

Palladium(II)-catalysed Cascade Cyclisation–Cycloaddition Reactions of Alkenyl Oximes

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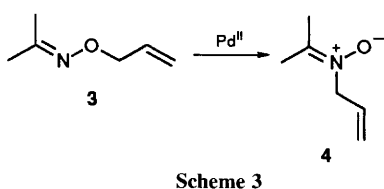
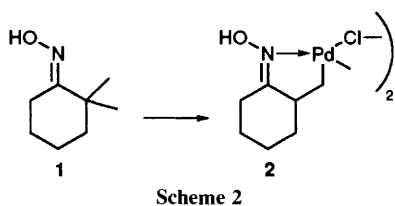
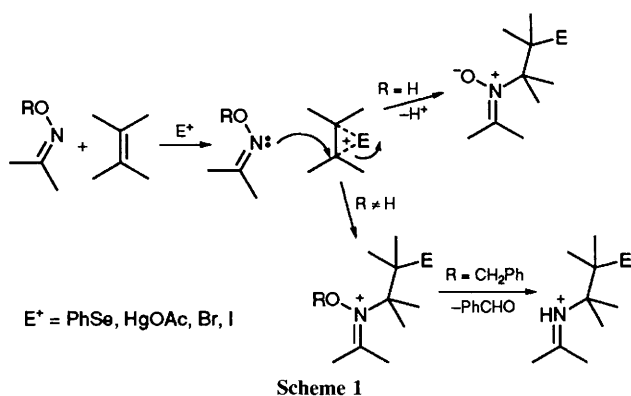
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Palladium(II) chloride-catalysed cascade cyclisation–cycloaddition reactions of δ -alkenyl oximes occur regio- and facially-specifically in high yield via intermediate six-membered cyclic nitrones; preliminary studies of γ -alkenyl oximes show they are reluctant to cyclise; four potential synthetic variants of the cascade process are identified and examples of two of the classes are provided.

We are developing a range of electrophile induced oxime–alkene¹ and oxime ether–alkene² reactions that generate nitrones and their salts or iminium salts respectively (Scheme 1) at ambient temperature in excellent yield. These processes occur regio- and stereo-specifically, result in incorporation of the synthetically valuable electrophile into the product and can be developed into oxime \rightarrow nitronone \rightarrow cycloaddition cascades or other ring forming protocols furnishing a wide range of nitrogen heterocycles.^{1,2}

Our interest in developing new palladium-catalysed reactions directed our attention to palladium(II) salts as potential electrophiles for Scheme 1. Palladium(II) species are known to promote a range of inter- and intra-molecular additions of nucleophiles to alkenes.³ Palladium(II)-induced reactions of certain oximes and oxime *O*-allyl ethers have also been reported. Thus the Shaw reaction⁴ involves insertion of palladium into an unactivated oxime β C–H bond **1** \rightarrow **2** and is driven by steric compression (Scheme 2). This is a potentially valuable synthetic method⁵ but is stoichiometric in palladium as is the briefly reported cyclisation of several α,β -unsaturated ketoximes to isoxazoles.⁶ We have developed a Pd^{II}-catalysed cascade rearrangement–cycloaddition reaction of oxime *O*-allyl ethers **3** which proceeds via the *N*-allyl nitronone **4** (Scheme 3).⁷ Thus Pd^{II} chemistry is compatible with oxime functionality.



Initial studies showed that both alkenyl aldoximes and alkenyl ketoximes undergo the desired Pd^{II}-catalysed cyclisation. The cyclisation reaction can be conducted in either boiling THF or benzene. The latter, higher boiling solvent, results in a faster reaction. Thus aldoxime **5** (Scheme 4) undergoes a cyclisation–cycloaddition cascade in boiling THF with **6** in the presence of 10 mol% PdCl₂ or 10 mol% [PdCl₂(MeCN)₂]. The intermediate nitronone **7** undergoes facially specific cycloaddition to *N*-methylmaleamide (NMM) **6** to give **8** (81%) as a 10 : 1 mixture of *exo*- and *endo*-isomers.† Ketoxime **9** undergoes an analogous reaction {C₆H₆, 80 °C, 7 h; 10 mol% [PdCl₂(MeCN)₂]} to give **10** (85%) as a 2 : 1 mixture of *exo*- and *endo*-isomers (Scheme 5).

There are potentially four synthetic variants of the Pd^{II}-catalysed oxime \rightarrow nitronone \rightarrow cycloaddition cascade (Table 1).⁸ Cascades **5** \rightarrow **8** and **9** \rightarrow **10** are class III processes. Examples of class IV processes are provided {C₆H₆, 80 °C, 6 h; 10 mol% [PdCl₂(MeCN)₂]} by the cyclisation–cycloaddition cascades **11a, b** \rightarrow **13** (85%) and **13b** (82%). Note that for **11b** the cyclisation is regioselective and involves the least substituted alkene (Scheme 6).

Preliminary studies of the scope of the reaction show it can be used to generate nitrones at a ring junction, e.g. oxime **14** cyclises {THF, 66 °C, 4 h; 10 mol% [PdCl₂(MeCN)₂]} to a 2 : 1 mixture of diastereoisomers of **15** in 70% yield (Scheme 7).

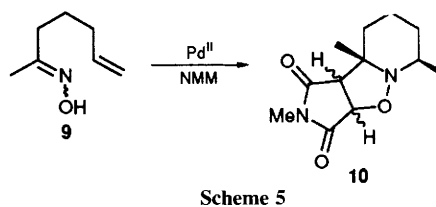
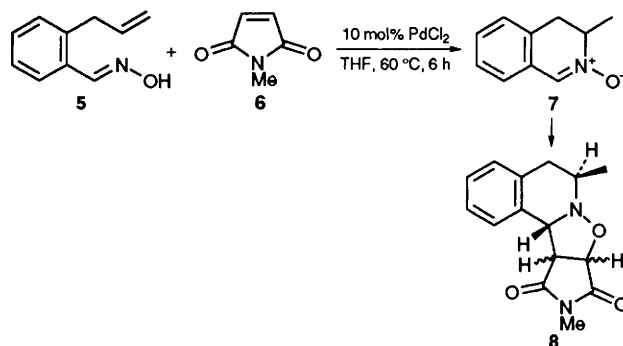
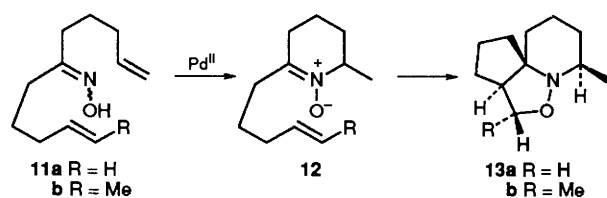


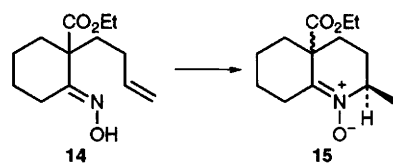
Table 1 Synthetic variants of the Pd^{II}-catalysed oxime–nitronone cycloaddition cascade

Class	Nitronone generation	Cycloaddition
I	Intermolecular	Intermolecular
II	Intermolecular	Intramolecular
III	Intramolecular	Intermolecular
IV	Intramolecular	Intramolecular

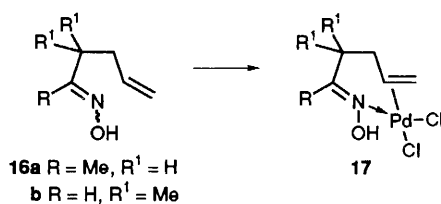
An observation of mechanistic importance is that oximes **16a,b** do not undergo Pd^{II}-catalysed cyclisation to the corresponding nitrones whilst reaction of **16a** with a stoichiometric amount of [PdCl₂(MeCN)₂] leads (THF, 25 °C, 16 h) to the isolation of a Pd^{II} complex formulated as **17** (70%) (Scheme 8). This result contrasts with the facile Pd^{II}-catalysed aminocyclisation of *N*-protected unsaturated amines to form five-membered nitrogen heterocycles. Analogous cyclisations of this type of substrate to form six-membered rings are comparatively rare.⁹ Another feature of mechanistic interest is that no products arising from the δ-alkenyl oximes by a cyclisation-β-hydride elimination sequence were detected. A possible reason for lack of β-hydride elimination is that species such as **19**, in which β-hydride elimination is geometrically impossible, play an important role in the catalytic cycle. Protolysis of the Pd-C bond in **19** would then generate product. The nitrono products from the Pd^{II}-catalysed cyclisations are analogous to those derived from alkenyl oximes by thermal 1,3-azaprotio cyclotransfer (**18**, arrows), a concerted 2n + 2π + 2σ process.¹⁰ Appropriate experiments showed that the reactions described above do not occur to any significant extent in the absence of PdCl₂ or by substituting either HCl or Pd(OAc)₂ for PdCl₂.



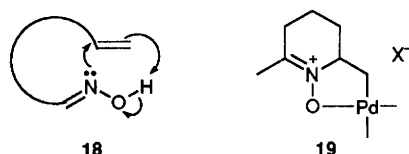
Scheme 6



Scheme 7



Scheme 8



Further studies on the relationship between these latter two reactions and related processes are underway.

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Footnote

† The stereochemistry of all products is assigned on the basis of NOE data. All new compounds gave satisfactory microanalytical and spectroscopic (¹H NMR, MS) data.

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- Note that Class II processes can be carried out in two tactically distinct ways. The dipolarophile can be attached to the carbon atom or the nitrogen atom of the nitrono (*C*-alkenyl- and *N*-alkenyl-nitronos respectively), e.g. P. Armstrong, R. Grigg, F. Heaney, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4495; R. Grigg, M. J. Dorrity, F. Heaney, J. F. Malone, S. Rajviroongit, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1991, **47**, 8297.
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