N-Sulfonyloxy carbamates as reoxidants for aminohydroxylation reactions

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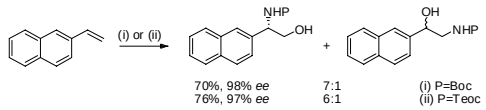
Introduction

The Sharpless asymmetric aminohydroxylation (AA) reaction is a powerful method for the synthesis of enantioenriched *syn*-1,2-amino alcohols from alkenes (**Scheme 1**).[1,2]

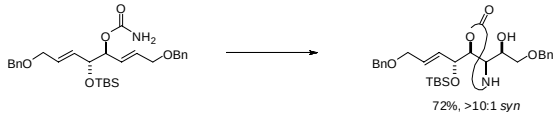


Scheme 1 – Reagents & conditions: *t*BuOCl (3.05 eq.), NaOH (3.05 eq.), $K_2[OsO_2(OH)_4]$ (4 mol%); (i) $BocNH_2$ (3.10 eq.), $(DHQ)_2PHAL$ (6 mol%), *n*PrOH:H_2O (2:1), 0 °C ; (ii) $TeocNH_2$ (3.10 eq.), $(DHQ)_2PHAL$ (5 mol%), *n*PrOH:H_2O (1:1).

This methodology has two principal drawbacks: (i) poor regioselectivity with some unsymmetrical alkenes; (ii) requirement of 3 equivalents of nitrogen source to obtain satisfactory product yields.

The Donohoe group has made efforts to address both of these issues:

(i) Tethered Aminohydroxylation (TA) – allows for complete regiocontrol and high diastereoselectivity with chiral alcohols (**Scheme 2**).[3]



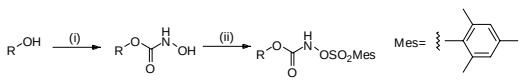
Scheme 2 – Reagents & conditions: *t*BuOCl (1.00 eq.), NaOH (0.92 eq.), $K_2[OsO_2(OH)_4]$ (4 mol%), *i*Pr_2NEt (5 mol%), *n*PrOH:H_2O (1:1).

The reaction is limited by modest yields and largely confined to allylic alcohols, homoallylic substrates afford poor product yields (<40%).

(ii) Novel reoxidants – this project examined alternative leaving groups on nitrogen in the nitrene equivalent reoxidant.

N-Sulfonyloxy carbamate reoxidants

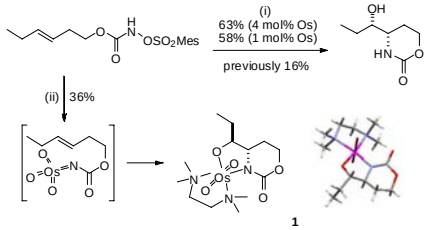
It was found that *N*-chlorocarbamates have a limited lifetime in aminohydroxylation reactions; this cannot be compensated for by use of excess reagent in the intramolecular TA reaction. In some TA substrates, competing chlorination of the alkene was observed as a detrimental side reaction.



Scheme 3 – Reagents & conditions: (i) CDI (1.50 eq.), MeCN, then imidazole (4.00 eq.), $NH_2OH.HCl$ (5.00 eq.); (ii) $MesSO_2Cl$ (1.00 eq.), Et_3N (1.00 eq.), toluene:DMF (4:1), 0 °C.

N-Sulfonyloxy carbamates have been developed as superior reoxidants for the TA reaction.[4] These were readily prepared in good yields in a two-pot procedure by sequential reaction of the corresponding alcohol with CDI and hydroxylamine, followed by sulfonylation (**Scheme 3**).

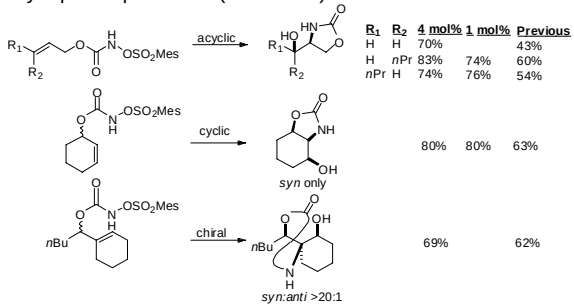
The modified procedure removes the need for both base and chlorinating agent and allows lower catalyst loading. Use of stoichiometric potassium osmate allowed isolation of the intermediate osmium azaglycolate **1**, providing strong evidence for oxidation of Os (VI) by the *N*-sulfonyloxy carbamate, and *syn*-addition across the double bond (**Scheme 4**).



Scheme 4 – Reagents & conditions: (i) $K_2[OsO_2(OH)_4]$, *i*Pr_2NEt (5 mol%), *n*PrOH:H_2O (1:1); (ii) $K_2[OsO_2(OH)_4]$ (1.00 eq.), TMEDA (1.00 eq.), *n*PrOH.

Allylic systems

In all tested cases, yields of the oxazolidinones were higher than with the previously reported procedure (**Scheme 5**).

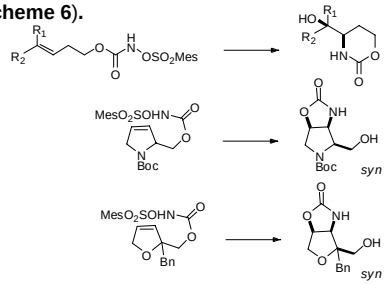


R_1	R_2	4 mol%	1 mol%	Previous
H	H	70%		43%
H	*n*Pr	83%	74%	60%
*n*Pr	H	74%	76%	54%
		80%	80%	63%
		69%		62%

Scheme 5 – Reagents & conditions: (i) $K_2[OsO_2(OH)_4]$, *i*Pr_2NEt (5 mol%), *n*PrOH:H_2O (1:1).

Homoallylic systems

A slower reaction to form 6-membered oxazinones meant that homoallylic substrates were particularly susceptible to alkene chlorination. The new procedure shows more marked improvement than the allylic series **(Scheme 6).**

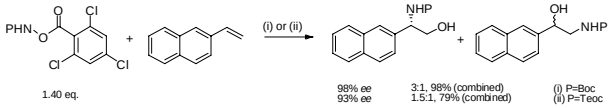


R_1	R_2	4 mol%	1 mol%	Previous
H	H	59%	47%	20%
H	*n*Pr	63%	58%	16%
*n*Pr	H	73%	69%	33%
			63%	35%
			70%	42%

Scheme 6 – Reagents & conditions: (i) $K_2[OsO_2(OH)_4]$, *i*Pr_2NEt (5 mol%), *n*PrOH:H_2O (1:1).

Intermolecular aminohydroxylations

N-Sulfonyloxy carbamates give poor regio- and enantioselectivities compared with conventional AA procedures, due to their incompatibility with hydroxide bases. However, ester-based leaving groups allow comparable selectivities and yields to be obtained using half the quantity of nitrogen source. The 2,4,6-trichlorobenzoyl derivative was found to be optimal (**Scheme 7**).



Scheme 7 – Reagents & conditions: $K_2[OsO_2(OH)_4]$ (4 mol%), LiOH (1.32 eq.) (i) P=Boc - $(DHQ)_2PHAL$ (6 mol%), *n*PrOH:H_2O (2:1), 0 °C ; (ii) P=Teoc - $(DHQ)_2PHAL$ (5 mol%), *n*PrOH:H_2O (1:1).

Acknowledgements

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References

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