

Efficient Acyclic Stereocontrol Using the Tethered Aminohydroxylation Reaction

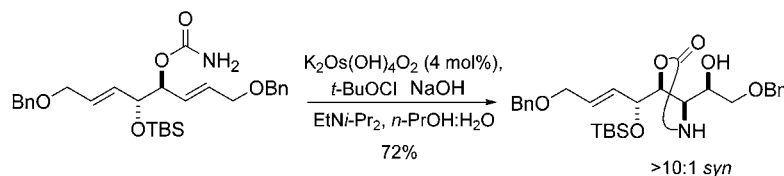
Timothy J. Donohoe,^{*,†} Peter D. Johnson,[†] Richard J. Pye,[†] and Martine Keenan[†]

Department of Chemistry, University of Oxford, Chemistry Research Laboratory,
Mansfield Road, Oxford OX1 3TA, U.K., and Eli Lilly and Company, Ltd.,
Lilly Research Centre, Erl Wood Manor, Sunninghill Road,
Windlesham, Surrey GU20 6PH, U.K.

timothy.donohoe@chem.ox.ac.uk

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ABSTRACT



The tethered aminohydroxylation (TA) of acyclic allylic carbamates has been achieved in a stereospecific and stereoselective manner. Unusually high levels of stereocontrol were observed in the oxidation of 1,1-disubstituted substrates.

The widespread occurrence of amino alcohols in biologically active molecules and natural products¹ has led to the need for simple, efficient, and reliable methodology for the introduction of such functional groups. The pioneering asymmetric aminohydroxylation (AA) reaction developed by Sharpless is a powerful method for the stereospecific preparation of vicinal amino alcohols using catalytic potassium osmate in the presence of a nitrogen source (typically a carbamate) and *tert*-butyl hypochlorite as the oxidant.² Despite its utility, the variability of regiocontrol during the oxidation of several unsymmetrical olefins within the AA remains a problem. Other workers have addressed this issue by manipulating the steric and electronic properties of various alkenes in an attempt to bias the aminohydroxylation reaction, but without finding a general solution.^{3–5} Our

method for achieving reliable regiocontrol during aminohydroxylation involves tethering the carbamate nitrogen source to the substrate, which, in the presence of *tert*-butyl hypochlorite and catalytic potassium osmate, constitutes an intramolecular AA reaction (described as the tethered aminohydroxylation, TA).⁶ Investigation of the TA reaction on achiral allylic carbamates confirmed that this novel approach gave total regioselectivity (Scheme 1)⁷ and an extension to cyclic allylic alcohol systems proved successful; the reaction proved to be both regio- and stereoselective.⁸

This paper describes our efforts to apply the TA reaction to flexible, chiral, acyclic substrates. In this case, achieving acyclic stereoselectivity would provide us with a powerful and novel method of preparing linear amino diols with fixed and predictable stereochemistry. Consequently, a series of *cis* and *trans* acyclic allylic carbamates were prepared from their respective alcohols and duly subjected to the TA conditions. As Scheme 2 illustrates, the reaction proceeded smoothly to furnish protected amino alcohols with complete regiocontrol and with excellent *syn* stereoselectivity. In all

[†] University of Oxford.

[‡] Eli Lilly and Company, Ltd.

(1) Bergmeier S. C. *Tetrahedron* **2000**, *56*, 2561.

(2) For representative references, see: Chang, H.-T.; Li G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813. Brunko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1483. Rubins, A. E.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2637. For a recent review on the AA reaction, see: Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, *24*, 2733.

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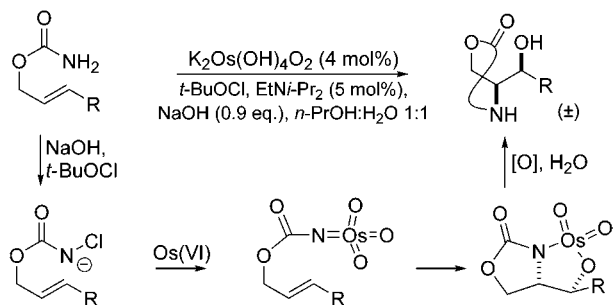
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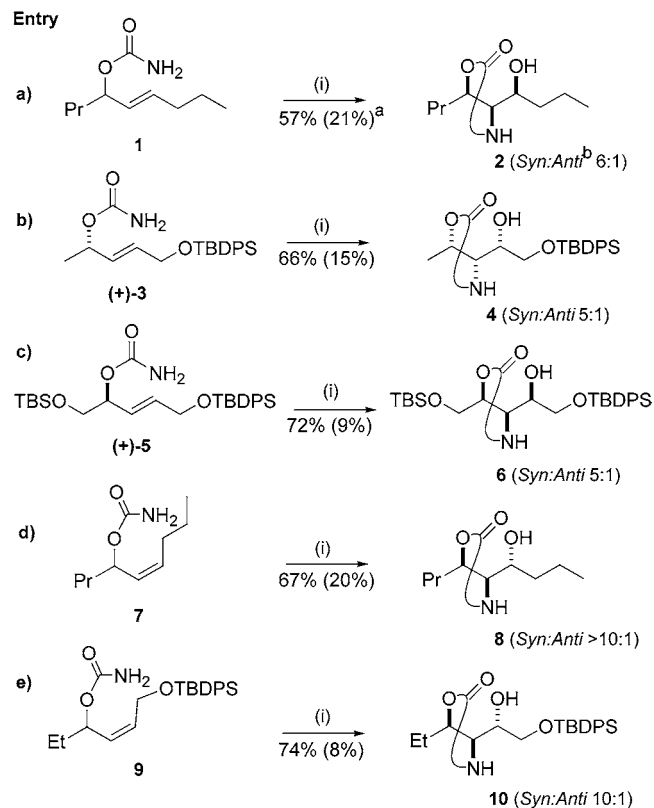
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Scheme 1

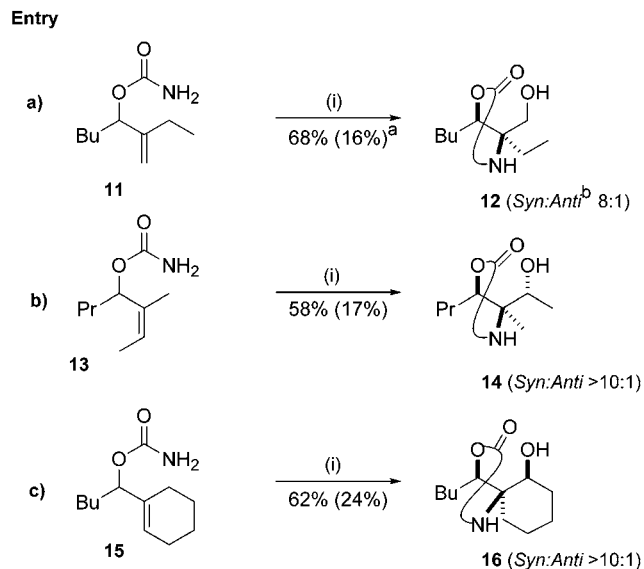


examples, good yields, mass recovery, and functional group tolerance were found. It is of note that *cis*-substituted allylic carbamates (entries **d** and **e**) gave nearly total stereocontrol in comparison to their *trans* counterparts.⁹ The stereochemical outcome of the reactions in Scheme 2 was proven by X-ray crystallography on compounds **6**, **8**, and **10** with the stereochemistry of compound **2** identified by symmetry properties¹⁰ and **4** by analogy. These results show that (i) the addition of nitrogen and oxygen was suprafacial (stereospecific) and (ii) the reaction was *syn* selective (stereoselective) in each case.

Scheme 2^a

^a Conditions: (i) $\text{K}_2\text{Os}(\text{OH})_4\text{O}_2$ (4 mol %), *t*-BuOCl (1.0 equiv), NaOH (0.92 equiv), EtN-*i*-Pr₂ (5 mol %), *n*-PrOH/H₂O (1:1). (a) Recovered starting material in parentheses. (b) All ratios calculated by ¹H NMR spectroscopy on the crude reaction mixture.

Syn-selective stereocontrol within 1,1-disubstituted acyclic alkene substrates is rare¹¹ because of the competing influence of A^[1,2] over A^[1,3] strain. Three 1,1-di or 1,1,2-trisubstituted allylic carbamates were synthesized in order to assess the degree of stereocontrol that could be induced using the TA reaction. Reaction of **11**, **13**, and **15** under standard TA conditions furnished three oxidized products with nearly complete *syn* stereoselectivity (entries **a–c**, Scheme 3). The

Scheme 3^a

^a Conditions: (i) $\text{K}_2\text{Os}(\text{OH})_4\text{O}_2$ (4 mol %), *t*-BuOCl (1.0 equiv), NaOH (0.92 equiv), EtN-*i*-Pr₂ (5 mol %), *n*-PrOH/H₂O (1:1). (a) Recovered starting material in parentheses. (b) All ratios calculated by ¹H NMR spectroscopy on the crude reaction mixture.

stereochemistry of **12**, **14**, and **16** was confirmed in each case by X-ray analysis. The yields for the reactions were good, and the overall mass recovery was excellent. This is a remarkable and useful set of results demonstrating that the factors controlling the stereoselectivity of the TA reaction are not unduly affected by the presence of a geminal substituent on the alkene.

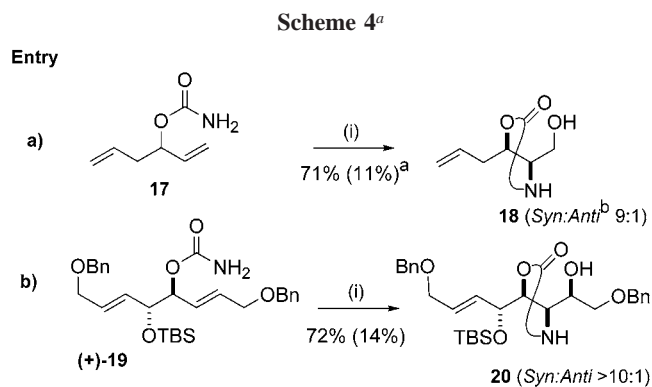
The synthesis of a set of structurally more complex acyclic carbamates was undertaken so that we might probe not only the stereo- and regiocontrol of the TA but also the chemoselectivity. Aminohydroxylation of **17**⁶ and **19** proved to be an efficient, stereospecific, and stereoselective reaction which was also totally regio- and chemoselective. Analysis of the product by ¹H NMR spectroscopy revealed formation of only

(9) Ratios of >10:1 mean that we could not detect the other diastereoisomer in the NMR spectra of the products.

(10) The stereochemistry of **2** was deduced by hydrolysis of the oxazolidinone ring and conversion of the stereoisomers to their respective triacetates which were separable. Symmetry properties then allowed assignment of the *syn* and *anti* products.

(11) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. See also: Adam, W.; Mitchell, C. M.; Saha-Möller, C. R. *J. Org. Chem.* **1999**, *64*, 3699. Donohoe, T. J.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1999**, *40*, 6881. Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917.

the kinetically favored five-membered oxazolidine ring in both instances (Scheme 4). The preference for *syn* stereo-



^a Conditions: (i) $\text{K}_2\text{Os}(\text{OH})_4\text{O}_2$ (4 mol %), *t*-BuOCl (1.0 equiv), NaOH (0.92 equiv), EtNi-Pr₂ (5 mol %), *n*-PrOH:H₂O (1:1). (a) Recovered starting material in parentheses. (b) All ratios calculated by ¹H NMR spectroscopy on the crude reaction mixture.

chemistry in **18** was proven by derivization to a previously reported compound,¹² while the stereochemistry of **20** was assigned by analogy with the previous examples.

To rationalize these results, a model was proposed which supports the *syn* selectivity observed during the reaction. The key step is intramolecular addition of the RN=Os=O fragment across the alkene, which could lead to *syn* or *anti* relative stereochemistry (Figure 1).

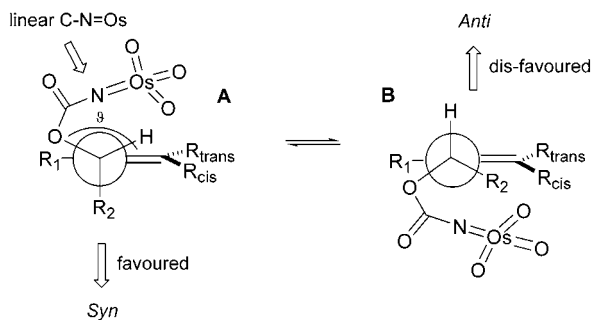


Figure 1. Transition states which rationalize the *syn* selectivity observed during the TA reaction.

It has been shown by X-ray crystallography that related transition-metal complexes form linear metal–nitrogen–carbon arrangements (with the metal forming a double bond to an acyl-substituted nitrogen).¹³ We suggest, therefore, that

(12) The stereochemistry of TA product **18** was deduced by base cleavage of the oxazolidinone ring and conversion of the stereoisomers to their respective triacetates. Hydrogenation of the double bond formed a common intermediate from previous studies.⁷

(13) Thomas, S.; Lim, P. J.; Gable, R. W.; Young, C. G. *Inorg. Chem.* **1998**, *37*, 590.

such a linear arrangement is present during the TA reaction (Figure 1). The nitrogen and oxygen then overlap with the π -orbitals of the alkene, with deformation of the linear (C–N=Os) arrangement occurring as the reaction proceeds to furnish an azaglycolate osmate ester.⁸ A consequence of starting with a linear osmium–nitrogen–carbon bond is that the initial dihedral angle (ϑ) required to give good orbital overlap between the oxidant and alkene must be large. Therefore, only two reactive conformations need be considered, which lead to the *syn* or *anti* product respectively (Figure 1).

Assuming the presence of a linear osmium–nitrogen–carbon arrangement and the subsequently large angle (ϑ) required for a successful reaction to occur, the factors which will govern the reactivity of these conformations, and hence the outcome of the TA reaction, can now be considered. Primarily, there will be A^[1,3] strain between the R_{cis} group and the allylic substituent in the inside position. Clearly, this is minimized in **A** (H inside, leading to *syn*) versus **B** (R inside, leading to *anti*). This factor also predicts greater *syn* selectivity when the R_{cis} group is not hydrogen.

Second, we suggest that any A^[1,2] strain between R₁ and R₂ is relatively unimportant and the level of A^[1,2] strain is approximately equivalent in both reactive conformations (because of the large angle (ϑ) in the transition state). Finally, the presence of a large group in the inside allylic position (see R₂ in **B**) may also hinder approach of the active osmium species to the alkene and slow the rate of oxidation via this conformation.

Therefore, inspection of our results indicates that reaction via conformation **A** (which leads to the *syn* product) is preferred. There is also greater *syn* selectivity during the oxidation of *cis*- versus *trans*-carbamates, as predicted by the model. The unusually high levels of *syn* selectivity observed in the 1,1-disubstituted series is (with A^[1,2] strain similar in both conformations) also explained by our model.

In conclusion, we report a successful application of the stereoselective TA reaction to chiral acyclic systems. The reaction displays excellent levels of *syn* stereoselectivity while providing complete control over the regio- and chemoselectivity of the oxidation. The high level of stereocontrol displayed in the 1,1-disubstituted systems is particularly exciting. A simple mechanistic model has been proposed which rationalizes the stereochemical outcome of the reaction. We believe these developments to the TA reaction will allow this methodology to find a wider application in an important area of organic synthesis.

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Supporting Information Available: Experimental procedures and analytical and spectroscopic characterization of all starting materials and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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