COMMUNICATION

Unusually facile palladium catalysed oxidation of imidazolidines and oxazolidines

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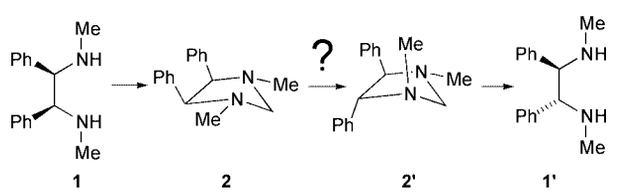
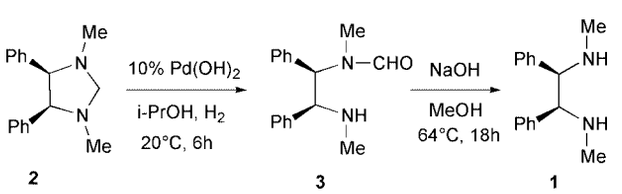
An unusually facile palladium catalysed oxidation of imidazolidines is described, affording in good yield, the monoamide of the corresponding diamine or the corresponding imidazolines. Oxazolidines derived from ephedrine react similarly.

In the course of our studies to find a method for the isomerisation of *meso* C_2 symmetrical diamines into their (+),(−) isomers,[1] we thought that the formation of an imidazolidine ring (an aminal) would help in this process. Indeed, in such a ring, the driving force would be the transformation of the *cis* relationship of the two substituents into a *trans* one (Scheme 1).



Scheme 1

A possible route for such an epimerisation, could be to take advantage of the benzylic position and to use a transition metal, the most obvious being palladium. When aminal **2** was treated with 10% $Pd(OH)_2$, in i-PrOH, under a hydrogen atmosphere, a rapid reaction took place, and, within 6 h at room temperature, all of the starting material disappeared in favor of a new very polar compound. This new compound was the monoformamide **3** of the starting diamine **1** (Scheme 2).



Scheme 2

Moreover, no isomerisation took place in this process, as was checked by hydrolysing amide **3**.

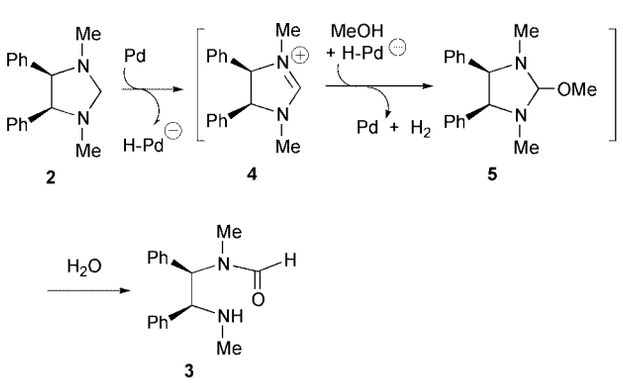
This net oxidation process of aminals has been achieved by electrochemical[2] or biogenetic[3] means, and more generally, by chemical oxidation.[4] In particular, palladium oxidation of amines has been described, but a high temperature (200 °C) is usually required.[5] This oxidation is also catalysed by other metals (see Table 1). However, the most practical and efficient was Pd/C (entry 3) which allows, by simple filtration and evaporation of the solvent, the easy obtention of the product. Of course there is no need to run the reaction under a hydrogen atmosphere. The reaction also occurs in open air, but a cleaner product is obtained under inert atmosphere (N_2 or Ar). Obviously, overoxidation products may be formed with oxygen. Solvents other than i-PrOH or MeOH were tried. No reaction at all was noticed in aprotic solvents such as cyclohexane, DCM, THF and toluene, or protic solvents such as ethanethiol or dimethylamine. In contrast, alcohols, such as methanol, ethanol, propan-2-ol, or even *n*-decanol may be used. Toluene containing MeOH is also possible, but no reaction occurred with water.

Table 1 Catalysts (5%) used for the oxidation of **2** to **3**

Entry	Catalyst (5%)	Conditions[a]	Conversion (%)
1	$Pd(OH)_2$	i-PrOH, H_2, 20 °C, 6 h	85
2	$Pd(PPh_3)_4$	MeOH, 20 °C, 30 min	100
3	10% Pd/C	MeOH, 20 °C, 5 h	100
4	Raney Ni	MeOH, 60 °C, 6 h	47
5	Pt/C	MeOH, 20 °C, 5 h	100
6	$RuCl_3$	MeOH, 65 °C, 24 h	20
7	Rh/C	MeOH, 20 °C, 15 h	65
8	$RhCl(PPh_3)_3$	MeOH, 20 °C, 15 h	50

[a] *Allowed solvents:* MeOH, EtOH, i-PrOH, $PhCH_3$ + 10% MeOH. *Not allowed solvents:* THF, CH_2Cl_2, $PhCH_3$, benzene, cyclohexane, EtSH, i-Pr_2NH, H_2O.

By analogy to Grigg and Heaney,[5b] we tentatively hypothesise that a palladium catalysed dehydrogenation occurs, leading to the imidazolinium **4**. This step is followed by addition of methanol to form a 2-alkoxy-1,3-imidazolidine **5**. In the case of these *meso* aminals, intermediates **4** and **5** were not observed since they are probably easily hydrolysed, even by moisture, to the monoamide **3** (Scheme 3).[6] That a dehydrogenation is involved, was checked by measuring the volume of gas evolution, and also by running a experiment with the aminal



Scheme 3

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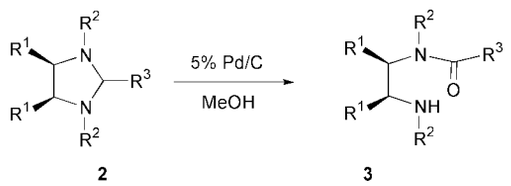
Table 2 Oxidation of *meso* aminals, according to Scheme 4

Entry	R^1	R^2	R^3	Conditions[a]	Product	Yield[b] (%)
1	Ph	Me	H	20 °C, 5 h	**3a**	89
2	Ph	Me	i-Pr	20 °C, 8 h	**3b**	83
3	Ph	Me	Ph	60 °C, 18 h	**3c**	70
4	Ph	Me	-CH=CH–CH_3	20 °C, 8 h	**3d**	70[c]
5	Ph	i-Pr	H	20 °C, 6 h	**3e**	73
6	Cy	Me	H	20 °C, 5 h	**3f**	84

[a] 3 Å Molecular sieves were usually added. [b] Isolated by SiO_2 column chromatography. [c] The saturated compound was obtained (R^3 = Pr).

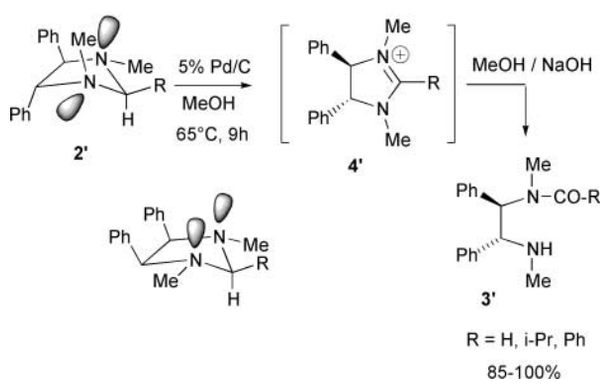
of crotonaldehyde, whereupon saturation of the double bond was observed (entry 4, Table 2).

In addition several other imidazolidines derived from *meso* diamines were treated under the above conditions. The results are summarised in Table 2 (Scheme 4).



Scheme 4

We also examined the case of the aminal **2′**, obtained from the (+),(−) diamine **1′**. The oxidation does not occur at all at room temperature, but only after heating at 65 °C for 9 h. In this aminal, the preferred conformation allows only one nitrogen lone pair to be *anti* to the C–H bond (Scheme 5),

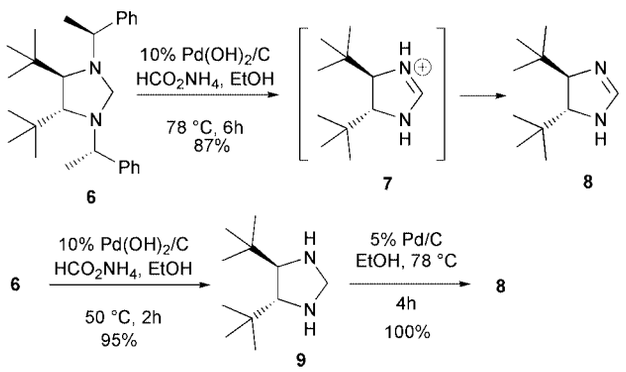


Scheme 5

whereas the all-*cis* aminal, seen above, allows the lone pairs of both nitrogens to adopt such a conformation. In this reaction, the imidazolinium **4′** seems more stable than its *meso* analogue **4** since it could be observed in the crude reaction mixture. The use of sodium hydroxide is then necessary, in addition to methanol and water, to have a complete hydrolysis into **3′**.

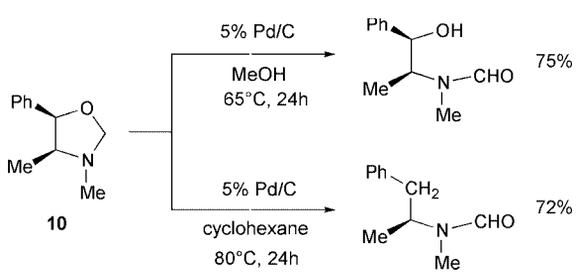
We also observed the same palladium mediated oxidation reaction on the (+),(−) aminal **6**.[7] Indeed, in the hydrogenolysis of the chiral benzylic groups, we obtained very cleanly the imidazoline **8** instead of the expected imidazolidine **9**. As above, this reaction probably proceeds through the imidazolinium **7** which is neither sensitive to addition of EtOH nor to hydrolysis by moisture in contrast to the intermediate **4′**. This hydrogenolysis/oxidation process occurred in one step in refluxing EtOH, using ammonium formate and palladium hydroxide as the catalyst. Nevertheless, the imidazolidine **9** could be obtained as the single product by performing the reaction at 50 °C with the same reagents. The palladium oxidation of **9** is then quantitative using Pd/C in refluxing ethanol without a hydrogen donor (Scheme 6).

Finally, we extended this reaction to oxazolidines. Thus, when the oxazolidine **10**, formed with ephedrine and formaldehyde, was treated under the standard conditions, the expected



Scheme 6

formamide was obtained in 75% isolated yield. Interestingly, when the same reaction was performed in an aprotic solvent, such as cyclohexane, a reaction occurred giving the formamide with cleavage of the benzylic C–O bond, in 72% isolated yield (Scheme 7).



Scheme 7

In summary, we have disclosed an interesting palladium catalysed oxidation of aminals,[8] which may find several synthetic applications, due to its mild conditions and efficiency. We are studying the extension of this reaction to other cyclic or acyclic aminals, as well as its potential in asymmetric synthesis.

Notes and references

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aminal **6** can also be obtained by the modified following procedure: To a solution of crude diamine (1 mmol) in Et_2O or CH_2Cl_2 (10 ml), were added a solution of formaldehyde (37% aq, 5 mmol), $MgSO_4$ (0.5 g) and acetic acid (one drop). The mixture was stirred at 20 °C for 6 h, filtered and concentrated. The crude was recrystallised in acetonitrile to give 50–60% of the expected aminal as colourless crystals.

8 **Typical Procedures**: *Oxidation of aminals*, **2** and **2′**: To a suspension of 10% Pd/C (0.053 g, 0. 05 mmol) and molecular sieves 3 Å (0.5 g), under argon, in MeOH (10 ml), was added the imidazolidine (1 mmol). The suspension was stirred for the time and the temperature stated in Table 2. After completion of the reaction, the Pd/C was filtered off through Celite, the solvents were evaporated and the crude product was purified by silica gel chromatography (Et_2O–MeOH, 50 : 50). *Oxidation of aminal*, **6**: To a solution of imidazolidine (1 mmol) in EtOH (20 ml), were added $Pd(OH)_2/C$ (0.1 mmol) and ammonium formate (10 mmol). The mixture was refluxed for 6 h, filtered and concentrated. To the residue were added Et_2O (15 ml) and K_2CO_3 (0.5 g) and the suspension was stirred for 1 h, filtered and concentrated to give the imidazoline **8** as a white solid. ^{1}H NMR: δ_H ($CDCl_3$) 0.86 (s, 18H), 3.27 (s, 2H), 4.8 (s, 1H), 7.05 (s, 1H). ^{13}C NMR: δ_C 24.5, 33.2, 69.1, 150.7.