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N-Sulfonyloxy Carbamates as Reoxidants for the Tethered Aminohydroxylation Reaction

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The Sharpless aminohydroxylation reaction has proven itself to be an extremely useful method of oxidizing alkenes to form vicinal amino alcohols. The scope of this chemistry is greatly enhanced by the fact that the reaction is stereospecific (strictly syn addition) and also capable of forming single enantiomers of amino alcohol products when performed in the presence of cinchona alkaloid ligands.[1] Our contribution to the development of this reaction was to address the regioselectivity problems that arose when unsymmetrical alkenes were oxidized. We recognized that tethering the nitrogen souce for an aminohydroxylation (such as a carbamate) to an allylic alcohol would allow an intramolecular aminohydroxylation to ensue with complete control of regioselectivity (and high levels of stereoselectivity when chiral allylic carbamates were subjected to the tethered aminohydroxylation, TA, reaction; Scheme 1).[2]

The reoxidant for an aminohydroxylation reaction is typically an *N*-halocarbamate salt prepared in situ by the action of NaOH and *t*BuOCl on a primary carbamate (Scheme 1).[3] In our hands, we found that the *N*-chlorocarbamates thus produced have a limited lifetime in the reaction. In an AA reaction, one can compensate for this by using 3−3.5 equiv of carbamate (and NaOH and *t*BuOCl). Clearly, we do not have this luxury in the TA reaction and thus we sometimes have difficulty in driving the reaction to completion.

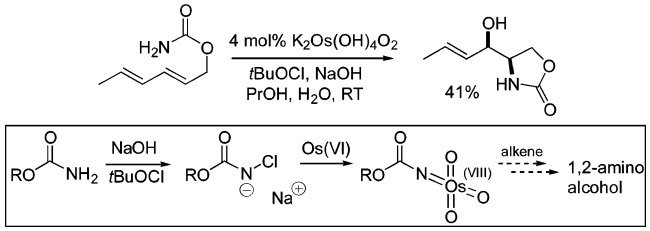
Furthermore, in detailed studies on the TA reaction we discovered that, occasionally, chlorination of the alkene unit was a competing side reaction (promoted by *t*BuOCl) that was responsible for lowering the yields. This problem is especially pronounced with homoallylic carbamates, and this substrate class is barely compatible with the TA conditions.

We have just completed an investigation into alternative reoxidants for the TA reaction with our efforts centered around replacement of the chloride leaving group on the *N*-halocarbamate salt.[4] It soon became apparent that *N*-sulfonyloxy derivatives were superior reoxidants for this process. Recently, Lebel et al. have shown that NHOTs derivatives of carbamates are effective nitrene precursors for C−H insertion and alkene aziridination.[5]

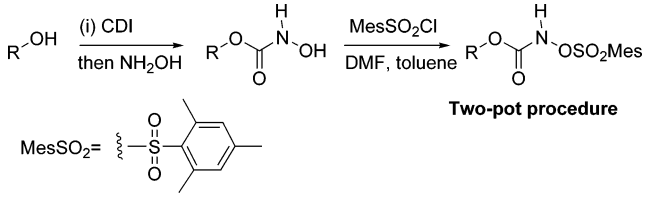
The requisite *N*-sulfonyloxy carbamates were readily prepared, in generally good yields, in a two-pot procedure by sequential reaction of an alcohol with CDI and hydroxylamine, followed by sulfonylation (Scheme 2). While we discovered that a variety of *O*-sulfonyl groups (e.g. OTs) were generally efficient as leaving groups in the TA reaction, we chose to use mesitylsulfonyl as a common standard.

Our studies into the aminohydroxylation reaction commenced with **1** (Scheme 3). Note that the corresponding carbamate of **1**

Scheme 1



Scheme 2



gave a yield of 43% of **2** in the TA reaction. Of course, there is no need to add a chlorinating agent to this TA reaction, and consideration of the likely pK_a of the NH proton[7] within **1** led us to run the hydroxyamination not just without *t*BuOCl but also without any hydroxide base.[8] Pleasingly, the reaction worked as planned and gave 70% yield of oxazolidone **2** (Scheme 3).

Next, a range of allylic alcohols was converted to the corresponding *N*-sulfonyloxy derivatives and then subjected to the chlorine-free TA reaction conditions (Scheme 3). In each case, the product of the reaction was identical to that obtained by conventional TA oxidation of the corresponding carbamate, but the yields were always higher. All of the main classes of allylic alcohol were examined, showing that the reaction works well for derivatives of achiral and chiral (both cyclic and acyclic) allylic alcohols.

The new regimen is much easier to perform and has none of the complications that arise when excess chlorinating agent is present in situ. As a testament to the extra simplicity of the reaction, it could be run at much lower catalyst loadings (1 mol % Os) and still gave acceptable yields of products; in our experience, this low catalyst loading is well out of range of a typical TA reaction.[9]

Extra information on the mechanism of reaction was gleaned by conducting a reaction on homoallylic alcohol derivative **11** using both catalytic and then stoichiometric potassium osmate (Scheme 4).

As expected, the catalytic reaction gave six-membered carbamate **12**, which was identical to that formed from the corresponding $ROCONH_2$ derivative, but with a yield greatly increased from 16 to 63%. Performing a reaction with 1 equiv of osmium, in the presence of TMEDA,[2b] allowed us to isolate osmium azaglycolate **13** in 36% yield (syn addition across the alkene was proven by

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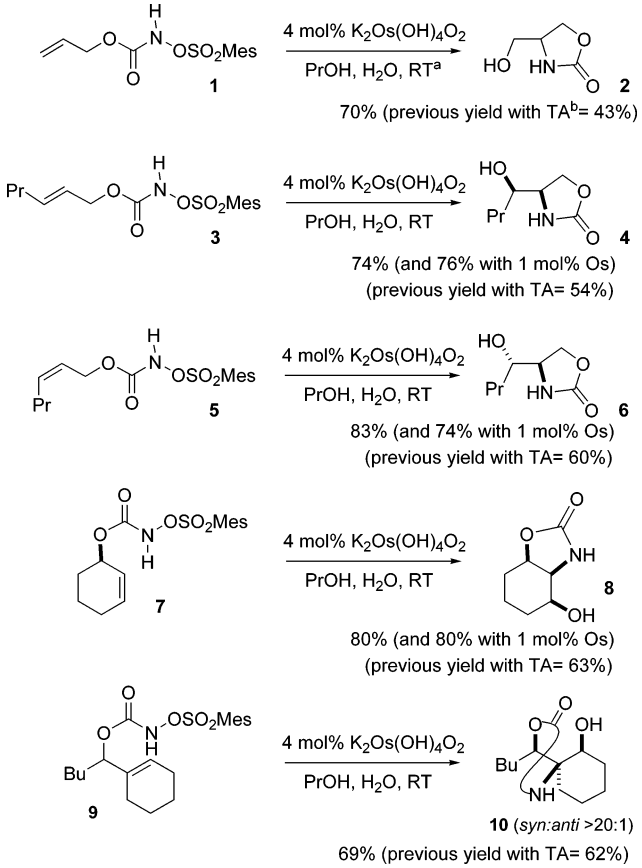
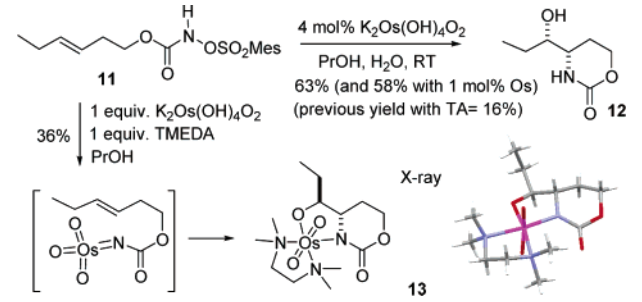
Scheme 3



[a] 5 mol % *i*Pr$_2$NEt was added to each reaction.[6] [b]All TA reactions were run with 4 mol % osmium.

Scheme 4. X-ray Structue of an Osmium Azaglycolate Intermediate

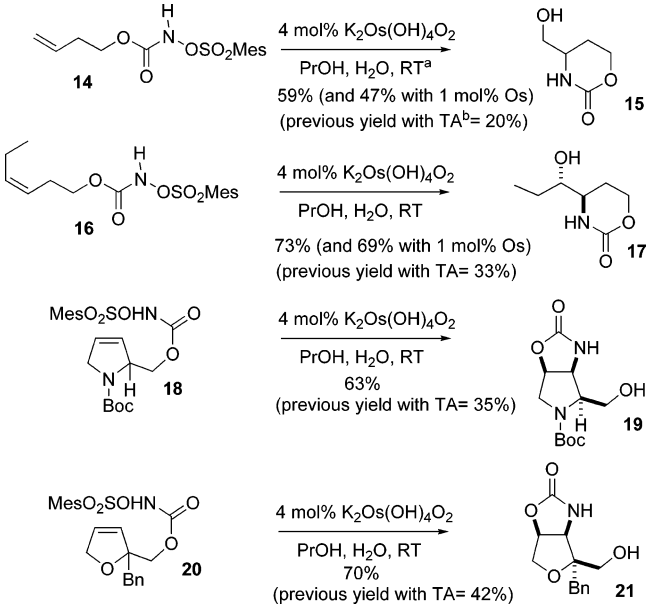


X-ray crystallography). The isolation of **13** is strong evidence in favor of the general mechanism of oxidation of Os(VI) using an *N*-sulfonyloxy carbamate.

We then investigated the new catalytic TA reaction as applied to extra homoallylic alcohol derivatives (Scheme 5). Our early work on the TA reaction of homoallylic carbamates was thwarted by competing chlorination of the alkene. Of course, now that we have access to a chlorine-free protocol we were able to obtain the desired TA oxidation products in good yields; certainly the improvement in this area is even more marked than in the allylic alcohol series. The complete stereoselectivity (followed by carbamate migration) in the TA reaction of both **18** and **20** is noteworthy.[10]

To conclude, we have shown that the *N*-chlorocarbamate reoxidant in an aminohydroxylation reaction can be replaced with an *N*-sulfonyloxy carbamate. This advance has removed the requirement to add chlorinating agent and hydroxide to TA reactions. Homoallylic derivatives that were previously untenable

Scheme 5



[a] 5 mol % *i*Pr$_2$NEt was added to each reaction. [b]All TA reactions were run with 4 mol % osmium.

substrates for the TA reaction have become compatible with these new conditions. Moreover, the reaction is cleaner, more efficient, and can be run with much lower catalyst loadings than before. These developments may also be of use in the formation of enantiopure amino alcohols via the Sharpless AA reaction.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Some small amount of base is present in this reaction: 8 mol % hydroxide from the catalyst and 5 mol % *i*Pr$_2$NEt. The pH of this reaction varies from 8 to 6 as MesSO$_3$H is liberated during the timecourse.

(9) Typically, the TA reaction of carbamates derived from allylic alcohols gave products in <30% yield with 1 mol % osmium cat. For specialized aminohydroxylation reactions with low catalyst loadings, see: Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3455.

(10) The stereochemistry of **17** and **21** was confirmed by X-ray crystallography on a derivative. The rearrangement of six- to five-membered carbamates from the TA reaction has been noted before: (a) Curtis, K. L.; Fawcett, J.; Handa, S. *Tetrahedron Lett.* **2005**, *46*, 5297. (b) Kenworthy, M. N.; McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 6661.

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