# On the Mechanism of Carbohydroxypalladation of Enynes. Additional Insights on the Cyclization of Enynes with Electrophilic Metal Complexes

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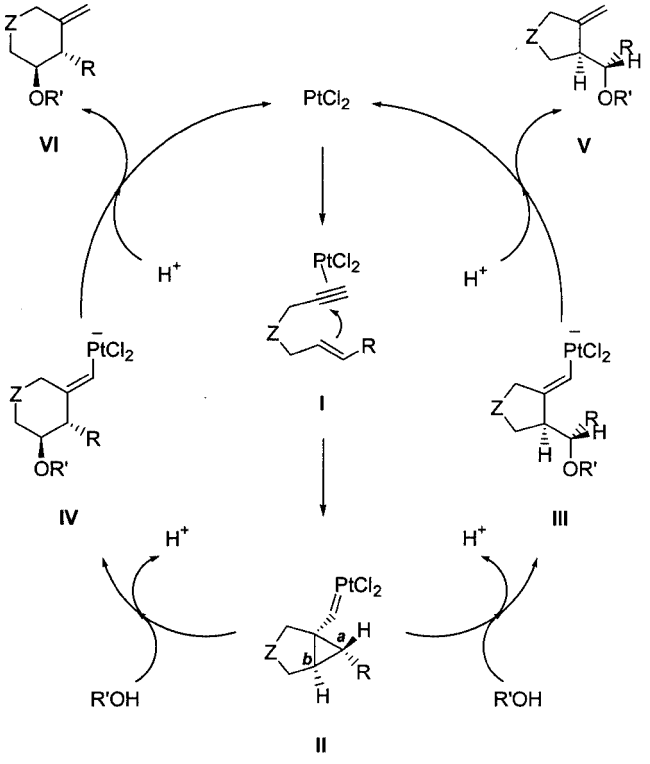
Different mechanisms have been proposed for the cyclization of enynes catalyzed by electrophilic metal halides or complexes. We present evidence to indicate that the previously reported "carbohydroxypalladation" and the "hydroxycyclization catalyzed by $Pt^{II}$" are closely related reactions. Thus, palladium complexes formed in situ from $PdCl_2$ and trisulfonated phosphane TPPTS or cyclic phosphite $P(OCH_2)_3CEt$ as the ligands catalyze the methoxy- or hydroxycyclization of enynes with selectivities similar to those observed with $Pt^{II}$ complexes. Deuteration studies indicate that activation of the alkyne by $Pd^{II}$ promotes an anti-addition of the alkene.


## Introduction

The coordination of electrophilic $PtCl_2$ to an enyne through the alkyne (**I**, Scheme 1) may promote the intramolecular reaction of the alkene to form a cyclopropyl Pt-carbene intermediate **II**.[1] Subsequent attack of the nucleophile (alcohol or water) at the cyclopropyl carbons labeled ***a*** and ***b*** of **II** presumably gives rise to the formation of five- (**III**) or six-membered (**IV**) intermediates, which evolve under catalytic conditions to afford the carbo- or heterocycles **V** or **VI**, respectively.[1] Although some of these reactions are also catalyzed by $AuCl_3$ and $Ru^{II}$ complexes, the cyclization with these catalysts is more limited in scope.[1] A similar mechanism has been suggested for the intramolecular reaction of allylsilanes and allylstannanes with alkynes, a process that is catalyzed by $Pt^{II}$, $Pd^{II}$, $Ru^{II}$, and, in some cases, by $Au^{III}$, $Cu^{I}$, and $Ag^{I}$.[2]

Cyclopropyl Pd carbenes have been proposed by Trost and Murai as intermediates for the reaction of some enynes which give cyclopropane derivatives.[3,4] Similar intermediates might be involved in the skeletal rearrangement of enynes that yield conjugated dienes.[5−8] Related intermediates have been proposed on the basis of DFT calculations for the intramolecular reaction of furans with alkynes catalyzed by $Pt^{II}$.[9]




Scheme 1

In competition with the above pathway, a different mechanism may operate if $PtCl_2$ coordinates both functional

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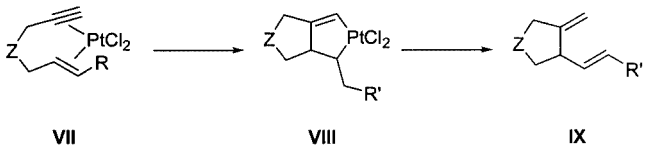
groups of the enyne, as shown in **VII** (Scheme 2). In this case the oxidative metallacycloaddition of **VII** would form metallacyclopentene **VIII**,[1b] which then evolves by β-hydride elimination to give the 1,4-diene cycloisomerization products **IX**. The cycloisomerization pathway is favored in the presence of polar non-nucleophilic solvents such as acetone or 1,4-dioxane.




Scheme 2

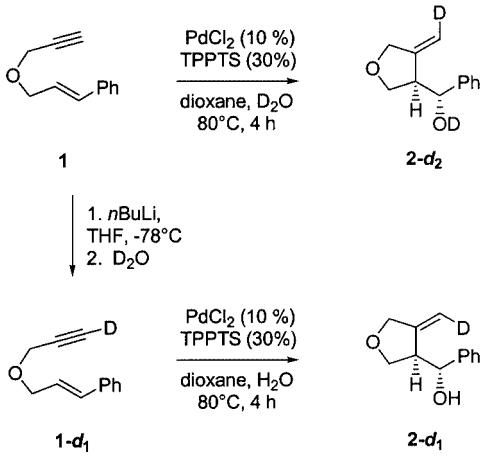
Palladium complexes $[Pd(L_2)X_2]$ favor the cycloisomerization pathway to give dienes **IX**.[10,11] However, when the reaction of certain enynes was carried out with a catalyst formed from $PdCl_2$ and the trisulfonated phosphane TPPTS in the presence of water, a new carbohydroxypalladation was observed.[12] Although the first mechanistic hypothesis for this new reaction was different from that proposed for the $PtCl_2$-catalyzed process, subsequent experiments indicate that the "carbohydroxypalladation" and the "hydroxycyclization" catalyzed by $Pt^{II}$ and other electrophilic metals are indeed related processes. Herein we report results that demonstrate that the Pt-catalyzed hydroxycyclization of enynes and the carbohydroxypalladation are similar reactions, which presumably proceed by the same mechanism.

## Results and Discussion

### Hydroxy- and Methoxycyclization vs. Cycloisomerization

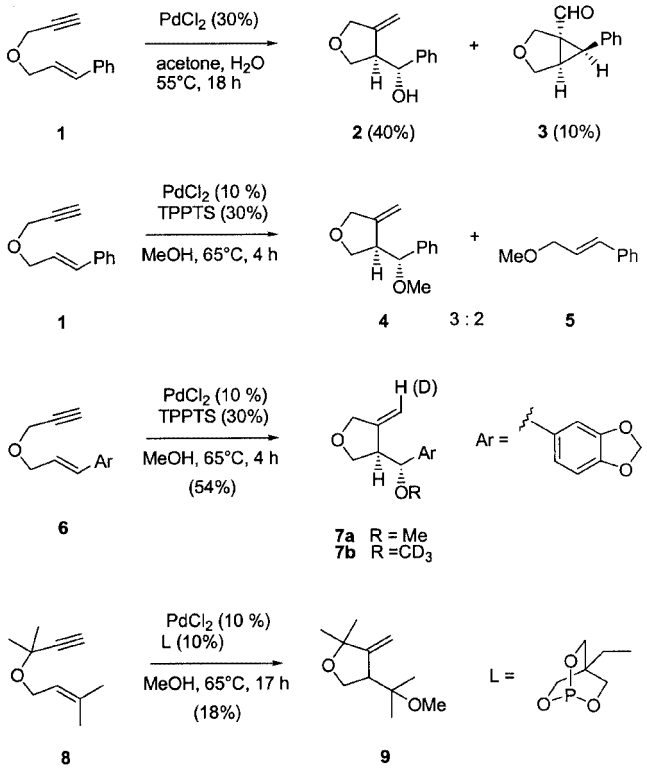
A key issue in the mechanism of the Pd-catalyzed cyclization of enynes is the determination of the stereochemistry of the key C−C bond formation step. This aspect can easily be resolved by performing the cyclization reaction in the presence of $D_2O$. Thus, reaction of propargyl cinnamyl ether (**1**) with $PdCl_2$ and TPPTS as the ligand in a mixture of 1,4-dioxane and $D_2O$ at 80 °C afforded selectively deuterated **2-*d*$_2$** (Scheme 3). The same result was obtained before in the reaction of **1** catalyzed by $PtCl_2$.[1b] We have also prepared the deuterated alkyne **1-*d*$_1$** by *n*BuLi deprotonation followed by $D_2O$ quenching. The reaction of **1-*d*$_1$** with $PdCl_2$ and TPPTS afforded the corresponding adduct **2-*d*$_1$**.

Interestingly, when the reaction of **1** was carried out with $PdCl_2$ in aqueous acetone at 55 °C for 17 h, in the absence of a phosphane ligand, a 4:1 mixture of hydroxycyclized derivative **2** and cyclopropyl aldehyde **3** was obtained in 50% yield (Scheme 4). Bicyclic aldehyde **3** has been obtained before in 12% yield, along with **2**, in the reaction of **1** with $PtCl_2$ as the catalyst.[1b] Reaction of **1** in MeOH at 80 °C with $PdCl_2$/TPPTS as the catalyst led to methoxycyclized derivative **4**, along with **5**, which can result from the reaction of methanol with a π-allyl palladium intermediate.



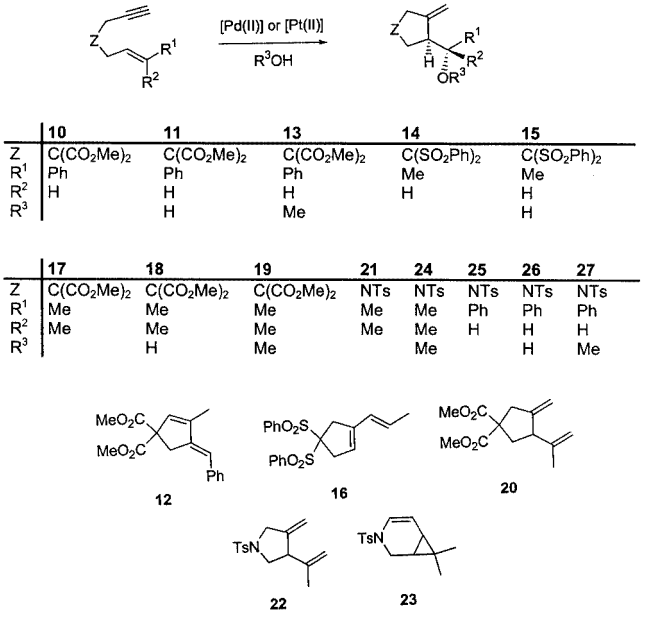

Scheme 3

Reaction of substrate **6**, bearing a more electron-rich aryl ring, favors the addition of methanol to form **7a**. Reaction of **6** in [$D_4$]methanol afforded **7b**, selectively monodeuterated at the alkenyl as in **2-*d*$_2$**. However, the reaction of more hindered **8** under these conditions gave complex reaction mixtures. When the cyclization of **8** was carried out with a catalyst prepared in situ from $PdCl_2$ (10 mol %) and cyclic phosphite $P(OCH_2)_3CEt$ (10 mol %)[13] as the ligand, **9** was obtained in 18% yield. The low yield might be due to decomposition of **9** under the reaction conditions, since increasing the loading of palladium catalyst leads to lower yields.




Scheme 4

We compared the cyclization of several enynes with $Pd^{II}$ and $Pt^{II}$ catalysts (Scheme 5 and Table 1). Enyne **10** reacted with $PdCl_2$/TPPTS in aqueous 1,4-dioxane to afford hydroxycyclized **11** (26%) and diene **12**[14] (25%) (Table 1, entry 1). A similar result was obtained in aqueous acetonitrile.[15] It is noteworthy that when the reaction was carried out with $PtCl_2$/TPPTS, under otherwise identical conditions, **11** could be obtained in 60% yield (entry 2). Similarly, reaction of **10** in methanol with $PdCl_2$/TPPTS afforded an inseparable 1:1 mixture of diene **12** and methoxycyclized **13** in 42% yield (entry 3). With palladium catalysts, the best results were obtained with the $P(OCH_2)_3CEt$ ligand, which led to **13** in 70% yield (entry 4). The use of a platinum catalyst gave **13** in 76% yield (entry 5). We also demonstrated that neither **11** nor **13** evolve to form diene **12** in the presence of $PdCl_2$/TPPTS (MeOH or aqueous dioxane at 80 °C). Since no elimination of water or methanol takes place under the reaction conditions, formation of diene **12** could be explained by isomerization of the primary cycloisomerized diene catalyzed by palladium or traces of acid. Semiempirical calculations (PM3)[16] show that **12** is the most stable among all the possible dienes.




Scheme 5

The reaction of enyne **14** with $PdCl_2$/TPPTS failed to give any cyclized derivative. However, reaction of **14** with $[PtCl_2(MeCN)_2]$ as the catalyst in aqueous acetone led to **15** in 44% yield together with rearrangement product **16** (entry 6). The hydroxycyclization of **17** was carried out with $PtCl_2$/TPPTS to give **18**, albeit in only 47% yield (entry 7). On the other hand, reaction of **17** with $PdCl_2$ and $P(OCH_2)_3$-CEt as the ligand in methanol under reflux for two days led to **19** (30%) along with cycloisomerization derivative **20** (60%) (entry 8). Addition of $AgBF_4$ or AgOTf suppressed the cycloisomerization, although the yield of **19** was low (10−20%). The best results were obtained with $PtCl_2$/TPPTS as the catalyst, which gave carbocycle **19** in 94% yield (entry 9).

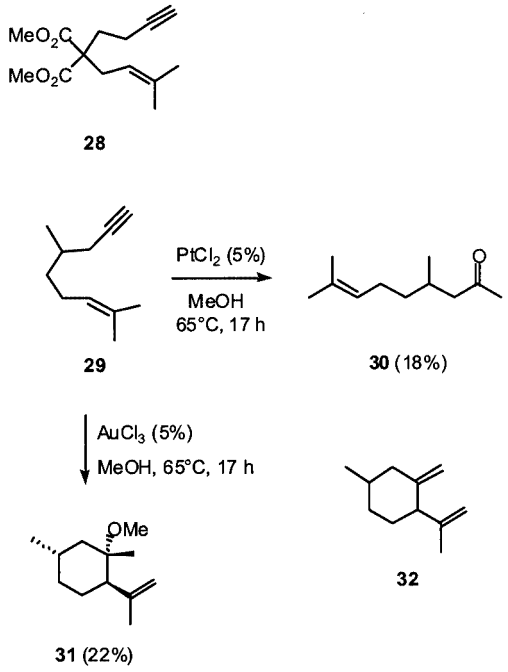
Table 1. $Pd^{II}$- vs. $Pt^{II}$-catalyzed cyclization of enynes

| Entry | Enyne | Catalyst | Reaction conditions | Product(s) (yield) |
|---|---|---|---|---|
| 1 | **10** | $PdCl_2$ (10%) TPPTS (30%) | 1,4-dioxane, $H_2O$ 80 °C, 46 h | **11** (26%) + **12** (25%) |
| 2 | **10** | $PtCl_2$ (10%) TPPTS (30%) | 1,4-dioxane, $H_2O$ 80 °C, 108 h | **11** (60%) |
| 3 | **10** | $PdCl_2$ (10%) TPPTS (30%) | MeOH, 80 °C, 113 h | **12** (21%) + **13** (21%) |
| 4 | **10** | $PdCl_2$ (10%) $P(OCH_2)_3CEt$ (30%) | MeOH, 65 °C, 17 h | **13** (70%) |
| 5 | **10** | $PtCl_2$ (10%) TPPTS (30%) | MeOH, 80 °C, 68 h | **13** (76%) |
| 6 | **14** | $Pt(MeCN)_2Cl_2$ (5%) | acetone, $H_2O$, 55 °C, 17 h | **15** (44%) + **16** (30%) |
| 7 | **17** | $PtCl_2$ (10%) TPPTS (30%) | 1,4-dioxane, $H_2O$ 80 °C, 87 h | **18** (47%) |
| 8 | **17** | $PdCl_2$ (10%) $P(OCH_2)_3CEt$ (30%) | MeOH, 65 °C, 48 h | **19** (30%) + **20** (60%) |
| 9 | **17** | $PtCl_2$ (10%) TPPTS (30%) | MeOH, 80 °C, 17 h | **19** (94%) |
| 10[1] | **21** | $PtCl_2$ (5%) | acetone, 55 °C | **22** (35%) + **23** (31%) |
| 11 | **21** | $PdCl_2$ (10%) TPPTS (30%) | MeOH, 65 °C, 17 h | **22** (65%) |
| 12 | **21** | $Pt(MeCN)_2Cl_2$ (5%) | MeOH, 65 °C, 17 h | **24** (62%) |
| 13 | **25** | $PtCl_2$ (10%) TPPTS (30%) | 1,4-dioxane, $H_2O$ 80 °C, 204 h | **26** (50%) |
| 14 | **25** | $PdCl_2$ (10%) TPPTS (30%) | MeOH, 80 °C, 22 h | **27** (34%) |
| 15 | **25** | $PtCl_2$ (10%) TPPTS (30%) | MeOH, 80 °C, 40 h | **27** (81%) |

We also examined the reaction of enyne **21**, which has been shown to react with $PtCl_2$ in acetone to give a 1.1:1 mixture of **22** and cyclopropane **23** in 66% yield (entry 10).[1] The reaction of **21** with $PdCl_2$/TPPTS in methanol afforded selectively cycloisomerization product **22** in 65% yield (entry 11). In contrast, the reaction of **21** with $[PtCl_2(MeCN)_2]$ as the catalyst in methanol gave **24** in 62% yield (entry 12). Hydroxycyclization of **25** with $PtCl_2$/TPPTS in aqueous dioxane afforded **26** in 50% yield (entry 13). Methoxycyclization of **25** proceeded with $PdCl_2$/TPPTS in low yield (entry 14), while the reaction with the platinum catalyst gave **27** in 81% yield (entry 15).

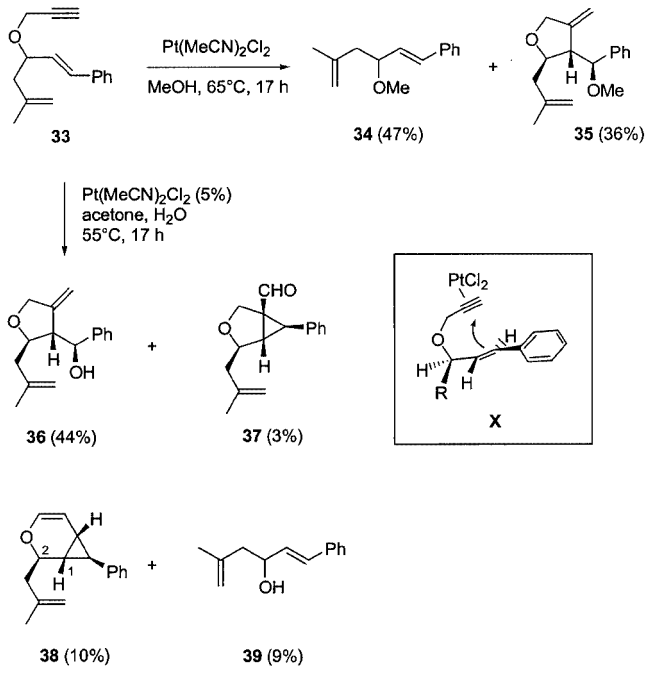
All attempts to cyclize enynes **28** and **29** with $Pd^{II}$ or $Pt^{II}$ catalysts in the presence of water or methanol failed to give any cycloisomerization product or any hydroxy- or methoxycyclized derivatives (Scheme 6). The only compound that could be isolated from **29** was methyl ketone **30**, which is the product of the alkyne hydration reaction.[15] Presumably, addition of MeOH catalyzed by $Pt^{II}$ gives the enol ether, which is subsequently hydrolyzed during work-up. However, when enyne **29** was submitted to the methoxycyclization reaction using $AuCl_3$ as catalyst, the unexpected carbocycle **31** was isolated in low yield. This product could result from the cycloisomerized carbocycle **32** by addition of MeOH to the exocyclic methylene catalyzed by the Lewis

acid $AuCl_3$. Indeed, semiempirical PM3 calculations[16] on model carbocations indicate that protonation of the exocyclic methylene of **32** is more favorable than at the isopropenyl side chain.




Scheme 6

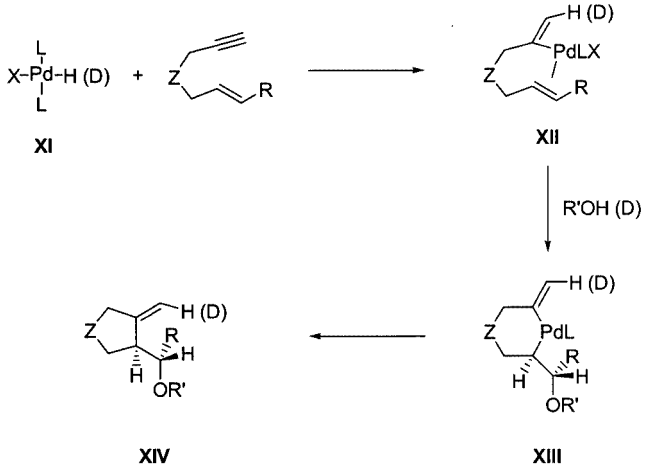
The reaction of dienyne **33** with $Pt^{II}$ afforded **34** (47%) and methoxycyclization derivative **35** (36%) (Scheme 7). The depropargylation product **34** was the only product when **33** was heated with 5 mol % $[PdCl_2(MeCN)_2]$ in MeOH. When the reaction was performed in the presence of water, carbocycle **36** was obtained in 44% yield, together with bicyclic aldehyde **37**, oxabicyclo[4.1.0]hept-4-ene **38** and alcohol **39**[17] as minor products. Although a mixture of compounds is obtained, the stereoselectivity of the process is high since none of the stereoisomers of **35**−**38** were formed in significant amounts. The configurations of **35**, **36**, and **37** were confirmed by NOE experiments. The configuration of **38** was assigned on the basis of the small vicinal coupling constant ($^3J$ = 1.8 Hz) between the bridgehead hydrogen at C-1 and the hydrogen at C-2, in agreement with a calculated dihedral angle of 81° (PM3 calculations) with a coupling constant $^3J$ of about 2 Hz (Karplus equation[18]). The dihedral angle of the alternative 2-epi configuration would be 45° (calculated $^3J$ = 6.3 Hz). Formation of **35**−**38** can be explained by attack of the alkene on the alkyne coordinated to $PtCl_2$, as shown in model **X**.




Scheme 7

## Mechanistic Hypothesis

A reasonable hypothesis for the palladium-catalyzed cyclization based on the insertion of a palladium hydride **XI** on the terminal alkyne to form **XII** is outlined in Scheme 8. Hydrides of type **XI** could be formed in situ by the oxidative addition of $Pd^0$ complexes to methanol or water. Subsequently, intermediate **XII** might be attacked by methanol or water in a Wacker-type process to form **XIII**, which would evolve to **XIV** after reductive elimination to form **XIV**. However, the deuteration results shown in Scheme 3 are not consistent with the configuration of the expected deuterated **XIV-*d***.

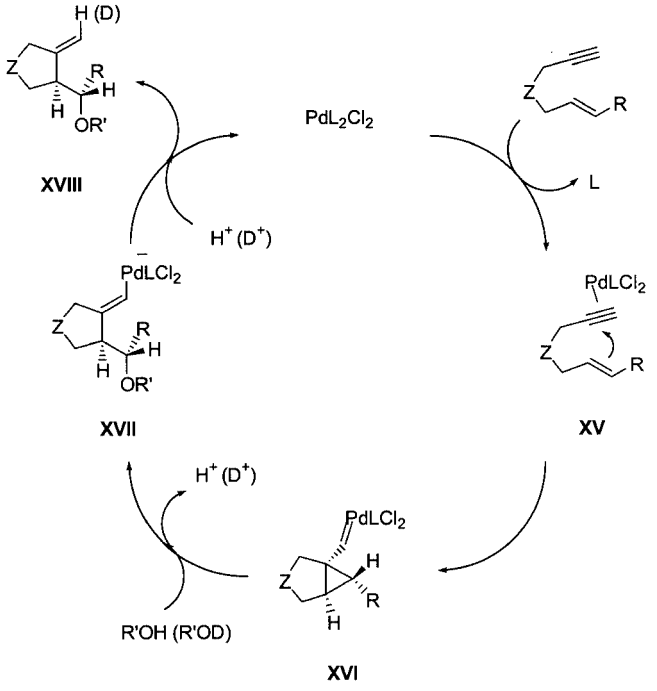



Scheme 8

Formation of cyclopropyl aldehydes **3** and **37** from **1** and **33**, respectively (Schemes 4 and 7) strongly suggests that a cyclopropyl Pd-carbene similar to **II** (Scheme 1) is involved as an intermediate in the Pd-catalyzed process. Additionally, the fact that **2** is also obtained with $PdCl_2$ as the catalyst indicates that this reaction is actually catalyzed by $Pd^{II}$. Thus, even though one cannot rule out a competing pathway, a mechanism similar to that proposed for the $Pt^{II}$-catalyzed cyclization can also be postulated for the process cata-

lyzed by palladium (Scheme 9). In this case, a square planar $PdCl_2L_2$ complex (L = TPPTS, $P(OCH_2)_3CEt$, MeCN) would coordinate to the enyne through the more reactive alkyne to form complex **XV**, which would evolve to give cyclopropylpalladium carbene complex **XVI**. Opening of this intermediate by methanol or water would then give rise to **XVII**, which would undergo protonolysis to form **XVIII**. This mechanism accounts for the deuteration pattern found in the reactions of **1** and **1-$d_1$**.

In agreement with the mechanism proposed in Scheme 9, no cyclization was observed with freshly prepared $Pd^0$ complexes $[Pd(PPh_3)_4]$ or $[Pd_2(dba)_3]$·dba. Phosphanes such as TPPTS are known to reduce $PdCl_2$ or $Pd(OAc)_2$, leading to $Pd^0L_n$ complexes.[19] Indeed, these complexes catalyze a number of cross-coupling reactions,[20] as well as Heck alkenylations,[20c] metal-catalyzed ene-reaction,[21] and Tsuji−Trost reactions.[22] However, the cyclizations of enynes are apparently catalyzed by small amounts of unreduced $[PdCl_2(TPPTS)_2]$ or other $Pd^{II}$ complexes formed in situ from $Pd(TPPTS)_3$.




Scheme 9

## Conclusion

Although different mechanisms have been proposed for the cyclization of enynes catalyzed by $Pd^{II}$ and $Pt^{II}$ complexes, the experimental evidence suggest that the "carbohydroxypalladation", and the hydroxy- and methoxycyclization catalyzed by electrophilic metals are closely related reactions.

Although both $Pd^{II}$ and $Pt^{II}$ catalysts cyclize 1,6-enynes, $Pt^{II}$ complexes are usually more reactive. A limitation has been found in the cyclization of 1,7-enynes **28** and **29**, which could not be cyclized with $Pd^{II}$ or $Pt^{II}$ catalysts (Scheme 6). In the case of **29**, $AuCl_3$ was moderately successful, leading to the formation of six-membered ring **31**.

The present work also demonstrates that palladium or platinum complexes bearing phosphanes or phosphites as the ligands can catalyze the cyclization of enynes with addition of methanol or water to the alkene. This suggests that chiral ligands of this type could be used to control the enantioselectivity of the process. Efforts to further develop this maximum atom-economy reaction are in progress.

## Experimental Section

**General Remarks:** The NMR determinations were carried out at 23 °C. $R_f$ were determined on TLC aluminum sheets coated with 0.2 mm $GF_{254}$ silica gel. Elemental analyses were performed at the SIdI (UAM), at the "Service Regional de Microanalyse" (Université Pierre et Marie Curie), and at the "Service de spectrométrie de masse" (Ecole Normale Supérieure). All reactions were carried out under an atmosphere of Ar. Solvents were purified, dried by standard methods and degassed prior to use. Column chromatography was performed with E. Merck 0.040−0.063 mm, Art. no. 11567, silica gel. Florisil (100−200 Mesh) was purchased from Acros or Avocado. $[Pt(MeCN)_2Cl_2]$ was prepared by the procedure described for the synthesis of $[Pt(PhCN)_2Cl_2]$.[21] $AuCl_3$ (Aldrich) was dried under reduced pressure.

The following compounds have been described before: **1**−**3**,[1] **6**,[12b] **8**−**11**,[1] **13**,[1] **14**,[1] **16**,[1] **17**,[24] **18**,[1] **19**,[1] **20**,[25] **21**,[1] **22**−**24**,[1] **28**,[26] **30**,[27] and **39**.[28] Known enyne **29**[29] was prepared by the Corey−Fuchs procedure.[30]

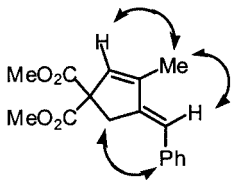
**General Procedure for the Palladium- or Platinum-Catalyzed Alkoxy- and Hydroxycyclization of Enynes:** A mixture of the enyne and the catalyst was heated at 55−80 °C in methanol (screw-capped tube at 80 °C), 14% aqueous 1,4-dioxane or 10% aqueous acetone. After being cooled to room temperature, the solvent was evaporated and the residue was chromatographed (hexanes/EtOAc mixtures) to give the desired carbocycles. The hydroxycyclization reactions were carried out in acetone/$H_2O$ (ca. 9:1) at 60 °C and the reaction mixtures were either dried with $MgSO_4$ or extracted ($Et_2O$) prior to chromatography. The cyclization reactions in the presence of TPPTS ligand were directly filtered through a short pad of florisil gel (EtOAc) and the solvents evaporated under reduced pressure.

**4-[1-Methoxy-(3,4-methylenedioxy)phenylmethyl]-3-methylenetetrahydrofuran (7a):** This compound was obtained from enyne **6** as a colorless oil following the general procedure (54%): $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.90 (m, 1 H), 3.18 (s, 3 H), 3.95 (m, 2 H), 4.16 (dd, $J$ = 9.0, 3.9 Hz, 1 H), 4.27 (m, 3 H), 4.81 (br. s, 1 H), 5.98 (s, 2 H), 6.81 (m, 3 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$; DEPT): δ = 50.80 ($CH_3$), 56.38 (CH), 71.53 ($CH_2$), 84.17 (CH), 100.87 ($CH_2$), 106.79 ($CH_2$), 107.52 (CH), 121.60 (CH), 133.84 (C), 147.07 (C), 147.65 (C) ppm. DCI/$NH_3$-MS: $m/z$ = 249 $[M + H]^+$, 266 $[M + NH_4]^+$. DCI/$NH_3$-HRMS calcd for $C_{14}H_{17}O_4$, 249.1127; found 249.1122.

**Dimethyl (*E*)-3-Benzylidene-4-methylcyclopent-2-ene-1,1-dicarboxylate (12):** This compound was obtained from enyne **10** following the general procedure (25% by using $PdCl_2$/TPPTS) as a colorless oil: $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 3.51 (br. s, 2 H), 3.76 (s, 6 H), 5.98 (br. s, 1 H), 6.32 (br. s, 1 H), 7.32 (m, 5 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$; DEPT): δ = 12.94 ($CH_3$), 37.71

($CH_2$), 52.85 ($CH_3$), 64.26 (C), 120.27 (CH), 126.55 (CH), 128.33 (CH), 129.63 (CH), 137.34 (C), 144.06 (C), 145.60 (C), 171.11 (C) ppm. CI-MS: *m*/*z* = 287 [M + H$^+$], 304 (M + $NH_4^+$). DCI/$CH_4$-HRMS calcd for $C_{17}H_{19}O_4$: 287.1283; found 287.1284.

The structure of **12** was confirmed by COSY, NOESY and HMQC experiments. The most significant NOE enhancements are shown below.




**(3*R**)-1,1-Bis(phenylsulfonyl)-3-[(1*R**)-1-hydroxyethyl]-4-methylenecyclopentane (15):** This compound was obtained from enyne **14** as a white solid (44%) following the general cyclization procedure: m.p. 125−127 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.5 Hz, 3 H), 2.63 (dd, *J* = 18.2, 12.2 Hz, 1 H), 2.84 (dd, *J* = 18.2, 8.9 Hz, 1 H), 2.85 (m, 1 H), 3.12 (d, *J* = 18.2 Hz, 1 H), 3.38 (dq, *J* = 18.2, 2.0 Hz, 1 H), 4.15−4.05 (m, 1 H), 4.94 (dd, *J* = 4.4, 2.4 Hz, 1 H), 5.04 (dd, *J* = 4.4, 2.0 Hz, 1 H), 7.60−7.57 (m, 4 H), 7.76−7.64 (m, 2 H), 8.10−7.80 (m, 4 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 20.72, 30.68, 39.36, 49.95, 66.96, 91.19, 108.15, 128.75, 131.22, 131.33, 134.65, 134.76, 135.40, 136.43, 147.48 ppm. $C_{20}H_{22}O_5S_2$: calcd. C 59.09, H 5.45, S 15.78; found C 58.38, H 5.42, S 15.71.

**(*N*,*N*)-Propargylcinnamyl-*p*-tosylamine (25):** This known compound[31] was obtained by an improved procedure in three high yielding steps.

**Step 1. Synthesis of (*N*,*N*)-*tert*-Butoxycarbonyl-cinnamyl-*p*-tosylamine:** NaH (295 mg, 7.37 mmol) was added portionwise at 0 °C to a THF/DMF (2:1) solution (0.16 M) of *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (2.00 g, 7.37 mmol). The mixture was allowed to warm to room temperature. Then, *trans*-cinnamyl bromide (1.6 g, 8.11 mmol) was added. The resulting mixture was heated under reflux 12 h. The suspension was quenched with water and extracted three times with $CH_2Cl_2$. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (cyclohexane/EtOAc, 95:5 to 90:10) to give a white solid (2.18 g, 79%): m.p. 118−120 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 9 H), 2.41 (s, 3 H), 4.59 (dd, *J* = 6.4, 0.9 Hz, 2 H), 6.27 (dt, *J* = 15.8, 6.4 Hz, 1 H), 6.65 (d, *J* = 15.8 Hz, 1 H), 7.32 (m, 7 H), 7.79 (d, *J* = 8.3 Hz, 2 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$, DEPT): δ = 21.47 ($CH_3$), 27.82 ($CH_3$), 48.42 ($CH_2$), 84.22 (C), 124.21 (CH), 126.48 (CH), 127.77 (CH), 128.00 (CH), 129.11 (CH), 133.79 (CH), 136.38 (C), 137.19 (C), 144.02 (C), 150.72 (C) ppm. $C_{20}H_{25}NO_4S$: calcd. C 63.98, H 6.71, N 3.73; found C 64.82, H 6.72, N 3.32.

**Step 2. Synthesis of (*N*)-Cinnamyl-*p*-tosylamine:** Trifluoroacetic acid (2.4 mL and then 1 mL, 43.1 mmol) was added at 0 °C to a solution (0.3 M) of the resulting sulfonamide (2.16 g, 5.75 mmol) in anhydrous $CH_2Cl_2$. The resulting mixture was stirred at room temperature, until completion of the reaction. Solvents were then evaporated in vacuo. The residue was partitioned between $CH_2Cl_2$ and water and NaOH pellets were added. The aqueous layer was extracted three times with $CH_2Cl_2$ and the combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated to give a white solid (1.52 g, 92%): m.p. 105−107 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.77 (td, *J* = 6.3, 1.3 Hz, 2 H), 4.53 (m, 1 H), 6.02 (dt, *J* = 15.8, 6.3 Hz, 1 H), 6.45 (d, *J* = 15.8 Hz, 1 H), 7.29 (m, 7 H), 7.79 (d, *J* = 8.3 Hz, 2 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$, DEPT): δ = 21.41 ($CH_3$), 45.40 ($CH_2$), 123.97 (CH), 126.31 (CH), 127.11 (CH), 127.84 (CH), 128.45 (CH), 129.65 (CH), 132.99 (CH), 135.99 (C), 137.00 (C), 143.45 (C) ppm. $C_{16}H_{17}NO_2S$: calcd. C 66.87, H 5.96, N 4.87; found C 66.53, H 6.11, N 4.71.

**Step 3:** Sodium hydride (205 mg, 5.11 mmol) was added portionwise at 0 °C to a THF solution (0.13 M) of the resulting deprotected sulfonamide (2.00 g, 5.11 mmol). The mixture was allowed to warm to room temperature. Then propargyl bromide (629 μL, 5.63 mmol) was added. The resulting mixture was heated under reflux overnight and then quenched with water and extracted three times with $CH_2Cl_2$. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel flash chromatography (cyclohexane/EtOAc, 90:10) to give a white solid (1.26 g, 76%): m.p. 79−81 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.07 (s, 1 H), 2.44 (s, 3 H), 4.00 (d, *J* = 6.8 Hz, 2 H), 4.14 (m, 2 H), 6.09 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.58 (d, *J* = 15.8 Hz, 1 H), 7.32 (m, 7 H), 7.78 (d, *J* = 8.3 Hz, 2 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$, DEPT): δ = 21.46 ($CH_3$), 35.81 ($CH_2$), 48.49 ($CH_2$), 73.76 (CH), 76.53 (C), 122.81 (CH), 126.45 (CH), 127, 69 (CH), 127.98 (CH), 128.52 (CH), 129.43 (CH), 134.82 (CH), 135.98 (C), 143.53 (C) ppm. $C_{19}H_{19}NO_2S$: calcd. C 70.12, H 5.88, N 4.30; found C 70.00, H 5.91, N 4.30.

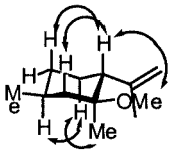
**(3*R**)-3-[(1*R**)(1-Hydroxy)phenylmethyl]-4-methylene-*N*-tosylpyrrolidine (26):** This compound was obtained from enyne **25** as a pale yellow oil (50%) following the general procedure: $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.98 (m, 1 H), 3.23 (dd, *J* = 9.8, 7.2 Hz, 1 H), 3.55 (dd, *J* = 9.8, 5.2 Hz, 1 H), 3.80 (m, 2 H), 4.55 (br. s, 1 H), 4.67 (d, *J* = 6.5 Hz, 1 H), 4.93 (br. s, 1 H), 7.31 (m, 7 H), 7.71 (d, *J* = 8.3 Hz, 2 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$; DEPT): δ = 21.45 ($CH_3$), 49.42 ($CH_2$), 50.40 (CH), 52.53 ($CH_2$), 73.74 (CH), 109.33 ($CH_2$), 126.19 (CH), 127.82 (CH), 128.33 (CH), 129.58 (CH), 132.41 (C), 141.73 (C), 143.63 (C), 144.11 (C) ppm. DCI/$NH_3$-MS: *m*/*z* = 344 [M + H]$^+$, 361 [M + $NH_4$]$^+$. DCI/$CH_4$-HRMS calcd for $C_{19}H_{22}NO_3S$: 344.1320; found 344.1319.

**(3*R**)-3-[-[(1*R**)(1-Methoxy)phenylmethyl]-4-methylene-*N*-tosylpyrrolidine (27):** This compound was obtained from enyne **25** following the general procedure (34% with $PdCl_2$/TPPTS and 81% with $PtCl_2$/TPPTS) as a pale yellow oil: $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.85 (m, 1 H), 3.10 (s, 3 H), 3.25 (dd, *J* = 8.9, 6.9 Hz, 1 H), 3.71(dd, *J* = 8.9, 5.0 Hz, 1 H), 3.91 (m, 2 H), 4.20 (br. s, 1 H), 4.76 (br. s, 1 H), 7.31 (m, 7 H), 7.73 (d, *J* = 8.3 Hz, 2 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 21.43 ($CH_3$), 50.38 ($CH_3$), 52.20 ($CH_2$), 56.72 (CH), 83.65 (CH), 109.91 ($CH_2$), 127.44 (CH), 127.77 (CH), 127.92 (CH), 128.14 (CH), 129.56 (CH), 132.74 (C), 139.30 (C), 143.33 (C), 143.52 (C) ppm. DCI/$NH_3$-MS: *m*/*z* = 358 [M + H]$^+$, 375 [M + $NH_4$]$^+$. DCI/$CH_4$-HRMS calcd for $C_{20}H_{24}NO_3S$: 358.1477; found 358.1476.

**(1*R**,2*S**,5*R**)-2-Isopropenyl-1-methoxy-1,5-dimethylcyclohexane (31):** This compound was obtained from enyne **29** as a colorless oil (22%) following the general cyclization procedure: $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.91 (m, 1 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 1.14 (s, 3 H), 1.16 (t, *J* = 12.3 Hz, 1 H), 1.45 (m, 1 H), 1.55 (td, *J* = 12.9, 3.8 Hz, 1 H), 1.63 (bd, *J* = 13.3 Hz, 1 H), 1.72 (d, *J* = 13.3 Hz, 1 H), 1.82 (ddd, *J* = 12.2, 3.4, 2.0 Hz, 1 H), 1.87 (t, *J* = 1.0 Hz, 3 H), 2.15 (dd, *J* = 12.8, 3.8 Hz, 1 H), 3.24 (s, 3 H), 4.66 (m, 1 H), 4.92 (m, 1 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 18.85, 23.02, 25.97, 29.83, 30.42, 35.55, 46.15, 48.62, 50.97, 78.13,

111.99, 148.50 ppm. EI-HRMS calcd. for $C_{12}H_{22}O$: 182.1761; found 182.1761.

The structure of **31** was confirmed by COSY, NOESY, HMBC and HMQC experiments. The most significant NOE enhancement are shown below.

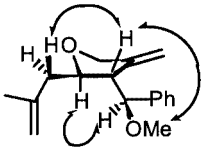



**5-Methyl-1-phenyl-3-(2-propynyloxy)-1,5-hexadiene (33):** A solution of 5-methyl-1-phenyl-1,5-hexadien-3-ol[32] (2.0 g, 10.63 mmol) in DMF (10 mL) was added to a suspension of NaH (60% in mineral oil, 467 mg, 11.69 mmol) in DMF (25 mL) at 0 °C, followed by propargyl bromide (80%, 1.3 mL, 11.69 mmol). The mixture was stirred for 17 h at 23 °C and then quenched with $H_2O$ and extracted ($Et_2O$). The organic layer was washed three times with 10% HCl, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexane/EtOAc, 9:1) to give **32** as a pale yellow oil (1.04 g, 42%). $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.78 (s, 3 H), 2.30 (dd, *J* = 14.1, 6.1 Hz, 1 H), 2.41 (t, *J* = 2.4 Hz, 1 H), 2.48 (dd, *J* = 13.7, 6.9 Hz, 1 H), 4.09 (dd, *J* = 15.8, 2.4 Hz, 1 H), 4.23 (d, *J* = 15.8, 2.4 Hz, 1 H), 4.28 (q, *J* = 6.1 Hz, 1 H), 4.80 (m, 2 H), 6.02 (dd, *J* = 16.2, 8.5 Hz, 1 H), 6.61 (d, *J* = 16.2 Hz, 1 H), 7.42−7.21 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$; DEPT): δ = 22.78 ($CH_3$), 43.98 ($CH_2$), 55.11 ($CH_2$), 74.07 (C), 77.70 (CH), 80.04 (CH), 112.94 ($CH_2$), 127.89 (CH), 128.59 (CH), 128.67 (CH), 133.39 (CH), 136.29 (C), 141.78 (C) ppm. $C_{16}H_{18}O$: calcd. C 84.91, H 8.10; found C 84.38, H 8.02.

**(*E*)-3-Methoxy-5-methyl-1-phenyl-1,5-hexadiene (34):** This compound was obtained from enyne **33** as a by-product of the reactions catalyzed by $PtCl_2$ and was isolated in the cyclization catalyzed by $[PdCl_2(MeCN)_2]$ as a colorless oil (47%): $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.76 (d, *J* = 1.2 Hz, 3 H), 2.25 (dd, *J* = 14.2, 6.2 Hz, 1 H), 2.43 (ddd, *J* = 14.2, 7.3, 1.2 Hz, 1 H), 3.31 (s, 3 H), 3.87 (m, 1 H), 4.76 (m, 1 H), 4.79 (m, 1 H), 6.04 (dd, *J* = 16.2, 8.1 Hz, 1 H), 6.53 (d, *J* = 16.2 Hz, 1 H), 7.40−7.21 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$; DEPT): δ = 22.84 ($CH_3$), 44.18 ($CH_2$), 56.31 ($CH_3$), 80.88 (CH), 112.76 ($CH_2$), 126.48 (CH), 127.70 (CH), 128.57 (CH), 129.86 (CH), 132.27 (CH), 136.57 (C), 142.09 (C) ppm. EI-MS: *m*/*z* = 186 (1) [$M^+$ − 16], 170 (14), 147 (100).

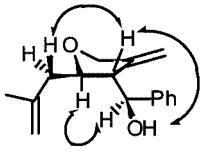
**(2*R**,3*S**)-3-[(1*S**)-(1-methoxy)phenylmethyl]-4-methylene-2-(2-methyl-2-propenyl)tetrahydrofuran (35):** This compound was obtained from enyne **33** as a pale yellow oil (36%) following the general cyclization procedure: $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.74 (d, *J* = 1.2 Hz, 3 H), 2.08 (dd, *J* = 14.1, 4.9 Hz, 1 H), 2.18 (ddd, *J* = 14.1, 9.3, 1.2 Hz, 1 H), 2.63 (m, 1 H), 3.21 (s, 3 H), 4.10 (d, *J* = 8.1 Hz, 1 H), 4.25 (m, 1 H), 4.29 (m, 2 H), 4.47 (m, 1 H), 4.72 (m, 1 H), 4.78 (m, 1 H), 4.80 (q, *J* = 2.0 Hz, 1 H), 7.37−7.24 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$; DEPT): δ = 22.31 ($CH_3$), 42.87 ($CH_2$), 55.49 (CH), 56.89 ($CH_3$), 70.28 ($CH_2$), 79.93 (CH), 84.69 (CH), 107.26 ($CH_2$), 112.08 ($CH_2$), 127.64 (CH), 127.95 (CH), 139.75 (C), 142.90 (C), 147.33 (C) ppm. FAB-HRMS cacld for $C_{17}H_{21}O_2$: 257.1541 [$M^+$ − H]; found 257.1539.

The structure of **35** was confirmed by COSY and NOESY experiments (the most significant NOE enhancement are shown below).




**(2*R**,3*S**)-3-[(1*S**)-(1-Hydroxy)phenylmethyl]-2-(2-methyl-2-propenyl)-4-methylenetetrahydrofuran (36):** This compound was obtained from enyne **33** in 44% yield as a colorless oil following the general cyclization procedure: $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 3 H), 1.87 (dd, *J* = 14.1, 5.1 Hz, 1 H), 2.10 (ddd, *J* = 14.1, 8.2, 0.8 Hz, 1 H), 2.18 (d, *J* = 3.5 Hz, 1 H), 2.73 (m, 1 H), 4.34 (m, 2 H), 4.40 (dt, *J* = 8.1, 4.7 Hz, 1 H), 4.64 (m, 1 H), 4.69 (dd, *J* = 4.2, 2.2 Hz, 1 H), 4.73 (br. s, 1 H), 4.86 (dd, *J* = 6.1, 3.4 Hz, 1 H), 5.00 (q, *J* = 4.0 Hz, 1 H), 7.61−7.20 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$; DEPT): δ = 22.25 ($CH_3$), 42.97 ($CH_2$), 55.67 (CH), 75.02 (CH), 70.59 ($CH_2$), 78.91 (CH), 106.76 ($CH_2$), 112.31 ($CH_2$), 126.28 (CH), 127.63 (CH), 128.27 (C), 142.10 (C), 142.77 (C), 148.52 (C) ppm. IR (neat): $\tilde{\nu}$ = 3418, 3073, 3030, 2967 $cm^{-1}$.

The structure of **36** was confirmed by COSY and NOESY experiments (the most significant NOE enhancements are shown below).




**(1*R**,4*S**,5*R**,6*S**)-1-Formyl-4-(2-methyl-2-propenyl)-6-phenyl-3-oxabicyclo[3.1.0]hexane (37):** This compound was obtained from enyne **33** as a colorless oil (3%) following the general cyclization procedure: $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.82 (s, 3 H), 2.17 (ddd, *J* = 13.7, 6.9, 1.2 Hz, 1 H), 2.29 (ddd, *J* = 14.2, 7.2, 1.0 Hz, 1 H), 2.90 (d, *J* = 5.7 Hz, 1 H), 2.93 (d, *J* = 5.7 Hz, 1 H), 3.97 (d, *J* = 9.3 Hz, 1 H), 4.32 (d, *J* = 9.3 Hz, 1 H), 4.35 (t, *J* = 7.3 Hz, 1 H), 4.79 (m, 1 H), 4.89 (m, 1 H), 7.36−7.25 (m, 5 H), 8.94 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$; DEPT): δ = 22.76 (CH), 34.67 (CH), 35.99 (CH), 42.00 (CH), 46.79 ($CH_2$), 65.88 ($CH_2$), 77.95 (CH), 113.24 ($CH_2$), 127.50 (CH), 128.82 (CH), 128.87 (CH), 133.92 (CH), 141.56 (C), 198.22 (CH) ppm. EI-HRMS calcd for $C_{16}H_{18}O$: 242.1307; found 242.1308.

**(1*R**,2*R**,6*S**,7*R**)-2-(2-Methyl-2-propenyl)-7-phenyl-3-oxabicyclo[4.1.0]hept-4-ene (38):** This compound was obtained from enyne **33** as a colorless oil (10%) following the general cyclization procedure: $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.56 (m, 1 H), 1.82 (s, 3 H), 1.94 (ddd, *J* = 9.0, 5.1, 1.9 Hz, 1 H), 2.32 (dd, *J* = 4.5, 4.3 Hz, 1 H), 2.39 (dd, *J* = 14.1, 6.0 Hz, 1 H), 2.50 (dd, *J* = 14.1, 7.4 Hz, 1 H), 4.03 (ddd, *J* = 7.6, 7.5, 1.8 Hz, 1 H), 4.81 (br. s, 1 H), 4.87 (br. s, 1 H), 5.35 (dd, *J* = 5.3, 5.5 Hz, 1 H), 6.23 (d, *J* = 5.8 Hz, 1 H), 7.32−7.05 (m, 5 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$; DEPT): δ = 19.44 (CH), 22.80 ($CH_3$), 29.17 (CH), 29.69 (CH), 32.21 (CH), 43.85 ($CH_2$), 69.06 (CH), 104.97 (CH), 113.06 ($CH_2$), 125.71 (CH), 128.37 (CH), 141.35 (CH), 141.54 (CH), 141.75 (C) ppm. EI-HRMS: *m*/*z* = 226.1 (17) [$M^+$], 171.1 (79), 143 (70), 141 (64), 128 (100). APCI-MS: *m*/*z* = 227.3 [$M^+$ + 1]. Calcd for $C_{16}H_{18}O$: 226.1357; found 226.1358.

The structure of **38** was confirmed by COSY and NOESY experiments.

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