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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 yields functionalized 7-membered carbocycles.

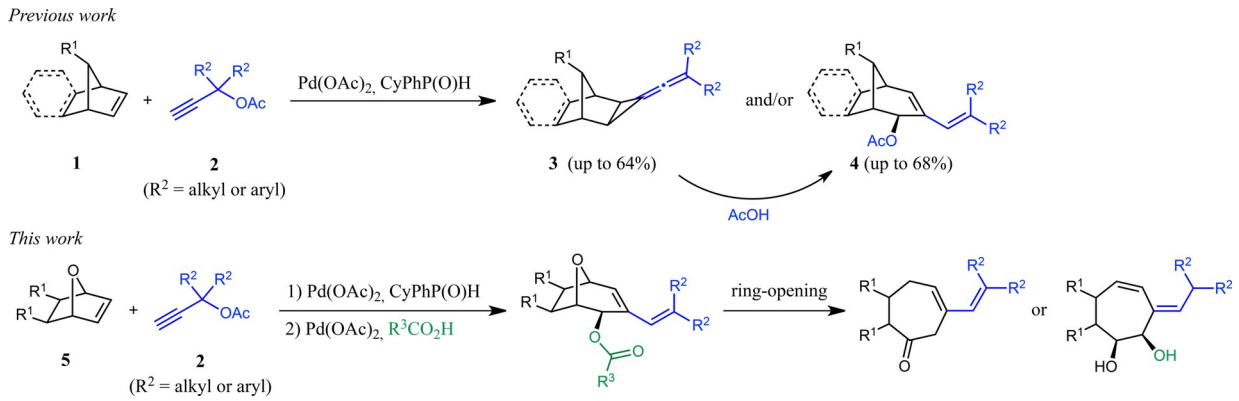
Keywords: carbocycles; cycloaddition; palladium; secondary phosphine oxide; vinylidenecyclopropane

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.

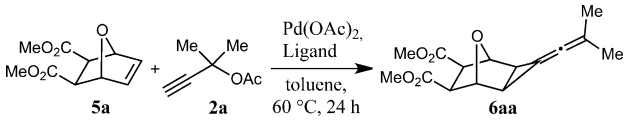
As a part of our research program dedicated to the coordination chemistry of secondary phosphine oxides (SPOs)[6] with transition metals[7] and the use of the resulting complexes to develop new synthetic transformations,[8] we reported in 2008 an intriguing vinylidenecyclopropane formation and a ring-expansion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



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

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



Entry	Ligand	Yield (%)
1	$Ph_2P(O)H$	60
2	$tBu_2P(O)H$	NP
3	$Cy_2P(O)H$	10
4	$Me_2P(O)H$	NP
5	Ph*t*BuP(O)H	10
6	PhCyP(O)H	76
7	PhBnP(O)H	58
8	Ph*n*BuP(O)H	32
9	PhMeP(O)H	Complex mixture
10	None	NP
11	PPh_3	NP
12	$P(OPh)_3$	NP
13	Ph_2PO_2H	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, 0.2 M), 60 °C, 24 h. NP = No Product.

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 oxanorbonene 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 $Ph_2P(O)H$ 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 sterical hindrances of SPO preligands seem to be a key parameter to reach good yields in **6aa** (entries 6 and 7). Importantly, control experiments without ligand or using triphenylphosphine, triphenylphosphite or phosphinic acid highlighted the crucial role played 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, an attempt was made to mimic it using the 1,3-bis(diphe-

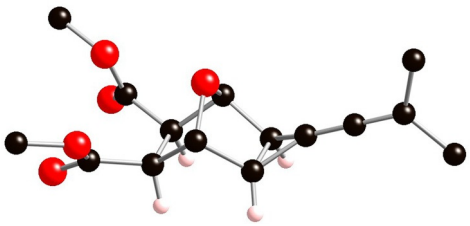
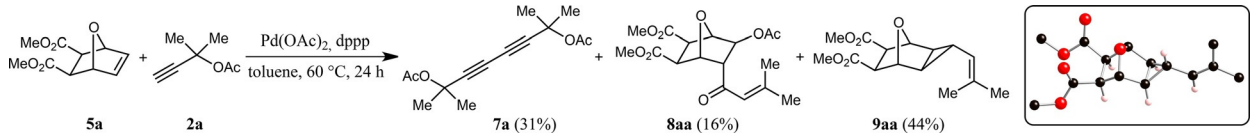
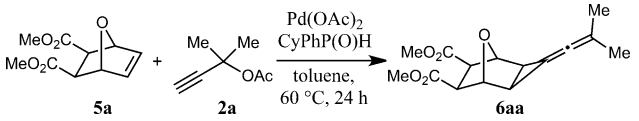


Figure 1. Ball-and-stick representation of compound **6aa** (most of the hydrogen atoms have been omitted for clarity).



Scheme 2. Control experiment using dppp (1,3-bis(diphenylphosphino)propane) as ligand and ball-and-stick representation of compound **9aa** (most of the 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 $Pd(OAc)_2$	20
3	Pt(OAc)(PhCyPOHOPPhCy) 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	$ClCH_2CH_2Cl$ 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, 0.2 M), 60 °C, 24 h. NP = No Product.

nylphosphino)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.

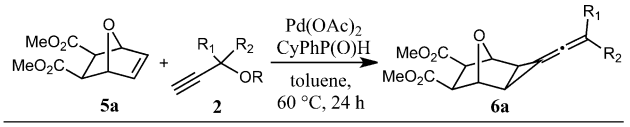
We then surveyed an array of parameters to identify the optimal reaction conditions for the VDCP formation (Table 2). The use of $Pd(OTFA)_2$ instead of $Pd(OAc)_2$ led to a severe decrease of the reaction yield (entries 1 and 2). Whereas platinum complexes bearing a phosphinito–phosphinous acid ligands 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).

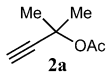
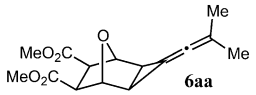
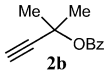
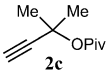
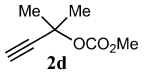
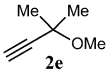
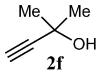
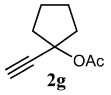
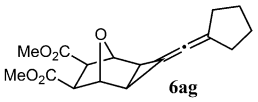
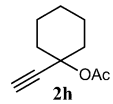
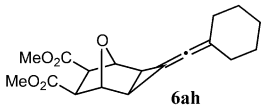
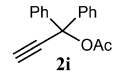
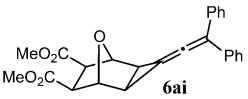
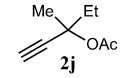
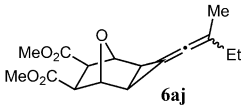
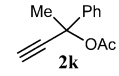
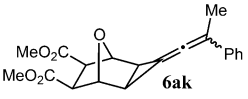
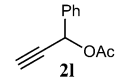
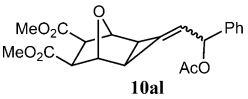
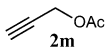
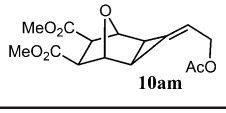
Having established the optimal reaction conditions, we investigated the scope of the catalytic system with a range of alkynes (Table 3). Leaving groups such as benzoate, pivalate or carbonate could be used and similar yields in VDCP **6aa** were isolated (entries 2–4). However, with methoxy- or hydroxy-substituted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

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 enantiomorphic 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 **5j** 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.

Table 3. Pd-mediated vinylidenecyclopropane formation with various alkynes **2**.[a]



Entry	Alkyne	Product	Yield (%)
1	 **2a**	 **6aa**	81
2	 **2b**		85
3	 **2c**		74
4	 **2d**		84
5	 **2e**		NP
6	 **2f**		NP
7	 **2g**	 **6ag**	82
8	 **2h**	 **6ah**	92
9	 **2i**	 **6ai**	44
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, 0.2 M), 60 °C, 24 h. NP = No Product.
[b] dr = 1:1.0. [c] dr = 1:1.5. [d] dr = 1:1.3.

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 a few months at 0 °C.

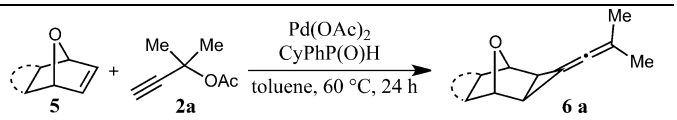
The oxabicyclo[3.2.1]oct-2-ene formation from VDCP through a ring-expansion was then examined (Table 5). The treatment of the VDCP **6aa** with one equivalent of acetic acid in presence of 5 mol% of $Pd(OAc)_2$ gave 84% of the expected product **11aa** (entry 1).[19] Importantly, under these reaction 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 1 and 8–11).

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 (entry 10, Table 6).

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 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 *endo* diastereomer 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

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



5 2a 6 a

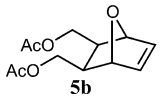
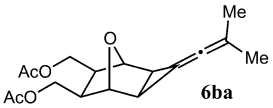
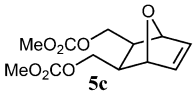
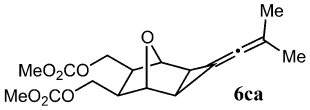
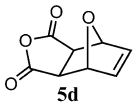
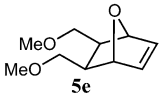
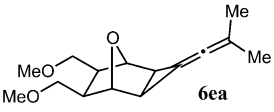
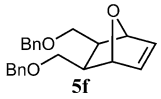
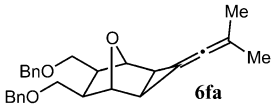
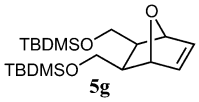
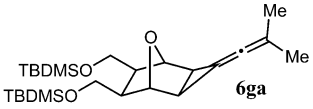
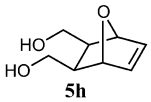
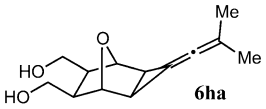
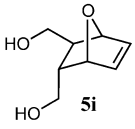
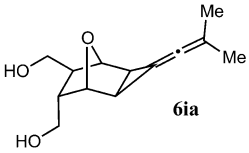
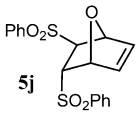
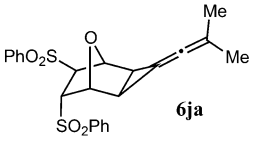
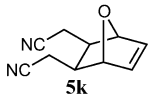
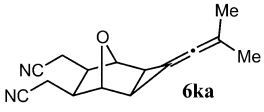
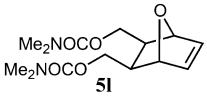
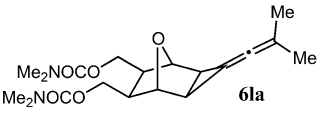
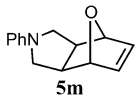
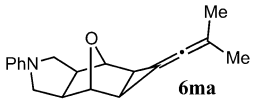
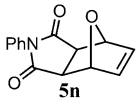
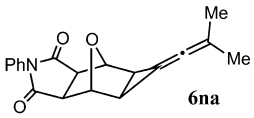
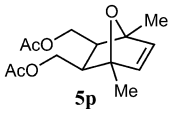
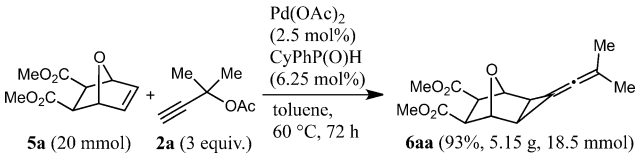
Entry	Oxanorbornene	Product	Yield (%)
1	 5b	 6ba	80
2	 5c	 6ca	77
3	 5d		NP
4	 5e	 6ea	89
5	 5f	 6fa	87
6	 5g	 6ga	90
7	 5h	 6ha	91
8	 5i	 6ia	76
9	 5j	 6ja	23[b]
10	 5k	 6ka	72
11	 5l	 6la	95

Table 4. (Continued)

Entry	Oxanorbornene	Product	Yield (%)
12	 **5m**	 **6ma**	96
13	 **5n**	 **6na**	58
14			77[b]
15	 **5p**		NP

[a] Standard reaction conditions: **5** (1 mmol), **2a** (3 mmol), $Pd(OAc)_2$ (5 mol%), PhCyP(O)H (12.5 mol%), toluene (5 mL, 0.2 M), 60 °C, 24 h. NP = No Product.
[b] Dichloroethane as solvent.



Scheme 3. Multi-gram scale vinylidenecyclopropane synthesis.

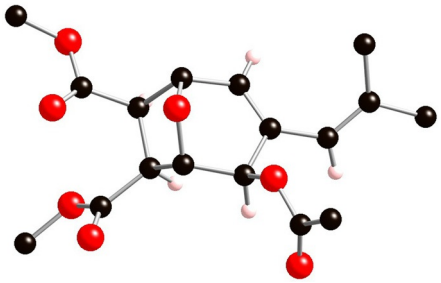
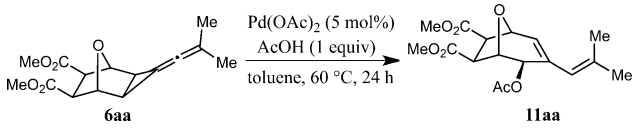


Figure 2. Ball-and-stick representation of compound **11aa** (most of the hydrogen atoms have been omitted for clarity).

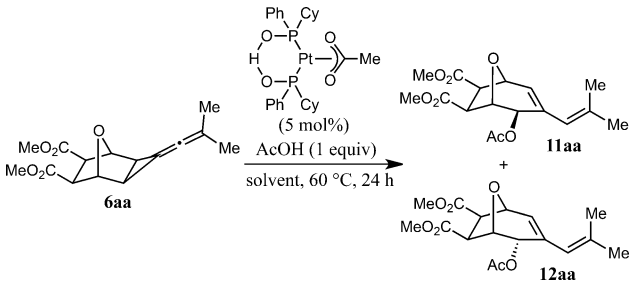
Table 5. Optimization of the reaction condition for the ring-expansion.[a]



Entry	Change from "standard conditions"	Yield (%)
1	None	84
2	0.2 M instead of 1 M	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	$ClCH_2CH_2Cl$ 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.

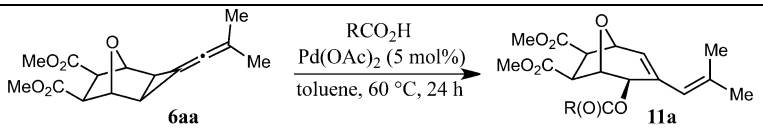
Table 6. Optimization of the reaction condition for the ring-expansion.[a]



Entry	Solvent	Yield (%)	**11aa/12aa**
1	toluene	84	0.7:1
2	dioxane	75	0.7:1
3	$ClCH_2CH_2Cl$	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.

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



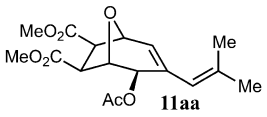
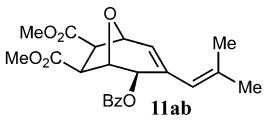
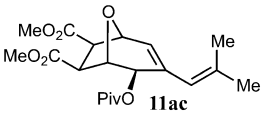
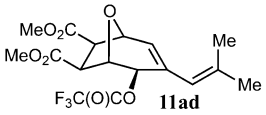
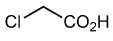
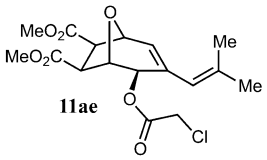
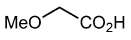
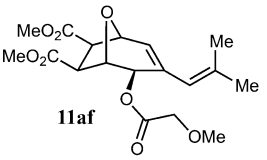
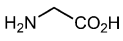
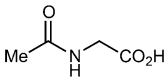
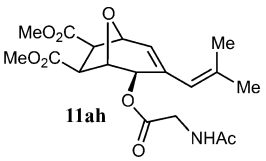
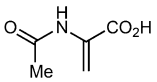
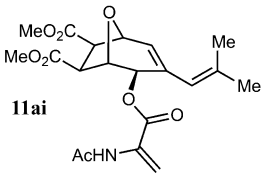
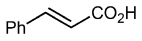
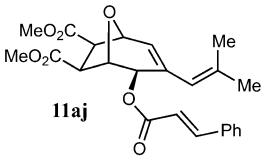
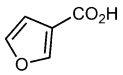
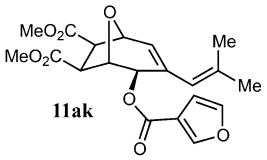
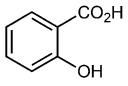
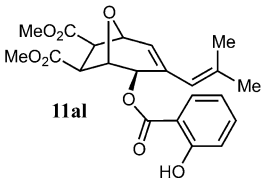
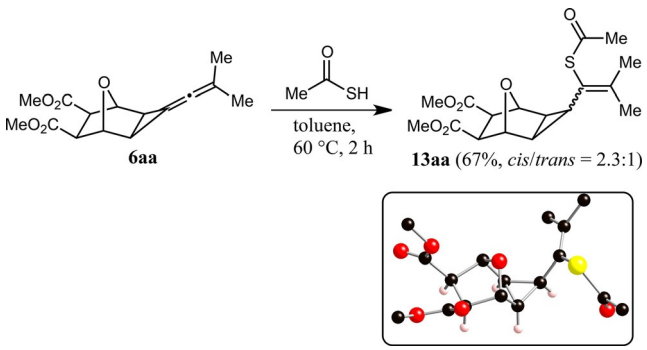
Entry	Carboxylic Acid	Product	Yield (%)
1	AcOH		84
2	$PhCO_2H$		56
3	PivOH		22
4	CF_3CO_2H		37
5			64
6			58
7			NP
8			36
9			42

Table 7. (Continued)

Entry	Carboxylic Acid	Product	Yield (%)
10		 **11aj**	66[b]
11		 **11ak**	68
12		 **11al**	71

[a] Standard reaction conditions: **6aa** (0.5 mmol), RCO_2H (0.5 mmol), $Pd(OAc)_2$ (5 mol%), toluene (0.5 mL, 1 M), 60 °C, 24 h. NP = No Product.
[b] *exo*/*endo* = 9:1.



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

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]

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.

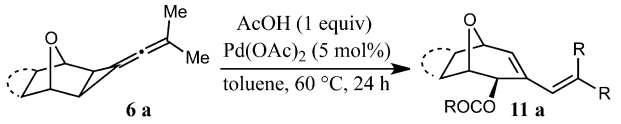
Finally, we tackled the oxa bridge opening. Whereas numerous methods are described for ring-opening reactions of [2.2.1] oxabicycles,[21] for [3.2.1] oxabicycles the ring-opening is much more challenging.[15,22] Following Föhlisch[22d] and Mascareñas[22g,j] procedure, we treated ester **11ea** with sodium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

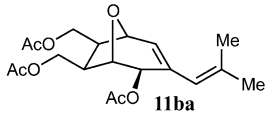
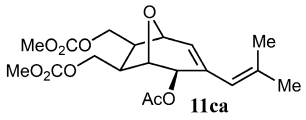
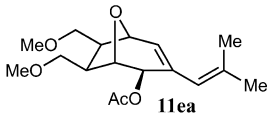
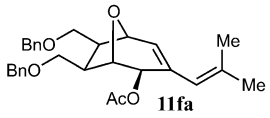
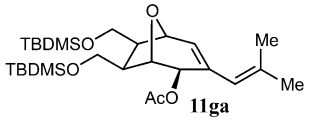
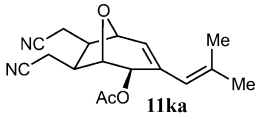
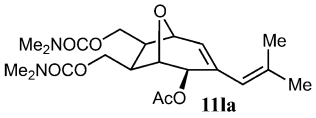
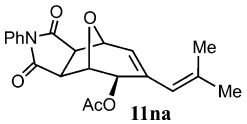
Moreover, as depicted in Scheme 6, in situ generated nickel hydride from $Ni(acac)_2$ and magnesium ethyl bromide, was efficient to ring-open the oxa bridge with concomitant isomerization of the dienic system. To our delight, diol **17fa** containing 4 contiguous stereocenters was isolated in 43% yield.

Conclusions

In summary, we developed a new strategy giving access to highly functionalized 7-carbocycles using palladium-mediated catalysis and simple raw substrates. First a [2+1] cycloaddition between oxanorbornenes and tertiary propargyl esters or carbonates

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



Entry	Product	Yield (%)
1	 11ba	59
2	 11ca	70
3	 11ea	68
4	 11fa	84
5	 11ga	96
6	 11ka	72
7	 11la	66
8	 11na	71

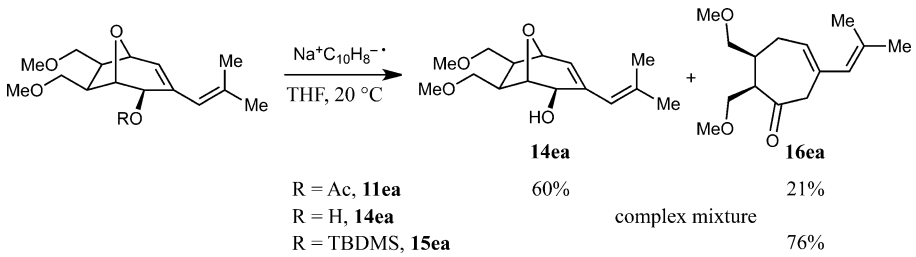
[a] Standard reaction conditions: **6aa** (0.5 mmol), AcOH (0.5 mmol), $Pd(OAc)_2$ (5 mol%), toluene (0.5 mL, 1 M), 60 °C, 24 h.

[b] *exo*/*endo* = 3.5:1.

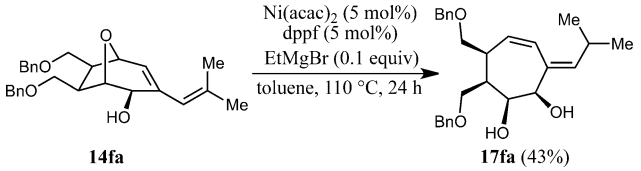
mediated by a phosphinito–phosphinous acid palladium complex afforded VDCPs **6** with high yields. It was demonstrated that this transformation is specific to the phosphinito–phosphinous acid ligand and is compatible with numerous functional groups. Then, we achieved a diastereoselective palladium-catalyzed 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) glassware. 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, Et_2O and toluene) were purified and dried with a Braun solvent purification system (MB-SPS-800). Analytical Thin Layer Chromatography (TLC) was carried out on Merck silica gel 60 F_{254}. 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, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ 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 monochormated 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] CCDC-1414754, -1414755, -1414756, and -1414757 contain the supplementary crystallographic data for compounds **6aa**, **9aa**, **11aa**, and **13aa**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.



Scheme 5. Reductive cleavage of the oxa bridge.



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

General procedure A: Palladium-catalyzed [2+1] Cycloaddition – Formation of Vinylidenecyclopropane 6.

In a 5 mL flame-dried Schlenk tube, $Pd(OAc)_2$ (11.2 mg, 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 tube, were introduced in turn under argon, $Pd(OAc)_2$ (5.6 mg, 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 $NaHCO_3$. The product was extracted with DCM and the organic phase was washed with brine, dried over $MgSO_4$, 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). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.59$ (t, J(H,H) = 6.8 Hz, 1H, C=C*H*-CH_2), 5.53 (s, 1H, C*H*=C$(CH_3)_2$), 3.64 (dd, J(H,H) = 9.5 and 7.8 Hz, 1H, CH_2-OMe), 3.34 (dd, J(H,H) = 9.5 and 5.8 Hz, 1H, CH_2-OMe), 3.27 (s, 3H, CH_3-O), 3.20 (s, 3H, CH_3-O), 3.19–3.16 (m, 3H, CH_2-OMe and CH_2-CO), 3.06 (dd, J(H,H) = 9.4 and 7.6 Hz, 1H, C*H*-CO), 3.00 (d, J(H,H) = 16.1 Hz, 1H, CH_2-CO), 2.49–2.41 (m, 1H, C*H*-CH-CO), 2.35–2.28 (m, 1H, CH_2-CH=C), 2.21–2.13 (m, 1H, CH_2-CH=C), 1.67 (d, J(H,H) = 1.4 Hz, 3H, C-CH_3), 1.66 (d, J(H,H) = 1.4 Hz, 3H, C-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.3$ (*C*O), 134.3 (*C*), 134.1 (*C*), 126.83 (*C*H), 126.80 (*C*H), 72.9 (*C*H_2), 70.0 (*C*H_2), 58.9 (*C*H_3), 58.8 (*C*H_3), 53.5 (*C*H), 48.8 (*C*H_2), 38.6 (*C*H), 29.2 (*C*H_2), 26.5 (*C*H_3), 19.5 (*C*H_3). HRMS (ESI): *m/z*: calcd for $C_{15}H_{24}NaO_3$: 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 1 M 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 16 h at 110 °C. The reaction was quenched with a saturated solution of $NaHCO_3$. The product was extracted with Et_2O and the organic phase was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The product was purified by column chromatography on silica gel to afford **17fa** as a yellow oil. (90 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$–7.18 (m, 10H, H^{Ar}), 6.17 (dt, J(H,H) = 11.7 and 2.0 Hz, 1H, CH=C*H*-C=CH), 5.44 (dd, J(H,H) = 11.7 and 1.1 Hz, 1H, C*H*=CH-C=CH), 5.38 (d, J(H,H) = 9.6 Hz, 1H, C=C*H*), 4.43 (d, J(H,H) = 4.4 Hz, 2H, CH_2-Ph), 4.36 (d, J(H,H) = 7.7 Hz, 2H, CH_2-Ph), 4.15 (dd, J(H,H) = 8.1 and 3.7 Hz, 1H, CH=C-C*H*-OH), 3.96–3.92 (m, 1H, CH=C-CH(OH)-C*H*-OH), 3.73 (d, J(H,H) = 7.7 Hz, 1H, CH-O*H*), 3.68 (dd, J(H,H) = 9.6 and 7.4 Hz, 1H, CH_2-OBn), 3.50–3.44 (m, 2H, CH_2-OBn), 3.39 (dd, J(H,H) = 9.4 and 6.7 Hz, 1H, CH_2-OBn), 3.19 (d, J(H,H) = 8.3 Hz, 1H, CH-O*H*), 2.69–2.65 (m, 1H, C*H*-CH_2-OBn), 2.52–2.44 (m, 2H, C*H*-CH_2-OBn and C*H*$(CH_3)_2$), 0.88 (dd, J(H,H) = 6.7 and 1.2 Hz, 6H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 138.6$ (*C*H), 137.7 (*C*), 137.6 (*C*), 133.5 (*C*), 130.6 (*C*H), 128.48 (*C*H), 128.46 (*C*H), 127.85 (*C*H), 127.81 (*C*H), 127.79 (*C*H), 127.73 (*C*H), 127.70 (*C*H), 127.0 (*C*H), 76.7 (*C*H), 75.1 (*C*H), 73.4 (*C*H_2), 73.3 (*C*H_2), 70.9 (*C*H_2), 69.3 (*C*H_2), 41.4 (*C*H), 38.9 (*C*H), 27.3 (*C*H), 22.8 (*C*H_3), 22.6 (*C*H_3). HRMS (ESI): *m/z*: calcd for $C_{27}H_{34}NaO_4$: 445.2349 [M+Na]$^+$; found 445.2352.

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