Directed Dihydroxylation of Allylic Trichloroacetamides

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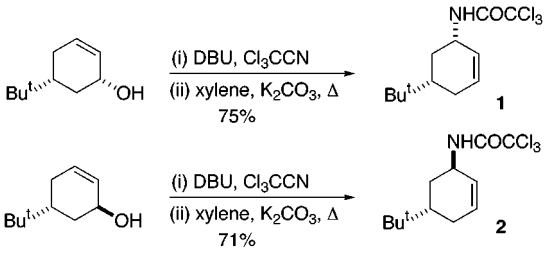
The dihydroxylation of alkenes using osmium tetraoxide is the most reliable and efficient method of *cis*-1,2-diol formation.[1] Oxidation of alkenes that contain chiral centers can lead to high levels of stereoselectivity in the glycol-forming step. Kishi noted that the oxidation of cyclic allylic alcohols led to formation of a *syn-anti* triol with high levels of stereoselectivity.[2] Other allylic functional groups have been shown to influence the dihydroxylation reaction, and we wish to address the oxidation of cyclic allylic amides with osmium tetraoxide. Although several acyclic allylic amides have been subjected to the dihydroxylation reaction,[3] a systematic survey of cyclic systems has not been reported.[4] In particular, we wanted to address the issue of *syn*/*anti* selectivity as we suspected that oxidation under Upjohn conditions[5] would give predominantly the *syn-anti* isomer, whereas directed dihydroxylation with our recently developed OsO_4/TMEDA oxidant should deliver the *syn-syn* isomer *via* a hydrogen-bonding mediated process.[6] Our studies focused on allylic trichloroacetamides for two reasons. First, these derivatives are easy to prepare *via* the Overman rearrangement of allylic alcohols,[7] and second, the trichloro group was expected to acidify the RCON*H* position and make it effective for directed dihydroxylation.[8]

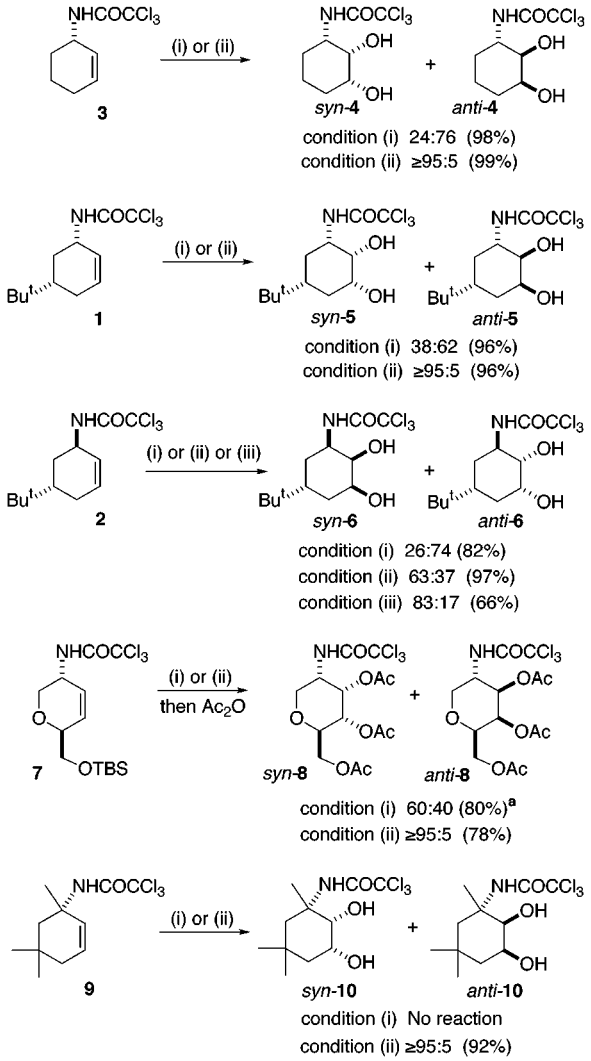
The Overman rearrangement strategy is illustrated in Scheme 1 with the formation of the novel *cis*- and *trans*-*tert*-butyl-substituted cyclohexenes **1** and **2**.

A range of six-membered allylic trichloroacetamides was thus prepared and oxidized under both Upjohn and OsO_4/TMEDA conditions (Scheme 2). The results in Scheme 2

Scheme 1



Scheme 2[a]



[a] Key: (i) OsO_4 (5 mol %), NMO, acetone/water, rt; (ii) OsO_4 (1 equiv), TMEDA (1 equiv), CH_2Cl_2, −78 °C, then MeOH/HCl, rt; (iii) OsO_4 (1 equiv), quinuclidine (1 equiv), CH_2Cl_2, −78 °C, then MeOH/HCl, rt. (a) The product from oxidation retained the TBS group; this was removed for comparison with the product from condition ii.

(condition i) show that under Upjohn conditions these particular substrates generally give low stereoselectivity for the *anti* diol. However, oxidation with 1 equiv of OsO_4 and TMEDA at −78 °C (condition (ii)) gives very high selectivity for the *syn* diastereoisomer.

The stoichiometric osmium tetraoxide conditions specified above lead directly to formation of an osmate ester; this derivative could be easily hydrolyzed to the diol by reaction with acidic methanol at room temperature. The stereo-

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† To whom correspondence regarding the crystal structure should be addressed.

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(8) Other amide derivatives bearing less acidic protons were screened (e.g., CH_3CONHR, $Bu^tOCONHR$) and found to be less effective hydrogen-bond donors.

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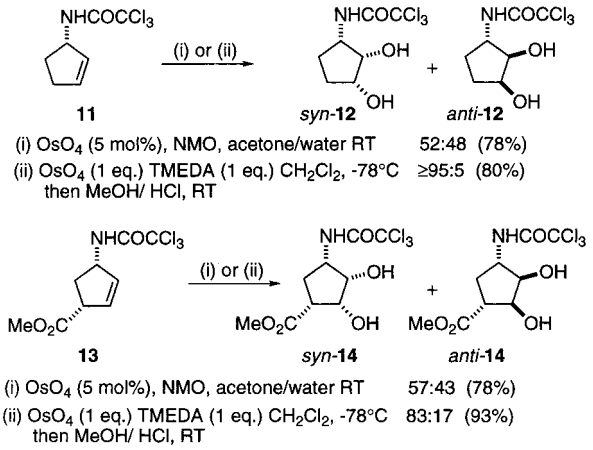
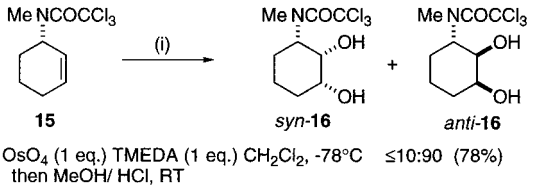
Scheme 3



selectivity of the OsO_4/TMEDA reaction was checked in two ways. First, the crude osmate esters produced from the reaction were analyzed by ^{1}H NMR spectroscopy, and the *syn*/*anti* ratio was judged (in comparison with an authentic sample of the *anti* osmate ester made *via* analogous oxidation in acetone/water). In addition, the crude diol products from cleavage were analyzed by ^{1}H NMR spectroscopy so that they could be compared with the compounds produced from the Upjohn reaction: a ratio of ≥ 95:5 means that the *anti* isomer could not be detected using these two assays. In most cases we also found it convenient to form the acetonide derivatives of the products as these were usually crystalline and easy to handle.[9] The relative stereochemistry of *syn*- and *anti*-**4** was proven by examination of ^{1}H NMR spectra of the corresponding osmate esters formed before acidic cleavage. X-ray crystallographic analysis secured the relative stereochemistry of *syn*-**5**, *syn*-**6**, *syn*-**8**, and *syn*-**10**.[10] Compound **2** (Scheme 2) contains a pseudoaxially "locked" amide group and is not particularly *syn* selective under hydrogen-bonding conditions. We presume that the active oxidizing agent in the OsO_4/TMEDA mixture is a bidentate complex formed between the two reagents[11] (electron donation from both nitrogen atoms of TMEDA increases the hydrogen-bonding acceptor capability of the oxo ligands on osmium).[6] A corollary of this assumption is that the oxidant is relatively bulky, and it is reluctant to oxidize hindered faces of alkenes. Previously, we have found that osmium tetraoxide with a *monodentate* ligand (such as quinuclidine) provides a compromise by displaying reduced hydrogen bonding acceptor ability but also reduced steric bulk.[12] Gratifyingly, this reagent combination provided reasonable (83:17) *syn* selectivity in the oxidation of **2**.

We prepared and oxidized two five-membered allylic trichloroacetamides to examine the generality of the process (Scheme 3). Both examples displayed good levels of *syn* stereoselectivity under directed dihydroxylation conditions; in each case the diastereoselectivity of the reaction was measured by the two methods described earlier. Note that oxidation of **11** and **13**[13] under Upjohn conditions is not partiularly (*anti*) stereoselective. These results are in agreement with previous reports of *syn* selectivity during the dihydroxylation of susbstituted cyclopentenes.[14] The relative stereochemistry of the four diols shown in Scheme 3 was assigned by X-ray crystallographic analysis on a trifluoromethyl analogue of *syn*-**12** and on the acetonide of *anti*-**14**.[10]

Scheme 4



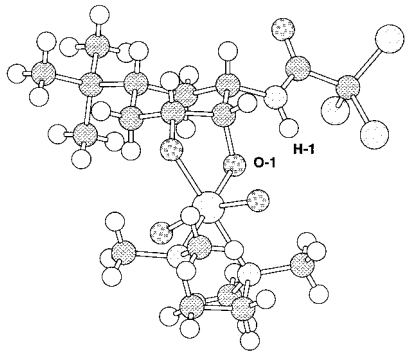


Figure 1. X-ray of **17**. H-1−O-1 distance is 2.30 Å.

To prove that hydrogen bonding was the driving force behind the *syn* selectivity observed in these systems, we prepared the *N*-methyl derivative **15** and oxidized it with OsO_4/TMEDA (Scheme 4). The result was selective formation of only *anti*-**16**, and we can report that the reaction of **15** under these conditions was several times slower than the corresponding *N*H derivative **3**.

The first stage of the directed dihydroxylation reaction with TMEDA involves formation of an osmate ester. These species are generally quite stable and can be purified by chromatography on silica and also crystallized.[15] We were able to obtain an X-ray crystallographic structure of the *syn* product **17**, derived from reaction of **1** with OsO_4 and TMEDA at −78 °C (Figure 1). Note that the TMEDA ligand is chelated to the osmium and also that the N*H* and the glycol oxygen are in close proximity. Indeed, the position of the N*H* could be determined with certainty, and a distance of 2.30 Å between the hydrogen and oxygen makes an intramolecular hydrogen bond seem likely.

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Supporting Information Available: Experimental details and spectroscopic data for compounds **1**,**2**, *syn*/*anti*-**4** (acetonide), *syn*/*anti*-**5**, *syn*/*anti*-**6** (acetonide), *syn*-**8**, *syn*-**10**, *syn*/*anti*-**12** (acetonide), *syn*/*anti*-**14** (acetonide), and *anti*-**16** (acetonide).

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(9) Acetonides were formed by taking the diol products in acetone and adding 2,2-dimethoxypropane and CF_3COOH (cat.): yields were 80−90%.

(10) All new compounds were fully characterized. Full details of the X-ray structures of *syn*-**6** (acetonide), *syn*-**8**, *syn*-**10,** and *anti*-**14** (acetonide) will be published in a full account of this work.

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