Palladium-Catalyzed Oxidation of Monoterpenes: Novel Aerobic Pd(II)/Cu(II)-Catalyzed Oxidation of Linalool under Chloride-Free Nonacidic Conditions

Marcelo G. Speziali, Patrícia A. Robles-Dutenhefner, and Elena V. Gusevskaya*

Departamento de Química, Universidade Federal de Minas Gerais, Belo Horizonte 31270-901, MG, Brazil

Received March 21, 2007

Linalool, a monoterpenic allylic alcohol, has been efficiently and selectively oxidized by dioxygen in methanol and ethanol solutions using a chloride-free $Pd(OAc)_2$/$Cu(OAc)_2$ catalytic system under nonacidic conditions. Corresponding allylic ether arising from the exclusive oxidation of a trisubstituted internal double bond has been characterized as a major product in each alcohol. In methanol, this product, 7-methoxyhotrienol, was obtained in virtually quantitative yield. It is remarkable that a monosubstituted terminal double bond of the substrate remains intact. In acetic acid, catalytic palladium turnover was achieved only by using benzoquinone as a terminal oxidant, with the regioselectivity of allylic oxidation being completely switched from that in alcohols. A major product is 8-linalyl acetate, formed with up to 85% selectivity. All linalool derivatives obtained have a pleasant scent with a flower or fruit tinge and are natural products found either in exotic plants or in grape wines. To the best of our knowledge, the present work reports a first synthesis of these functionalized monoterpenes, potentially useful as components of synthetic perfumes. On the basis of the results obtained, the mechanism of this unusual oxidation reaction involving the formation of various organometallic intermediates is discussed, with bimetallic Pd−Cu catalysis being suggested.

Introduction

Monoterpenes constitute a class of natural products that can be transformed into compounds commercially important for industrial production of fragrances, perfumes, flavors, and pharmaceuticals as well as synthetic building blocks.[1−4] For example, linalool, a monoterpenic allylic alcohol with a pleasant lily odor, is a key intermediate for the synthesis of various vitamins and fragrance chemicals, such as citral, geraniol, and citronellol.[1,5] This compound is available from essential oils of some plants and flowers, like lavender, but most linalool is produced synthetically from α-pinene, an inexpensive major constituent of turpentine oils obtained from coniferous trees.[1,5] Although linalool is itself a fragrance ingredient and can be found in many fine fragrances, cosmetics, and noncosmetic products, such as household cleaners and detergents,[6] the use of this compound can be significantly extended by its oxyfunctionalization.

Palladium complexes are remarkably versatile reagents for the selective oxidation of organic molecules. These reactions can be made catalytic with the use of reversible co-oxidants for the reoxidation of Pd(0), with $CuCl_2$ being the most convenient one (Wacker catalyst). However, the system with $CuCl_2$ and chloride ions is highly corrosive because of its acidic conditions and often causes the formation of chlorinated side products. Hence, much effort has been devoted to the development of alternative cocatalysts, such as heteropoly acids, nitrates, and benzoquinone,[7,8] as well as palladium catalysts containing oxidatively robust ligands to stabilize the palladium catalyst and promote dioxygen-coupled catalytic turnover.[9−13] In the latter systems, catalyst regeneration occurs by the direct reaction of molecular oxygen with reduced palladium species.

For several years, we have been interested in catalytic transformations of monoterpenes, in particular, their palladium-catalyzed oxidations.[14−18] The most abundant nonfunctionalized monoterpenes, such as limonene, pinenes, camphene, and myrcene, have been mainly used as substrates in our work. On the other hand, diversification of substrates by using oxygenated terpenoids can afford products bearing several functional groups hardly accessible by conventional synthetic routes. These products can show interesting olfactory characteristics and also can be useful as bi- or polyfunctionalized intermediates for organic syntheses, thus opening new entries to many valuable compounds. For example, we have recently studied the process

---

* Corresponding author. E-mail: elena@ufmg.br.

(1) Erman, W. E. *Chemistry of the Monoterpenes: An Encyclopedic Handbook*; Marcel Dekker: New York, 1985.

(2) Monteiro, J. L. F.; Veloso, C. O. *Top. Catal.* **2004**, *27*, 169.

(3) Bauer, K.; Garbe, D.; Surburg, H. *Common Fragrance and Flavor Materials: Preparation, Properties and Uses*; Wiley: New York, 1997.

(4) *The Chemistry of Fragrances*; Pybus, D. H., Sell, C. S., Eds.; RSC Paperbacks: Cambridge, 1999.

(5) Swift, K. A. D. *Top. Catal.* **2004**, *27*, 143.

(6) Letizia, C. S.; Cocchiara, J.; Lalko, J.; Api, A. M. *Food Chem. Toxicol.* **2003**, *41*, 943.

(7) Heumann, A.; Jens, K. J.; Reglier, M. *Prog. Inorg. Chem.* **1994**, *42*, 542.

(8) Jira, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996; p 374.

(9) ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636.

(10) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551.

(11) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201.

(12) Stahl, S. S. *Angew. Chem. Int.* **2004**, *43*, 3400.

(13) Muzart, J. *Chem.−Asian J.* **2006**, *1*, 508.

(14) da Silva, M. J.; Gusevskaya, E. V. *J. Mol. Catal. A* **2001**, *176*, 23.

(15) Gonçalves, J. A.; Howarth, O. W.; Gusevskaya, E. V. *J. Mol. Catal. A* **2002**, *185*, 95.

(16) Gonçalves, J. A.; Gusevskaya, E. V. *Appl. Catal. A* **2004**, *258*, 93.

(17) Gonçalves, J. A.; da Silva, M. J.; Piló-Veloso, D.; Howarth, O. W.; Gusevskaya, E. V. *J. Organomet. Chem.* **2005**, *690*, 2996.

(18) Gonçalves, J. A.; Bueno, A. C.; Gusevskaya, E. V. *J. Mol. Catal. A* **2006**, *252*, 5.

10.1021/om700264w CCC: $37.00

of the hydroformylation of linalool and achieved a good control of chemo- and stereoselectivity through the appropriate choice of reaction variables.[19] The main product was cyclic hemiacetal, which can be easily converted in acetal or lactone or dehydrated giving a dihydrofuran derivative.

The aim of the present study was to investigate the applications of the homogeneous catalytic combinations "Pd(II) + reversible co-oxidant" for the aerobic oxidation of linalool (**1**) in various solvents. The co-oxidants used were $CuCl_2$, $Cu(OAc)_2$, and benzoquinone. To the best of our knowledge, palladium-promoted reactions of linalool have not been studied hitherto. Here we wish to report a novel highly selective oxidation of linalool by dioxygen using a chloride-free $Pd(OAc)_2/Cu(OAc)_2$ catalytic system. The reaction occurs smoothly in methanol and ethanol, giving methyl (**2a**) and ethyl (**2b**) ethers of 7-hydroxyhotrienol (a natural constituent of *Cinnamomum camphora*),[20] respectively. In acetic acid, catalytic palladium turnover was achieved by using benzoquinone as the terminal oxidant. Under such conditions, regioselectivity of the allylic oxidation is completely switched, with 8-acetoxylinalool (**3**) being the main product. It is remarkable that in all solvents a trisubstituted internal double bond of the linalool molecule undergoes oxidation, whereas a terminal monosubstituted double bond remains intact.

All linalool derivatives obtained have a pleasant scent with a flower or fruit tinge and are natural products found either in some grape wines (**2b**)[21] or in flower extracts of the exotic plant *Boronia megastigma* (Rutaceae) (**2a** and **3**).[22,23] It should be mentioned that the odor of the *Boronia* flowers is tremendously rich, and for this reason, their extract is commercially used in high-class chypre and fougère perfumes.[22] To the best of our knowledge, the present work reports a first synthesis of these functionalized monoterpenes, potentially useful as components of synthetic perfumes.

Experimental Section

All reagents were purchased from commercial sources and used as received. $CuCl_2{\cdot}2H_2O$ LiCl was dehydrated by heating. Glacial acetic acid was used as a solvent. Benzoquinone was purified by column chromatography (silica).

The reactions at atmospheric pressure were carried out in a magnetically stirred glass reactor equipped with a condenser and followed by measuring a dioxygen uptake (if any) and by gas chromatography (GC). The reactions at higher pressures were carried out in a magnetically stirred stainless steel 100 mL autoclave and followed by GC using a sampling system. In a typical run, the solution of palladium and copper (if any) complexes, benzoquinone (if any), *p*-toluenesulfonic acid (if any), and bornyl acetate (internal standard, 0.20 M) in a corresponding solvent (20 mL) was stirred at the reaction temperature and oxygen pressure of 1−10 atm for 15 min. Concentrations of the components are given in the tables. Then, linalool was added (0.50 M) and the mixture was stirred. At appropriate time intervals, aliquots were taken and analyzed by GC using a Shimadzu 17B instrument fitted with a Carbowax 20 m capillary column and a flame ionization detector. Conversions and selectivities were determined by GC and based on reacted linalool. The Arrhenius activation energy was determined using reaction rates calculated on the basis of kinetic curves "substrate conversion versus reaction time" for the reactions performed at different temperatures. Products were identified by GC-MS (Hewlett-Packard MSD 5890/Series II, 70 eV) and NMR. The GC mass balance was based on the substrate charged using bornyl acetate as an internal standard.

Compounds **2a**, **2b**, and **3** were isolated by column chromatography (silica) using mixtures of hexane and CH_2Cl_2 as eluents and identified by ^1H and ^{13}C NMR spectroscopy (Bruker DRX-400, tetramethylsilane, $CDCl_3$, COSY, HMQC, and DEPT experiments).

Spectroscopic data for 2a, 3,7-dimethyl-7-methoxyocta-1,5-dien-3-ol (7-methoxyhotrienol) (light yellow oil): MS (*m/z*/rel int) 152/1 ($M^+ - CH_3OH$); 99/25; 83/25; 82/100, 71/86, 67/61, 55/34. δ_C: 144.75 (C^2), 139.85 (C^6), 124.81 (C^5), 112.02 (C^1), 74.85 (C^7), 72.64 (C^3), 50.24 (OCH_3), 45.42 (C^4), 27.45 (C^{10}), 25.96 and 25.85 (C^8 and C^9). δ_H: 5.93 (dd, 1H, C^2H, $^3J_{2-1a} = 17.3$ Hz, $^3J_{2-1b} = 10.7$ Hz); 5.49−5.60 (m, 2H, C^5H_1, C^6H_1); 5.21 (d, 1H, $C^1H_aH_b$, $^3J_{1a-2} = 17.3$ Hz); 5.06 (d, 1H, $C^1H_aH_b$, $^3J_{1b-2} = 10.7$ Hz); 3.14 (s, 3H, OCH_3); 2.21−2.35 (m, 2H, C^4H_2); 1.28 (s, 3H, $C^{10}H_3$); 1.26 (s, 6H, C^8H_3, C^9H_3). Carbon numbering is given in Scheme 1. Compound described by Weyerstahl et al. (extracted from natural sources).[23]

Spectroscopic data for 2b, 3,7-dimethyl-7-ethoxyocta-1,5-dien-3-ol (7-ethoxyhotrienol) (light yellow oil): MS (*m/z*/rel int) 83 (20); 82/100; 71/82; 67/40; 55/25. δ_C: 144.91 (C^2), 140.16 (C^6), 124.22 (C^5), 111.37 (C^1), 73.15 (C^7), 72.41 (C^3), 57.59 (OCH_2CH_3), 45.27 (C^4), 26.41 (C^{10}), 27.63 (C^8 and C^9), 15.95 (OCH_2CH_3) δ_H: 5.91 (dd, 1H, C^2H, $^3J_{2-1a} = 17.4$ Hz, $^3J_{2-1b} = 10.6$ Hz); 5.49−5.55 (m, 2H, C^5H_1, C^6H_1); 5.20 (d, 1H, $C^1H_aH_b$, $^3J_{1a-2} = 17.4$ Hz); 5.04 (d, 1H, $C^1H_aH_b$, $^3J_{1b-2} = 10.6$ Hz); 3.32 (q, 2H, OCH_2CH_3 $^3J = 6.8$ Hz); 2.27−2.32 (m, 2H, C^4H_2); 1.31 (t, 3H, OCH_2CH_3 $^3J = 6.8$ Hz); 1.26 (s, 3H, $C^{10}H_3$); 1.17 (s, 6H, C^8H_3, C^9H_3). Carbon numbering is given in Scheme 1. Compound described by Strauss et al. (extracted from natural sources).[21]

Spectroscopic data for 3, 3,7-dimethyl-8-acetoxyocta-1,6-dien-3-ol (8-linalyl acetate) (yellow oil): MS (*m/z*/rel int) 152/12 ($M^+ - CH_3COOH$); 137/25 ($M^+ - CH_3COOH - CH_3$); 119/29; 110/57; 96/80; 82/100, 71/95, 68/75, 67/80; 55/75. δ_C: 170.11 ($C{=}O$), 143.85 (C^2), 129.26 (C^7), 128.46 (C^6), 110.86 (C^1), 72.17 (C^3), 69.17 (C^9), 40.54 (C^4), 26.89 (C^{10}), 21.51 (C^5), 19.96 ($OCOCH_3$), 12.90 (C^8). δ_H: 5.91 (dd, 1H, C^2H, $^3J_{2-1a} = 10.8$ Hz, $^3J_{2-1b} = 17.4$ Hz); 5.46 (t, 1H, C^6H, $^3J_{6-5} = 7.2$ Hz); 5.21 (d, 1H, $C^1H_aH_b$, $^3J_{1a-2} = 10.8$ Hz); 5.06 (d, 1H, $C^1H_aH_b$, $^3J_{1b-2} = 17.4$ Hz), 4.44 (s, 2H, C^9H_2); 2.06−2-11 (m, 2H, C^5H_2); 2.06 (s, 3H, $OCOCH_3$); 1.64 (s, 3H, C^8H_3); 1.56−1.62 (m, 2H, C^4H_2); 1.29 (s, 1H, $C^{10}H$). Carbon numbering is given in Scheme 2. Compound described by Weyerstahl et al. (extracted from natural sources).[22]

Results and Discussion

Oxidation of Linalool in Methanol Solutions. The conventional Wacker catalytic system promotes a rapid conversion of linalool (**1**); however, not even moderate selectivity has been observed for any particular product. When a solution of $NaPdCl_4$ (0.01 M) and $CuCl_2$ (0.05 M) in methanol containing 0.5 M linalool was stirred at 80 °C and 5 atm oxygen pressure, near 50% of linalool reacted for the first hour, giving a complex mixture of more than 10 products. A palladium mirror was observed on the walls of the autoclave. When the reaction was performed in the absence of palladium, with $CuCl_2$ alone, the concentration of linalool also decreased at nearly the same rate, giving a number of products. Some of these products showed the same GC retention time as those formed with the Wacker system. Due to the difficulty of separation and a complex composition of the crude product, the structures of these numerous compounds were not clarified. Instead, we decided to invest in the development of $CuCl_2$-free catalysts. Representative results of this study are given in Table 1.

---

(19) da Silva, J. G.; Barros, H. J. V.; dos Santos, E. N.; Gusevskaya, E. V. *Appl. Catal. A* **2006**, *309*, 169.

(20) Guittet, E.; Sylvestre, J. *Synth. Commun.* **1981**, *11*, 723.

(21) Strauss, C. R.; Wilson, B.; Rapp, A.; Guentert, M.; Williams, P. J. *J. Agric. Food Chem.* **1985**, *33*, 706.

(22) Weyerstahl, P.; Marschall, H.; Bork, W.-R.; Rilk, R. *Liebigs Ann. Chem.* **1994**, 1043.

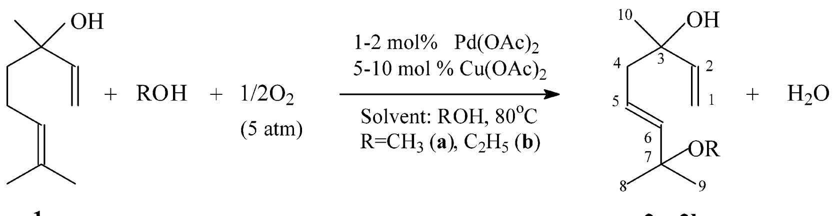
(23) Weyerstahl, P.; Marschall, H.; Bork, W.-R.; Rilk, R.; Schneider, S.; Wahlburg, H. C. *Flavour Fragr. J.* **1995**, *10*, 297.

Table 1. Palladium-Catalyzed Oxidation of Linalool with Dioxygen in Alcohols[a]

run	[Pd(OAc)$_2$] (M)	[Cu(OAc)$_2$] (M)	pressure (atm)	temp (°C)	time (h)	conversion (%)	selectivity **2a** or **2b** (%)	rate[b] (M h^{-1})
				Solvent: Methanol				
1	0.01	none	5	80	5	65	40	
2[c]	0.01	0.05	5	80	1	8	52	
					5	10	50	
3[d]	0.01	none	5	80	5	40	10	
4	0.01	0.05	5	80	2	40	97	0.10
					5	96	95	
5	0.01	0.05	10	80	5	92	95	0.09
6	0.01	0.05	5	65	5	45	94	0.05
7	0.01	0.05	5	50	5	25	97	0.02
8	0.005	0.05	5	80	9	98	93	0.05
9	0.01	0.025	5	80	2	27	97	
					5	82	85	0.07
10[e]	0.01	0.05	10	80	10	90	80	0.15
11[f]	0.01	0.05	5	80	5	85	35	
12[g]	0.01	0.05	5	80	2	36	86	0.10
					5	95	53	
				Solvent: Ethanol				
13	0.01	0.05	5	80	7	70	75	0.05

[a] [linalool] = 0.50 M. Conversion and selectivity were determined by GC and based on reacted linalool. [b] Average rates of the conversion of linalool are given, as the kinetic curves for these runs are nearly straight lines (Figure 1). [c] [benzoquinone] = 0.01 M. [d] [benzoquinone] = 0.5 M. [e] [linalool] = 1.50 M. 3,6-Linalool oxide was also formed as a mixture of *cis*/*trans* isomers (8%). [f] H_2O was added (15 vol %). [g] [*p*-toluenesulfonic acid] = 0.01 M.

Scheme 1



1 **2a**, **2b**

In methanol solutions, the reaction of linalool with Pd(OAc)$_2$ alone at 5 atm oxygen pressure appeared to be catalytic in palladium (Table 1, run 1). Although at least 10 GC distinguishable products were detected, one of them was formed in much higher concentration, showing 40% selectivity based on the reacted linalool. This major product was isolated from the reaction solution by column chromatography and identified by GC-MS and NMR spectroscopy as ether **2a** (Scheme 1). It was formed in run 1 with a dioxygen-coupled catalytic turnover number (TON) of near 10, considering its selectivity. Benzoquinone (BQ) is known to reoxidize readily Pd(0) during the catalytic cycle under chloride-free conditions.[7] Although the oxidation of hydroquinone (HQ) back to BQ by dioxygen is a slow reaction, it can be, in principle, accelerated by the use of some catalysts such as cobalt, iron, and copper complexes or heteropoly compounds.[7,24,25] For example, we have recently developed a multistep electron-transfer catalytic system Pd(OAc)$_2$/BQ/(Cu or Mn acetates) for the aerobic oxidation of limonene.[16] We have tested this Pd(OAc)$_2$/BQ catalyst in the oxidation of linalool using Cu(OAc)$_2$ as a redox mediator (Table 1, run 2). Unexpectedly, the reaction had virtually ceased after 1 h at a 10% conversion (Figure 1, run 2), though it gives **2a** with near 50% selectivity. With stoichiometric amounts of BQ (Table 1, run 3), the conversion of linalool is faster; however the reaction results, likewise with the Pd/Cu/chloride system, in a mixture of several products with comparable GC peak areas and shows negligible selectivity for **2a**.

When we performed the experiment removing BQ, using only Pd(OAc)$_2$ (2 mol %) and Cu(OAc)$_2$ (10 mol %) (Table 1, run 4), to our surprise, the reaction occurred much faster than in the presence of BQ (cf. kinetic curves for runs 2 and 4 given in Figure 1)! Moreover, the reaction resulted in almost quantitative formation of ether **2a** (95% selectivity at a virtually complete conversion). This result is quite unexpected, as it is well-known that the presence of chloride ions is necessary to make the reoxidation of Pd(0) by Cu(II) thermodynamically favorable: coordination with Cl$^-$ decreases the redox potential of the

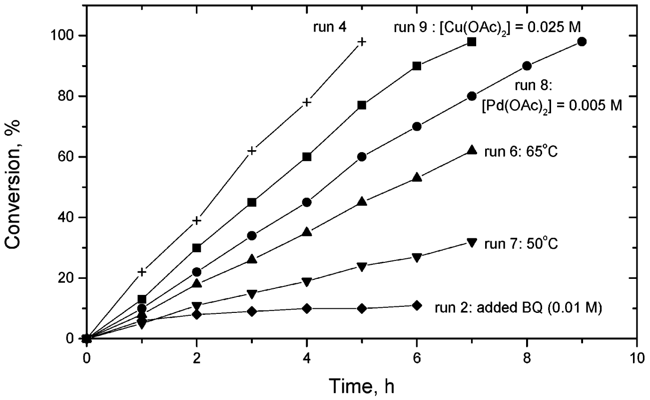


Figure 1. Palladium−copper-catalyzed oxidation of linalool with dioxygen in methanol. Curve numbering corresponds to the runs in Table 1. Conditions for run 4: linalool (0.50 M), Pd(OAc)$_2$ (0.01 M), Cu(OAc)$_2$ (0.05 M), 5 atm (O_2), 80 °C. In the other runs one of the variables was changed as indicated.

---

(24) Bystrom, S. E.; Larsson, E. M.; Akermark, B. *J. Org. Chem*. **1990**, *55*, 5674.

(25) Bergstad, K.; Grennberg, H.; Backvall, J.-E. *Organometallics* **1998**, *17*, 45.

Pd^{2+}/Pd^0 couple, while increases that of the Cu^{2+}/Cu^+ couple.[26] Nevertheless, in methanol (and in ethanol, as described below) linalool is readily oxidized by dioxygen over the chloride-free Pd/Cu catalyst without palladium black formation. Thus, under such conditions the zerovalent palladium ether is not formed at all or, if formed, is stabilized toward clustering through interaction with the solvent and available ligands. It is also important that the reaction proceeds under nonacidic conditions.

It is remarkable that the main product, allylic ether **2a** (Scheme 1), arises from the oxidation of the trisubstituted double bond of linalool, whereas a terminal monosubstituted double bond remains intact. It is also noteworthy that the kinetic curves for these reactions are nearly straight lines from 0 to 100% conversion (Figure 1). This means that the rate is virtually independent of the concentration of the substrate. In other words, linalool reacts with palladium quite readily and most of the metal centers always, even at high conversions, contain strongly coordinated linalool or fragments derived from linalool. This also shows that no catalyst deactivation occurs throughout the reaction. Judging from the structure of **2a**, interaction of linalool with palladium in our system should proceed via a η^3-allyl complex formed by the abstraction of hydrogen from carbon C-5. On the other hand, as there is no hydrogen at carbon C-3, activation of the terminal double bond can occur only via η^2-bonding with palladium. Apparently, the latter coordination is weaker than the η^3-allylic one; thus the more accessible terminal double bond loses a competition for palladium to the internal double bond.

Further increase in the oxygen pressure up to 10 atm showed no appreciable effect on both reaction rate and selectivity (Table 1, run 5). Thus, it seems that the reaction is zero-order in oxygen under the conditions used. The treatment of the kinetic data revealed the temperature dependence for this reaction. The data on the reaction rates (runs 4, 6, and 7 in Table 1 and Figure 1) expressed by means of the Arrhenius equation yield the activation energy of ca. 47 kJ mol^{-1} in the range of 50−80 °C. The reaction selectivity for ether **2a** varies quite slightly with temperature, being above 90%.

With respect to the concentration of $Cu(OAc)_2$, the reaction shows a positive order (Table 1 and Figure 1, runs 4 and 9). There is also an appreciable effect on selectivity. In the run with a half amount of $Cu(OAc)_2$ (5 mol %, run 9), selectivity for **2a** steadily decreases, with the reaction progress to 85% at 82% conversion (cf. with run 4). The reaction is also accelerated by the increased Pd(II) concentration, with an approximately first-order rate dependence being observed (Table 1 and Figure 1 cf. run 8 vs run 4). A TON of near 100 was achieved in run 8 using 5×10^{-3} M $Pd(OAc)_2$ (1 mol %) with a constant turnover frequency of 5 h^{-1} up to the complete conversion. In run 10, only 0.66 mol % of $Pd(OAc)_2$ was used at a relatively high substrate concentration of 1.5 M. In this run, all linalool has been converted for ca. 10 h (TON = 150); however the selectivity for **2a** decreases to 80%, mainly due to the concomitant formation of 3,6-linalool oxide. A possible explanation of this result is the increase in water concentration due to the main reaction, which inhibits the palladium-catalyzed oxidation (Scheme 1).

Water was found to exert a deleterious effect on the formation of ether **2a**: in aqueous methanol, selectivity dropped to 35% (run 11) versus 96% under anhydrous conditions (run 4). Therefore, it is understandable that water formed along with **2a** upon the oxidation of linalool (Scheme 1) negatively affects selectivity of the reaction with palladium at high substrate concentrations, especially at high conversions.

Table 2. Palladium-Catalyzed Oxidation of Linalool with Benzoquinone in Acetic Acid[a]

run	[additive] (M)	temp (°C)	time (h)	conversion (%)	selectivity for **3** (%)
1[b]	$Cu(OAc)_2$ (0.05)	40	6	14	traces
2	none	40	30	53	85
3	none	80	5	50	57
4	*p*-TsOH (0.01)	80	5	65	0
5	$Cu(OAc)_2$ (0.05)	40	22	85	23

[a] $[Pd(OAc)_2]$ = 0.01 M; [benzoquinone] = 0.50 M; [linalool] = 0.50 M; 1 atm (O_2). Conversion and selectivity were determined by GC and based on reacted linalool. *p*-TsOH = *p*-toluenesulfonic acid. [b][benzoquinone] = 0.04 M.

It is known that the addition of small amounts of strong acids can, in some cases, benefit palladium-catalyzed reactions, preventing palladium black precipitation and increasing reaction rates.[16,18,27] For example, we have observed a great accelerative effect of *p*-toluenesulfonic acid (*p*-TsOH) on various oxidations of limonene.[16,18] Thus, we have added *p*-TsOH to our system (Table 1, run 12). Although the average rate of the linalool conversion remains the same as without the acid in run 4, selectivity decreases markedly at high conversions, being 53% at the end of the reaction. Moreover, further transformations of the primarily formed product **2a** occur: the concentration of **2a** passes a maximum, after which it slowly declines.

Oxidation of Linalool in Ethanol Solutions. The oxidation of linalool with dioxygen in the presence of 2 mol % $Pd(OAc)_2$ and 10 mol % $Cu(OAc)_2$ (80 °C, 5 atm) occurs smoothly also in ethanol solutions, albeit at a lower rate than in methanol (cf. runs 4 and 13 in Table 1). A major product was isolated from the reaction solution by column chromatography and identified by GC-MS and NMR spectroscopy as the ethyl ether of 7-hydroxyhotrienol, **2b**, analogous to methyl ether **2a** (Scheme 1). Thus, the reaction in ethanol seems to follow the same mechanism as in methanol. Under nonoptimized conditions, 75% selectivity for product **2b** was obtained (Table 1, run 13), although such conditions were found to show the best results in methanol (Table 1, run 4). Nevertheless, it seems that a solvent scope for this aerobic oxidation can be extended to other alcohols. It should be mentioned that no co-oxidation of ethanol or methanol is observed under the conditions used in the present work.

Oxidation of Linalool in Acetic Acid Solutions. We attempted to perform palladium-catalyzed oxidation of linalool in acetic acid, a solvent commonly used in Wacker-type oxidations along with water. It was found that in this solvent, as in methanol, the conventional $PdCl_2/CuCl_2$ catalyst promoted a rapid conversion of linalool into a mixture of more than 10 products, most of them in low selectivity (40−80 °C, 1 atm). Near the same conversions and product distribution were observed in the absence of $PdCl_2$. A major product (30−50% selectivity) was identified as α-terpineol acetate formed due to the nonoxidative transformation of linalool: acid-catalyzed isomerization accompanied by esterification. Therefore, once again we devoted our efforts to the development of catalysts free of $CuCl_2$, as it catalyzed undesirable reactions of linalool (Table 2).

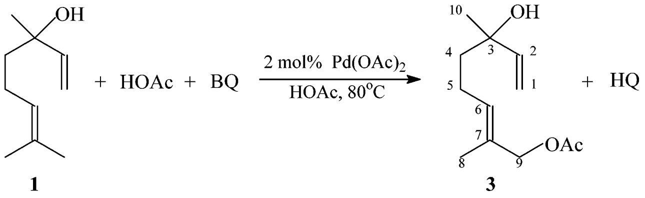
With the $Pd(OAc)_2/Cu(OAc)_2$ catalyst, effective in methanol and ethanol for the linalool oxidation, a palladium mirror is rapidly formed on the walls of the glass reactor, which is not

---

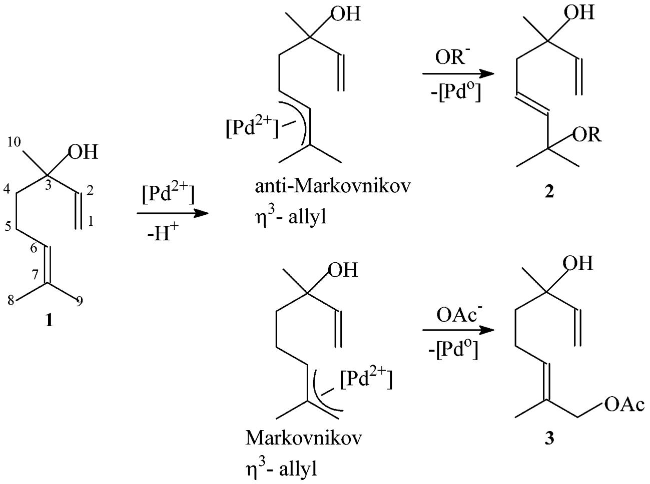
[26] Huheey, J. E. *Inorganic Chemistry: Principles of Structure and Reactivity*, 3rd ed.; Harper: New York, 1983.

[27] Grennberg, H.; Gogoll, A.; Backvall, J.-E. *Organometallics* **1993**, *12*, 1790.

Scheme 2



Scheme 3



unexpected in chloride-free solutions of acetic acid. The $Pd(OAc)_2/BQ/Cu(OAc)_2$ catalytic system, effective for the limonene aerobic oxidation in acetic acid,[16] promotes several transformations of linalool, resulting in numerous unidentified products, in low selectivity each (Table 2, run 1). Better results were obtained using stoichiometric amounts of benzoquinone as a terminal oxidant. At 40 °C, the reaction with 2 mol % of $Pd(OAc)_2$ gives one major product in 85% selectivity, although only 53% conversion has been attained in 30 h (Table 2, run 2). This product was isolated from the reaction solution by column chromatography and identified by GC-MS and NMR spectroscopy as 8-linalyl acetate (**3**) (Scheme 2).Compound **3** is also the product of the allylic oxidation of the internal double bond of linalool. However, its structure implies that under the conditions used in acetic acid the regioselectivity of the allylic oxidation is completely switched from that in alcohols. Interaction of linalool with palladium in this system seems to proceed via the abstraction of hydrogen from carbon C-9, giving an η^3-allyl precursor of **3**.

Our attempts to accelerate the reaction without heavy losses of selectivity were fruitless: raising the temperature (Table 2, run 3) or the addition of *p*-TsOH (Table 2, run 4) or $Cu(OAc)_2$ (Table 2, run 5), indeed, benefits the reaction rate; however the selectivity for **3** drops down. At 80 °C, only 57% selectivity was achieved at 50% conversion. On the other hand, although the reaction occurs quite slowly at 40 °C, the high selectivity for **3** at reasonable conversions makes the method synthetically useful.

Reaction Mechanism. Thus, the structures of **2** and **3** imply that these products arise, unexpectedly, from the interaction of palladium with the internal double bond of linalool, i.e., its allylic oxidation. Palladium is known to be the catalyst of choice for the allylic oxidation of olefins and dienes.[28,29] The accepted mechanism of these reactions involves η^3-allyl palladium complexes as key intermediates; thus, it seems reasonable to suggest their formation in the case of linalool. Hydrogen abstraction from C-5 would result in the internal η^3-allyl and from C-9 in the terminal one, as depicted in Scheme 3, i.e., oxidative addition of the olefin to palladium(II) occurs. The terminal complex is formed when the addition follows a Markovnikov-like orientation; that is, the hydrogen allylic to the more substituted end of the olefin is abstracted. A subsequent nucleophilic attack of alkoxy or acetate groups affords ether **2** from the internal complex and acetate **3** from the terminal one.

In the terminal η^3-allyl, the nucleophile addition is expectedly directed to the less hindered terminal carbon C-9. However, in the internal η^3-allyl, the nucleophile bonds to the more alkyl substituted carbon C-7. To explain the formation of ether **2**, we have to make two suggestions: (i) in the η^3- allyl palladium complexes depicted in Scheme 3, at least in the internal one, there is the interaction of the second olefinic bond with palladium via η^2-bonding and (ii) a coordinated alkoxy group on palladium rather than an external one participates in the formation of **2**. Such coordination of the terminal double bond on the same palladium atom would hamper the access to carbon C-5, as the attacking alkoxy group must be coordinated *trans* to carbon C-5 but *cis* to carbon C-7 in the square-planar palladium complex. Thus, the nucleophilic attack at C-7 giving ether **2** would become sterically favored.It is also remarkable that the terminal double bond remains intact under the reaction conditions, while the sterically hindered internal double bond undergoes the oxidation. In principle, as the degree of alkyl substitution increases, the ability of the double bond to form the η^2-olefin−Pd(II) complex should increase because of higher electron density. However, terminal olefins are usually much more reactive than internal ones due to steric factors. Due to the electron-withdrawing effect of the hydroxyl group, allylic alcohols should be less reactive toward palladium than simple olefins; nevertheless, it is known that allylic alcohols with a terminal double bond can be oxidized by $PdCl_2$.[30] Why is the terminal double bond in linalool not oxidized at all in our reaction?

A possible explanation may be the fact that, despite steric crowding, the internal double bond in linalool could be more prone to react with palladium due to the electronic factors. Really, HOMO coefficients calculated by Ishii et al. for linalool are nearly 6 times higher for the internal double bond than for the terminal one.[31] In other words, the chemoselectivity of the interaction of linalool with palladium may be determined by the intrinsic reactivity of its two C═C bonds for η^2-bonding, which, in its turn, is dominated by the electron density. However, it seems to be also important the possibility of the η^3-allyl formation from the internal η^2-complex, in contrast to the terminal one. A fast transformation of the primarily formed η^2-complex into an η^3-allyl intermediate might account for the preferential oxidation of the internal double bond.

As seen from the structure of products **2** and **3**, regioselectivity of this $\eta^2-\eta^3$-transformation, i.e., hydrogen abstraction from C^9H_3 versus C^5H_2, depends on the reaction conditions. In acetic acid solutions, when benzoquinone is used as reoxidant for palladium, the Markovnikov-like η^3-allyl complex is formed by the abstraction of more acidic methyl hydrogen, as ex-

---

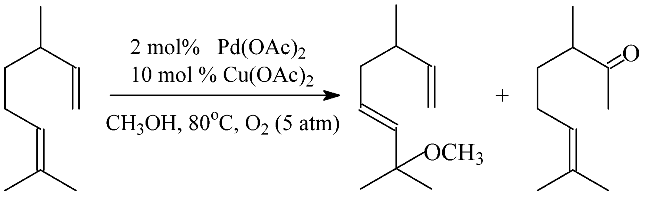
(28) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959.

(29) Grennberg, H.; Gogoll, A.; Backvall, J. E. In *Transition Metals for Organic Synthesis−Building Blocks and Fine Chemicals*; Bolm, C., Beller, M., Eds.; Wiley: Weinheim, 1998; Vol. 2, p 200.

(30) Zaw, K.; Lautens, M.; Henry, P. M. *Organometallics* **1984**, *4*, 1286.

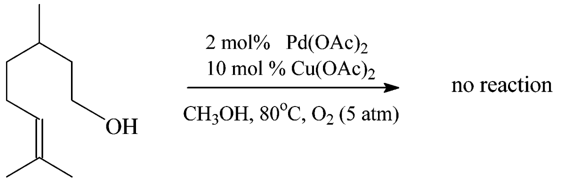
(31) Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1996**, *61*, 5307.

Scheme 4



4 **5** **6**

Scheme 5



7

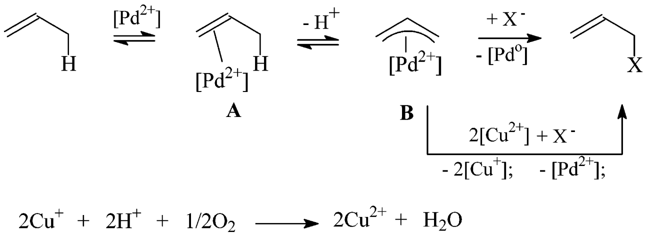
pected.[32] In addition, benzoquinone, as a large coordinating reoxidant, should favor the formation of less sterically demanding terminal η^3-allyls. On the other hand, the regioselectivity of the insertion is completely opposite in the alcoholic solutions, where $Cu(OAc)_2$ is used as the cocatalyst. In alcohols, the internal η^3-allyls are exclusively formed, judging from the structure of products **2a** and **2b**. Such a result is also not unexpected, as it is known that copper complexes, used to assist the formation of η^3-allyls from olefins, strongly affect the regiochemistry of this reaction and can favor the formation of more substituted complexes.[32,33]

To support the mechanistic suggestions, we have tested the reactivity of two other substrates, dihydromyrcene (β-citronellene) (**4**) and citronellol (**7**), in methanol solutions under the conditions used for linalool in run 4 in Table 1 (Schemes 4 and 5). These substrates also have a myrcene skeleton and a trisubstituted internal double bond, like linalool, but substrate **4** contains no allylic hydroxyl group, whereas substrate **7** contains no terminal double bond. It has been observed that both double bonds of substrate **4** are oxidized to give allylic ether **5** and ketone **6** in a ratio of near 1.5:1 (Scheme 4). The reaction is slower than that with linalool (70% and 96% conversions for 5 h, respectively) and much less selective: a combined selectivity for products **5** and **6** is near 40%.

On the other hand, substrate **7** (Scheme 5) showed almost no reactivity under similar conditions, revealing the importance of the terminal double bond for the activation of the internal double bond in the linalool molecule. The results obtained support the suggestion that there is the interaction of the second olefinic bond with palladium in the η^3-allyl palladium intermediates in the course of the linalool oxidation. These experiments also demonstrate the important role of the allylic hydroxyl group in decreasing the reactivity of the terminal double bond toward oxidation, which confers such a high selectivity on the oxidation of linalool compared to that of dihydromyrcene.

The accelerative effect of $Cu(OAc)_2$ in the oxidation of linalool in methanol is also noteworthy. This effect can be explained by bonding of Cu(II) (or Cu(I)) to Pd(II) via bridging ligands (e.g., acetate or alkoxy). The formation of bimetallic Pd−Cu complexes was suggested in various olefin oxidations in both chloride and chloride-free systems.[17,34−37] It is known that η^3-allyl palladium complexes (**B**) are formed from olefins via the intermediate formation of η^2-olefin complexes **A** (Scheme 6).[32] The presence of electrophilic Cu(II) ions bound to palladium via bridging ligands should favor the olefin coordination to palladium bearing now a more positive partial charge. Then a formal oxidative addition of the olefin to palladium(II) occurs through allylic C−H cleavage to give η^3-allyl complexes **B**.

Scheme 6



We have recently studied a specific function of $CuCl_2$ in the palladium-catalyzed allylic oxidation of various monoterpenes by *in situ* NMR.[17] In that work, the accelerative effect of $CuCl_2$ on the formation and decomposition of η^3-allyl palladium complexes was spectroscopically confirmed. In some cases, the formation of these intermediates occurred at a significant rate only in the presence of $CuCl_2$. In particular, NMR experiments have indicated that palladium η^3-allyls specifically interact with Cu(II) ions in the reaction solutions through Cu(II) bonding to Pd(II), which accelerates their decomposition by reductive elimination, as shown in Scheme 6. Once again, withdrawing copper ions can favor this step, decreasing the electron density on palladium. We suppose that such Pd−Cu bimetallic catalysis is also of critical importance for the linalool oxidation in alcohol solutions. NMR *in situ* studies of this system are in progress in our laboratory.

There is another observation that seems to collaborate the importance of the palladium−copper bonding. The addition of benzoquinone to the $Pd(OAc)_2/Cu(OAc)_2$ system almost inhibits catalytic turnover in methanol: only 10% of linalool was converted during 5 h in the presence of small amounts of BQ (Pd/BQ = 1:1), while without BQ for the same time the reaction was complete (cf. runs 2 and 4 in Figure 1 and Table 1). This can be explained by the fact that bulky BQ coordinates on palladium and prevents the Pd−Cu interaction. Indeed, BQ is known to behave as a ligand in palladium systems, especially in the absence of strongly coordinating chloride ions.[16,18,38]

Reoxidation of reduced palladium species in acetic acid is performed by benzoquinone, which is used in stoichiometric amounts. However, it is not so obvious how dioxygen-coupled catalytic turnover is achieved in alcohols, as $Cu(OAc)_2$ is used as the only cocatalyst along with $Pd(OAc)_2$. The conventional Pd/Cu redox catalysis, depicted in Scheme 6, seems to us unlikely, as the redox potentials of the Pd^{2+}/Pd^0 and Cu^{2+}/Cu^+ couples are not compatible in the absence of chloride ions.[26] Moreover, the reaction is catalytic on palladium even in the absence of the copper salt, albeit slow and not as selective as with the bicomponent system.

---

(32) Trost, B. M.; Strege, Weber, P. E. L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407.

(33) Suggs, J. W. In *Encyclopedia of Inorganic Chemistry*; King, R. B., Ed.; Wiley: Chichester, U.K., 1994; Vol. 6, p 3023.

(34) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S. I. *J. Am. Chem. Soc.* **1981**, *103*, 2318.

(35) Takehira, K.; Hayakawa, T.; Orita, H.; Shimizu, M. *J. Mol. Catal.* **1989**, *53*, 15.

(36) Hosokawa, T.; Murahashi, S. I. *Acc. Chem. Res.* **1990**, *23*, 49.

(37) Karandin, A. V.; Gusevskaya, E. V.; Likholobov, V. A.; Stepanov, A. G.; Talzi, E. P. *Kinet. Catal.* **1990**, *31*, 506.

(38) Backvall, J.-E.; Gogoll, A. *Tetrahedron Lett.* **1988**, *29*, 2243.

Thus, we have to assume that under the conditions used in alcohol solutions (but not in acetic acid) regeneration of the oxidized palladium is performed directly by molecular oxygen. In this regard, it should be mentioned that a growing class of palladium-catalyzed aerobic oxidations are known that do not require conventional co-oxidants, such as copper chloride.[9−13] In these reactions, coordinating solvents or oxidatively stable ligands prevent zerovalent palladium species, Pd^0L_n, from clustering into inactive bulk metal, thus promoting their oxidation by molecular oxygen. We suppose that in our system aerobic oxidation of the palladium(0) resting state also occurs faster than aggregation. As far as $Cu(OAc)_2$ is concerned, it seems that copper ions participate in the palladium-mediated oxidation of linalool (i.e., bimetallic catalysis takes place) rather than play a fundamental role in the palladium regeneration.

We have tested in the oxidation of linalool a $PdCl_2$/dimethylacetamide (DMA) system, recently discovered by Kaneda et al., active for the aerobic oxidation of terminal olefins under cocatalyst-free conditions in DMA solutions.[39] Only 15% of linalool was converted in 6 h; however, no products were detected by GC ($PdCl_2$, 0.5 mol %; H_2O, 15 vol %; 80 °C, 10 atm of oxygen). A similar result was obtained with the system for the allylic oxidation of monosubstituted olefins recently discovered by White et al.: $Pd(OAc)_2$/BQ/HOAc/dimethylsulfoxide (DMSO).[40] The concentration of linalool in the solution gradually decreased, showing a 30% conversion in 48 h ($Pd(OAc)_2$, 10 mol %; BQ, 2 equiv, 4 Å MS, DMSO/HOAc = 1:1 (v/v), 40 °C, 1 atm of air); however, no GC-detectable products were also observed, suggesting the formation of high molecular weight oligomerization products. These results once again show the important role of copper cocatalyst in the oxidation of linalool.

Conclusions

In summary, a novel selective $Pd(OAc)_2$/$Cu(OAc)_2$-catalyzed oxidation of linalool, which is a readily available natural raw material, by dioxygen under chloride-free nonacidic conditions has been developed. The reaction occurs in methanol and ethanol and results in unexpected allylic ethers arising from the exclusive oxidation of the trisubstituted internal double bond of the substrate. Bimetallic Pd−Cu catalysis is suggested in this unusual oxidation of linalool. In acetic acid, catalytic palladium turnover was achieved by using benzoquinone as a terminal oxidant, with the regioselectivity of allylic oxidation being completely switched from that in alcohols.

Acknowledgment. We acknowledge the financial support from the CNPq, CAPES, and FAPEMIG (Brazil) and scholarships from CNPq (M.G.S.) and CAPES (P.A.R.D.). The authors wish to thank Dr. José Ailton Gonçalves for the helpful discussion.

OM700264W

---

[39] Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori. K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481.

[40] Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.