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Palladium-catalyzed [2+1] cycloadditions affording vinylidenecyclopropanes as precursors of 7-membered carbocycles

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Abstract. Palladium(II) acetate in association with secondary phosphine oxides provides an efficient catalytic system for [2+1] cycloadditions starting from oxanorbornene derivatives and tertiary propargyl esters giving rise to vinylidenecyclopropanes. This reaction is specific to bidentate phosphinito-phosphinous acid ligands generated from secondary phosphine oxides. The [2+1] cycloaddition was found broad in scope with a high tolerance to various functional groups. Moreover, vinylidenecyclopropanes were

straightforwardly converted into oxabicyclo[3.2.1]oct-2-ene derivatives through a palladium-catalyzed ring-expansion. Finally, the oxa bridge cleavage of oxatricyclic compounds allows the obtention of functionalized 7-membered carbocycles.

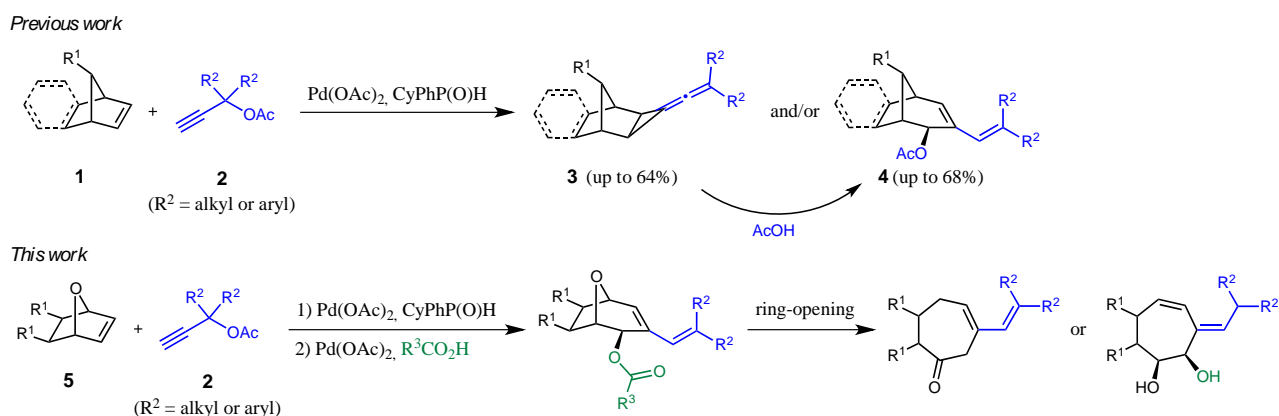
Keywords: Carbocycles; Cycloaddition; Palladium; Vinylidenecyclopropane; Secondary Phosphine Oxide

Introduction

The importance of seven-membered rings as ubiquitous structural subunits in natural products and biologically relevant compounds continues to inspire the development of novel methodologies for their preparation.^[1] However, due to unfavorable entropic and enthalpic factors, the synthesis of these compounds through ring-closure reactions remains challenging.^[2] Among the various synthetic methodologies to prepare cycloheptane derivatives,

cycloaddition routes^[2,3] such as [4+3] or [5+2] cycloadditions with transition-metal catalysts,^[4,5] have appeared to be competitive.

As a part of our research program dedicated to the coordination chemistry of secondary phosphine oxides (SPOs)^[6] with transition metals^[7] and the use of the resulting complexes to develop new synthetic transformations,^[8] we reported in 2008 an intriguing vinylidenecyclopropane formation and a ring-expansion giving rise to functionalized bicyclo[3.2.1]octanes (Scheme 1).^[9] Palladium(II) complexes bearing a phosphinito-phosphinous acid



Scheme 1. Palladium-mediated [2+1] Cycloaddition – ring expansion sequences.

bidentate ligand, generated from SPOs, catalyze [2+1] cycloadditions between strained carbon-carbon double bonds, typically norbornene derivatives **1**, and terminal alkynes to form methylenecyclopropanes.^[8a]

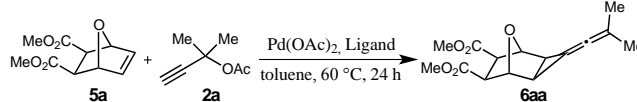
With tertiary propargyl acetates **2**, a further reactivity occurred with the release of acetic acid from the adducts and led to the formation of vinylidenecyclopropanes (VDCPs) **3** in up to 64% yield (Scheme 1).^[10] As by-products, bicyclo[3.2.1]octadienes **4** were also produced and, under more drastic reaction conditions, they could be isolated in good yields (up to 68% yield). Of note, it was demonstrated that VDCPs **3** are intermediates in the synthesis of bicyclo[3.2.1]octadienes **4**. This is a rare example of cleavage of one C-C bond of a bicyclo[4.1.0]heptane unit affording a 7-membered ring,^[11] especially starting from VCDPs.^[12] Moreover, NMR analyses showed that compounds **4** were obtained as a mixture of two diastereomers, with the *exo* acetoxy group for the major diastereomer. In view of the usefulness of functionalized bicyclo[3.2.1]octane skeletons in modern chemistry,^[13] this palladium-mediated [2+1] cycloaddition – ring expansion sequence represents a valuable methodology for their preparation.

Nevertheless, oxa-bridged [3.2.1] bicycles have shown a more significant importance in medicinal chemistry^[14] such as potency towards HIV-1 inhibition and central nervous system diseases. Moreover, the oxa bridge could operate as temporary tether which after an appropriate carbon-oxygen bond cleavage will release the functionalized 7-membered carbocycle (Scheme 1).^[15] Therefore, we decided to study therein, the palladium-catalyzed [2+1] cycloaddition – ring-expansion sequence starting from oxanorbornene derivatives **5**.

Results and Discussion

We started by the examination of the palladium-based catalytic system for the [2+1] cycloaddition using tertiary propargyl acetate **2a** and oxanorbornene **5a** as benchmark substrates. As depicted in Table 1, various ligands or preligands, mainly secondary phosphine oxides were screened and only the VDCP **6aa** was observed without traces of ring-expanded product **11aa** (Table 5). Single-crystal X-ray analysis of **6aa** unambiguously confirmed the atom connectivity (Figure 1). Of note, a slight excess of SPOs related to palladium (2.5:1) was used to ensure the formation of the bidentate phosphinito-phosphinous acid ligands. With symmetrical SPO preligands, we noticed drastic differences as a function of the nature of substituents on the phosphorus atom (entries 1-4). Whereas Ph₂P(O)H gave 60% yield of **6aa**, other symmetrical SPOs led to up to 10% yield. In a general manner, dissymmetrical SPOs provides better results with still a sharp contrast as function the P-substituents (entries 5-9). Moderate sterically hindrances of SPO preligands seem to be a key parameter to reach good

Table 1. Ligand screening for the Pd-catalyzed [2+1] cycloaddition.^[a]



Entry	Ligand	Yield (%)
1	Ph ₂ P(O)H	60
2	<i>t</i> Bu ₂ P(O)H	NP
3	Cy ₂ P(O)H	10
4	Me ₂ P(O)H	NP
5	Ph <i>t</i> BuP(O)H	10
6	PhCyP(O)H	76
7	Ph <i>n</i> BuP(O)H	58
8	Ph <i>n</i> BuP(O)H	32
9	PhMeP(O)H	Complex mixture
10	None	NP
11	PPh ₃	NP
12	P(OPh) ₃	NP
13	Ph ₂ PO ₂ H	NP
14	Ph(OEt)P(O)H	18

^[a]Reaction conditions: **5a** (1 mmol), **2a** (2 mmol), Pd(OAc)₂ (5 mol%), Ligand (12.5 mol%), toluene (5 mL, 0.2M), 60 °C, 24 h. NP = No Product.

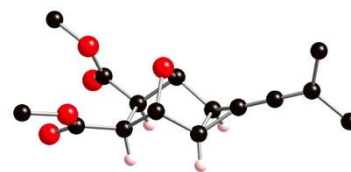
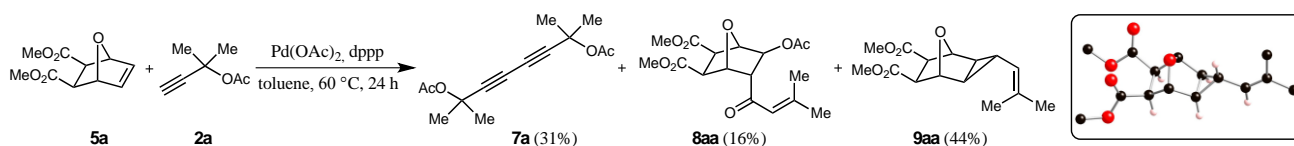


Figure 1. Ball-and-stick representation of compound **6aa** (most of hydrogen atoms have been omitted for clarity).

yields in **6aa** (entries 6 and 7). Importantly, control experiments without ligand or using triphenylphosphine, triphenylphosphite or phosphinic acid highlighted to crucial role plays by SPOs and precisely by bidentate phosphinito-phosphinous acid ligands (entries 10-13).^[16] Only with the ethyl phenylphosphinate, we were able to isolate the expected VDCP **6aa** in low yield; in this case, it is also possible to generate *in situ* a phosphinito-phosphinous acid ligand (entry 14). In order to probe again the specificity of the phosphinito-phosphinous acid ligand, it was attempted to mimic it using the 1,3-bis(diphenylphosphino)propane (Scheme 2). Several products were isolated: the Hay-Glaser coupling product **7a** in 31% yield, the enone **8aa** in small amount and a vinylcyclopropane **9aa** as major product (44%) for which the structure has been confirmed by single-crystal X-ray analysis. No VDCP **6aa** was detected in the crude mixture.

We then surveyed an array of parameters to identify the optimal reaction conditions for the VDCP formation (Table 2). The use of Pd(OTFA)₂ instead of Pd(OAc)₂ led to a severe decrease of the reaction yield (entries 1 and 2). Whereas platinum complexes



Scheme 2. Control experiment using dppp (1,3-bis(diphenylphosphino)propane) as ligand and ball-and-stick representation of compound **9aa** (most of hydrogen atoms have been omitted for clarity).

Table 2. Optimization of the reaction conditions for Pd-mediated [2+1] cycloaddition.^[a]

Entry	Change from “standard conditions”	Yield (%)
1	none	76
2	Pd(OTFA) ₂ instead of Pd(OAc) ₂ Pt(OAc)(PhCyPOHOPhCy)	20
3	instead of Pd(OAc) ₂ /PhCyP(O)H	NP
4	25 °C instead of 60 °C	11
5	40 °C instead of 60 °C	41
6	80 °C instead of 60 °C	NP
7	72 h instead of 24 h	81
8	dioxane instead of toluene	48
9	ClCH ₂ CH ₂ Cl instead of toluene	40
10	MeCN instead of toluene	34
11	DMF instead of toluene	85
12	1.5 equiv. of 2a	51
13	3 equiv. of 2a	81
14	5 equiv. of 2a	Complex mixture

[a] Standard reaction conditions: **5a** (1 mmol), **2a** (2 mmol), Pd(OAc)₂ (5 mol%), PhCyP(O)H (12.5 mol%), toluene (5 mL, 0.2M), 60 °C, 24 h. NP = No Product.

bearing a phosphinito-phosphinous acid ligands are efficient catalysts to promote the [2+1] cycloaddition,^[8b] no VDCP could be detected using oxanorbornenes **5** (entry 3). At room temperature or at 40 °C the VDCP formation occurred slowly and at 80 °C mainly degradation products were observed (entries 4-6). Increasing the reaction time to 3 days improved slightly **6aa** yield (entry 7). The solvents screening revealed that the VDCP formation could be achieved in various solvents, DMF being the most efficient but for practical reasons, toluene was chosen for the rest of our investigations (entries 8-11). Finally, the increase of the alkyne amount to 3 equivalents gave a maximum of 81% yield in VDCP **6aa** (entry 13); with higher quantities of **2a**, a complex mixture was obtained (entry 14).

Having established the optimal reaction conditions, we investigated the scope of the catalytic system with a range of alkynes (Table 3). Leaving groups such as benzoate, pivalate or carbonate could be used and similar yields in VDCP **6aa** were isolated (entries 2-4). However, with methoxy- or hydroxy-substituted alkynes, no reaction occurred (entries 5 and 6).

Table 3. Pd-mediated vinylidene cyclopropane formation with various alkynes **2**.^[a]

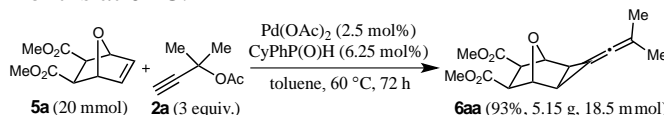
Entry	Alkyne	Product	Yield (%)
1	2a	6aa	81
2	2b	6aa	85
3	2c	6aa	74
4	2d	6aa	84
5	2e		NP
6	2f		NP
7	2g	6ag	82
8	2h	6ah	92
9	2i	6ai	42
10	2j	6aj	68 ^[b]
11	2k	6ak	74 ^[c]
12	2l	10al	88 ^[d]
13	2m	10am	65

[a] Standard reaction conditions: **5a** (1 mmol), **2** (3 mmol), Pd(OAc)₂ (5 mol%), PhCyP(O)H (12.5 mol%), toluene (5 mL, 0.2M), 60 °C, 24 h. [b] dr = 1:1.0. [c] dr = 1:1.5. [d] dr = 1:1.3. NP = No Product.

Various tertiary propargyl acetates are also competent (entries 7-11) and the best yield was reached with alkyne **2h** (92%, entry 8). Of note, VDCPs **6aj** and **6ak** were isolated as an inseparable mixture of diastereomers with a ratio close to 1:1. With secondary and primary propargyl acetates, only methylenecyclopropanes (MCP) **10** were isolated (entries 12 and 13). For MCP **10al**, a 1:1.3 mixture of diastereomers was observed due to the geometrical enantiomeric isomerism (*cis-trans* enantiomerism or *Z-E* enantiomerism).^[17,18]

A wide range of 7-oxanorbornenes **5** were then tested in order to determine the limits of catalytic system (Table 4). The VDCP formation was found compatible with various functional groups such as esters (entry 1), carbonate (entry 2), ethers (entries 4 and 5), silyl ether (entry 6) or even free hydroxyl groups, independently of the *endo/exo* position of the oxanorbornene substituents (entries 7 and 8). One of the limitations is the competitive retro Diels-Alder reaction of **5d** which is faster than the [2+1] cycloaddition (entry 3). This trend was also observed with bis-sulfone **5j** giving rise to VDCP **6ja** in only 23% yield along with the retro D-A product (ca 45%, entry 9). In this run, dichloroethane was used due to the poor solubility of **6j** in toluene. Similar solubility issues were also encountered with imide derivative **5n** (entries 13 and 14). Otherwise, N-containing functional groups such as nitrile (entry 10), carbamate (entry 11) or tertiary amine (entry 12) are well tolerated and in a general manner high yields have been obtained.

To fully demonstrate the usefulness on preparative scale, a reaction was performed on 20-mmol scale. As shown in Scheme 3, using 2.5 mol% of palladium, it was possible to get up to 5 g (93 %) of VDCP **6aa** after 3 days at 60 °C. Importantly, VDCPs were found perfectly stable and could be stored for few months at 0 °C.



Scheme 3. Multi-gram scale vinylidenecyclopropane synthesis.

The oxabicyclo[3.2.1]oct-2-ene formation from VDCP through a ring-expansion was then examined (Table 5). The treatment of the VDCP **6aa** with one equivalent of acetic acid in presence of 5 mol% of Pd(OAc)₂ gave 84% of the expected product **11aa** (entry 1).^[19] Importantly, under these reaction conditions only the *exo* diastereomer was observed. Its structure was unambiguously determined by single-crystal X-ray analysis (Figure 2). The concentration and the temperature were found to be key parameters to achieve the transformation with high yields (entries 2-4). It was possible to obtain **11aa** without Pd(OAc)₂, but this required 5 equiv. of AcOH to isolate a satisfactory yield (entries 5 and 6). Of note, the well-defined palladium complex bearing the phosphinito-phosphinous acid ligand gave

product **11aa**, but only in low yield (entry 7). The examination of reaction media showed that various solvents could be used; the best yields were reached with toluene and dichloroethane (entries 8-11).

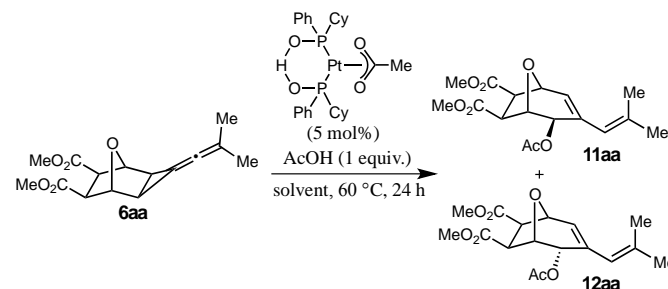
Table 5. Optimization of the reaction condition for the ring-expansion.^[a]

Entry	Change from “standard conditions”	Yield (%)
1	None	84
2	0.2 M instead of 1M	43
3	20 °C instead of 60 °C	31
4	40 °C instead of 60 °C	55
5	No Pd(OAc) ₂	12
6	No Pd(OAc) ₂ , 5 equiv. AcOH	69
7	Pd(OAc)(PhCyPOHOPPhCy) (5 mol%), instead of Pd(OAc) ₂	27
8	dioxane instead of toluene	53
9	ClCH ₂ CH ₂ Cl instead of toluene	78
10	MeCN instead of toluene	54 ^[b]
11	DMF instead of toluene	47

[a] Standard reaction conditions: **6aa** (0.5 mmol), AcOH (0.5 mmol), Pd(OAc)₂ (5 mol%), toluene (0.5 mL, 1 M), 60 °C, 24 h. [b] *exo/endo* = 3.5:1.

Surprisingly, the platinum-based counterpart of phosphinito-phosphinous acid palladium complex was efficient to promote the formation oxabicyclo[3.2.1]oct-2-ene **11**, unfortunately as a mixture of *exo* and *endo* diastereomers, respectively **11aa** and **12aa**. The nature of the solvent influenced *exo/endo* ratios but not enough to reach a good diastereoselectivity (Table 6).

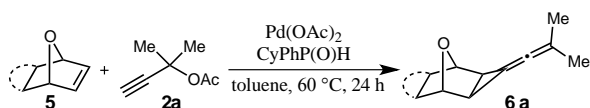
Table 6. Optimization of the reaction condition for the ring-expansion.^[a]



Entry	Solvent	Yield (%)	11aa/12aa
1	toluene	84	0.7:1
2	dioxane	75	0.7:1
3	ClCH ₂ CH ₂ Cl	84	1.0:1
4	MeCN	58	1.4:1
5	DMF	31	>20:1

[a] Standard reaction conditions: **6aa** (0.5 mmol), AcOH (0.5 mmol), Pt(OAc)(PhCyPOHOPPhCy) (5 mol%), solvent (2.5 mL, 0.2 M), 60 °C, 24 h. NP = No Product.

Table 4. Pd-catalyzed [2+1] cycloaddition with various oxanorbornenes.^[a]



Entry	Oxanorbornene	Product	Yield (%)
1			80
2			77
3			NP
4			89
5			87
6			90
7			91
8			76
9			23 ^[b]
10			72
11			95
12			96
13			58
14			77 ^[b]
15			NP

[a] Standard reaction conditions: **5a** (1 mmol), **2** (3 mmol), Pd(OAc)₂ (5 mol%), PhCyP(O)H (12.5 mol%), toluene (5 mL, 0.2M), 60 °C, 24 h. [b] dr = 1:1.0. [c] dr = 1:1.5. [d] dr = 1:1.3. NP = No Product.

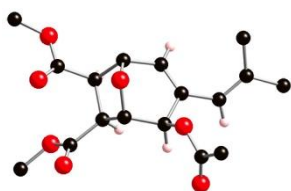
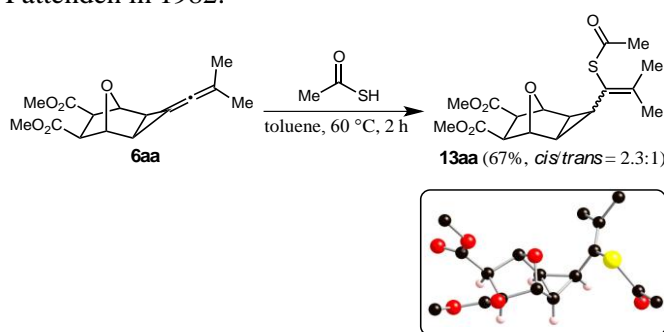


Figure 2. Ball-and-stick representation of compound **11aa** (most of hydrogen atoms have been omitted for clarity).

The scope examination of the Pd-mediated ring-expansion of VDCP disclosed a good tolerance to various carboxylic acids (Table 7). A wide range of oxabicyclo[3.2.1]oct-2-enes were prepared with low to good yields as a function of the nature of the carboxylic acid. Sterically hindered or strong acids such as pivalic acid or trifluoroacetic acid led to low yields (entries 3 and 4). With glycine, a protection of the amine function was necessary to form the corresponding oxabicyclo[3.2.1]oct-2-ene compound (entries 7 and 8). Otherwise, the ring-expansion is compatible with functional groups such as halide, ether, C-C double bonds as well as heterocycles or phenol derivatives. The unique case where the *endodiastereomer* was detected was with cinnamic acid yet in minute amounts (entry 10).

Compared to carboxylic acids, thioacetic acid exhibited a totally different reactivity with the formation of the vinylthioester **13aa** as a 2.3:1 mixture of diastereomers (Scheme 4). Interestingly, no catalyst was required and the consumption of VDCP **6aa** was much faster. The structure of **13aa** determined by single-crystal X-ray analysis confirmed the addition of thioacetic acid on the diagonal carbon atom of the allene moiety. This transformation proceeds probably according to a radical process and is related to the thiophenol addition to VDCPs described by Crombie and Pattenden in 1982.^[20]



Scheme 4. Reaction of VDCP with thioacetic acid and ball-and-stick representation of compound **13aa** (most of hydrogen atoms have been omitted for clarity).

To further examine the scope of the palladium-catalyzed ring-expansion, several functionalized VDCPs **6** were tested with acetic acid (Table 8). As good to almost quantitative yields were obtained with carbonate-, ether-, silyl ether-, nitrile or carbamate-substituted VDCPs, we believe this transformation

does not present issues of functional groups compatibility.

Finally, we tackled the oxa bridge opening. Whereas numerous methods are described for ring-opening reactions of [2.2.1] oxabicycles,^[21] for [3.2.1] oxabicycles the ring-opening is much more challenging.^[15,22] Following Föhlsch^[22d] and Mascareñas^[22g,j] procedure, we treated ester **11ea** with sodium naphthalenide in THF at room temperature and mainly reduction into alcohol **14ea**

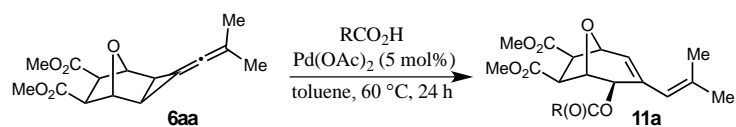
Table 8. Scope of the Pd-mediated ring-expansion with various VDCPs.^[a]

Entry	Product	Yield (%)
1		59
2		70
3		68
4		84
5		96
6		72
7		66
8		71

[a] Standard reaction conditions: **6aa** (0.5 mmol), AcOH (0.5 mmol), Pd(OAc)₂ (5 mol%), toluene (0.5 mL, 1 M), 60 °C, 24 h. [b] *exo/endo* = 3.5:1.

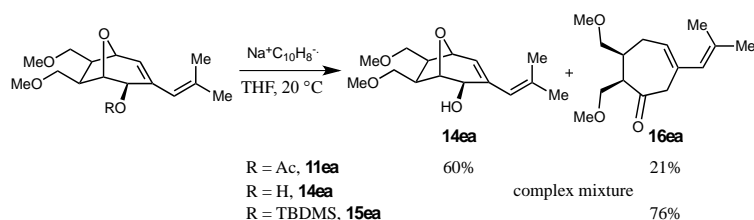
was observed (Scheme 5). However, as a by-product, ketone **16ea** was isolated in 21% yield. A control experiment showed that alcohol **14ea** is not an intermediate for the ketone formation. With silyl ether **15ea**, the sodium naphthalenide-mediated reductive cleavage of the oxa bridge gave a satisfactory yield of 76% in ketone **16ea**.

Table 7. Pd-mediated ring-expansion with various carboxylic acid.^[a]



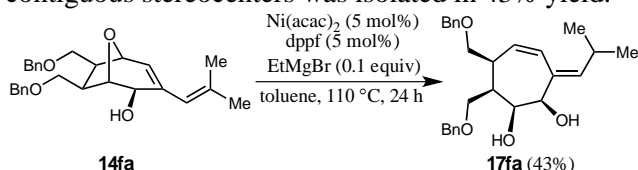
Entry	Carboxylic acid	Product	Yield (%)
1	AcOH		84
2	PhCO ₂ H		56
3	PivOH		22
4	CF ₃ CO ₂ H		37
5			64
6			58
7			NP
8			36
9			42
10			66 ^[b]
11			68
12			71

[a] Standard reaction conditions: **6aa** (0.5 mmol), RCO₂H (0.5 mmol), Pd(OAc)₂ (5 mol%), toluene (0.5 mL, 1 M), 60 °C, 24 h. [b] *exo/endo* = 9:1. NP = No Product.



Scheme 5. Reductive cleavage of the oxa bridge.

Moreover, as depicted in Scheme 6, *in situ* generated nickel hydride from Ni(acac)₂ and magnesium ethyl bromide, were efficient to ring-open the oxa bridge with concomitant isomerization of the dienic system. To our delight, diol **17fa** containing 4 contiguous stereocenters was isolated in 43% yield.



Scheme 6. Nickel-hydride mediated reductive cleavage of the oxa bridge.

Conclusion

In summary, we developed a new strategy giving access to highly functionalized 7-carbocycles using palladium-mediated catalyses and simple raw substrates. First a [2+1] cycloaddition between oxanorbornenes and tertiary propargyl esters or carbonates mediated by a phosphinito-phosphinous acid palladium complex afforded VDCPs **6** with high yields. It was demonstrated that this transformation is specific to the phosphinito-phosphinous acid ligand and is compatible with numerous functional groups. Then, we achieved a diastereoselective palladium-catalyzed ring-expansion with various carboxylic acids giving rise to [3.2.1] oxabicycles **11**. Finally, the oxa bridge was cleaved either under reductive conditions or by nickel hydride species to afford 7-membered carbocycles. Further studies on the reactivity of VDCPs and more precisely mechanistic investigations on palladium-mediated ring-expansion are currently undergoing in our laboratory.

Experimental Section

General considerations. Unless otherwise stated, all reactions were carried out in an atmosphere of dry nitrogen or argon using oven-dried (120 °C) glasswares. All reagents were obtained from commercial sources and used as received. SPO preligands were obtained from a chemical supplier or by following literature procedures.^[7a] Solvents (THF, DCM, Et₂O and toluene) were purified and dried over Braun solvent purification system (MB-SPS-800). Analytical Thin Layer Chromatography (TLC) was carried out on Merck silica gel60 F₂₅₄. Products were revealed by ultraviolet light (254 or 366 nm) and stained with dyeing reagents solutions such as 5% phosphomolybdic acid solution, potassium permanganate

solution or *p*-anisaldehyde solution in ethanol followed by gentle heating. Flash chromatography purifications were performed on Combiflash® Companion or with Merck silica gel 60 (230-400 mesh). ¹H, ¹³C and ³¹P NMR spectra were recorded in CDCl₃ at ambient temperature on Bruker Avance III 300 or 400 spectrometers operating at 300 and 400 MHz respectively for ¹H. Solvent residual signals were used as internal standard.^[23]

Chemical shifts (δ) and coupling constants (*J*) are given in ppm and Hz respectively. The peaks patterns are indicated as the following format multiplicity (s: singlet; d: doublet; t: triplet; q: quartet; sept: septuplet; m: multiplet; dd: doublet of doublet; dt: doublet of triplet; etc.). The prefix br. indicates a broadened signal. HRMS were recorded on SYNAPT G2 HDMS (Waters) or on QStar Elite (Applied Biosystems SGIEX) equipped with an Atmospheric Pressure Ionization (API) source. Mass spectra were obtained a Time Of Flight (TOF) analyser. Intensity data were collected on a Bruker-Nonius KappaCCD diffractometer using graphite monochromated MoKα radiation (0.71073 Å) at 293(2) K. The collected frames were processed with the software HKL-2000, structures were resolved by the direct methods and refined using the SHELXL-97 software package.^[24] The CIF files of compounds **6aa**, **9aa**, **11aa** and **13aa** have also been deposited with the CCDC as, respectively, No. CCDC 1414754 – 1414757.

General procedure A: palladium-catalyzed [2+1] cycloaddition – formation of vinylidenecyclopropane **6**. In a 5 mL flame-dried Schlenk, Pd(OAc)₂ (11.2mg, 0.05 mmol, 5 mol %) and CyPhP(O)H (26.0 mg, 0.125 mmol, 12.5 mol %) were introduced under argon and dissolved in dry and degassed toluene (2 mL). The resulting orange solution was stirred at 60 °C during 30 min until the orange color disappears. Then, oxanorbornene **5** (1 mmol, 1 equiv.), alkyne **2** (3 mmol, 3 equiv.) and 3 mL of dry and degassed toluene were added. The resulting mixture was stirred at 60 °C for 24 h. Then, volatiles were removed under reduced pressure. The crude mixture was purified by flash chromatography on silica gel to obtain the desired product **6**.

General procedure B: palladium-catalyzed ring expansion giving rise to oxabicyclo[3.2.1]oct-2-ene **11**. In a 5 mL flame-dried Schlenk, were introduced in turn under argon, Pd(OAc)₂ (5.6mg, 0.025 mmol, 5 mol%), vinylidenecyclopropane (0.5 mmol), carboxylic acid (0.5 mmol, 1 equiv.) and dry toluene (0.5 mL). The resulting orange solution was stirred at 60 °C for 24 h. Then, volatiles were removed under reduced pressure. The crude mixture was purified by flash chromatography on silica gel to obtain the desired product **11**.

(±)-6,7-bis(methoxymethyl)-3-(2-methylprop-1-en-1-yl)cyclohept-3-enone **16ea**. To a solution of compound **15ea** (125 mg, 0.47 mmol) in dry THF (5 mL), sodium naphthalenide (prepared by stirring overnight at RT naphthalene (640 mg) and sodium (230 mg) in dry THF (10 mL)), was added until the green color persisted. Then, the reaction mixture was stirred 15 min at rt and quenched with a saturated solution of NaHCO₃. The product was extracted with DCM and the organic phase was washed with brine, dried over MgSO₄, and concentrated to dryness. The product was purified by column chromatography on silica gel to afford **16ea** as a colorless oil (88 mg, 76% yield). ¹H NMR (400 MHz, CDCl₃): δ = 5.59 (t, *J*(H,H) = 6.8 Hz, 1H, C=CH-CH₂), 5.53 (s, 1H, CH=C(CH₃)₂), 3.64 (dd, *J*(H,H) = 9.5 and 7.8 Hz, 1H, CH₂-OMe), 3.34 (dd, *J*(H,H) = 9.5 and 5.8 Hz, 1H, CH₂-OMe), 3.27 (s, 3H, CH₃-O), 3.20 (s, 3H, CH₃-O), 3.19-3.16 (m, 3H, CH₂-OMe and CH₂-CO), 3.06 (dd, *J*(H,H) = 9.4 and 7.6 Hz, 1H, CH-CO), 3.00 (d, *J*(H,H) = 16.1 Hz, 1H, CH₂-CO), 2.49-2.41 (m, 1H, CH-CH-CO), 2.35-2.28 (m, 1H, CH₂-CH=C), 2.21-2.13 (m, 1H, CH₂-CH=C), 1.67 (d, *J*(H,H) = 1.4 Hz, 3H, C-CH₃), 1.66 (d, *J*(H,H) = 1.4 Hz, 3H, C-CH₃). ¹³C NMR (100 MHz, CDCl₃): δ = 208.3 (CO), 134.3 (C), 134.1 (C), 126.83

(CH), 126.80 (CH), 72.9 (CH₂), 70.0 (CH₂), 58.9 (CH₃), 58.8 (CH₃), 53.5 (CH), 48.8 (CH₂), 38.6 (CH), 29.2 (CH₂), 26.5 (CH₃), 19.5 (CH₃).HRMS (ESI): *m/z*: calcd for C₁₅H₂₄NaO₃; 275.1618[M+Na]⁺; found 275.1616.

(±)-(1*S*,2*R*,6*S*,7*R*,*E*)-6,7-bis((benzyloxy)methyl)-3-(2-methylpropylidene)cyclohept-4-ene-1,2-diol **17fa**. To a solution of Ni(acac)₂ (6.5 mg, 0.025 mmol, 5 mol%) and dppf (13.6 mg, 0.025 mmol, 5 mol%) in toluene 10 mL, EtMgBr 1M in THF (50 μL, 0.05 mmol, 0.1 equiv.) was added at RT. After 30 min, alcohol **14fa** (210 mg, 0.5 mmol) was added and the reaction mixture was stirred 16h at 110 °C. The reaction was quenched with a saturated solution of NaHCO₃. The product was extracted with Et₂O and the organic phase was washed with brine, dried over MgSO₄, and concentrated to dryness. The product was purified by column chromatography on silica gel to afford **17fa** as a yellow oil. (90 mg, 43%). ¹H NMR (400 MHz, CDCl₃): δ = 7.28-7.18 (m, 10H, H^{Ar}), 6.17 (dt, *J*(H,H) = 11.7 and 2.0 Hz, 1H, CH=CH-C=CH), 5.44 (dd, *J*(H,H) = 11.7 and 1.1 Hz, 1H, CH=CH-C=CH), 5.38 (d, *J*(H,H) = 9.6 Hz, 1H, C=CH), 4.43 (d, *J*(H,H) = 4.4 Hz, 2H, CH₂-Ph), 4.36 (d, *J*(H,H) = 7.7 Hz, 2H, CH₂-Ph), 4.15 (dd, *J*(H,H) = 8.1 and 3.7 Hz, 1H, CH=C-CH-OH), 3.96-3.92 (m, 1H, CH=C-CH(OH)-CH-OH), 3.73 (d, *J*(H,H) = 7.7 Hz, 1H, CH-OH), 3.68 (dd, *J*(H,H) = 9.6 and 7.4 Hz, 1H, CH₂-OBn), 3.50-3.44 (m, 1H, CH₂-OBn), 3.39 (dd, *J*(H,H) = 9.4 and 6.7 Hz, 1H, CH₂-OBn), 3.19 (d, *J*(H,H) = 8.3 Hz, 1H, CH-OH), 2.69-2.65 (m, 1H, CH-CH₂-OBn), 2.52-2.44 (m, 2H, CH-CH₂-OBn and CH(CH₃)₂), 0.88 (dd, *J*(H,H) = 6.7 and 1.2 Hz, 6H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ = 138.6 (CH), 137.7 (C), 137.6 (C), 133.5 (C), 130.6 (CH), 128.48 (CH), 128.46 (CH), 127.85 (CH), 127.81 (CH), 127.79 (CH), 127.73 (CH), 127.70 (CH), 127.0 (CH), 76.7 (CH), 75.1 (CH), 73.4 (CH₂), 73.3 (CH₂), 70.9 (CH₂), 69.3 (CH₂), 41.4 (CH), 38.9 (CH), 27.3 (CH), 22.8 (CH₃), 22.6 (CH₃).HRMS (ESI): *m/z*: calcd for C₂₇H₃₄NaO₄; 445.2349[M+Na]⁺; found 445.2352.

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Palladium-catalyzed [2+1] cycloadditions affording vinylidenecyclopropanes as precursors of 7-membered carbocycles

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