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Tethered Aminohydroxylation (TA) Reaction of Amides

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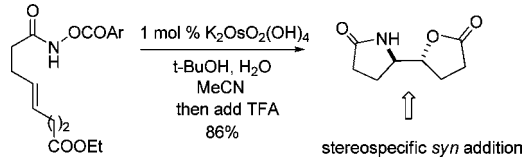
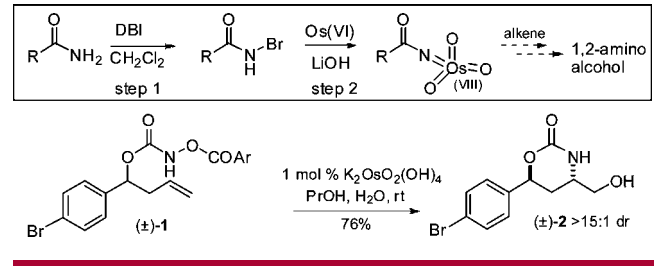
ABSTRACT



The first examples of amide-tethered aminohydroxylation reactions, catalyzed by osmium, showing that the use of N−O-based reoxidants are essential for success, are reported. The system that is described is compatible with a variety of different alkene substitution patterns and ring sizes and works with low loadings in both cyclic and acyclic systems. The levels of diastereoselectivity that were observed for substituents at both the allylic and homallylic position bode well for the use of stereoselective TA reactions in organic synthesis.

The osmium-catalyzed aminohydroxylation reaction has proven to be a valuable method for the introduction of two adjacent heteroatoms by the (stereospecific-*syn*) oxidation of an alkene.[1] In the intermolecular reaction, Sharpless has shown that both carbamates and amides are suitable nitrogen sources for the asymmetric aminohydroxylation (AA) when they are used as their corresponding *N*-halo derivative (which acts as the reoxidant in the catalytic cycle). For carbamate-based aminohydroxylation, chlorination of the parent ($ROCONH_2$) carbamate can be carried out in situ by the use of *t*BuOCl.[2] However, for AA reactions involving amides, the in situ generation of an *N*-halo amide (bromo derivatives are required) is not yet achievable, and these must be generated in a prior step from the amide ($RCONH_2$) and DBI (dibromoisocyanuric acid) (Scheme 1).[3] We recently extended the aminohydroxylation reaction of carbamates to proceed in an intramolecular fashion to access synthetically useful amino diol units in both cyclic and acyclic systems.[4] However, we had no success in performing an intramolecular TA of an *N*-bromo amide onto a pendant alkene. The problems that we encountered stemmed from unwanted

Scheme 1



[†] Author to whom correspondence regarding X-ray crystallography should be addressed.

(1) (a) Kolb, H. C.; Sharpless, K. B. *Transition Met. Org. Synth.* **1998**, *2*, 243. While other useful aminohydroxylation reactions based on metals such as copper and palladium have emerged, it is fair to say that none can match the stereospecificity and functional group tolerance offered by osmium. (b) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. (c) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (d) Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 1866. (e) Fuller, P. H.; Kim, J.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638.

(2) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1997**, *35*, 2813.

(3) (a) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1997**, *36*, 1483. (b) Demko, Z. P.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 2221.

(4) (a) Donohoe, T. J.; Helliwell, M.; Johnson, P. D.; Keenan, M. *Chem. Commun.* **2001**, 2078. (b) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934. (c) Donohoe, T. J.; Johnson, P. D.; Pye, R. J. *Org. Biomol. Chem.* **2003**, *1*, 2025. (d) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2004**, *6*, 2583.

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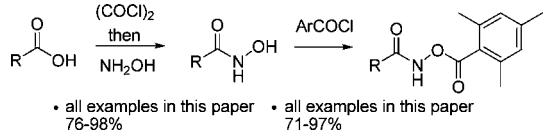
oxidation of the alkene by DBI which was necessary to form the *N*-bromo amide prior to the TA reaction. Herein, we report a solution to this problem using N−O reoxidants derived from amides.

Recently, we have reported an improvement of our original TA reaction that allowed N-OCOAr based substrates to act as the reoxidant for the reaction, thus removing the need for chlorine-based reagents in the reaction (see **1** → **2**).[5] This protocol was very successful for carbamates and allowed TA reactions to become higher yielding, cleaner, and compatible with low catalyst loadings. In this paper, we examine the viability of perfoming TA reactions of amides that have been preactivated as RCONHOCOAr derivatives so as to circumvent the problems of alkene bromination that were previously encountered.

In each case, our synthesis of the requisite *N*-OCOAr amides began with the corresponding acid which was converted into the hydroxamic acid in one pot (oxalyl chloride then NH_2OH), followed by reaction with trimethybenzoyl chloride. In our hands, this was the best aryl derivative, and acylation using pentafluorobenzoyl chloride gave decomposition products that appeared to originate from the Lossen rearrangement.[5b] This sequence proved to be reliable and high yielding across a wide range of substrates Scheme 2.

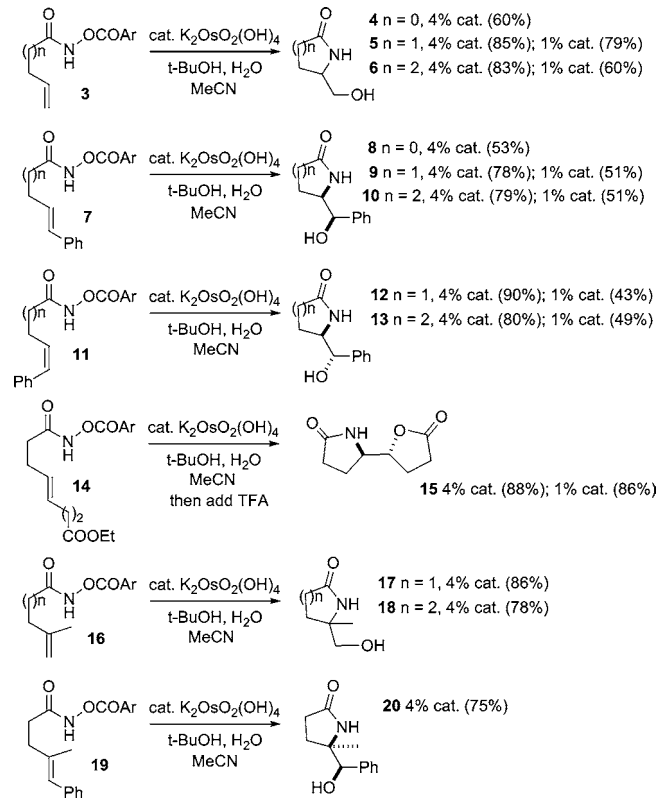
Scheme 2



With the requisite *O*-aryloyl hydroxamic acids in hand, we examined their reaction with catalytic osmium(VI) in the form of potassium osmate, in a mixture of tert-butyl alcohol and aqueous MeCN, Scheme 3 (Ar = $Me_3C_6H_3$).

Bearing in mind that the substrate itself is the reoxidant for Os(VI) to Os(VIII) then no other additives were required and these are very clean reactions. The results shown in Scheme 3 reveal that the tethered aminohydroxylation reaction of amides is an efficient process capable of forming β-lactams ($n = 0$), pyrrolidinones ($n = 1$), and piperidinones ($n = 2$) in good yields and with low catalyst loadings (1% in some cases, with the remaining mass being recovered starting material).[6] Moreover, the results of oxidation of **7** and **11** show that the reaction is stereospecific for the *syn*-addition of the two heteroatoms across the alkene, as

Scheme 3



predicted, vide infra.[7] The oxidation of substrate **14** was followed by in situ lactonisation of the newly installed hydroxyl group to form the lactam/lactone **15** which is the basis of several natural products.[8] Finally, oxidation of 1,1-disubstituted alkenes revealed the potential of this TA to provide highly substituted lactams.

We next examined the idea of diasteroselective cyclization reactions on chiral substrates; therefore, a series of chiral acids were converted into the oxidation precursors and then subjected to the TA reaction in a search for stereoselectivity, Scheme 4. Early studies showed that even a Me group adjacent to the carbonyl gave decent levels of diastereoselectivity for the *cis*-1,3-disubstituted pyrrolidinones **22** and *trans*-piperidinones **23**.[9] Moving the stereodirecting methyl group to an allylic position was not as successful and compounds **25** and **26** were formed with little selectivity. However, introducing a larger (Ph) group at this position did impart significant levels of diastereoselectivity upon the TA reaction (**27** → **28**), and this process should have application in natural product synthesis.[10]

Finally, we examined this TA sequence on cyclic alkenes in order to assess the full scope of the methodology, Scheme

(5) (a) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514. (b) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725. see also. (c) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (d) Lebel, H.; Lectard, S.; Parmentier, M. *Org. Lett.* **2007**, *9*, 4797.

(6) The TA reaction to form 7- and 8-membered lactam rings was unsuccessful.

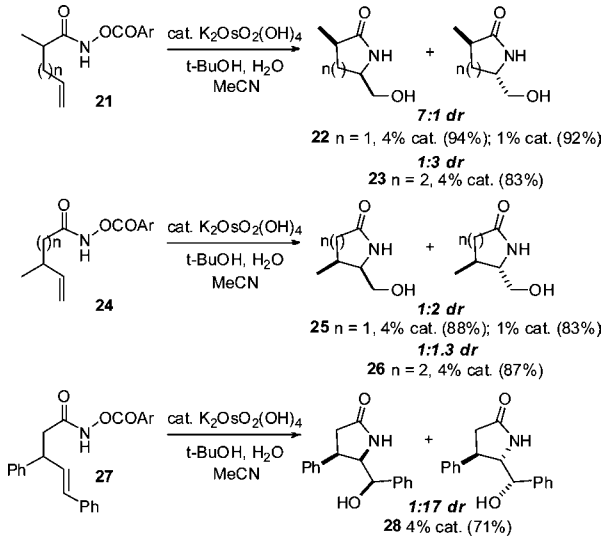
(7) The stereochemistry of **8**−**10**, **12**, **13**, **17**, **20**, **28**, **30**, **32**, and **35** was determined by X-ray analysis and of **15**, **25**, and **34** by analogy. The stereochemistry of **22** and **23** was assigned by NMR experiments.

(8) Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117.

(9) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.

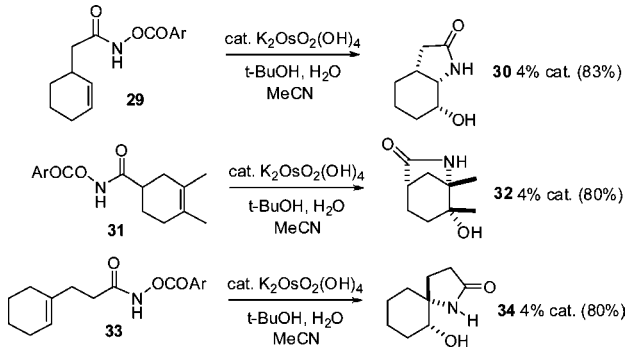
(10) See, for example, the epiclausinamides: Wu, Y.; Liu, L.; Wei, H.; Liu, G. *Acta Pharmacol. Sin* **2006**, *27*, 1024.

Scheme 4



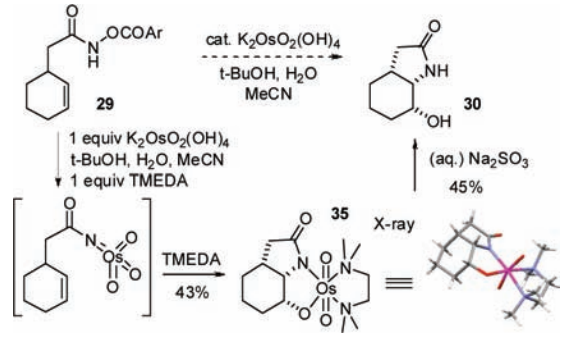
5. The results show that a variety of stereoselective *syn* addition reactions are possible giving access to useful cyclic amino alcohols.

Scheme 5



We propose the following mechanism for this reaction, Scheme 6. Indeed, we were able to trap out an Os(VI) intermediate[11] generated in a model stoichiometric oxidation of **29** using TMEDA as a stabilizing ligand (compound **35** was characterized by X-ray crystallography and lends considerable weight to the proposed mechanism). The X-ray structure of **35** is significant because it is the first time that we have been able to observe an azaglycolate osmate ester derived from an amide, rather than a carbamate. As expected, **35** was transformed into genuine product **30** in a separate hydrolysis experiment.

Scheme 6



To conclude, we have reported the first examples of amide tethered aminohydroxylation reactions and shown that the use of N−O-based reoxidants are essential. The system is compatible with a variety of different alkene substitution patterns and ring sizes (4, 5, 6) and works with low loadings in both cyclic and acyclic systems. The levels of diastereoselectivity that we observed bode well for the use of stereoselective TA reactions in synthesis.[12]

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

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(11) Griffith, W. P.; Pawson, D. *J. Chem. Soc., Dalton Trans.* **1973**, *12*, 1315.

(12) For example: (a) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2005**, *7*, 1275–1277. (b) Kenworthy, M. N.; McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 6661–6664. (c) Cohen, J. L.; Chamberlin, A. R. *Tetrahedron Lett.* **2007**, *48*, 2533–2536.