

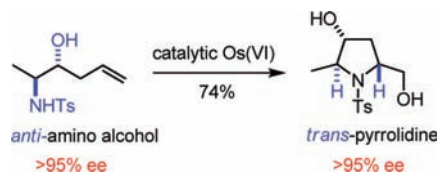
New Modes for the Osmium-Catalyzed
Oxidative CyclizationTimothy J. Donohoe,^{*,†} Peter J. Lindsay-Scott,[†] Jeremy S. Parker,[‡] and Cedric K. A. Callens^{†,§}

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Received January 8, 2010

ABSTRACT



The osmium-catalyzed oxidative cyclization of amino alcohol initiators formally derived from 1,4-dienes is an effective method for the construction of pyrrolidines, utilizing a novel reoxidant (4-nitropyridine *N*-oxide = NPNO). The cyclization of enantiopure *syn*- and *anti*-amino alcohols gives rise to enantiopure *cis*- and *trans*-2,5-disubstituted pyrrolidines, respectively. Moreover, the cyclization of *bis*-homoallylic amines bearing an exocyclic chelating group is shown to be a complementary method for *trans*-pyrrolidine formation.

Various metal–oxo species have been reported to catalyze the oxidative cyclization of 1,5-dienes to the corresponding 2,5-disubstituted THFs, with varying degrees of success.¹

While most metals give *cis*-THF products exclusively, ruthenium has been shown to afford *trans*-THFs as minor products in certain circumstances.²

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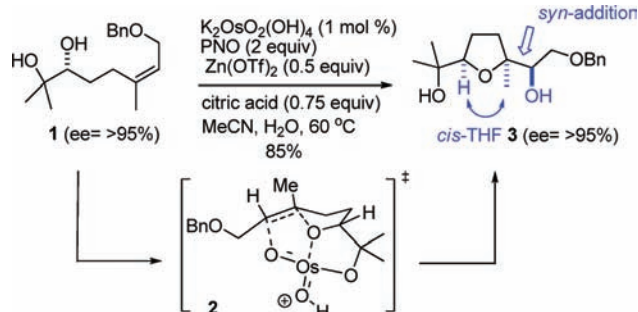
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In recent years, the osmium-catalyzed oxidative cyclization of diols and amino alcohols formally derived from 1,5-dienes has emerged as a powerful method for the construction of enantiopure THFs **3** and pyrrolidines, respectively (Scheme 1).³ The reaction is stereoselective for the formation of *cis*-2,5-disubstituted heterocycles and stereospecific with regards to *syn*-addition across the tethered alkene, providing efficient access to stereodefined THFs and pyrrolidines.

Recent studies from our laboratory have shown that only Os(VI) is required to perform these cyclization reactions, while Os(VIII) leads to unwanted dihydroxylation of the starting material.⁴ Hence, the optimal reoxidant for this transformation was shown to be pyridine *N*-oxide (PNO), since this was able to oxidize Os(IV) to Os(VI), but not to Os(VIII) under the reaction conditions.^{3c} In addition, citric acid was postulated to stabilize Os(VI) with respect to disproportionation and aid in the hydrolytic release of product

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Scheme 1. The Osmium-Catalyzed Oxidative Cyclization Reaction



molecules from osmium complexes.⁵ Ongoing research in our group has also revealed that metal triflates are capable of promoting the cyclization of bound osmium species **2** at higher temperatures, where the use of traditional protic acids gives lower yields of cyclized products and degrades the starting material.^{3d} Thus, the use of PNO in concert with citric acid and metal triflates provides a powerful, yet controlled, system for the oxidative cyclization of suitable initiators.

In stark contrast, the oxidative cyclization of 1,4-dienes to THFs has been reported only once in the literature, with just two examples quoted (both cyclizations proceeded in 30% yield).⁶ Moreover, the cyclization of diols or amino alcohols formally derived from 1,4-dienes has yet to be documented. We were intrigued by the possibility of utilizing our potent oxidative conditions (that had performed admirably for the cyclization of 1,5-diene derived initiators, Mode A) in the context of substrates derived from 1,4-dienes, Mode B (Figure 1). Both modes of cyclization would involve a

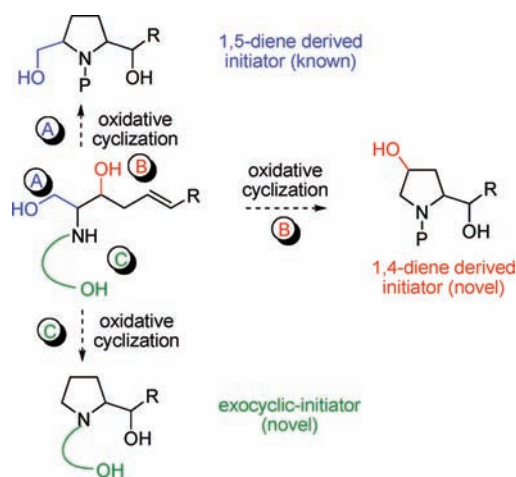


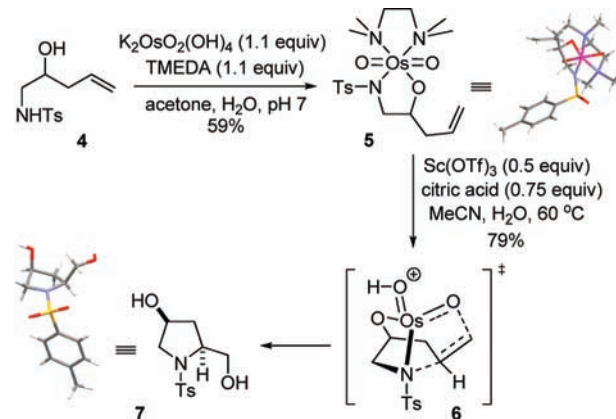
Figure 1. Possible modes of oxidative cyclization.

bidentate coordination of the substrate to Os(VI), leading to the protected amine becoming *fused* to the heterocycle and the other coordinating function becoming *appended*

to the heterocycle. We postulated that a third system (akin to the rhenium-mediated oxidative cyclization of *bis*-homoallylic alcohols)⁷ might also be possible, in which the chelating alcohol function was part of the amine protecting group, Mode C. If these new modes of oxidative cyclization could be unlocked with osmium, they might enable the formation of *trans*-2,5-disubstituted pyrrolidines.

With this in mind, we examined the oxidative cyclization of *N*-Ts amino alcohol **4**, since these types of substrate had proven to be the most reactive toward Os(VI) in the analogous 1,5-diene series (Scheme 2).⁸ Treatment of **4** with

Scheme 2. Initial Stoichiometric Studies



stoichiometric Os(VI) and TMEDA at pH 7 furnished osmate ester **5** in 59% yield, whose structure was proven unambiguously by X-ray crystal structure analysis.⁹ When complex **5** was exposed to a variety of protic acids and solvents, no oxidative cyclization occurred. However, stirring with substoichiometric scandium(III) triflate and citric acid in aqueous acetonitrile at 60 °C delivered the target pyrrolidine **7** in 79% yield. The relative stereochemistry of **7** was confirmed by X-ray crystal structure analysis, providing evidence for the postulated transition structure **6**, since the alcohol and hydroxymethylene groups in the product were shown to be on the same face of the pyrrolidine. Interestingly, no cyclization of **5** was observed when Lewis acids were used without citric acid.

The reaction was rendered catalytic by utilizing PNO as reoxidant, and a variety of olefins were shown to be suitable substrates for oxidative cyclization (Scheme 3).

(5) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421–433.

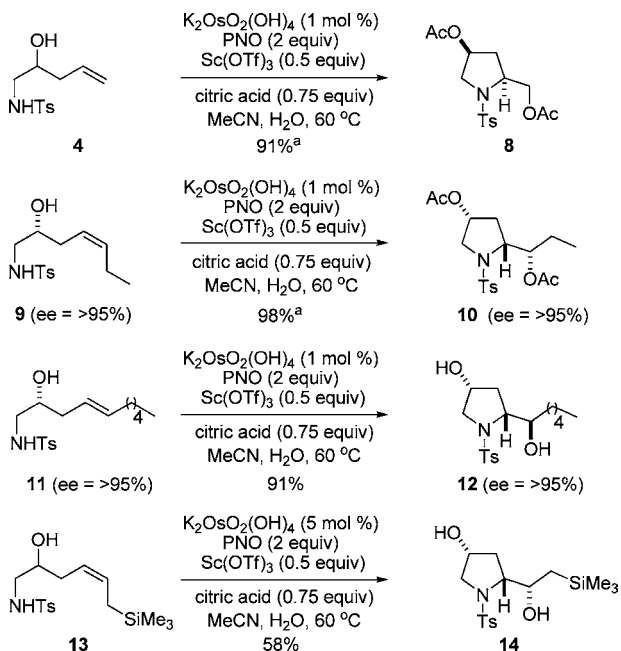
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(7) (a) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 3729–3732. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299–5302.

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(9) X-ray crystal structure analyses were performed on compounds **5**, **7**, **14**, and **20**, and on derivatives of compounds **16** and **18** (see the Supporting Information).

Scheme 3. Oxidative Cyclization of *N*-Ts Amino Alcohols^a



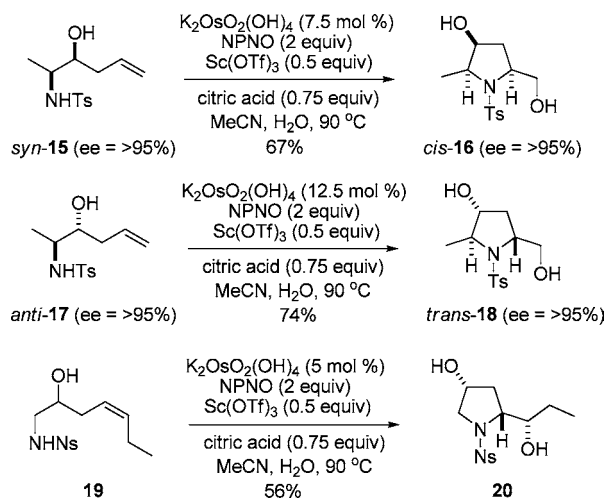
^a After acetylation (Ac₂O, pyridine) of the crude material.

While other Lewis acids required reaction times of up to 48 h to fully consume the starting materials, substoichiometric scandium(III) triflate consistently achieved full conversions for all examples in Scheme 3 in only 16 h. Notably, amino alcohols **4**, **9**, and **11** all cyclized efficiently to pyrrolidines **8**, **10**, and **12** in high yields as single diastereomers with catalyst loadings of only 1 mol %. Moreover, enantiopure amino alcohols **9** and **11** cyclized with no erosion of enantiopurity in the products.¹⁰ It was found advantageous to isolate pyrrolidines **8** and **10** as their corresponding diacetates to aid purification. The structure of **8** was proven by deprotection to diol **7** (see the Supporting Information), while amino alcohols **9** and **11** were assumed to have undergone stereospecific *syn*-oxidations with respect to alkene geometry (based on significant literature precedent for the oxidation of amino alcohols derived from 1,5-dienes, evidenced by extensive X-ray crystal structures).^{3b} Allyl silane **13** was also shown to undergo oxidative cyclization to pyrrolidine **14** in 58% yield, although this substrate required a catalyst loading of 5 mol % to achieve full conversion (Scheme 3). The relative stereochemistry of pyrrolidine **14** was secured by X-ray crystal structure analysis, clearly highlighting the stereospecific (*syn*) nature of the alkene oxidation.⁹

Next, the reactivity of amino alcohols bearing substitution α - to nitrogen was investigated (Scheme 4). These substrates were significantly less reactive toward Os(VI) and required higher temperatures, increased catalyst loadings, and longer

(10) Enantiomeric excess measurements were conducted by either (a) ¹⁹F NMR spectroscopy on Mosher's ester derivatives or (b) ¹H NMR spectroscopy with an enantiopure additive, with comparison to racemic standards in both cases.

Scheme 4. Oxidative Cyclization of Challenging Amino Alcohols



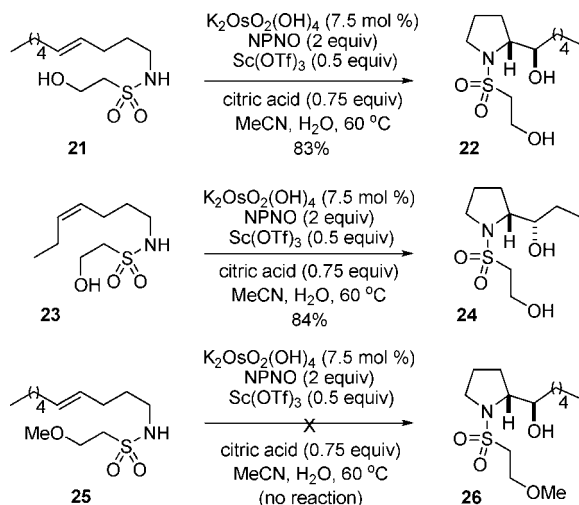
reaction times for full consumption of the starting materials. However, under these conditions competing dihydroxylation was also observed because either (i) the disproportionation of Os(VI) in acid was vastly accelerated at 90 °C or (ii) PNO was eventually capable of oxidizing Os(VI) to Os(VIII) at 90 °C. To tackle this problem, these reactions were conducted with 4-nitropyridine *N*-oxide (NPNO) as reoxidant, which gave higher yields of cyclized products, presumably as a result of its attenuated oxidizing power toward osmium. Notably, *syn*-amino alcohol **15** cyclized to *cis*-pyrrolidine **16** in 67% yield (36 h), while *anti*-amino alcohol **17** afforded *trans*-pyrrolidine **18** in 74% yield (48 h, the first example of an osmium-catalyzed *trans*-selective oxidative cyclization reaction), with no erosion of enantiopurity. Also, the use of *N*-Ns protecting groups was tolerated under the reaction conditions. However, amino alcohol **19** also required the more forcing conditions (16 h) to cyclize effectively, probably due to the electron-withdrawing effect of the nitro group. The structures of compounds **16**, **18**, and **20** were all proven by X-ray crystal structure analysis.⁹ Unfortunately, the cyclization of diols and transposed amino alcohols derived from 1,4-dienes failed to give any THF products when exposed to similar reaction conditions.

With an effective protocol established for the formation of pyrrolidines by cyclization Mode B (see Figure 1 above), the use of exocyclic-initiator functionalities was examined next (Mode C). Initial studies revealed that a novel β -hydroxy sulfonamide protecting group was ideal for this task (after cyclization, deprotection could be accomplished by *O*-methylation and subsequent reduction, see the Supporting Information). However, 1,3-initiators have been shown to be less reactive toward Os(VI) than their 1,2-counterparts, since the large metal atom has a preference for five-membered chelates over six, due to more favorable bond angles.¹¹ Hence, the cyclization of amino alcohols **21** and

(11) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875–1914.

23 also required relatively high catalyst loadings and long reaction times (48 h) to achieve full conversion of starting materials, affording pyrrolidines **22** and **24** in high yields (Scheme 5). It was assumed that these oxidations had

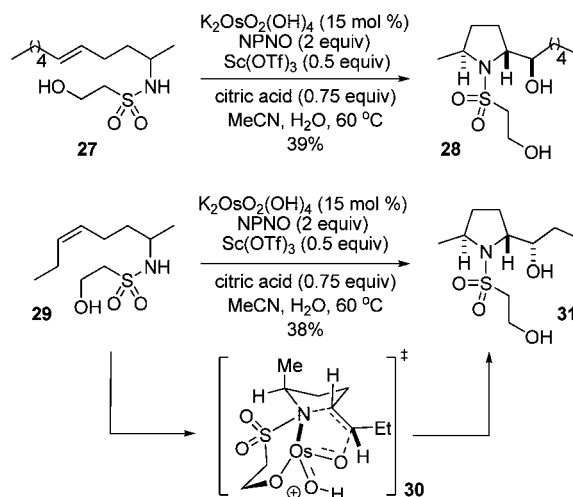
Scheme 5. Oxidative Cyclization of Exocyclic Initiators



occurred in a *syn*-stereospecific manner with respect to alkene geometry (based on significant literature precedent for the oxidation of amino alcohols derived from 1,5-dienes).^{3b} When *O*-Me compound **25** was exposed to the reaction conditions, only starting material was recovered, suggesting that osmium must be coordinated in a bidentate fashion during cyclization (see transition structure **30**, Scheme 6).

Secondary *bis*-homoallylic amines **27** and **29** also underwent oxidative cyclization to give *trans*-pyrrolidines **28** and **31** as single diastereomers (48 h, Scheme 6), albeit in lower yields due to competing dihydroxylation of these less reactive substrates. We suggest that the observed stereoselectivity was a consequence of the bystander methyl group electing to be *trans* disposed to the alkene during cyclization (transition structure **30**) to minimize steric congestion, as in the

Scheme 6. Formation of *trans*-Pyrrolidines



analogous rhenium-mediated process.⁷ The *trans* nature of **28** and **31** was confirmed by gradient NOE enhancements, while it was assumed that the oxidations had occurred in a stereospecific (*syn*) fashion, as before.

In conclusion, two new modes of osmium-catalyzed oxidative cyclization have been explored for the construction of pyrrolidines. As a result, *trans*-2,5-disubstituted heterocycles can be accessed directly from acyclic precursors by using a novel reoxidant for osmium. This methodology should find use in the synthesis of natural products.

Acknowledgment. We thank the EPSRC and AstraZeneca for funding this project and the Oxford Chemical Crystallography Service for the use of their instrumentation.

Supporting Information Available: Experimental procedures and spectroscopic/X-ray data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL100046A