Synthetic Methods

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Stereoselective Synthesis of Pyrrolidines: Catalytic Oxidative Cyclizations Mediated by Osmium**

Timothy J. Donohoe, Gwydion H. Churchill, Katherine M. P. Wheelhouse (née Gosby), and Paul A. Glossop*

Since its discovery by Klein and Rojahn in 1965, the oxidative cyclization of 1,5-dienes to give 2,5-disubstituted tetrahydrofurans has received a considerable amount of attention with a number of metal oxo species now capable of accomplishing this transformation.[1] We have recently developed the use of catalytic OsO_4 under acidic conditions to give *cis*-tetrahydrofurans (THFs) in high yields.[2] Attempts to induce asymmetric induction in this reaction with the addition of chiral amine ligands failed, presumably owing to the low pH of the reaction. However, we subsequently reported that vicinal diols derived from 1,5-dienes undergo cyclization in a regio- and stereoselective manner to give *cis*-THFs under conditions comparable to diene cyclization (Scheme 1).[3] We have evidence to suggest that Os complexes to the diol (chelation is essential) before perfoming an intramolecular, and stereo-

[*] Prof. T. J. Donohoe, Dr. G. H. Churchill, K. M. P. Wheelhouse (née Gosby)
Department of Chemistry
University of Oxford
Chemistry Research Laboratory
Mansfield Road, Oxford OX1 3TA (UK)
Fax: (+44) 1865-275-708
E-mail: timothy.donohoe@chem.ox.ac.uk
Homepage:
http://www.chem.ox.ac.uk/researchguide/tjdonohoe.html
P. A. Glossop
Pfizer Global R&D
Pfizer Limited
Ramsgate Road, Sandwich, Kent CT13 9NJ (UK)

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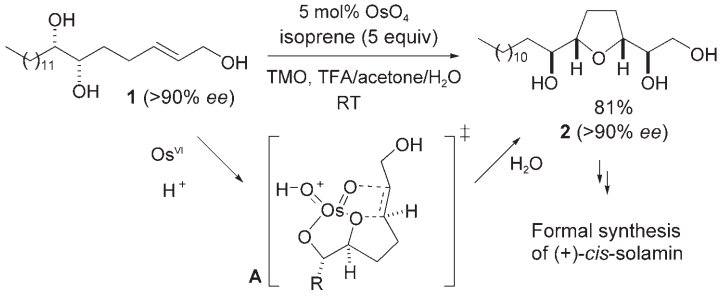


Scheme 1. Stereoselective oxidative cyclization of diols. TMO = Me_3NO; TFA = trifluoroacetic acid.

specific, oxidation of the pendant alkene (**A**). Furthermore, there is no loss of stereochemical integrity during the cyclization, and enantiopure diols give enantiopure THFs; this methodology was then applied to a formal synthesis of (+)-*cis*-solamin.[3]

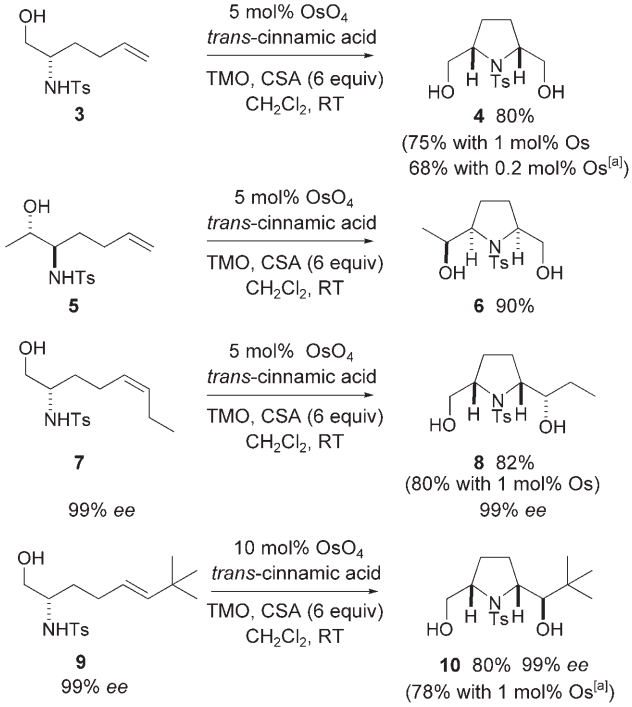
The results shown above extend the possibility to take this reaction in a fundamentally new direction and allow the formation of *nitrogen* heterocycles via oxidative cyclization of amino alcohols. Although the oxidative cyclization of 1,5-dienes has not been modified to form pyrrolidines, we chose to examine the cyclization of vicinal amino alcohols as our starting point.[4] Our rationale was that in synthesizing enantiopure amino alcohols separately, we would be able to obtain enantiopure pyrrolidines by oxidative cyclization. If successful, we would uncover a new catalytic reaction capable of making important heterocycles in a stereoselective fashion.[5]

Substrates **3**, **5**, **7**, **9** were readily prepared and subjected to the oxidation conditions;[6] pleasingly, *cis*-pyrrolidines **4**, **6**, **8**, **10** were formed in 80–90% yield (Scheme 2). The reaction is stereoselective, giving *cis*-pyrrolidines in all cases, and stereospecific (see oxidation of **7**, **9**). Moreover, the *syn* addition of nitrogen and oxygen atoms across the distal alkene was proven rigorously.[7]

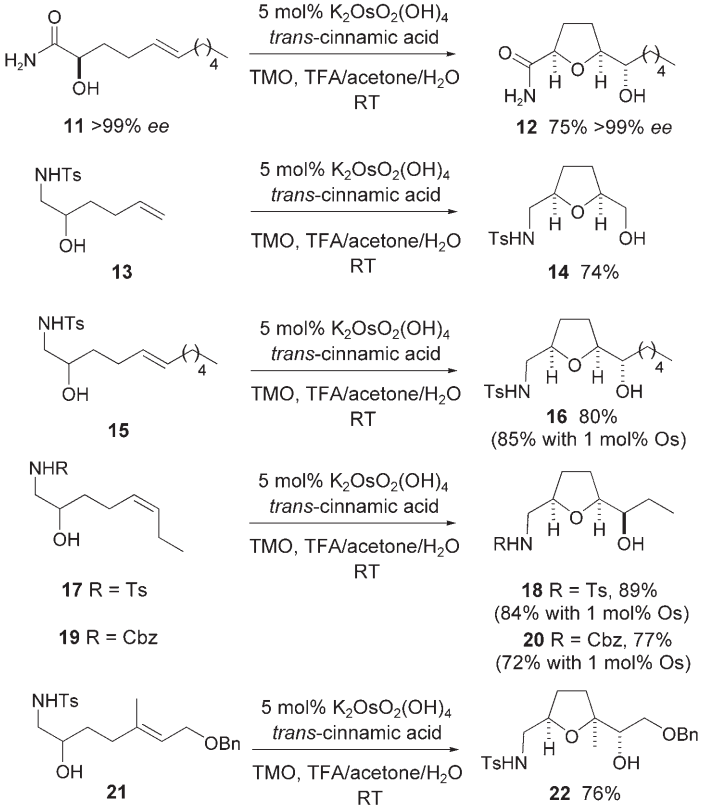
The cyclization of the sterically bulky alkene **9** to give **10** is also notable for its high yield. Catalyst loadings were successfully reduced to 1 mol% osmium (**4**, **8**, and **10**) and even as low as 0.2 mol% for **3**, giving compound **4** in 68% yield. Furthermore, we have applied these conditions to the cyclization of enantiopure starting materials (**7**, **9**)[6] without loss of enantiomeric purity during the reaction. Note that *trans*-cinnamic acid is added to these oxidations as a sacrificial alkene[3] and was found to be optimal for these transformations (see below).

The information detailed above reveals that the range of potentially chelating substrates that can undergo oxidative cyclization is large. We were intrigued by the possibility of subjecting other chelating derivatives to this procedure, to give differently substituted THFs.

Therefore, enantiopure hydroxy amide **11** was subjected to oxidative conditions and cyclized in high yield to give the amido THF **12** (Scheme 3).[8] This result



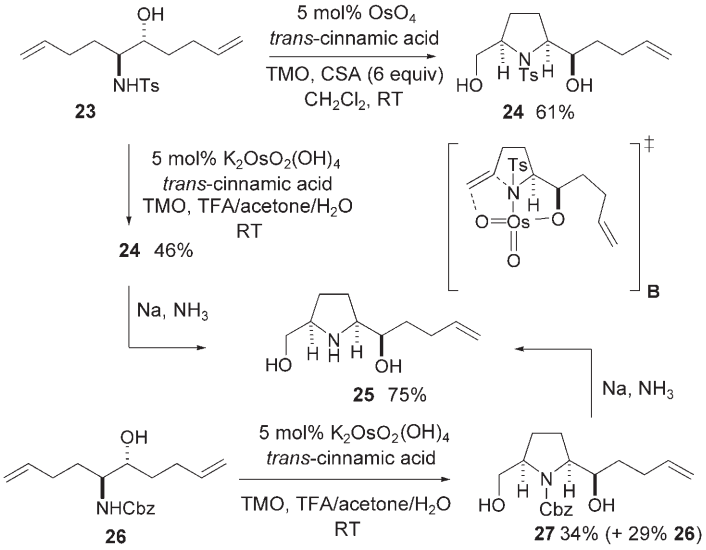
Scheme 2. Oxidative cyclization to form pyrrolidines. [a] Reactions carried out at 40 °C. Ts = toluene-4-sulfonyl; CSA = camphorsulfonic acid.



Scheme 3. Alternative chelating functionality for cyclization. Cbz = benzyloxycarbonyl; Bn = benzyl.

demonstrates the generality possible in the initiating functionality. Next, the amino alcohol substrates shown were subjected to oxidative cyclization to give *cis*-THFs in good to excellent yields. The stereospecific *syn* addition is exemplified by the stereochemistry of the products **16** and **18**.[7] The *N*-Ts group was found to be optimal for these cyclizations, although carbamates do cyclize, albeit in lower yields (see **19**).

We investigated the mechanism of cyclization by preparing the competition substrate **23** (Scheme 4), which bears the 1,2-hydroxysulfonamide functionality and two distal terminal alkenes. Oxidative cyclization of **23** should form an osmium chelate (see **B**),[4] and then cyclization will reveal a preference for formation of either N- or O-heterocycles. We also wished



Scheme 4. Mechanistic probes for pyrrolidine formation.

to examine the role of solvent on any competitive cyclization, and in this regard it is worth noting that formation of oxygen and nitrogen heterocycles works best in different solvents (compare Scheme 2 and Scheme 3).

When **23** was subjected to the OsO_4/CSA conditions, the *cis*-pyrrolidine **24** was formed in 61% yield. The structure of **24** was proven by X-ray crystallography and none of the corresponding THF was observed during this reaction. It was then anticipated that use of the $K_2OsO_2(OH)_4$/TFA conditions (that is, those which have proved optimal for the synthesis of THFs; see Scheme 3) would provide the THF congener of **24**. These conditions also returned the pyrrolidine **24**, but in a lower yield (46%). The carbamate derivative **26** proved completely inert to OsO_4/CSA conditions, but gave a low yield of the *cis*-pyrrolidine **27** when subjected to $K_2OsO_2(OH)_4$/TFA cyclization. These reactions serve to underline the overriding preference for cyclization to nitrogen-containing heterocycles over those containing oxygen, and provide further evidence for the enhanced participation of Os–N bonds over Os–O bonds whenever there is a choice.[9] The removal of N-protecting groups with Na in liquid NH_3 then established the formation of pyrrolidine **25** from both substrates **24** and **27**.

Examination of the reaction of **23** revealed interesting information about the nature of the catalyst involved in chelation and cyclization (Table 1). In entry 1 it is seen that stoichiometric Os^{VI} is capable of chelating and then cyclizing

Table 1: Reaction of **23** to give **24**.

Entry	Conditions	Yield of **24**
1	1 equiv $K_2OsO_2(OH)_4$, CSA, CH_2Cl_2	63%
2	1 equiv OsO_4, CSA, CH_2Cl_2	<20%[a]
3	cat. OsO_4, CSA, TMO, CH_2Cl_2	<5%
4	cat. OsO_4, CSA, *trans*-cinnamic acid, TMO, CH_2Cl_2	61%

[a] Products derived from dihydroxylation of **23** were observed.

($Os^{VI} \rightarrow Os^{IV}$).[10] Moreover, entry 2 reveals that Os^{VIII} preferentially dihydroxylates an alkene rather than cyclizes a diol onto it.[11] We suspect that the small amount of **24** formed here comes from dihydroxylation and subsequent ligand exchange on Os^{VI} and cyclization. Thus, the role of the sacrificial alkene becomes clear; it must be dihydroxylated in preference to the alkene in the substrate. In so doing it prevents unwanted diol by-products and forms Os^{VI}, which is a more competent catalyst (compare entries 3 and 4, Table 1). *trans*-Cinnamic acid is ideal because the diol formed from dihydroxylation is polar and easily separable from the cyclized products.

To conclude, we have shown that N-protected 1,2-amino alcohols are excellent substrates for catalytic oxidative cyclization. The synthesis of pyrrolidines and THFs is both stereoselective and stereospecific, high-yielding, and governed by the position of the heteroatoms in the starting material. Enantiopure starting materials are readily accessible and give enantiopure products after cyclization.

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[6] The enantiopure amino alcohols reported here were made by a convenient route that involved: 1) reaction of OTr glycidol with an allyl Grignard reagent, 2) Mitsunobu inversion with BocNHTs, and then 3) deprotection. OTr = *O*-trityl, Boc = *tert*-butoxycarbonyl.
[7] The structures of **6**, **8**, **10**, **16**, **18**, **22**, and **24** were proven unambiguously by X-ray crystallography.
[8] Although the yields are sensitive to the solvent used and the pH, they are not influenced unduly by the source of osmium.
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[11] J. R. Ragazzo, E. J. Behrman, *Bioinorg. Chem.* **1976**, *5*, 343 – 352; while the studies here indicate that Os^{VI} is desirable for formation of a chelate, we have unpublished results which show that both Os^{VI} and Os^{VIII} osmate esters can cyclize under acidic conditions.

