Tandem [2+1] Cycloaddition–Ring Expansion of Bicyclic Alkenes with Tertiary Propargylic Acetates Catalyzed by Palladium(II)-Coordinated Phosphinous Acid

Julie Bigeault,[a] Innocenzo de Riggi,[a] Yves Gimbert,[b] Laurent Giordano,*[a] Gérard Buono*[a]

[a] Université d'Aix-Marseille, ECM, Institut des Sciences Moléculaires de Marseille (ISM2), CNRS UMR 6263; Avenue Escadrille Normandie Niemen, Case A 62, 13397 Marseille Cedex 20, France
Fax +33(491)282742; E-mail: gerard.buono@univ-cezanne.fr; E-mail: laurent.giordano@univ-cezanne.fr

[b] Université Joseph Fourier de Grenoble, Département de Chimie Moléculaire, UMR CNRS 5250, ICMG FR-2607, 38041 Grenoble Cedex 9, France

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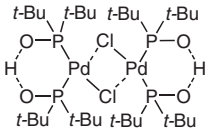
Abstract: Palladium–SPO complex catalyzed the tandem [2+1] cycloaddition–ring expansion of norbornene derivatives with tertiary propargylic acetates to afford bicyclo[3.2.1]octadienes.

Key words: palladium, secondary phosphine oxides, tertiary propargylic acetate, bicyclic alkene, tandem reaction

Secondary Phosphine Oxides (SPO) are excellent preligands for transition metals.[1] To date, the SPO are largely employed as preligands in catalytic reactions.[2] The pioneering work involving SPO for transition-metal-catalyzed cross-coupling reactions was reported by Li.[3] Since 2001, the field of application of SPO in cross-coupling reactions has considerably extended.[4] Transition-metal-coordinated chiral phosphinous acid have also found applications in asymmetric allylic amination[5] or alkylation[6] and asymmetric hydrogenation of imines[7] or functionalized olefins.[8] Recently, a bridged phosphinous acid dimer POPd1 (Figure 1) proved to be an efficient catalyst for the conjugate addition of arylsiloxanes to a wide range of α,β-unsaturated substrates.[9]



POPd1

Figure 1 Li's catalyst

In our previous works, we reported that palladium or platinum–phosphinous acid catalysts are active for the [2+1] cycloaddition of terminal alkynes and norbornene derivatives.[10,11] These classes of complexes also show an activity in a [4+2] cycloaddition involving alkylidenecyclopropanes.[11] These results led us to examine the behavior of vinylidenecyclopropanes in the presence of nucleophilic reagent and catalytic amounts of $Pd(OAc)_2$/SPO. In this letter, we describe the direct preparation of bicyclo[3.2.1]octadienes via an in situ rearrangement of allenylidenecyclopropanes catalyzed by palladium(II)-coordinated phosphinous acid. We firstly decided to reexamine the reaction of tertiary acetates **2a** and **2b** with norbornadiene **1a** in the presence of 5 mol% of $Pd(OAc)_2$ associated with cyclohexylphenylphosphine oxide (1:2 molar ratio) at room temperature using toluene instead of THF as solvent.[10] In contrast with the reaction carried out in THF (Table 1, entries 1 and 2) the expected cycloadducts **3a** and **3b** were obtained in lower yield, 22% and 8%, respectively (Table 1, entries 3 and 5). However, ^{1}H NMR analysis of the crude reaction mixture revealed a complete conversion (based on **2**) and the formation of a new adduct **4** obtained as a 9:1 mixture of diastereomers.

The structure of **4a** and **4b** were established by ^{1}H NMR and ^{13}C NMR and the *exo* stereochemistry of the acetoxy group for the major diastereomer **4b** was assigned by comparison with literature data.[12] Interestingly, when the reaction was performed at 60 °C for 60 hours, **3a** and **4a** were obtained with an overall yield of 86% and the molar ratio of **4a/3a** raised to 3.8:1 (Table 1, entry 4). The variation of the molar ratio in favor of **4a** when increasing the temperature suggested **3a** as a precursor of **4a**. Indeed, **3a** could react with AcOH released in the medium during the first step of the reaction (Scheme 1). It is important to note that the reaction performed with Ph_3P in place of SPO ligands did not afford **3**.[13]

This observation was supported by the reaction of **3a** and AcOH in the presence of $Pd(OAc)_2$/CyPhP(O)H as a catalytic system affording **4a** as a single adduct in 48% yield (Scheme 2).[14]

However, under these conditions the diastereomeric excess decrease to 68%, probably due to a large amount of AcOH (1 equiv) compared to the catalytic system (0.05 equiv). Finally, using the tertiary acetate **2b** in the same conditions, **4b** was obtained selectively in 60% yield (Table 1, entry 6). Secondly, having established the feasibility of this transformation, various bicyclic alkenes were tested to extend the scope of the above reaction (Table 2).

Almost all bicyclic substrates were transformed into their corresponding bicyclo[3.2.1]octadienes **4**. For instance, norbornene **1c** and functionalized norbornadienes **1d–g** afforded **4d–g** in moderate yields. However, the whole transformation should be considered as two successive steps with fairly good yields (Table 2, entries 1–6). It is

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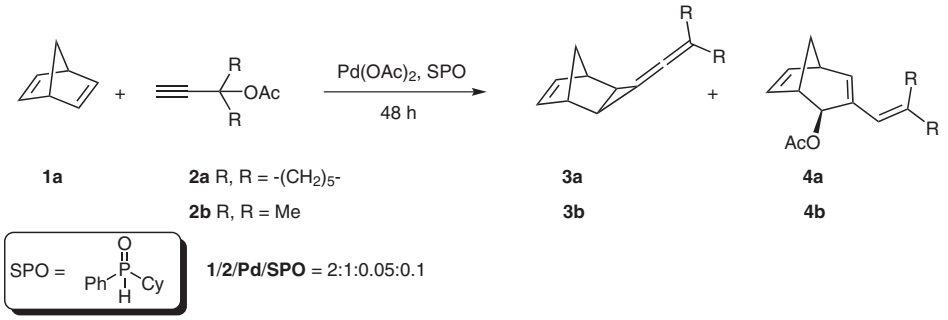
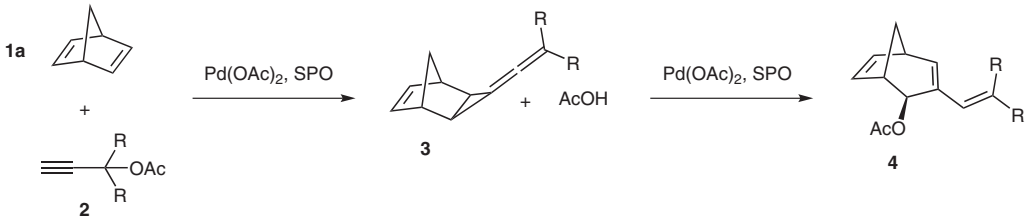
Table 1 Synthesis of Bicyclo[3.2.1]octadiene **4** from Tertiary Acetates **2** and Norbornadiene **1a**[a]

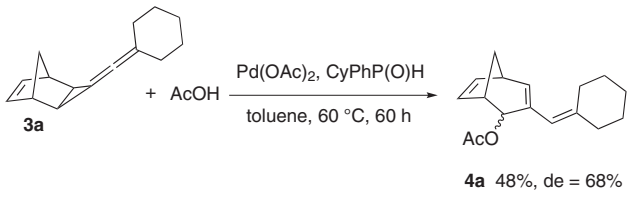


Entry	Alkyne	Solvent	Temp (°C)	Product	Yield (%)[b]
1	**2a**	THF	25	**3a**	64
2	**2b**	THF	25	**3b**,	27
3	**2a**	Toluene	25	**3a** **4a**	22 33
4	**2a**	Toluene	60	**3a** **4a**	18 68
5	**2b**	Toluene	25	**3b** **4b**	8 32
6	**2b**	Toluene	60	**3b** **4b**	≤ 5 60

[a] All reactions were carried out with 1 mmol of **2a** or **2b** for 48 h.
[b] Isolated yield.



Scheme 1 A possible formation of bicyclo[3.2.1]octadiene **4** from alkyne **2** and norbornadiene **1a**



Scheme 2 $Pd(OAc)_2$–SPO-catalyzed rearrangement of allenylidenecyclopropane

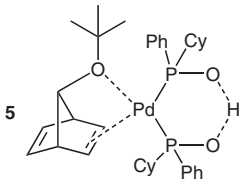
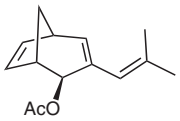
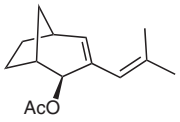
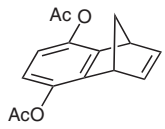
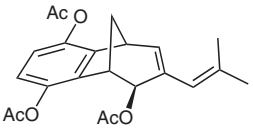
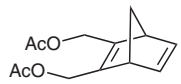
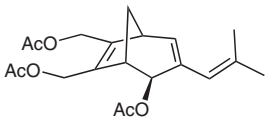
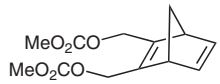
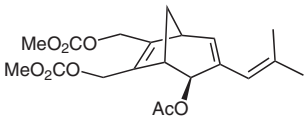
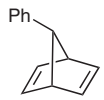
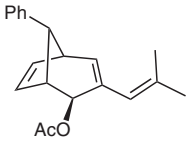
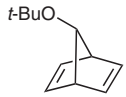
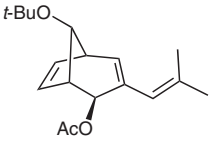


Figure 2 Formation of a possible stable complex **5**

worth noting that these reaction conditions were suitable for every compound except for 7-*tert*-butoxynorbornadiene (**1h**, Table 2, entry 7). In this case, the possibility of the coordination of the oxygen atom carried by *tert*-butoxy group and the double bond of the norbornadiene moiety could yield a stable complex **5**, unreactive for the [2+1] cycloaddition (Figure 2).[15]

A possible pathway for the palladium-catalyzed [2+1] cycloaddition of norbornadiene **1a** with tertiary propargylic acetates **2** was proposed in our previous work.[10] The mechanism of the present ring expansion involving Pd(II) cationic species **A** as the active catalyst is suggested (Scheme 3).[16] Complex **A** is able to coordinate the allene partner by the most available *endo* face to give **B**. At this stage, the activation of the double bond branched on cyclopropane ring generates a cyclopropyl cation **C** which rearranges into an allylic cation **D**. Nucleophilic attack of the acetate[17] and protonolysis of **D** release the product **4** and the active catalyst **A**.

Table 2 Pd–SPO-Catalyzed Tandem [2+1] Cycloaddition–Ring Expansion of **1** with **2b**[a]

Entry	Alkene	Time (h)	Product (de, %)	Yield (%)[b]
1	 **1a**	48	 **4b** (80)	60
2	 **1c**	24	 **4c** (80)	54
3	 **1d**	60	 **4d** (95)	55
4	 **1e**	60	 **4e** (93)	53
5	 **1f**	50	 **4f** (92)	33
6	 **1g**	60	 **4g** (95)	49
7	 **1h**	14	 **4h**	NR

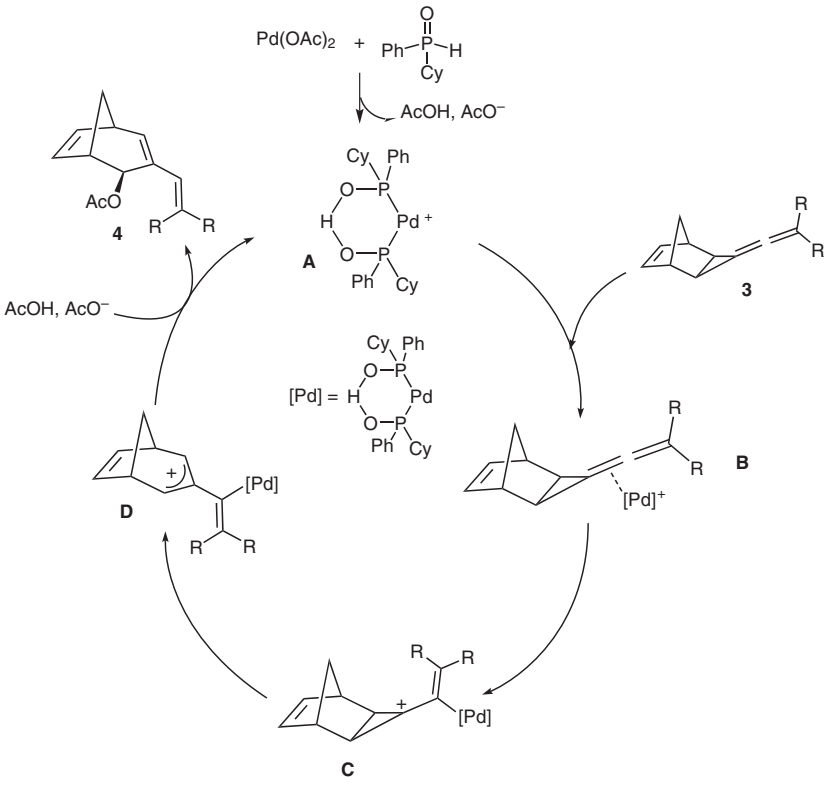
[a] All reactions were carried out with 1 mmol of **2b** at 60 °C in toluene. Ratio: **1/2b**/Pd/CyPhP(O)H = 2:1:0.05:0.1.
[b] Isolated yield.

We intended to compare the effect of Ph_3P ligand and SPO on the outcome of the reaction of **3a** with AcOH. When using Pd(0)/PPh_3 as a catalyst, the reaction was not selective, affording **4a** together with **6** (Scheme 4).

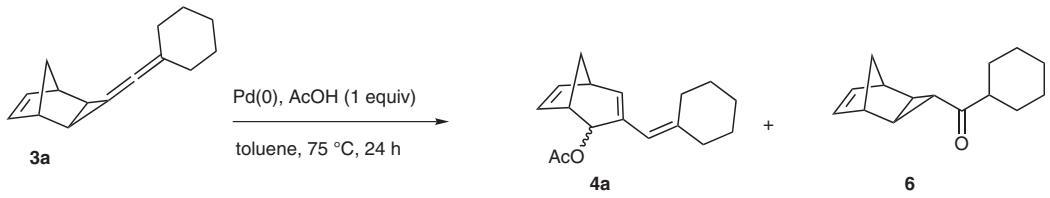
Although the Pd(0)/Ph_3P catalyzes this rearrangement with modest selectivity, it turns out that the SPO ligands showed a better efficiency and selectivity for the second step of this reaction. On the basis of these results, another mechanistic pathway involving HPd(OAc)$(PPh_3)_2$ must be considered (Scheme 5).[18]

The formation of both products could be explained by two distinct elemental steps: A hydropalladation (i)[19] and an acetoxypalladation (ii). Intermediate **E** isomerizes to a π-allyl Pd **F** precursor of **4** whereas intermediate **G** undergoes reductive elimination to afford the ketone **6** after hydrolysis.

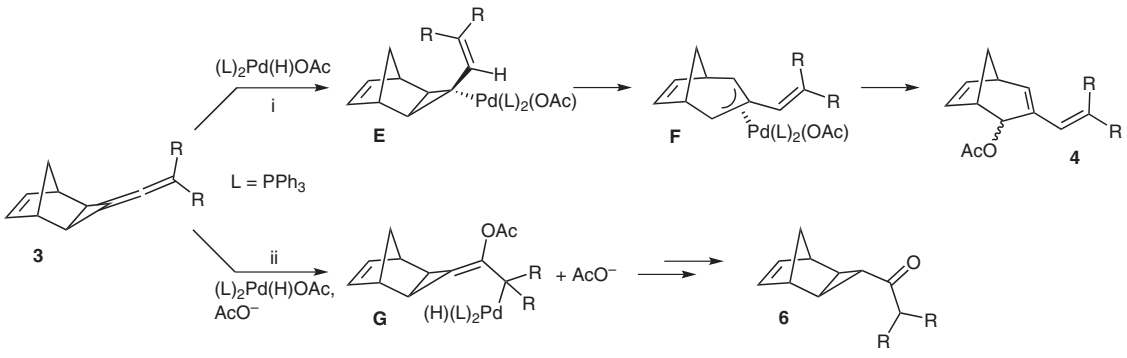
In conclusion, a new tandem [2+1] cycloaddition–ring expansion of norbornene derivatives with tertiary propargylic acetates using a Palladium–SPO complex as a catalyst have been developed. This simple catalytic procedure provides various functionalized bicyclo[3.2.1]octadienes. Since enantiomerically enriched SPO preligands[20] can be used for this transformation, an asymmetric domino reaction is expected to occur. These studies will be reported in due course.



Scheme 3 Proposed reaction pathway for the palladium–SPO-catalyzed ring expansion of **3**



Scheme 4 Palladium(0)-catalyzed ring expansion of **3a**



Scheme 5 Possible pathway for Pd(0)-catalyzed ring expansion of **3**

Typical Procedure

In a 10mL flame-dried Schlenk flask, $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%) and CyPhP(O)H (0.1 mmol, 20.8 mg, 10 mol%) were dissolved under argon in dry and degassed toluene (2 mL), then, the resulting yellow solution was stirred at r.t. After 30 min, a solution of **1** (2 mmol) and 2-methybut-3-yn-2-yl acetate (**2b**, 1 mmol, 125.1 mg), respectively, in 1 mL and 2 mL of dry and degassed toluene were added successively. The resulting mixture was stirred at 60 °C for 24–60 h. The solvent was then concentrated in vacuum to afford a yellow or dark crude mixture. Purification of the

crude by flash chromatography using Et_2O–light PE as eluent afforded 33–60% of **4**.

All new compounds exhibited satisfactory ^1H NMR, ^{13}C NMR, and IR spectral data. The following physical data are representative.

3-(2-Methyl-propenyl)-exo-bicyclo[3.2.1]oct-3,6-dien-2-yl Acetate (4b)

Diastereomeric excess: 80%; yield 60%; pale yellow oil. TLC: $R_f = 0.48$ (Et_2O–light PE, 1:9). IR (thin film, NaCl plate): ν_{max} = 3059, 3028, 2971, 2945, 2867, 1737, 1648, 1446, 1368, 1327, 1239, 1015, 974 cm^{-1}. ESI-MS (low resolution): *m/z* calcd for $C_{14}H_{18}O_2$ $[M + H]^+$: 219; found: 219 $[M + H]^+$, 236 $[M + NH_4]^+$, 241 $[M + Na]^+$.

Major Diastereomer

^1H NMR (200 MHz, $CDCl_3$): δ = 1.68 (d, *J* = 1.3 Hz, 3 H), 1.69 (d, *J* = 1.3 Hz, 3 H), 1.83–1.92 (m, 1 H), 1.97 (d, *J* = 9.6 Hz, 1 H), 2.03 (s, 3 H), 2.69–2.75 (m, 1 H, H_1), 2.81–2.87 (m, 1 H), 4.97 (d, *J* = 1.3 Hz, 1 H, HCO), 5.28 (m, 1 H), 5.86 (dd, *J* = 3.1, 5.5 Hz, 1 H), 6.10 (d, *J* = 6.6 Hz, 1 H), 6.48 (dd, *J* = 2.8, 5.5 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.4 (q), 21.2 (q), 26.4 (q), 38.4 (t), 39.2 (d), 43.7 (d), 70.9 (d), 123.5 (d), 129.5 (d), 130.5 (s), 135.6 (s), 136.9 (d) 145.4 (d), 170.4 (s).

Minor diastereomer

NMR signals from the *exo*/*endo* mixture: ^1H NMR (200 MHz, $CDCl_3$): δ = 1.69–1.71 (m, 6 H), 3.19 (td, *J* = 5.1, 2.8 Hz, 1 H), 5.46 (d, *J* = 5.5 Hz, 1 H, HCO), 5.74 (dd, *J* = 5.5, 2.6 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.5 (q), 20.7 (q), 21.1 (q), 39.0 (d), 44.2 (t), 71.4 (d), 123.4 (d), 129.4 (d), 131.9 (s), 135.6 (d).

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