

Palladium-catalyzed oxidation of monoterpenes: novel tandem oxidative coupling–oxidation of camphene by dioxygen

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Abstract

The Pd-catalyzed stereoselective oxidative coupling of (–)-camphene gives mainly (*E,E*)-diene, i.e., bis(3,3-dimethyl-2-norbornylidene)ethane, which can be oxidized into the corresponding α,β -unsaturated ketone, i.e. (3,3-dimethyl-2-norbornyl)(8-camphenyl)ketone, with LiNO_3 being used as a reoxidant and dioxygen as a final oxidant; these two reactions are performed in a one port process with up to 90% selectivity for ketone. The applications of the Pd(II)/NO_3^- catalytic system to the oxidation of limonene and β -pinene have also been studied. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Palladium; Monoterpenes; Oxidative coupling; Oxidation

1. Introduction

Metal complex catalyzed functionalization of inexpensive naturally occurring monoterpenes can provide the oxygenated products of interest to perfumery and pharmaceutical industries. We have recently been involved in oxidation and carbonylation of monoterpenes, such as limonene, β -pinene and camphene [1–4]. Although the Pd-catalyzed reactions of olefin oxidation have been developed as an important synthetic methods, their applications to natural product synthesis are rather scarce [5–8]. We described [1] the selective $\text{PdCl}_2/\text{CuCl}_2$ catalyzed allylic oxidation of limonene by dioxygen, however, failed to extend this methodology to bicyclic monoterpenes due to their skeletal rearrangements promoted by CuCl_2 acting as a Lewis acid [1,2]. Then, we developed a CuCl_2 -free system for the selective oxidation of

β -pinene and camphene into allylic and glycol derivatives, respectively, using H_2O_2 as a final oxidant and Pd(OAc)_2 as a catalyst [2]. This work describes the applications of the Pd(II)/NO_3^- catalytic system to the oxidation of monoterpenes by dioxygen, which in some cases offers valuable alternatives to the Wacker catalyst [9–13]. We wish to report a novel palladium-catalyzed chemo and stereoselective oxidative coupling of (–)-camphene and tandem oxidative coupling–oxidation of (–)-camphene (C_{10}) resulting in an α,β -unsaturated ketone (C_{20}). In both reactions, the new diterpene derivatives are formed and dioxygen is involved as a terminal oxidant.

2. Results and discussion

The results on the oxidation of (–)-camphene (**1**) are collected in Table 1. First, we studied the reactions of **1** with $\text{Pd(NO}_2)\text{ClL}_2$ and $\text{Pd(NO}_3)\text{ClL}_2$ ($\text{L} = \text{CH}_3\text{CN}$) in chloroform and acetic acid

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Table 1
Oxidation of camphene in the presence of palladium complexes (L = CH₃CN)^a

| Run | Palladium complex | Reoxidant (mol l ⁻¹) | Camphene (mol l ⁻¹) | Time (h) | Conversion (%) | TON ^b | Selectivity ^c (%) | |
|------------------------------|--------------------------------------|----------------------------------|---------------------------------|----------|----------------|------------------|------------------------------|----------|
| | | | | | | | 2 | 3 |
| <i>Solvent (chloroform)</i> | | | | | | | | |
| 1 ^d | Pd(NO ₂)ClL ₂ | None | 0.10 | 1 | 11 | 0.7 | 78 | 22 |
| 2 | Pd(NO ₂)ClL ₂ | None | 0.10 | 1 | 18 | 1.5 | 34 | 66 |
| 3 ^d | Pd(NO ₃)ClL ₂ | None | 0.10 | 1 | 29 | 1.5 | 95 | 5 |
| 4 | Pd(NO ₃)ClL ₂ | None | 0.10 | 1 | 40 | 2.5 | 77 | 23 |
| <i>Solvent (acetic acid)</i> | | | | | | | | |
| 5 | Pd(NO ₃)ClL ₂ | None | 0.20 | 1.5 | 40 | 4.0 | 98 | Trace |
| 6 ^e | Pd(NO ₂)ClL ₂ | None | 0.20 | 1.5 | 25 | 2.5 | 98 | Trace |
| | | LiNO ₃ (0.18) | | 3.0 | 60 | 11.4 | 6 | 92 |
| 7 | Pd(NO ₃)ClL ₂ | LiNO ₃ (0.18) | 0.20 | 1.5 | 54 | 9.0 | 22 | 76 |
| 8 | Pd(OAc) ₂ | LiNO ₃ (0.18) | 0.25 | 1 | 27 | 5.9 | 18 | 78 |
| | | | | 6 | 77 | 17.7 | 12 | 86 |
| 9 | Pd(OAc) ₂ | LiNO ₃ (0.36) | 0.50 | 1 | 46 | 21.2 | 8 | 88 |
| | | | | 8.5 | 80 | 33.4 | Trace | 92 |
| 10 | Pd(OAc) ₂ | None | 0.50 | 1.5 | 4 | 0.9 | 94 | 0 |
| 11 | Pd(OAc) ₂ | Benzoquinone (0.05) | 0.50 | 6 | 22 | 5 | 96 | 0 |
| 12 ^f | PdCl ₂ | CuCl ₂ (0.20) | 0.50 | 3 | 10 | 0 | 0 | 0 |
| | | LiCl (0.50) | | | | | | |

^a Conditions: [Pd complex] = 1.0 × 10⁻² mol l⁻¹; 60°C; 0.1 MPa (O₂).

^b Turnover number is calculated as a ratio between the amounts (mol) of **2** and **3** formed and the charged Pd complex, considering that **3** is formed from **1** via **2** and both steps are Pd-catalyzed (TON = [2] + 2[3]/[Pd]).

^c Determined by GC and based on reacted camphene. In acetic acid, the main by-product is bornyl acetate.

^d Nitrogen is used as a gas phase.

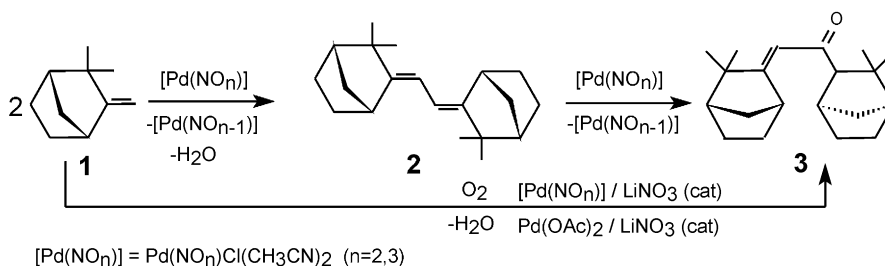
^e After 1.5 h, LiNO₃ was added.

^f The main products are bornylacetate and tricyclene.

solutions, in the absence and in the presence of dioxygen. Camphene reacts with both complexes giving two major products, identified as bis(3,3-dimethyl-2-norbornylidene)ethane (**2**) and (3,3-dimethyl-2-norbornyl)(8-camphenyl)ketone (**3**). The **2**/**3** ratio and reaction rate are strongly dependent on the ligand and solvent nature (runs 1–6). Diene **2** results from the oxidative coupling of camphene

and the further oxidation of one of its double bonds gives α,β-unsaturated ketone **3** (Scheme 1). As far as we know, this is the first example of the palladium-catalyzed oxidation of dienes into α,β-unsaturated ketones.

Direct coupling of alkenes is not general reaction and only a few examples have been reported [14–18]. To the best of our knowledge, diterpene derivatives **2**



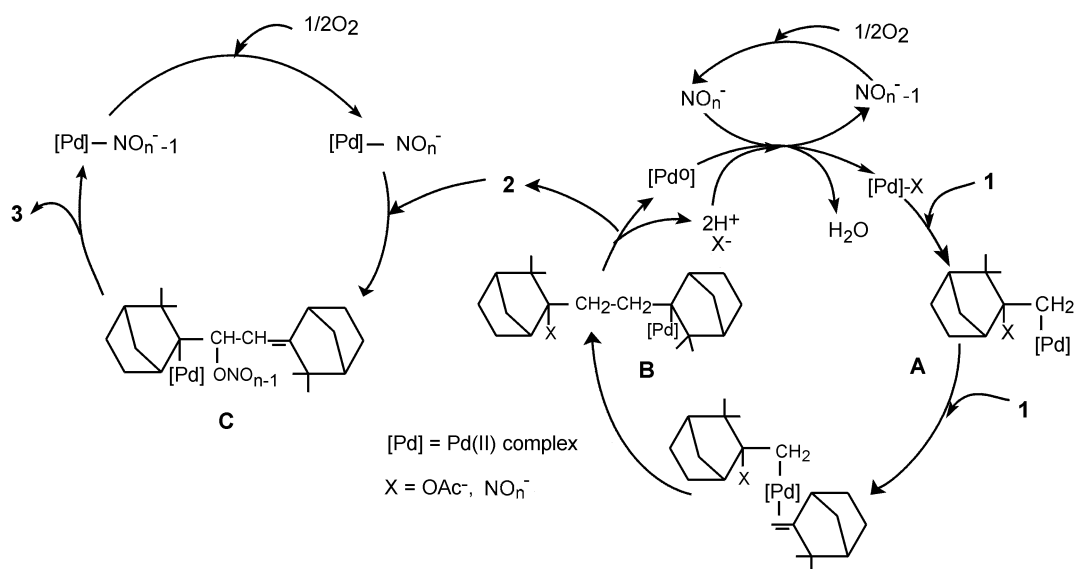
Scheme 1.

and **3** are the new compounds and the reactions depicted in Scheme 1 have not been described earlier. In acetic acid, the reaction is highly selective (98%) for **2** (runs 5 and 6), with only traces of tricyclene and bornyl acetate being detected. Products **2** and **3** are not formed with PdCl_2L_2 neither in chloroform nor in acetic acid even in the presence of water and/or dioxygen. The formation of enone **3** is observed under the oxygen-free conditions in chloroform (runs 1 and 3) indicating that a direct oxygen transfer from the nitrate/nitro group to diene **2** seems to occur. However, additional oxygen labeling experiments are needed to confirm this conclusion. In the absence of dioxygen, the total amounts of the products formed correspond to the reduction of all NO_n^- ligands into nitrosyl groups, then at longer reaction time, a palladium black is precipitated. In the presence of dioxygen, the reaction becomes catalytic in both palladium and nitrate. Primarily formed **2** can be rapidly and selectively converted into **3** by the addition of LiNO_3 to the reaction solutions containing Pd(II) ions (run 6). This clearly shows the consecutive character of the reactions. The synthesis of enone **3** by the combined oxidative coupling–oxidation of camphene with dioxygen has been performed in a one port reaction using $\text{Pd(NO}_3)_2\text{Cl}_2/\text{LiNO}_3$ or $\text{Pd(OAc)}_2/\text{LiNO}_3$ catalytic systems (runs 7–9). The selectivity of up to 92% at a 80% conversion is achieved. It should be

mentioned that the rate drops rapidly with the decrease in camphene concentration because the reaction is probably second order in the amounts of substrate.

The reaction mechanism proposed is shown in Scheme 2. The only allylic hydrogen in camphene molecule is at the bridgehead position and not easily abstractable to form a π -allylic complex. Furthermore, there are no hydrogens at β -carbon of the double bond. Thus, σ -organopalladium intermediate **A**, formed via a palladation of the π -coordinated camphene, seems to be stable enough to react with another molecule of camphene, which inserts into the Pd–C bond in an anti-Markovnikov fashion due to the large steric hindrance of two bulky bicyclic fragments. Resulting complex **B** decomposes via a β -hydride and HX ($\text{X} = \text{NO}_n^-, \text{OAc}$) elimination giving diene **2** and reduced palladium species. The latter are oxidized back to Pd(II) in the presence of nitrate or nitro groups, which, in their turn, are reoxidized with dioxygen. The formation of **3** can be interpreted as an anti-Markovnikov oxidation of one of the double bonds of **2**, with the other one being intact, via the formation of σ -organopalladium intermediate **C** and subsequent β -hydride rearrangement.

The oxidative coupling of camphene is highly stereoselective and results mainly in (*E,E*)-isomer of **2** (ca. 90%). We detected two atropisomers **2a** and **2b**



Scheme 2.

(ca. 40/60) which seems to be separable because of the sterical restriction on the rotation about the central C–C bond. The stereoselectivity of the oxidation of diene **2** is rather low; two isomers of enone **3** have been detected: (*E*)-*exo* (**3a**) and (*E*)-*endo* (**3b**) (ca. 60/40). Pd(OAc)₂ alone also promotes the stoichiometric oxidative coupling of camphene (run 10), differently from PdCl₂(CH₃CN)₂, however, no trace amounts of **3** are observed, even in the presence of water and/or dioxygen.

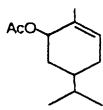
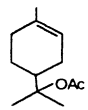
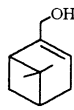
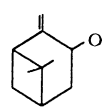
The specific function of nitrate/nitro groups in the oxidation of **2** has been further confirmed by the runs, in which other reoxidants for Pd have been used. With benzoquinone (run 11), the highly selective (96%) and catalytic in Pd-oxidative coupling of camphene occurs, while the Wacker system (run 12) promotes essentially the skeletal isomerization of camphene, with not even traces of products **2** and **3** being detected. Thus, nitrate and nitro groups show behavior far exceeding that of simple reoxidation agents. As earlier confirmed by oxygen labeling experiments [19], a distinctive feature of the systems based on the palladium–nitro/nitrosyl redox couple is an oxygen atom transfer from the nitro group to the alkene. According to our preliminary data this should also occur with camphene.

We have also examined the activity of the Pd(NO₃)ClI₂ complex and Pd(OAc)₂/LiNO₃ catalytic system in the oxidation of limonene and β-pinene (Table 2) and found the strong effect of the

structure of monoterpene on its reactivity. A very low conversion of limonene is observed (runs 1, 3 and 5), with small amounts of α-carveyl acetate (**4**) and α-terpenyl acetate (**5**) being detected. The former is the product of allylic oxidation and the latter of the addition of acetic acid to the exocyclic double bond. Under all conditions used, β-pinene undergoes a significant double bond isomerization into α-pinene and also skeletal isomerization (up to 50% based on reacted substrate). In chloroform solutions, the allylic oxidation products with the pinane structure are formed, i.e., myrtenol (**6**) and pinocarveol (**7**) (run 2). In acetic acid solutions, the main product, i.e., α-terpenyl acetate (**5**), arises from the nucleophilic attack by acetate on the carbonium ion formed from original β-pinene (runs 4 and 6).

In summary, a novel palladium-catalyzed tandem oxidative coupling–anti-Markovnikov oxidation of camphene by dioxygen using LiNO₃ as a reoxidant has been developed. The (*E*)-*exo* and (*E*)-*endo* isomers of α,β-unsaturated ketone are formed exclusively. A palladium-catalyzed chemo and stereoselective oxidative coupling of camphene giving rise mainly to (*E,E*)-diene has also been realized using benzoquinone as a reoxidant. We are presently pursuing catalytic processes showing higher turnover numbers and studying the mechanism of these reactions resulted in new diterpene derivatives.

Table 2
Reactions of monoterpenes in the presence of palladium complexes

| Run | Terpene | Solvent | Conversion (%) | Product distribution ^a (%) | | | |
|------------------|----------|-------------------|----------------|---|--|---|---|
| | | | |  |  |  |  |
| 1 ^b | Limonene | CHCl ₃ | <1 | | | | |
| 2 ^{b,c} | β-Pinene | CHCl ₃ | 16 | | | 31 | 23 |
| 3 ^b | Limonene | HOAc | <3 | 54 | 23 | | |
| 4 ^{b,c} | β-Pinene | HOAc | 32 | Trace | 90 | | |
| 5 ^d | Limonene | HOAc | 4 | 60 | 40 | | |
| 6 ^{c,d} | β-Pinene | HOAc | 48 | 4 | 96 | | |

^a Determined by GC and based on reacted terpene.

^b Conditions: [terpene] = 1.0 × 10⁻¹ mol l⁻¹; [Pd(NO₃)Cl(CH₃CN)₂] = 1.0 × 10⁻² mol l⁻¹; 60°C; 0.1 MPa (N₂); 5 h. Chlorides of the corresponding main products are also formed as by-products.

^c Due to isomerization of β-pinene (mainly to α-pinene), only conversion into oxygenated products is given.

^d Conditions: [terpene] = 1.00 mol l⁻¹; [Pd(OAc)₂] = 1.0 × 10⁻² mol l⁻¹; [LiNO₃] = 0.40 mol l⁻¹; 60°C; 0.1 MPa (O₂); 2 h.

3. Experimental

The reactions were carried out in a stirred glass reactor and followed by measuring the dioxygen uptake (if any) and/or by gas chromatography (GC) (Shimadzu 14B, Carbowax 20 M). Pd(NO_n)Cl₂ (L = CH₃CN, n = 2, 3) were synthesized from PdCl₂L₂ and Ag(NO_n) in analogy to Ref. [19]. Products **2** and **3** were isolated as mixtures **2a/2b** and **3a/3b** by column chromatography (silica) and identified by GC/MS (Hewlett-Packard MSD 5890/Series II, 70 eV), IR (Mattson FTIR 3000/Galaxy Series), ¹H and ¹³C-NMR spectroscopy (Bruker DRX-400, tetramethylsilane, CDCl₃, COSY, HMQC and DEPT experiments). The stereochemistry was determined using NOESY experiments (the complete report will be published elsewhere).

Selected spectroscopic data for 2: m.p. = 182–184°C; ν_{max}(KBr)/cm⁻¹: 3020 [ν (=C–H)], 1625 [ν (C=C)], 810 [δ (=C–H)]; (m/z/rel. int.): **2a** (shorter GC retention time): 270/70 [M]⁺, 255/100 [M–CH₃]⁺; **2b**: 270/79 [M]⁺, 255/100 [M–CH₃]⁺; δ_H for **2a**: 1.06 (s, 6H, Me), 1.02 (s, 6H, Me), 5.73 (s, 2H, =C–H); δ_H for **2b**: 1.05 (s, 6H, Me), 1.03 (s, 6H, Me), 5.71 (s, 2H, =C–H); δ_C for **2a**: 26.05 (Me), 29.31 (Me), 113.30 (C=C–H), 155.44 (C=C–H); δ_C for **2b**: 26.00 (Me), 29.25 (Me), 113.22 (C=C–H), 155.44 (C=C–H).

Selected spectroscopic data for 3: ν_{max}(film)/cm⁻¹: 3025 [ν (=C–H)], 1700 [ν (C=O)], 1630 [ν (C=C)], 800 [δ (=C–H)]; (m/z/rel. int.): **3a** (*exo*, shorter GC retention time): 67/100, 286/70 [M]⁺, 271/35 [M–CH₃]⁺; **3b** (*endo*): 286/100 [M]⁺, 67/98, 271/44 [M–CH₃]⁺; δ_H for **3a**: 0.84 (s, 3H, Me), 0.96 (s, 3H, Me), 1.04 (s, 3H, Me), 1.09 (s, 3H, Me), 2.99 (d, 1H, ⁴J_{H–H} = 9.6 Hz, CH–COCH=), 4.97 (d, 1H, ⁴J_{H–H} = 9.6 Hz, CH–COCH=); δ_H for **3b**: 0.80 (s, 3H, Me), 0.95 (s, 3H, Me), 1.01 (s, 3H, Me), 1.11 (s, 3H, Me), 2.95 (d, 1H, ⁴J_{H–H} = 9.6 Hz, CH–COCH=), 4.97 (d, 1H, ⁴J_{H–H} = 9.6 Hz, CH–COCH=); δ_C for **3a**: 23.13 (Me), 26.34 (Me), 27.33 (Me), 29.59 (Me), 53.81 (CH–COCH=C), 109.25 (CH–COCH=C), 158.87

(CH–COCH=C), 214.73 (CH–COCH=C); δ_C for **3b**: 22.85 (Me), 25.82 (Me), 26.15 (Me), 29.68 (Me), 53.38 (CH–COCH=C), 109.00 (CH–COCH=C), 158.81 (CH–COCH=C), 214.68 (CH–COCH=C).

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References

- [1] E.V. Gusevskaya, J.A. Gonsalves, J. Mol. Catal. 121 (1997) 131.
- [2] E.V. Gusevskaya, V.S. Ferreira, P.A. Robles-Dutenhefner, Appl. Catal. A 174 (1998) 177.
- [3] A.O. Dias, R. Augusti, E.N. Santos, E.V. Gusevskaya, Tetrahedron Lett. 31 (1997) 41.
- [4] E.V. Gusevskaya, E.N. dos Santos, R. Augusti, A.O. Dias, C.M. Foca, J. Mol. Catal. A 152 (2000) 15.
- [5] J.-L. Malleron, J.-C. Fiaud, J.-Y. Legros, Handbook of Palladium-catalyzed Organic Reactions, Academic Press, London, 1997.
- [6] J. Tsuji, Top. Curr. Chem. 91 (1980) 29.
- [7] L. El Firdoussi, A. Benharref, S. Allaoud, A. Karim, Y. Castanet, A. Mortreux, F. Petit, J. Mol. Catal. 72 (1992) L1.
- [8] L. El Firdoussi, A. Baqqa, S. Allaoud, B.A. Allal, A. Karim, Y. Castanet, A. Mortreux, J. Mol. Catal. A 135 (1998) 11.
- [9] M.A. Andrews, T.C.-T. Chang, C.-W.F. Cheng, K.P. Kelly, Organometallics 3 (1984) 1777.
- [10] F. Chaulet, A. Heumann, B. Waegell, J. Org. Chem. 52 (1987) 1916.
- [11] T.T. Wenzel, J. Chem. Soc., Chem. Commun. (1989) 932.
- [12] N.H. Kiers, B.L. Feringa, Tetrahedron Lett. 33 (1992) 2403.
- [13] I.E. Beck, E.V. Gusevskaya, A.G. Stepanov, V.A. Likhobolov, J. Mol. Catal. 73 (1992) 115.
- [14] K. Kikukawa, K. Sakai, K. Asada, T. Matsuda, J. Organomet. Chem. 77 (1974) 131.
- [15] R. Huttel, J. Kratzer, M. Bechter, Chem. Ber. 94 (1961) 766.
- [16] H.C. Volger, Rec. Trav. Chim. Pays-Bas 86 (1967) 677.
- [17] R.S. Shue, J. Chem. Soc., Chem. Commun. (1971) 1510.
- [18] R.F. Heck, Palladium Reagents in Organic Synthesis, Academic Press, London, 1985, p. 204.
- [19] M.A. Andrews, K.P. Kelly, J. Am. Chem. Soc. 103 (1981) 2894.