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Tethered Aminohydroxylation: Dramatic Improvements to the Process

Timothy J. Donohoe,*,† Carole J. R. Bataille,† William Gattrell,‡ Johannes Kloesges,† and Emilie Rossignol†

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, U.K., and Prosidion Ltd., Watlington Road, Oxford OX4 6LT, U.K.

timothy.donohoe@chem.ox.ac.uk

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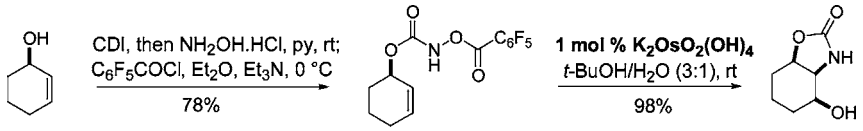
ABSTRACT

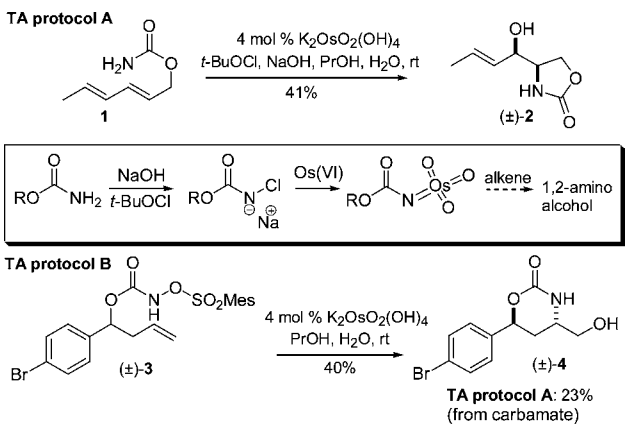


Changing the identity of the N leaving group on a hydroxylamine-based reoxidant gives a dramatic improvement to the tethered aminohydroxylation reaction. Using $OCOC_6F_5$ as a leaving group means that only 1 mol % of osmium is required and yields as high as 98% can be obtained. Acyclic homoallylic alcohols were substrates considered too unreactive for effective use in the tethered aminohydroxylation reaction; improved reaction conditions mean that they have now become viable substrates for oxidation.

The widespread occurrence of amino alcohols and amino acids in biologically active molecules and natural products has led to the need for a simple, efficient, and reliable methodology for the introduction of such functional groups. The pioneering asymmetric aminohydroxylation (AA) reaction, as developed by Sharpless, is a powerful method for the stereospecific preparation of vicinal amino alcohols using substoichiometric potassium osmate in the presence of a nitrogen source (typically a carbamate) and *tert*-butyl hypochlorite as a reoxidant.[1] We have extended the scope of this method by tethering the carbamate unit to an allylic alcohol, thus constituting a tethered aminohydroxylation (TA). This approach solves one of the drawbacks of the AA reaction, which is control of regioselectivity during the oxidation of unsymmetrical alkenes.[2]

Initially, allylic carbamates were oxidized with *t*-BuOCl using Sharpless' original conditions[3] (named TA protocol A hereafter), and the desired products were obtained in moderate yields and with total regioselectivity (Scheme 1). These results were encouraging, and further investigation was undertaken to improve the yields. We observed that chlorination of the alkene unit was a competing side reaction in the TA reaction under protocol A and is partly responsible for lowering the yield. Therefore, a screen of alternative reoxidants for the TA reaction was conducted, focusing on

Scheme 1



† University of Oxford.
‡ Prosidion.

(1) For reviews, see: Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley: New York, 1998; Vol. 2, pp 243. Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733.
(2) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934.

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replacement of the chlorine of the *N*-halocarbamate salt that is generated in situ during oxidation with *t*-BuOCl and NaOH.

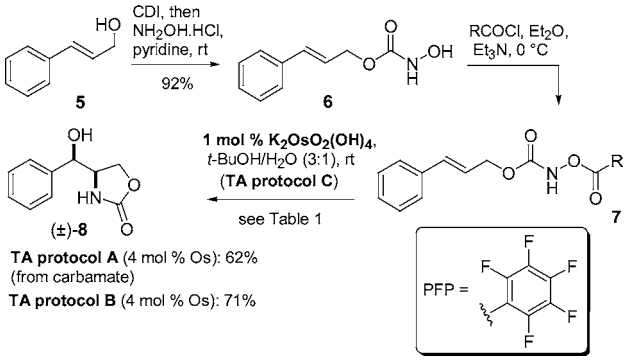
This study led to the discovery of *N*-mesitylsulfonyloxy derivatives as valuable reoxidants for osmium. In these cases, the *N*-Cl unit had been replaced by a *N*-*O*-SO_2Mes group, which was introduced before the aminohydroxylation rather than being formed in situ. Allylic and homoallylic substrates were successfully oxidized using the novel and chlorine-free TA (named hereafter TA protocol B); the corresponding products were usually obtained in good yields.[4] Although this new protocol was significantly better than the original TA reaction based on *t*-BuOCl, the reaction sometimes proved capricious; that is, lower yields were obtained for no apparent reason on some substrates (Scheme 1). In addition, the formation of the TA precursors from the corresponding alcohols could be problematic, leading to moderate yields and fairly unstable compounds. It was, therefore, decided to investigate the reaction further and to especially focus our attention on these particular issues, as they constitute an obstacle to the widespread utilization of the TA reaction in the chemistry community.

Although encouraging results were obtained with the *O*-SO_2Mes reoxidant, no trend emerged as to which substrates would work well, or poorly, in the reaction. It was, therefore, decided to screen a wider range of leaving groups on the carbamate nitrogen. Cinnamyl alcohol **5** was chosen as a test substrate for this investigation as this alcohol is commercially available and a good example of a class of compounds (primary alcohol, *trans*-alkene) which were less than ideal under previous protocols.[5]

Previously, the preparation of hydroxycarbamates, from the corresponding alcohol, was performed using CDI and hydroxylamine hydrochloride in acetonitrile in the presence of imidazole; this method sometimes led to moderate yields due to the formation of byproducts. A judicious switch to pyridine solvent allowed the reduction of byproducts and led to dramatic increases in the yields. For example, cinnamyl alcohol **5** was reacted with CDI in pyridine, followed by the addition of hydroxylamine hydrochloride, to afford hydroxycarbamate **6** in excellent yields (Scheme 2). The resulting hydroxycarbamate **6** was then treated with several acid chlorides, in ether, to yield the corresponding O-derivatized hydroxycarbamates **7**, which were subjected to the new TA conditions (named TA protocol C hereafter), to test their potential as reoxidants (Table 1).

Interestingly, the *O*-pentafluorobenzoyl group (*O*-PFB) emerged as a superior reoxidant for the TA reaction, giving a dramatically improved yield (see entry **7d**).[6,7] When

Scheme 2



pentafluorobenzoyl substrate **7d** was subjected to the new TA protocol, the desired oxazolidinone **8** was obtained in excellent and reproducible yield. It is noteworthy that the amount of potassium osmate could be significantly reduced to 1 mol % without lowering the yields; this change was not always possible before, especially with protocol A. These improvements render the novel TA protocol C very attractive as a synthetic route to vicinal amino alcohols.

Table 1. Effect of Acyl-Based Leaving Groups on the Yield of the TA

entry	R	yield of **7a**−**f**	yield of **8** (protocol C)
7a	Me	81%	52%
7b	2,4,6-$Cl_3C_6H_2$	85%	73%
7c	2,4,6-$Me_3C_6H_2$	81%	86%
7d	**C_6F_5**	**95%**	**86%**
7e	*p*-ClC_6H_4	90%	86%
7f	*t*-Bu	94%	0%

To confirm the potential of this improved procedure, it was decided to oxidize a series of allylic alcohol derivatives using the new protocol C (Scheme 3). The alcohols **11**−**14** were treated with CDI in pyridine followed by the addition of hydroxylamine hydrochloride to afford the hydroxycarbamate intermediates, which were then converted to the

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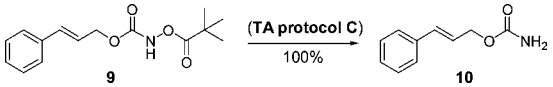
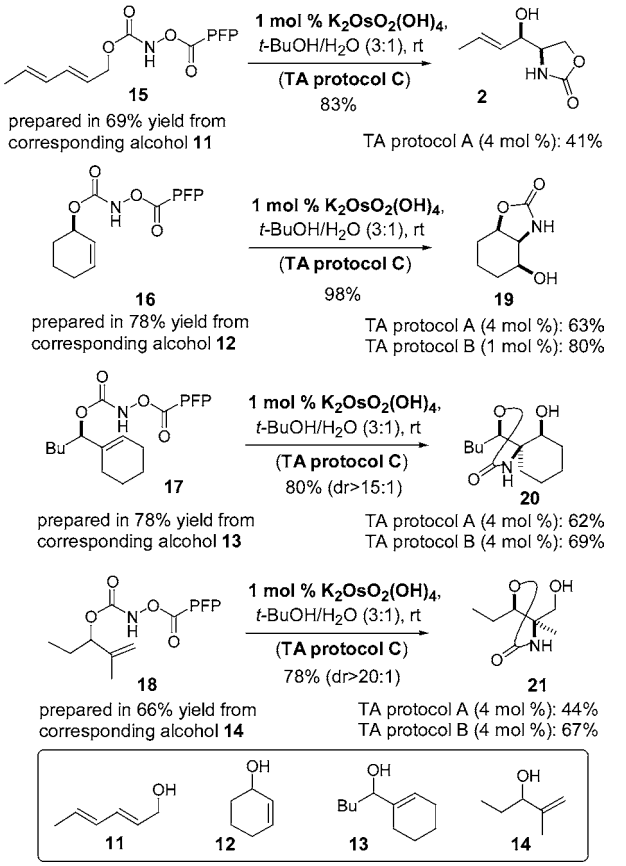
(6) Kloesges, J. Part II thesis; Oriel College: Oxford, 2006.

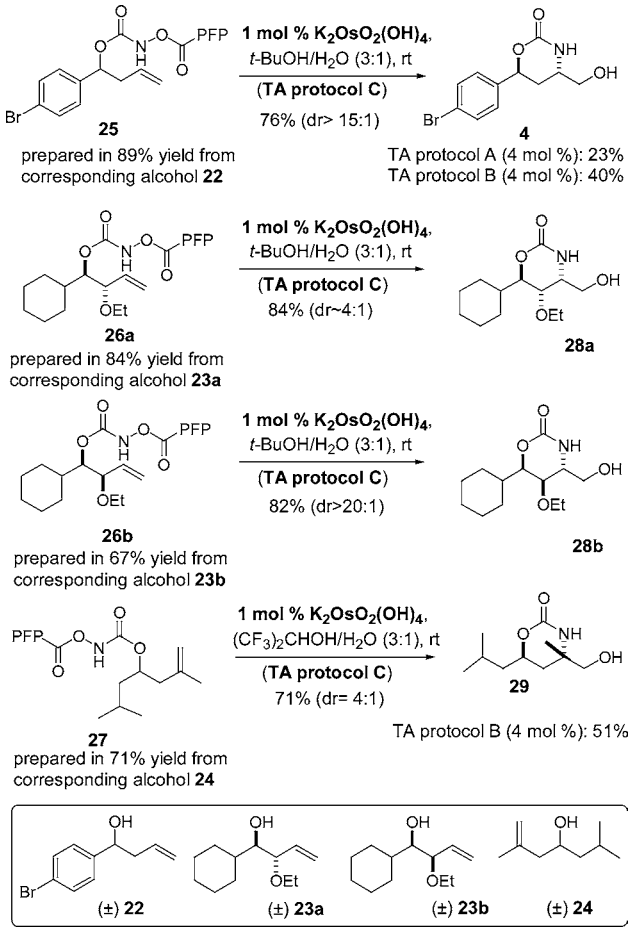
(7) During the screening of nitrogen leaving groups, we discovered that often the TA adduct **8** was obtained with the carbamate **10** as a byproduct. It is interesting that the ratio of TA product **8** to carbamate **10** depends on the nature of the R group positioned on the *O*-acyl group of the hydroxycarbamate derivatives. The formation of the carbamate was surprising. It is proposed that the isolation of **10** could be due to two factors. First, the influence of a particular R group on the solubility of the substrate may play a role in determining the outcome of the reaction. Second, the pK_a of the conjugate acid of the leaving group ($RCOO^-$) may be important in determining the fate of the starting material. For example, the *O*-PFB moiety (R = C_6F_5) is one of the best leaving groups examined here (and this gave no carbamate in the TA reaction) whereas the *O*-Piv group (see **9**, R = *t*-Bu) is the worst leaving group studied. This led to the formation of carbamate **10** in quantitative yield.



Scheme 3



Scheme 4



corresponding pentafluorobenzoyl derivatives **15**−**18** in good to excellent yields. The PFB substrates **15**−**18** were oxidized using protocol C to afford the desired products **2** and **19**−**21** in good to very good yields and with good diastereoselectivity where applicable.

The identities of oxazolidinones **2** and **19**−**21** were confirmed by comparison with the analytical data of authentic samples previously synthesized using protocol A and/or B.[2,5,8] Pleasingly, all the yields obtained with protocol C were significantly higher than the ones afforded by the two previous methods, using only *1 mol % of potassium osmate* instead of the 4 mol % utilized exclusively in protocol A and for the most part with protocol B.

We then attempted to apply this novel methodology to homoallylic alcohol derivatives that have previously been unsuitable for a TA reaction under both earlier sets of conditions. Pentafluorobenzoyl derivatives **25**−**27** were prepared in good to excellent yields from the corresponding homoallylic alcohols (±)-**22**−**24** via the previously described method (Scheme 4) and then submitted to TA protocol C, affording the desired oxazinanones **4**, **28**, and **29** in good to excellent yields and good to excellent diastereoselectivity. It is noteworthy that, again, all the reactions were performed with only 1 mol % of potassium osmate. Consider the outcome of the TA reaction of **25**; this gave oxazinanone **4** in only 23% yield using protocol A and in 40% yield using protocol B. However, using protocol C (1 mol %), this yield was improved dramatically. The high level of 1,3-acyclic stereocontrol in favor of the anti diastereoisomer is also noteworthy.

Relative stereochemistries in this series were confirmed by X-ray crystallography for oxazinanone **4** and by NOE experiments for oxazinanones **28** and **29**. None of these acyclic homoallylic alcohols gave synthetically useful yields in the TA reaction using the previous two procedures.

We also propose here a simple model that could serve as an explanation for the stereoselectivity observed in this system. On the basis of the lack of asymmetric induction in the TA reaction in the presence of a chiral ligand, we have previously suggested that the TA reaction works through the second catalytic cycle.[5,9] So, we assume that the diastereoselectivity obtained above arises from an intermediate such as **A** or **B**, where the osmium atom has already undergone addition across an alkene unit and then been reoxidized (Figure 1). To rationalize the stereochemical outcome of the

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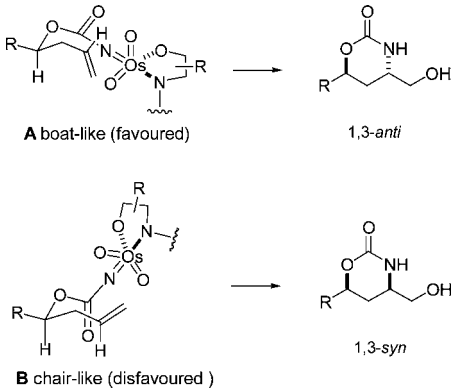

Figure 1. Transition state model for 1,3-anti diastereoselectivity.

oxidation, we make the assumption that the Os═N−C linkage is a linear one without much change in shape in the transition structure.[8,10] Examination of molecular models then shows that a boatlike conformation **A** (with an equatorial R group) allows the best overlap between the oxidant and the π-bonds of the alkene (this gives rise to 1,3-anti diastereoselectivity). The corresponding chairlike transition state **B** (which would give the syn isomer) suffers because this arrangement puts a larger distance between the orbitals of the alkene and the imido-osmium complex and is, therefore, disfavored.

The matching and mismatching effects of a second stereogenic center on the carbon backbone (see **28a** and **b**) are difficult to understand because the less selective derivative **26a** could readily put the OEt group in an equatorial position on the six-membered ring. It may be that this type of conformation is relatively unreactive because the equatorial ethoxy group is placed close to antiperiplanar to the alkene where it can deactivate it by stereoelectronic effects.[11]

To conclude, we have shown that the nature of the leaving group attached to the N−O reoxidant for aminohydroxylation is crucial in promoting an efficient reaction. Positioning the pentafluorobenzoyl group on the oxygen turns an acyl hydroxylamine into an extremely efficient reoxidant capable of giving yields as high as 98% for the tethered aminohydroxylation reaction, all with just 1 mol % of osmium catalyst. Each of the major classes of substrates has been shown to be compatible with this change, and acyclic homoallylic alcohols have, for the first time, become viable compounds for the TA reaction, proceeding with high levels of 1,3-asymmetric induction.

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Supporting Information Available: Copies of ^{1}H NMR spectra and detailed spectroscopic data for all new compounds and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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