# A novel oxidative cyclisation onto vinyl silanes†

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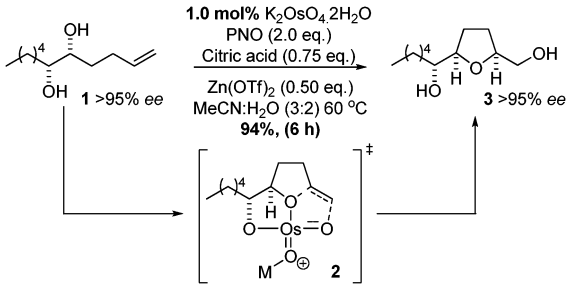
**A novel osmium-catalysed oxidative cyclisation of 1,2-diols bearing a pendant vinyl silane affords THFs that contain silicon functionality at the ring junction. When the cyclisation occurs onto a vinyl benzyldimethylsilyl group, the resulting silyl group can act as a masked hydroxyl group and undergo a Fleming–Tamao type oxidation at a later stage to form the corresponding lactol. The scope of this reaction can also be extended beyond 1,2-diols and applied to the cyclisation of α-hydroxy-sulfonamides and α-hydroxy-amides.**

We have previously shown that vicinal diols and amino alcohols derived from 1,5-dienes will cyclise in the presence of a catalytic amount of osmium to form 2,5-*cis*-THFs and pyrrolidines with excellent stereoselectivity.[1,2] This oxidative cyclisation required an acid and a catalytic amount of Os(VI), which was provided by the *in situ* dihydroxylation of a "sacrificial alkene" (usually *trans*-cinnamic acid) by Os(VIII).

Recently this process was improved significantly by the introduction of pyridine-*N*-oxide (PNO) as a reoxidant capable of oxidizing Os(IV) to Os(VI) but not to unwanted Os(VIII), thus eliminating the need for a sacrificial alkene.[3] It was also found that the addition of a catalytic amount of citric acid further improved the reaction, presumably by stabilizing Os(VI) with respect to disproportionation in acidic media.[4]

More recently, it was discovered that replacing the Brønsted acid promoter with a catalytic amount of Lewis acid [either $Zn(OTf)_2$ or $Cu(OTf)_2$] resulted in higher yielding reactions that proceeded nearly an order of magnitude faster than before (Scheme 1).[5] Under these improved conditions, the osmium loading could be reduced to as little as 0.2 mol%. Furthermore, these mildly acidic cyclisation reactions were found to tolerate a range of acid sensitive functional groups when a pH 6.5 phosphate buffer was incorporated. Under these conditions, methoxymethyl ether (MOM), *p*-methoxy-benzyl (PMB) and *tert*-butyl dimethyl silyl (TBS) protected primary alcohols, and *tert*-butyl carbamate (Boc) protected amines remained intact throughout the cyclisation.

Attention turned to the possibility of performing the cyclisation onto heteroatom-substituted pendant alkenes that would have been unstable under previous acidic cyclisation conditions. It is proposed that one of the key components of

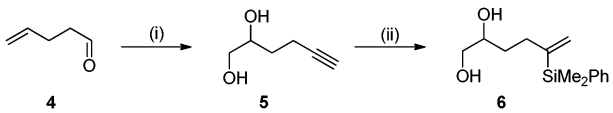



**Scheme 1** The osmium-catalysed oxidative cyclisation under Lewis acid conditions.

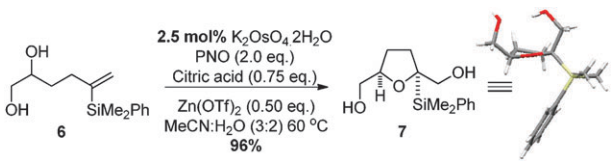
the osmium-catalysed oxidative cyclisation is an inverse electron demand [4 + 2] cycloaddition between the osmate ester, and the pendant alkene (Scheme 1, transition structure **2**).[6] Consequently it was predicted that vinyl silanes, despite an increase in steric bulk would provide sufficiently electron-rich π-bonds to enable a successful oxidative cyclisation. Pleasingly, we can report herein that a range of vinyl silanes will undergo the osmium-catalysed oxidative cyclisation to form the corresponding silyl substituted *cis*-THFs.[7]

Our initial investigations concentrated on the cyclisation of terminal vinyl silane **6**. This substrate was easily accessible by the sequential dihydroxylation of commercially available 4-pentenal followed by subsequent Seyferth–Gilbert homologation using the Bestmann–Ohira reagent (Scheme 2). Regioselective hydrosilylation of the resulting terminal alkyne furnished cyclisation precursor **6**.[8]

Oxidative cyclisation of **6** using the recently-developed Lewis acid conditions furnished the corresponding THF **7** in 96% yield (Scheme 3).§




**Scheme 2** Synthesis of a cyclisation precursor. *Reagents and conditions*: (i) $OsO_4$ (5.0 mol%), NMO, $H_2O$/THF/$^t$BuOH (1 : 10 : 8), rt, then $H_3CCOC(N_2)PO(OEt)_2$, $K_2CO_3$, MeOH, rt, 66% (over 2 steps); (ii) Cp*Ru$(MeCN)_3PF_6$ (2.0 mol%), $HSiMe_2Ph$, $CH_2Cl_2$, 0 °C to rt, 86%.




**Scheme 3** Novel oxidative cyclisation onto a heteroatom-substituted alkene.

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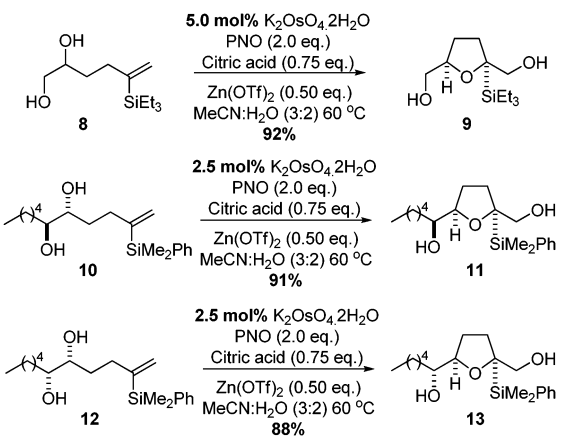
The *cis* 2,5-relationship was proven by X-ray crystal structure analysis, which is consistent with the hypothesised chelated transition structure **2** (Scheme 1).[7,9] To our knowledge, this is the first reported example of an oxidative cyclisation onto a heteroatom-substituted alkene promoted by a metal–oxo species. Attempts to apply previous cyclisation conditions to the cyclisation of **6** [5.0 mol% $K_2OsO_4{\cdot}2H_2O$, PNO, citric acid, acetone : water : trifluoroacetic acid (9 : 1 : 5)], reduced the yield to 61%.

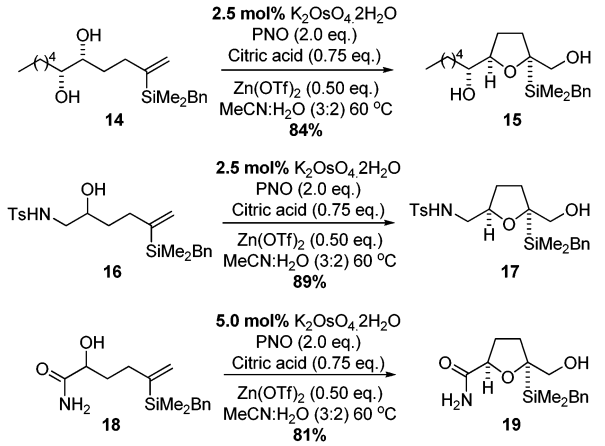
Using an analogous approach to that shown in Scheme 2, a range of vinyl silanes were synthesised in 3 steps from commercially available 4-enals (Scheme 4). Upon subjection of these vinyl silanes to Lewis acid cyclisation conditions, THFs **9**, **11** and **13** were formed in excellent yields. Again, the resulting THFs exhibited a *cis* 2,5-relationship as expected.[10]

The application of organosilanes as masked hydroxyl groups has been widely reported in recent years.[11] However, our attempted oxidations of the 2-dimethylphenylsilyl THFs were unsuccessful under Fleming–Tamao conditions, resulting in either no reaction or over-oxidation to a lactone.[12] At this point, our attention turned to the cyclisation of vinyl silanes bearing a benzyldimethylsilyl group which can be readily oxidised using mild conditions.[13] This transformation would enable the silyl-substituted THFs formed in the oxidative cyclisation to act as masked lactols. With this in mind, vinyl benzyldimethylsilanes with different cyclisation initiators were synthesised from the corresponding terminal alkynes [with $Cp^*Ru(MeCN)_3PF_6$, $HSiBnMe_2$, $CH_2Cl_2$]. Pleasingly, 1,2-diol **14**, α-hydroxy sulfonamide **16** and α-hydroxy amide **18** all cyclised onto the vinyl benzyldimethylsilane in excellent yields (Scheme 5).[10]

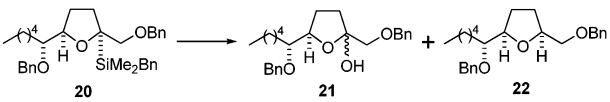
Initial attempts to oxidise **15** using standard Fleming–Tamao conditions resulted in immediate protodesilylation (with retention) following the addition of tetrabutylammonium fluoride (TBAF); this process afforded the corresponding 2,5-*cis*-THF in 78% yield.[14] We propose that this unusually fast rate of protodesilylation occurs due to the α-hydroxyl group acting as either an intramolecular nucleophile for silicon or a proton source. Therefore, it was found that subjecting benzyl-protected THF **20** to the same Fleming–Tamao conditions (the addition of tetrabutylammonium fluoride, followed by aqueous hydrogen peroxide) led to the formation of the




**Scheme 4** Cyclisations of a range of vinyl silanes.




**Scheme 5** Cyclisation of different initiators.




**Scheme 6** Fleming–Tamao oxidation of protected THF.

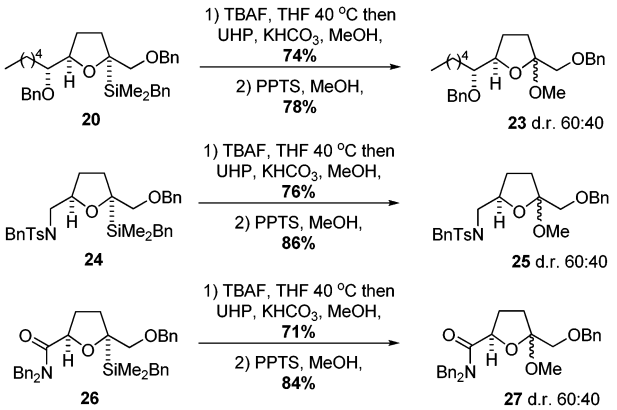
expected lactol **21** as a mixture of isomers (Scheme 6).[15] Despite this initial success, significant amounts of protodesilylation product **22** were still observed. In order to suppress this side reaction, we adapted an approach originally reported by Trost *et al.*, whereby tetrabutylammonium fluoride was added *via* syringe pump in order to maintain a low fluoride concentration. This slow addition protocol, in combination with anhydrous urea–hydrogen peroxide (UHP) led to the formation of **21** in good yield (Table 1). Crucially, smaller amounts of protodesilylation were observed.

With these optimised conditions available, oxidation of the benzyl protected THFs **24** and **26** also provided the corresponding lactols as mixtures of cyclic and open chain isomers. Pleasingly, treatment of the lactol intermediates with PPTS in $MeOH/CH_2Cl_2$ furnished the desired lactol ethers in good yields as a mixture of diastereomers (Scheme 7).

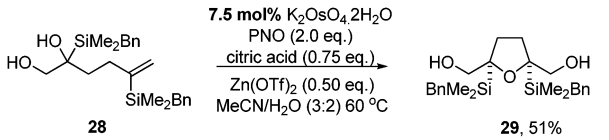
An alternative approach to the formation of silyl-substituted THFs was to dihydroxylate a vinyl silane precursor followed by oxidative cyclisation onto a pendant alkene. This approach was taken with diol **28** which was formed by doubly hydrosilylating commercially available 1,5-hexadiyne [with $Cp^*Ru(MeCN)_3PF_6$, $HSiBnMe_2$, $CH_2Cl_2$], followed by mono-dihydroxylation of the resulting diene [with $OsO_4$ (5.0 mol%), 4-methylmorpholine *N*-oxide, water/tetrahydrofuran/*tert*-butanol (1 : 10 : 8)]. In this case, the pendant alkene is also a vinyl silane and the pseudo-*trans*-diaxial steric interaction between the two benzyldimethylsilyl groups during cyclisation might be expected to be unfavourable. Consequently, it was unclear whether this interaction would cause the osmium-mediated oxidative cyclisation to deviate from consistently forming THFs with *cis*-selectivity or supress the cyclisation altogether. Using a slightly higher catalyst loading, diol **28** was subject to standard cyclisation conditions and furnished THF **29** in 51% yield after 24 h (Scheme 8). The relative stereochemistry of the benzyldimethylsilyl groups was proven to be *cis* by NOE enhancements on the corresponding mono-acetate.

**Table 1** Optimisation of the Fleming–Tamao oxidation

| Entry | Reagents and conditions | Yield of **21** (%) | Yield of **22**[16] (%) |
|---|---|---|---|
| 1 | TBAF, THF, 40 °C, 0.5 h, then $H_2O_2$, MeOH, $KHCO_3$, 40 °C, 1 h | 43 | 32 |
| 2 | TBAF, THF, 40 °C, 0.5 h then UHP, MeOH, $KHCO_3$, 40 °C, 1 h | 64 | 24 |
| 3 | TBAF (over 30 min) THF, 40 °C, then UHP, MeOH, $KHCO_3$, 40 °C, 1 h | 74 | 15 |




**Scheme 7** Oxidation of the benzyldimethylsilyl group.




**Scheme 8** Double-silyl cyclisation.

This result further demonstrates the stereochemical rigidity of the osmium-mediated oxidative cyclisation.

To conclude, we have extended the scope of the osmium-mediated oxidative cyclisation by performing the first such cyclisations by metal–oxo species onto heteroatom-substituted alkenes. This process is stereoselective for the formation of silyl-substituted *cis*-THFs and proceeds with excellent yields. We have also demonstrated the potential of benzyldimethylsilyl-substituted THFs to act as masked lactols, which can be oxidised under mild conditions at a later stage. Furthermore, this methodology can be applied beyond 1,2-diols as cyclisation initiators and has been extended to both α-hydroxy-sulfonamides and α-hydroxy-amides.

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## Notes and references

§ *General experimental procedure*: Potassium osmate dihydrate (mol% as specified) was added to a solution of the cyclisation substrate (1.0 eq.), PNO (2.0 eq.), citric acid (0.75 eq.) and zinc triflate (0.50 eq.) in $MeCN/H_2O$ (3 : 2, 20 mL per mmol substrate) and the resulting mixture was stirred at 60 °C until the reaction had gone to completion by TLC. The reaction was quenched with $Na_2SO_3$ (0.1 g) and after 30 minutes, water (20 mL) was added. The mixture was extracted with EtOAc (3 × 25 mL) and washed with brine (20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent removed *in vacuo* to give the crude product which was purified by flash column chromatography.

1 (*a*) T. J. Donohoe and S. Butterworth, *Angew. Chem., Int. Ed.*, 2005, **44**, 4766; (*b*) T. J. Donohoe, G. H. Churchill, K. M. P. Wheelhouse and P. A. Glossop, *Angew. Chem., Int. Ed.*, 2006, **45**, 8025.
2 This is in contrast to other metals where either stereoselectivity is lower or stoichiometric quantities of metal are required. For examples see: V. Piccialli, *Synthesis*, 2007, 2585–2607.
3 T. J. Donohoe, K. M. P. Wheelhouse, P. J. Lindsay-Scott, P. A. Glossop, I. A. Nash and J. S. Parker, *Angew. Chem., Int. Ed.*, 2008, **47**, 2872.
4 P. Dupau, R. Epple, A. A. Thomas, V. V. Fokin and K. B. Sharpless, *Adv. Synth. Catal.*, 2002, **344**, 421.
5 T. J. Donohoe, P. C. M. Winship and D. S. Walter, *J. Org. Chem.*, 2009, **74**, 6394.
6 For a related inverse electron demand cycloaddition see: L. Domingo, *Eur. J. Org. Chem.*, 2000, 2265–2272.
7 The THF products in this paper are referred to as *cis* based upon the relative stereochemistry of the two carbon substituents at C2 and C5. However, the mono-silyl-substituted THFs would be officially designated *trans* under IUPAC nomenclature guidelines.
8 B. M. Trost and Z. T. Ball, *J. Am. Chem. Soc.*, 2001, **123**, 12726.
9 X-Ray crystallography data are available in the ESI†.
10 In each case, the relative stereochemistry proven by NOE enhancements.
11 I. Fleming, R. Henning, D. C. Parker, H. E. Plaut and P. E. J. Sanderson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 317.
12 It is thought that the unexpected lactone product originates from a Baeyer–Villiger type oxidation of the intermediate lactol.
13 B. M. Trost, Z. T. Ball and K. M. Laemmerhold, *J. Am. Chem. Soc.*, 2005, **127**, 10028.
14 Protodesilylation of **15** gave a compound that was spectroscopically identical to **3**, formed previously from the cyclisation onto a terminal alkene (see ref. 5).
15 Acetylating the complex mixture of **21** provided the open chain ketone as a single compound in 98%.
16 Protodesilylation again occurred with retention of stereochemistry to afford a compound spectroscopically identical to the product obtained upon doubly benzylating compound **3**.

 