorbornadiene and 7-substituted norbornadiene with similar yields but as a nearly single diastereomer: the *exo*.



Scheme 15. Selected examples of tandem [2+1] cycloaddition/ring-expansion.

Recently, we reported a new methodology for the preparation of functionalized 7-membered carbocycles based on the [2+1] cycloaddition/ring-expansion sequence.²⁵ Thus, starting from oxanorbornenes, this transformation would lead to the formation of oxa-bridged [3.2.1] bicycles and, after an appropriate cleavage of the temporary oxygen tether, interesting 7-membered carbocycles will be obtained. Reaction parameters have been optimized for the formation of VDCP **13a** (Table 6). First of all, oxa-bridged VDCP **13** were found less reactive than carba-bridged VDCP **12**, despite analogous reactions conditions (toluene, 60 °C, 24 h). No ring-expansion occurred; only VDCP **13a** was obtained from the [2+1] cycloaddition. Once again, the key parameter of this transformation was found to be the nature

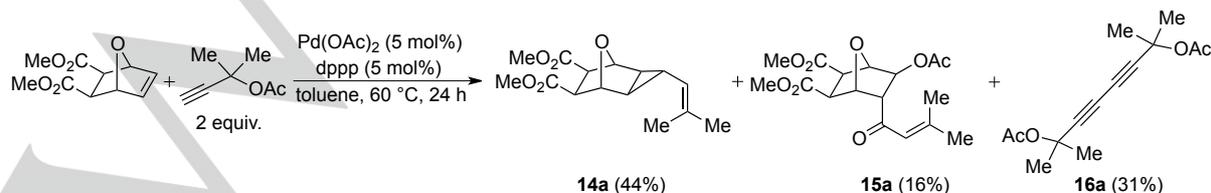
of the substituents on the phosphorus atom (Table 6). With diphenyl- and phenylbenzyl-substituted SPOs **3a** and **3e** good yields were reached (entries 1 and 5) but once more PhCyP(O)H **3d** gave better results (76%, entry 4). Other SPOs afforded either complex mixture (entry 7) or low yields (entries 2, 3 and 8). With triphenylphosphine or phosphite, no reaction occurred. Only with ethyl phenylphosphinate **3f**, it was possible to obtain the expected product **13a** but in low yield and with various unidentified by-products (entry 6). This is due to the fact that a phosphinito-phosphinous acid ligand can also be formed from SPO **3f**.

Table 6. SPO screening for the palladium-promoted [2+1] cycloaddition affording VDCPs **13**.^[a]

Entry	SPO 3	Yield (%)
1	3a , R ¹ = R ² = Ph	60
2	3b , R ¹ = R ² = Cy	10
3	3c , R ¹ = Ph, R ² = <i>t</i> Bu	10
4	3d , R ¹ = Ph, R ² = Cy	76
5	3e , R ¹ = Ph, R ² = Bn	58
6	3f , R ¹ = Ph, R ² = OEt	18
7	3g , R ¹ = Ph, R ² = Me	Complex mixture
8	3h , R ¹ = Ph, R ² = <i>n</i> Bu	32

[a] Reaction conditions: Pd(OAc)₂ (5 mol%), SPO **3** (12.5 mol%), oxanorbornadiene (1 mmol), tertiary propargyl acetate (2 mmol), toluene (5 mL), 60 °C, 24 h.

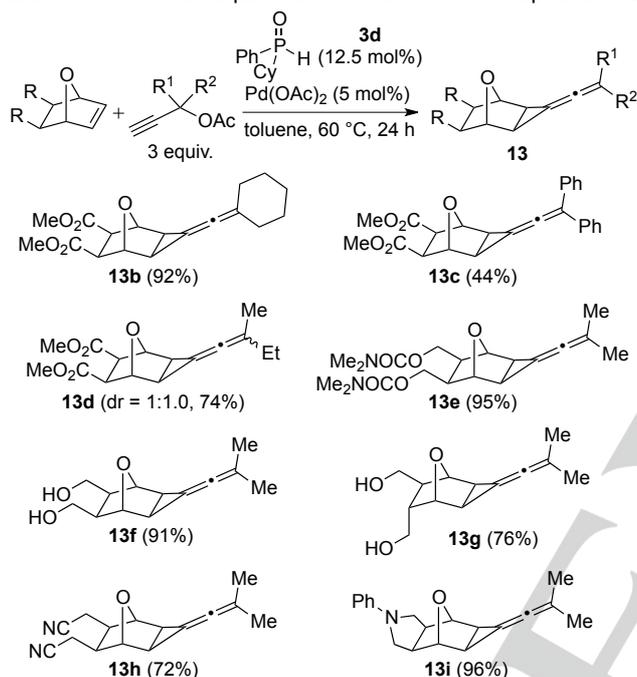
In order to demonstrate the specificity of the phosphinito-phosphinous acid ligand, a control experiment was carried out with the 1,3-bis(diphenylphosphino)propane (dppp) which can be seen as a mimic of our bidendate ligand (Scheme 16). No VDCP could be detected, however several products were



Scheme 16. Control experiments using 1,3-bis(diphenylphosphino)propane (dppp) as ligand.

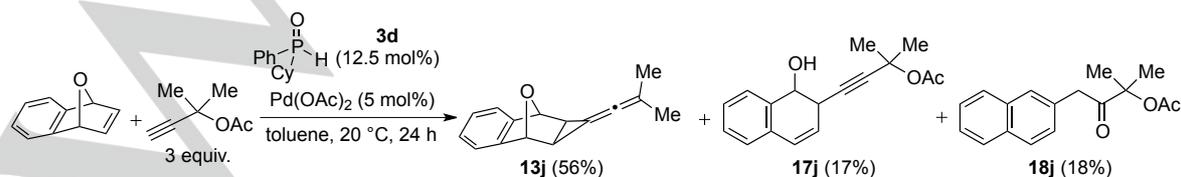
isolated: the vinylcyclopropane **14a** as the major product (44%), the enone **15a** (16%) and substantial amounts of Hay-Glaser coupling product **16a** (31%).

The scope of the [2+1] cycloaddition affording VDCPs **13** was found particularly broad (Scheme 17). In addition of acetate, benzoate, pivalate or methylcarbonate could be used as leaving groups with a comparable efficiency. As long as the propargyl acetate was tertiary, various substituents were well tolerated; a moderate yield was only obtained for diphenyl-substituted VDCP **13c**. When the two substituents of the propargyl acetate were different, the VDCP was isolated as a mixture of two diastereomers in an equimolar ratio such as for compound **13d**.



Scheme 17. Survey of the [2+1] cycloaddition scope affording VDCPs **13**.

As well, various functional groups were well tolerated, such as carbamates (**13e**), alcohols (**13f** and **13g**), nitriles (**13h**) or tertiary amines (**13i**), and high yields were generally reached. On the other hand, the use of benzoxanorbornene as substrate led to a different outcome (Scheme 18).²⁶ First, this compound exhibited a higher reactivity allowing to proceed at room temperature. Second, the expected VDCP **13j** was isolated albeit in lower yield than usual (56%), due to the competitive formation of by-products **17j** and **18j**. **17j** resulted from a hydroalkylation followed by a β -alkoxyelimination. At first sight, **18j** seemed to come from compound **17j** though an intramolecular hydration of the carbon-carbon triple bond.



Scheme 18. [2+1] cycloaddition with benzoxanorbornene and tertiary propargyl acetate.

However, rising the reaction time to 3 days or the temperature to 60 °C did not change the ratio between the three products.

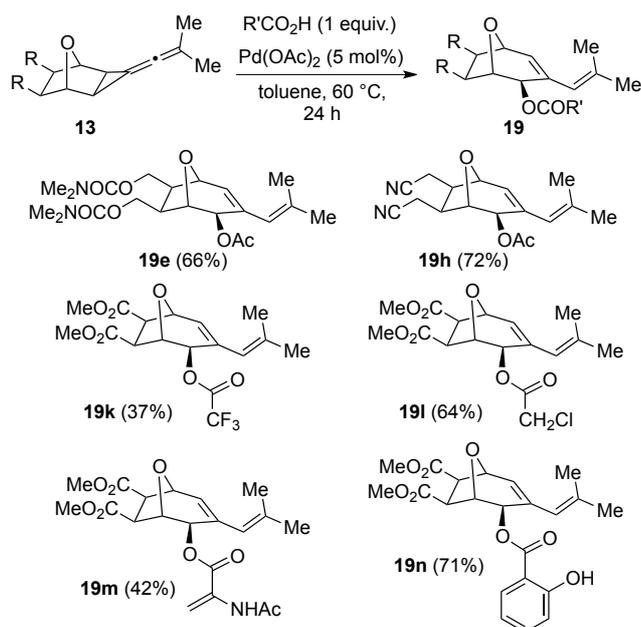
Oxa-bridged VDCPs **13** were less reactive for the ring-expansion than their carba-bridged counterparts (Table 7).²⁵ By increasing the reaction media concentration to 1M, the ring-expansion could occur at 60 °C without any catalyst, but only small quantities of the expected oxa-bridged [3.2.1] bicycle **19a** were isolated (12%, entry 1). Under the same conditions, the use of the phosphinito-phosphinous acid ligand-containing palladium complex **2d** allowed a slight enhancement of the yield (27%, entry 2). A real breakthrough was achieved when Pd(OAc)₂ was simply used as catalyst and **19a** could be obtained in 84% yield as a single diastereomer *exo* (entry 3). At lower concentration, the reaction performed more slowly (entry 4).

Table 7. Optimization of the ring-expansion of VDCP **13a** giving rise to oxa-bridged [3.2.1] bicycle **19a**.^[a]

Entry	Catalyst	Yield (%)
1	None	12
2	[Pd(OAc)(PhCyPOHOPPhCy)] ₂ 2d	27
3	Pd(OAc) ₂	84
4 ^[b]	Pd(OAc) ₂	43

[a] Reaction conditions: Catalyst (5 mol%), VDCP (0.5 mmol), acetic acid (0.5 mmol), toluene (0.5 mL, 1M), 60 °C, 24 h. [b] Reaction performed in 2.5 mL of toluene (0.2M).

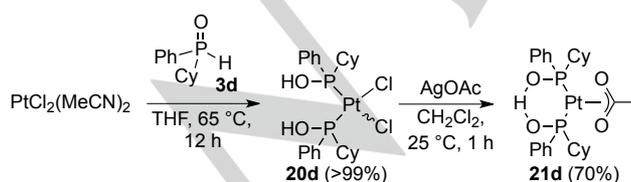
The ring-expansion was then broadened to several VDCPs **13** and various carboxylic acids. Selected examples are depicted in Scheme 19. This transformation worked well with functional groups such as carbamates or nitriles on VDCPs **13**. In the same manner, a wide range of carboxylic acids, such as trifluoroacetic acid, chloroacetic acid, 2-acetamidoacrylic acid or salicylic acid, could be used. Overall, the expected oxabicyclo[3.2.1]oct-2-ene **19** were isolated in good yields and as single diastereomers.



Scheme 19. Selected examples of ring-expansion of VDCPs **13**.

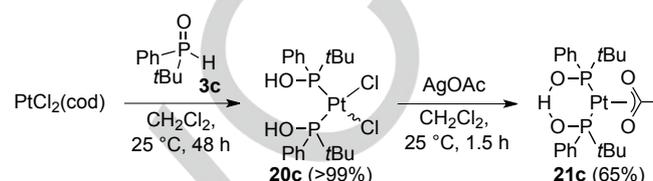
5. Platinum-Phosphinito-Phosphinous Acid Promoted Synthesis of ACPs

Given the parallelism between the coordination chemistry of palladium and platinum, we attempted to prepare platinum-based complexes bearing a phosphinito-phosphinous acid ligand following the synthetic procedures developed for palladium. As depicted in Scheme 20, the reaction of $\text{PtCl}_2(\text{MeCN})_2$ with 2 equivalents of secondary phosphine oxides **3d** required a thermal activation at 65 °C to afford quantitatively the bis phosphinous acid platinum complex **20d** as a 1:1 mixture of *cis* and *trans* isomers.²⁷ A subsequent treatment of **20d** with 2 equivalents of silver acetate gave the desired phosphinito-phosphinous acid platinum complex **21d** in good yield. Of note, this complex was isolated under a monomeric form whereas in the palladium series only dimers were obtained. The compulsory thermal activation for the synthesis of **20d** had an unexpected drawback with the partial racemization of the phosphorus stereogenic center when enantiopure SPOs were used. Therefore, the preparation of bis phosphinous acid platinum complexes **20** has been tested starting from other platinum salts.



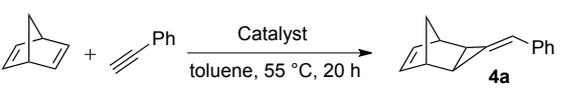
Scheme 20. Preparation of platinum complex **21d** bearing phosphinito-phosphinous acid ligands from $[\text{PtCl}_2(\text{MeCN})_2]$.

The use of the more soluble $\text{PtCl}_2(\text{cod})$ allowed to carry out the reaction at room temperature and, after 2 days complex **20c** was isolated in quantitative yield and as a 1:1 mixture of *cis* and *trans* isomers (Scheme 21).^{5a,27} In this case, no racemization of the phosphorus stereogenic center occurred. Addition of silver acetate led to the formation of complex **21c** in 65% yield. Advantageously, with this procedure, the preparation of complexes **21** could be performed one pot from $\text{PtCl}_2(\text{cod})$ and SPO preligands.



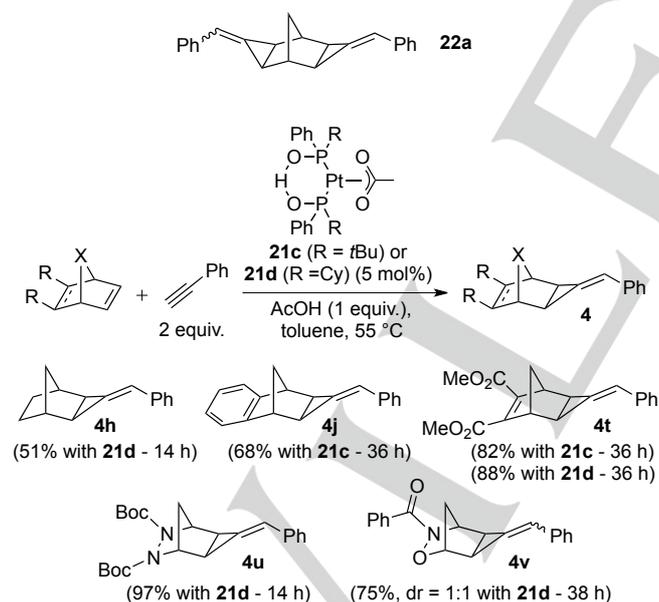
Scheme 21. Synthesis of phosphinito-phosphinous acid platinum complex **21c** starting from $[\text{PtCl}_2(\text{cod})]$.

The performances of complexes **20** and **21** were tested in the [2+1] cycloaddition using norbornadiene and phenylacetylene as model substrates (Table 8).²⁷ As anticipated, no reaction occurred in presence of the bis phosphinous acid platinum complex **20c** (entry 1) but addition of AgOAc to trigger the formation of the phosphinito-phosphinous acid ligand allowed to isolate **4a** in 65% (entry 2). Since the well-defined phosphinito-phosphinous acid ligand-containing platinum complex **21c** was found to display a lower catalytic activity (entry 3), we assumed that the presence of acetic acid - one equivalent is released during the formation of complexes **21** - was required to enhance the yield of **4a**. Thus, addition of 10 mol% or up to 1 equiv. of AcOH boosted the formation of **4a** (entries 4 and 5). The platinum-based system was found much more efficient than the analogous palladium catalyst (entries 5 and 6). A slight yield improvement and a cleaner reaction could even be obtained in reversing the ratio norbornadiene/phenylacetylene (entry 7). In this case, with the most efficient catalyst **21d** (possessing phenyl and cyclohexyl substituents on the phosphorus atoms), we observed the formation of the dicycloadduct **22a** in a 1:1.2 diastereomeric ratio along with the expected cycloadduct **4a** (entry 8).^{27,28} Importantly, dicycloadducts **22** were never detected in the case of palladium-mediated [2+1] cycloadditions. Similarly to palladium, the platinum-catalyzed formation of ACPs was successfully widened to norbornene, benzonorbornene or diazabicyclic alkene (Scheme 22). For ACP **4t**, the yield was found in the same range using either catalyst **21c** or **21d**. Cycloadduct **4v** was isolated as a 1:1 mixture of diastereomers and the N-O bond was subsequently cleaved with $\text{Mo}(\text{CO})_6/\text{NaBH}_4$ to give the corresponding amidoalcohol.

Table 8. Optimization of the catalytic system for the Pt-mediated [2+1] cycloaddition.^[a]


Entry	Catalytic system	Yield (%)
1	20c (5 mol%)	-
2	20c (5 mol%), AgOAc (10 mol%)	65
3	21c (5 mol%)	29
4	21c (5 mol%), AcOH (10 mol%)	68
5	21c (5 mol%), AcOH (1 equiv.)	80
6	Pd(OAc) ₂ (5 mol%), SPO 3c (10 mol%)	42
7 ^[b]	21c (5 mol%), AcOH (1 equiv.)	81
8 ^[b]	21d (5 mol%), AcOH (1 equiv.)	17 ^[c]

[a] Reaction conditions: [Pt] (5 mol%), norbornadiene (1 mmol), phenylacetylene (0.5 mmol), toluene (5 mL), 55 °C, 20 h. [b] Reactions performed with norbornadiene (0.5 mmol), phenylacetylene (1 mmol) [c] Dicycloadduct **22a** was isolated as the major product (52%) in 1:1.2 ratio of diastereomers.

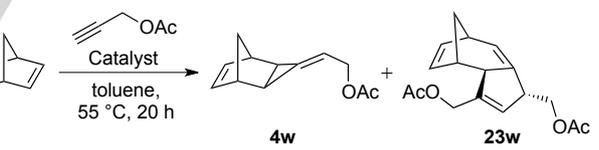
**Scheme 22.** Selected examples of Pt-catalyzed [2+1] cycloadditions.

From a mechanistic point of view, it seemed that the platinum-catalyzed [2+1] cycloaddition differed from the palladium one. Indeed, combined mass spectrometry experiments (Collision-Activated Reaction (CAR)/Sustained Off-Resonance Irradiation

(SORI)) and density functional theory calculations suggested the formation of platinum-vinylidene species instead of palladium-acetylide intermediates **C** (Scheme 8).²⁹ The transformation would occur by a [2+2] cycloaddition between the platinum-vinylidene and the olefin followed by a platinum extrusion. However these results have to be carefully considered since the ACPs formation works only with strained olefins.

6. Pt-Phosphinito-Phosphinous Acid Catalyzed [2+1]/[3+2] Cycloadditions

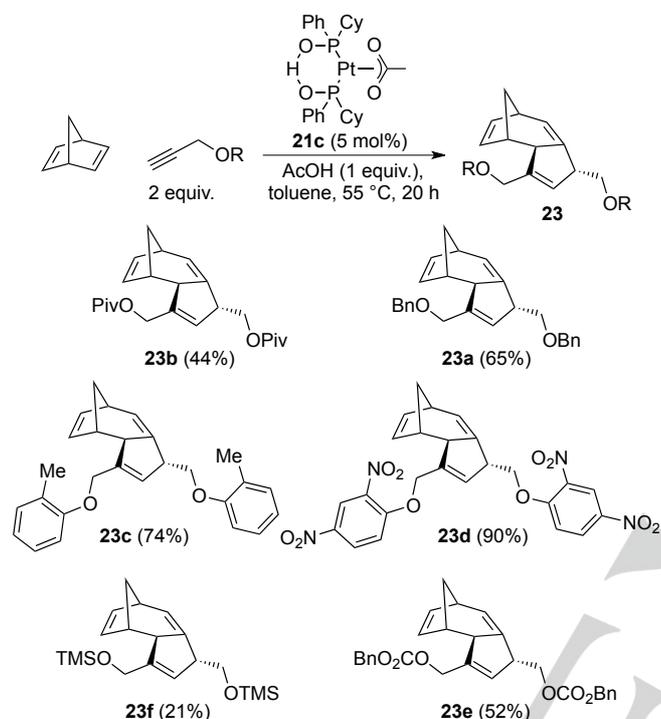
During the scope investigation of the platinum-catalyzed [2+1] cycloaddition, we observed the formation of an unexpected product when propargyl acetate was used as alkyne partner.²⁸ As shown in table 9, entry 1, only small quantities of ACP **4w** were isolated, while the tricyclic compound **23w** was the major product (62%). Compound **23w** was obtained as a single regio- and stereoisomer, and its relative configuration was determined by NMR spectroscopies and X-ray diffraction analysis. Formation of **23w** as single product upon increase of the reaction time to 3 days, suggested that **4w** is an intermediate in the formation of **23w** (entry 2). With catalyst **21c**, both **4w** and **23w** were observed albeit in much lower quantities (entry 3). On the same manner, in absence of acetic acid or using an *in-situ* generated catalyst from bis phosphinous acid platinum complex **20d**, silver acetate and triethylamine, the catalytic activities were found very low even though **23w** was been always isolated as the major product (entries 4 and 5).

Table 9. Optimization of platinum-catalyzed tandem [2+1]/[3+2] cycloaddition sequence.^[a]


Entry	Catalyst	Yields (%)	
		4w	23w
1	21d (5 mol%), AcOH (2 equiv.)	10	62
2 ^[b]	21d (5 mol%), AcOH (2 equiv.)	-	71
3	21c (5 mol%), AcOH (2 equiv.)	4	6
4	21d (5 mol%)	5	20
5	20d (5 mol%), AgOAc (10 mol%), Et ₃ N (10 mol%)	-	30

[a] Reaction conditions: [Pt] (5 mol%), norbornadiene (0.5 mmol), propargyl acetate (1 mmol), toluene (5 mL), 55 °C, 20 h. [b] Reaction time: 72 h.

This unusual platinum-catalyzed tandem [2+1]/[3+2] cycloaddition sequence was successfully applied to various substrates at the condition that the alkyne partner possessed an oxygen atom on the propargylic carbon (Scheme 23). With alkynes containing either esters, ethers (alkyl-, aryl- and silylethers) or carbonates, the transformation occurred and tricyclic compounds **23** were isolated in fair to excellent yields.



Scheme 23. Selected examples of Pt-catalyzed [2+1]/[3+2] cycloadditions.

In order to probe that ACP **4w** is an intermediate in the formation of **23w**, we treated it with 2 equivalents of propargyl acetate under the optimized reaction conditions (Table 10, entry 1). Pleasingly, **23w** was isolated as a single regio- and stereoisomer in 48% yield. With this result in hands, we further examined the scope of the [3+2] cycloaddition by setting reactions with **4w** and various alkynes (Table 10). This time, no requirement concerning the nature of the alkyne was observed and overall good yields of [3+2] cycloadducts **23** were obtained with propargylic alcohol, trimethylsilylacetylene, 1-hexyne, phtalimide- or sulfone-containing alkynes. Nevertheless, this transformation took place with the formation of by-products **24**, which might result from the formation of a platinum π -allyl intermediate and incorporation of the alkyne moiety. Compounds **24** were isolated as *exo* isomers with yields up to 26%.

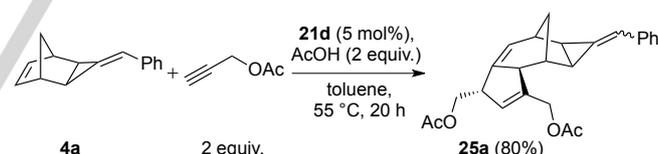
The necessity of the oxygen atom on the allylic carbon of alkylidenecyclopropane was confirmed by the reaction presented in Scheme 24. When ACP **4a** was submitted to the conditions of the Pt-catalyzed [2+1]/[3+2] cycloaddition sequence, no reaction took place on the ACP moiety. Instead

the carbon-carbon double bond of the norbornene reacted to afford the polycycle **25a** as a 1:1 mixture of diastereomers.

Table 10. Selected scope for the [3+2] cycloaddition.^[a]

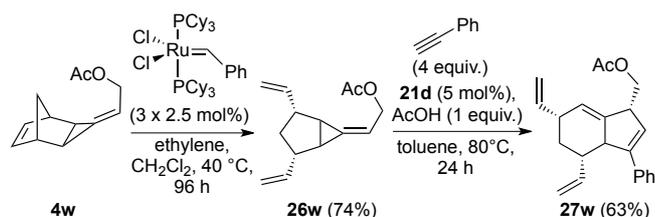
Entry	Alkyne	Yield (%)	
		23	24
1		48	-
2		39	7
3		61	-
4		70	25
5		61	12
6		63	26

[a] Reaction conditions: **21d** (5 mol%), ACP **4w** (0.5 mmol), alkyne (1 mmol), AcOH (1 mmol), toluene (10 mL), 55 °C, 20 h.



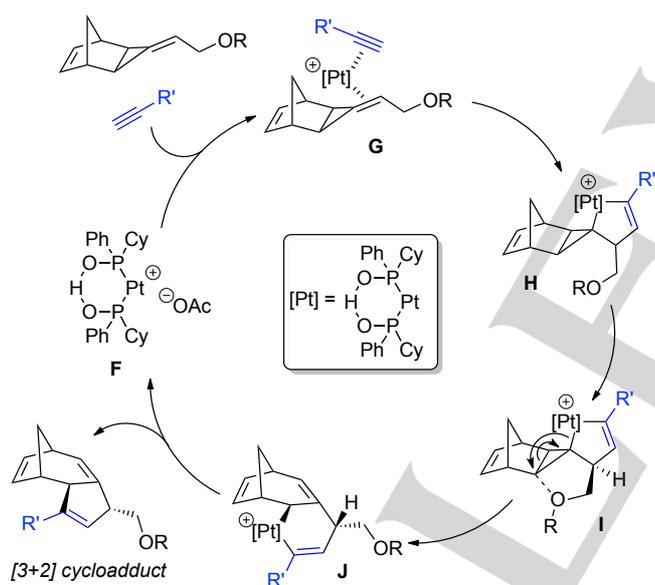
Scheme 24. Control experiment highlighting the necessity of the oxygen atom on the allylic carbon of ACPs.

In order to check whether the [3+2] cycloaddition could be achieved in the absence of the bicyclo[2.2.1]heptane moiety, an ethenolysis was performed on **4w** and after 4 days of reaction at 40 °C and regular addition of first generation Grubbs catalyst, ACP **26w** was isolated in 74% yield (Scheme 25).³⁰ Compared to **4w**, **26w** was less reactive and the reaction temperature had to be increased to 80 °C. Nonetheless, after a brief optimization (4 equivalents of phenylacetylene added dropwise for 16 hours), the expected tetrahydro-indene **27w** was obtained as a single diastereomer in good yield.



Scheme 25. Pt-catalyzed [3+2] cycloaddition in the absence of the norbornene structure.

A mechanism was proposed to rationalize both regio- and diastereoselectivities (Scheme 26).²⁸ We assumed that the cationic platinum species **F** coordinates both the alkyne and the carbon-carbon double bond of the ACP on its *exo* face and an oxidative coupling would form the platinacyclopentene **H**. Due to steric interactions between substrates and ligands, **H** would be obtained as a single regioisomer. For more clarity and to explain the diastereoselectivity, **H** has been drawn as a single enantiomer **I**. The cyclopropane fragmentation would occur by a 1,2 shift of



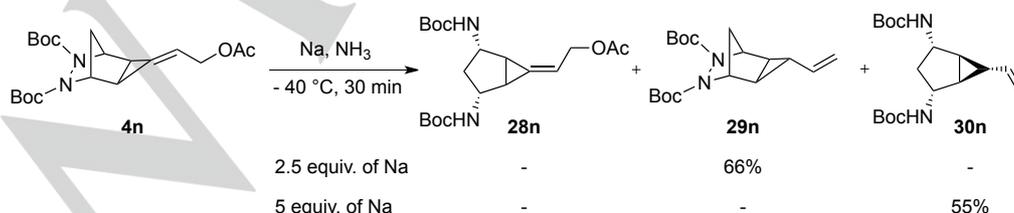
Scheme 26. Postulated mechanism for the platinum-mediated [3+2] cycloaddition.

the platinum assisted and oriented by the oxygen atom to generate the platinacyclohexene **J**. Finally, a reductive elimination would afford the [3+2] cycloadduct and regenerate the catalytically active species **F**. This proposed mechanism highlights a stereochemical relation between the enantiomer **G** and the final product.

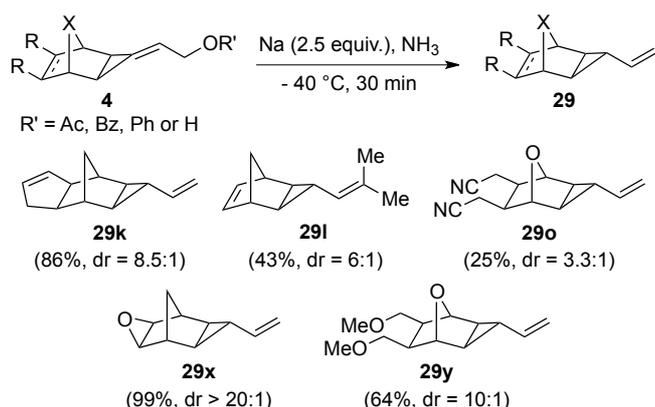
7. Related Reactivities of ACPs

During the project directed toward the study of the platinum-mediated [3+2] cycloaddition with ACPs that do not contain the bicyclo[2.2.1]heptane moiety, we discovered an unusual reactivity of ACPs. As an alternative to the ethenolysis, the reductive cleavage of the nitrogen-nitrogen bond of cyclic hydrazines was investigated.¹³ Among the several methodologies reported to carry out the reductive N-N cleavage of hydrazines, we chose to study the one involving the use of sodium metal in liquid ammonia. When ACP **4n** was treated with 2.5 equiv. of Na, the formation of the expected product **28n** was not detected (Scheme 27). Only the vinylcyclopropane **29n**, resulting from a reductive isomerization, was obtained in 66% yield as a single diastereomer with the vinyl *trans* to the other substituents of the cyclopropane. The desired cleavage of the N-N bond was achieved by increasing the quantity of Na to 5 equivalents. However in this case, only the compound **30n** was isolated indicating that the N-N cleavage was subsequent to the reductive isomerization.

The scope of this transformation was found broad since a range of vinylcyclopropanes **29** could be prepared with good overall yields and selectivities (Scheme 28). In addition of acetate, several leaving groups could be used in this reaction: benzoate, phenoxy and even hydroxyl groups. With the gem-dimethyl substituted alcohol **4l**, the formation of compound **29l** required 6 equivalents of sodium. Despite a moderate yield and a low selectivity, it was even possible to prepare a nitrile-containing vinylcyclopropane **29o**. To our delight, the reductive isomerization was found compatible with epoxide and **29x** was quantitatively isolated as a single diastereomer.



Scheme 27. Reductive cleavage of the nitrogen-nitrogen bond of cyclic hydrazine **4n**.



Scheme 28. Selected examples of reductive isomerization affording vinylcyclopropanes.

8. Conclusions and outlook

In summary, our group has developed straightforward and powerful synthetic routes to alkylidenecyclopropanes and vinylidenecyclopropanes from terminal acetylenic compounds and norbornadiene or oxanorbornadiene derivatives. These methods lie on [2+1] cycloadditions which require the use of palladium- and platinum-based complexes bearing a phosphinito-phosphinous acid ligand. Only few exceptions have been noticed in the case of strongly polarized alkynes (ynamides, ynones, propiolates) for which [2 + 1] cycloaddition reactions could be achieved with phosphapalladacycles **1**. Palladium and platinum complexes bearing phosphinito-phosphinous acid ligands can be easily prepared by treatment of appropriate metal salts with secondary phosphine oxides. The specificity of this ligand relies on the fact the two phosphorus atoms are non-equivalent but interchangeable and as a result, the electronic properties of the metal center can be finely adjusted.

With these catalytic systems in hand, we investigated the reactivity of norbornene derivatives with terminal alkynes. As noted through this manuscript, this chemistry suffers from low predictive aspects but the serendipitous findings achieved make it extremely fascinating. Indeed, as a function of the catalyst, the reaction conditions, or the nature of the reagents, different synthetic transformations were discovered. With alkyl- and aryl-substituted alkynes, both palladium and platinum complexes gave rise to ACP derivatives. With alkyne partners possessing an oxygen atom on the propargylic carbon, platinum-based complexes catalyzed a [2+1]/[3+2] cycloadditions sequence. With tertiary propargyl acetates, palladium-mediated [2+1] cycloadditions afforded VDCPs. The reaction of the latter was further investigated and an unusual ring expansion discovered. Considering the unique catalytic properties of metal complexes bearing phosphinito-phosphinous acid ligands and the clearly under exploited enantioselective potential of these ligands – as highlighted by the interesting results presented therein – it can be confidently stated that they possess a bright future.

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Keywords: cycloaddition • palladium • platinum • secondary phosphine oxide • methylenecyclopropane

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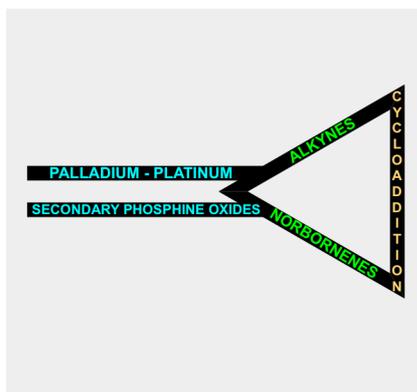
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Layout 1:

PERSONAL ACCOUNT

This Account describes our group's contribution toward the preparation of alkylidene- and vinylidenecyclopropanes by [2+1] cycloaddition using metal-phosphinito-phosphinous acid-promoted catalyses and the associated reactivities of these useful synthons.

*Hervé Clavier* and Gérard Buono***Page No. – Page No.****[2+1] Cycloaddition Affording Methylene- and Vinylidenecyclopropane Derivatives: A Journey around the Reactivity of Metal-Phosphinito-Phosphinous Acid Complexes**