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An efficient catalytic system for cyclocarbonylation of terpenes into lactones†

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Three different kinds of representative monoterpenic alcohol are involved in the palladium-catalysed cyclocarbonylation reaction. Lactone formation is shown to occur when cyclic (1), tertiary (3) and primary allylic alcohol (7) functions are reacted, in the presence of CO with [$HPd(SnCl_3)L_2$] as the active catalytic species. Good yields and selectivities can easily be reached for isopulegol (1), and dihydromyrcenol (3). However, more modest results are obtained for the functionalization of geraniol into the original lactone (9). This lactone can be largely favoured by using a basic chelating diphosphine ligand such as 1,4-bis(diphenylphosphino)butane. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: cyclocarbonylation; lactone; monoterpenes; homogeneous catalysis; palladium hydride

INTRODUCTION

Hemi-synthesis is a powerful strategy to combine tandem reactions and retro-synthesis, and to produce relatively sophisticated molecules that display biological activity.[1,2] For several years now, we have been interested in the design of selective tools using coordination catalysis and we have demonstrated that, in some cases, it is possible to combine two successive steps to transform a relatively complicated substrate into a functionalized and useful product; thus, the palladium-catalysed cyclocarbonylation of isolimonene produces, in somewhat mild conditions, a cyclopentanone fused to the starting cyclohexyl moiety.[3]

We have been concerned with the definition of versatile palladium precursors to catalyse this type of reaction using various representative C_{10} starting materials in order to obtain lactones of different sizes selectively. Based on our experience on the carbonylation of isopulegol, (which provides a six-membered lactone with a quasi-quantitative yield, a complete regioselectivity, and a good diastereoselective excess[4]), we investigated the reaction starting from dihydromyrcenol (a terminal alkene containing a tertiary alcoholic function) and from geraniol (an allylic alcohol for which the first step requires an isomerization reaction of the C=C double bond).

RESULTS AND DISCUSSION

The cyclocarbonylation of isopulegol has recently been described. This is interesting to summarize, because it provides our first entry into the synthesis of lactones by this type of reaction (Fig. 1).[3]

The catalytic precursor is [$PdCl_2L_2$] in the presence of a slight excess of tin(II) chloride and the L phosphine ligand. From [$PdCl(SnCl_3)(PPh_3)_2$], a palladium hydride active species is generated in the medium, with hydrogen arising from the water-gas-shift reaction (Eqn (1)) and water coming from traces of water in the medium or from dehydration of the alcohol:[5]

$$CO + H_2O \rightleftharpoons CO_2 + H_2 \qquad (1)$$

In some cases the substrate itself can assist the formation of the hydride, especially when an allylic function is present.[6,7]

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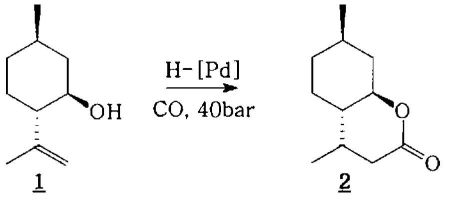

Figure 1. Cyclocarbonylation of isopulegol **1**.

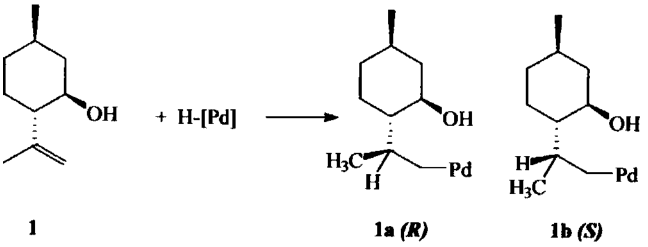

Figure 2. Hydride transfer from palladium complex to isopulegol **1**.

We have learned in this chemistry that the ligand is preferably a bidentate diphosphine and not necessary chiral. The enantioselectivity is, in fact, induced by the chirality of the substrate itself when the hydride is transferred onto the exocyclic C=C double bond (carbon C5).[4] Moreover, we suspect that an interaction, rather than a coordination, of the hydroxyl group assists the stereodifferentiation along this step (Fig. 2).

Further coordination of CO, then CO migratory insertion, cyclization to produce the lactone and regenerate the palladium hydride have no influence on the stereodifferentiation. The catalytic cycle is summarized in Fig. 3.

Dihydromyrcenol is interesting because it is representative of an acyclic terpene containing a terminal C=C bond and a tertiary hindered alcohol. Cyclocarbonylation of this substrate under the same mild conditions and with the same catalytic system is a little bit more complicated because. This is because dehydration of the tertiary alcoholic function can occur, leading to a hydroxycarbonylation reaction, transforming the resulting dihydromyrcene into the corresponding acid (Fig. 4).

In order to ensure the lactone route, it is necessary to avoid not only the dehydration step, but also the presence of any water in the medium. We have observed that any trace of hydrochloric acid in the solvent induces dehydration, and we discovered that the simple addition of molecular sieves removes both HCl and water. Thus, at 40 bar of CO, and 75 °C, chemo- and regio-selectivities of 100% and 98% respectively can be reached for a conversion of 60% over 40 h.[7] Thus, the nine-membered lactone can be produced by a one-pot reaction.

Geraniol presents an allylic alcohol functionality, and we were interested in exploring its reactivity in the present

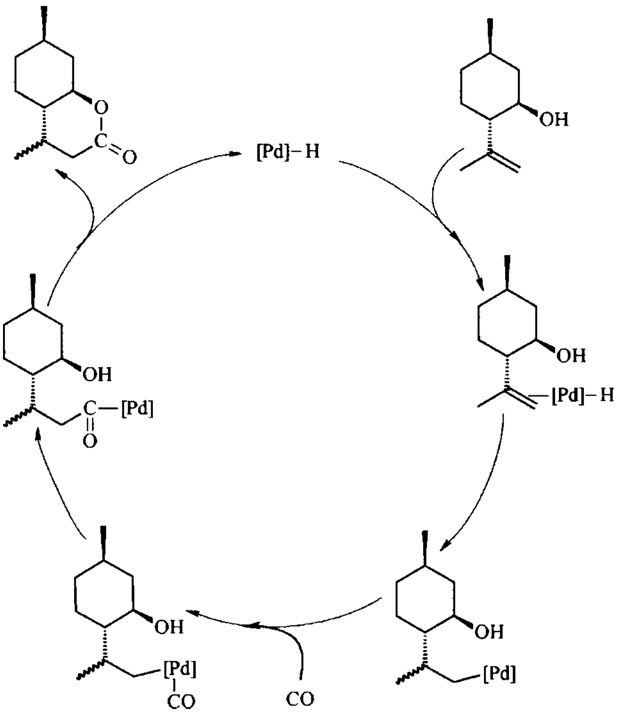

Figure 3. Catalytic cycle proposed for the cyclocarbonylation of isopulegol **1**.

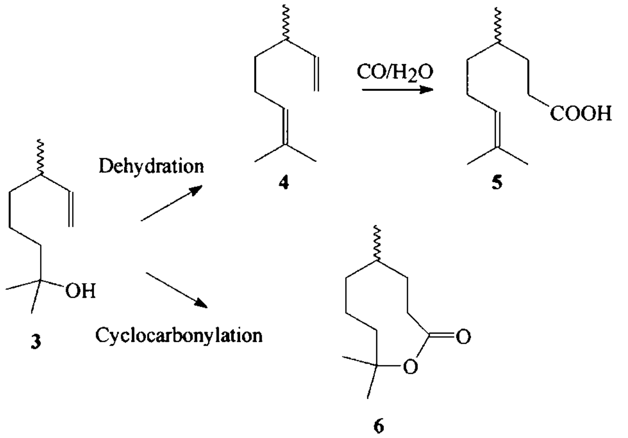

Figure 4. Competitive pathways during the carbonylation reaction of dihydromyrcenol **3**.

carbonylation reaction. Starting from $[HPd(SnCl_3)(PPh_3)_2]$ generated *in situ*, pressures as high as 80–100 bar are necessary to convert the substrate. In fact, three carbonylated products are synthesized, as shown in Fig. 5.

Table 1 displays some results for reactions performed between 60 and 100 °C for 16–40 h. Run 2 is representative of such a carbonylation, since at 100 bar and 80 °C (16 h) a conversion of *ca* 72% of geraniol is observed, providing roughly 13% of acid **8**, 2% of lactone **9**, and 65% of the ester **10**, which results from the esterification by **7**

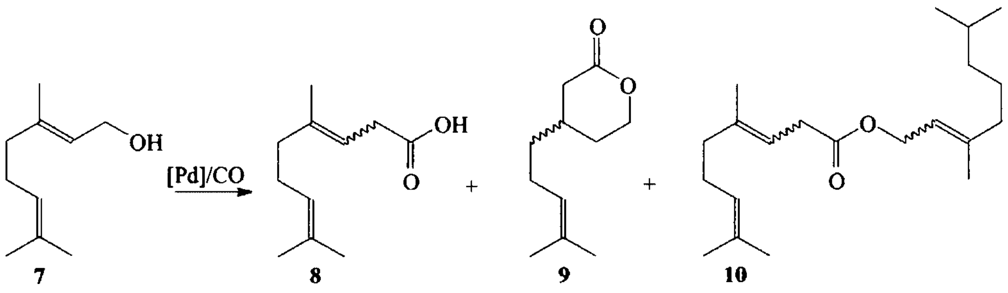

Figure 5. Main products obtained during the carbonylation of geraniol **7**.

Table 1. Carbonylation of geraniol with [PdCl$_2$(PPh$_3$)$_2$] precursor

Entry	P_{CO} (bar)	T (°C)	Time (h)	Conversion (%)[a]	**8** (%)[a,b]	**9** (%)[a,b]	**10** (%)[a,b]
1	100	60	16	48.1	11.5	2.7	67.6
2	100	80	16	71.8	13.3	1.6	64.6
3	100	80	40	74.2	10.2	1.4	75.5
4	100	100	16	67.6	14.7	4.7	51.7
5	80	80	16	59.9	13.3	2.5	68.5

Conditions: catalytic precursor, 1 mmol; excess of PPh$_3$, 2 mmol; SnCl$_2$, 2.5 mmol; toluene, 25 ml, substrate/catalyst ratio S/C = 50.
[a] Determined by GC.
[b] Selectivity (%).

of acid **8**. Other non-carbonylated products arising from isomerization, dehydration of the allylic alcohol function or etherification of the substrate are not taken into account here (*ca* 20%). This reaction, in fact, has some flexibility, as even at 80 bar a 75% conversion can be gained in 40 h.

Introduction of a diphosphine ligand, such as 1,4-bis-(diphenylphosphino)butane (dppb) or 1,1′-bis-(diphenylphosphino)ferrocene (dppf), into the coordination sphere of palladium moves the selectivity. Table 2 shows the main results observed during our study.

The chelating dppf ligand has a deceptive behaviour, because the yield in acid is increased, as well as the by-products, and it is necessary to operate at a lower pressure to obtain 7% of lactone **9**. Interestingly, dppb allows a more satisfactory yield in lactone versus acid **8** and ester **10**, although significant amounts of the ether and isomerized products are still present. Thus, at 100 bar, 80 °C and for 16 h, a conversion of 40% of geraniol gives a selectivity of 22% in lactone **9**. At lower pressure, such as 50 bar, the conversion is 60% and the selectivity in lactone is increased slightly to 25%.

This carbonylation reaction provides interesting insights into the mechanism. Indeed, the lactone formation involves the reactivity of the palladium hydride species, as shown in Fig. 6.

Moreover, a first step of migration of the C=C double bond to form a methylidene group substituting the C8 chain is necessary. This involves hydride transfer followed by a β-H elimination, then a further hydride transfer to reach

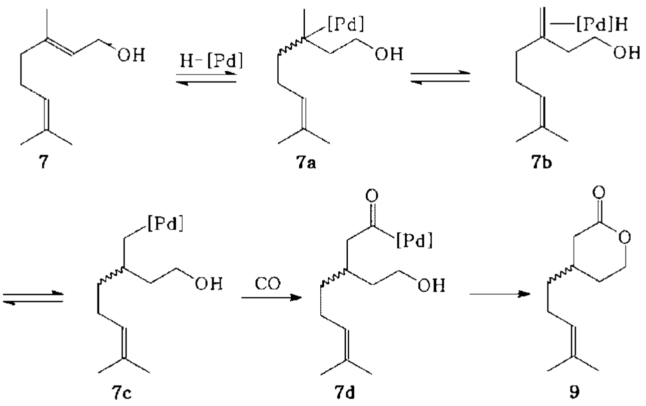

Figure 6. Mechanism proposed for the cyclocarbonylation of geraniol **7** into the lactone **9**.

Table 2. Carbonylation of geraniol with [PdCl$_2$(diphos)] precursor

Entry	Ligand	P_{CO} (bar)	T (°C)	Time (h)	Conversion (%)[a]	**8** (%)[a,b]	**9** (%)[a,b]	**10** (%)[a,b]
1	dppf	65	100	16	50	27	3	7
2	dppf	80	100	16	70	20	4	0
3	dppb	100	80	16	40	Traces	22	Traces
4	dppb	50	80	24	60	Traces	25	Traces

Conditions: catalytic precursor, 1 mmol; excess of diphosphine, 1 mmol; SnCl$_2$, 2.5 mmol; toluene, 25 ml; S/C = 50.
[a] Determined by GC.
[b] Selectivity (%).

the intermediate **7c**. CO migratory insertion gives the acyl species, and intramolecular reaction of the alcohol function restores the palladium hydride active species and the lactone **9**. In addition, this hydride route explains the formation of isomerized products. Figure 7 shows one of the isomers obtained.

Analysis of the mechanism by which acid **8**, and thus ester **10**, is formed dictates the involvement of a palladium(0) species, which reacts with geraniol by an oxidative addition reaction (see Fig. 8).

This mechanism is supported by the identification of myrcene **11**, which results from the dehydration of the intermediate **7e**. Carbonylation and CO migratory insertion provide the acyl species **7f**, which gives directly acid **8** by reductive elimination. Similarly, reaction of one more molecule of geraniol on **7f** produces the ester **10**.

There are a few results in the literature concerning the carbonylation of allylic-alcohol-containing monoterpenes. Alper and co-workers[8,9] have shown that $Pd(dba)_2$ and dppb is an efficient entry for the cyclocarbonylation of tertiary allylic alcohols into the corresponding γ-butyrolactones. Similarly, they investigated the cyclocarbonylation of β,γ-disubstituted allylic alcohol. The related catalytic system $\{Pd(OAc)_2 + \text{dppb}\}$ allows, in the same experimental conditions (~55 bar, 110 °C), provided a small partial pressure of hydrogen is introduced, the conversion of perillyl alcohol (a terpene in which the C=C double bond related to the allylic moiety is endocyclic) into a bicyclicfuranone, as shown in Fig. 9.

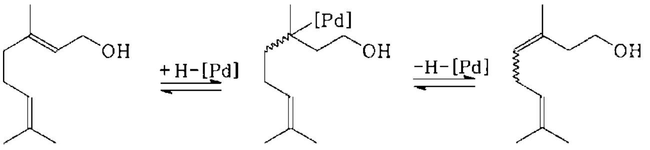

Figure 7. Isomerization reaction of geraniol **7**.

El Ali and Alper observed that lactones are only produced when dihydrogen is present in the medium and when the allylic function is β,γ-substituted; they assumed that a palladium hydride species is responsible for the lactone formation.[8]

CONCLUSIONS

We generated properly in the reaction conditions the active species $[HPd(SnCl_3)(PPh_3)_2]$, which is very efficient at converting a terpenic alcohol into the corresponding lactone. The yields and selectivity in lactone remain at a modest level for geraniol, due to the fact that the C=C double bond needs to be shifted during a preliminary isomerization step. The hydride route, for which intermediate species are under investigation, is presumably favoured when the $(SnCl_3)^-$ ligand is introduced in the coordination sphere.[10] No hydrogen is necessary in this case. As we succeeded in the successive isomerization–carbonylation–cyclization steps for geraniol and that we dispose of a convenient tool for tandem carbonylations, studies are under way to improve and extend this reaction to various terpenic allylic alcohols in the reaction.

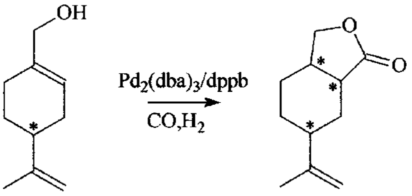

Figure 9. Palladium-catalysed carbonylation of perillyl alcohol, adapted from Ref. 9.

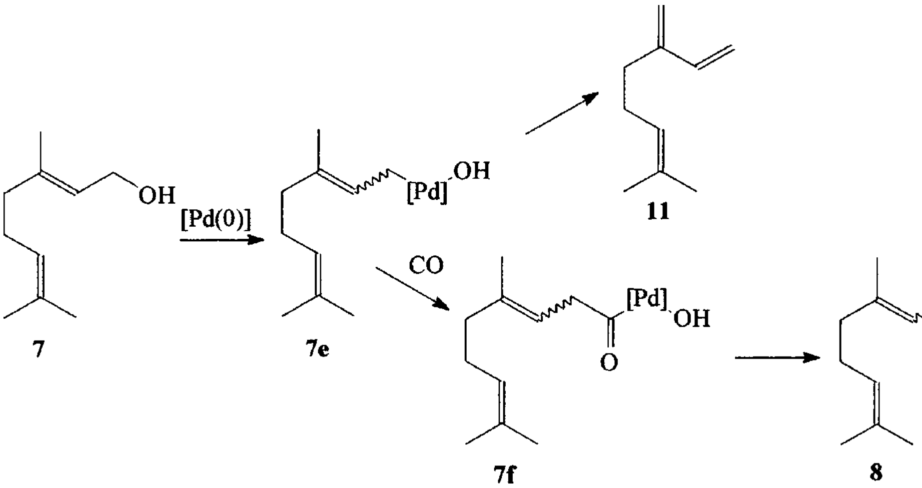

Figure 8. Palladium-catalysed carbonylation of geraniol into acid **8** and dehydration into myrcene **11**.

EXPERIMENTAL

General procedure: a mixture of $[PdCl_2(PPh_3)_2]$ (0.702 g, 1 mmol), or $[PdCl_2(dppf)]$ (0.732 g, 1 mmol) or $[PdCl_2(dppb)]$ (0.604 g, 1 mmol), $SnCl_2 \cdot 2H_2O$ (0.564 g, 2.5 mmol) and PPh_3 (0.524 g, 2 mmol), or dppf (0.554 g, 1 mmol) or dppb (0.435 g, 1 mmol), was introduced into a 250 ml Hastelloy autoclave with mechanical stirring. A solution of geraniol (50 mmol, 7.71 g) in freshly distilled toluene (25 ml) was added. The autoclave was sealed, flushed with nitrogen and then heated under CO pressure. At the end of the reaction, the autoclave was allowed to cool and then slowly depressurized. The crude mixture withdrawn was treated with a few drops of CCl_4 to precipitate organometallic compounds and the phosphine excess. Then the solution was analysed by gas chromatography (GC).

GC analyses were performed on a Perkin Elmer 8500 apparatus equipped with a J&W Scientific DB-5 (30 m, 0.53 mm, 0.25 μm) capillary column and a flame ionization detector. Products were identified by GC–mass spectrometry (MS) on a Perkin Elmer TurboMass, with a J&W Scientific DB-5MS (30 m, 0.25 mm, 0.25 μm).

Spectral data for **2**: see Ref. 4. Spectral data for **5** and **6**: see Ref. 7.

Spectral data for **8**. ^1H NMR (200 MHz, $CDCl_3$): δ 9.32 (s, 1H, OH), 5.23 (t, $J = 7$ Hz, 1H), 5.00 (t, 1H), 2.98 (d, $J = 7.1$ Hz, 2H), 1.97 (m, 4H), 1.58 (s, 3H), 1.54 (s, 3H), 1.50 (s, 3H). $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$): δ 172.4, 142.1, 131.7, 123.9, 118.4, 39.5, 33.7, 26.4, 25.6, 17.6, 16.4.

Spectral data for **9**. IR (CH_2Cl_2): ν 1735 cm^{-1} (C=O), 1184 cm^{-1} (C–O). GC–MS (CI) m/z (rel. int.): 183 ($M + 1$, 5.4), 200 ($M + 18$, 33.8).

Spectral data for **10**: IR (CH_2Cl_2): ν 1736 cm^{-1} (C=O), 1135 cm^{-1} (C–O). GC–MS (CI) m/z (rel. int.): 319 ($M + 1$, 4.9), 336 ($M + 18$); 46.9. ^1H NMR (200 MHz, $CDCl_3$): δ 5.34 (t, $J = 7$ Hz, 2H), 5.09 (t, 2H), 4.60 (d, $J = 7.2$ Hz, 2H), 3.05 (d, $J = 7$ Hz, 2H), 2.04 (m, 8H), 1.68 (s, 6H), 1.60 (s, 12H). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 172.4, 142.1, 138.9, 131.7, 123.9, 118.4, 115.8, 61.4, 39.5, 33.7, 26.4, 25.6, 17.6, 16.4.

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