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Tandem catalysis in the polycyclisation of dienes to produce multi-substituted tetrahydrofurans

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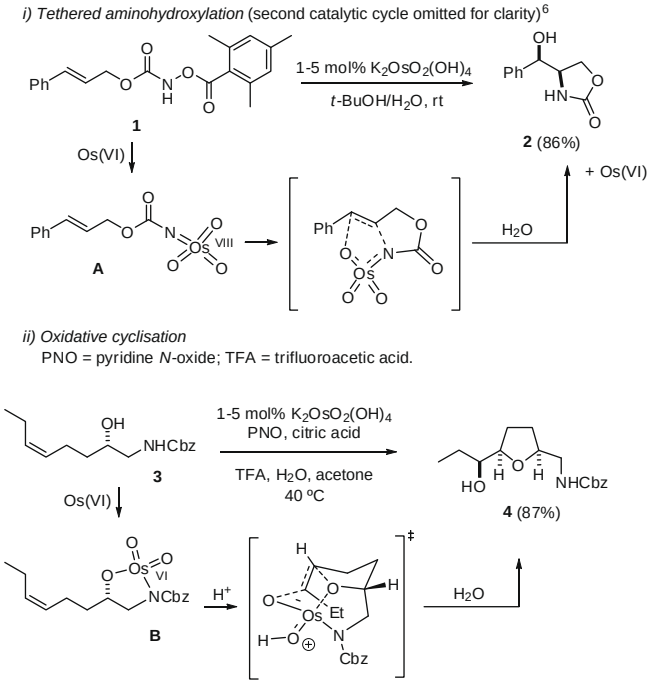
ABSTRACT

A new catalytic protocol has been established by using two separate oxidation reactions, catalysed by osmium, in tandem. Control of the pH and oxidation state of the metal is crucial in controlling this new sequence, which begins with a tethered aminohydroxylation reaction (Os(VIII) is active) and is followed by an oxidative cyclisation under acidic conditions (Os(VI) is active). The result of this work is an extremely quick route (five steps from commercially available materials) to complex THF rings containing an adjacent oxazolidinone and four new stereogenic centres.

In recent years, we have developed a research programme aimed at expanding the scope of osmium-catalysed oxidation procedures, most notably the addition of two heteroatoms across an alkene unit. There are two main strands to this work, which consist of the tethered aminohydroxylation (TA)[1] and oxidative cyclisation reactions, respectively.[2] In the TA reaction, a substrate based upon a carbamate is transformed into an imido-osmium(VIII) complex[3] which is then able to aminohydroxylate a proximal alkene, often with high regio- and stereoselectivity. Recent discoveries showed that the key to a successful TA reaction was to embed the reoxidant into the substrate in the form of an N–OCOAr carbamate (see **1**, Scheme 1).[4] The second string to this programme involves an oxidative cyclisation reaction promoted by osmium(VI), in which a metal-chelated diol, or amino alcohol, unit forms a THF ring when treated with acid: cyclisation shows stereoselectivity for cis-2,5-disubstituted rings and stereospecificity for *syn* addition across the alkene (see **4**). In this cyclisation, Os(VI) is the most active catalyst and the reduced osmium (presumably Os(IV)) can be re-oxidised to Os(VI) afterwards by the use of pyridine N-oxide (PNO).[5] In fact, the use of PNO is greatly beneficial for the yields because it does not over oxidise the osmium to Os(VIII) where it can dihydroxylate the alkene in the cyclisation substrate.

It became apparent that we might be able to couple these two oxidative processes in a tandem catalytic sequence,[7] starting with carbamate **C** and adding catalytic Os(VI). This should then be oxidised to the imido Os(VIII) **D** and then undergoe a TA reaction onto



Scheme 1. The osmium-catalyzed oxidation reactions. (See above-mentioned reference for further information.)

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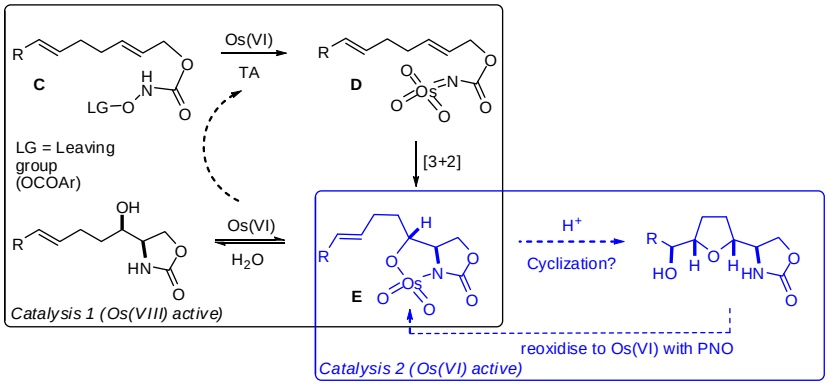
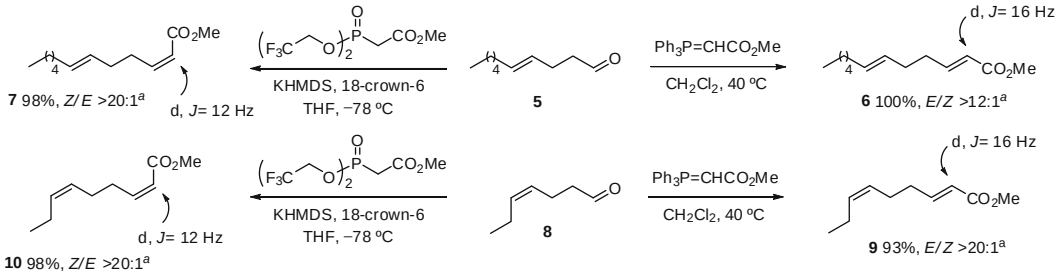
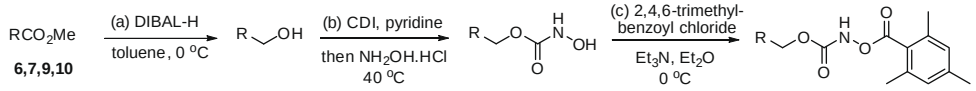
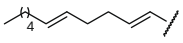
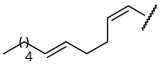
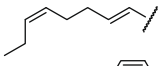
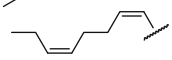


Scheme 2. Two catalytic reactions in one-pot.



Scheme 3. Stereocontrolled alkene synthesis. [a]Isomer ratios measured by ^{1}H NMR. KHMDS = potassium bis(trimethylsilyl)amide. *J* values for the methine proton adjacent to the ester groups are shown.



Entry	R =	Yield (step a) %	Yield (step b) %	Yield (step c) %
1		95	69 + 25 rsm	98 **11**
2		97	67 + 32 rsm	93 **12**
3		92	71 + 23 rsm	86 **13**
4		93	66 + 30 rsm	89 **14**

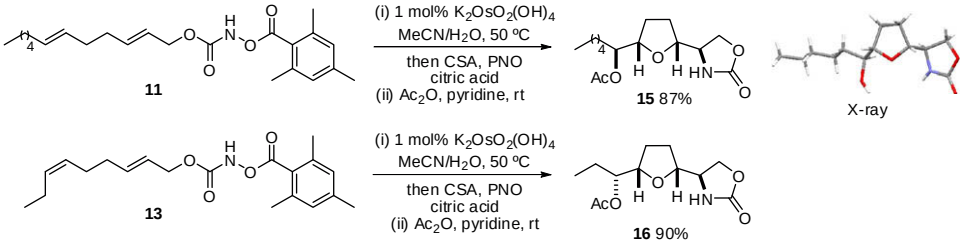
Scheme 4. Substrate synthesis. DIBAL-H = diisobutylaluminium hydride. rsm = recovered starting material.

the nearby alkene (and in doing so be reduced back down to Os(VI) ready for another TA reaction). Then, after the TA process was complete, acidification of the reaction mixture (the hydroxy-oxazolidinone should make an ideal chelating substrate for oxidative cyclisation) should facilitate the formation of a THF ring in the usual manner using the Os(VI) complex **E** formed from the initial TA reaction, Scheme 2. The addition of PNO here would be ideal as it acts as a re-oxidant that would not form Os(VIII) in situ and would reduce the amount of unwanted dihydroxylation of the alkene within the TA product. The result would be a one-pot formation of a THF with a pendant oxazolidinone and four new stereogenic centres.

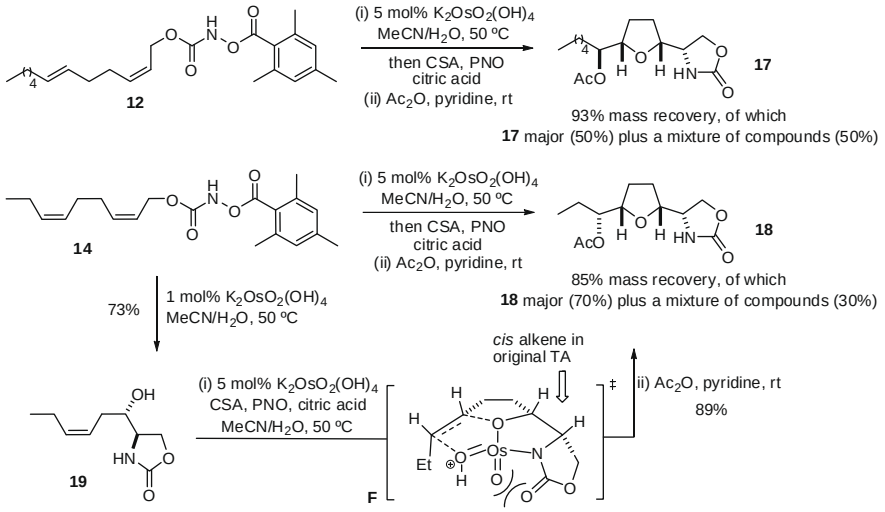
The project began with the synthesis of four stereochemically defined diene substrates on which we would test the idea of tandem catalysis using osmium; the diverse stereochemical array of substrates would allow us to probe the stereospecificity and stereoselectivity of this process at the same time. Consequently, commercially available alkene *E*-**5** was olefinated using a stabilised ylide or the Still-Gennari[8] reaction to provide *E,E*-**6** and *E,Z*-**7**, respectively, Scheme 3. A similar sequence, starting with commercial *Z*-**8** gave *Z,E*-**9** and *Z,Z*-**10** as expected.

Then, each ester was reduced to an allylic alcohol, which was then activated for the TA reaction by conversion into an N–OCOAr carbamate via a two-pot protocol, which involved formation of the N–OH carbamate followed by reaction with 2,4,6-trimethylbenzoyl chloride, Scheme 4.[4] In general, the yields for this procedure were good and enabled us to prepare reasonable quantities of the requisite starting materials **11**–**14**.

The stage was now set for the tandem TA/oxidative cyclisation reaction, which would be initiated by the addition of potassium osmate [$K_2OsO_2(OH)_4$] in aqueous acetonitrile, Scheme 5. Then, after the aminohydroxylation reaction was complete, the reaction was acidified (to encourage oxidative cyclisation) and pyridine N-oxide re-oxidant was added to allow the catalyst to turn over.[9] Examina-



Scheme 5. One-pot tethered aminohydroxylation/oxidative cyclisation. CSA = (±)-camphorsulfonic acid; Ac_2O = acetic anhydride.



Scheme 6. One-pot tethered aminohydroxylation/oxidative cyclisation. CSA = (±)-camphorsulfonic acid; Ac_2O = acetic anhydride.

tion of this sequence with substrates **11** and **13**, showed that the idea had worked as planned and the resulting oxazolidinone-substituted THF ring systems **15** and **16** were isolated in excellent yields, after acetylation of the crude reaction mixture;[10] both reactions proceeded well with 1% catalyst loadings. The stereoselectivity of the reaction was confirmed by X-ray crystal structure analysis of the alcohol derived from **15**,[11] which clearly showed double *syn*-addition across both alkenes. The other cyclisation product **16** was an oil and so the stereochemistry was assigned by analogy to **15** (note that there is substantial precedent for the *syn* stereospecificity of both the TA and oxidative cyclisation reactions and that the ^{1}H and ^{13}C NMR spectra of the two compounds were very similar).

Interestingly, the tandem TA/oxidative cyclisation reaction on substrates **12** and **14** was not as successful. We noted that the oxidative cyclisation (not TA) of both took much longer to reach completion and that consequently, higher catalyst loadings were required. After isolation, the THF products **17** and **18** were clearly contaminated with several other products, which had very similar NMR spectra to the parent compound and which were inseparable. In order to investigate further, we performed a TA reaction on substrate **14** and examined the subsequent product **19**, Scheme 6. NMR analysis of this compound showed that it consisted of only one diastereoisomer; therefore, this compound was re-subjected to the oxidative cyclisation reaction to yield the THF **18**, again formed as a mixture of compounds. This experiment reveals that the problematic step is oxidative cyclisation, and indeed examination of molecular models for the putative transition structure **F** reveals undue steric strain in the THF-forming reaction when the original alkene for the TA reaction was cis configured.

Unfortunately, it was not possible to determine the exact nature of the other products arising from cyclisation of **12** and **14**, however, we speculate that formation of *trans*-THFs originating from mono-dentate coordination of the initial TA product is the most likely possibility.[12] Indeed, in light of the lack of selectivity during oxidative cyclisation, the stereochemical assignments of **17** and **18**, shown as the major expected product, must remain tentative.

Therefore, the results illustrated in Scheme 5 show that the notion of a tandem TA reaction, followed by oxidative cyclisation is a valid one, capable of making heterocyclic THF compounds and four stereogenic centres with control of relative stereochemistry in just five steps from commercially available starting materials. The *syn* addition of both cyclisations, added to the predilection for forming *cis*-THF rings means that the stereochemistry of the THF product can be predicted with accuracy from that of the starting material. However, the sequence does not give clean diastereoisomers if the initial alkene for the TA reaction is cis-configured; steric strain in the transition structure is thought to be responsible for a less than completely selective oxidative cyclisation reaction. Control of the oxidation state of osmium is achieved throughout by the use of a substrate-derived re-oxidant for the TA and then PNO as a weak re-oxidant incapable of forming Os(VIII) during the oxidative cyclisation. It is hoped that the tandem catalytic cyclisation sequence described herein will find use in the synthesis of natural products.[13]

Acknowledgements

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9. *General procedure 1*: One-pot TA/oxidative cyclisation: potassium osmate dihydrate (0.01 equiv) was added to a solution of the hydroxamic ester (1 equiv) in a 3:1 mixture of acetonitrile–water (20 mL per mmol substrate) and the reaction mixture stirred at 50 °C for 2 h. (±)-Camphor-10-sulfonic acid (6 equiv), pyridine N-oxide (2 equiv) and citric acid (0.75 equiv) were added and the reaction mixture stirred at 50 °C for a further 16 h. The reaction was quenched by addition of solid sodium sulfite (10 mg), stirred for 30 min, washed with aqueous 2 M sodium hydroxide (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The residue was dissolved in pyridine (1 mL) and acetic anhydride (1 mL) and the resultant mixture stirred at room temperature for 16 h. The reaction mixture was concentrated and the crude product purified by flash column chromatography. The beneficial effect of citric acid on osmium-catalysed processes has been documented; see Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421.
10. *Data for compound* **15**: hydroxamic ester **11** (111 mg, 0.286 mmol) was subjected to general procedure 1. Purification by flash column chromatography (SiO_2, eluting with 7:3 petrol/ethyl acetate, R_f 0.38 in ethyl acetate) gave *tetrahydrofuran* **15** (75 mg, 0.250 mmol, 87%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.92 (1H, s), 4.81 (1H, ddd, *J* 8.6, 6.3, 4.6 Hz), 4.38 (1H, t, *J* 8.7 Hz), 4.02 (1H, dd, *J* 9.0, 5.2 Hz), 3.99–3.94 (1H, m), 3.92–3.87 (1H, m), 3.72 (1H, td, *J* 8.5, 5.2 Hz), 2.09 (3H, s), 2.04–1.96 (2H, m), 1.65–1.47 (4H, m), 1.33–1.21 (6H, m), 0.86 (3H, t, *J* 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 159.1, 81.0, 80.8, 75.9, 66.3, 56.1, 31.6, 30.9, 27.6, 27.6, 24.9, 22.5, 21.3, 14.0; ν_{max} (thin film)/cm^{-1} 3287, 2955, 2931, 2861, 1758, 1466, 1408, 1374, 1243, 1126, 1058, 1026, 946, 922; *m/z* (ESI$^+$) 358 (100%, $[M+NH_4+MeCN]^+$); HMRS (ESI$^+$) $C_{15}H_{25}O_5NNa$ requires $[M+Na]^+$ 322.1630, found 322.1641 (2.5 ppm).
Data for compound **16**: hydroxamic ester **13** (135 mg, 0.391 mmol) was subjected to general procedure 1. Purification by flash column chromatography (SiO_2, eluting with 7:3 petrol/ethyl acetate, R_f 0.30 in ethyl acetate) gave *tetrahydrofuran* **16** (90 mg, 0.350 mmol, 90%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.06 (1H, s), 4.89–4.85 (1H, m), 4.41 (1H, t, *J* 8.8 Hz), 4.08 (1H, dd, *J* 8.9, 5.5 Hz), 4.00–3.96 (1H, m), 3.92–3.86 (1H, m), 3.76–3.70 (1H, m), 2.06 (3H, s), 2.01–1.93 (2H, m), 1.84–1.75 (1H, m), 1.67–1.50 (3H, m), 0.89 (3H, t, *J* 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 159.4, 80.8, 80.4, 75.5, 66.4, 56.2, 26.9, 26.6, 24.0, 21.1, 9.7; ν_{max} (thin film)/cm^{-1} 3286, 2970, 1749, 1411, 1373, 1240, 1080, 1023, 963, 925; *m/z* (ESI$^+$) 258 (60%, $[M+H]^+$), 532 (90%, $[2M+NH_4]^+$), 537 (100%, $[2M+Na]^+$); HMRS (ESI$^+$) $C_{12}H_{19}O_5NNa$ requires $[M+Na]^+$ 280.1155, found 280.1155 (0.08 ppm).
11. Data were collected at low temperature using an Enraf-Nonius KCCD diffractometer [Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode, In *Methods Enzymol.* Carter, C. W., Sweet, R. M., Eds.; Academic Press, 1997, Vol. 276.]. The Crystal structures were solved using SIR92 [Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M.C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.] and refined using the CRYSTALS software suite [Betteridge, P.W.; Carruthers, J.R.; Cooper, R.I.; Prout, K.; Watkin, D.J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.], as per the CIF. Crystallographic data (excluding structure factors) for this compound have been deposited with the Cambridge Crystallographic Data Centre (CCDC 721466) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
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