OBC
www.rsc.org/obc

The tethered aminohydroxylation (TA) reaction†

Timothy J. Donohoe,* Peter D. Johnson and Richard J. Pye
The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: timothy.donohoe@chem.ox.ac.uk

Received 9th May 2003, Accepted 19th May 2003
First published as an Advance Article on the web 28th May 2003

Since Sharpless' discovery of the asymmetric aminohydroxylation (AA) reaction, a major challenge for chemists has been to find ways of controlling the regio- and stereochemical outcome of this important reaction. Detailed herein is a review of our novel approach towards gaining reliable and predictable regio- and stereocontrol through the use of a tethered carbamate to promote an intramolecular AA reaction, along with a description of the mechanism proposed for this new methodology.

Introduction

The asymmetric aminohydroxylation (AA) reaction was developed in the mid-nineties by Sharpless and has emerged as a powerful method for the synthesis of chiral amino alcohols from alkenes.[1] Importantly, the reaction is catalytic in both osmium and a cinchona alkaloid ligand, with various sources of nitrogen being developed since the reaction's discovery.[2] While this reaction has many similarities to the more prominent asymmetric dihydroxylation (AD) process,[3] it has an added complication in that control of the regiochemistry is necessary when oxidising unsymmetrical olefins.

In order to address this issue, several efforts have been made to provide regiocontrol within the AA reaction and a few relevant studies on alkenes with an allylic heteroatom are now summarised (Scheme 1). Landais and co-workers reported that it was possible to direct aminohydroxylation through the use of cyclic allyl silanes in their work towards the synthesis of amino-cyclitols.[4] It was observed that the aminohydroxylation of dienylsilane (**1**) using EtO_2CNH_2 as the source of nitrogen furnished (**2**) with complete regio- and diastereoselectivity. It was suspected that electronic effects were responsible for the preference for the nitrogen group to be positioned α to the silyl group at the more hindered C2 position. Meanwhile, Janda and co-workers examined a range of unsymmetrical allylic alcohol derivatives and explored the role that steric and electronic effects of substituents on either side of the olefin had upon the AA reaction (Scheme 1).[5] Through careful design of the substrate it was demonstrated that complementarity between the catalyst binding pocket and the alkene substituents could be maximised thus resulting in the promotion of regio- and enantioselectivity. For example, reaction of the naphthyl ester

† Electronic supplementary information (ESI) available: Figure: The tethered aminohydroxylation reaction. See http://www.rsc.org/suppdata/ob/b3/b305189g/

Timothy J. Donohoe studied for a first degree in chemistry at the University of Bath (1985–1989). In 1989 he moved to Oxford to study for a D. Phil. with Professor Steve Davies and then in 1992 went to the US for postdoctoral work with Professor Phil Magnus. In October 1994 he took up his first independent job as lecturer in Chemistry at the University of Manchester being promoted to Reader in 2000. In 2001 he moved to the Dyson Perrins Laboratory, Oxford as Lecturer in Chemistry and Fellow of Magdalen College.

Peter Johnson graduated with first class honours from the University of Cambridge in 2000. He then moved to the University of Manchester to begin his PhD under the supervision of Tim Donohoe. In September 2001 he transferred with Tim to his present position as a DPhil student at the University of Oxford.

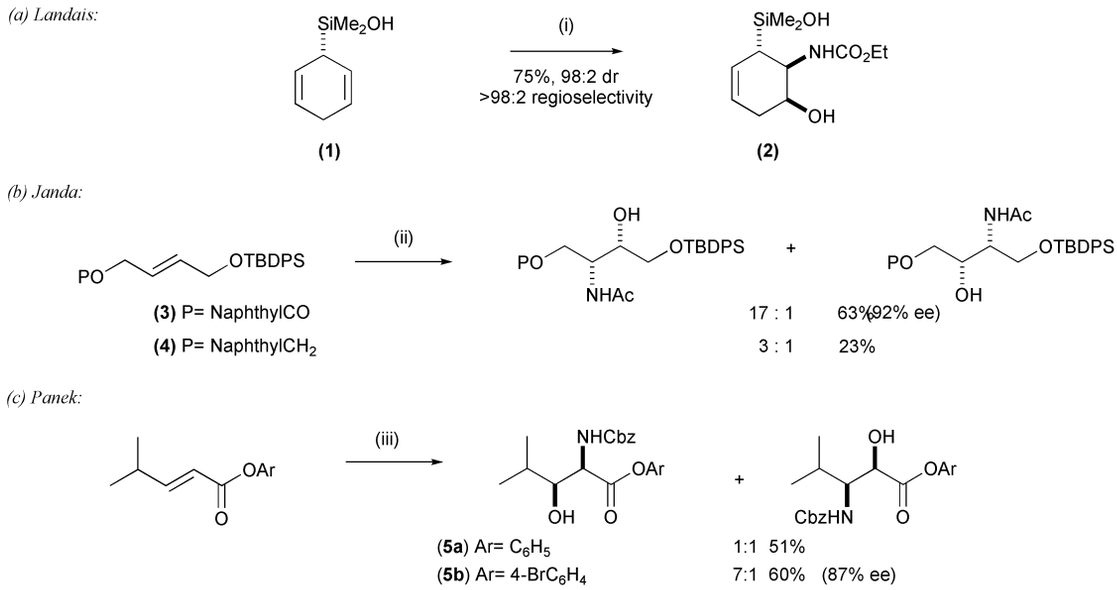
Richard Pye completed his Masters of Chemistry degree in 1999 at the University of Sheffield. He then moved to the University of Reading where he studied for his PhD under the supervision of Professor Laurence Harwood, working on the total synthesis of mycaperoxide B. On completion of his studies, he took up his current position as a postdoctoral research assistant with Dr Tim Donohoe at the University of Oxford.

Timothy J. Donohoe

Peter Johnson

Richard Pye

DOI: 10.1039/b305189g



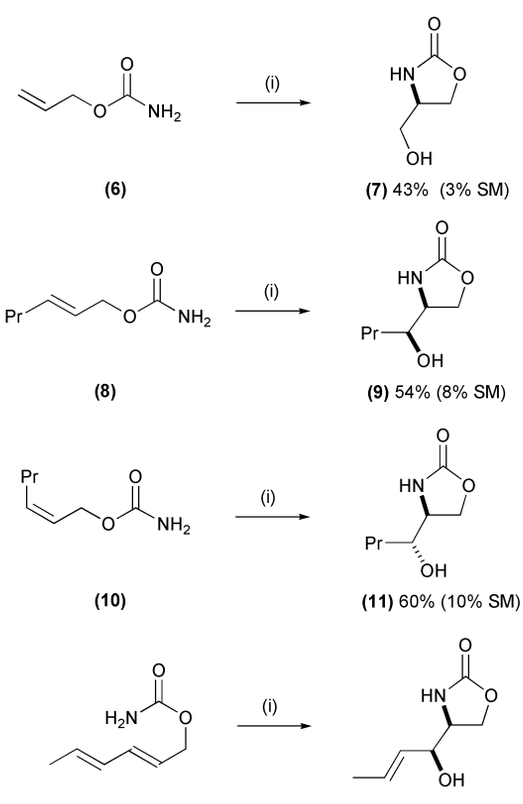
Scheme 1 *Reagents and conditions:* (i) $K_2OsO_2(OH)_4$, $(DHQ)_2PYR$, $H_2NCOOEt$, NaOH, ^{t}BuOCl, ^{i}PrOH–H_2O (1 : 1), rt 1 h; (ii) $K_2OsO_2(OH)_4$ (5 mol%), $(DHQD)_2PHAL$ (6 mol%), $CH_3CONHBr$, LiOH, H_2O, ^{t}BuOH–H_2O (2 : 1); (iii) $K_2OsO_2(OH)_4$ (4 mol%), $(DHQ)_2AQN$ (5 mol%), Cbz-NH_2, ^{t}BuOH, ^{t}BuOCl, NaOH, ^{i}PrOH–H_2O (1 : 1) rt.

(**3**) proceeded with excellent regiocontrol and provided material with a high level of enantioselectivity. However, the sensitivity of the binding pocket to the electronic nature of the substrates and the subsequent effect this had upon the regio- and enantiocontrol of the reaction were demonstrated by the reaction of naphthyl derived ether (**4**), which occurred in poor yield and with significantly less regiocontrol (Scheme 1). Panek and coworkers have also exploited the variable electronic properties of substituents within substrates for the AA reaction when synthesising β-hydroxy-α-amino cinnamate esters.[6a] The delicate balance between the factors that control regioselectivity is illustrated by the different product ratios from oxidation of **5a** *versus* **5b** (Scheme 1). Moreover, during the oxidation of substituted cinnamates Sharpless noted that the nature of the chiral catalyst (linker) itself had a direct influence on the regioselectivity.[6b]

The tethered aminohydroxylation (TA) reaction

Acyclic systems[7]

Despite these promising advances in controlling the regiochemistry of the AA reaction, all the results to date have been very dependent on the nature of the substrate and there is still a need for reliable and predictable methodology for dictating the regiochemical outcome of the reaction. We decided to attempt to control the oxidation of allylic alcohols by tethering the nitrogen source (a carbamate) onto the hydroxy group. Oxidation under appropriate conditions would promote an AA and the intramolecular nature of the reaction would completely control the regiochemistry. ‡ Accordingly, allyl alcohol was converted ($Cl_3CCONCO$ then K_2CO_3, aq. MeOH) to its carbamate (**6**) and subjected to standard Sharpless AA conditions with catalytic potassium osmate (Scheme 2). Hydroxyoxazolidinone (**7**) was isolated as a single regioisomer in an acceptable yield (with 3% recovered starting material, SM). The presence of an amine ligand was found to accelerate the reaction modestly, with Hünig's base proving optimum. Building upon this promising result, a range of allylic alcohols were converted to their corresponding carbamates and subjected to the tethered aminohydroxylation (TA) conditions. With substrates (**8**) and



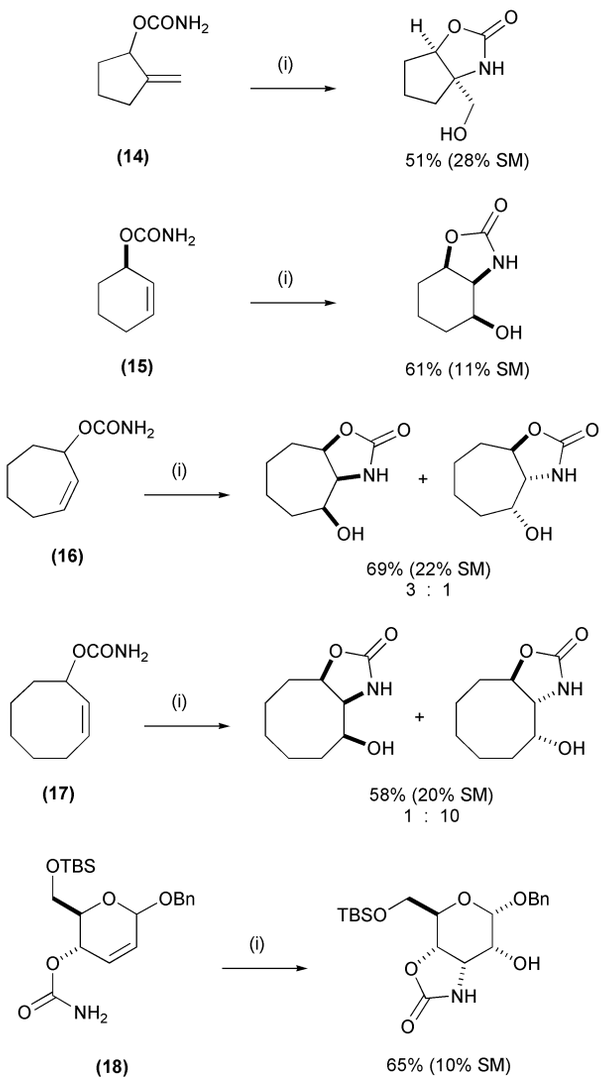
Scheme 2 *Reagents and conditions*: (i) $K_2OsO_2(OH)_4$ (4 mol%), NaOH (0.92 eq.), ^{t}BuOCl (1 eq.), EtN^iPr_2 (5 mol %), ^{n}PrOH–H_2O (2 : 1), rt.

(**10**) a completely regio- and stereospecific reaction occurred with *syn* addition of the nitrogen and oxygen functionalities. Despite showing modest rate acceleration, Sharpless' chiral cinchona-based ligands failed to induce any enantioselectivity in this oxidation. While the cyclisations proceeded in good yields, starting material was always recovered from the reaction and it has proved difficult to push the reaction to completion, even with additional *tert*-butylhypochlorite, NaOH or transition metal catalyst. Regioselective conversion of the carbamate of the *trans*, *trans*-hexadiene (**12**) under the TA conditions further proved the applicability of the methodology with no other oxazolidinone products being detected.

‡ Aminohydroxylation of a range of allylic alcohols showed that they were not oxidised with any appreciable regiocontrol under Sharpless' AA conditions.

Cyclic systems[8]

The scope of this novel tethered carbamate approach to the AA reaction was extended by examining the *stereoselectivity* in cyclic systems (Scheme 3). The reaction proved optimum with 6-membered rings, with formation of the aminohydroxylation products occurring with complete stereo- and regioselectivity and in high yields. The TA reaction with 7-membered cyclic carbamates was found to be high yielding although the stereocontrol was diminished, with formation of the *syn* product favoured by 3 : 1. The TA reaction of 8-membered rings displayed an interesting reversal of diastereoselectivity with the *anti* product being produced (≥10 : 1). The TA reaction of 5-membered rings revealed some incompatibilities of the methodology, with only exocyclic alkenes (**14**) forming cyclisation products. It is believed the strain resulting from the formation of the osmate ester in such endocyclic substrates is prohibitive, *vide infra*. As with the acyclic examples, the yields for the TA are reasonable, especially when the recovered starting material is taken into account.



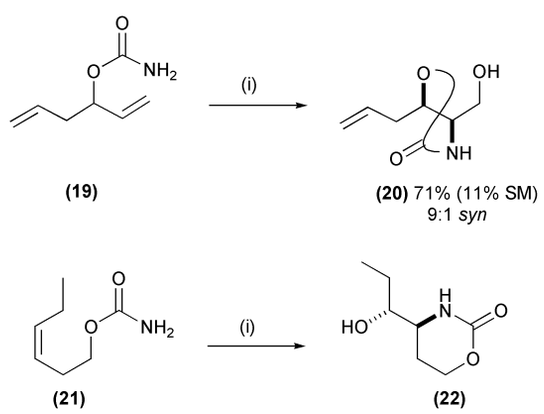
Scheme 3 *Reagents and conditions*: (i) $K_2OsO_2(OH)_4$ (4 mol%), NaOH (0.92 eq.), ^{t}BuOCl (1 eq.), EtN^iPr_2 (5 mol%), ^{n}PrOH–H_2O (2 : 1), rt.

Mechanism

The mechanism we suggest for the TA reaction is analogous to that proposed by Sharpless[2] for the AA reaction (which in turn closely resembles that of its forerunner, the asymmetric dihydroxylation reaction).[9,10] The main difference in our mechanism is the tether between the olefin substrate and the carbamate (Fig. 1). After chlorination and deprotonation of the carbamate, the nitrene equivalent (**A**) combines with potassium osmate to form the active osmium species (**B**), which then adds to the alkene (under the influence of an amine ligand) to form the azaglycolate species (**C**). We presume that the osmium is first reoxidised through the addition of a second nitrene equivalent (**A**) to form a second glycolate species (**D**). At this juncture, hydrolysis of the glycolate species (**D**) releases the hydroxyamination product and regenerates the initial active osmium species (**B**), so completing the primary catalytic cycle. It is speculated that combination of the osmium species (**D**) with the second olefin would allow entry into a second catalytic cycle and that the loss of enantioselectivity in the TA reaction may be a consequence of this divergence.[11] However, we have been able to provide support for the primary cycle through the isolation and recrystallisation of the osmate ester species (**E**). Previous work within the group has identified chelating diamines, in particular TMEDA, as having the ability to stabilise osmate esters.[12] Consequently, the TA reaction shown in Fig. 1 was performed with minimal water present in the reaction; addition of TMEDA to the mixture led to the formation of osmate ester (**E**). X-Ray crystallographic analysis of (**E**) unequivocally confirmed that this tethered aminohydroxylation had proceeded with complete *syn* stereoselectivity. In a separate step, (**E**) was hydrolysed to form the TA product.

Future work

The current focus of our work involves examination of the scope of the tethered aminohydroxylation reaction. A greater understanding of the reaction with more complex substrates and its tolerance towards various functional groups is required. One current avenue of investigation is the reaction of chiral acyclic carbamate systems in the TA reaction (Scheme 4). When the secondary carbamate (**19**) was subjected to the TA reaction conditions, oxazolidinone (**20**) was isolated in good yield and with high stereoselectivity for the *syn* diastereoisomer. Another offshoot is the formation of 6-membered hydroxyamination products from the oxidation of homoallylic alcohols. While the result from the TA reaction on alkene (**19**) shows that allylic alkenes are oxidised faster than homoallylic ones, when we remove the option of forming a 5-membered oxazolidinone (see **21**) then homoallylic systems can be oxidised in 30–65% yield depending upon the substitution pattern.



Scheme 4 *Reagents and conditions*: (i) $K_2OsO_2(OH)_4$ (4 mol%), NaOH (0.92 eq.), ^{t}BuOCl (1 eq.), EtN^iPr_2 (5 mol%), ^{n}PrOH–H_2O (2 : 1), rt.

Summary

In conclusion, an efficient regio- and stereospecific methodology has been developed to synthesise protected amino alcohols. Moreover, the reaction displays excellent levels of stereoselectivity when chiral substrates are oxidised. Formation of the carbamate starting material is straightforward, high

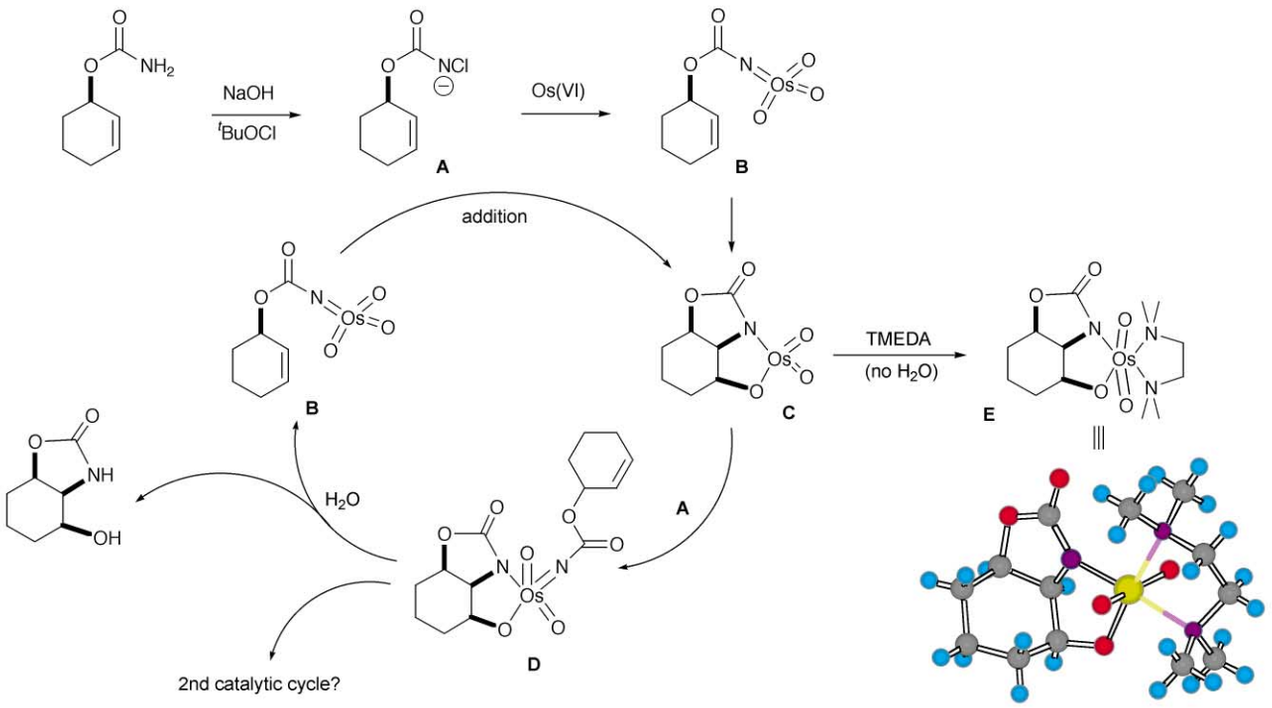


Fig. 1 Proposed mechanism for the TA reaction; ligands omitted for clarity.

yielding and can be performed on a multigram scale. The tethered carbamate approach to the reaction requires only catalytic potassium osmate, a cheap and convenient oxidant (*tert*-butylhypochlorite) and a mild base and results in the formation of amino alcohols with excellent regio- and stereocontrol. Whilst a method for controlling the enantioselectivity, potentially through a chiral auxiliary or ligand, remains unresolved, the early developments made to date on the TA methodology indicate that the reaction has an exciting future in modern synthetic organic chemistry.

References

1 For representative references see: H.-T. Chang, G. Li and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 1996, **35**, 451; H. Angcit, G. Li and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2813; M. Brunko, G. Schlingloff and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1483; A. E. Rubin and K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2637.

2 For reviews see: H. C. Kolb and K. B. Sharpless. in *Transition Metals For Organic Synthesis*, ed. M. Beller and C. Bolm, vol. 2, Wiley-VCH, Weinheim. 1998, p. 243; J. A. Bodkin and M. D. McLeod, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2733; for recent developments see : D. M. Jerina, A. S. Pilcher and H. Yagi, *J. Am. Chem. Soc.*, 1998, **120**, 3520; K. R. Dress, L. J. Goosen, H. Lin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 1999, **38**, 1080.

3 H. C. Kolb, M. S. VanNienwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.

4 R. Angelaud and Y. Landais, *Tetrahedron Lett.*, 1997, **38**, 1407.

5 C.-W. Cho, H. Han and K. D. Janda, *Chem. Eur. J.*, 1999, **5**, 1565.

6 (*a*) C. E. Masse, A. J. Morgan and J. S. Panek, *Org. Lett.*, 1999, **1**, 1949; (*b*) B. Tao, G. Schlingloff and K. B. Sharpless, *Tetrahedron Lett.*, 1998, **39**, 2507.

7 T. J. Donohoe, M. Helliwell, P. D. Johnson and M. Keenan, *Chem. Commun.*, 2001, 2078.

8 T. J. Donohoe, A. Cowley, P. D. Johnson and M. Keenan, *J. Am. Chem. Soc.*, 2002, **124**, 12934.

9 D. W. Nelson, A. Gypser, P. T. Ho, H. C. Kolb, T. Kondo, H.-L. Kwong, D. V. McGrath, A. E. Rubin, P.-O. Norrby, K. P. Gable and K. B. Sharpless, *J. Am. Chem. Soc.*, 1997, **119**, 1840.

10 R. Criegee, *Justus Liebigs Ann. Chem.*, 1936, **522**, 75.

11 J. S. M. Wai, I. Markó, J. M. Svendsen, M. G. Finn, E. N. Jacobsen and K. B. Sharpless, *J. Am. Chem. Soc.*, 1989, **111**, 1123.

12 T. J. Donohoe, P. R. Moore, N. J. Newcombe and M. J. Waring, *Tetrahedron Lett.*, 1997, **38**, 5027.