Palladium(II)-catalysed Oxidation of Allylic Amines with Molecular Oxygen

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The palladium(II)-catalysed oxidative cyclization of the adducts of *N*-Boc-protected allylic amines with methyl glyoxylate proceeds well in the presence of molecular oxygen as the stoichiometric oxidant without the need of a co-oxidant, if Me_2SO is used as the solvent.

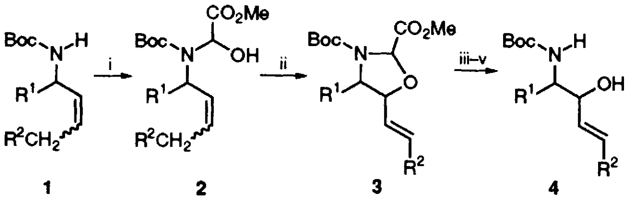
We recently reported a facile and stereoselective synthesis of *N*-Boc-1-aminoalk-3-en-2-ols **4** from *N*-Boc-protected allylic amines **1**.[1] This methodology (Scheme 1) involves (*i*) conversion of the *N*-Boc-protected amines **1** into the stable methyl glyoxylate adducts **2**, (*ii*) oxidative 5-*exo* cyclization of **2** to alkenyl oxazolidines **3**, and (*iii*) detachment of the original methyl glyoxylate moiety by using anodic oxidation to provide **4**. The key oxidation step was carried out in Me_2SO with $Pd(OAc)_2$ as the catalyst and $Cu(OAc)_2$ as the stoichiometric oxidant.

In order to improve the oxidation step we investigated the use of molecular oxygen as a clean alternative for $Cu(OAc)_2$. We also tested numerous other solvents for this reaction and examined the effects of these changes on regio- and stereochemistry. Herein, we report that the key oxidative cyclization proceeds well by using molecular oxygen without a co-catalyst in Me_2SO as the solvent.

There are numerous examples of palladium(II)-catalysed oxidations that employ molecular oxygen as the stoichiometric reagent.[2] The vast majority of these examples, however, require the presence of a co-catalyst, as palladium is not readily oxidized by molecular oxygen itself. The energetic barrier for electron transfer from palladium(0) to molecular oxygen can be considerably lowered by coupling with a cascade redox system[3] allowing aerobic reactions to be carried out even at room temperature. Only in a very few cases is palladium reported to be recycled by molecular oxygen without an additional redox aid.[4] As $Cu(OAc)_2$ is also known to act as co-catalyst in some cases,[5] an obvious modification to our published method[1] was to reduce the amount of $Cu(OAc)_2$ and conduct the reaction under atmospheric pressure of pure oxygen.

The results of our experiments are listed in Table 1. All the starting hydroxymethylamine starting derivatives have been described before.[1] Stereochemical assignments of the individual product oxazolidines were based on crystallographic data (**13**)[6] and/or ^1H NMR NOE experiments. In order to establish the stereochemistry of the ring junctions of **14** and **15** beyond doubt, a mixture of these oxazolidines was convered to the single crystalline *N*-Boc-protected aminoalcohol **18** (m.p. 122–123 °C).[1] X-Ray crystallography† showed this compound to be *trans*-1-*N*-Boc-aminocyclooct-3-en-2-ol (Fig. 1).‡

The cyclopentenylamine derivative **5** which earlier proved[1] to be an excellent substrate in the reaction with stoichiometric $Cu(OAc)_2$ with regard to both stereoselectivity and reaction rate (see Table 1, entry 1) was investigated first. It cyclized in satisfactory yield under an oxygen atmosphere with 10% of both $Pd(OAc)_2$ and $Cu(OAc)_2$ at 65–70 °C in Me_2SO. Surprisingly, however, this reaction proceeded equally well without any added copper salts (entry 2). In addition, the precipitation of palladium black (*i.e.* loss of catalyst) that was characteristic for the copper-mediated reactions was less pronounced. Encouraged by these observations we also lowered the amount of the palladium catalyst to 5 and 2% (entries 3 and 5). The reaction mixtures now remained clear throughout the course of the reaction and no precipitation was observed. Although these reactions did proceed at room temperature, the optimum temperature with respect to reaction rate again turned out to be 65–70 °C.



Scheme 1 *Reagents and conditions*: i, $HOCH(OMe)CO_2Me$, CH_2Cl_2 reflux, 4 Å molecular sieve; ii, $Pd(OAc)_2$, 10%, $Cu(OAc)_2$ (3 equiv.), Me_2SO, 70 °C; iii, LiOH, MeOH, reflux; iv, anodic oxidation, MeOH; v, hydrolysis.

Under these conditions the cyclohexenylamine derivative **6** which showed[1] a slower cyclization rate than **5** in the reaction with stoichiometric $Cu(OAc)_2$ (entry 6) gave similar reaction rates and yields as **5** (entries 7–9). Furthermore the cyclization of the cyclooctenylamine derivative **7** which earlier appeared[1] to be a difficult substrate (entry 10) proceeded readily (entry 11). Albeit not complete, this reaction gave an appreciably higher yield in a much shorter reaction time. In order to force this reaction to completion the catalyst was added in two portions (entry 14), giving the same cyclization products as before in the expected 1:2 ratio reflecting the ratio of the starting diastereoisomers. The use of smaller amounts of catalyst or unfavourable conditions (see *e.g.* entry 13) led to a different ratio, indicating that diastereoisomer **15** was more readily formed than **14**.§

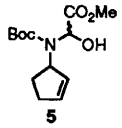
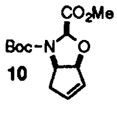
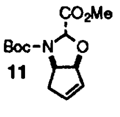
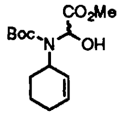
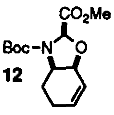
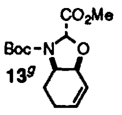
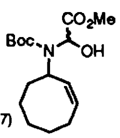
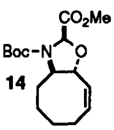
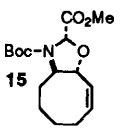
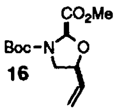
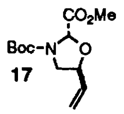
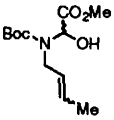
In contrast with the cyclic substrates **5**–**7** the stereochemical outcome of the cyclizations of the non-cyclic **8** and **9** is not determined by the isomer ratio of the starting material. This might provide information on the nature of the catalytically active palladium species. As shown in Table 1 the variation in stereoselectivity was small in the oxidative cyclization of *Z*- and *E*-crotylamine derivatives **8** and **9** under the different conditions. Interestingly, the difference in reactivity between the *Z*- and the *E*-olefin was more pronounced with molecular oxygen than with $Cu(OAc)_2$ as the oxidant (compare entries 16 and 19 with 15 and 18).

With substrates **5**, **6** and **7** we tested a wide range of solvents for the oxidative cyclization catalysed by 2–10% of $Pd(OAc)_2$. Most solvents, however, allowed the catalyst to perform only one turnover as was easily inferred from TLC, and precipitation of Pd-black resulted. Amides such as DMF, *N*-methylacetamide and formamide, and glymes (dimethoxy ethane, di- and tri-glyme) did allow more than one catalytic cycle but the reaction was considerably slower than in Me_2SO and did not go to completion because of extensive precipitation of Pd-black. Me_2SO was thus shown to perform a unique role as the solvent.[9]

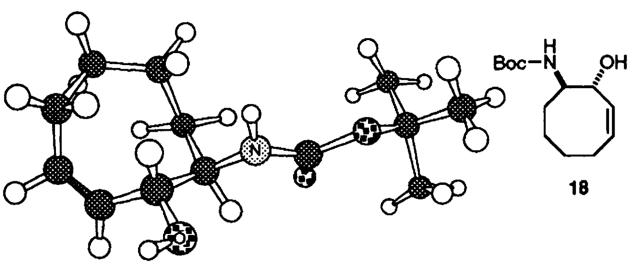
Efforts to use Me_2SO in catalytic amounts along with $Pd(OAc)_2$ by using other solvents were equally unsuccessful. However, dilution of Me_2SO with glymes was possible to some extent. The use of a 9:1 mixture of triglyme and Me_2SO did not alter the reaction rate (entries 4 and 8) except with substrate **7**. In the latter case precipitation of the catalyst became dominant and the yield dropped dramatically (entry 13).

In general, satisfactory catalytic activity was found only when the reaction mixtures were clear and without precipitate. These solutions initially adopted an orange-red colour

Table 1 Results of the Palladium(II) catalysed oxidations of *N*-Boc protected allylic amine derivatives **5–9**

Entry	Substrate[a]	Catalyst % $Pd(OAc)_2$	Conditions[b]	Reaction time/h[c]	Yield (%)[d]	Product oxazolidines[e]	Ratio[f]
1	 **5**	10	**A**	2	85	 **10**  **11**	50:50
2		10	**B**	2	87		50:50
3		5	**B**	2	89		50:50
4		5	**C**	2	87		50:50
5		2	**B**	2	91		50:50
6	 **6**	10	**A**	5	70	 **12**  **13**[g]	50:50
7		5	**B**	2	90		50:50
8		5	**C**	2	89		50:50
9		2	**B**	2	90		50:50
10	 (33:67) **7**	10	**A**	24*	49	 **14**  **15**	25:75
11		10	**B**	1*	62		33:67
12		5	**B**	4*	58		33:67
13		5	**C**	4*	27		16:84
14		5 + 5	**B**	4 + 4	70		33:67
15		10	**A**	2	76	 **16**  **17**	23:77
16	**8** *Z* 	5	**B**	2	80		24:76
17		2	**B**	4*	69		24:76
18		10	**A**	5	64		50:50
19		5	**B**	4*	43		50:50
20	**9** *E*	5 + 5	**B**	4 + 4*	63		50:50

[a] Isomer ratios are 50:50 unless otherwise stated. [b] **A**: 3 equiv. $Cu(OAc)_2$, Me_2SO, 65–70 °C. **B**: Me_2SO, O_2, 65–70 °C. **C**: Me_2SO–triglyme (1:9), O_2, 65–70 °C. [c] Reactions were run until complete according to TLC. An asterisk denotes an incomplete reaction. [d] Yields refer to isolated and purified (flash chromatography) mixtures of diastereoisomers. [e] Diastereoisomers could also be isolated (flash chromatography) and characterized separately[6] except **14** and **15**, and **16** and **17**, which were inseparable. [f] Isomer ratios were determined by ^1H NMR (OC*H*CH=C signals integrated). [g] Mp 78–79 °C.



18

Fig. 1 Chem 3D™ perspective view of the crystal structure of **18**

which gradually turned pale yellow as the reaction proceeded further. A possible explanation for these observations is the formation of stabilized colloidal metal species or so-called 'giant clusters'[10] under the reaction conditions. Transition metal clusters (normally < 5 nm in size) are well known as homogeneous catalysts in many different reactions,[11] as are colloids (generally > 10 nm). For example, platinum colloid is believed to be involved as the catalytically active species in platinum-mediated hydrosilylations causing the characteristic yellow colour of the homogeneous reaction mixture.[12] The presence of molecular oxygen is essential for its formation. 'Giant' palladium acetate clusters[13] are used as homogeneous catalysts in various oxidative reactions employing molecular oxygen.[14] For their preparation *via* partial reduction of $Pd(OAc)_2$ both molecular oxygen and a stabilizing ligand are needed.[13,14] We believe that in our case the solvent Me_2SO is essential in this respect. Me_2SO is known[15] to be a versatile ligand for palladium because of its ambidentate character. Apparently, after initial reduction of $Pd(OAc)_2$ by oxidative cyclization, no palladium species is formed that can carry the reaction further in other solvents.

In conclusion, we have shown that $Cu(OAc)_2$ can be replaced by molecular oxygen as the stoichiometric oxidant in a $Pd(OAc)_2$-catalysed oxidative cyclization.¶ This modification requires less catalyst and gives considerably higher yields in shorter reaction times. The solvent Me_2SO performs a unique role.

We thank J. Fraanje and K. Goubitz of the Laboratory of Crystallography of this University for the X-ray structure determination and Prof. P. W. N. M. van Leeuwen for useful discussions. This investigation was supported by the Innovation Oriented Research Program on Catalysis of the Dutch Ministry of Economic Affairs.

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Footnotes

† *Crystal data*: $C_{13}H_{23}NO_3$, M_r = 241.3, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 6.3908(4), b = 11.006(2), c = 20.769(2)Å, U = 1460.8(3) Å^3; Cu-Kα radiation, λ(Cu-Kα) = 1.5418 Å, μ = 5.9 cm^{-1}; $F(000)$ = 528. 1625 reflections were measured on an Enraf-Nonius CAD-4 diffractometer. 1257 reflections with $I > 2.5\sigma(I)$ were used in the structure solution and refinement. Corrections were applied for Lorentz and polarisation effects. The Flack[16] absolute structure parameter refined to X_{abs} = 0.04(86). Final R = 0.079, R_w = 0.059. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‡ Thus, the earlier stereochemical assignments[1] of **14**, **15** and **18** were wrong. A comparable yet not as pronounced stereoselectivity trend in 5-annulation onto cyclohexene and cyclooctene was reported by Fristad and Peterson.[7] The stereochemical course of our cyclizations is in agreement with results of epoxidation and cyclopropanation on cyclohex-2-enol and cyclooct-2-enol.[8]

§ Such a preference was also observed in the reaction of **5** and **6** (the *exo* diastereoisomers **11** and **13**, respectively, were formed faster as was easily inferred from TLC) but this was not reflected in the product oxazolidine ratio because these reactions were complete.

¶ *Note added in proof*: This work was reported (by R. A. T. M. v. B.) at the 7th IUPAC Symposium on Organometallic Chemistry directed toward Organic Synthesis, 19–23 September 1993, Kobe, Japan. Related results were independently published by R. C. Larock and T. R. Hightower, *J. Org. Chem.*, 1993, **58**, 5298.

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