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Palladium (II) Catalysed Oxime-Metallo-Nitrone-Isoxazolidine Cascade Reactions of α-Imino Aldoximes

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Abstract: Palladium (II) salts catalyse stereospecific and highly facially selective oxime-nitrone-isoxazolidine cascade reactions between α-imino aldoximes and *N*-methylmaleimide *via* intermediate *N*-metallo-aldonitrones. These processes occur at room temperature in a range of polar solvents through the chelation of both α-imino and aldoxime nitrogen atoms to the palladium (II) centre.
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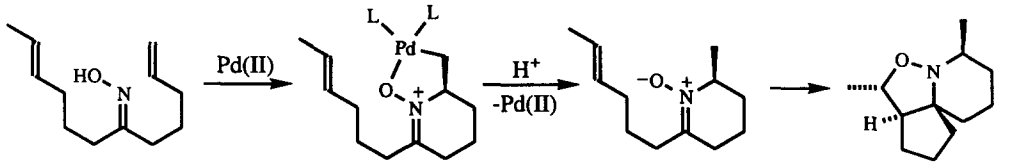
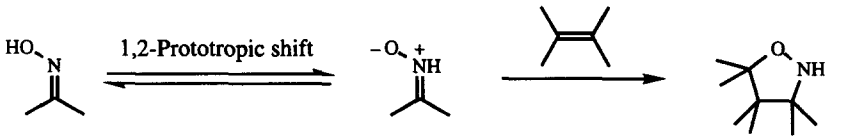
We have recently reported[1,2] the use of palladium (II) salts as catalysts to promote oxime-nitrone-isoxazolidine cascades and have noted that either $PdCl_2$ or $PdCl_2(MeCN)_2$ catalyse oxime-nitrone-isoxazolidine cascades in unactivated terminally unsaturated oximes (*Scheme 1*). These formal 1,3-azaprotio cyclotransfer (APT) processes occur with regio-, stereo- and facio-specificity in the subsequent cycloaddition step under relatively mild conditions and at a much enhanced rate compared to the purely thermal reactions.[3] Thus in unactivated systems Pd(II) catalysed processes typically proceed over 6-8 hours in THF or benzene at reflux (66-80°C) whereas identical uncatalysed reactions require more elevated temperatures (xylene, 140°C) and extended reaction times (up to three days). Recently we have also developed efficient $ZnBr_2$ catalysed oxime-nitrone-isoxazolidine cascades.[4]



Scheme 1



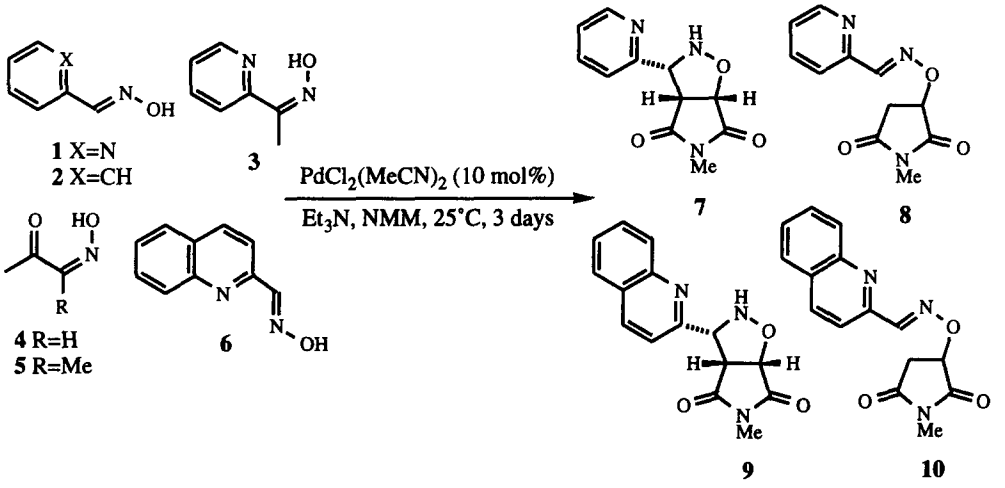
Scheme 2

We have been similarly interested in the development of methods by which to enhance the rate of what is generally the most energetically demanding of our cascade routes from oximes to heterocycles *via* nitrones, namely the 1,2-prototropic route[5] (*Scheme 2*). This route to cycloadducts has been extensively developed in

our laboratories to prepare isoxazolidine derived heterocyclic systems in which further elaboration of the resulting heterocycle is possible by subsequent manipulation of the N-O bond.

We have thus screened a wide range of metal salts with varying aza- and oxa-philicities to determine their effectiveness as catalysts to enhance the rate of nitrone formation from oximes by the selective complexation of the oxime sp^2 nitrogen atom thereby generating *N*-metallo-nitrones upon deprotonation. We now report on our studies using $PdCl_2(MeCN)_2$ to catalyse metallo-nitrone-cycloaddition cascades in α-imino aldoximes. These cascades proceed at room temperature *via* the intermediacy of *N*-metallo-aldonitrones through chelation of both α-imino and oxime sp^2 nitrogen atoms to the palladium centre.

In contrast to our Pd(II) assisted APT-cycloaddition cascades[1,2] in which only $PdCl_2$ and $PdCl_2(MeCN)_2$ were found to be active as catalysts, several Pd(II) salts are effective in these metallo-nitrone cascades; $PdCl_2$, $PdCl_2(MeCN)_2$, $Pd(OAc)_2$, $Pd(H_2O)_4(ClO_4)_2$[6] and $(Ph_3P)_2PdCl_2$ are all active to varying degrees, interestingly $Pd(MeCN)_4(BF_4)_2$[7] is not an active catalyst. Of the Pd(II) catalysts the chloride (and its more soluble acetonitrile complex) are by far the most active; the acetate and perchlorate catalysed processes are noticeably slower with reactions catalysed by $(Ph_3P)_2PdCl_2$ occuring extremely slowly.



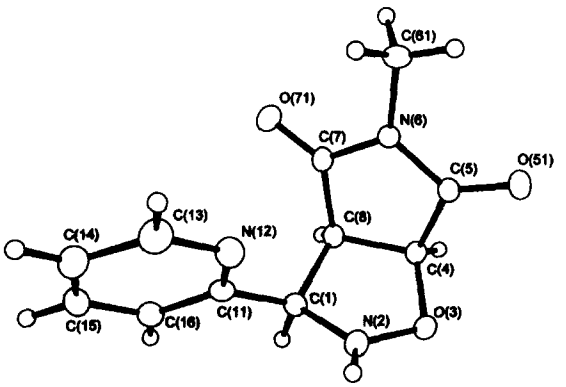
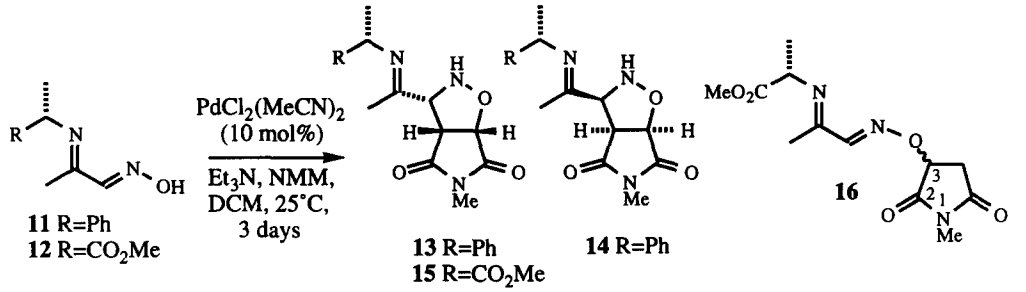


Figure 1: X-ray crystallographic structure of **7**

Thus (*E*)-aldoxime **1** when treated with $PdCl_2(MeCN)_2$ (10 mol%) and triethylamine (1·00 eq) in dichloromethane at room temperature smoothly underwent a stereospecific metallo-nitrone cycloaddition cascade with *N*-methylmaleimide (NMM) over 3 days to afford *endo*-adduct **7** (75%) the structure of which was confirmed by X-ray crystallography (*Figure 1*). The reaction was similarly stereospecific when performed at 20°C in more polar solvents (THF, MeCN and DMF) and occurred at substantially faster rates at more elevated temperatures (THF, 66°C, 40 h; MeCN, 80°C, 18 h). However, higher temperatures also encouraged the formation of *O*-Michael adduct **8** which was isolated as the sole product when the reaction was performed under similar conditions but in the absence of the Pd(II) salt. Subsequent treatment of **8** with $PdCl_2(MeCN)_2$ did not result in the formation of cycloadduct **7** indicating that **8** is not a precursor of **7**.

The corresponding (*E*)-benzaldoxime **2**, the (*Z*)-α-pyridyl ketoxime **3** and both (*Z*)-α-keto-aldoxime **4** and (*Z*)-α-keto-ketoxime **5** all failed to afford analogous 1:1 cycloadducts under identical reaction conditions (CH_2Cl_2, 25°C) whilst (*E*)-aldoxime **6** reacted only slowly in acetonitrile over three days (80% conversion) to afford **9** (20%) and *O*-Michael adduct **10** (45%). These results suggest that the success of this metal assisted route to nitrones is dependent on the presence of α-imino functionality and is only applicable to (*E*)-aldoximes.

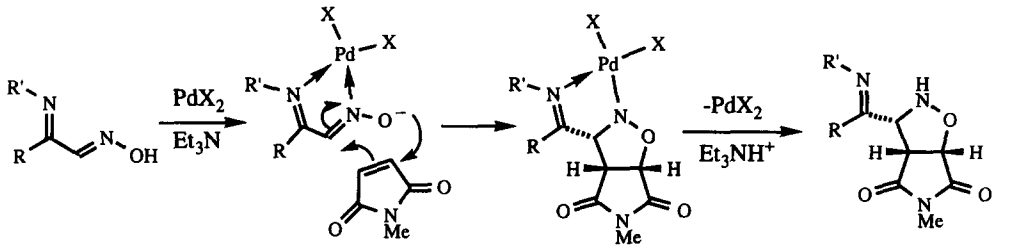
(*E*,*E*)-Aldoxime **11** underwent a stereospecific and highly facially selective cascade under identical conditions (three days) to afford enantiopure *endo*-adducts **13** and **14** (80%; 9:1 ratio) as evidenced by ^1H nmr analysis of the reaction mixture. The (*E*,*E*)-L-alanine derived ester **12** reacted facially specifically under similar conditions to afford enantiopure cycloadduct **15** (55%) over three days (80% conversion) together with an *O*-Michael adduct **16** [10% by ^1H nmr, stereochemistry at C(3) unknown]. In the reaction employing ester **12**, cycloadducts arising from possible alternative *N*-metallo-azomethine ylide cycloaddition processes[8] (deprotonation α- to CO_2Me) were not observed in the ^1H nmr spectrum of the reaction mixture.



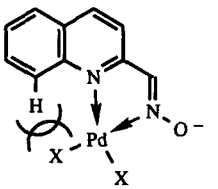
It is thought that the palladium (II) centre forms a five-membered chelate with the α-imino aldoxime to generate an (*E*)-*N*-metallo-nitrone intermediate which subsequently undergoes stereospecific cycloaddition (*Scheme 3*). Intramolecularly hydrogen bonded (*Z*)-α-imino ketoximes such as **3** do not isomerize at an appreciable rate under the reaction conditions to their less sterically encumbered (*E*)-isomers and thus are geometrically precluded from chelation by the palladium (II) centre in a similar fashion. Aldoxime **6** reacts slowly (and hence gives poor yields of cycloadduct **9**) due to poor solubility and because of the difficulty in formation of the *N*-metallo-aldonitrone **17** as a result of a high degree of steric compression caused by the buttressing effect of the *peri*-hydrogen atom at C-8 of the quinoline ring.

In the cases involving chiral imines **11** and **12** we believe that the intermediate *N*-metallo-aldonitrones **18** and **19** exist exclusively as their rotamers in which steric interactions between the chiral

moieties and the ligands attached to the square planar palladium (II) centre are minimized (hydrogen and ligand X contiguous) with cycloaddition proceeding preferentially *syn* to the smaller methyl group of the sidechain (and *anti*- to the larger phenyl or carbomethoxy group) to afford mostly isomers **13** and **15**. The high facial selectivity in the cycloaddition step in these two cases can be rationalized by inspection of molecular models of **18** and **19** from which it becomes apparent that cycloaddition *via* a kinetically favoured *endo*-transition state results in steric interactions between the α-imino side chain and NMM which are pronounced on only one of the two diastereotopic faces of the intermediate *N*-metallo-aldonitrones **18** and **19** (namely the ones bearing the larger Ph or CO_2Me substituents) so encouraging cycloaddition to occur preferentially *anti* to these groups.



Scheme 3



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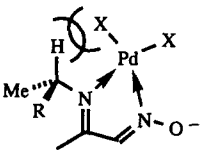

18 R=Ph
19 R=CO_2Me

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