

The Tethered Aminohydroxylation (TA) of Cyclic Allylic Carbamates

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The Sharpless aminohydroxylation reaction has recently emerged as a powerful method of preparing vicinal amino alcohols from alkenes using osmium catalysts.¹ Using a carbamate as the source of nitrogen and (basic) *tert*-butyl hypochlorite as the oxidant, good yields of amino alcohol products can be obtained in the presence of catalytic amounts of potassium osmate ($K_2OsO_2(OH)_4$).²

One of the complications with this methodology is a lack of regiochemistry when some unsymmetrical alkenes are oxidized;³ in response to this issue we tethered the source of nitrogen (carbamate) to an achiral allylic alcohol and discovered a method of controlling completely the regiochemistry of the product (**1** → **2**, Scheme 1).⁴

This work describes our efforts to control not only the regioselectivity but also the stereoselectivity of hydroxyamination reactions. Although the basic hydroxyamination reaction is stereospecific, there are currently no good strategies for the stereoselective hydroxyamination of chiral substrates. With this goal in mind, oxidation of a carbamate such as **3** (Scheme 1) should lead to a single regio- and stereoisomer. This outcome would represent a significant increase in the degree of control possible during the oxidation of allylic alcohol substrates.⁵

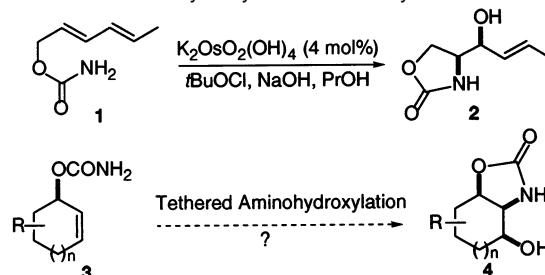
To test our hypothesis, we prepared a range of carbamates from five- and six-membered cyclic allylic alcohols ($Cl_3CCON=C=O$ then K_2CO_3 (aq), 78–99%). These derivatives were then subjected to hydroxyamination, Scheme 2.

As the results show, there is one incompatibility in the tethered aminohydroxylation of five-membered rings, with only exocyclic alkenes being viable substrates; we believe this is because of undue strain in the azaglycolate osmate ester that would be formed from **5**, vide infra. However, the TA reaction on six-membered rings proved to be versatile and completely stereoselective; entries 5 and 6 show that 3-aminosugars can be prepared easily from alkene precursors.

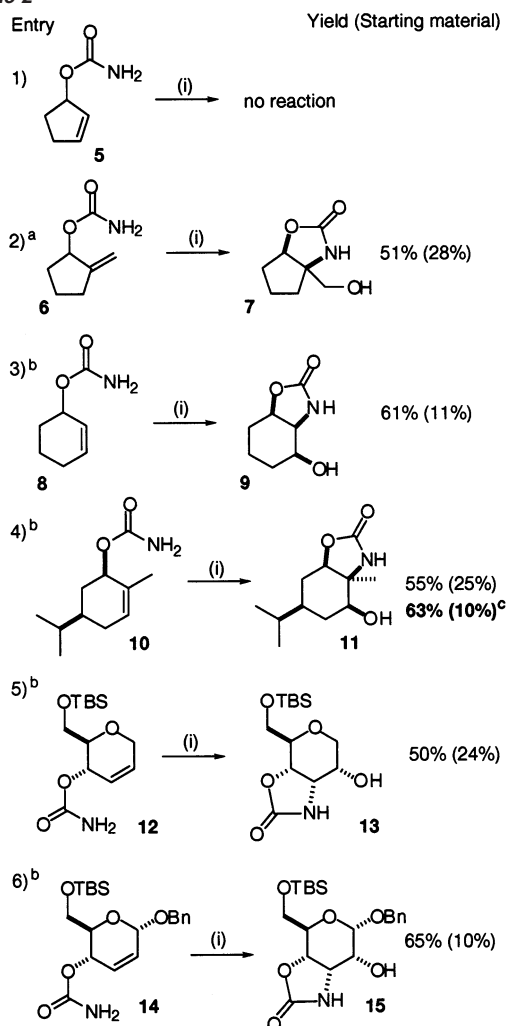
In general, the yields for the TA reaction are good, especially when one considers the amount of recovered starting material, which can easily be recycled through the oxidation regime.

During development of the reaction conditions, we examined the role of various amines as promoters for the TA of compound (+)-**10**, Table 1. The presence of an amine is beneficial to the rate, with Sharpless' catalysts and *i*-Pr₂NEt giving the highest yields.⁶ Surprisingly, quinuclidine is not good at accelerating the reaction, and we suspect that it is destroyed by one of the chlorinating agents present in solution. Importantly, there was no significant difference in rate (or yield) for oxidation using (DHQD)₂PHAL and its pseudoenantiomer (DHQD)₂PHAL; this points to a role for the chiral ligand that does not include stereochemical induction and fits well with our observations using achiral allylic carbamates.⁴

Scheme 1. Tethered Hydroxyamination of Allylic Carbamates



Scheme 2^a



^a (i) $K_2OsO_2(OH)_4$ (4 mol %), *t*-BuOCl (1 equiv), NaOH (0.9 equiv), amine (5 mol %), PrOH, H₂O. (a) EtNiPr₂. (b) (DHQD)₂PHAL. (c) Yield after one recycle.

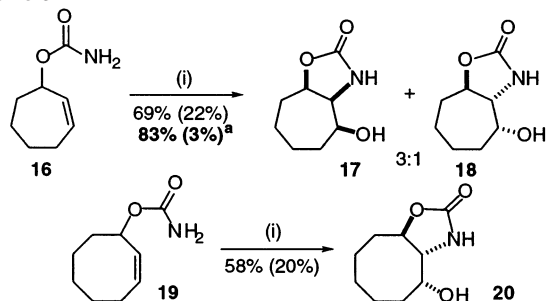
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[†] Author for correspondence regarding the crystal structure.

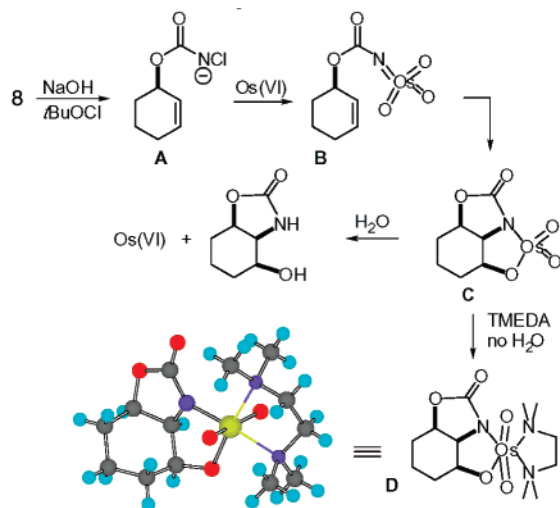
[‡] Lilly Research Centre.

Table 1. Oxidation of **10** → **11** (Recovered Starting Material)

entry	additive	time	yield %
1	(DHQ) ₂ PHAL (5%)	2.3 h	55 (25)
2	(DHQD) ₂ PHAL (5%)	2.5 h	46 (29)
3	<i>i</i> -Pr ₂ NEt (5%)	2.5 h	48 (29)
4	<i>i</i> -Pr ₂ NEt (100%)	—	45 (17)
5	quinuclidine (5%)	>7 h	35 (40)
6	quinuclidine (100%)	—	6 (74)
7	none	5.5 h	43 (37)

Scheme 3^a

^a (i) $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol %), *t*-BuOCl (1 equiv), NaOH (0.9 equiv), (DHQ)₂PHAL (5 mol %), PrOH, H₂O. (a) Yield after one recycle.

**Figure 1.**

Naturally, we examined the recovered starting material from oxidation of racemic substrates, and they had a specific rotation of zero, which rules out a kinetic resolution.

Next, we examined the tethered aminohydroxylation reaction on both seven- and eight-membered rings and found that the oxidation worked well, giving predominantly the all syn isomer with the seven-membered ring and the anti isomer ($\geq 10:1$ dr) with the eight,⁷ Scheme 3.

In terms of mechanism, we suggest that in situ chlorination and deprotonation of the allylic carbamate gives a species **A** (a nitrene equivalent) that is capable of oxidizing potassium osmate (Os(VI)) to the osmium tetroxide analogue **B** (Os(VIII), Figure 1). Addition to the alkene (amine accelerated as in dihydroxylation?) gives

azaglycolate osmate ester **C** (Os(VI)) which is oxidized and hydrolyzed in situ (second cycle notwithstanding).

We present two pieces of experimental evidence in support of this hypothesis: (1) repetition of the TA reaction using optimum conditions, but no potassium osmate, gave no cyclized products, (2) the osmate ester **C** could be intercepted by the addition of TMEDA to the reaction mixture to give **D** (no water was present here to avoid hydrolysis of **C**).

Previously, we have used diamines to improve the hydrogen-bonding ability of OsO_4 ;⁸ one consequence of this combination is the extra stability that TMEDA confers to the osmate ester, making them difficult to hydrolyze during the reaction.⁹ Thus, we were able to obtain an X-ray crystal structure of complex **D**,¹⁰ and its structure fits exactly with our predictions. In a separate step, intermediate **D** could be hydrolyzed (aq Na_2SO_3) to alcohol **9**.

To conclude, we have shown the utility of the tethered amino-hydroxylation reaction toward cyclic substrates. The regio- and stereoselective synthesis of all syn amino-diol motifs in protected form is now straightforward, and this methodology will prove its utility in synthesis. Moreover, we have probed the reaction mechanism and obtained an X-ray crystal structure of an azaglycolate osmate ester. This rare example provides key information about the nature of one of the many intermediates in aminohydroxylation reactions.

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Supporting Information Available: Representative experimental procedures and spectroscopic data for all new compounds, plus proof of stereochemistry and X-ray data for compound **D** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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