# Intramolecular Oxidative Pd(II)-Catalyzed Alkoxylation of 3-Aza-5-alkenols with $O_2$ as Sole Oxidant: Mild Conditions for the Synthesis of 1,4-Oxazine Derivatives

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*Received 17 October 2010*

Dedicated to Professor Alberto Brandi on occasion of his 60th birthday

**Abstract:** Synthesis of 1,4-2*H*-oxazine derivatives was performed by Pd(II)-catalyzed aerobic oxidative cyclization of 3-aza-5-alkenols, prepared from easily available 1,2-amino alcohols. The reaction proceeds in very mild conditions with a simple catalytic system consisting of $PdCl_2(MeCN)_2$ in THF at room temperature with molecular oxygen as the sole stoichiometric oxidant.

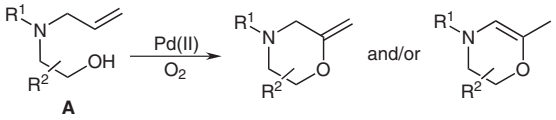
**Key words:** palladium, heterocycles, alkenols, alkoxylation, molecular oxygen

Oxidative palladium(II) catalysis has gained a remarkable role in functionalization of $sp^2$-carbon atoms.[1] Significant success has been achieved for carbon–carbon[2] and carbon–heteroatom[3] bond formation either by inter- or intramolecular reactions. In terms of versatility, economic cost, and environmental impact, one of the key requirements for their success is played by the oxidant, essential to restart a new catalytic cycle.[4] A fruitful approach is the use of procedures involved with a terminal oxidant such as molecular oxygen. This offers both economical and practical advantages, making attractive the challenge in this field to use molecular oxygen as the sole oxidant without any other co-oxidants.[5,6]

The intramolecular version of palladium-catalyzed oxidative reactions has had a growing impact on heterocyclic synthesis.[7] Also in our laboratories some cyclization procedures have been previously performed as convenient routes to access various heterocycle systems.[8]

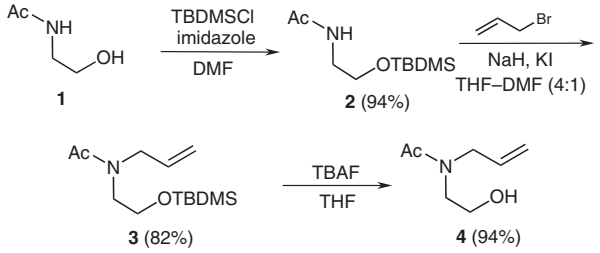
Herein, we describe a practical procedure for the synthesis of 2*H*-1,4-oxazine derivatives by palladium-catalyzed aerobic oxidative cyclization of 3-aza-5-alkenols **A** (Scheme 1), which are readily accessible from 1,2-amino alcohols. This reaction was made possible by use of a very simple catalyst system consisting of $PdCl_2(MeCN)_2$ in THF, which is able to promote the cyclization at room temperature with molecular oxygen as the sole stoichiometric oxidant.

The interest towards 2*H*-1,4-oxazine skeleton arises from its presence in compounds having biological activities as well as from the potential use as building blocks in various useful synthesis.[9]




**Scheme 1** Synthesis of 1,4-2*H*-oxazine derivatives by Pd(II)-catalyzed aerobic oxidative cyclization of alkenols

The initial efforts to develop the desired reaction were made on alkenol **4**, prepared in satisfactory overall yields starting from (*N*-acetyl)aminoethanol (**1**).[10] After O-protection with TBDMSCl, the resulting amide **2** was functionalized by reaction with allyl bromide in the presence of NaH and KI to give **3**. The subsequent removal of TBDMS group in classical conditions (tetrabutylammonium fluoride in THF) as final step furnished the target compound **4** (Scheme 2).



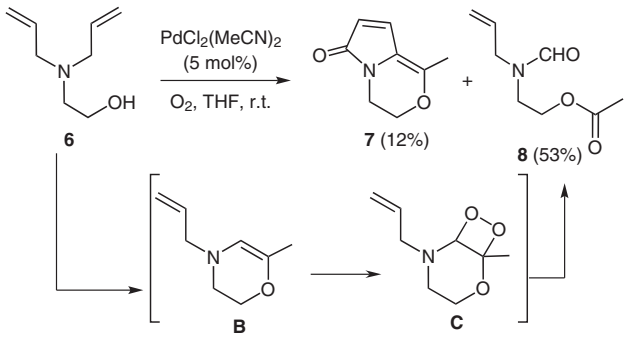

**Scheme 2** Synthesis of alkenol **4**

Alkenol **4** was firstly tested under a number of conditions potentially suitable for aerobic oxidative heterocyclization reactions (entries 1–8, Table 1). $Pd(OAc)_2$ in THF and in DMSO afforded the desired 3,4-dihydro-2*H*-oxazine **5** in 15% and 37% yield, respectively, beside unreacted or degradation materials (entries 1 and 2). Since a better result was obtained by using $PdCl_2(MeCN)_2$ in DMSO (entry 3), we privileged the use of the latter catalyst and examined the influence of solvent and temperature on the product yield (entries 4–7). Disappointingly, when the reaction took place with air as terminal oxidant, compound **5** was formed in lower yield (entry 8). The reaction was found to be feasible with other oxidant agents such as $Cu(OAc)_2$, 1,4-benzoquinone, $H_2O_2$, $CuCl_2/O_2$,

*SYNLETT* 2011, No. 2, pp 0227–0230
Advanced online publication: 04.01.2011
DOI: 10.1055/s-0030-1259295; Art ID: G31210ST

and *t*-BuOOH (entries 9–13, Table 1). However, sizeable amounts of degradation products were generally formed. As a matter of fact, the overall account of the investigated catalytic systems show as the most effective the mild conditions of entry 5, namely $PdCl_2(MeCN)_2$ in THF at room temperature in the presence of molecular oxygen.[11]

Subsequently, we investigated the efficiency of molecular oxygen to promote intramolecular alkoxylation of a few differently N-substituted 3-aza-5-hexenols. When a tosyl group replaced the acetyl group of compound **4**, a satisfactory reaction occurred providing the cyclization product in higher yield (81% vs. 75% yield). Conversely, the reaction of (*N*,*N*-diallyl)-2-aminoethanol (**6**) in the presence of 0.05 equivalents of $PdCl_2(MeCN)_2$ in THF under oxygen atmosphere led to a synthetically useless mixture of the bicyclic fused-ring product **7** and the acyclic compound **8** (Scheme 3). A tentative suggestion for the formation of **7** implies an insertion of the endocyclic olefin of **B** into a Pd–H bond affording an intermediate which could evolve through 5-*endo* cyclization, isomerization to an enamine, adventitious water attack, and final oxidation. Conversely, compound **8** plausibly arises by an oxidative degradation of the first-formed 3,4-dihydro-2*H*-1,4-oxazine **B** through the intermediacy of the dioxetane species **C** susceptible to [2+2] retrocycloaddition.[12]

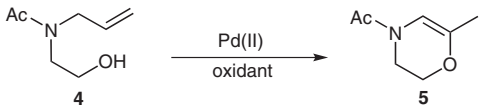



**Scheme 3** Pd(II)-catalyzed reaction of (*N*,*N*-diallyl)aminoethanol **6**

At this stage of our study, we explored the scope of the intramolecular alkoxylation procedure onto a variety of 2-substituted 3-aza-alkenols. Starting from the easily available L-alaninol, L-valinol, L-leucinol, L-phenylalaninol, and (*S*)-2-aminobutanol, we synthesized the substrates **9a–g** and transformed them into the optically active dihydrooxazines **10a–g** in fair to good yields.

A plausible pathway accounting for the formation of the 1,4-oxazine product is depicted in Scheme 4. The first formed Pd(II) coordination species **E** undergoes intramolecular nucleophilic attack of the hydroxy group to generate the σ-alkylpalladium complex **F** via a 6-*exo*-trig cyclization process. Subsequent β-hydride elimination results in the formation of the *exo*-methylene compound **G**, which isomerizes to the final product **5**, and the complex **H** which eliminates HCl giving the Pd(0) species **I**. At this point, in the light of previous literature reports,[5b,d] the role of molecular oxygen may be interpreted as follows. Oxygenation of **I** generates the dioxygen complex **J**, susceptible to protonation and ring opening to the Pd(II)-

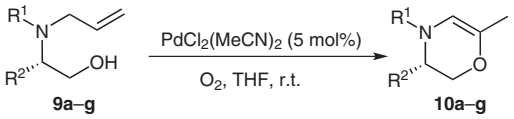
**Table 1** Optimization of Reaction Conditions




| Entry | Catalyst (5 mol%) | Oxidant | Solvent | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $O_2$ | THF | 25 | 24 | 15 |
| 2 | $Pd(OAc)_2$ | $O_2$ | DMSO | 70 | 2 | 37 |
| 3 | $PdCl_2(MeCN)_2$ | $O_2$ | DMSO | 70 | 4 | 61 |
| 4 | $PdCl_2(MeCN)_2$ | $O_2$ | THF | 60 | 2 | 58 |
| 5 | $PdCl_2(MeCN)_2$ | $O_2$ | THF | 25 | 5 | 75 |
| 6 | $PdCl_2(MeCN)_2$ | $O_2$ | 1,4-dioxane | 25 | 2 | 72 |
| 7 | $PdCl_2(MeCN)_2$ | $O_2$ | MeCN | 25 | 2 | 52 |
| 8 | $PdCl_2(MeCN)_2$ | air | THF | 25 | 24 | 45 |
| 9 | $PdCl_2(MeCN)_2$ | $Cu(OAc)_2$[a] | THF | 25 | 24 | 70 |
| 10 | $PdCl_2(MeCN)_2$ | 1,4-BQ[a] | THF | 25 | 1 | 38 |
| 11 | $PdCl_2(MeCN)_2$ | $H_2O_2$[a] | THF | 25 | 3 | 25 |
| 12 | $PdCl_2(MeCN)_2$ | $CuCl_2$,[b] $O_2$ | THF | 25 | 2 | 65 |
| 13 | $PdCl_2(MeCN)_2$ | *t*-BuOOH[a] | THF | 25 | 3 | 27 |

[a] 1.5 equiv.
[b] 10 mol%.

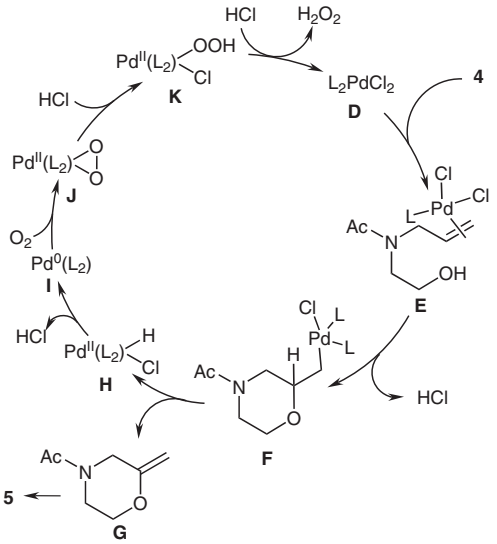
**Table 2** Reaction Scope




| Entry | $R^1$ | $R^2$ | Yield of **10** (%) |
|---|---|---|---|
| 1 | Ac | *i*-Bu | 75 |
| 2 | Ac | Et | 63 |
| 3 | Ac | Bn | 63 |
| 4 | Tos | *i*-Pr | 82 |
| 5 | Tos | Me | 75 |
| 6 | Tos | Et | 74 |
| 7 | Tos | Bn | 67 |

hydroperoxide intermediate **K**. A second protonation step can finally convert **K** in $H_2O_2$ and the active Pd(II) catalyst **D**.

Since some literature papers described the Pd-catalyzed isomerization of the ethylenic double bond of alkenols,[13] one could devise a different mechanism involving an initial migration of the ethylenic double bond and subsequent 6-*endo*-trig cyclization. However, we tend to exclude such mechanism because in no case we observed the formation of the isomerization substrate or the plausible 5-*exo*-trig cyclization product. Moreover, the attempts to promote the Pd-catalyzed migration of the double bond on O-protected compound **3** and on alkenol **4** failed.[14]




**Scheme 4** Proposed mechanism for the oxidative palladium(II)-catalyzed heterocyclization

In conclusion, we have developed an intramolecular oxidative alkoxycyclization of 3-aza-5-alkenols in very mild conditions to give 3,4-dihydro-2*H*-1,4-oxazine products, which are useful intermediates to access more complex structures containing a morpholine ring. Investigations towards dihydroalkoxylation reactions to directly produce optically active variously substituted morpholines are now in progress.

## Acknowledgment

The authors thank the Ministero dell'Università e della Ricerca for financial support (PRIN 2008KRBX3B).

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(11) **Experimental Procedure**
A solution of **4** (1.0 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol, 13 mg), in THF (5 mL) was stirred under oxygen atmosphere for 5 h at r.t.. The solvent was evaporated under reduced pressure. The crude mixture was diluted with brine (10 mL) and extracted with $CH_2Cl_2$ (2 × 25 mL). The organic layer was dried over $Na_2SO_4$ and the solvent removed under reduced pressure. The residue was chromatographed on a silica gel column with light PE–EtOAc (5:1) as eluent to give **5** (75%).
**Data for 4-Acetyl-6-methyl-3,4-dihydro-2*H*-1,4-oxazine (5)**
Colourless oil. IR (nujol): 1676 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.75 (3 H, s), 2.12 (3 H, s), 3.48 (2 H, t, *J* = 4.7 Hz), 3.55 (2 H, t, *J* = 4.7 Hz), 5.89 (1 H, s). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 17.9 (q), 22.0 (q), 43.1 (t), 64.1 (t), 98.9 (d), 137.9 (s), 163.7 (s). MS: *m/z* = 141 [$M^+$]. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found C, 59.33; H, 7.96; N, 9.88.

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(14) Reaction conditions used to attempt the isomerization process: (*i*) $PdCl_2$ (10 mol%) in $H_2O$–MeOH (1:1) at 80 °C for 24 h; (*ii*) $PdCl_2$(TMEDA) (10 mol%) in $H_2O$–MeOH (1:1) at 80 °C for 24 h; (*iii*) $PdCl_2(MeCN)_2$ (10 mol%) in $CH_2Cl_2$ at r.t. for 24 h.