Oxidation of Unactivated Methyl Groups *via* a Cyclopalladation Reaction

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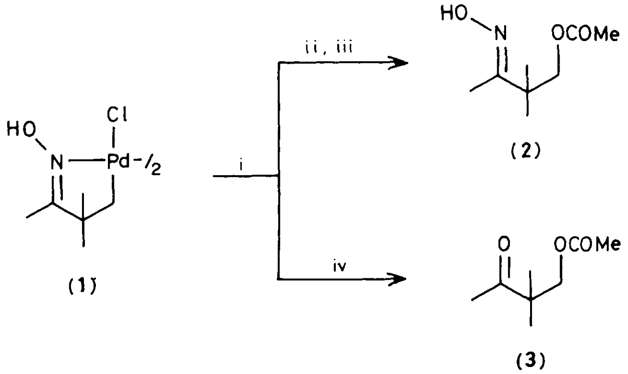
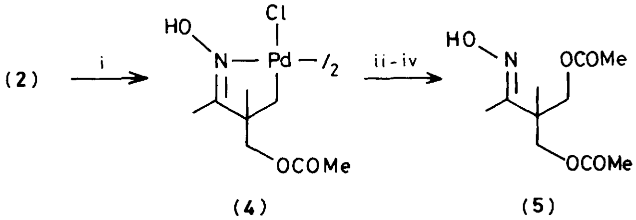
The successive cyclopalladation–oxidation of *E*-pinacolone, *E*-2,2-dimethylcyclohexanone, 2,2,6,6-tetramethylcyclohexanone, and *E*-lupanone oxime led to the corresponding β-acetoxy derivatives; the second palladation in the case of the acetoxy compounds (**2**) and (**8**) takes place in one of the remaining methyl groups, being a regiospecific process, and in the case of the cyclic oximes the palladation occurs in the equatorial methyl group.

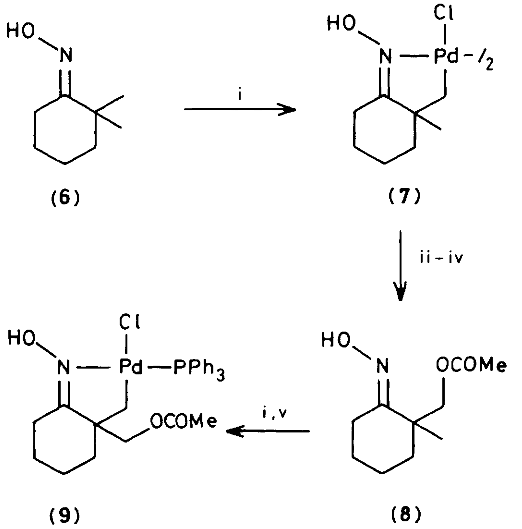
The cyclopalladation of *E*-pinacolone oxime leading to the dimeric organopalladium compound (**1**) has been described.[1]



Scheme 1. *Reagents*: i, pyridine; ii, $Pb(OAc)_4$; iii, $NaBH_4$; iv, 2 equiv. $Pb(OAc)_4$.



Scheme 2. *Reagents*: i, Na_2PdCl_4–NaOAc; ii, pyridine; iii, $Pb(OAc)_4$; iv, $NaBH_4$.



Scheme 3. *Reagents*: i, Na_2PdCl_4; ii, pyridine; iii, $Pb(OAc)_4$; iv, $NaBH_4$; v, PPh_3.

Very recently, the application of this reaction to the cyclopalladation of lanost-8-en-3-one oxime and its further deuteriation or iodination has been published.[2] These results prompt us to report our independent findings in this field.

The oxidation of the pyridine complex derived from the compound (**1**) with lead tetra-acetate (1 equiv.) in acetic acid at room temperature led after reduction with sodium borohydride‡ to the acetoxy oxime (**2**) (*ca.* 100% yield).§ In the absence of pyridine the reaction did not work. If the same process was carried out with double the stoicheiometric amount of lead tetra-acetate the corresponding compound (**3**) was isolated (64% yield)§ (Scheme 1).

A second palladation–oxidation of compound (**2**) was done in order to study the regiochemistry of this process. Thus, when compound (**2**) was palladated the organopalladium dimer (**4**) was isolated (83% yield),§ and subsequent oxidation of this compound led to the diacetoxy oxime (**5**) (86% yield)§ (Scheme 2).

The palladation of *E*-2,2-dimethylcyclohexanone oxime (**6**) yielded the corresponding dimer (**7**) (85% yield)§ which was oxidized through its pyridine complex to give the compound (**8**) (96% yield).§ When this compound was again palladated the metallation took place on the remaining methyl group[3] affording the organopalladium compound (**9**) after treatment with triphenylphosphine (82% yield)§ (Scheme 3).

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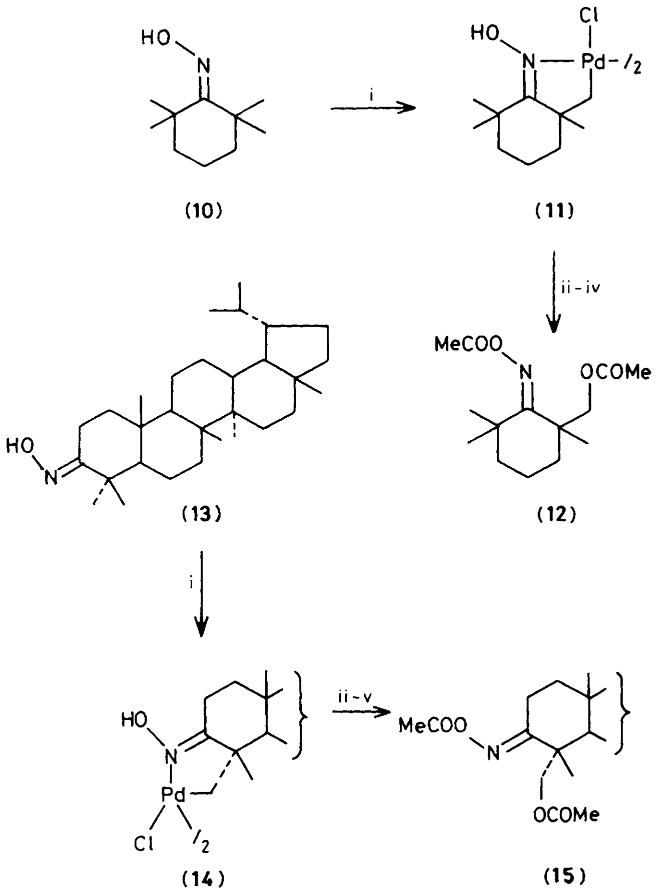
‡ When the reaction product bears the oxime group the reduction of Pd^{II} to Pd^0 was carried out to avoid the trapping of the Pd^{II} by the oxime.

§ All new compounds have yielded satisfactory analytical and/or spectral data. Selected data: (**2**), m.p. 85—86 °C; ν 1 730 cm^{-1} (C=O); δ_H 4.07 (CH_2O); δ_C 70.01 (CH_2O) and 170.98 (C=O); *m/z* 174 (M^+ +1). (**3**), b.p. 100 °C (0.1 mmHg, Kugelrohr); ν 1 750 and 1 710 cm^{-1} (C=O); δ_H 2.16 (MeCO) and 4.10 (CH_2O); δ_C 69.82 (CH_2O), 170.66 (CO_2), and 210.89 (C=O); *m/z* 159 (M^+ +1). (**4**), m.p. 135–138 °C; δ_H 2.34, 2.63 (2 d, *J* 8.4 Hz, CH_2Pd), 3.96, and 4.01 (2d, *J* 11.3 Hz, CH_2O); δ_C 33.67 (CH_2Pd) and 68.84 (CH_2O). (**5**), m.p. 45—47 °C; δ_H 4.18 (CH_2O); δ_C 65.70 (CH_2O). (**7**), m.p. 182—185 °C (decomp.); δ_H 2.51 and 2.57 (2d, *J* 8.2 Hz, CH_2Pd); δ_C 26.48 (Me) and 40.40 (CH_2Pd); *m/z* 562 (M^+). (**8**), m.p. 125 °C (0.1 mmHg, Kugelrohr); ν 1 740 cm^{-1} (C=O); δ_H 4.08 and 4.20 (2d, *J* 11.0 Hz, CH_2O); δ_C 69.10 (CH_2O) and 171.07 (C=O); *m/z* 199 (M^+). (**9**), m.p. 156—158 °C (decomp); δ_H 1.40, 1.87 (2d, *J* 10.0 Hz, CH_2Pd), 3.81, 4.28 (2d, *J* 10.8 Hz, CH_2O), and 10.67 (d, J_{HP} 3.0 Hz, OH); δ_C 42.30 (CH_2Pd) and 68.29 (CH_2O); δ_P 30.49 p.p.m. (**11**), m.p. 177—179 °C (decomp.); δ_H 2.33 and 2.46 (2d, *J* 7.1 Hz, CH_2Pd); δ_C 41.22 (CH_2Pd). (**12**), oil; ν 1 745 cm^{-1} (C=O); δ_H 2.06, 2.19 (2 × MeCO), 4.07, and 4.31 (2d, *J* 10.7 Hz, CH_2O); δ_C 20.07, 20.87 (2 × CH_3CO), 71.34 (CH_2O), 169.16, 170.78, and 172.85 (C=N and 2 × C=O). (**14**), m.p. > 210 °C; δ_H 2.50 and 2.61 (br. s and d, *J* 7.5 Hz, CH_2Pd); δ_C 43.15 (CH_2Pd). (**15**), oil; ν 1 740 cm^{-1} (C=O); δ_H 2.06, 2.17 (2 × MeCO), 4.09, and 4.19 (2d, *J* 11.0 Hz, CH_2O); δ_C 68.29 (CH_2O), 169.65, and 170.84 (C=N and 2 × C=O); *m/z* 542 (M^+ +1).



Scheme 4. *Reagents*: i, Na_2PdCl_4–NaOAc; ii, Ac_2O; iii, pyridine; iv, $Pb(OAc)_4$; v, $NaBH_4$.

The palladation of 2,2-dimethylcyclopentanone oxime fails owing to the difficulty in achieving planarity of the oxime and methyl groups necessary for palladation within the constraints applied by the five-membered ring.[3]

We have also studied the palladation–oxidation in a hindered ketone. Thus, when 2,2,6,6-tetramethylcyclohexanone oxime (**10**) was palladated the expected organopalladium dimer (**11**) was obtained (86% yield).§ In this case the oxime group must be acetylated in order to avoid its isomerization during the oxidation; the acetylation and further oxidation of compound (**11**) led to the product (**12**) (76% yield)§ (Scheme 4).

Finally, we have palladated lupanone oxime (**13**), isolating the expected dimer (**14**) (76% yield),§ which after acetylation and oxidation led to the expected 23-acetoxy derivative (**15**) (90% yield)§ (Scheme 4). The stereochemistry of (**14**), and hence the acetoxy derivative (**15**), was established by nuclear Overhauser effect (n.O.e.) studies at 500 MHz.

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