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Perspective

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Osmium-Catalyzed Oxidative Cyclization of Dienes and Their Derivatives

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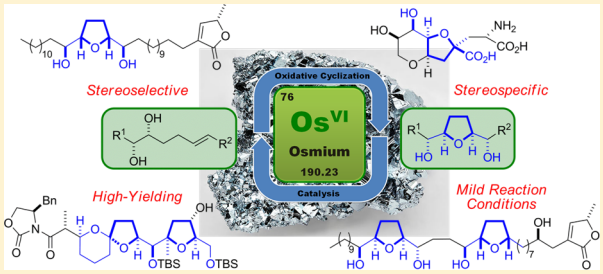
ABSTRACT: The development and application of novel methods for accomplishing the synthesis of heterocycles via osmium-catalyzed oxidative cyclization onto an alkene is described in this Perspective. Beginning with a fortuitous discovery, an extensive examination of the possible mechanism of cyclization has been carried out, and the method was continuously developed until it had been transformed into an extremely efficient and powerful new catalytic reaction for the formation of tetrahydrofurans and pyrrolidines with complete control over all aspects of relative and absolute stereochemistry. By working with Os(VI) rather than the more familiar Os(VIII), a highly potent yet mild set of reaction conditions were developed. In addition to the method development studies, this work also sets out some synthetic challenges against which the methodology was tested. Pleasingly, the catalytic oxidative cyclization has proved itself to be an efficient and functional group tolerant process that was pivotal to the completion of several natural product syntheses.



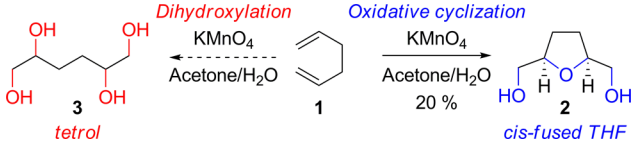
INTRODUCTION

There are many reactions of alkenes that fall under the broad banner of oxidative cyclization. Diene cyclizations promoted by a metal−oxo species constitute a particularly interesting subclass of these reactions, both mechanistically and synthetically. This transformation is known to be promoted by a number of different metals, with the use of any particular one having specific stereochemical ramifications and consequences for reactivity. In our laboratory, we have concentrated on the use of osmium to mediate this transformation. As a comprehensive review on this area was written by Piccialli in 2007,[1] this Perspective will concentrate on how we undertook the development of the osmium-catalyzed version of this transformation in our laboratory, focusing on both our mechanistic insights into the reaction and its synthetic applications. However, where appropriate, we will make key contrasts between the behavior of osmium and other metals and offer some insight into the differences in their reactivities.

DISCOVERY OF DIENE OXIDATIVE CYCLIZATION

The first reported example of the oxidative cyclization of a diene mediated by a metal−oxo species was disclosed by Klein and Rojahn in 1965.[2] It was found that treatment of 1,5-hexadiene **1** with potassium permanganate ($KMnO_4$) led to the formation of the *cis*-fused tetrahydrofuran (THF) **2** in 20% yield via an oxidative cyclization, rather than providing the expected tetrol **3** via double dihydroxylation (Scheme 1). The authors concurrently elucidated the structure of the permanganate oxidation products of both geranyl acetate and neryl acetate; remarkably, all of these products were *cis*-fused THFs as opposed to tetrols. These findings were all in contrast to the known behavior of permanganate toward isolated alkenes.

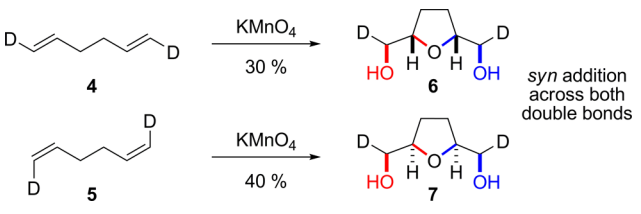
Scheme 1. Klein and Rojahn's Discovery of Oxidative Cyclization



INITIAL MECHANISTIC STUDIES

Several years later, the research groups of both Baldwin[3] and Walba[4] independently conducted experiments to elucidate the mechanism of the reaction. Through the cyclization of two diastereomeric deuterium-labeled dienes **4** and **5**, Baldwin showed that the addition of the two oxygen atoms was *syn* stereospecific across both double bonds, and hence, THFs **6** and **7** were the sole products, respectively (Scheme 2).

Scheme 2. Baldwin's Oxidative Cyclization of Diastereomeric Dienes 4 and 5



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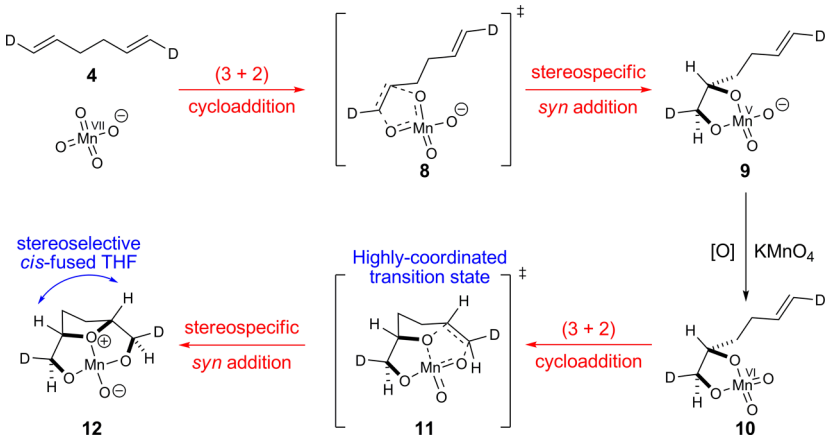
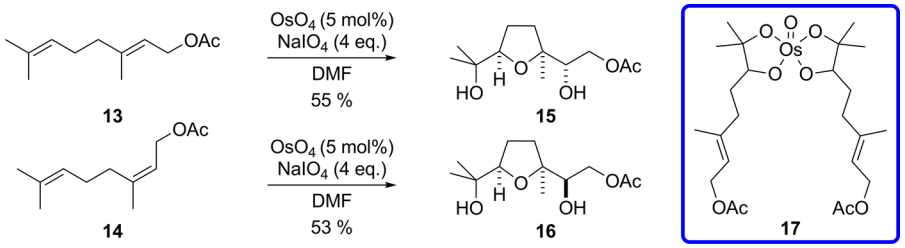
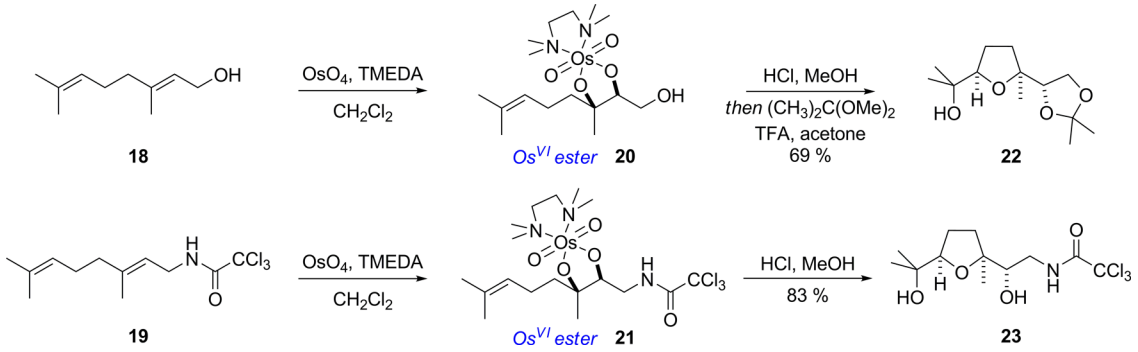
Scheme 3. Baldwin's Initial Mechanistic Proposal



Scheme 4. Piccialli's Catalytic Cyclizations of Geranyl and Neryl Acetates



Scheme 5. Oxidative Cyclization of TMEDA Osmate Esters



This result led Baldwin to suggest that the reaction proceeded via an initial (3 + 2) cycloaddition of MnO_4^- across the first alkene, with the bond formation in transition state **8** taking place in a concerted suprafacial manner. This resulted in Mn^V ester **9**, in which the two oxygen atoms had been added in a *syn* manner across the original alkene. Oxidation of this species to Mn^{VI} ester **10** presumably preceded a subsequent intramolecular (3 + 2) cycloaddition onto the second alkene. Once again, the suprafacial nature of this cycloaddition resulted in a *syn* relationship between the two oxygen atoms across the second alkene, with the stereoselectivity for a *cis*-fused THF being proposed to arise from bidentate coordination in transition state **11** (Scheme 3).

Although alternative mechanisms were proposed by others, it is now generally accepted that the Baldwin mechanism is in operation here and also in the osmium and ruthenium versions of these reactions. Evidence supporting the first step of this mechanism includes labeling studies,[5] spectroscopic evidence for the intermediacy of Mn^V esters,[6] DFT calculations,[7] and the isolation and characterization of other intermediates, such as Os^{VI} esters, within our laboratory vide infra.

OSMIUM-PROMOTED PROCESSES

In 1998, Piccialli was first to report the osmium-catalyzed cyclization of 1,5-dienes using catalytic osmium tetraoxide with sodium periodate as a reoxidant, whereby geranyl acetate **13** and neryl acetate **14** were converted to their corresponding THFs **15** and **16** in moderate yields (Scheme 4).[8] Piccialli also reported the structure of osmate ester **17** containing two molecules of mono-oxidized geranyl acetate and showed that this could be subsequently converted into THF **15**. This osmate ester is analogous to a second cycle intermediate in the asymmetric dihydroxylation of olefins,[9] and its isolation lends support to the Baldwin mechanism; however, it is not known whether the catalytic version of the oxidative cyclization reaction must proceed via this exact intermediate.

We first encountered the osmium-promoted version of this reaction shortly afterward during our investigations into the hydrogen bond-directed dihydroxylation of olefins.[10] Oxidation

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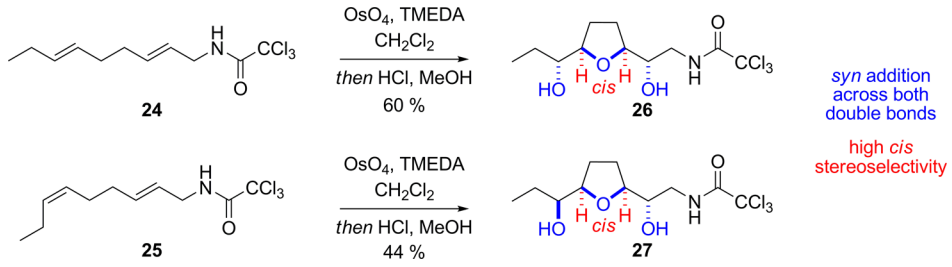
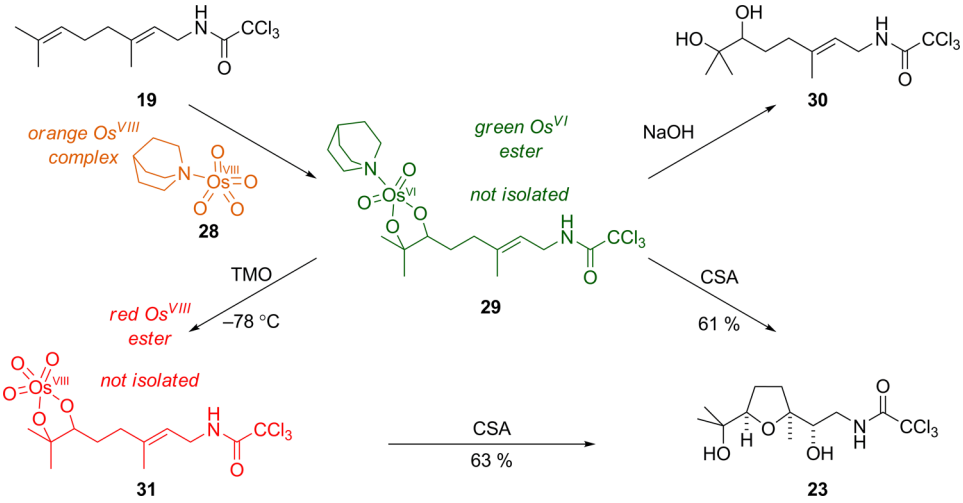
Scheme 6. Stereospecificity and Stereoselectivty in the Osmium-Promoted Cyclization



Scheme 7. Stoichiometric Investigations into the Osmium Oxidation State during the Cyclization



of geraniol **18** and geranyl trichloroacetamide **19** proceeded to give the osmate esters **20** and **21** as expected, but upon hydrolysis under acidic conditions, THFs **22** and **23** were isolated rather than the expected triol or amido diol (Scheme 5).[11]

The isolation of **20** and **21** provided further strong evidence to support the initial step of the Baldwin mechanism, but implied an Os^{VI} to Os^{IV} transformation in the second step of the mechanism, due to the absence of an external oxidant. This is in stark contrast to standard dihydroxylation chemistry where the Os^{VI} to Os^{IV} couple is not usually implicated, and alkenes are largely unreactive toward Os^{VI}. It is believed that both the intramolecular nature of this second addition and the strongly acidic conditions are factors required to facilitate this otherwise difficult cyclization step. These processes proceeded with the same stereospecificity for *syn* addition across each double bond in **24** or **25** as the documented permanganate reaction and also gave extremely high stereoselectivity for the formation of *cis*-fused THF rings (**26** and **27**). No *trans*-fused THF stereoisomers were detected (Scheme 6).

A RELIABLE CATALYTIC REACTION

Piccialli's discovery of the cyclization with catalytic osmium tetraoxide represented an important discovery; however, the use of the strong reoxidant sodium periodate led to the formation of overoxidized side products, and only two dienes had been shown to be amenable to the reaction conditions. In order to develop a reliable catalytic version of the reaction, we first examined the requirement for acid that we had observed in our earlier studies. A strong acid was necessary for any cyclized products to be observed, with camphorsulfonic acid (CSA) giving the best results; mildly acidic, neutral, or basic conditions failed to promote cyclization or cleave the osmate ester. However, it was not known whether strongly acidic conditions were needed to promote the cyclization step itself or simply to first cleave the TMEDA ligand from the osmium prior to cyclization.

To further probe the mechanism, some stoichiometric experiments were undertaken. Geranyl trichloroacetate **19** was reacted with quinuclidine and osmium tetraoxide. The initial orange-red solution at −78 °C was indicative of the formation of complex **28** between quinuclidine and osmium tetraoxide, and as this was warmed to −50 °C the color changed to green as an Os^{VI} ester **29** was formed. Compound **29** was not isolated, but NaOH cleavage furnished diol **30** indicating that the *distal* alkene had been oxidized. Compound **29** could be oxidized, via treatment with trimethylamine *N*-oxide (TMO), to presumably give the red Os^{VIII} ester **31** before being subsequently cyclized with CSA to THF **23** in 63% yield. However, treating **29** itself with CSA also afforded THF **23** in 61% yield, again illustrating that the Os^{VI} intermediate could cyclize in the absence of an external oxidant. These results showed that (i) TMEDA was not necessary for oxidative cyclization; (ii) both Os^{VI} and Os^{VIII} esters could cyclize onto the pendant alkene; and (iii) THF **23** could be formed from an osmate ester derivative of either double bond (e.g., **21** or **29**) vide supra (Scheme 7).

With these results in hand, the search began for a suitable reoxidant that would enable osmium tetraoxide to be used in a catalytic amount, but that was also mild enough to prevent overoxidation of the products which often contained primary alcohols. It was found that TMO, a known reoxidant for osmium in the dihydroxylation of olefins (Poli's conditions[12]), in conjunction with a catalytic amount of osmium tetraoxide

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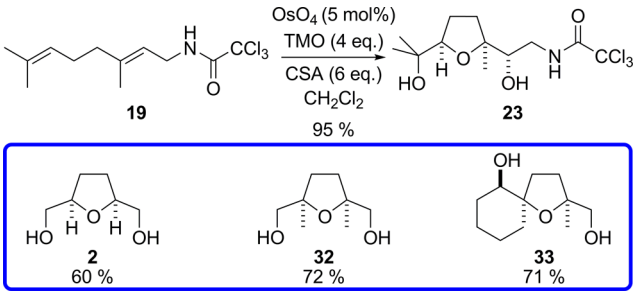
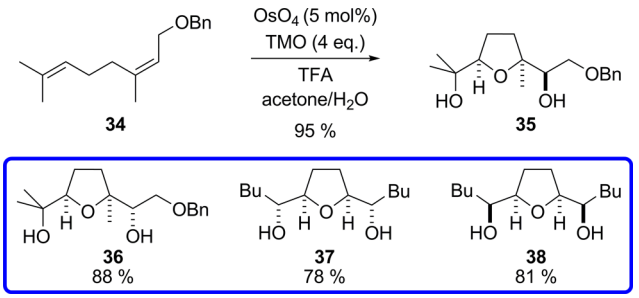
promoted the cyclization of geranyl trichloroacetamide **19** in 95% yield under acidic conditions (Scheme 8).[13]

Scheme 8. Catalytic Oxidative Cyclization Using TMO as a Reoxidant



While these conditions mediated the cyclization of several classes of dienes, furnishing THFs **2**, **32**, and **33** without deleterious over oxidation reactions, a number of dienes were unreactive and instead returned diols that had not undergone cyclization. After screening a range of solvents for the cyclization of nerol benzyl ether **34** it was found that using an excess of trifluoroacetic acid (TFA) in a 9:1 mixture of acetone/water promoted cyclization to **35** in 95% yield. THFs **36**, **37**, and **38** were also synthesized in good yields under these conditions (Scheme 9). The successful cyclization of mono and disubstituted alkenes is particularly notable as these substrates are frequently overoxidized when treated with other metal−oxo species.

Scheme 9. Catalytic Oxidative Cyclization under Aqueous Conditions



The precise role of the acid in the cyclization step is not known for certain. The second (3 + 2) cycloaddition in the reaction mechanism is one of inverse electron demand (the alkene is the electron-rich 2e$^-$ component and the :O−Os═O moiety the electron-poor 4e$^-$ component.) The dominant orbital interaction is thus likely to involve the LUMO on the osmium moiety and the HOMO of the alkene, and hence by protonating an oxo group on the osmium center, the energy of the LUMO would be expected to be lowered and the energy gap between that and the alkene HOMO reduced; making cyclization more favorable. This is analogous to (for example) the Lewis acid catalyzed (3 + 2) cyclization of vinyl ethers with nitrones whereby initial studies have indicated that coordination of the oxygen of the nitrone to a Lewis acid, lowers the LUMO energy and facilitates an inverse electron demand cyclization.[14]

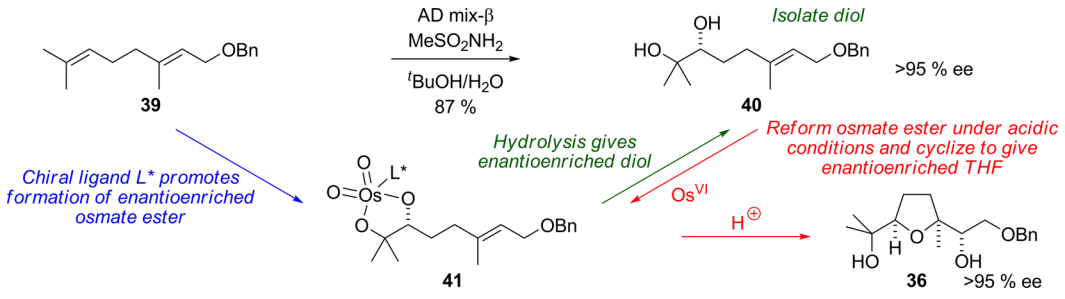
DEVELOPING AN ENANTIOSELECTIVE PROTOCOL

Although a catalytic cyclization process had now been realized, the THF products were generally formed as racemic mixtures and so efforts switched to making this process enantioselective. The asymmetric dihydroxylation of olefins with OsO_4 is well-known, where the cinchona alkaloid ligands first utilized by Sharpless allow a range of alkenes to be dihydroxylated with high enantiomeric excess.[15] However, when these ligands were employed in our cyclization conditions, only racemic THF products were obtained. Presumably, the chiral amine ligands are protonated at the low pH of the reaction mixture and are unable to coordinate to the osmium center and exert their influence on the first oxidation. Hence, a different route to obtaining a highly enantioenriched osmate ester was designed. The regioselective asymmetric dihydroxylation of certain polyenes such as **39** allows the preparation of enantioenriched diols bearing a pendant alkene such as **40**. We hypothesized that if, under acidic conditions, these isolated diols were able to form their corresponding osmate esters **41** then cyclization to form enantioenriched THFs should ensue (Scheme 10).

This strategy raised an issue regarding the oxidation state of the osmium metal throughout the cyclization. During studies on nucleotide derivatives such as **42**, Behrman had shown that Os^{VI} preferentially bound to a diol on the sugar portion of the molecule to furnish osmate ester **43**, whereas Os^{VIII} reacted with the alkene portion of the molecule to furnish **44** (Scheme 11).[16]

Hence, in the catalytic oxidative cyclization of diol **40**, it would be desirable to have a system based around Os^{VI} rather than Os^{VIII}. Although potassium osmate dihydrate ($K_2OsO_2(OH)_4$) is a readily available source of Os^{VI}, the TMO present should rapidly reoxidize this up to Os^{VIII}, leading to unwanted dihydroxylation of the pendant alkene and tetrol formation. We therefore decided to add another reactive alkene to the reaction mixture, in the hope that this would be dihydroxylated in preference to the pendant alkene in our substrate, returning any Os^{VIII} produced back to Os^{VI}. Precedent from the second cycle in Sharpless asymmetric

Scheme 10. Cyclization of Enantioenriched Diols Leading to Enantioenriched THFs



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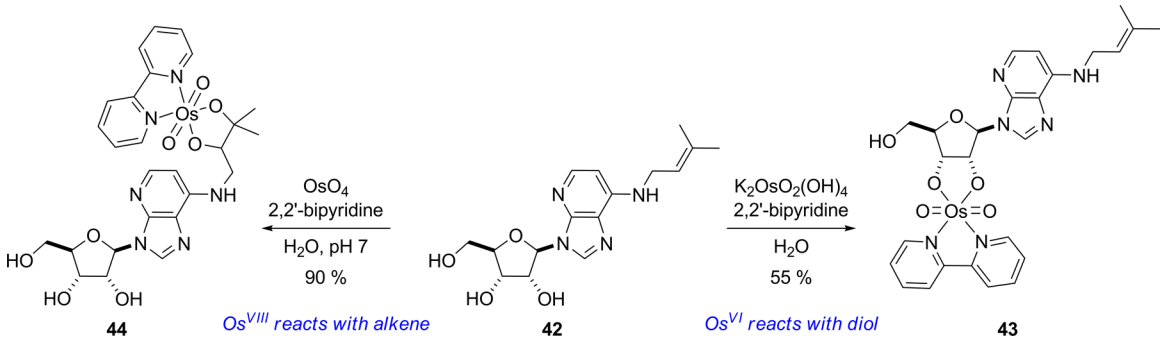
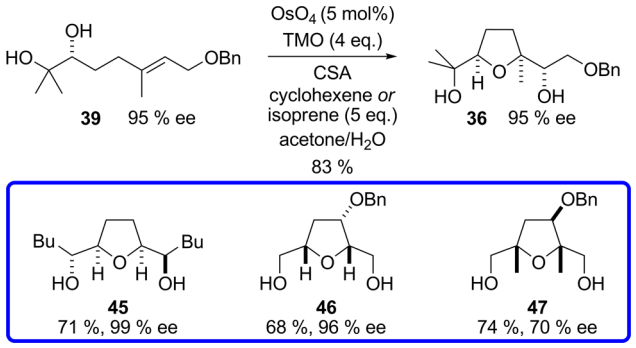
Scheme 11. Contrasting Reactivity of Os^{VI} and Os^{VIII} as Illustrated by Behrman



dihydroxylations indicated that the bound Os^{VI} should readily exchange between the substrate diol and the diol from the "sacrificial" alkene. Experimentation showed that cyclohexene, isoprene, and *trans*-cinnamic acid all proved to be suitable sacrificial alkenes and that subjecting a range of enantioenriched diols to the cyclization conditions in the presence of one of these alkenes allowed a variety of THFs to be synthesized, without any erosion in enantiopurity from the diol starting materials (Scheme 12).[17] In each case, the sacrificial alkene was chosen so that its resulting diol did not hinder purification of the THF product.

Scheme 12. Use of a Sacrificial Alkene to Synthesize Enantioenriched THFs

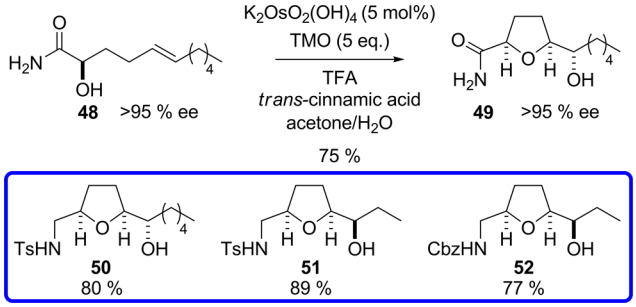


SYNTHESIZING PYRROLIDINES FROM AMINO ALCOHOLS

In the literature, all oxidative cyclizations reported thus far were limited to synthesizing oxygen-based heterocycles, most commonly THFs or tetrahydropyrans (THPs). However, it was postulated that a greater variety of chelating functionality (other than 1,2-diols) would be able to condense with Os^{VI} and subsequently cyclize to form a wider range of heterocyclic motifs. Exchanging the hydroxyl group at the tris-homoallylic position for a suitable nitrogen-containing substituent allowed the synthesis of a range of THFs flanked with amide **49**, sulfonamide **50** and **51** or carbamate functionality **52** (Scheme 13).[18]

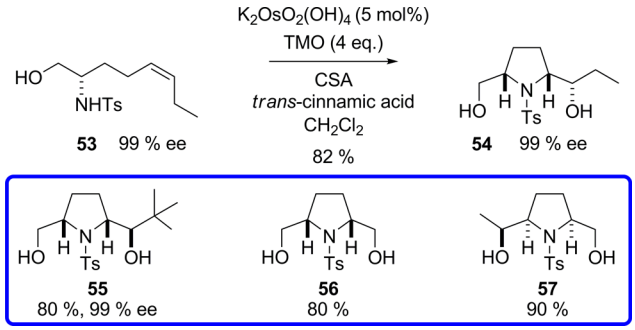
In an analogous fashion, exchanging the bis-homoallylic hydroxyl group for a sulfonamide-protected nitrogen atom enabled a number of pyrrolidines to be synthesized under similar reaction conditions (a change of solvent to CH_2Cl_2 was found to be beneficial here). We observed solely *syn* addition of oxygen and nitrogen across the *distal* alkene, and as in the THF case, there was complete stereoselectivity for the formation of

Scheme 13. Synthesis of Amide, Sulfonamide, and Carbamate-Flanked THFs



cis-fused pyrrolidines (**54**–**57**). In enantioenriched substrates, there was again no loss of enantiomeric purity (Scheme 14). This was a key development, allowing for the first time access to an entirely different class of heterocycle via this methodology.

Scheme 14. Synthesis of Pyrrolidines from Amino Alcohols



The 1,2-hydroxysulfonamide substrate **58** was synthesized to probe the reaction's preference for formation of either *N*- or *O*-heterocycles when a choice existed. Under the optimized conditions for both pyrrolidine formation (Scheme 15, (i)) and for THF formation (Scheme 15, (ii)), it was found that **58** cyclized to give purely pyrrolidine **59**, with none of THF **60** being detected. This result illustrated that it was more favorable for Os–N bonds than Os–O bonds to participate in the cyclization reaction, leading to the formation of nitrogen-containing heterocycles, in agreement with previous work in the area by Sharpless.[19]

TAMING THE REACTION CONDITIONS

Although the addition of a sacrificial alkene largely prevented unwanted dihydroxylation by in situ produced Os^{VIII}, it was

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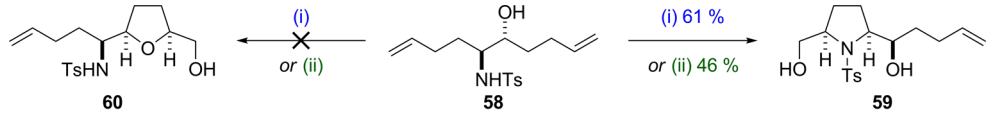
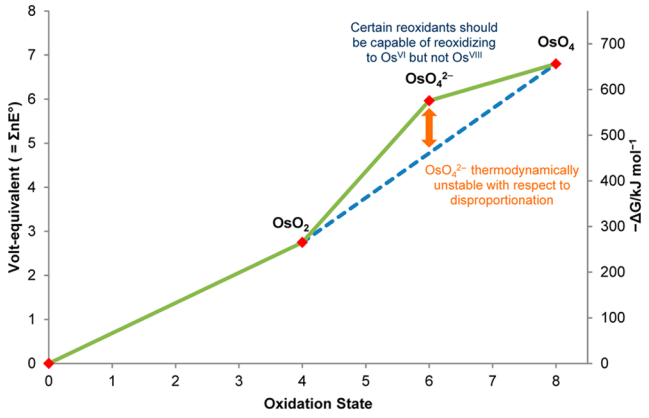
Scheme 15. Investigating the Preference for O- vs N-Heterocycle Formation



desirable to develop a milder catalytic system whereby the formation of Os^{VIII} (and hence the need for a sacrificial alkene) could be avoided entirely. It became instructive at this point to examine the redox potentials (and the corresponding plot of volt-equivalent against oxidation state) for various osmium oxides in acidic aqueous solution (Figure 1).[20] These redox



Half Equation	E°/V	Volt-equivalent
$OsO_2 + 4H^+ + 4e^- \leftrightarrows Os + 2H_2O$	0.687	2.748
$(OsO_4)^{2-} + 8H^+ + 6e^- \leftrightarrows Os + 4H_2O$	0.994	5.964
$OsO_4 + 8H^+ + 8e^- \leftrightarrows Os + 4H_2O$	0.850	6.800

Figure 1. Plot of volt-equivalent against oxidation state for osmium in acidic aqueous solution.

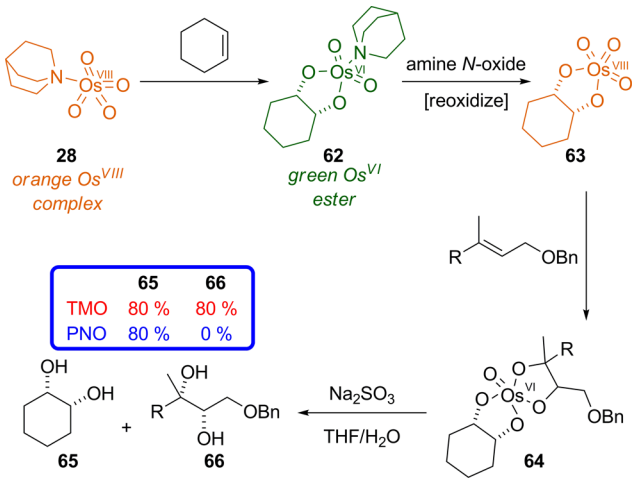
potentials can of course be altered by the presence of ligands in the reaction vide infra. The potentials indicated that it should be possible to find a reoxidant that would be capable of oxidizing Os^{IV} to Os^{VI} (the redox couple needed for cyclization), but not Os^{VI} to Os^{VIII} (the dihydroxylation redox couple). The use of such a reoxidant would retard the formation of OsO_4, but may not eliminate it entirely, as OsO_4^{2-} is thermodynamically unstable with respect to disproportionation into OsO_2 and OsO_4, as evidenced from Figure 1 (where OsO_4^{2-} lies above the line joining OsO_2 and OsO_4).

Nevertheless, aqueous solutions of OsO_4^{2-} are "stable" at room temperature; i.e., no visible precipitation of the poorly soluble disproportionation product OsO_2 is observed. Hence, we thought it probable that the rate of this disproportionation under reaction conditions at (or close to) ambient temperature should be sufficiently slow to virtually eliminate OsO_4 from a catalytic oxidative cyclization reaction with a suitably mild reoxidant.

After screening a wide range of reoxidants, it was found that pyridine *N*-oxide (PNO) allowed the cyclization of **61** to **56** to proceed in high yields without any sacrificial alkene being necessary (Scheme 16, (ii)).[21] The presumed increased concentration of active Os^{VI} also meant that the reaction time was substantially shortened (from 16 to 4 h) when compared with the previous TMO conditions (Scheme 16, (i)).

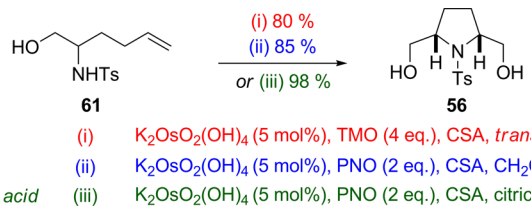
Further stoichiometric studies were undertaken to confirm the milder oxidizing properties of PNO compared with TMO (Scheme 17). When the orange OsO_4·quinuclidine complex **28**

Scheme 17. Stoichiometric Experiments with TMO and PNO



was treated with cyclohexene the green Os^{VI} ester **62** was formed. When this complex was treated with TMO a color change occurred during conversion to putative Os^{VIII} complex **63**.[22] The formation of Os^{VIII} was confirmed by the ability of **63** to react with a second alkene to give proposed Os^{VI} complex **64**. Reductive hydrolysis of **64** furnished two diols **65** and **66** in a 1:1 ratio and 80% yield. In contast, no color change was observed upon treatment of **62** with PNO, and the resulting complex was unable to oxidize the second alkene. Hence, on

Scheme 16. Improvement in Reaction Conditions with PNO and Citric Acid



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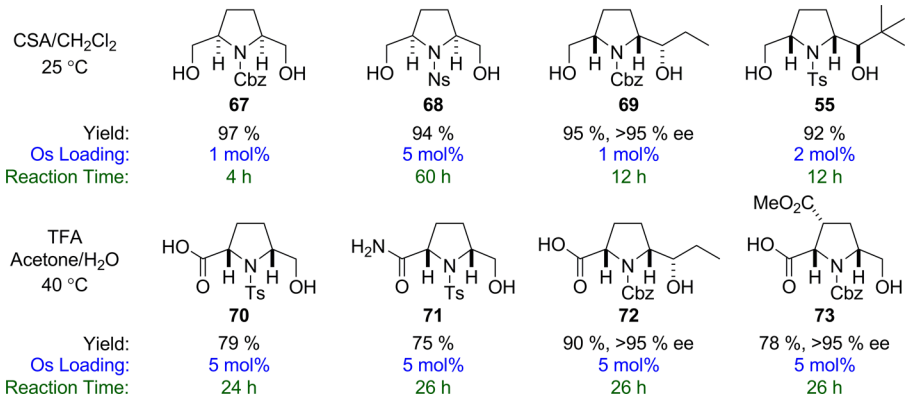

Figure 2. Pyrrolidines synthesized under PNO/citric acid conditions.

hydrolysis the second alkene was recovered with none of diol **66** observed.

Although PNO was not a powerful enough oxidizing agent to oxidize Os^{VI} to Os^{VIII}, disproportionation under the reaction conditions may still have led to the unwanted formation of Os^{VIII}, albeit slowly. Sharpless and co-workers had previously investigated this disproportionation during their studies on dihydroxylation,[23] wherein they reported that the addition of citric acid gave large improvements in product yield and purity. They proposed that the citric acid coordinated to the osmium center, helping to stabilize the Os^{VI} species against disproportionation. It was also hypothesized that once ligated, the two pendant carboxylate groups would increase the hydrophilicity of the Os^{VI} species and so aid the hydrolytic release of product molecules from osmium, increasing the rate of this step in a catalytic cycle.

In the event, the addition of citric acid greatly improved the oxidative cyclization reaction of **61** to **56**, with a yield of 98% obtained in a reaction time of just 2 h, with no dihydroxylated product being detected (Scheme 16, (iii)). Furthermore, in control experiments, a number of alkenes were recovered untouched after reaction under these new catalytic reaction conditions. Thus, all evidence we had gathered pointed to a lack of any Os^{VIII} under PNO conditions.[24]

Applying these improved reaction conditions to other substrates allowed the synthesis of a range of pyrrolidines in high yields (Figure 2). Sulfonamide and carbamate-protected amino alcohols, which often required high catalyst loadings and long reaction times under the old conditions, now cyclized much more efficiently and with reduced osmium loadings (see pyrrolidines **55**, **67** and **69**). The new conditions were also compatible with a number of initiating motifs that were not tolerated under previous conditions. These included a nitrobenzenesulfonyl group (Ns) (pyrrolidine **68**) and a number of amino acids and amino amides (pyrrolidines **70**–**73**). The change in the nature of the acid and the solvent enabled us to maximize the solubility of these more polar substrates, heat the reaction to increase the rate and aided purification procedures.

It is probable that, depending on the exact reaction conditions used for the oxidative cyclization, the oxidation states of the osmium centers involved in the catalytic cycle may vary. Piccialli initially proposed that in the diene cyclizations the intermediate Os^{VI} ester was first reoxidized to an Os^{VIII} ester prior to cyclization to the THF. Recent DFT calculations in more simple systems also concluded that the cyclization of an Os^{VIII} ester would proceed via a lower energy pathway than that of the analogous Os^{VI} ester.[25] However, the body of evidence obtained during our investigations has revealed that Os^{VI} species are perfectly capable of reacting with alkenes and hence cyclizing without the need for prior oxidation. The ability of non-Os^{VIII} species to react with alkenes is further supported by the very recent work by Sugimoto et al. who were able to dihydroxylate alkenes with cationic Os^{V} complex **74** (Figure 3).[26] The catalytic cycle is proposed to involve an Os^{V}–Os^{III} redox couple, with hydrogen peroxide acting as the reoxidant.

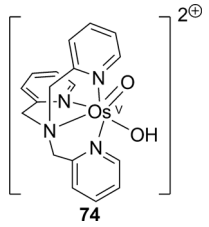

Figure 3. Sugimoto's Os^{V} dihydroxylation catalyst.

We have also shown conclusively that free Os^{VIII} can be avoided by the use of PNO reaction conditions. Hence, it is perfectly plausible that under PNO conditions the entire catalytic cycle is mediated by an Os^{VI}–Os^{IV} redox couple, where the ligating ability of citric acid helps stabilize these lower oxidation state intermediates in aqueous solution. This allows us to propose a more detailed catalytic cycle for the system under our new, milder conditions (Figure 4). In this cycle, a molecule of citric acid is shown coordinated to the osmium center throughout the reaction. Although there may be other osmium species present (with no other ligand than the substrate or a second diol), the continued ligation of citric acid seems plausible given its highly beneficial effect on the reaction.

A molecule of enantioenriched diol **75** (synthesized separately) first coordinates to the Os^{VI}–citric acid species **76** to form complex **77**. Protonation by acid is required to form the key Os^{VI} oxidative cyclization precursor **78**, which undergoes an inverse electron demand (3 + 2) cycloaddition to give Os^{IV}–product complex **79**. As mentioned earlier, the need for protonation is analogous to the coordination of the oxygen of a nitrone to a Lewis acid, prior to a (3 + 2) cyclization with a vinyl ether.[14] The THF product **80** is then furnished by hydrolysis (presumably aided by the pendant carboxylic acid groups of the ligated citric acid), and the Os^{IV}–citric acid species is oxidized back to Os^{VI} species **76**. Under these milder reaction conditions, it is likely that the formation

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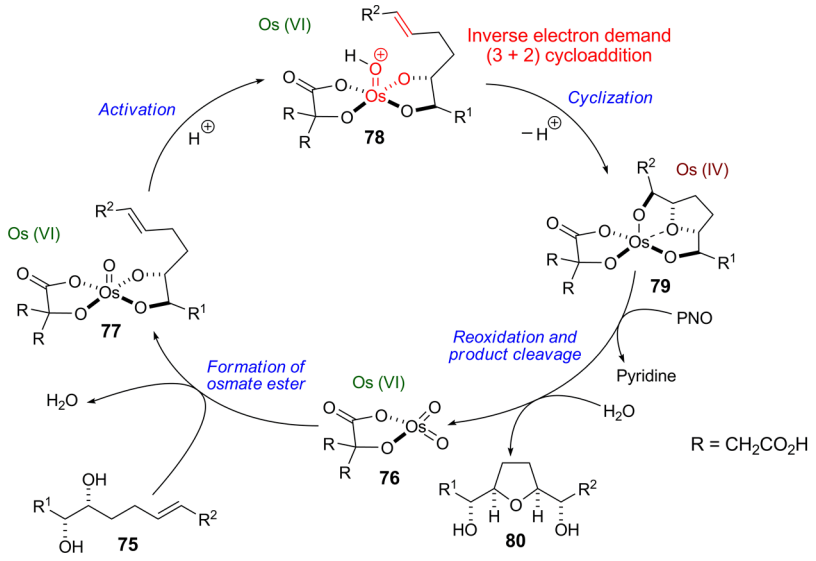

Figure 4. Proposed catalytic cycle under PNO conditions.

Table 1. Optimization of the Reaction Conditions

entry	$K_2OsO_2(OH)_4$ (mol %)	oxidant	additives	solvent	temp (°C)	yield (%)	time (h)
1	5.0	TMO	*trans*-cinnamic acid, TFA	acetone/H_2O (9:1)	20	72	20
2	5.0	PNO	citric acid, TFA	acetone/H_2O (9:1)	20	78	16
3	5.0	PNO	citric acid, $Sc(OTf)_3$ (6.0 equiv)	acetone/H_2O (9:1)	20	84	16
4	5.0	PNO	citric acid, $Cu(OTf)_2$ (0.5 equiv)	MeCN/H_2O (4:1)	60	87	8
5	5.0	PNO	citric acid, $Zn(OTf)_2$ (0.5 equiv)	MeCN/H_2O (4:1)	60	89	8
6	1.0	PNO	citric acid, $Zn(OTf)_2$ (0.5 equiv)	MeCN/H_2O (3:2)	60	92	6
7	0.2	PNO	citric acid, $Zn(OTf)_2$ (0.5 equiv)	MeCN/H_2O (3:2)	60	90	72

of Os^{VIII} species, including OsO_4, is completely suppressed. Free OsO_4^{2-} may be a catalytically active species itself, but is probably not as efficient a catalyst as Os^{VI}-citric acid species **76**. Free OsO_2 is presumed not to be a reaction intermediate, due to its low solubility in water. The formation of OsO_2 is a potential decomposition pathway for the active catalyst and we believe it is responsible for the observation that reactions without citric acid turn black over time due to lower valent osmium species precipitating out of solution.

LEWIS ACIDIC CONDITIONS

The newly developed PNO/citric acid conditions led to significant improvements in the cyclization of amino alcohol substrates, but the more challenging diol substrates still required high catalyst loadings. The highly acidic reaction conditions often led to complications during workup and meant that many functional groups were not compatible with the reaction. We envisaged, by analogy to the Lewis acid catalyzed (3 + 2) cyclization of vinyl ethers with nitrones, that a Lewis acid could also be employed in place of the Brønsted acid to promote the oxidative cyclization reaction. The key would be to find an oxophilic Lewis acid which would be able to coordinate to the osmium oxo ligand and reduce the LUMO energy without sequestering the pyridine *N*-oxide. After screening a range of Lewis acids, it was discovered that a range of metal triflates were highly proficient at this task.[27] Initial optimization focused on the cyclization of diol **81**, which had proceeded under Brønsted acid conditions in 72% yield (Table 1, entry 1), albeit with a relatively high loading of osmium catalyst.

Initial improvements were achieved when TMO was replaced with PNO as the reoxidant, in combination with the addition of citric acid (entry 2). Replacing TFA with an excess of $Sc(OTf)_3$ led to a further enhancement in yield (entry 3); however, acetonide side products were also formed between the diol and the acetone solvent. After screening a range of different reaction solvents to avoid this, an MeCN/H_2O mixture was found optimal. This system could be heated up to 60 °C, which increased the rate of the reaction, without leading to a reduction in yield due to disproportionation of Os^{VI} or other detrimental side reactions. A number of different triflates, including $Cu(OTf)_2$ and $Zn(OTf)_2$, were all found to work well in the reaction and had the benefits of being cheaper and milder than $Sc(OTf)_3$. The use of either $Cu(OTf)_2$ or $Zn(OTf)_2$ led to increased yields in a much shorter time of 8 h (entries 4 and 5). Further optimization showed that a MeCN/H_2O ratio of 3:2 was optimal, and this made the reactions sufficiently rapid that the catalyst loading could be reduced to 1.0 mol % (entry 6) or even 0.2 mol % (entry 7) while still attaining excellent yields. These Lewis acidic reactions were found to have a pH of 2. However, conditions without the Lewis acid metal ion whereby the pH was adjusted to 2 with TfOH only led to decomposition of the starting material, showing that under Lewis acid

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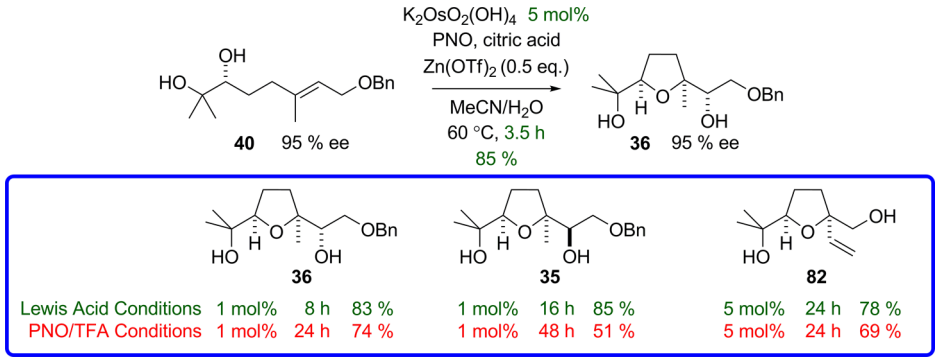
Scheme 18. Improvement in Yield for Cyclization under Lewis Acidic Conditions

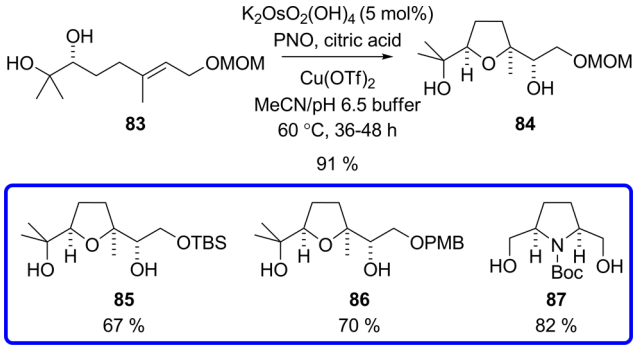


conditions the reactions were being promoted by the metal ion and not simply by the low pH. Similarly, citric acid mediated a far greater rate acceleration than other carboxylic acids that were screened, supporting the idea that its ligating ability was key vide supra.

These new reaction conditions led to improvements in reaction yields for almost all substrates and allowed a number of demanding substrates that had previously cyclized only in low yields or not at all to now be converted efficiently (Scheme 18).

The key advantage of removing the TFA from the reaction mixture was that the cyclization reaction was now compatible with a number of functional groups that otherwise would not have endured the harshly acidic conditions. The water in the reaction mixture could be replaced by a pH 6.5 phosphate buffer (1:1 NaH_2PO_4/Na_2HPO_4). These conditions, while essentially neutral, still promoted cyclization well due to the Lewis acidity of the metal ions. A number of acid-sensitive protecting groups (including MOM **84**, TBS **85** and PMB-protected alcohols **86** and Boc-protected amines **87**) could now be tolerated under the reaction conditions (Scheme 19). All

Scheme 19. Cyclization of Acid-Sensitive Substrates under Lewis Acidic Conditions



molecules containing these protecting groups had decomposed under TFA conditions, and no cyclized products were observed. The tolerance of these protecting groups makes this methodology far more attractive for endeavors in total synthesis, vide infra.

REDUCED TOXICITY

It is well-known that osmium tetraoxide is highly toxic, and because of its volatility, strict precautions must be taken when it is used or formed in a reaction. However, it is a common misconception that "all osmium is equally toxic". In fact, if we compare the toxicity of osmium tetraoxide and potassium osmate by examining the median lethal oral dose in rats (the LD_{50}), we see a greater than 200-fold reduction in toxicity for potassium osmate compared to osmium tetraoxide (Table 2).[28] Also as potassium osmate is not volatile, its usage presents significantly less operational risk to the user than that of OsO_4.

Table 2. Relative Toxicity of Osmium Tetraoxide and Potassium Osmate

OsO_4	$K_2OsO_2(OH)_4$
R26/27/28, R34	R23/24/25
LD_{50} rat (oral)	LD_{50} rat (oral)
0.01 g/kg	2.69 g/kg

Hence, our new mild cyclization conditions, which do not require the user to add OsO_4 and also virtually eliminate any Os^{VIII} species from the reaction, make these reactions much safer to carry out as well as improving the reaction yields and reducing reaction times.

HETEROATOM-SUBSTITUTED DOUBLE BONDS

Up until this point, all oxidative cyclizations performed in our group had involved double bonds bearing only hydrogen- or carbon-based substituents and other groups had not been examined. We became intrigued to determine whether heteroatom-substituted double bonds **88** could be tolerated under the now much milder Lewis acidic reaction conditions we had developed. In particular, installation of a heteroatom at the ring junction (see **89**) would be particularly valuable as it would allow further manipulation of this center after the cyclization **90**, an otherwise tricky process. The oxidative cyclization reaction proceeds most efficiently onto electron rich double bonds, due to the inverse electron demand nature of the second mechanistic step. However, these double bonds are also the most susceptible to decomposition or hydrolysis to **92** under the acidic aqueous cyclization conditions (via a species such as **91**). This meant careful selection of the heteroatom would be required (Scheme 20).

After investigations into a range of possible heteroatom substituents, it was found that vinylsilanes were amenable to the reaction conditions. The silicon group is sufficiently electropositive to render the alkene electron-rich enough to promote the cyclization while sufficiently robust to remain stable under the Lewis acidic cyclization conditions. This cyclization is particularly remarkable given the considerably increased steric bulk during the cyclization due to the presence of a substituent

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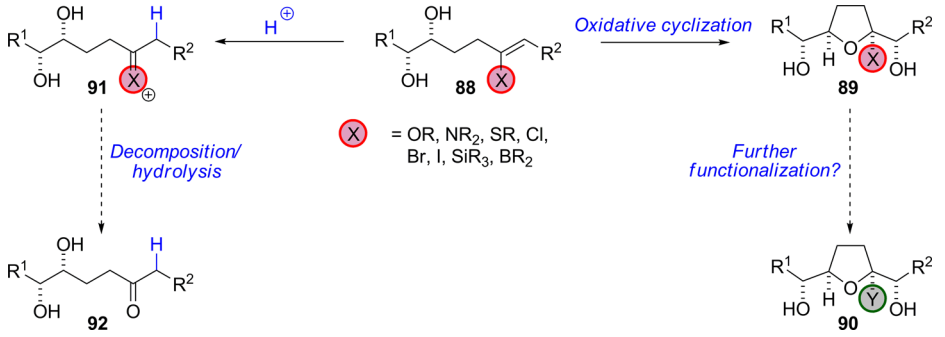
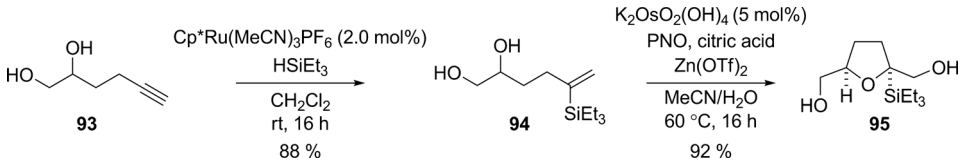
Scheme 20. Cyclization onto Heteroatom-Substituted Double Bonds and Possible Decomposition Pathways



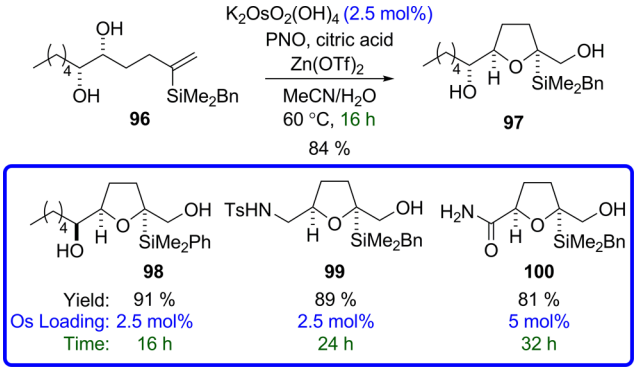
Scheme 21. Synthesis and Oxidative Cyclization of a Vinylsilane



at this position. The requisite vinyl silane diol **94** could be readily synthesized as a single regioisomer from the corresponding alkyne diol **93** using a ruthenium-catalyzed hydrosilylation reaction recently developed by Trost et al.[29] When subjected to the reaction conditions this vinyl silane cyclized in excellent yield to form the resulting THF **95** (Scheme 21).[30]

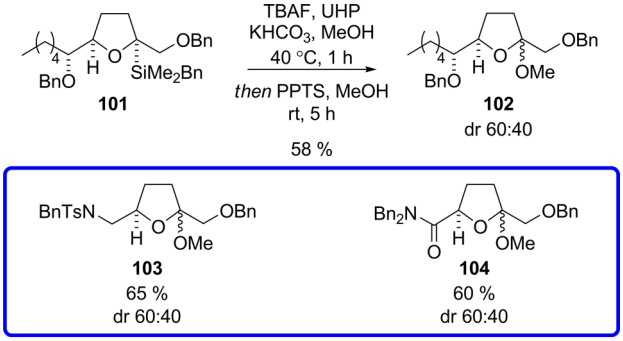
In addition to a triethylsilyl group, both a dimethylphenylsilyl group **98** and benzyldimethylsilyl groups **97**, **99**, and **100** could be incorporated in an analogous fashion in similarly high yield; a range of activating groups could also be used to facilitate the cyclization (Scheme 22).

Scheme 22. Cyclization of a Range of Vinylsilanes



The successful integration of dimethylphenylsilyl and benzyldimethylsilyl groups onto the THF ring junction was particularly noteworthy as these organosilanes have recently seen extensive use as masked hydroxyl groups,[31] and so this route offered potential for further manipulation of the ring junction carbon center postcyclization. Attempts to oxidize the dimethylphenylsilyl group after the cyclization proved unsuccessful, often leading to overoxidized products. However, more success was achieved with the oxidation of the benzyldimethylsilyl group using another procedure recently developed by Trost et al., which uses milder oxidizing conditions.[32] Prior to oxidation of the benzyldimethylsilyl group it was necessary to benzyl protect the hydroxyl groups, to prevent protodesilylation occurring instead (presumably via an intramolecular mechanism involving the neighboring hydroxyl group). Oxidation to the lactol was carried out with tetrabutylammonium fluoride (TBAF) followed by anhydrous urea-hydrogen peroxide (UHP). As the lactols existed as mixtures of cyclic and open chain isomers, they were converted into their lactol ethers (**102**–**104**) prior to isolation as the presumed thermodynamic mixture of diastereoisomers (Scheme 23). Hence, these silyl-substituted THFs can act as lactol synthons which can be unmasked under mild conditions at a late stage in a chemical synthesis.

Scheme 23. Oxidation of Benzyldimethylsilyl THFs and Isolation as Lactol Ethers



ALTERNATIVE CHELATING MODES AND MOTIFS

Our studies had begun with the oxidative cyclization of 1,5-dienes, but the advent of the Os^{VI} conditions led to 5,6-dihydroxyalkenes becoming the cyclization substrates of choice. The 1,2-diol moiety in these substrates typically originated from an alkene itself, but it is also possible to envisage the use of other chelating moieties without a 1,2-relationship between the functional groups. 1,3-Diols were tested and were indeed found to be competent cyclization substrates.[33] Much of the work on 1,3-diols was initially carried out under the older TMO reaction conditions (Scheme 24), where reasonable yields were obtained for some substrates (**106**–**109**); the 1,3-diols were noticeably more sluggish to react than the corresponding 1,2-

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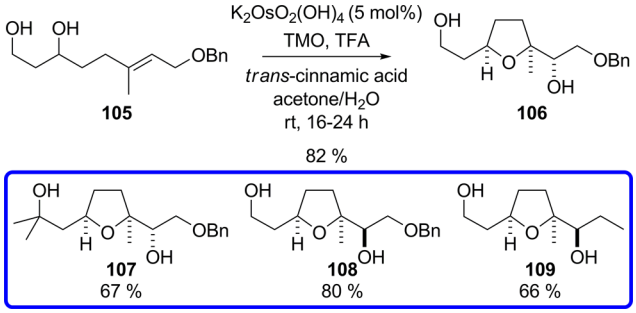
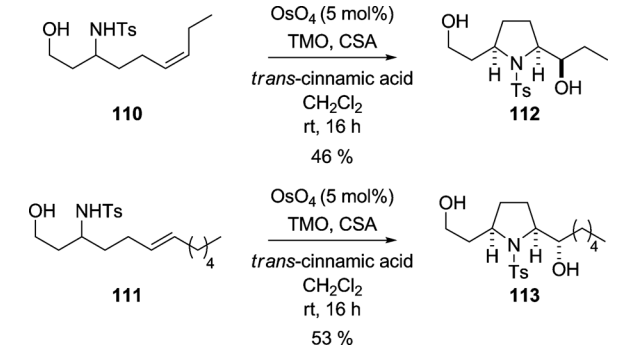
Scheme 24. Cyclization of 1,3-Diols under TMO Conditions



diols, which was attributed to their weaker chelating ability. Larger metals such as osmium are known to preferentially form five-membered chelate rings over six-membered rings due to more favorable bond angles in the five-membered case.[34] These cyclization reactions proceeded with the same stereospecificity for *syn* addition across the alkene as in the 1,2-diol case, as well as stereoselectivity for producing *cis*-fused THFs.

Likewise, 1,3-amino alcohols **110** and **111** could be cyclized to the corresponding pyrrolidines **112** and **113** (Scheme 25).

Scheme 25. Cyclization of 1,3-Amino Alcohols under TMO Conditions



Again, the lower yields and longer reaction times were attributed to the less favorable chelate ring size formed during the cyclization step. Some of these 1,3-chelating examples were revisited after we had developed the much more powerful Lewis acidic cyclization conditions, when they could be converted in significantly higher yields with lower osmium loadings, although still not as efficiently as 1,2-chelating substrates.[27]

In oxidative cyclizations promoted by rhenium, there is no requirement for two atoms to chelate to the metal prior to cyclization. Indeed both bis-homoallylic alcohols and tris-homoallylic alcohols have been cyclized to THFs and THPs respectively.[35−38] Therefore, it was conceivable that 1,4-diol **114** might cyclize under the action of osmium by coordination of only the bis-homoallylic group or alternatively by chelation of both groups in a seven-membered chelate with osmium. However, when **114** was subjected to the optimized reaction conditions no product was formed (Figure 5). Bis-homoallylic alcohol **115** was also synthesized and subjected to oxidative cyclization conditions. However, no THF was formed from this substrate or indeed any other monodentate bis-homoallylic alcohol that was tested, strongly implying the necessity for osmium to be bound to the substrate in a bidentate fashion in order to mediate cyclization.

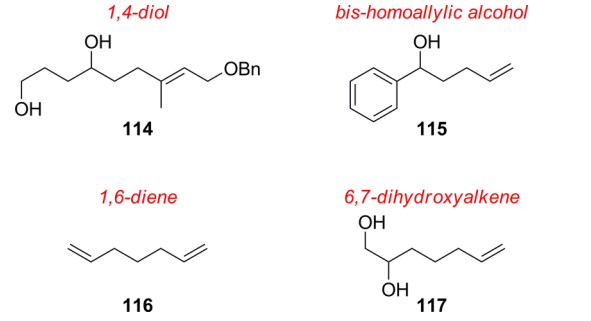


Figure 5. Unreactive substrate classes toward oxidative cyclization with osmium.

Similarly, precedent from cyclization with other metals suggested that 1,6-dienes and their derivatives could undergo analogous cyclizations to form THPs, but no reactivity was seen when either 1,6-diene **116** was subjected to our Os^{VIII} cyclization conditions or 6,7-dihydroxy-alkene **117** to our Os^{VI} cyclization conditions.

The contrasting reactivity of osmium to other metals merits further discussion here. Our experiments have illustrated that osmium has to be chelated in a bidentate fashion by the substrate in order to mediate a cyclization. In the five-membered ring case, this chelation in transition state **118** results in the exclusive production of *cis*-THFs (Figure 6).

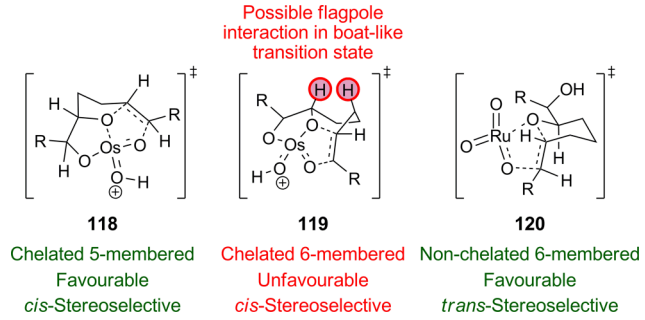


Figure 6. Possible transition states for five- and six-membered ring formation.

Manganese and chromium cyclizations are proposed to proceed via analogous transition states and hence also give *cis*-THFs. Rhenium cyclizations from a bis-homoallylic alcohol deliver *trans*-THFs; as there is now no opportunity for chelation, there is much greater flexibility in the transition state. These more "open" transition states are believed to suffer from less steric hindrance en route to *trans* rather than *cis*-THFs. With ruthenium cyclizations a mixture of *cis* and *trans*-THFs are formed, typically with the *cis* predominating in a ratio of 95:5. It is postulated that ruthenium can cyclize via either a chelated transition state (major) to furnish the *cis*-THF or a nonchelated transition state (minor) to furnish the *trans*-THF. The chelated transition state is believed to be lower in energy and hence *cis*-THFs are the major products.

When we move to the six-membered ring case, osmium will not catalyze any cyclization and no THP formation was observed. Molecular models constructed in our group of the possible chelated transition state structure **119** have indicated that the six-membered ring may adopt a highly strained boat-like conformation in order to ensure a geometry around the metal ion that is similar to the five-membered case, which is

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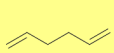
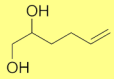
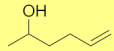
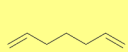
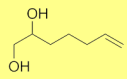
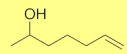
Table 3. Substrate Scope and Stereoselectivity in Oxidative Cyclization with Other Metals

	Five-Membered Rings			Six-Membered Rings		
Initiator	1,5-Diene	5,6-Dihydroxy-alkene	Bis-homo-allylic alcohol	1,6-Diene	6,7-Dihydroxy-alkene	Tris-homo-allylic alcohol
Metal						
Osmium [8,11,13,17,21,27,33]	*cis*	*cis*	unreactive	unreactive	unreactive	unreactive
Manganese [2,39]	*cis*	–	–	*cis*	–	–
Rhenium [35-38,40-42]	–	–	*trans*	–	–	*trans*
Ruthenium [43-49]	*cis:trans* up to 95:5	*cis:trans* > 95:5	unreactive	*trans:cis* > 95:5	–	–
Chromium [50,51]	–	*cis*	unreactive	–	–	–

obviously a highly favorable geometry for cyclization. Thus, it may be the case that an unfavorable flagpole interaction across the forming THP ring makes this cyclization unfavorable. Manganese, however, does promote cyclization to form *cis*-THPs and by implication can overcome such a barrier. Here the authors proposed a chelated chairlike transition state to account for the *cis*-selectivity.[39] The inconsistency in reactivity between these two metals, which both seem to require a chelated transition state for THP formation, is possibly due to the significant size difference between them.

Note that rhenium will cyclize tris-homoallylic alcohols and ruthenium 1,6-dienes to form *trans*-THPs. In the nonchelated rhenium case, the open transition state leading to the *trans*-THP is believed to be sufficiently lower in energy on steric grounds. With ruthenium, which is believed to be able to cyclize via either chelated or nonchelated transition states; it is postulated that it prefers nonchelated chairlike transition state **120** in the six-membered case on steric grounds (in contrast to the chelated transition state which is preferred in the five-membered case) which accounts for the reversal in the stereoselectivity of ruthenium cyclizations between five and six-membered rings. A brief summary of the contrasting reactivity of different metals is given in Table 3. In addition to the different stereochemical preferences, the compatibility with different initiating motifs is also listed. These differences are determined not only by the redox potentials of the metal oxo species involved, but also by any reoxidant present and the nature of the cyclization conditions (pH, temperature, etc.). Where control experiments in our group or by others have illustrated that certain substrates would not cyclize under the action of a particular metal, we have listed these substrates as "unreactive". Where there is no published account (to the best of our knowledge) of the reactivity of a particular substrate, we have indicated this with a "–", although it is likely that in most of these gaps the substrate is either unreactive or would undergo deleterious side reactions.

At this point, we had thoroughly explored a variety of groups that could chelate to osmium to promote the oxidative cyclization reaction. However, we realized that these all cyclized via essentially the same mode, whereby one of the two chelating atoms became the heteroatom in the heterocycle and the other became affixed to the carbon chain external to the newly formed ring (cyclization "Mode A", **121** → **122**, Figure 7).

An alternative "Mode B", **123** → **124**, was envisaged whereby the chelating atom of the initiating pair nearest to the double

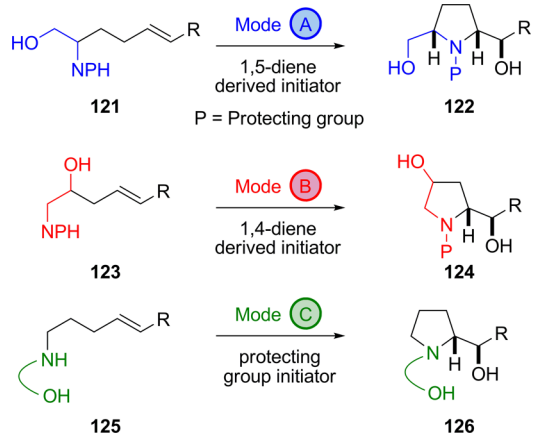


Figure 7. Different modes of cyclization for bidentate chelating groups.

bond in the starting material ends up on the 3-position of the heterocyclic ring backbone. This initiator was formally derived from a 1,4-diene. The oxidative cyclization of 1,4-dienes to form THFs had only been disclosed once before with two low yielding examples being reported.[52] Furthermore, a "Mode C", **125** → **126**, was possible in the case of pyrrolidine synthesis, whereby the nitrogen protecting group also acted as a second chelating group. The possibilities offered by Mode B and Mode C were thus explored to further extend this methodology. In particular, it was hoped that unlocking these modes would allow access to *trans*-pyrrolidines *via* osmium cyclizations for the first time. To this end, hydroxysulfonamide **127** was subjected to the optimized Lewis acidic cyclization conditions (Scheme 26).[53] In the product **129** (which was acetylated to aid purification), the hydroxyl group on the ring backbone and the hydroxymethylene group were located on the same face of the pyrrolidine ring, as confirmed by X-ray crystallography. This led us to postulate that the cyclization had proceeded through highly organized chelated transition state **128**. A number of amino alcohols could be cyclized with this procedure. Pyrrolidines **130** and **131** were synthesized without any erosion in enantiomeric excess from the amino alcohol starting materials, and again exclusively *syn* addition occurred across the double bond. Electron rich allyl silanes were also compatible substrates and pyrrolidine **132** was synthesized by cyclization onto an allyl silane in 58% yield.

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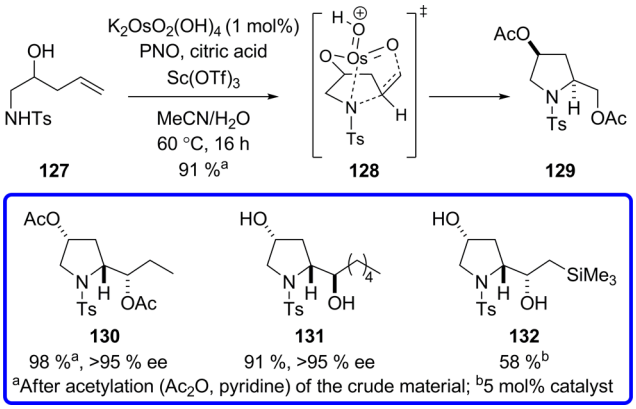
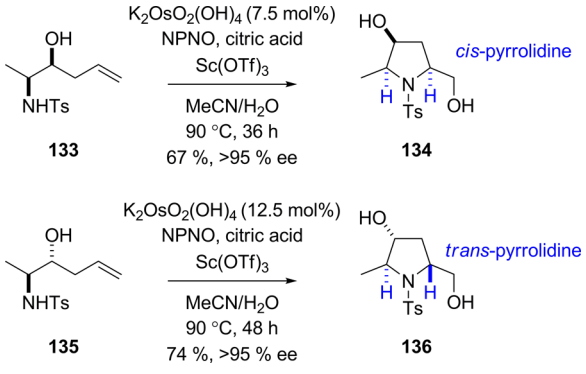
Scheme 26. Mode B Cyclizations of Unhindered Substrates



When attention was turned to substrates with substitution α- to the nitrogen atom, it was found that these were considerably less reactive toward Os^{VI}, possibly due to unfavorable steric interactions in the highly compact transition state required for cyclization. In an effort to improve this reactivity higher temperatures were investigated. However, at these higher temperatures, competing dihydroxylation of the substrate became a problem, presumably due to either the elevated oxidizing ability of PNO at these temperatures or an increased rate of disproportionation of Os^{VI}. It was therefore decided to screen for a new, even weaker oxidizing agent to attempt to overcome this limitation and it was discovered that 4-nitropyridine *N*-oxide (NPNO) was suitable for this task. The reduction in reactivity is most likely due to the greater N−O bond strength in NPNO versus PNO. When NPNO was used as the reoxidant in higher temperature cyclizations, superior yields of cyclized products were obtained without competing dihydroxylation. Under these conditions, *syn* amino alcohol **133** cyclized to furnish *cis*-pyrrolidine **134** in 67% yield, while *anti* amino alcohol **135** cyclized to furnish *trans*-pyrrolidine **136** in 74% yield. This was the first time a *trans*-selective oxidative cyclization had been documented with osmium and hence was a key advance (Scheme 27). Unfortunately, diols derived from 1,4-dienes and amino alcohols with the two chelating groups transposed failed to cyclize to THFs under these conditions.

Focus then shifted to Mode C cyclizations. Due to sulfonamide-protected nitrogen atoms displaying the greatest reactivity under our oxidative cyclization conditions, a novel β-hydroxy sulfonamide chelating protecting group was designed;

Scheme 27. More Challenging Mode B Cyclizations with NPNO



this motif would form a six-membered chelate with osmium. Although a five-membered chelate would be significantly more favorable, the corresponding α-hydroxy sulfonamides are not stable functional groups and rapidly decompose. Hydroxysulfonamide **137** underwent cyclization to form *trans*-pyrrolidine **139** via proposed transition state **138** (Scheme 28). We hypothesized that the *trans*-stereoselectivity was a result of the methyl group and the alkene preferring to be orientated as far apart during the cyclization as possible, as in related processes with rhenium catalysts. Due to the steric bulk in the substrates, higher osmium catalyst loadings and longer reaction times were required. When primary rather than secondary bis-homoallylic amine substrates were subjected to the reaction conditions, the reduced hindrance led to much greater product yields being obtained (pyrrolidines **140** and **141**). If the hydroxyl group on the β-hydroxy sulfonamide was methylated prior to the reaction, the substrate became unreactive to the reaction conditions, again illustrating that bidentate chelation is a requirement for osmium-catalyzed oxidative cyclization.

With these results we could conclude that after a decade of optimizing this reaction we had developed a highly reactive set of conditions that had been tested to the limit. The osmium-catalyzed oxidative cyclization process has now been scrutinized extensively against a wide assortment of substrates. This cyclization gives high yields in many systems, with complete control of absolute and relative stereochemistry. The mild reaction conditions mean that an array of functional groups and protecting groups can be carried through the reaction. The potency of the system also enables it to construct extremely complicated structural motifs, including many that are sterically hindered, from simple precursors.

APPLICATIONS IN SYNTHESIS

As this reaction underwent development in our laboratory, we felt it pertinent to assess the capabilities of this new methodology in the synthesis of important targets such as biologically active natural products. While our initial targets were more straightforward, as the reaction conditions were simultaneously refined and made more potent, we were able to apply them to more complex targets. Some of the natural products or fragments of natural products accessed are shown in Figure 8.

Each of the natural products that we have worked on is examined separately. Rather than describing the entirety of each synthesis, we have focused our discussion around the construction of the key precursor for the oxidative cyclization reaction, the cyclization itself and the subsequent major reactions to convert the resulting THF from this reaction into the natural product. For more detailed discussions, readers should refer to the individual synthesis papers or to a recent review.[54]

(+)-ANHYDRO-D-GLUCITOL AND (+)-D-CHITARIC ACID

In 2003 we published the syntheses of (+)-anhydro-D-glucitol and (+)-D-chitaric acid (Scheme 29).[13] The readily available C_2-symmetric diene (+)-**143** was oxidized to give enantiomerically pure (+)-**144**. Compound (+)-**144** could be converted to (+)-anhydro-D-glucitol in one step or (+)-D-chitaric acid in three steps *via* simple protecting group and redox transformations.

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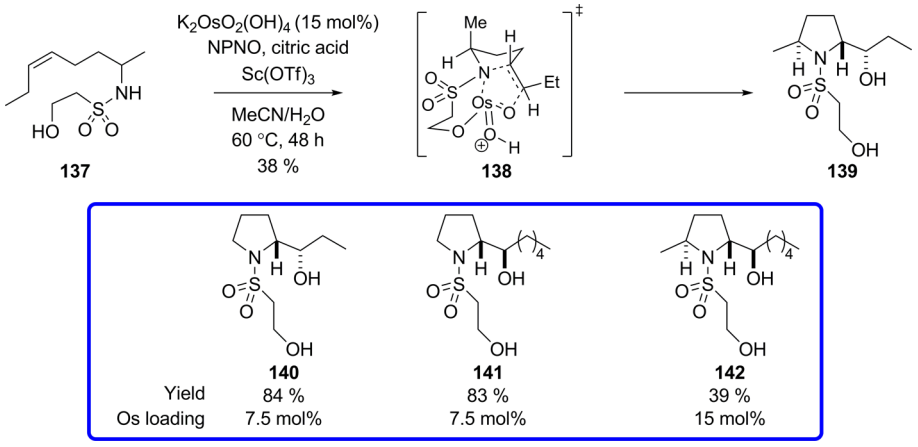
Scheme 28. Mode C Cyclizations with Protecting Group initiators



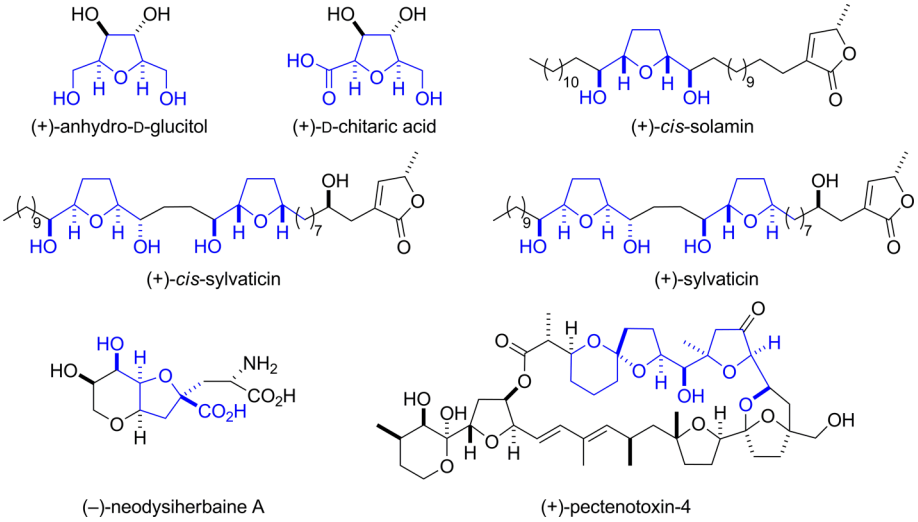
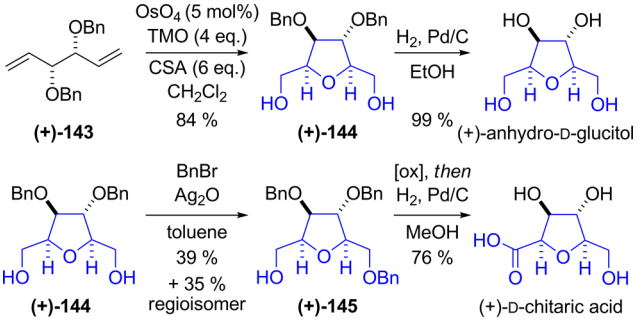


Figure 8. THF-containing natural products, and fragments, successfully prepared using oxidative cyclization.

Scheme 29. Synthesis of (+)-Anhydro-D-glucitol and (+)-D-Chitaric Acid



■ (+)-*CIS*-SOLAMIN

In 2005, we had demonstrated that chiral diols were suitable substrates to subject to the reaction conditions and this greatly expanded the diversity of motifs available. Natural products could potentially now be accessed as single enantiomers without having to rely on the substrate to direct the facial selectivity of the initial osmate ester formation. Diene **146** was prepared in four steps via a literature route. Following reduction to the alcohol, a Sharpless AD reaction furnished diol **147** with a high degree of both regio- and enantioselectivity. Oxidative cyclization of **147** proceeded in excellent yield to give THF **148**. Compound **148** could be almost quantitatively converted into tosylate **149**, an intermediate in Brown's synthesis of (+)-*cis*-solamin (which employed a permanganate oxidative cyclization),[55] thus completing a formal synthesis of this molecule (Scheme 30).[17] Stark has also more recently synthesized (+)-*cis*-solamin via a ruthenium-catalyzed oxidative cyclization.[56]

■ (+)-*CIS*-SYLVATICIN

A more challenging test for this new methodology was to determine whether it was possible to perform a double oxidative cyclization reaction to synthesize two THF rings in one reaction. In 2006, our group utilized this idea en route to (+)-*cis*-sylvaticin.[57] Commercially available tetradecatetraene **150** was converted into key oxidative cyclization precursor **151** in five steps. Although **150** was only available as a mixture of the *EE*, *EZ* and *ZZ* isomers, the inherent preference of the AD reaction for *trans* alkenes (over both *cis* and monosubstituted) meant that the desired isomer was the most reactive; the unwanted isomers could be separated chromatographically at a later stage. Importantly, the AD reaction gave high selectivity (>98% ee, >90% de) for the all *syn* isomer. The bisacetonide precursor **151** underwent double deprotection in situ under the

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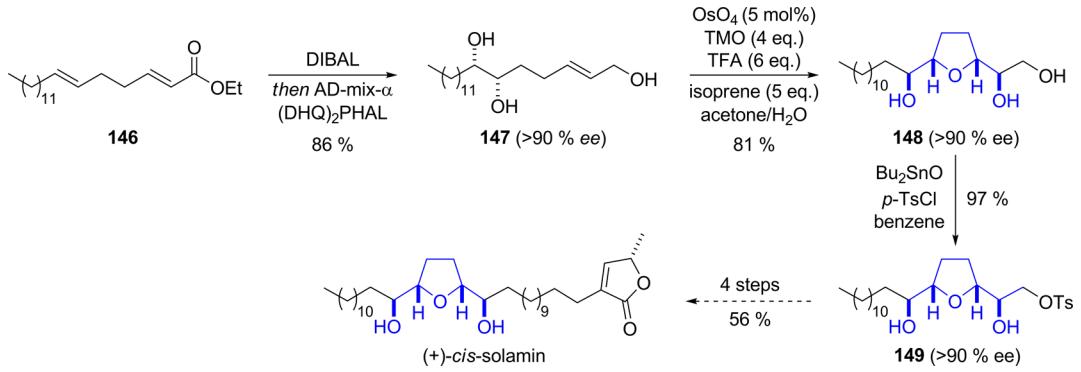
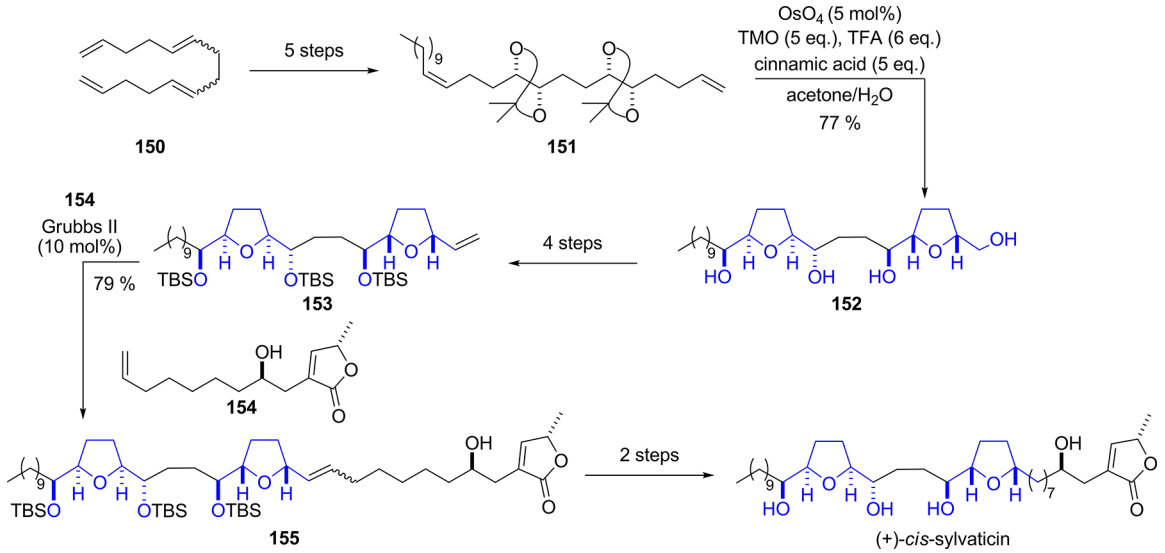
Scheme 30. Formal Synthesis of (+)-*cis*-Solamin



Scheme 31. Synthesis of (+)-*cis*-Sylvaticin



oxidative cyclization reaction conditions and bis-THF **152** was furnished as a single diastereoisomer in 77% yield, meaning two new rings were formed and three new stereogenic centers were set in one operation. In four further steps compound **152** was converted to intermediate **153**, which was subjected to a cross metathesis with alkene **154** to attach the butenolide fragment. A further two transformations then delivered (+)-*cis*-sylvaticin (Scheme 31).

■ (+)-SYLVATICIN

In 2009, we also disclosed the first total synthesis of (+)-sylvaticin, a natural product epimeric to (+)-*cis*-sylvaticin at the C-12 position.[58] The *trans*-THF ring in (+)-sylvaticin required some alterations to the synthetic approach. Diene **150** was converted to a more elaborate oxidative cyclization precursor **156** in eight steps. The use of our newly developed Lewis acidic oxidative cyclization conditions was crucial at this stage, as they were able to cleave the bis acetonide in situ, while the pH was high enough to allow the PMB group to be retained in the cyclization conditions. Cyclization to produce bis THF **157** proceeded in 76% yield, but due to the nature of the oxidative cyclization reaction, the C-12 stereocenter had the opposite configuration to that of the target, (+)-sylvaticin. However, we had planned to use other recently developed methodology in the Donohoe group in this regard.[59] Compound **157** was converted in five steps to **158**, a precursor for our hydride shift methodology. Treatment of **158** with zinc acetate in hexafluoroisopropanol led to an intramolecular hydride shift to expel the mesylate leaving group and generate oxocarbenium ion **159**. Hydride was then transferred intramolecularly to the lower face of this oxocarbenium ion from the appended silyl hydride to furnish *trans*-THF **160**. The remaining hydroxyl groups were then reprotected as their TBS ethers prior to a cross metathesis to attach the butenolide fragment **161** to give **162**. A further two steps then yielded (+)-sylvaticin (Scheme 32).

■ (−)-NEODYSIHERBAINE A

In 2011, we again utilized the Lewis acidic cyclization conditions en route to (−)-neodysiherbaine A.[60] Vinyl bromide **163** and alkyl iodide **164** (both obtained in one step from commercially available materials) were combined in a Negishi coupling, and the resulting product was treated with sodium methoxide in methanol to give oxidative cyclization precursor **165** in 79% yield over two steps. The ability of **165** to cyclize to **166** with complete stereochemical control was a rigorous test for the cyclization methodology given the bicyclic nature of the product formed, the presence of the acid sensitive NBoc group and *t*Bu ester and the potential of the triol to chelate to osmium in a number of modes. Gratifyingly, cyclization proceeded in 88% yield (**165** → **166**). Following this oxidative cyclization only three more steps (including an oxidation of the primary

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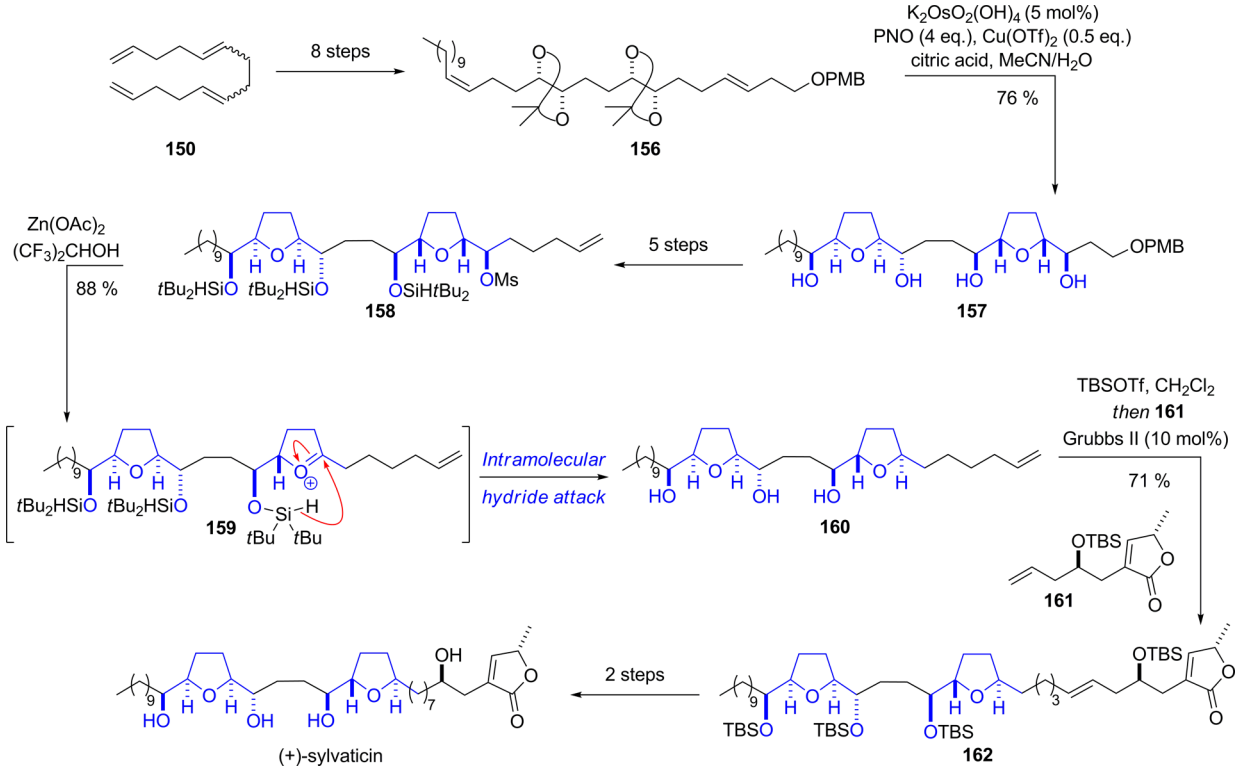
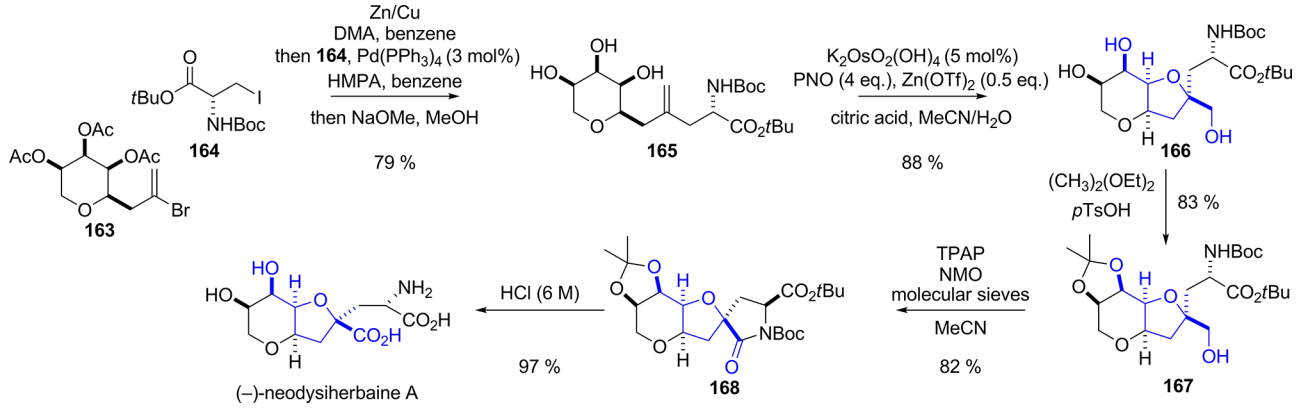
Scheme 32. Synthesis of (+)-Sylvaticin



Scheme 33. Synthesis of (−)-Neodysiherbaine A



alcohol produced during the cyclization) were needed to synthesize (−)-neodysiherbaine A (Scheme 33).

The synthesis of (−)-neodysiherbaine A, was completed in seven linear steps (eight steps in total) and in an excellent overall yield of 24%, clearly illustrating how powerful this reaction had become.

■ (+)-PECTENOTOXIN-4

In 2012, our group published the synthesis of the ABC fragment of (+)-pectenotoxin-4.[61] In this fragment of the macrolide both the B and C rings were constructed in one operation via two oxidative cyclization reactions in a cascade process, and then subsequently the A ring was installed utilizing hydride shift/spiroketalization methodology that had also been developed in our group. Whereas simultaneous double oxidative cyclizations had been accomplished in previous syntheses, in those cases the two cyclizations were essentially independent events within the same molecule. With the ABC fragment of (+)-pectenotoxin-4 a cascade cyclization was required, whereby the first oxidative cyclization (**172** → **173**) afforded the requisite diol needed to chelate to osmium and promote the second cyclization (**173** → **174**) (Scheme 34). The synthesis of (+)-pectenotoxin-4 began with the combination of aldehyde **169** and alkyne **170** (available from commercial precursors in four and three steps, respectively) in a Carreira reaction. This proceeded with high stereoselectivity (dr 96:4) to furnish intermediate **171** in 54% yield. A Ready methylation followed by a deprotection using TBAF then delivered key oxidative cyclization precursor **172**. Subjecting **172** to the buffered cyclization conditions at a slightly elevated temperature of 80 °C led to the cascade oxidative cyclization reaction. The vicinal diol in **172** presumably chelated to Os^{VI} and first cyclized to deliver the C ring. The hydroxyl group added by the first cyclization in **173** now meant that there was a diol appropriately placed relative to the second double bond for a further cyclization to ensue.

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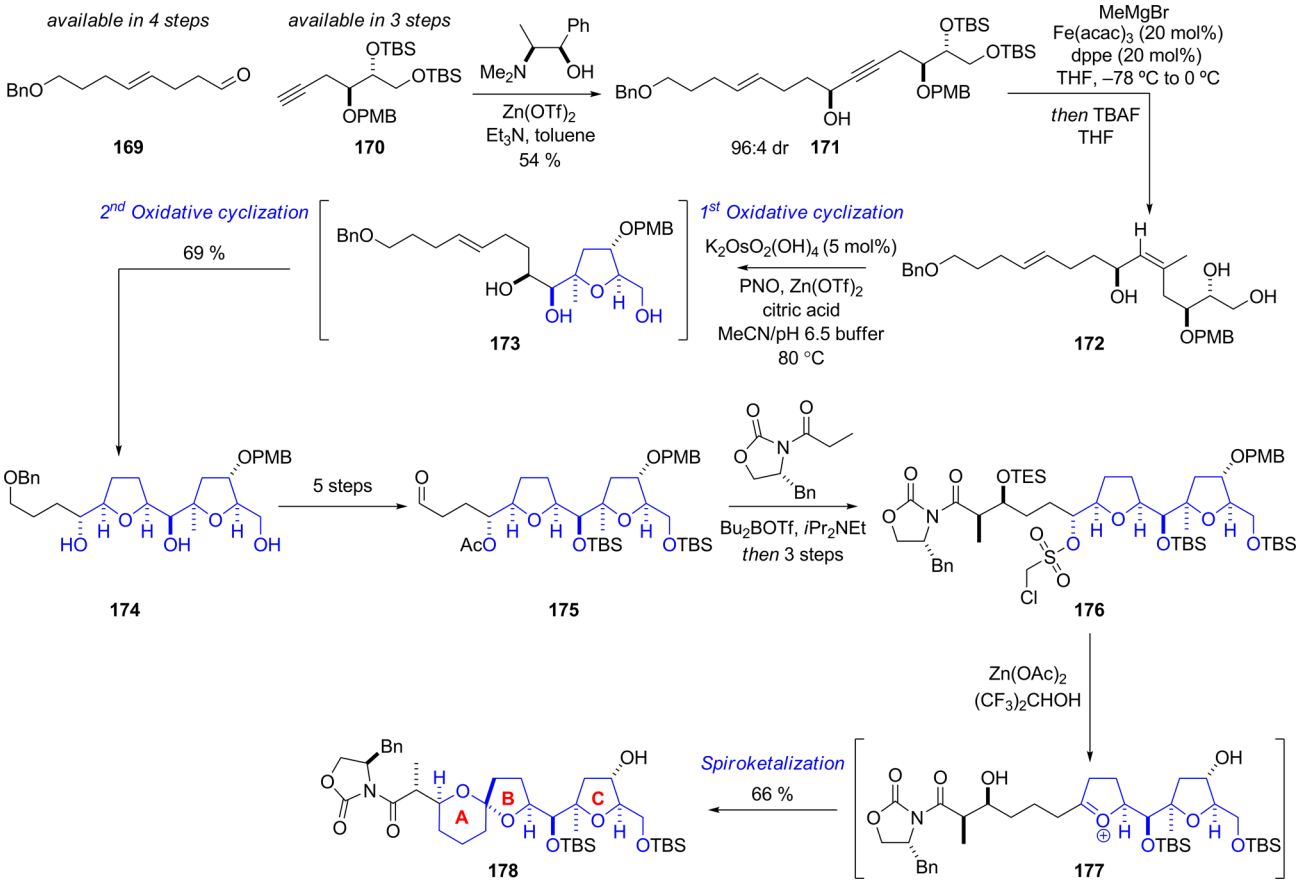
Scheme 34. Synthesis of the ABC Ring Fragment of (+)-Pectenotoxin-4



Compound **173** was not characterized or isolated but a compound presumed to be **173** was observed by TLC analysis of the reaction mixture. It is not known in general whether the same osmium atom catalyzes both cyclizations in one substrate molecule via reoxidation after the first reaction and then translocation on to the newly created vicinal diol or whether all double cyclizations proceed via the osmium-free species **173**. After the second cyclization to give **174**, two new rings and four new stereogenic centers had been created in one operation. Following protecting group manipulation and oxidation to **175**, an Evans aldol reaction was employed to attach the remainder of the fragment. Three further steps, including the addition of a key α-chloromesylate leaving group, gave precursor **176** for our hydride shift/spiroketalization methodology. Treatment of **176** with zinc acetate in hexafluoroisopropanol led to an intramolecular hydride shift to expel the chloromesylate leaving group, with the resulting cation **177** being stabilized by the neighboring oxygen lone pair. The pendant TES-protected hydroxyl group, having been deprotected under the reaction conditions, subsequently trapped out cation **177** to give **178**, the ABC fragment of (+)-pectenotoxin-4.

This success in these syntheses was hard to imagine when we embarked upon our study into this reaction just over a decade ago. The ability to rapidly generate molecular complexity in one operation, and to set multiple stereocenters with high levels of both stereospecifity and stereoselectivity, together with the now much milder and safer reaction conditions makes this reaction, in our opinion, an extremely useful part of any chemist's toolkit. We are currently applying this reaction to even more challenging synthetic endeavors within our laboratory, and we hope that after reading this Perspective, others may be inclined to do the same.

■ CONCLUSIONS

This Perspective has described the development of a novel catalytic process that enables the controlled synthesis of five-membered heterocycles. By continuously probing the details of the mechanism our work has uncovered a new and powerful set of cyclization conditions that could not have been envisaged at the start of our studies. The use of pyridine *N*-oxide to control the oxidation state of osmium, coupled with the addition of a Lewis acid promoter, has meant that a truly useful new synthetic reaction has been uncovered. Of course, the best test of a new synthetic method is to apply it in total synthesis, and in this regard we have probed the limits of the cyclization with applications in the syntheses of several complex natural products. The satisfaction gained from completing a successful (i.e., short and efficient) synthesis using a newly developed method helps to drive the search for yet more powerful and useful methodology, especially that based around catalysis.

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Notes

The authors declare no competing financial interest.

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Biographies

Timothy J. Donohoe completed his BSc at the University of Bath and his DPhil at the University of Oxford before undertaking a postdoctoral position with Prof. P. D. Magnus. He started his independent career at the University of Manchester in 1994. In 2001, he moved to the University of Oxford, being promoted to Professor in 2004. His research interests include total synthesis, the synthesis of both aromatic and saturated heterocycles, and catalysis and redox reactions.

Ben S. Pilgrim obtained his MChem from the University of Oxford in 2009, undertaking his final year research project in the laboratory of Prof. Timothy J. Donohoe on the osmium-catalyzed oxidative cyclization reaction. Ben remained in the Donohoe group at Oxford University for his DPhil studies, which he is due to complete in 2013.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) Piccialli, V. *Synthesis* **2007**, *2007*, 2585.
(2) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353.
(3) Baldwin, J. E.; Crossley, M. J.; Lehtonen, E.-M. M. *J. Chem. Soc., Chem. Commun.* **1979**, 918.
(4) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396.
(5) Wolfe, S.; Ingold, C. F.; Lemieux, R. U. *J. Am. Chem. Soc.* **1981**, *103*, 938.
(6) Lee, D. G.; Brownridge, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 3033.
(7) Houk, K. N.; Strassner, T. *J. Org. Chem.* **1999**, *64*, 800.
(8) de Champdoré, M.; Lasalvia, M.; Piccialli, V. *Tetrahedron Lett.* **1998**, *39*, 9781.
(9) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.
(10) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.
(11) Donohoe, T. J.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *Tetrahedron Lett.* **2001**, *42*, 971.
(12) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385.
(13) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 948.
(14) Domingo, Luis R. *Eur. J. Org. Chem.* **2000**, *2000*, 2265.
(15) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(16) Ragazzo, J. A.; Behrman, E. J. *Bioinorg. Chem.* **1976**, *5*, 343.
(17) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766.
(18) Donohoe, T. J.; Churchill, G. H.; Wheelhouse, K. M. P.; Glossop, P. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 8025.
(19) Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628.
(20) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*; Elsevier: New York, 1998; p 1077.
(21) Donohoe, T. J.; Wheelhouse, K. M. P.; Lindsay-Scott, P. J.; Glossop, P. A.; Nash, I. A.; Parker, J. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2872.
(22) Wu, P.; Hilgraf, R.; Fokin, V. V. *Adv. Synth. Catal.* **2006**, *348*, 1079.
(23) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421.
(24) Muldoon, J.; Brown, S. N. *Org. Lett.* **2002**, *4*, 1043.
(25) Poethig, A.; Strassner, T. *J. Org. Chem.* **2010**, *75*, 1967.
(26) Sugimoto, H.; Kitayama, K.; Mori, S.; Itoh, S. *J. Am. Chem. Soc.* **2012**, *134*, 19270.
(27) Donohoe, T. J.; Winship, P. C. M.; Walter, D. S. *J. Org. Chem.* **2009**, *74*, 6394.
(28) Oral toxicity data is readily available from most common chemical suppliers. This information was gathered from Merck and Fischer Scientific.
(29) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726.
(30) Donohoe, T. J.; Winship, P. C. M.; Pilgrim, B. S.; Walter, D. S.; Callens, C. K. A. *Chem. Commun.* **2010**, *46*, 7310.
(31) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317.
(32) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028.
(33) Donohoe, T. J.; Wheelhouse, K. M. P.; Lindsay-Scott, P. J.; Churchill, G. H.; Connolly, M. J.; Butterworth, S.; Glossop, P. A. *Chem.—Asian J.* **2009**, *4*, 1237.
(34) Hancock, R. D. *J. Chem. Educ.* **1992**, *69*, 615.
(35) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299.
(36) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303.
(37) McDonald, F. E.; Singhi, A. D. *Tetrahedron Lett.* **1997**, *38*, 7683.
(38) Kennedy, R. M.; Tang, S. *Tetrahedron Lett.* **1992**, *33*, 3729.
(39) Cecil, A. R. L.; Brown, R. C. D. *Tetrahedron Lett.* **2004**, *45*, 7269.
(40) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995**, *60*, 5750.
(41) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022.
(42) Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc.* **1998**, *120*, 1633.
(43) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(44) Piccialli, V.; Cavallo, N. *Tetrahedron Lett.* **2001**, *42*, 4695.
(45) Albarella, L.; Musumeci, D.; Sica, D. *Eur. J. Org. Chem.* **2001**, *2001*, 997.
(46) Roth, S.; Göhler, S.; Cheng, H.; Stark, C. B. W. *Eur. J. Org. Chem.* **2005**, *2005*, 4109.

(47) Cheng, H.; Stark, C. B. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1587.
(48) Roth, S.; Stark, C. B. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6218.
(49) Piccialli, V. *Tetrahedron Lett.* **2000**, *41*, 3731.
(50) Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727.
(51) Hammock, B. D.; Gill, S. S.; Casida, J. E. *J. Agric. Food Chem.* **1974**, *22*, 379.
(52) Travis, B.; Borhan, B. *Tetrahedron Lett.* **2001**, *42*, 7741.
(53) Donohoe, T. J.; Lindsay-Scott, P. J.; Parker, J. S.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 1060.
(54) Donohoe, T. J.; Pullin, R. D. C. *Chem. Commun.* **2012**, *48*, 11924.
(55) Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368.
(56) Göksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433.
(57) Donohoe, T. J.; Harris, R. M.; Burrows, J.; Parker, J. *J. Am. Chem. Soc.* **2006**, *128*, 13704.
(58) Donohoe, T. J.; Harris, R. M.; Williams, O.; Hargaden, G. i. C.; Burrows, J.; Parker, J. *J. Am. Chem. Soc.* **2009**, *131*, 12854.
(59) Donohoe, T. J.; Williams, O.; Churchill, G. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2869.
(60) Donohoe, T. J.; Winship, P. C. M.; Tatton, M. R.; Szeto, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7604.
(61) Donohoe, T. J.; Lipinski, R. M. *Angew. Chem., Int. Ed.* **2013**, DOI: 10.1002/anie.201208919.