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Selectivity controlled by ligand tuning in the palladium-catalysed cyclocarbonylation : synthesis of new γ and δ lactones from a natural sesquiterpene

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Graphical abstract

Highlights

- Palladium-catalyzed cyclocarbonylation of a natural sesquiterpene affords new gamma- and delta-lactones
- High conversions and good selectivities in lactones are obtained
- Regioselectivity can be controlled by the nature of the ligand and a control by the substrate itself is also observed
- It's an attractive catalytic transformation of a sesquiterpene easily available form bio-renewableressources

Abstract

The cyclocarbonylation of homoallylic alcohols, derived from α-atlantone, catalysed by $[Pd(Cl_2)L_2]/SnCl_2$] system, afforded new γ and δ lactones as the main products with high selectivities. The regiochemical control depends on the nature of phosphines involved. Catalysts based on monophosphines with large cone angles such as tricyclohexyl phosphine produce the six-membered ring lactones with selectivities up to 80%, while diphosphines with wide bite angle such as xantphos are found to favour the five-membered ring lactones with up to 99% selectivity. Monocrystals of the γ and δ lactones suitable for X-ray diffraction analysis have been obtained and the stereochemistry of the lactones **5a**,**a'** and **6** have been elucidated. This study is the first example of an attractive catalytic transformation of one single natural sesquiterpene easily available from bio-renewable resources to obtain either γ- or δ-lactones.

Keywords: homogeneous catalysis, cyclocarbonylation, palladium, terpenes, lactones

1. Introduction

Lactones are a broad family of compounds which can be very often found in nature [1] and have been largely studied because of their biological properties and as building blocks [2], like, for instance, Corey's lactone [3]. Because of their broad range of applications, many synthetic efforts have been devoted to the synthesis of lactones [4], in particular in enantiomerically enriched forms [5]. Out of the classical Baeyer-Villiger oxidation of cyclic ketones [6,7], palladium metal-catalysed cyclocarbonylation of unsaturated alcohols represents one of the most efficient and atom-economy approaches since it can provide access [8] to unsaturated [9] or saturated lactones [10,11,12] which are often difficult to selectively synthesise. Using Pd(II) catalytic system, 5-membered ring saturated lactones can be obtained from allylic alcohols [10] or homoallylic alcohols [11], while 6-membered ring saturated lactones are obtained from alkenol with 3 carbons between the alcohol and the alkene function (Scheme 1) [11a]. In addition, 2-allylphenols yield a mixture of 5-, 6- and 7-membered ring lactones [12]

As a possible way to use biomass as a source of valuable chemicals, various representative C10 monoterpenes have been also used as starting materials in the cyclocarbonylation reactions by us [13] and others authors [10c] yielding lactones. The palladium-based catalytic tool used permits to obtain these heterocycles with different ring sizes. Indeed from geraniol a 6-membered lactone is obtained while perillyl alcohol leads to a bicyclic 5-membered lactone and isopulegol to a bicyclic 6-membered one (Scheme 2).

More recently, as part of an ongoing program on the use of Moroccan essential oils as feedstocks for fine chemistry [14], we have been interested by the essential oil of the Atlas Cedar (*Cedrus Atlantica*), an interesting raw material for the perfume industry [15]. The main components of this essential oil are the sesquiterpenic bicyclic hydrocarbons, α-, β- and γ-

himachalene, and the oxygenated part, α-atlantone. We already worked on the catalytic transformation of the himachalenes by Lewis acid catalysed rearrangement of their monoepoxides [14].

In this paper, we will now focus on the oxygenated fraction which essentially contains the sesquiterpenic ketone α-atlantone easily isolated by fractional distillation. In the present contribution, we present an efficient way to obtain new chiral γ- or δ-lactones from this purified natural molecule based on palladium-catalysed cyclocarbonylation reaction as a key step.

2. Experimental

2.1. Materials and general procedure

All commercially available reagents were used as received without purification. All reactions were run under Argon using Schlenk techniques. Toluene, dichloromethane, pentane, THF were dried under N_2 using a solvent purification system (SPS).

Z, E α-atlantones were extracted according to the literature [16].

All palladium complexes were prepared according an already described method [17].

All NMR spectral data were recorded at 25 °C on a DPX300 or AV 500 spectrometers with TMS as internal reference for ^{1}H and ^{13}C, 85% H_3PO_4 as external reference for ^{31}P. Spectral assignments were made by means of routine one and two dimensional NMR experiments where appropriate, the data are reported as s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet) High-resolution mass spectra (HRMS) were recorded on GC/TOF using chemical ionisation by desorption in methane. IR analysis was performed using a FT-IR spectrometer. Analytical GC was carried out on a chromatograph with Stabilwax^{R}-AD column and flame ionisation detector. HPLC analysis was done using a prep 4000 Waters. Single crystal X-ray structures were determined on Gemini and Xcalibur diffractometers.

*2.2 Synthesis of 6-methyl-2-(p-tolyl)-hepta-4-one, **2***

In a 2-necked flask equipped with a magnetic stirrer, a thermometer and a condenser was charged a mixture of the two Z and E isomers of α-atlantone **1** (5 g, 23 mmol), and palladium on activated charcoal (10%) (0.1 eq, 250 mg). The reaction mixture was heated at 160°C for 12h. The reaction was then cooled. 20 mL of dichloromethane was added and the solution was filtered to remove palladium on activated charcoal. Then the solvent was removed and the residue was separated by column chromatography with hexane/ethyl acetate (v/v 99/1); the product was isolated in 80% yield as a yellow oil as a racemic mixture.

NMR ^{1}H (298K, $CDCl_3$, 500.33MHz): 7.12 (s, 2H, C11-H; C13-H); 7.12 (s, 2H, C10-H, C14-H); 3.32 (m, 1H, C2-H); 2.71 (d, 1H, *J*=5Hz, C3-H); 2,61 (d, 1H, *J*=11Hz, C3-H); 2.33 (s, 3H, C15-H); 2.22 (d, 2H, *J*=5Hz, C5-H); 2.11 (m, 1H, C6-H); 1.27 (d, 3H, *J*=5Hz, C1-H); 0.89 (s, 3H, C8-H); 0.88 (s, 3H, C7-H). NMR $^{13}C\{^{1}H\}$ (298K, $CDCl_3$, 100.613 MHz) : 209.8 (C4); 143.3 (C9); 135.4 (C12); 129.0 (C11 , C13); 126.9 (C10,C14); 52.7 (C3); 51.4 (C5); 35.5 (C2); 25.6 (C15); 22.8 (C1); 23.4 (C6); 24.5 (C7); 24.1 (C8). IR ν (C=O): 1710 cm^{-1}. HRMS (DCI-CH_4) (m/z) : calcd for $[C_{15}H_{22}O+H]^+$ $[M+H]^+$ 219.1749 found 219.1745

2.3 Synthesis of 6-p-tolyl-4-isobutylhept-1-en-4-ol, ***4a*** *and* ***4b***

Under dry N_2 atmosphere in a schlenk tube, compound **1** (1g, 4.58mmol) was dissolved in THF (10ml). The mixture was cooled to 0°C in an ice bath, and a solution of allylmagnesium bromide in THF 1M (1.1 eq, 5.04 mL) was added dropwise. The solution was warmed to room temperature and stirred for 2h. The reaction mixture was then quenched by addition of saturated aqueous NH_4Cl solution. Extraction with diethyl ether was done three times and the organic layers were collected and dried on anhydrous $MgSO_4$, then filtered and the solvent was removed. The residue was separated by column chromatography with hexane first and then a hexane/ ethyl acetate mixture (95/5, v/v). The product was isolated in 92% yield as a yellow oil. The partial separation of the two diastereoisomers was carried out by HPLC using

a Sunfire Silica chiral column type with a mixture petroleum ether/ diethylether ether (98:2) as eluent (**4b**, retention time=13.15 min; **4a,** retention time=13.20 min).

4a: NMR ^{1}H (298K, $CDCl_3$, 500.33MHz): 7.12 (s, 2H, C13-H, C17-H); 7.16 (s, 2H, C14-H, C16-H); 5.76 (m, 1H, C2-H); 5.16 (dd, 2H, C1-H, *J* = 5Hz, *J* = 11Hz); 2.99 (m, 1H, C6-H); 2.34 (s, 3H, C18-H); 2.23 (m, 2H, C3-H); 1.97 (m, 1H, C9-H); 1.80 (d, 1H, C5-H, *J*=11Hz); 1.85 (d,, 1H, C5-H, J=5Hz); 1.37 (m, 2H,C8-H); 1.29 (d, 3H, C7-H, J=5Hz); 0.97 (d, 3H, C11-H, 5Hz); 0.94 (d, 3H, C10-H, J=5Hz). NMR $^{13}C\{^{1}H\}$ (298K, $CDCl_3$, 100.613 MHz): 144.8(C12); 135.7(C15); 134.4 (C2); 129.4 (C14,C16) ; 127.1 (C13, C17); 118.4 (C1); 75.1 (C4); 48.24 (C8); 47.5 (C5); 44.8 (C3); 35.8 (C6); 25.2 (C7); 24.8 (C19); 24.7 (C10); 23.8 (C11) 21.0 (C18). IR ν (O-H) 3571 cm^{-1}, ν (C=C) 1640 cm^{-1}. HRMS (DCI-CH_4) (m/z) : calcd for $[C_{18}H_{28}O]^{+}$ $[M]^{+}$ 260.2140 found 260.2138

2.4. Catalytic tests

Under dry N_2 atmosphere in a tube schlenk a mixture of $PdCl_2L_2$ (0.02 mmol), tin chloride (0.05 mmol), and compound **4a-b** (1mmol) was added in 10mL of toluene/dichloromethane (1:1), then it was transferred in 100mL stainless steel autoclave with magnetic stirring. The autoclave was purged three times with carbon monoxyde, then stirred and heated in an oil bath at 80°C and pressurized under 40 bar of CO for 16h. After 16h, the autoclave was cooled to room temperature and then slowly depressurized. The crude residue was filtered through a pad of silica and then analysed by gas chromatography. The lactones were purified by column chromatography using hexane-ethyl acetate as eluent (v/v, 95/5). Lactones **6**, as mixture of the two diastereomers **6a** and **6b**, and **5**, as a mixture of the four diastereomers, **5a**, **5a'**, **5b** and **5b'**, were separated.

5a, 5a': NMR ^{1}H (298K, $CDCl_3$, 500.33MHz): 7.09 (s, 2H, C12-H, C14-H); 7.10 (s, 2H, C11-H, C15-H); 2.96 (s, 1H, C8-H); 2.73(s, 1H, C3-H); 2.35 (s, 3H, C16-H); 2.25 (m, 1H, C18-H);1.95 (d, 1H, C4-H, *J*=11Hz); 2.01 (d, 1H, C4-H, *J*=6.5Hz); 1,55(d, 2H, C7-H, *J*=5Hz);

1.44 (d, 2H, C17-H, *J*=5Hz); 1.29 (d, 3H, C9-H, *J* = 5Hz); 1.15 (d, 3H, C6-H, *J*=5Hz); 0.93 (d, 3H, C19-H, *J*=5Hz); 0.92(d, 3H, C20-H, *J*=5Hz). NMR $^{13}C\{^{1}H\}$ (298K, $CDCl_3$, 100.613 MHz): 179.3(C2); 144.8(C10); 135.9(C13); 129.4 (C12, C14); 126.8 (C11, C15); 87.0 (C5); 47.6 (C17); 45.9 (C7); 42.1 (C4); 36.0 (C8); 35 (C3); 29.7 (C18); 24.7 (C9); 24.2 (C20); 24.1 (C19); 21.0 (C16); 15.8 (C6). NMR ^{1}H (298K, $CDCl_3$, 500.33MHz): 7.12 (s, 2H,C12-H, C14-H); 7.14 (s, 2H, C11-H, C15-H); 2.96 (m, 1H,C8-H); 2.73 (m, 1H,C3-H); 2.35 (s, 3H, C16-H); 2.25 (m, 1H, C18-H);1.95 (d, 1H, C4-H, *J*=11Hz); 2.01 (d, 1H, C4-H, *J*=6.5Hz); 1.55(d, 2H, C7-H, *J*=5Hz); 1.44(d, 2H, C17-H, *J*=5Hz); 1.33 (d, 3H, C9-H, *J* = 5Hz); 1.18 (d, 3H, C6-H, *J*=5Hz); 0.98 (d, 3H, C19-H, *J*=5Hz); 0.95 (d, 3H, C20-H, *J*=5Hz). NMR $^{13}C\{^{1}H\}$ (298K, $CDCl_3$, 100.613 MHz): 179.2 (C2); 143.81 (C10); 135.8 (C13) ; 129.2 (C12, C14) ; 126.6 (C11, C15); 86.9 (C5); 47.3 (C17); 45.5 (C.7); 41.0 (C4); 35.7 (C8); 34.9 (C3); 29.6 (C18); 24.6 (C9); 24.2 (C20); 24.0 (C19); 21.0 (C16); 15.5 (C6). HRMS (DCI-CH_4) (m/z) : calcd for $[C_{19}H_{28}O_2 + H]^+$ $[M+H]^+$ 289.2168 found 289.2171.

6a: NMR ^{1}H (298K, $CDCl_3$, 500.33MHz): 7.11 (s, 2H,C12-H, C14-H); 7.11 (s, 2H, C11-H, C15-H); 2.85 (m, 1H,C8-H); 2.41 (m, 2H, C3-H); 2.34 (s, 3H, C16-H); 2.06 (d, 2H, C7-H, *J*=5.19Hz); 1.80 (m, 1H, C18-H); 1.67 (m, 2H, C4-H); 1.55 (m, 1H, C5-H); 1.45 (m, 1H, C5-H); 1.35 (d, 3H, C9-H, 5Hz); 0.98 (d, 3H, C19-H, *J*=5Hz); 0.96 (d, 3H, C20-H, *J*=5Hz). NMR $^{13}C\{^{1}H\}$ (298K, $CDCl_3$, 100.613 MHz): 171.1 (C2); 144.4 (C10); 135.7 (C13); 129.3 (C12, C14); 126.8 (C11, C15); 87.2 (C6); 47.1 (C17); 46.9 (C7); 35.6 (C8); 30.9 (C5); 29.2 (C18); 25.1 (C9); 24.6 (C20); 23.9 (C20,C19); 20.0 (C16); 16.3 (C4) . IR ν (C=O): 1776 cm^{-1}. HRMS (DCI-CH_4) (m/z) : calcd for $[C_{19}H_{28}O_2 + H]^+$ $[M+H]^+$289.2168 found 289.2158.

6b: NMR ^{1}H (298K, $CDCl_3$, 500.33MHz): 7.11 (s, 2H,C12-H, C14-H); 7.11 (s, 2H, C11-H, C15-H); 2.85 (m, 1H, C8-H); 2.41 (m, 2H, C3-H); 2.34 (s, 3H, C16-H); 2.06 (d, 2H, C7-H, *J*=5.19Hz); 1.80 (m, 1H, C18-H); 1.67 (m, 2H, C4-H); 1.65 (d, 2H, C17-H); 1.55 (m, 1H, C5-

H); 1.45 (m, 2H, C5-H); 1.35 (d, 3H, C9-H, *J*=5Hz); 0.98 (d, 3H, C19-H, *J*=5Hz); 0.96 (d, 3H, C20-H, *J*=5Hz). NMR $^{13}C\{^{1}H\}$ (298K, $CDCl_3$, 100.613 MHz): 171.3 (C-2); 144.8 (C-10); 135.6 (C-13); 129.2 (C-12, C-14); 126.8 (C-11, C-15); 87.0 (C-6); 47.6 (C-17); 46.9 (C-7); 35.2 (C-8); 30.9 (C-5); 29.7 (C18); 29.3 (C-3); 25.2 (C-9); 25.0 (C-20); 24.4 (C-19); 21.0 (C-16); 16.5 (C-4). HRMS (DCI-CH_4) m/z : calcd for $[C_{19}H_{28}O_2 + H]^+$ $[M+H]^+$ 289.2168 found 289.2158.

3. Results and discussion

*3.1. Chemical modification of α-atlantone **1***

To obtain lactones via a cyclocarbonylation catalytic route, α-atlantone **1** was chemically modified in order to synthesise a suitable homallylic alcohol. Heating the Z, E mixture of the two isomers of α-atlantone **1** to 160 °C in the presence of 5% palladium on activated carbon (Pd/C) quantitatively produces racemic ketone **2** which was transformed into alcohol **4** in the presence of allylmagnesium bromide **3** (Scheme 3).

4 is obtained in excellent yield (90%) as two diastereoisomers, **4a** and **4b**, in a 62:38 ratio (determined by GC) non-separable in the usual conditions of chromatography on silica gel.

3.2. Catalytic cyclocarbonylation

Previous studies in our group have shown that $[Pd(Cl_2)L_2]/SnCl_2.2H_2O$ catalytic system can be efficient in the cyclocarbonylation reaction on monoterpenes, such as isopulegol and isolimonene [13]. In a first step of experiments, the carbonylation reaction of this new substrate using $[Pd(Cl_2)(PPh_3)_2]/SnCl_2.2H_2O$ and conducted under optimised conditions18 [80°C, 40 bar of CO, 16h, toluene/DCM (dichloromethane) (1:1, v/v), P/Pd ratio of 2] affords a mixture of lactones such as the five-membered lactone **5** and the six-membered lactone **6** (Scheme 4). The six-membered lactone **6** is obtained as a mixture of two diastereoisomers **6a** and **6b** while the five-membered lactone **5** is formed as four diastereoisomers **5a**,**5a'**,**5b**,**5b'** due to the creation of a new asymmetric carbon.

It should be noted that high conversion (95%) and selectivity (80%) were obtained. We only observed a side reaction of dehydration giving a mixture of isomers [19].

As the steric and electronic properties of the phosphine ligands could play an important role in the selectivity of the cyclocarbonylation reactions [13a,**Error! Bookmark not defined.**] we have then investigated the influence of various monophosphine and diphosphine ligands (Figure 1).

Cyclocarbonylation using isolated palladium complexes of different monophosphines, including phosphole ligands, has been first studied. The results are compiled in Table 1.

The comparison of results show that the activities of these catalytic systems are strongly affected by the nature of the phosphine ligands as the conversion of the substrate ranges between 0 and 90%. The catalyst activity can be roughly correlated to the value of the phosphine cone angle. Indeed, ligands with cone angles between 145 and 212° (entries E11-E17) lead to active catalysts while ligands with smaller (entries E9-E10) and larger (entry E18) cone angles give less active or inactive catalysts. However, the electronic properties of the ligands also seem to influence the catalyst activity as phosphines having similar cone angles but different donating abilities [20,21] (entries E13-E14 and E15-E16) yield catalytic systems of different efficiencies.

However, all active catalytic systems are chemoselective producing a mixture of lactones **5** and **6** with high selectivities (80-85%) and regioselectivities in favor of lactone **6** with good diastereoselectivies (**6a**/**6b** ratio up to 82/18). It is interesting to note that $P(Cy)_3$ (entry E16) or $P(Mes)_3$ (entry E17) give the best catalysts in terms of chemo-, regio- and diastereoselectivities (up to a **6a/6b** ratio of 82/18 starting from a **4a/4b** mixture with a 62/38 ratio). It is worth to point out that diastereoisomer **4b** reacts with a lower rate than **4a** and accumulates in the remaining alcohol (Table 1).

Table 2 presents the results obtained with isolated palladium complexes of various diphosphine ligands. In the series of dppe, dppp, dppb ligands, which differ only by the number of methylene group in the linker between the two PPh_2 group (Figure 1b), conversions increased with the size of the linker from 10% to 49% (entries E19-E21). Similar trends with dppe and dppp were observed before in the cyclocarbonylation reaction [12a,22]. Interestingly, using dcpb (entry E22), with steric properties similar to the ones of dppb but different electronic properties, the conversions could be increased to 100% with even better chemoselectivity in favor of lactones (from 70% to 82%). The regioselectivity with these diphosphines is, contrary to the case of monophosphine ligand, now in favor of the five-membered lactone **5**. These results prompted us to try other wide bite angle diphosphines, namely dppf and xantphos. With dppf, the conversion could be increased but not the chemo- and regioselectivities (entry E23). However, it is interesting to note that the ratio of the two diastereoisomers **6a** and **6b** (65/35) is similar to that of the starting alcohol **4a, 4b** (62/38). With xantphos, excellent conversion of 100%, high chemoselectivity (82% for lactones) and excellent regioselectivity up to 99% in favor of the 5-membered ring lactones **5** is obtained (entry E24). We therefore find an excellent catalytic system to efficiently obtain the 5-membered ring lactone **5**.

As mentioned before, the 5-membered lactones **5** are obtained as a mixture of four diastereomers. The mixture resulting from the reaction with xantphos (entry 24) was analysed by GC and HPLC but unfortunately the ratio between the different isomers could not be precisely determined. In addition, the separation of the different products of the reaction proved to be difficult. Only the five-membered lactones could be separated from the six-membered lactones by column chromatography.

To get more insight into this cyclocarbonylation reaction, we have investigated the separation of the two diastereoisomers of alcohol **4**. These two diastereoisomers, **4a** and **4b**, are not

separable in the usual conditions of silica gel chromatography and difficult to separate by HPLC. By preparative HPLC, a pure sample of **4a** can be obtained as a racemic mixture but **4b** was always obtained with significant amounts of **4a** (>10%). The cyclocarbonylation reaction was then carried out with diastereoisomerically pure **4a** with the best catalytic systems, ie those with PCy_3 and xantphos (Tables 1 and 2, E16 and E24).

With PCy_3 catalytic system, alcohol **4a** can be converted to a mixture of only 3 lactones: **5a, 5a'** and **6a** (Table 3, entry E25*)* when 6 different lactones (**5a**, **5a'**, **5b**, **5b'**,**6a** and **6b**) are obtained starting from the **4a**/**4b** mixture **.** Similarly with xantphos, the reaction yields lactone **5** as a mixture of only **5a** and **5a',** while **5b** and **5b'** are also obtained from the **4a**/**4b** mixture. The catalytic tests have not been performed on alcohol **4b** but it must lead to **5b**, **5b'**and/or **6b**. This result shows that the racemic diastereoisomer **4a** yields only one single 6-membered lactone, **6a.** During this transformation, no new asymmetric carbon center is formed. We can suppose that the asymmetric carbons already present in **4a** are preserved during the catalytic reaction yielding only the lactones **6a.** Similarly, we can suppose that during the formation of lactones **5** the asymmetric carbons already present in **4a** are left untouched, producing only two lactones **5a** and **5a'** due to the creation of a new asymmetric carbon.

Compound **6a** could be isolated from the mixture obtained in E25 conditions but all attempts to separate **5a** and **5a'** failed, even from the mixture obtained in E26. In addition, the ratio of these 2 diastereoisomers could not be determined either by GC or HPLC in spite of several attempts.

3.3. Structural determination

Monocrystals of the six-membered ring compound **6a** suitable for X-ray diffraction analysis were obtained. Similarly, monocrystals were grown from a mixture of 5-membered ring lactones 5**a** and 5**a**'. The two compounds crystallised in a P2**1**/n centrosymmetric space

group, consistent with their racemic nature. A view of the two compounds is shown on Figures 2 and 3. Bond distances and angles are reported in Supporting Information. The difference between the two structures is the occurrence of pyran-2-one ring in compound **6a** and furan-2-one ring in compounds 5**a**/5**a'**. The geometry within the isobutyl and 2-p-tolylpropyl substituents is the same within experimental error as reported in Supporting Information.

The puckering parameters [23,24], θ= 134° and φ= 318.4°, observed for the pyran-2-one ring in **6a** are related to a half-chair conformation. In compound **6a**, there is a weak C-H π interaction between the C4 atom and the symmetry related tolyl ring: C-H = 0.96 Å; H---Cg = 2.83 Å; C4-H4---Cg = 163°(Cg is the centroid of the tolyl ring). From the molecular structure, depicted in Figure 2, the configurations could be determined. **6a** is the racemic mixture of (**6*S*,8*R***)-**6a** and (**6*R*,8*S***)-**6a**.

Owing to the disorder observed within the furan-2-one ring for compound **5**, the stereochemistry for the atom C5 could be (***R***) or (***S***): the two diastereomers **5a** and **5a'** are present in the unit cell. In addition, the two diastereoisomers cocrystallise in a 66/34 ratio, the major diastereoisomer, called **5a**, being the racemic mixture (**3*R***,***5S***,***8R***)/(**3*S***,***5R***,***8S***). Indeed, the minor diasteroisomer **5a'** is the (**3*R***,**5*R***,**8*S***)/(**3*S***,**5*S***,**8*R***) mixture. Whatever the disorder, the conformation of this ring is half-chair with puckering parameter φ= 89.8(5)°. Similar conformation has been also observed in related compounds [25].

Because the synthesis of **6a** from **4a** does not change the configuration of the asymmetric carbons (see above), we can conclude that the homoallylic alcohol **4a** is a racemic mixture of (**1*R*,6*R***)-**4a** and (**1*S*,6*S***)-**4a**. Therefore, **4b** is a racemic mixture of (**1*R*,6*S***) and (**1*S*,6*R***) isomers (see figure 4). We can also conclude that **6b**, the diastereoisomer of **6a**, is the racemic mixture of (**6*S***,**8*S***) and (**6*R***,**8*R***) isomers.

In the synthesis of five-membered lactones **5**, an additional asymmetric carbon is created yielding two different stereoisomers from **4a** (**5a** and **5a')** or **4b** (**5b** and **5b'**). As shown before, both **5a** and **5a'** cocrystallised. Indeed, the molecular structure confirms the configurations of the asymmetric carbons 5 and 8 already present in **4a** but the configuration of new asymmetric carbon 3 could not be determined (see Figure 4).

3.4 Influence of ligands and substrate on selectivities

Finally, the question arises on the control of the regioselectivity and the stereoselectivity for the formation of lactones which suggests that different intermediates might be involved in the catalytic cycle. From the commonly accepted catalytic cycle involving the formation of a Pd-H key intermediate [13d,26] (Figure 5), the regioselective determining step (step B) occurs during the insertion of the C-C double bond in the [Pd]-H bond and leads to the lactone **6** from the linear intermediate and lactone **5** from the branched intermediate. Our results show that the ligand is able to control this regioselectivity since diphosphine ligand such as xantphos gives mainly lactones **5** while monophosphine ligand such as PCy_3 promotes essentially lactone **6** formation. In addition, it is worth to point out that a control by the substrate itself is observed since the regioselectivities observed with diasteroisomers **4a** and **4b** are significantly different. Indeed lactone **6** is mainly derived from alcohol **4a** while the lactone **5** is mainly derived from alcohol **4b** (see table 4).

The substrates **4** could induce asymmetric induction but as the ratio of the four diastereoisomers of **5** could not be determined at this stage, we cannot validate this hypothesis.

4. Conclusions

In this article, we described efficient palladium-based catalytic systems for the cyclocarbonylation of homoallylic alcohols **4** obtained by straightforward chemical transformation of natural atlantone extracted from Moroccan Atlas Cedar. High catalytic

activities as well as high chemoselectivities in favour of lactones could be achieved. The regioselectivity can be easily switched by a judicious choice of ligands in favour of 5 membered ring lactone **5** or 6-membered ring lactone **6**. When monophosphines, such as PCy_3 ligand, are used, the major product is the lactone **6**. In contrast the use of diphosphines as auxiliary ligands affords the lactone **5**, with almost total regioselectivity when the ligand xantphos was used. The reversal of regioselectivity by changing monophosphines by diphosphines could be related to the geometry of the corresponding palladium complexes: *trans* relative geometry of the two phosphines in the square-planar complexes for monophosphines and *cis* geometry for diphosphines. To the best of our knowledge, this work is the second example of efficient synthesis and modulated regioselectivity into γ-lactone or δ-lactone starting from the same homoallylic alcohol [27]. Further studies including theoretical calculations are currently in progress to get more insights in the effect of both ligands and substrates on the outcome of the catalytic reaction.

Moreover in the general context of the use of biomass, obtention of enantiomerically pure lactones **5** and **6** is of high interest because they could be valuable intermediates in agrochemical and pharmaceutical industries. Two approaches involving either the resolution of racemic alcohols **4a** and **4b** or asymmetric catalytic carbonylation with chiral phosphines will be explored.

Acknowledegments

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Supplementary data

^{1}H and ^{13}C NMR, 2D NMR data for new compounds. Including also X-ray data for compounds **5a, 5a'** and **6b**.

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Figures And Tables:
Scheme 1 Selective cyclocarbonylation of various alkenols.

Scheme 2 Regioselectivity of cyclocarbonylation of various allylic and homoallylic terpenols

Scheme 3 Synthesis of homoallylic alcohol 4.

Scheme 4 Cyclocarbonylation reaction of compound 4. Figure 1 Phosphine ligands used in this study. Figure 2 Molecular structure of 6a. Only one enantiomer is represented Figure 3 Molecular structure of 5a. Only one enantiomer is represented. Figure 4 Stereochemistry of compounds 4a, 4b, 5a, 5a', 5b-b', 6a, 6b (only one enantiomer is represented for each compound).

Figure 5. Proposed catalytic cycle.

Table 1: Cyclocarbonylation of **4a**, **4b** catalysed by [$PdCl_2L_2$/$SnCl_2$,$2H_2O$], L=monophosphine

Entries	Ligand L	Cone Angle [1]	Conversion[a] (%)	Selectivity in lactones %[a,b,c]	**5**/**6** ratio[b]	**6a**/**6b** ratio[b]
E9	P(*n*-$Bu)_3$	130	0	/	/	/
E10	PPh_2Me	136	15	80	33/67	nd
E11	PPh_3	145	95	80	33/67	67/33
E12	P(*p*-$FC_6H_4)_3$	145	91	85	34/66	68/32
E13	DBP	147	60	80	32/68	68/32
E14	TMP	150	73	81	31/69	68/32
E15	TPP	167	61	82	34/66	67/33

E16	**$P(Cy)_3$**	**170**	**90**[c]	**85**	**20/80**	**82/18**
E17	**$P(Mes)_3$**	**212**	**85**[c]	**82**	**20/80**	**75/25**
E18	JohnPhos	246	0	/	/	/

Conditions : S/C =50, $SnCl_2$/C= 2.5, P_{CO}=40 bar, T(°C)=80, t(h)=16, 1 mmol **4a**,**4b** in 10mL (toluene/DCM:(1/1)). [a] selectivity: moles of lactones **5** and **6**/moles of converted substrate. [b] determined by GC. [c] the ratio of the four diastereoisomers of the minor lactone **5** could not be determined due to a difficult separation. [c] in the remaining alcohol, the **4a/4b** ratio is 30/70 for E16 and 33/67 for E17 starting from an initial **4a/4b** ratio of 62/38.

Table 2: Cyclocarbonylation of **4a, 4b** catalysed by [$PdCl_2(L_2)/SnCl_2,2H_2O$], L_2 =diphosphine

Entry	Ligand L	Bite angle [1]	Conversion (%)	Selectivity in lactones[a] (%)	**5/6** ratio[b]
E19	dppe	78	10	-	-
E20	dppp	86	15	-	-
E21	dppb	98	49	70	71/29
E22	dcpb[c]	-	100	82	68/32
E23	dppf[d]	99	81	69	62/38
E24	**xantphos**	**110**	**100**	**82**	**>99/1**

Conditions: S/C =50, acid/C= 2.5, P_{CO}=40 bar, T=80°C, t(h)=16 Solvent 10mL (toluene/DCM:(1/1). [a] selectivity: moles of lactones **5** and **6**/moles of converted substrate [b] determined by GC. [c] bite angle not determined. [d] for E23, the **4a/4b** ratio is 60/40 in the remaining alcohol, and the **6a/6b** ratio is 65/35.

Table 3 : Cyclocarbonylation of **4a** catalysed by [$PdCl_2L_2$ / $SnCl_2,2H_2O$] system

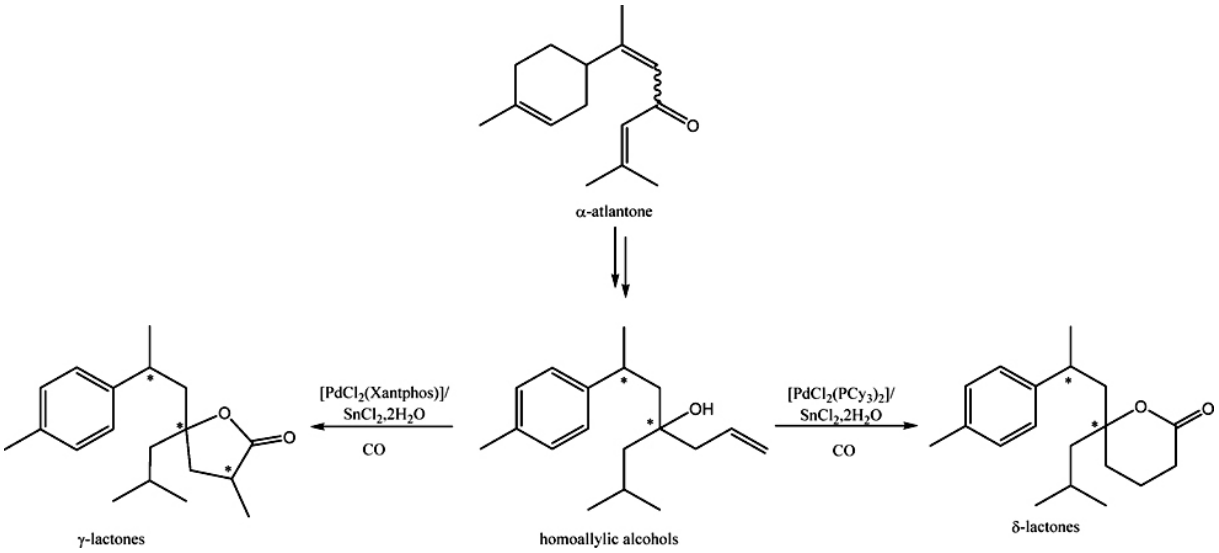
Entry	Ligand L	Conversion[b] (%)	Selectivity in lactones[a, b] (%)	**5/6** ratio[b]
E25	PCy_3	92	85	19(**5a+5a'**)/81(**6a**)
E26	**xantphos**	100	84	>99(**5a+5a'**)/1(**6a**)

Conditions : S/C =50, $SnCl_2$/C= 2.5, P_{CO}=40 bar, T(°C)=80, t(h)=16 Solvent 10mL (toluene/DCM:(1/1)). [a] selectivity: moles of lactones **5** and **6**/moles of converted substrate [b] determined by GC

Table 4: Products distribution in the reactions E16 and E17

		Products distribution			
	homoallylic alcohol	remaining alcohol	lactones **6**	Lactones **5**	byproducts[a]
E16 conversion 90% lactones 85% **(5/6=20/80) (6a/6b=82/18)**	**4a** 62%	**4a** 3%	**6a** 55,8%	**5a** 0-3,2%	0-5%
	4b 38%	**4b** 7%	**6b** 12,2%	**5b** 13,8-18,8%	0-5%
	100%	10%	68%	17%	5%
E17 conversion 85% lactones 82% **(5/6=20/80) (6a/6b=75/25)**	**4a** 62%	**4a** 4,95	**6a** 49,2%	**5a** 4,85-7,85%	0-3%
	4b 38%	**4b** 10,05	**6b** 16,4%	**5b** 8,55-11,55%	0-3%
	100	15%	65,6%	16,4%	3%

[a] dehydrated products from **4a** or **4b**.



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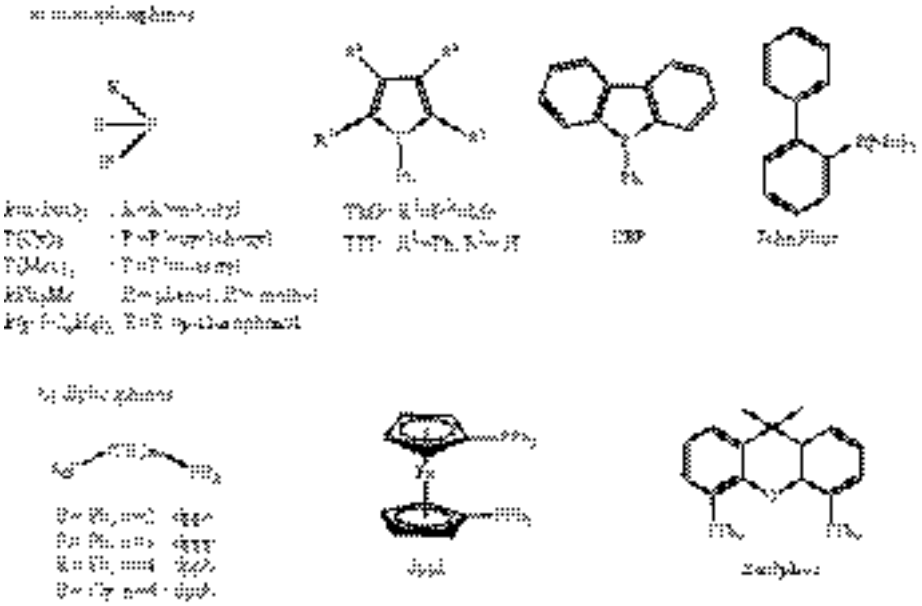

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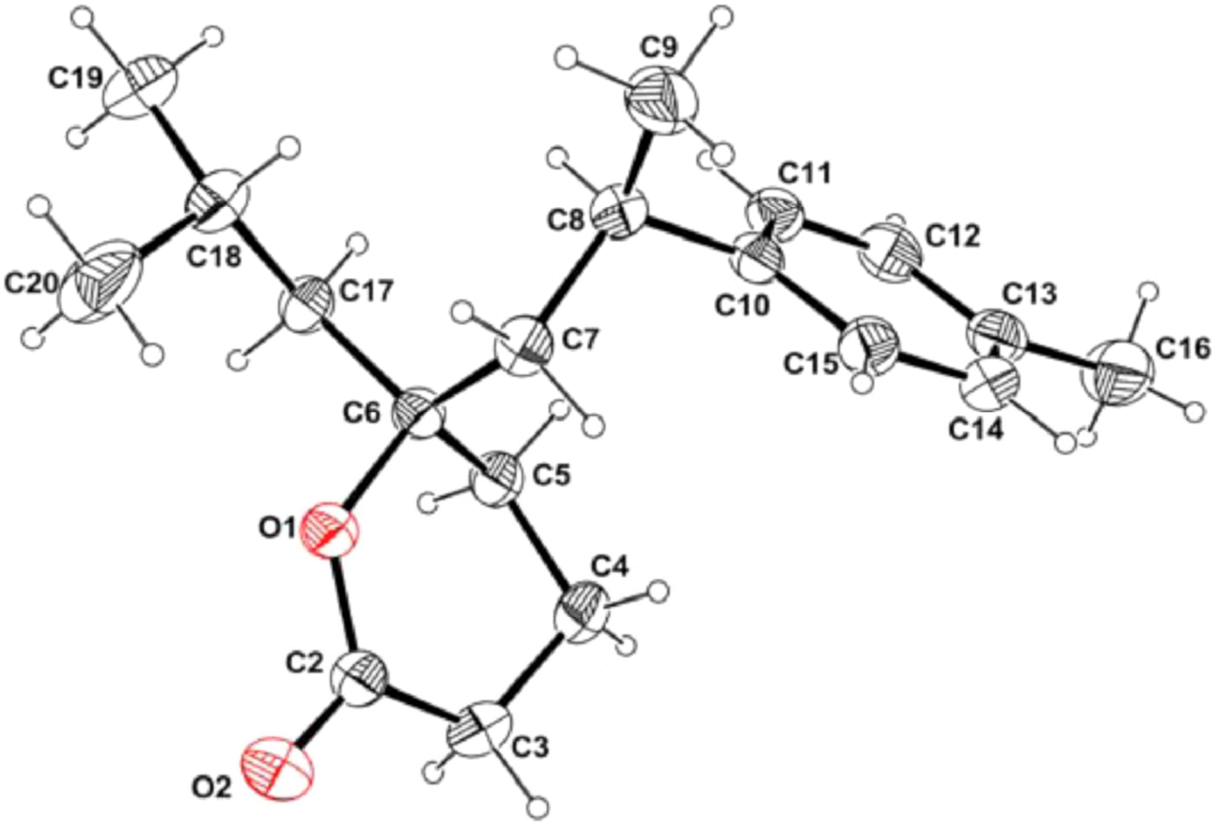

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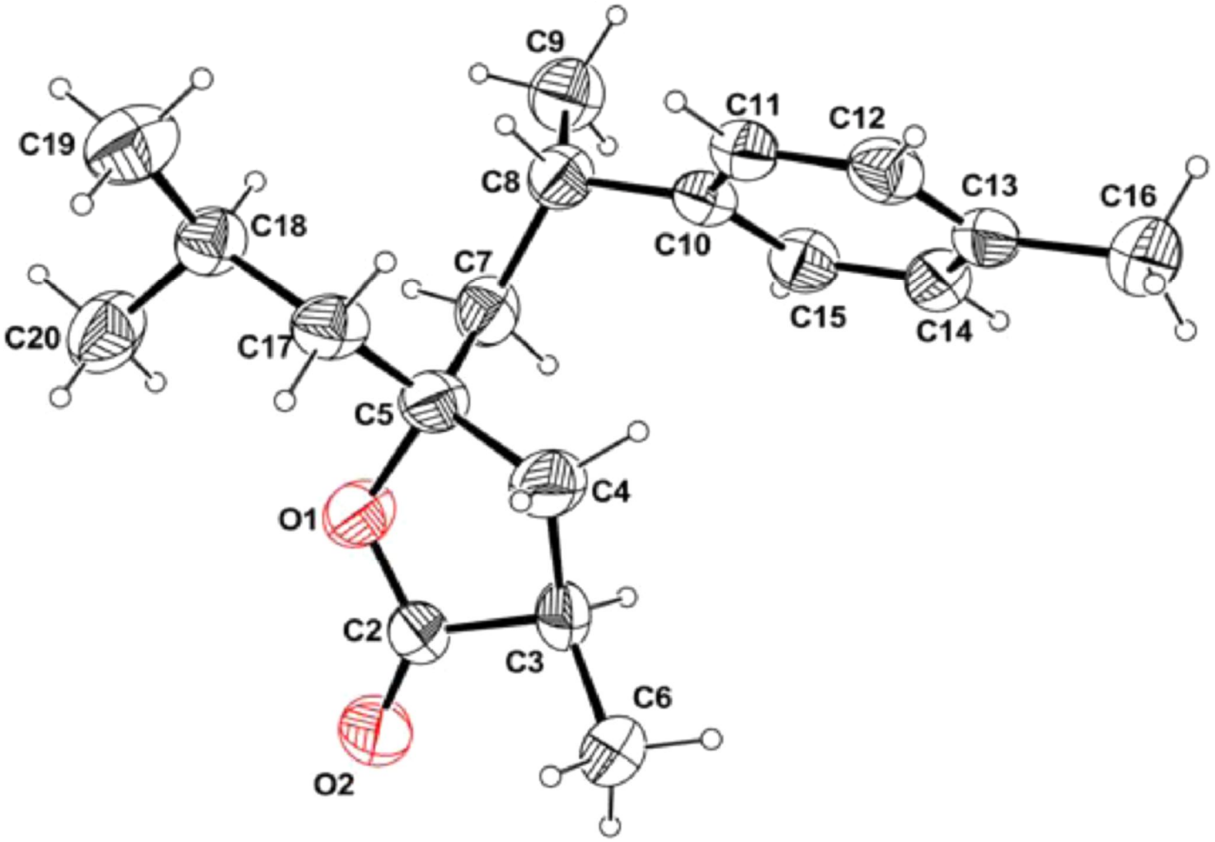

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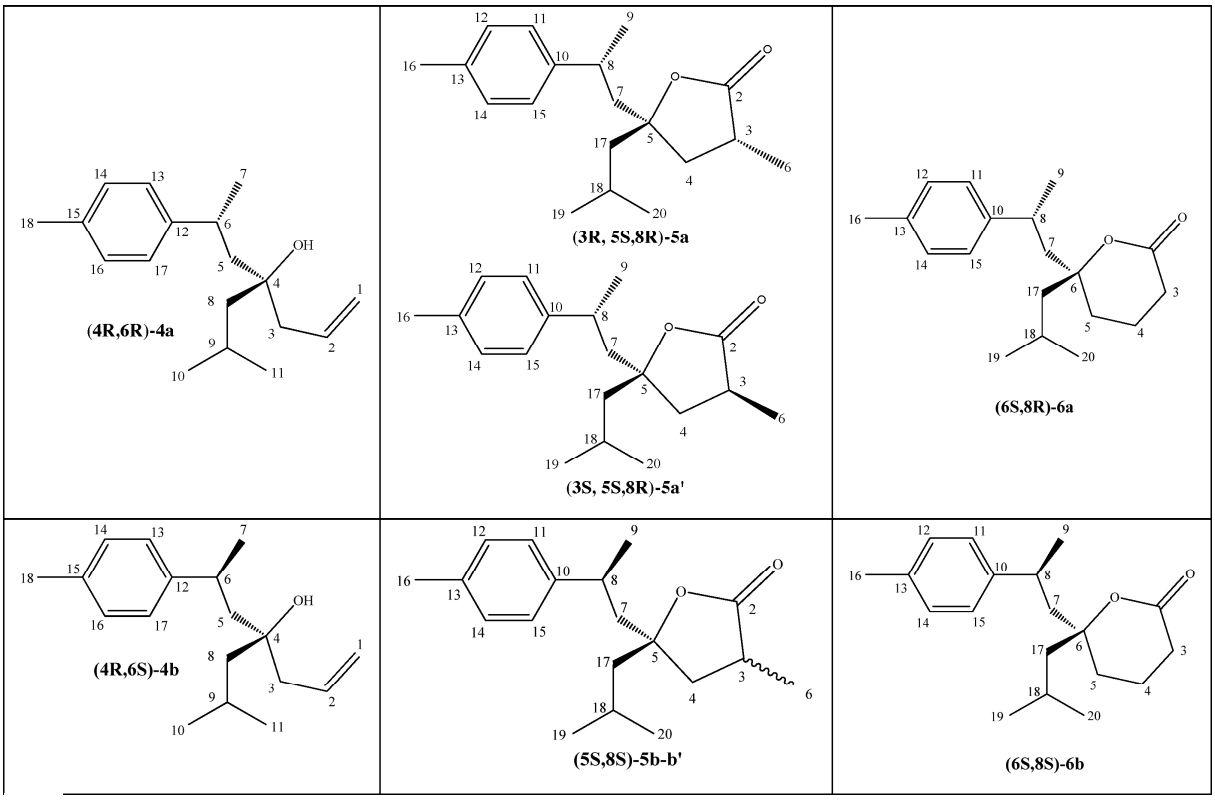

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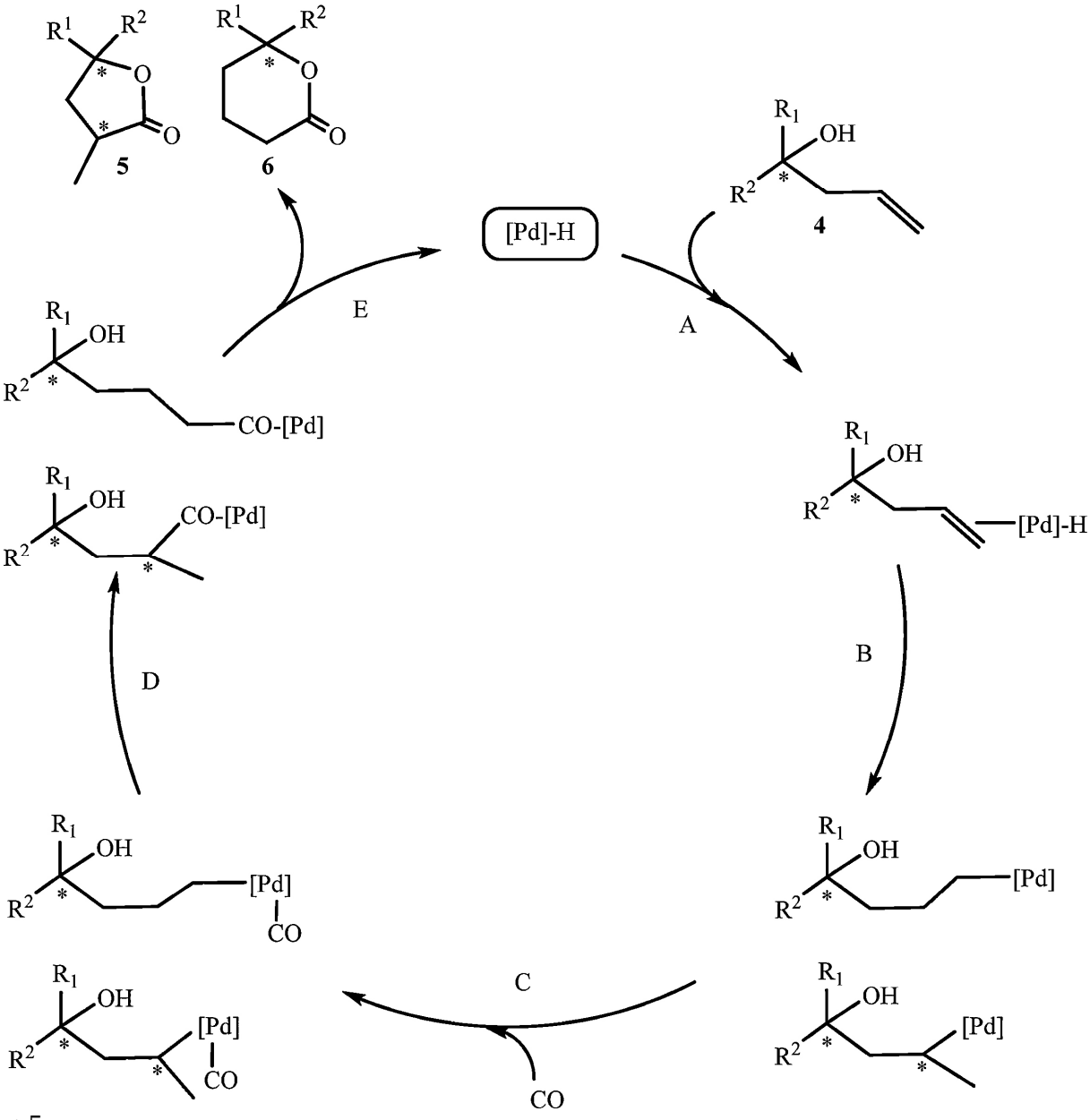

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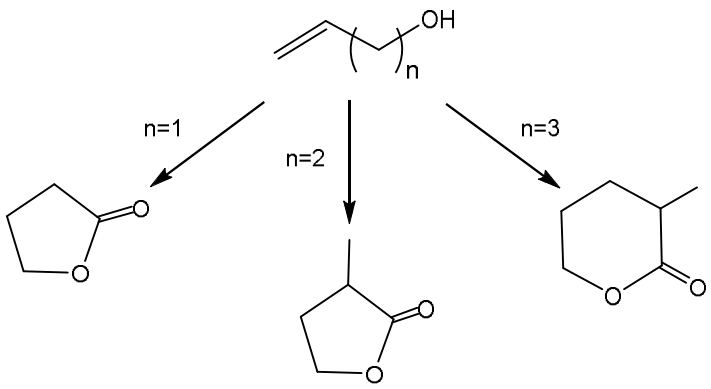
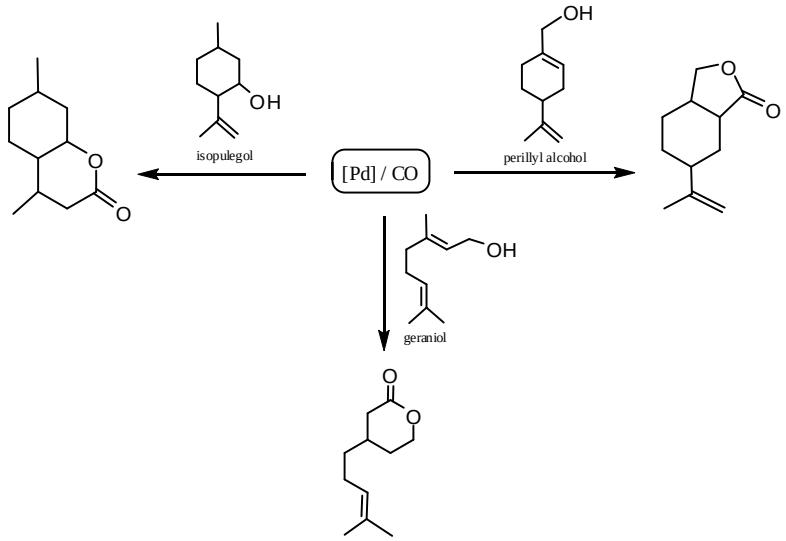
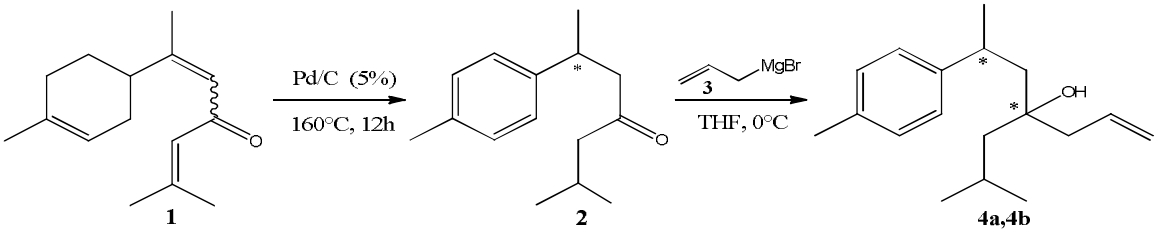


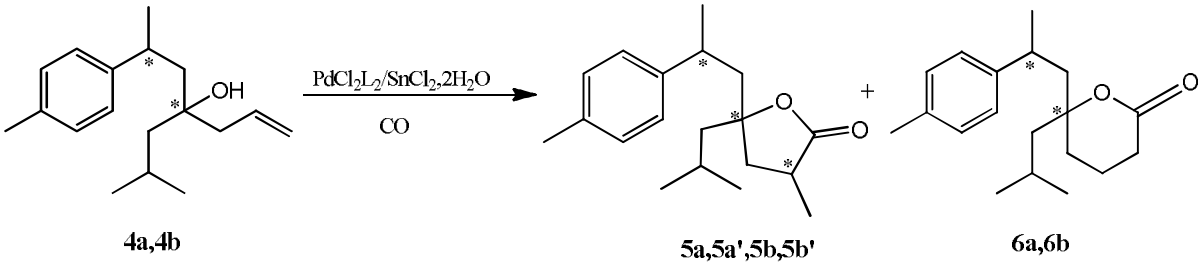
Scheme 1



Scheme 2



Scheme 3



Scheme 4