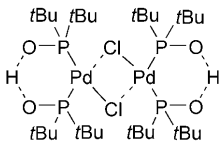
Palladium-Catalyzed Chemistry

[2+1] Cycloadditions of Terminal Alkynes to Norbornene Derivatives Catalyzed by Palladium Complexes with Phosphinous Acid Ligands**

*Julie Bigeault, Laurent Giordano, and Gérard Buono**

Secondary phosphine oxides (SPOs) have been widely used for the synthesis of tertiary phosphine oxides and have found applications as Wittig–Horner reagents[1–2] and, later, as effective ligands for transition-metal complexes.[3] Recently, Li et al. showed that SPOs form air-stable palladium complexes, such as POPd1, when they are mixed with $PdCl_2(MeCN)_2$ and then treated with Et_3N.[4] These complexes proved efficient as catalysts in several cross-coupling reactions[4–5] as well as in asymmetric allylic alkylations.[6] Recent reports showed also that these new ligands are suitable for other types of catalyzed reactions such as the hydrolysis of nitriles[7] and the asymmetric hydrogenation of imines[8] and alkenes.[9] Our continued interest in the metal-catalyzed cycloaddition reactions between alkynes and norbornadiene[10] prompted us to investigate the catalytic behavior of palladium(II) complexes coordinated by SPOs.



POPd1

First, we developed an easier way to synthesize the palladium catalyst **1**. Upon treatment of $Pd(OAc)_2$ with *tert*-butyl(phenyl)phosphane oxide (**L1**), dihydrogen di-μ-acetatotetrakis(*tert*-butylphenylphosphinito-κ-*P*)dipalladate (**1**) was quantitatively obtained without further treatment (Scheme 1).[11] Second, as a model we examined the reaction of phenylethyne (**3a**) with norbornadiene (**2**) in the presence of 2.5 mol% of **1** in toluene at 50°C for 24 h. Unexpectedly, the palladium(II) complex **1** coordinated by **L1** favored the formation of benzylidenecyclopropane (**4a**) as a single diastereomer in 17% yield (Scheme 2) and contaminated by an unidentified byproduct (5%). Surprisingly, a similar reaction using the known chloro-bridged analogue **5**[6a–12] as catalyst did not work. Furthermore, in the reaction catalyzed by **5**, the addition of 10 mol% of AgOAc (4 equiv relative to

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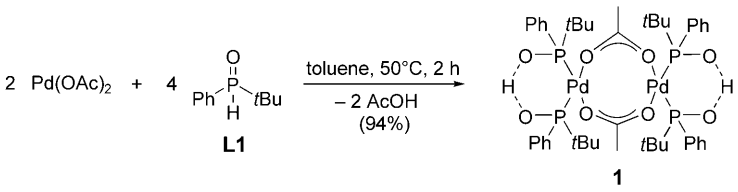
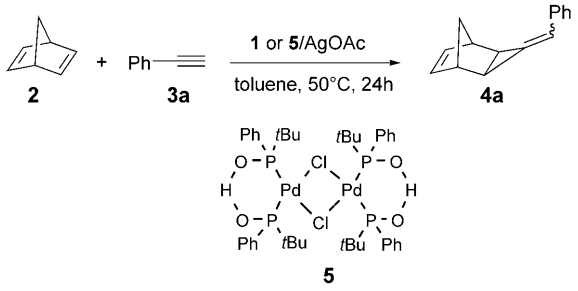
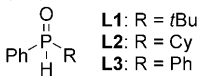


Scheme 1. Synthesis of the new air-stable palladium(II) complex **1** with phosphinous acid ligands.



Scheme 2. Palladium(II) complexes **1** or **5** catalyze an unusual [2+1] cycloaddition of **2** with **3a**. Conditions: **2**/**3a**/**1** = 2:1:0.025; **2**/**3a**/**5**/AgOAc = 2:1:0.025:0.1.

Table 1: Benzylidenecyclopropanation of **2** with **3a**.



Entry[a]	L	*T* [°C]	Yield [%][b]
1	**L1**	25	trace
2	**L1**	50	42
3	**L2**	50	76
4	**L2**	25	80
5	**L3**	25	21
6	**L3**	50	58

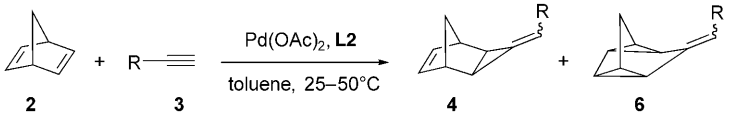
[a] All reactions were carried out with **2**/**3a**/$Pd(OAc)_2$/**L** in a ratio of 2:1:0.05:0.1 for 24 h. [b] Yield of isolated product. Cy = cyclohexyl.

Having established the feasibility of the cycloaddition reaction, we tested various terminal alkynes **3a**–**k** to extend its applicability. Under optimized conditions, all reactions proceeded cleanly and various functional groups such as ethers, esters, alcohols, sulfones, or tertiary amines present in the alkyne were tolerated (Table 2). Propargylic alcohols **3f** and **3g**, sulfone **3i**, and tertiary amine **3j** also reacted with **2** to afford **4f**, **4g**, **4i**, and **4j**, respectively, in 57–75% yields

catalyst **5**) led to the formation of **4a** in 15% yield.[13] Even if few examples of ruthenium-[14] or palladium-catalyzed[15] cyclopropanations of norbornene derivatives with alkynes are known, a catalytic process that is able to favor the direct formation of alkylidenecyclopropanes as illustrated in Scheme 2 has, to our knowledge, not been reported. Herein, we show that palladium(II) complexes stabilized by secondary phosphine oxides are active catalysts for an unusual [2+1] cycloaddition of norbornene derivatives with terminal alkynes to produce various alkylidenecyclopropanes.

In a preliminary study, we found that the addition of 5 mol% of acetic acid was beneficial to the reaction and led to the formation of **4a** as the exclusive product in 26% yield. This finding revealed that acetate plays an important role in the reaction. Indeed, AcOH was released in the reaction medium during the formation of catalyst **1**. This observation prompted us to test the formation of catalysts in situ. Two other SPOs, **L2** and **L3**, were tested under similar conditions by generating the catalyst in situ (Table 1). The best result was observed when $Pd(OAc)_2$ was associated with **L2** (1:2 molar ratio), affording **4a** in satisfactory yield at room temperature (entry 4).[16–17] Similarly, palladium catalyst systems generated with **L1**[18] or **L3** proved active but less efficient (entries 2 and 6).

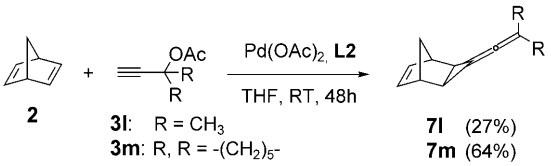
Table 2: Palladium-catalyzed alkylidenecyclopropanation of **2** with terminal alkynes **3**.



Entry[a]	Alkyne	R	*T* [°C]	*t* [h]	Cycloadduct	Yield [%][b]
1	**3a**	Ph	25	20	**4a**	80
2	**3b**	*n*Bu	50	20	**4b**	9
3	**3c**	CH_2TMS	50	48	**4c**	–
4	**3d**	CH_2OBn	25	50	**4d**	70
5	**3e**	CH_2OAc	25	50	**4e**	73
6	**3f**	CH_2OH	25	50	**4f**	34
7	**3f**	CH_2OH	50	48	**4f**	57
8	**3g**	$C(Me)_2OH$	50	36	**4g**	75
9	**3h**	$CH_2CH(CO_2Me)_2$	50	50	**4h**	52
10	**3i**	CH_2SO_2Ph	25	48	**4i**	66
11	**3j**	CH_2Mp	25	48	**4j**	34
12	**3j**	CH_2Mp	50	36	**4j**	60
13	**3k**	CO_2Me	25	60	**6k**	56

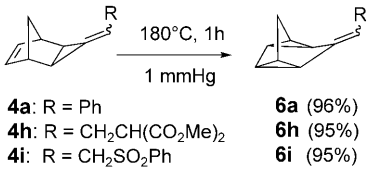
[a] Experiments were performed on a 1-mmol scale using 5 mol% of $Pd(OAc)_2$ and 10 mol% of **L2** (**2**/**3**/Pd/**L2** = 2:1:0.05:0.1). [b] Yield of isolated product. TMS = trimethylsilyl; Bn = benzyl; Mp = morpholinyl (C_4H_8NO).

(Table 2, entries 7, 8, 10, and 12). For an unknown reason, no product was obtained with propargylsilane **3c** (entry 3).[19] Likewise, with an unfunctionalized alkyne such as **3b**, the reaction was slow and conversion was very low (Table 2, entry 2). Surprisingly, an acetate group in a propargylic position such as in **3e** afforded the desired cyloadduct **4e** without formation of byproducts (entry 5).[20] A notable difference in reactivity was observed for tertiary acetates such as **3l** and **3m**. In this case, known allenylidenecyclopropanes[21] **7l** and **7m** were obtained in 27% and 64% yield, respectively (Scheme 3).



Scheme 3. Synthesis of allenylidenecyclopropanes **7l** and **7m** from tertiary acetates. Conditions: **2**/**3**/Pd/**L2** = 2:1:0.05:0.1.

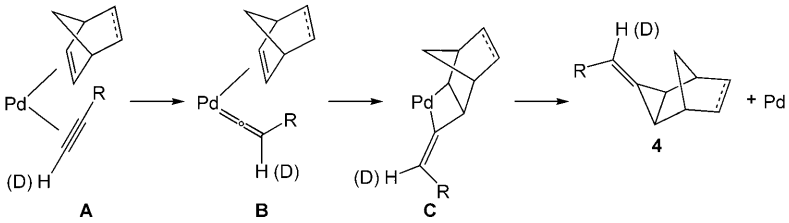
With the electron-deficient alkyne **3k** (Table 2, entry 13), the expected cycloadduct **4k** and the rearranged (valence isomerization) product **6k** were observed in 1:1 ratio in the crude reaction mixture. After purification by chromatography on silica gel, only **6k** was isolated in 56% yield. Valence isomerization proved to be effective on cycloadducts **4a**, **4h**, and **4i** under thermal conditions in the absence of solvent: heating these cycloadducts to 180 °C at 1 mm Hg resulted in clean and complete conversion after 1 h (Scheme 4).[22–23]



Scheme 4. Thermal rearrangements (valence isomerization) of **4**.

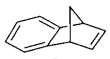
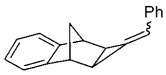
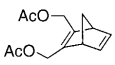
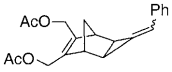
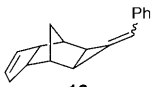
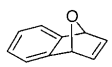
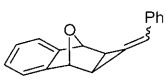
The cycloaddition reaction was extended to other norbornene derivatives by using phenylethyne (**3a**) as a partner (Table 3).[24] The cyclopropanation of alkenes **8**–**12** afforded expected benzylidenecyclopropanes **13**–**17** in moderate to good yields. The best yields were observed for norbornene (**8**) or benzonorbornene (**9**; entries 2 and 3). The cycloaddition with functionalized norbornenes gave the products in fair yields (entries 4 and 6). For cyclopentadiene dimer **11**, the cyclopropanation occurred exclusively at the most strained double bond to yield the cycloadduct **16** in 51% as a 1:1 mixture of diastereomers (Table 3, entry 5). Note the exclusive formation of cyclopropane **15** from **10** (entry 4). Indeed, diacetate **10** has been previously used in palladium(0)-catalyzed elimination[25] and alkylation[26] reactions and proceeds via an intermediate π-allyl complex.

Although the mechanism of this unusual cyclopropanation remains unclear at the moment, we assume that the reaction may involve palladium vinylidene species as key intermediates in a catalytic process that favors the formation of [2+1] cycloadducts over dimerization[27] products of alkynes (Scheme 5). Palladium vinylidene complex **B** may be generated from 1-alkyne **3**,[28,29] and **B** could allow a [2+2] cycloaddition with the double bond of the norbornene. The resulting 2-alkylidene palladacyclobutane (**C**) would release cycloadduct **4** after reductive elimination. The formation of this unprecedented Pd vinylidene complex is supported by results from deuterium-labeling experiments. Starting from monodeuterophenylacetylene [D$_1$]**3a** and **2**,



Scheme 5. A possible pathway for the palladium-catalyzed [2+1] cycloaddition of norbornadienes and alkynes. (D) denotes the proton exchanged for deuterium in labeling experiments.

Table 3: Cyclopropanation of various norbornenes **8**–**12** with phenylethyne (**3a**).

Entry[a]	Alkene	*T* [°C]	*t* [h]	Cycloadduct	Yield [%][b]
1	 **8**	25	60	 **13**	51
2		50	48		94
3	 **9**	25	60	 **14**	84
4	 **10**	50	36	 **15**	58
5	 **11**	50	72	 **16**	51
6	 **12**	50	48	 **17**	56

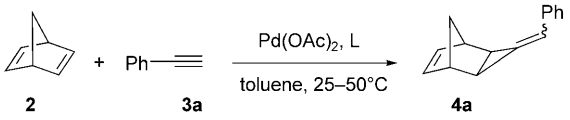
[a] Experiments were performed on a 1-mmol scale using 5 mol% of Pd(OAc)$_2$ and 10 mol% of **L2**. [b] Yield of isolated product.

under similar conditions the reaction led to compound [D$_1$]**4a** in 88% yield with 80% incorporation of deuterium on the external double bond (Scheme 5).[30] For the formation of allenylidenecyclopropanes **7l** and **7m**, the reaction is thought to proceed through a similar mechanism via a palladium allenylidene intermediate (Pd=C=C=CR$_2$).[31]

Finally, we briefly examined the interesting asymmetric version of this cycloaddition by using chiral secondary phosphine oxides (−)-**L1** and (−)-**L2** obtained by separation with chiral HPLC.[32] Indeed, alkylidenecyclopropanes synthesized from symetrical **2** showed geometrical enantiomorphic isomerism.[33–34] Preliminary results obtained are encouraging: an asymmetric induction of 59% *ee* was achieved with (−)-**L1** without optimization of the reaction conditions (Table 4, entry 1).

In conclusion, we have shown that palladium(II) complexes stabilized by secondary phosphine oxide ligands catalyze a very unique [2+1] cycloaddition of norbornene derivatives with various terminal alkynes to afford functionalized alkylidenecyclopropanes.[35–36] Moreover, our results suggest a Pd vinylidene complex as a key intermediate. A detailed investigation of the mechanism and the development

Table 4: Enantioselective benzylidenecyclopropanation of **2** with **3a** using a chiral secondary phosphine oxide ligand.



2 **3a** **4a**

Entry[a]	L	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	(−)-**L1**	50	60	53	59
2	(−)-**L2**	25	20	80	22

[a] Experiments were performed using 5 mol% of $Pd(OAc)_2$ and 10 mol% of ligand L. [b] Yield of isolated product. [c] *ee* values determined on a Daicel Chiralcel OJ-H column at $\lambda = 254$ nm using hexane/*i*PrOH 99:1 as eluent with a flow rate of 1 mL min^{-1}; $t_1 = 6.4$ min, $t_2 = 7.1$ min.

of asymmetric cycloaddition reactions are underway in our laboratory.

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[11] With enantiopure **L1**, the complex **1** was clearly identified by NMR spectroscopy. The acetato-bridged structure was supported by the ESI mass spectrum of the palladium complex **1** (see Supporting Information).

[12] Complex **5** was prepared according to Li's procedure[4] from **L1**. As shown by ^{31}P NMR spectra and X-ray crystallography, only one diastereomeric complex was obtained which exhibits C_2 symmetry and retention of configuration at phosphorus (see Supporting Information). During the course of our work, Leung and co-workers reported chiral bisphosphinite metalloligands derived from a P-chiral secondary phosphine oxide: E. Y. Y. Chan, Q. F. Zhang, Y.-K. Sau, S. M. F. Lo, H. H. Y. Sung, I. D. Williams, R. K. Haynes, W.-H. Leung, *Inorg. Chem.* **2004**, *43*, 4921–4926.

[13] Cycloadduct **3a** was also contaminated with 5% of an unidentified byproduct.

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[16] Other catalysts associated with two PPh_3 ligands such as $[PdCl\{\eta^3\text{-}(C_3H_5)\}_2]$, $Pd(OAc)_2$, and $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneacetone) did not promote the reaction at all.

[17] Toluene gave the best results. The [2+1] cycloaddition proceeded well in heterogeneous media in solvents such as Et_2O (74% yield), THF (59% yield), or CH_2Cl_2 (49% yield). The lowest yields were obtained with more polar solvents such as *N*,*N*-dimethylformamide (10% yield) or CH_3CN (6% yield).

[18] The catalytic system was stable under the experimental conditions described and could be recovered after the reaction by column chromatography.

[19] A difference in reactivity was observed by using trimethylsilylacetylene in place of propargylsilane **3c**: Only an adduct of hydroalkynylation was obtained as a single diastereomer in 68% yield.

[20] The reaction is probably catalyzed by a Pd^{II} catalyst. Indeed, Pd^0-catalyzed reactions of various propargylic compounds proceed by the formation of either σ-allenyl or σ-prop-2-ynylpalladium species; see: J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, Wiley, Chichester, **2004**, chap. 6, pp. 543–563; for the Pd^0- and Pd^{II}-catalyzed reactions of alkynes, see: J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, Wiley, Chichester, **2004**, chap. 7, pp. 565–599.

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[22] These rearrangments are geometrically constrained to occur by a $\sigma^2s + \sigma^2\pi$ mechanism, which is a symmetry-forbidden reaction.

They have therefore been generally interpreted to occur by cleavage to a diradical followed by rapid intramolecular trapping of the diradical by the π bond (see reference [21a]).
[23] The structure and stereochemistry of compounds **4i** and **6i** were confirmed by X-ray analysis (see reference [36]).
[24] The same reaction carried out with cyclopentene in place of norbornene derivatives did not work. No oligomers or self-coupling adducts of the phenylethyne **3a** have been observed.
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[29] There are two possible mechanisms for the formation of Pd vinylidene complexes **B** from η^2-coordinated alkyne intermediate **A**. The first involves a direct 1,2-hydrogen migration over the carbon triple bond. In contrast, the second mechanism occurs through a 1,3-shift of the hydride to the alkynyl ligand after oxidative addition of the C–H bond to Pd.
[30] The position of the deuterium was based on the disappearance of the signal of C_{sp^2}-H at $\delta = 6.55$ ppm (see Supporting Information).
[31] For recent reviews, see: a) H, Werner, *Chem. Commun.* **1997**, 903 – 910; b) D. Touchard, P. H. Dixneuf, *Coord. Chem. Rev.* **1998**, 178 – 180, 409 – 429; c) V. Cadierno, M. P. Gamasa, J. Gimeno, *Eur. J. Inorg. Chem.* **2001**, 571 – 591.
[32] Pure enantiomers were obtained by semipreparative chiral HPLC on chiralpak AD or AS (250×10 mm^2) columns using hexane/ethanol (90:10) or ethanol as eluents. For **L2**, the absolute configuration at phosphorus is currently unknown.
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[34] This type of chirality known under the name of "geometric enantiomerism" is also called *cis–trans* enantiomerism. *Stereochemistry of Organic Compounds* (Eds.: E. L. Eliel, S. H. Wilen), Wiley, New York, **1994**, chap. 14-3, pp. 1155 – 1156.
[35] Alkylidenecyclopropanes have served as useful building blocks in organic synthesis. For recent reviews, see: a) I. Nakamura, Y. Yamamoto. *Adv. Synth. Catal.* **2002**, *344*, 111 – 217; b) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213 – 1270.
[36] See Supporting Information for full synthetic details and characterization of new compounds. CCDC 265344–265346 (**4i**, **6i**, and **5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

