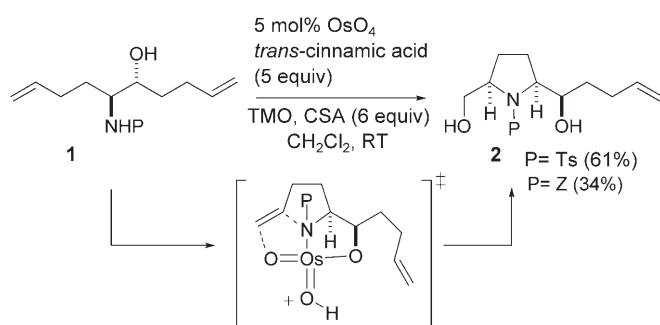


# Pyridine-*N*-Oxide as a Mild Reoxidant Which Transforms Osmium-Catalyzed Oxidative Cyclization\*\*

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Recent reports from our group showed that the catalytic oxidative cyclization of 1,5-dienes<sup>[1]</sup> directly to *cis* tetrahydrofurans (THFs) can be interrupted and that vicinal diols derived from 1,5-dienes also cyclize to give THF rings in excellent yields under the action of osmium tetroxide and an acid.<sup>[2]</sup> In addition, we also disclosed that the corresponding *N*-tosyl amino alcohols (tosyl = *p*-toluenesulfonyl) bearing a pendant alkene cyclize to give the relevant pyrrolidine ring systems **2**, the first time that such oxidative methodology had been used to form nitrogen heterocycles (Scheme 1).<sup>[3]</sup> Both



**Scheme 1.** Oxidative cyclization of hydroxysulfonamide substrates. Ts = *p*-toluenesulfonyl; Z = PhCH<sub>2</sub>OCO.

cyclization reactions are notable for their stereospecificity (*syn* addition across the tethered alkene) and stereoselectivity (*cis*-2,5-heterocycles are formed exclusively). As expected, the absolute stereochemistry of the starting materials is transferred to the products, thus providing a short route to valuable heterocycles with complete control of stereochemistry.

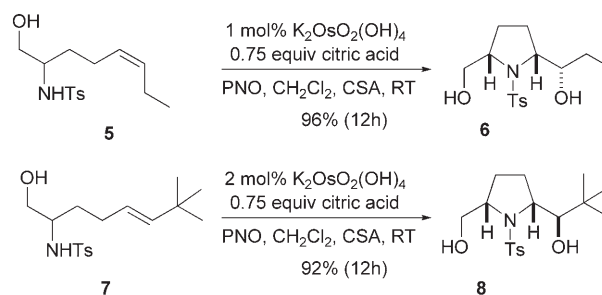
The advantage of using diols or amino alcohols as precursors to the cyclization is that it allows the direct formation of enantiopure heterocycles, including pyrrolidines, by a pathway that is simply not viable from the cyclization of 1,5-dienes.<sup>[4]</sup>

However, this catalytic reaction does have some limitations. Firstly, the cyclization of protected amines to form pyrrolidines is restricted to amino alcohols with a sulfonamide group on the nitrogen center; carbamates do not cyclize in acceptable yield. Secondly, our studies revealed that Os<sup>VI</sup> is the more active catalyst for the cyclization process, and the presence of Os<sup>VIII</sup> is to be avoided because it causes unwanted dihydroxylation of alkenes in the substrate.<sup>[3]</sup> A consequence of this observation is that it is necessary to add an excess of a sacrificial alkene (usually cinnamic acid) to the system so that it is dihydroxylated in preference to the substrate, and thereby increases the concentration of Os<sup>VI</sup> in the reaction. Such an internal conflict within the reaction mixture is clearly less than ideal.

**Table 1:** Cyclization reaction of *N*-tosyl-protected amino alcohols.

Entry	Conditions <sup>[a]</sup>	Yield of <b>4</b>
1	5% K <sub>2</sub> OsO <sub>2</sub> (OH) <sub>4</sub> , CSA, TMO, CH <sub>2</sub> Cl <sub>2</sub> (48 h)	69%
2	5% K <sub>2</sub> OsO <sub>2</sub> (OH) <sub>4</sub> , CSA, cinnamic acid, TMO, CH <sub>2</sub> Cl <sub>2</sub> (16 h)	79%
3	5% K <sub>2</sub> OsO <sub>2</sub> (OH) <sub>4</sub> , CSA, PNO, CH <sub>2</sub> Cl <sub>2</sub> (4 h)	85%
4	5% K <sub>2</sub> OsO <sub>2</sub> (OH) <sub>4</sub> , CSA, PNO, citric acid, <sup>[5]</sup> CH <sub>2</sub> Cl <sub>2</sub> (2 h)	98%

[a] Reactions run at room temperature. Tosyl = *p*-toluenesulfonyl; CSA = (±)-camphorsulfonic acid; TMO = trimethylamine-*N*-oxide.



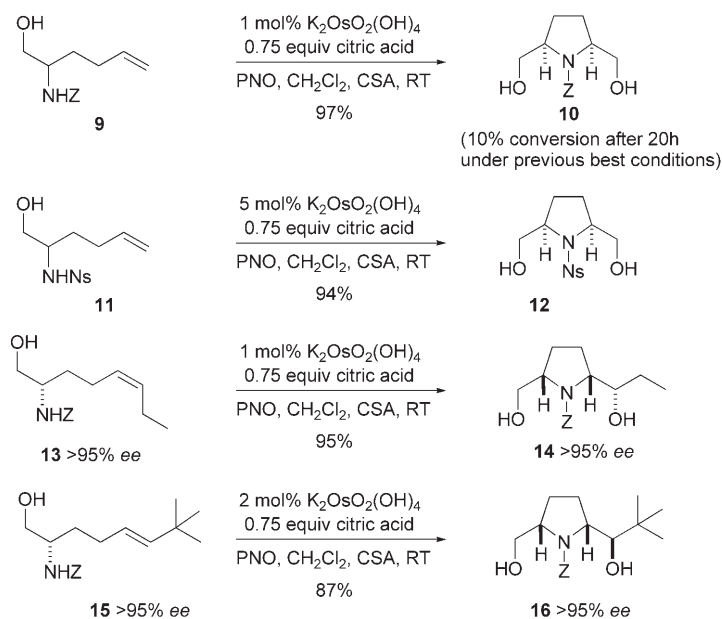
**Scheme 2.** Stereoselective oxidative cyclization.

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**Scheme 3.** Oxidative cyclization of carbamate-protected amino alcohols. Ns = nitrobenzenesulfonyl; Z = PhCH<sub>2</sub>OCO.

To overcome these problems we sought a reoxidant that would oxidize Os to the VI oxidation state (where it is capable of promoting an oxidative cyclization), but not to the VIII oxidation state (where it can also dihydroxylate the substrate). After screening a range of reoxidants for osmium, we can now report that pyridine-*N*-oxide (PNO) is an effective reoxidant for the oxidative cyclization reaction. The consequences of using this reoxidant are that it engenders a much more powerful oxidizing system, which does not require the addition of a sacrificial alkene and does not cause dihydroxylation of the substrate. A good example of this effect can be seen in the formation of pyrrolidine **4** from **3** (Table 1).

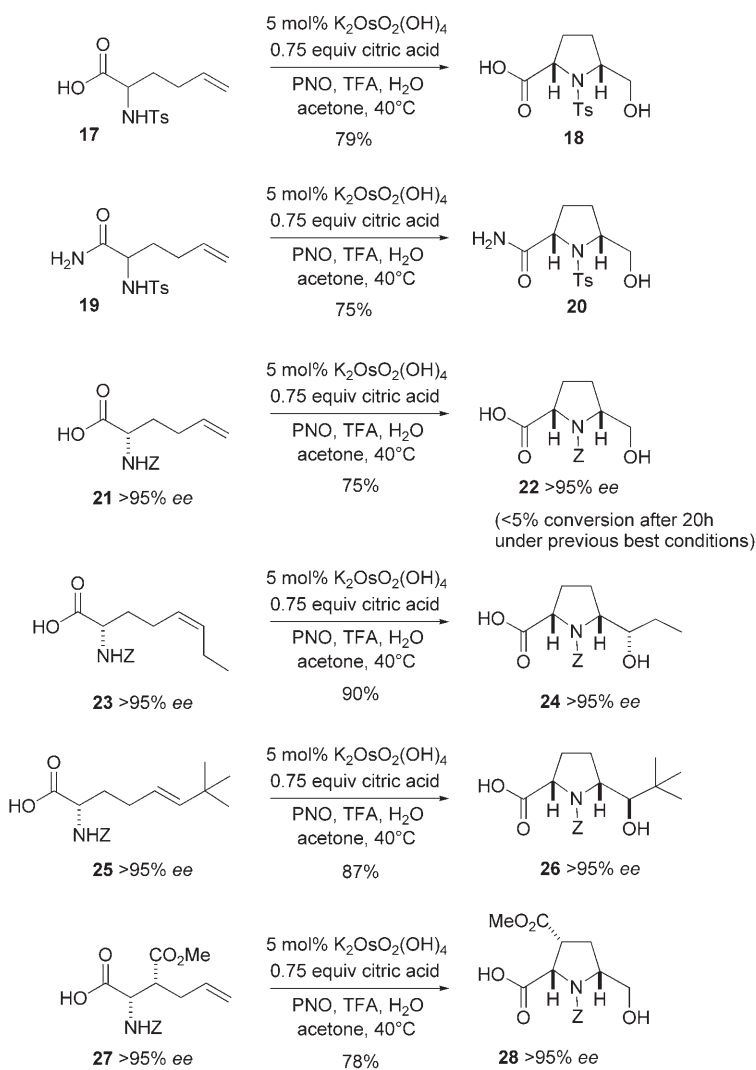
Hydroxysulfonamides **5** and **7**, which each took over 24 hours to react under the old conditions (yields 78–80%), cyclized most efficiently and with low catalyst loadings (Scheme 2).

In fact, the improvement that this new system lends to the oxidative cyclization is so marked that *N*-carbamate-protected amino alcohols can now be cyclized in excellent yields and with low loadings of the osmium catalyst (Scheme 3).<sup>[6]</sup> None of these reactions, including cyclization of *N*-nosyl-protected (nosyl = nitrobenzenesulfonyl) substrate **11**, gave viable (or often any) yields of pyrrolidine rings under the previous best set of conditions.

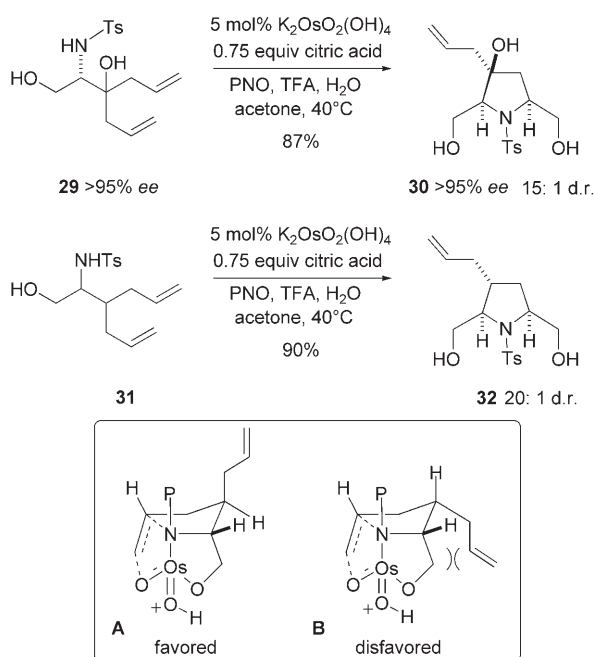
Armed with the new cyclization conditions we were able to re-examine cyclization substrates that were not successfully transformed in our early work. We concentrated on amino acid substrates because of the useful products that they form<sup>[7]</sup> and

the relative ease of preparing them in enantiopure form (Scheme 4). The cyclization reaction works well and allows the preparation of a series of useful, enantiopure cyclic amino acids; note also the successful cyclization of amino amide **19**. The change in the solvent and the acid for this reaction enabled us to maximize solubility, heating, and purification procedures.

The cyclization of aspartic acid derived amino acid **27**<sup>[8]</sup> reveals that substituents on the backbone are tolerated under the cyclization conditions. However, we were intrigued by the notion of cyclizing a compound containing two allyl groups in an attempt to induce a diastereoselective cyclization, thus gaining a free stereogenic center in the pyrrolidine product (Scheme 5). Substrates **29** and **31** were prepared easily and then cyclized by using the PNO conditions. In each case a major product was formed with excellent diastereoselectivity and X-ray crystallographic analysis confirmed the *trans* relationship between the remaining allyl group and the C2 methylene group.<sup>[9]</sup> From transition-state models this outcome can be rational-



**Scheme 4.** Oxidative cyclization of amino acids.

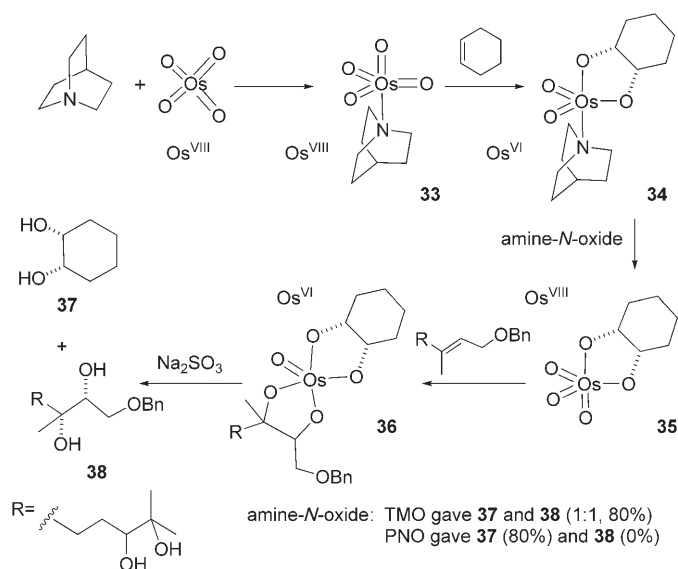


**Scheme 5.** Cyclization onto one of two diastereotopic allyl groups. P = protecting group.

ized by placing the bystander allyl group in the less crowded *exo* position (A), rather than the *endo* position (B), where it experiences a greater steric clash with the incipient pyrrolidine ring. The smaller hydrogen atom in **31** or hydroxy group in **29** is then forced to adopt this more crowded position with a smaller energetic penalty. The advantages of positioning an allyl group onto the pyrrolidine backbone are manifold when one considers opportunities for cross-metathesis, oxidative cleavage, or alkene isomerization.

Our next task was to investigate more fully the role of PNO in the above cyclization reactions. Initial observations centered around the hypothesis that this oxidant does not form  $\text{Os}^{\text{VIII}}$  in the reaction mixture. To support this idea, we report that PNO does not promote turnover in an UpJohn style dihydroxylation reaction of alkenes.<sup>[10]</sup>

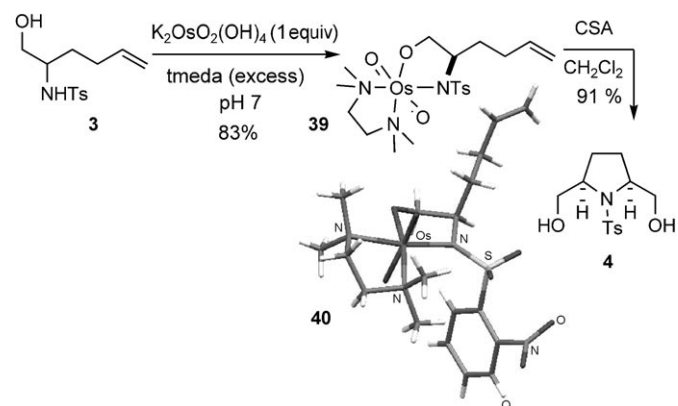
Next, we examined a stoichiometric model for the key oxidation of  $\text{Os}^{\text{VI}}$  to  $\text{Os}^{\text{VIII}}$  which was modeled after a system originally described by Sharpless and co-workers to probe the effect of the second catalytic cycle in the asymmetric dihydroxylation reaction.<sup>[11]</sup> The reaction of orange complex **33** with cyclohexene enabled the formation of (green)  $\text{Os}^{\text{VI}}$  compound **34** (Scheme 6).<sup>[12]</sup> When this complex was treated with TMO a color change was observed to give putative complex **35**;<sup>[13]</sup> the formation of  $\text{Os}^{\text{VIII}}$  was then verified as **35** was able to oxidize a second alkene that was added after the color change was complete. Reductive cleavage of the osmium gave **37** and **38** in a 1:1 ratio. Substitution of TMO with PNO in this reaction did not cause the color change/reoxidation of **34**, and the osmium complex that resulted was not able to oxidize a second alkene as observed in the first experiment; indeed the alkene could be recovered (this experiment was also repeated in the presence of six equivalents of CSA to replicate the acidic oxidative cyclization



**Scheme 6.** Mechanistic probes for osmium oxidation. Bn = benzyl.

conditions, but again no oxidation of  $\text{Os}^{\text{VI}}$  was observed). All of this evidence points to a lack of  $\text{Os}^{\text{VIII}}$  after the addition of PNO.<sup>[14]</sup>

Given the likely dominance of  $\text{Os}^{\text{VI}}$  in the above PNO-driven reactions, we also present data to confirm that this metal species is capable of accomplishing oxidative cyclization (Scheme 7). Hydroxytosylate **3** was subjected to reaction with one equivalent of  $\text{Os}^{\text{VI}}$  in the presence of tmeda as a stabilizing ligand.<sup>[15]</sup> Even at near neutral pH, condensation of the amino alcohol with Os was rapid, producing azaglycolate ester **39** in 83% yield. Subsequent cyclization of  $\text{Os}^{\text{VI}}$  ester **39** could be accomplished by reaction with an acid, thus producing the pyrrolidine **4**, as before, in a two step procedure that validates the ability of  $\text{Os}^{\text{VI}}$  to undergo both coordination with the substrate and oxidative cyclization under acidic conditions. Repetition of this sequence with the nosyl analogue **11** (not shown) enabled us to obtain a crystal structure (**40**) of the corresponding intermediate azaglycolate osmate ester, before it was cyclized with acid.



**Scheme 7.** Mechanistic probes for osmium oxidation. tmeda = *N,N,N',N'*-tetramethylethylenediamine.

To conclude, we have shown that PNO is a mild new reoxidant for oxidative cyclization that dramatically improves the range of substrates that are compatible with this reaction; N-Z carbamate-protected amino alcohols and amino acids were cyclized for the first time. The role of PNO was investigated and it appears to act as a reoxidant for osmium that does not produce  $\text{Os}^{\text{VIII}}$  in situ. This reoxidation has beneficial consequences for the efficiency of the cyclization and has ramifications for the use of this chemistry on a large scale.

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