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Aerobic oxidation at benzylic positions catalyzed by a simple $Pd(OAc)_2$/bis-triazole system†

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An efficient catalyst system for the Pd-catalyzed aerobic oxidation of benzylic positions has been developed. The combination of palladium(II) acetate and 3,5-bis((1*H*-1,2,4-triazol-1-yl)methyl)benzoate ligand allows the selective oxidation at carbon adjacent to arene rings (primary and secondary benzylic alcohols, and other benzyl compounds) to provide the corresponding carbonyl and carboxy derivatives, employing molecular oxygen as oxidizing agent and a very low metal loading (10^{-5} mol%).

Introduction

The selective oxidation of benzylic compounds is a transformation of great interest since aryl ketones and arenecarboxylic acids are not only ubiquitous substructures present in natural products and pharmaceutically active compounds but also versatile intermediates in the synthesis of agrochemicals, medicines and other functional materials.[1] Classical approach to such compounds by oxidation of aryl carbinols is a well established reaction performed by a wide range of oxidizers.[2]

In this context, molecular oxygen has displaced most of the existing oxidants as the reagent of choice, cheap and readily available, and with water as the only by-product.[3] Indeed, the relevance of carbonyl and carboxy compounds has encouraged research on this area, which *ab initio* encountered problems in the absence of catalysts. An alternative to these potentially risky procedures was the chain radical non-catalyzed oxidation, but without metal catalysts lower yields and mixtures of oxidation products are usually obtained.[3f–h] Therefore, a number of metal catalysts (Cu, Pd, Ru, Fe, V, Zn, Ni, Ir, Rh, Au, Mn, Co, and Pt *inter alia*) have been reported to promote such benzylic oxidations.[3–12] Among them, palladium catalysts stand out due to their slightly higher efficiency.[3,4] However, even in the latter case, relatively high catalyst amounts are required (>0.01 mol% of metal, usually 1–5 mol%) and, sometimes, oxygen pressures above 5 atm.[13]

Over the last decades, the design and tailoring of ligands and catalytic species has become a major strategy for improving the efficiency and even the sustainability of chemical processes.

In this context, several years ago we developed palladium CNC and NCN pincer complexes **1** and **2** (Fig. 1a) as efficient palladium sources (10^{-2} mol% of [Pd]) for the aerobic oxidation of secondary benzyl alcohols and benzylic methylene compounds at atmospheric pressure in a sustainable reaction medium such as PEG-400.[4i]

The excellent results provided by these palladium species encouraged us to investigate whether a preformed palladium complex was essential for the reaction, or more simple catalytic systems could show a similar activity. Taking into account the structure of mentioned palladacycles, we considered the evaluation of simple azoles or azole-type ligands.

This investigation led us to find a convenient, much more efficient system for such oxidation reactions based on the use of

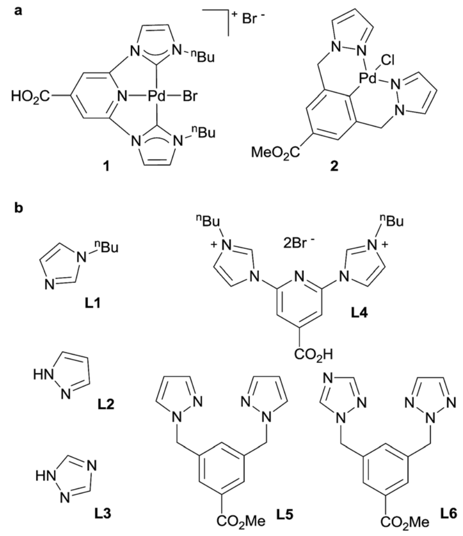

Fig. 1 (a) Palladium complexes employed in our previous works. (b) Azole-type ligands utilized in this study.

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a commercial palladium source ($Pd(OAc)_2$) and a readily available bis-(1,2,4)-triazolyl ligand.

Results and discussion

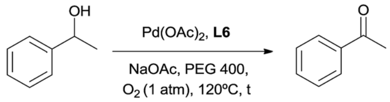
Considering our previous work,[4i] and the proven ability of pyrazoles, imidazoles and NHCs to form stable transition metal complexes,[14] **L1, L2** and **L4, L5** azole ligands[15] were chosen for the initial assays. **L3** and **L6** triazole derivatives were also included due to their singular coordinative properties.[16]

Our investigation started with the oxygen-mediated oxidation of 1-phenylethanol to acetophenone. Combinations of commercially available $Pd(OAc)_2$ and ligands **L1–L6** were tested in the presence of some bases and additives under 1 atm oxygen pressure and in aqueous or polyol solvents (Table 1), as other organic solvents (DMSO, Et_2O, ^{t}BuOMe, THF, DMF, EtOAc, 1,2-dichloroethane, 1,4-dioxane *inter alia*) provided negative results.

In no case was the target ketone detected when 1-butylimidazole **L1**, pyrazole **L2** or 1,2,4-1*H*-triazole **L3** were used as ligands. However, different results were achieved employing bis-azolyl compounds **L4–L6**. 1-Phenylethanol oxidation took place when an alkoxide or carboxylate base (KO^{t}Bu, NaOAc), $Pd(OAc)_2$ and bis-imidazolium salt **L4** or bis-(pyrazolylmethyl) arene **L5** were used in polyol media (entries 4–5, 7–10), although in moderate to low yields. Surprisingly, the bis-triazolyl derivative **L6**/$Pd(OAc)_2$ system provided much better results (entries 4–10), and acetophenone was obtained in an excellent yield (97%) when NaOAc and PEG-400 were employed as base and reaction solvent respectively (entry 5). The use of additives such as TBAB or pivalic acid did not have a positive effect. Interestingly, no product was observed in the absence of the palladium source or the N-heterocyclic ligand (entries 11–12),[17] so both species were needed to effect alcohol oxidation.

Once it had been proven that **L6**/$Pd(OAc)_2$ was a valuable catalyst system to carry out the aerobic oxidation of 1-phenylethanol, we decided to decrease the catalytic amount of both ligand and palladium source. To our delight, it could be decreased down to 10^{-4} mol% with no loss in the yield (Table 2, entry 3). Lower catalyst loadings required longer reaction times to achieve similar yields (entries 4–6). Therefore, although the metal and ligand amounts could be decreased to 10^{-7} mol%, we decided to employ a 10^{-5} mol% to get a proper balance between reaction time and substrate/catalyst ratio (TON and TOF values are displayed in Table 2).

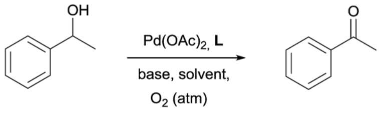
Table 2 Minimization of the amounts of $Pd(OAc)_2$ and **L6**



Entry[a]	[Pd]/**L6** mol%	*t* (h)	Yield[b] (%)	TON	TOF (h^{-1})
1	10^{-2}	24	97	9.7×10^3	404
2	10^{-3}	24	95	9.5×10^4	3958
3	10^{-4}	24	98	9.8×10^5	40 832
4	10^{-5}	48	99	9.9×10^6	206 250
5	10^{-6}	72	96	9.6×10^7	1 333 333
6	10^{-7}	72	89	8.9×10^8	12 361 111

[a] 1.0 mmol of substrate, NaOAc (0.1 eq.), PEG (1 mL $mmol^{-1}$), O_2 (1 atm). [b] Isolated yield.

Table 1 Optimization studies for the oxidation of 1-phenylethanol



		Ligand[b] (**L**) [%]					
Entry	Reaction conditions[a]	**L1**	**L2**	**L3**	**L4**	**L5**	**L6**
1	DMSO : H_2O (1 : 1), 120 °C, 24 h	—	—	—	—	—	—
2	$NaHCO_3$, DMSO : H_2O (1 : 1), 120 °C, 24 h	—	—	—	—	—	—
3	NaOAc, H_2O, 120 °C, 24 h	—	—	—	—	—	—
4	NaOAc, ETG, 120 °C, 15 h	—	—	—	25	30	80
5	NaOAc, PEG 400, 120 °C, 24 h	—	—	—	40	60	97(97)
6	K_2CO_3, PEG 400, 120 °C, 30 h	—	—	—	—	—	57
7	KO^{t}Bu, PEG 400, 120 °C, 30 h	—	—	—	35	30	76
8	NaOAc, PEG 400, 120 °C, 24 h, TBAB	—	—	—	20	10	65
9	NaOAc, PEG 400, 120 °C, 15 h, pivalic acid	—	—	—	19	15	43
10	NaOAc, PEG 400 : H_2O (1 : 1), 120 °C, 48 h	—	—	—	15	10	50
11[c]	NaOAc, PEG 400, 120 °C, 48 h	—	—	—	—	—	—
12[d]	NaOAc, PEG 400, 120 °C, 48 h	—	—	—	—	—	—

[a] 1.0 mmol of substrate, 0.1 eq. of base, 1 mL of solvent per mmol of substrate, O_2 (1 atm), 0.01 mol% of $Pd(OAc)_2$ and 0.01 mol% of ligand were employed. [b] Conversion rates measured by GS-MS. Isolated yields are shown in parentheses. [c] 0.01 mol% of $Pd(OAc)_2$ was employed without the addition of ligand. [d] No palladium source. Only 0.01 mol% of ligand was employed.

The scope of the methodology was evaluated by submitting a number of commercially available benzyl alcohols to the optimized conditions.

As displayed in Table 3, aryl ketones were obtained in high yields from secondary benzylic alcohols regardless of the electronic nature of the substituents, with the only exception of benzoyl cyanide (entry 4), which was obtained in a moderate 54%.[18] Longer reaction times (96 hours) were required in some cases, probably related to steric hindrance (entries 3, 5, 6, 13). It should be pointed out that hydrobenzoin provided the corresponding diketone (benzil) in excellent yield (entry 15) and 1,2-diphenylethanol was selectively oxidized to deoxybenzoin and no overoxidation products were observed (entry 16).

Our novel catalyst system could also be efficiently used in the aerobic oxidation of primary benzylic alcohols (Table 4). Carboxylic acids were obtained in good yields from benzylic alcohols bearing electron withdrawing, neutral or electron donating groups although longer reaction times were required in general to ensure complete conversion in this double oxidative process.

Delightedly, benzylic C–H oxidation also proceeded smoothly under the same reaction conditions. (Table 5). Moreover, complete conversion to the aryl ketone derivatives was observed in all cases and, in contrast with previous works with molecular oxygen or even other oxidants (H_2O_2, TBHP, MCPBA, NHPI)[19] no partial oxidation by-products (benzyl alcohols) were detected.

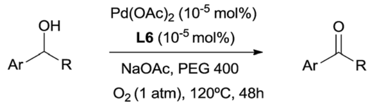
It cannot be ignored that deoxybenzoin provided benzil in almost quantitative yield (Table 5, entry 2) so, by means of the optimized reaction conditions and just controlling the reaction time deoxybenzoin (Table 3, entry 16) or benzil can be obtained from 1,2-diphenylethanol.

Several experiments were performed to extract information about the reaction mechanism and kinetics. A quasi-linear kinetic plot (conversion rate *vs.* time) was found for the aerobic oxidation of 1-phenylethanol in the presence of **L6**/Pd(OAc)$_2$ system. No induction time was observed, thus questioning the participation of heterogeneous catalysts (Fig. 2). The results for poisoning assays reinforced the hypothesis of active homogeneous catalytic species, since the addition of sub-stoichiometric or overstoichiometric amounts of Hg, CS_2, PPh_3, Py and PVPy had no influence in the outcome of the reaction (Table 6).[20]

No proof in support of the *in situ* formation of a palladium pincer complex was achieved, and in fact, all our attempts to synthesize such a complex from **L6** and several palladium sources resulted in unstable species even in solid state under argon at low temperature. Several authors have explained palladium-catalyzed aerobic oxidation of alcohols from mono- and dicoordinated palladium complexes.[21] We propose a similar mechanism for the **L6**/Pd(OAc)$_2$-catalyzed oxidative process (Scheme 1).

Thus, metal-alkoxide complex **A** is generated by a ligand displacement with starting alcohols. β-Elimination generates target carbonyl product and metal hydride **B**. The next step involves the transfer of a hydrogen atom to a dioxygen species,

Table 3 Oxidation of secondary benzylic alcohols



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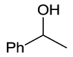
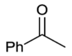
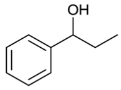
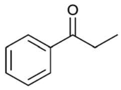
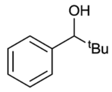
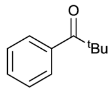
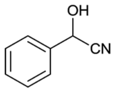
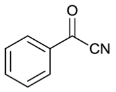
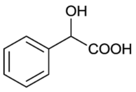
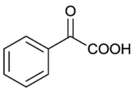
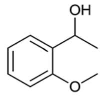
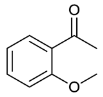
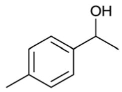
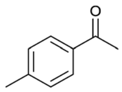
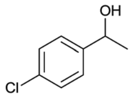
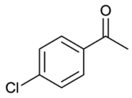
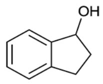
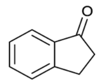
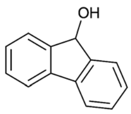
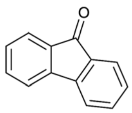
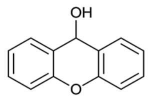
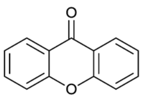
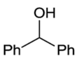
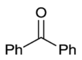
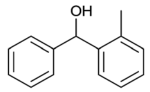
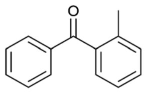
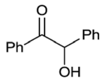
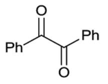
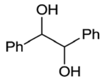
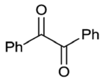
1			99
2			91
3^c			98
4			54
5^d			86
6^c			88
7			85
8			84
9			97
10			94
11			90
12			91
13^c			74
14			97
15			95

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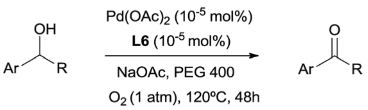

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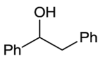
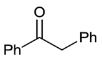
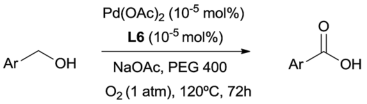
16			94

[a] 1.0 mmol of substrate, 0.1 eq. of NaOAc, PEG (1 mL mmol^{-1}), O_2 (1 atm), $Pd(OAc)_2$ (10^{-5} mol%), **L6** (10^{-5} mol%), 48 h. [b] Isolated yields. [c] 96 h. [d] 72 h.

Table 4 Oxidation of primary benzylic alcohols



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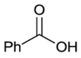
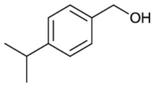
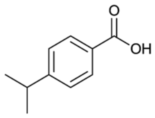
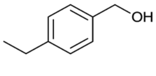
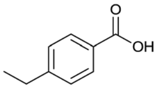
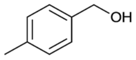
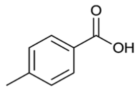
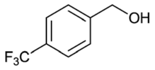
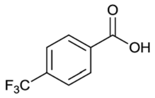
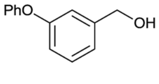
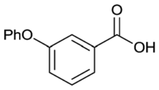
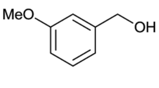
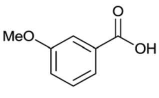
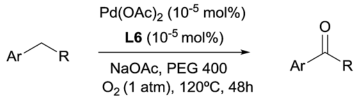
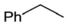
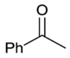
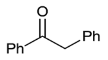
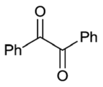
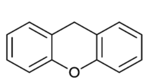
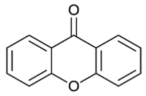
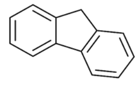
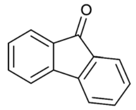
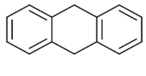
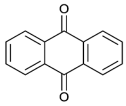
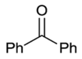
1[c]			83
2			94
3[c]			86
4			83
5			76
6			82
7[d]			91

[a] 1.0 mmol of substrate, NaOAc (0.1 eq.), PEG (1 mL mmol^{-1}), O_2 (1 atm), $Pd(OAc)_2$ (10^{-5} mol%), **L6** (10^{-5} mol%), 72 h. [b] Isolated yields. [c] 48 h. [d] 96 h.

Table 5 Catalytic oxidation of benzylic C–H bonds



Entry[a]	Substrate	Product	Yield[b] (%)
1			95
2			97
3[c]			97
4			97
5[c]			89
6			96

[a] 1.0 mmol of substrate, 0.1 eq. of NaOAc, PEG (1 mL mmol^{-1}), O_2 (1 atm), $Pd(OAc)_2$ (10^{-5} mol%), **L6** (10^{-5} mol%), 48 h. [b] Isolated yields. [c] 72 h.

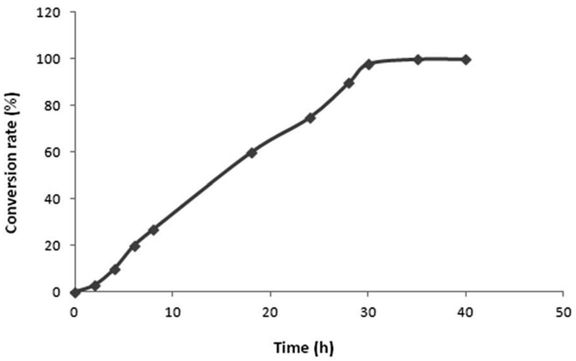
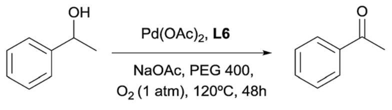


Fig. 2 Conversion rate (%) of 1-phenylethanol *vs.* time.

a process that can occur by two different pathways. Reductive elimination of acetic acid from **B** would provide metal(0) species **C**, which upon reaction with molecular oxygen would provide η-peroxide complex **D**. Hydroperoxide **E** would be generated by attack of acidic AcOH.[22]

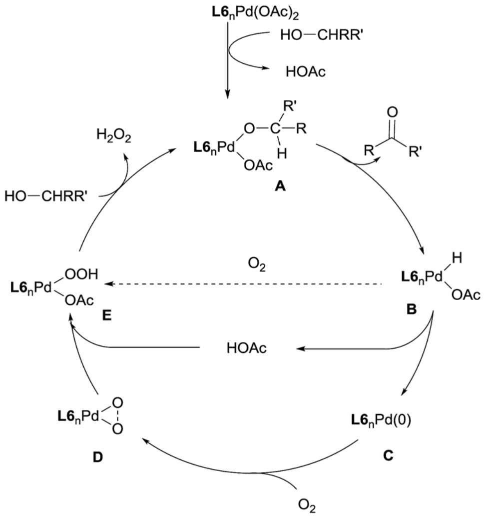
Recently it has been suggested that the hydride complex **B** may not decompose, but instead it might react directly with O_2 to afford the hydroperoxide **E** without involving Pd(0) intermediates.[23] Finally, ligand displacement by a molecule of starting alcohol would regenerate key alkoxide complex **A** and release hydrogen peroxide oxidizer, which could be also responsible for the further oxidation of aldehydes to carboxylic acids.

Table 6 Poisoning experiments



Entry[a]	Poisoning additive	Yield[b] (%)
1	Hg (1 drop)	95
2	CS_2 (0.5 equiv.)	93
3	CS_2 (2 equiv.)	94
4	PPh_3 (0.03 equiv.)	96
5	PPh_3 (0.3 equiv.)	95
6	PPh_3 (4 equiv.)	93
7	Py (150 equiv.)	94
8	PVPy (150 equiv.)	93

[a] 0 mmol of substrate, 0.1 eq. of NaOAc, PEG (1 mL $mmol^{-1}$), O_2 (1 atm), $Pd(OAc)_2$ (10^{-5} mol%), **L6** (10^{-5} mol%), 48 h. [b] Isolated yields.



Scheme 1 Proposed mechanism for the $Pd(OAc)_2$/**L6**-catalyzed aerobic oxidation of alcohols.

Experimental

Material and methods

Commercially available reagents were used throughout without purification unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^1H and 75.4 MHz for ^{13}C) at 20 °C. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) $CDCl_3$ (δ = 7.26 for ^1H and δ = 77.00 for ^{13}C). Coupling constants, J, are reported in hertz (Hz). Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230–400 mesh ASTM). IR spectra were recorded on a Perkin-Elmer 1600 FT and JASCO FTIR-4100 infrared spectrophotometer as thin films, and only noteworthy absorptions are reported in cm^{-1}. Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. MS and HR-MS were measured using a Waters GCT mass spectrometer.

General procedure for the aerobic oxidation of alcohols in the presence of $Pd(OAc)_2$ and L6. A round bottom flask equipped with a magnetic stirrer bar was charged with the alcohol (1 mmol), NaOAc (8.0 mg, 0.1 mmol), $Pd(OAc)_2$ (20 µL of a 5 × 10^{-6} M solution in PEG-400, 10^{-7} mmol), **L6** (20 µL of a 5 × 10^{-6} M solution in PEG-400, 10^{-7} mmol) and PEG 400 (1 mL) at room temperature. The system was purged with molecular oxygen, and an oxygen-filled balloon (1–1.2 atm) was connected. The mixture was heated at 120 °C under stirring until completion. The reaction outcome was monitored by ^1H-NMR. Afterwards, the mixture was cooled to room temperature and water was added (50 mL aprox.). The resulting solution was acidified with HCl 1 M (pH ≈ 1–2) and extracted with Et_2O (4 × 6 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexane:ethyl acetate as eluent.

General procedure for the aerobic oxidation of benzylic CH bonds in the presence of $Pd(OAc)_2$ and L6. A round bottom flask equipped with a magnetic stirrer bar was charged with the methylene compound (1 mmol), NaOAc (8.0 mg, 0.1 mmol), $Pd(OAc)_2$ (20 µL of a 5 × 10^{-6} M solution in PEG-400, 10^{-7} mmol), **L6** (20 µL of a 5 × 10^{-6} M solution in PEG-400, 10^{-7} mmol) and PEG 400 (1 mL) at room temperature. The system was purged with molecular oxygen, and an oxygen-filled balloon (1–1.2 atm) was connected. The mixture was heated at 120 °C under stirring until completion. The reaction outcome was monitored by ^1H-NMR. Afterwards, the mixture was cooled to room temperature and water was added (50 mL aprox.). The resulting solution was acidified with HCl 1 M (pH ≈ 1–2) and extracted with Et_2O (4 × 6 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexane:ethyl acetate as eluent.

Conclusions

In conclusion, we have presented an extremely active, more convenient system for the oxidation of primary and secondary benzylic alcohols based on the use of air stable and relatively inexpensive palladium acetate and a readily available bis-(1,2,4)-triazolyl ligand, a combination also suitable for the benzylic C–H oxidation. A variety of alcohols and benzylic methylene compounds are selectively oxidized under 1 atm oxygen pressure at catalyst loadings as low as 10^{-5} mol%.

Acknowledgements

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