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A survey of suitable protecting groups for the synthesis of hydroxylamines by Mitsunobu reactions

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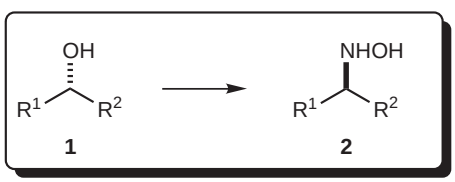
Abstract—A variety of protecting groups, commonly associated with peptide synthesis, are suitable for the *N*,*O*-protection of hydroxylamine; the resulting reagents are all suitable for *N*-alkylhydroxylamine synthesis using the Mitsunobu method. © 2001 Elsevier Science Ltd. All rights reserved.

In connection with our studies of the reverse-Cope reaction,[1,2] we required access to various *N*-alkylhydroxylamines **2** containing a suitably positioned alkene group, using an approach which was capable of delivering chiral, non-racemic material. While there are relatively limited but, in many cases viable approaches to such hydroxylamine derivatives,[3] the most suitable for the elaboration of single enantiomers appeared to be by Mitsunobu inversion[4,5] of the corresponding alcohols **1** using *N*,*O*-doubly protected hydroxylamines as the nucleophiles. Such species have been used before in related hydroxylamine synthesis: the bis-Boc reagent **3** can be *N*-allylated under PTC conditions[6] by allylic bromides and also by related allylic electrophiles using a Pd(0) catalyst,[7] and additions, both Pd-catalysed and uncatalysed, of its sodium salt to 1-chlorocyclohex-2-enes.[8] The Mitsunobu method itself has been used to *N*-alkylate the bis-phenoxycarbonyl reagent **4** by alcohols,[9] based on much earlier work by Miller et al.,[10] who first introduced this idea, using the *O*-benzyl reagent **5**. However, these derivatives contained protecting groups which were too stable for our purposes. For example, removal of the Boc functions from derivatives of reagent **3** also caused hydrolysis of other protecting groups and gave poor yields of the required hydroxylamines, phenylcarbamates derived from reagent **4** were too stable and hydrogenolysis of the *O*-benzyl group in derivatives of reagent **5** was incompatible with the presence of an alkene group in the projected reverse-Cope substrates, despite the fact that this can be done without N–O bond cleavage.[11]

In general bis-protected species related to reagent **3** should be good Mitsunobu nucleophiles, as the presence of two electron withdrawing groups should lower the pK_a of the N–H bond to be broken, a crucial enabling feature in such chemistry.[12] Herein, we report our study of a range of alternative hydroxylamine protecting groups which suggests that this should be a very widely applicable method.

As representative examples, offering a range of deprotection possibilities, we chose the symmetrically protected mixed carbamate–carbonates **6**–**9**, featuring Z,[13] Alloc,[14] Troc[15] and Teoc[15] functions, respectively. These were all readily prepared by a Schotten–Bauman procedure consisting of treating an ice-cold solution of hydroxylamine hydrochloride in aqueous tetrahydrofuran containing 3.3 equivalents of sodium carbonate with two equivalents of the respective



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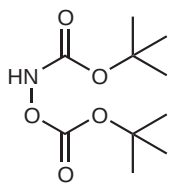

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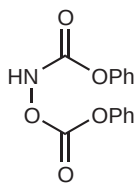

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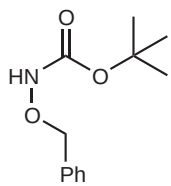

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Keywords: hydroxylamines; carbamates; carbonates; protection; Mitsunobu.

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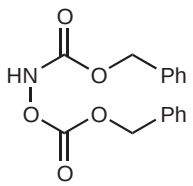
chloroformate. All four products were thus secured in 80–90% isolated yield after a simple extractive work-up. The only difficulty encountered was the ability of the Troc derivative **8** to retain water tenanciously.[15]

Mixed derivatives were also readily obtainable, due to the greater nucleophilicity of the amino group in hydroxylamine. Thus, using the same Schotten–Bauman protocol but with less than an equivalent of the chloroformate, reasonable 50–60% yields of the mono-*N*-protected derivatives were isolated; subsequent repetition, but with a different chloroformate, then gave representative mixed derivatives (e.g. **10** and **11**). Returning to the original procedure, the bis-9-fluorenyloxycarbonyl (Fmoc) species **12**, mp 129°C, was obtained in 79% isolated yield.

The key Mitsunobu displacements were carried out by the addition of diisopropyl azodicarboxylate to an ice-cold solution of triphenylphosphine, a hydroxylamine reagent **6**–**10** and an alcohol in tetrahydrofuran, followed by stirring without external cooling for a further 2 h. During this work, it was observed that older samples of the azodicarboxylate often delivered inferior yields, in which cases, substitution by a recently purchased sample usually restored good yields. The results obtained are presented in Table 1; yields refer to pure, isolated products which have been fully characterised. The yields obtained are mostly highly viable with primary alcohols, but were slightly lower with the two aliphatic secondary alcohols examined. In the case of the propargylic alcohol, the displacements appeared to proceed entirely by the expected S_N2 mechanism; in no



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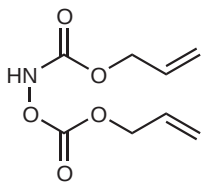

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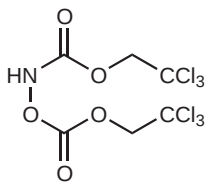

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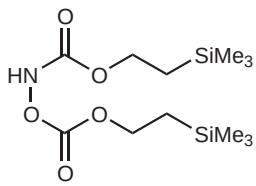

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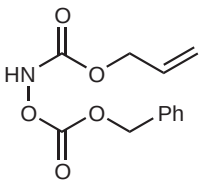

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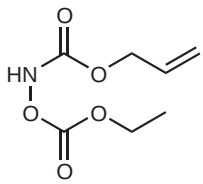

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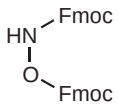

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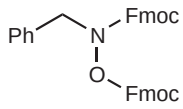

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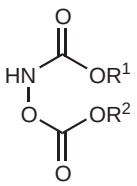
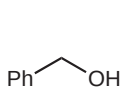
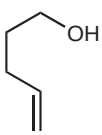
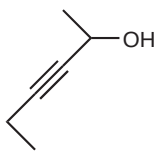
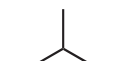
Table 1. Isolated yields from Mitsunobu reactions of protected hydroxylamines **3**, **6**–**10**

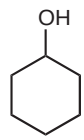












$R^1 = R^2 = PhCH_2$ **[6]**	87	73	69	55	22
$R^1 = R^2 = CH_2CH{:}CH_2$ **[7]**	96	91	80	61	38
$R^1 = R^2 = CH_2CCl_3$ **[8]**	83	75	69	--	38
$R^1 = R^2 = (CH_2)_2SiMe_3$ **[9]**	90	76	68	--	17
$R^1 = R^2 = Bu^t$ **[3]**	78	82			
$R^1 = CH_2CH{:}CH_2$; $R^2 = PhCH_2$ **[10]**	79	69	62	58	33

instances were any allenic products isolated, arising from S_N2' reactions. Most yields were comparable or slightly better than those obtained using the known bis-Boc derivative **3** and were not improved by either initial complexation of the phosphine and the azodicarboxylate or by using the reportedly more reactive tetramethyl azodiamide (TMAD) analogue.[16] In contrast, reactions involving cyclohexanol uniformly gave poorer yields. This is a phenomenon which has been observed previously[16,17] and it would seem, at this stage, that Mitsunobu reactions in general with cyclic secondary alcohols should be viewed as potentially inefficient. In no case was any decomposition of the various protecting groups observed. However, perhaps not surprisingly, the bis-Fmoc hydroxylamine **12** delivered a relatively lower 58% yield of the *N*-benzyl derivative **13** when coupled with benzyl alcohol, presumably due to the sensitivity of this functionality to various basic species present in the Mitsunobu mixture.

Deprotection was accomplished using standard methodology in the cases of derivatives of the reagents **7**–**10**. Firstly, in all examples, the carbonate could be cleaved regiospecifically by exposure to methanolic potassium carbonate to give singly protected carbamates in 90–95% isolated yields. This could offer a benefit in cases where the chloroformate is particularly valuable, as much cheaper analogues, such as ethyl chloroformate, can be used to elaborate in the carbonate function in the two-step protection method. Complete deprotection of derivatives of the hydroxylamines **7**–**10** was achieved, at least in the examples shown in Table 1, by using $Pd(Ph_3P)_4$ in the presence of dimedone, zinc metal or fluoride, respectively. Some examples of this are included in the following paper;[18] in general, the expected hydroxylamines were isolated in >70% yields, but the sensitive nature of these meant that the samples were not purified completely. The Troc deprotections gave lower yields (40–50%), presumably due to some N–O bond cleavage. In practise, such deprotections would usually be followed by the next synthetic step in a particular sequence, such as nitrone formation or, as outlined in the following paper, a reverse-Cope cyclisation.

In summary, we have demonstrated that a range of typical amine protecting groups are suitable for the protection of hydroxylamines and also compatible with the Mitsunobu reaction, suggesting that this could be a very general method, and that the exact protecting groups used could be tailored to the requirements of the subsequent chemistry. Of particular significance is that this method should allow ready access to enantiopure hydroxylamines from the corresponding secondary alcohols.

Acknowledgements

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