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## 2 Synthetic methods

### Part (v) Protecting groups

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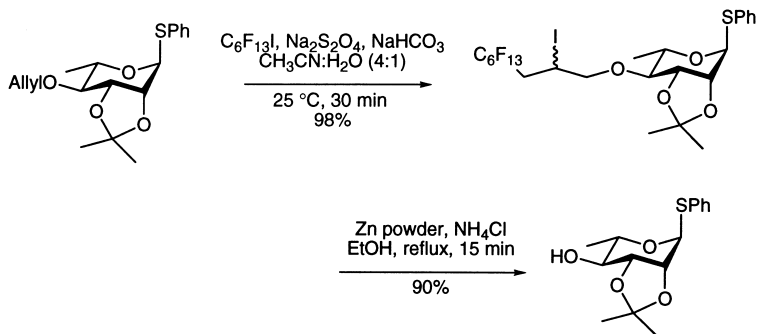
Another excellent and comprehensive 'update' review of protecting group strategies in organic synthesis has appeared this year.<sup>1</sup> Additionally, a useful review focusing on enzymes as 'reagents' for protecting group manipulation (mainly esters and amides) has been published.<sup>2</sup>

#### 1 Hydroxy protecting groups

The development of mild new methods for the cleavage of allyl ethers continues to attract attention. An interesting example is a new two-step procedure whereby sodium dithionate ( $\text{Na}_2\text{S}_2\text{O}_4$ )–sodium bicarbonate mediated (*i.e.* radical) addition of perfluorohexyl iodide ( $\text{C}_6\text{F}_{13}\text{I}$ ) in  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  (4: 1) affords the corresponding  $\beta$ -iodo- $\gamma$ -perfluoroalkyl derivatives which undergo reductive elimination on treatment with Zn-powder and ammonium chloride in refluxing EtOH to afford anomeric hemiacetals of carbohydrates,<sup>3</sup> secondary alcohols and carboxylic acids<sup>4</sup> from their respective allyl protected forms. Acetoxy and secondary hydroxy groups, isopropylidene and benzylidene acetals, thiophenyl ethers, and trisubstituted double bonds are inert under these conditions (Scheme 1).

Preliminary studies on the oxidative deprotection of allyl glycosides using *tert*-butyl hydroperoxide–copper(I) bromide in *t*-BuOH– $\text{H}_2\text{O}$  at 70 °C (*Kharasch–Sosnovsky* reaction *via* peroxyacetal intermediates) have also been disclosed but presently give moderate yields.<sup>5</sup>

Two new methods for the chemoselective *O*-methylation of phenols in the presence of alkyl alcohols have appeared: LiOH· $\text{H}_2\text{O}$  (1 equiv.), dimethyl sulfate (0.5 equiv.) in dry THF at 25 °C,<sup>6</sup> and  $\text{Cs}_2\text{CO}_3$  (0.25 equiv.) in neat dimethyl carbonate at 120 °C.<sup>7</sup> The former method, which uses a minimum of dimethyl sulfate, is compatible with benzylic primary amide and ester functionality and efficiently methylates (*R*)-*N*-Boc tyrosine methyl ester without loss of optical purity. The latter avoids the use of dimethyl sulfate (which is toxic) and can also be applied to the preparation of methyl esters. 3-Pentyl ether protection of tyrosine has been advocated during segment coupling as it is compatible with both fluoren-9-ylmethoxycarbonyl (Fmoc) and

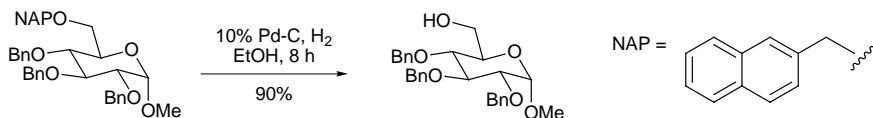


**Scheme 1**

*tert*-butoxycarbonyl (Boc) based peptide synthesis strategies.<sup>8</sup> Introduction employs NaH then 3-bromopentane in *N,N*-dimethylformamide (DMF) (no racemisation observed for *N*-Boc tyrosine) and cleavage employs neat trifluoroacetic acid (TFA), 25 °C. Cleavage could also probably be effected using AlCl<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> which has been reported to selectively cleave isopropyl aryl ethers in the presence of methyl aryl ethers.<sup>9</sup> Phenolic triisopropylsilyl (TIPS) ethers are not stable to these conditions. The Boc group has been shown to be a useful group for the protection of highly hindered phenols such as 2,6-di-*tert*-butylphenol.<sup>10</sup> The group is introduced using di-*tert*-butyl dicarbonate (Boc<sub>2</sub>O)-*N,N*-dimethyl-4-aminopyridine (DMAP) in CH<sub>3</sub>CN or CH<sub>2</sub>Cl<sub>2</sub> and deprotected using 3 M aq. HCl-dioxane (1: 1) at reflux. Deprotection using TFA was unsatisfactory due to competing dealkylation and *o*- and *p*-realkylation by the liberated *tert*-butyl cation.

Trityl ethers are popular acid labile protecting groups and a new method for their introduction under almost neutral conditions employs stoichiometric benzyl trityl ether (BTE) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) with 4 Å molecular sieves in ClCH<sub>2</sub>CH<sub>2</sub>Cl.<sup>11</sup> The expected selectivity for primary over secondary alcohols is observed. Non-acidic deprotection of both trityl and monomethoxytrityl ethers can be effected using 1% iodine in MeOH allowing preservation of acetate and *tert*-butyldimethylsilyl (TBDMS) ethers providing the temperature is kept below 40 °C.<sup>12</sup> A photo-labile trityl derivative, the 9-phenylxanthen-9-yl (pixyl) group, which undergoes heterolytic C–O bond cleavage on irradiation at 254 or 300 nm in CH<sub>3</sub>CN–H<sub>2</sub>O in excellent yields, has also been developed.<sup>13</sup>

Due to the enduring popularity of benzyl ether protection, particularly in the field of oligosaccharide synthesis, numerous new and selective methods for their deprotection continue to be reported. Of note is a new dual ‘primary benzyl ether deprotection and alkyl to thiophenylglycosyl’ conversion employing PhSSiMe<sub>3</sub>, ZnI<sub>2</sub>, Bu<sub>4</sub>Ni in ClCH<sub>2</sub>CH<sub>2</sub>Cl (a reagent combination introduced by Hanessian for the latter process).<sup>14</sup> Of more general utility is the extensive work that has been reported this year on the effect of additives (both promoters and dopants) on palladium-catalysed hydrogenolysis. Thus Ti-loaded hexagonal mesoporous silica (TiHMS) significantly accelerates the cleavage of primary and secondary benzyl ethers by hydrogen using 5% Pd–C in MeOH in the presence of acid-sensitive functionality such as TBDMS and

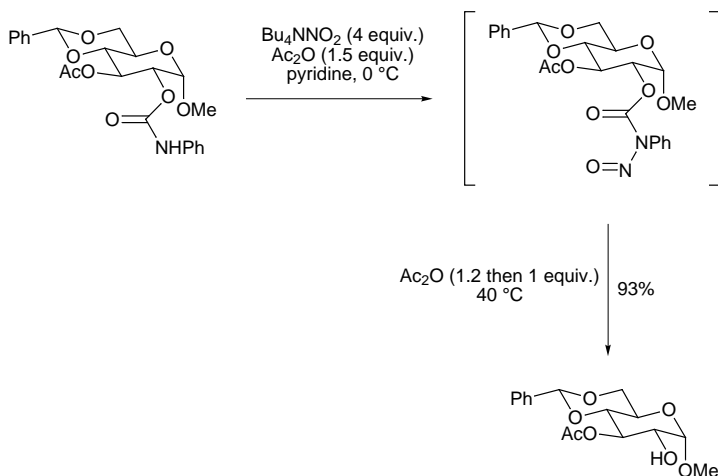


**Scheme 2**

tetrahydropyranyl (THP) ethers, and dimethyl acetals.<sup>15</sup> Elegant studies into the mechanistic details of hydrogenolysis with Pd–C (and homogeneous Pd systems) have highlighted the amphipolar nature of the Pd–H bond resulting in insights of use in synthesis.<sup>16</sup> For example, the use of specific amine dopants for tempering the reactivity of the Pd surface such that disubstituted alkenes, benzyl esters and nitro functions can be reduced in the presence of phenolic benzyl ethers,<sup>17</sup> mono-, di- and tri-substituted alkene hydrogenation in the presence of *O*-benzyl and *N*-benzyloxycarbonyl (Cbz) groups,<sup>18</sup> and the use of 2-naphthylmethyl (NAP) as a benzylic protecting group which is more labile to hydrogenolysis than the benzyl group, thereby allowing sequential deprotection of the two (Scheme 2).<sup>19</sup>

Use of fluorous ‘tagged’ benzyl protecting groups during oligosaccharide synthesis has been shown to allow rapid fluorous-organic separation techniques although presently the yields of introduction of these groups leave much to be desired (51% for standard tribenzylation of a monosaccharide).<sup>20</sup> Microwave thermolysis using clay supported ammonium nitrate (Clayan) in the absence of solvent offers a cost effective and environmentally benign method for the selective deprotection of alkyl and aryl *p*-methoxybenzyl (PMB) ethers in the presence of silyl ethers, acetates, esters, double and triple bonds and benzyl ethers.<sup>21</sup> *O*-2,4-Dimethoxybenzyl (DMB) protection of hydroxamic acids during parallel synthesis allows for clean deprotection by 5% TFA ( $\pm$  triethylsilane as benzyl cation scavenger) in  $\text{CH}_2\text{Cl}_2$ .<sup>22</sup> An economical method for the preparation of benzhydryl ethers would appear to be by refluxing equimolar quantities of alcohol and benzhydrol with catalytic *p*-TSA in benzene in a Dean–Stark trap.<sup>23</sup>

In the area of ester protection of alcohols there have been further advances in non-enzymatic kinetic resolution of secondary alcohols *via* acylation using ‘synthetic’ chiral catalysts based on DMAP derivatives,<sup>24–26</sup> *N*-alkylimidazole containing tripeptides,<sup>27,28</sup>  $\text{TaCl}_5$ –chiral diol complexes,<sup>29</sup> and chiral diamines.<sup>30,31</sup> Preparation of esters of highly hindered alcohols by reaction with an acid is frequently a challenging proposition but a number of excellent protocols have now been developed including the use of scandium triflate–DMAP<sup>32</sup> and *O,O'*-di(2-pyridyl) thiocarbonate–DMAP.<sup>33</sup> An alternative protocol employs the acid anhydride with trimethylsilyl triflate (TMS-OTf).<sup>34</sup> Selectivity for acylation of primary over secondary (or tertiary) alcohols is also challenging and stannoxane catalysed transesterification with alkenyl esters (*e.g.* vinyl acetate),<sup>35</sup> triphenylphosphine–carbon tetrabromide mediated transesterification with ethyl acetate (or formate),<sup>36</sup> and lanthanide triflate catalysed acylation with anhydrides<sup>37,38</sup> all display useful levels of such selectivity. The utility of cerium(III) chloride ( $\text{CeCl}_3$ ) and copper(I) chloride for promoting selective C-10 [over C-7] acylation in 10-deacetylbaccatin III has also been investigated.<sup>37</sup> Racemisation of optically labile secondary alcohols during esterification can also prove troublesome and *N*-acylpyridinium triflates are recommended in such situations.<sup>39</sup> Environment-



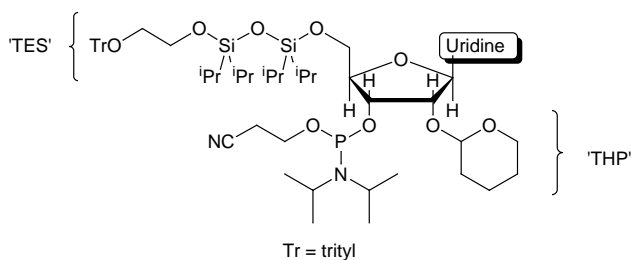
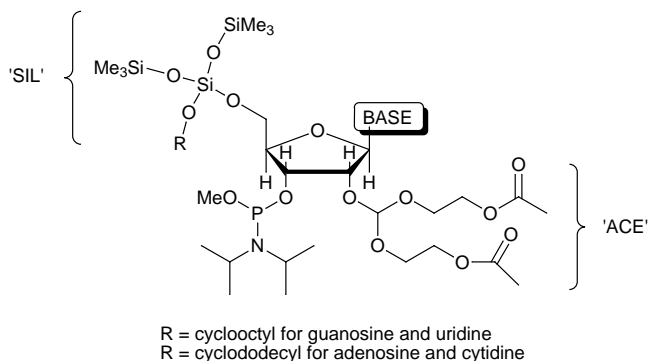
**Scheme 3**

ally benign methods for the per-*O*-acetylation of polyols (particularly sugars) include using neat acetic anhydride ( $\text{Ac}_2\text{O}$ ) with either Montmorillonite K-10<sup>40</sup> or Zeolite HSZ-360,<sup>41</sup> both of which are cheap solids which can be readily recycled. A new ester group, the 2,2-dimethylpent-4-enoate, has been introduced as an oxidatively labile pivaloate equivalent.<sup>42</sup> Use of pivaloate protection, particularly for tertiary alcohols, is often limited by the vigorous hydrolysis conditions required to effect cleavage. The 2,2-dimethylpent-4-enoate however, can be removed by intramolecular 6-*exo*-trig lactonisation following either hydroboration–oxidation [9-borabicyclo[3.3.1]nonane (9-BBN)– $\text{H}_2\text{O}_2$ ] or dihydroxylation [ $\text{OsO}_4$ –*N*-methylmorpholine oxide (NMO)].

The transformation of alcohols into *N*-phenylcarbamates using *e.g.* *N*-phenyl isocyanate is rarely considered as a protection step because deprotection requires drastic conditions (*e.g.*  $\text{LiAlH}_4$  in refluxing THF or sodium ethoxide in refluxing EtOH). However, *N*-nitrosation of alkyl *N*-arylcabamates at  $0^\circ\text{C}$  in pyridine using acetic nitrous anhydride [ $\text{AcONO}$ , generated *in situ* from  $\text{Ac}_2\text{O}$ –tetrabutylammonium nitrite ( $\text{Bu}_4\text{NNO}_2$ )] followed by addition of further  $\text{Ac}_2\text{O}$  and heating to  $40^\circ\text{C}$  allows for efficient deprotection of  $\alpha$ -D-glucofuranose derivatives without acetyl, benzoyl, pivaloyl or TBDMS migration.<sup>43</sup> This innovation makes *N*-phenylcarbamate protection of alcohols much more attractive in the context of organic synthesis (Scheme 3).

Toluene-*p*-sulfonates are generally prepared to enable  $\text{S}_{\text{N}}2$  type substitution rather than as an alcohol protection strategy. However, following the development of interesting asymmetric ketone  $\alpha$ -tosyloxylation and alkene 1,2-tosyloxylation protocols using hypervalent iodine reagents, mild methods for accomplishing their ‘deprotection’ have been developed utilising magnesium in dry MeOH.<sup>44</sup>

Methods for the selective deprotection of various silyl ethers are legion. Useful additions to the synthetic repertoire disclosed this year include: the use of 1% iodine in MeOH<sup>45,46</sup> and catalytic scandium triflate in  $\text{CH}_3\text{CN}$ – $\text{H}_2\text{O}$ <sup>47</sup> for selective deprotection of alkyl trialkylsilyl ethers in the presence of aryl trialkylsilyl ethers. Both systems are also successful for distinguishing different alkyl trialkylsilyl ethers in favourable



**Scheme 4**

cases. Carbon tetrabromide in refluxing MeOH or <sup>1</sup>PrOH is also useful in this regard and can be used for deprotection of primary TIPS ethers in the presence of secondary ones.<sup>48</sup> Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F), a commercially available anhydrous solid, also appears to be a useful reagent for mild silyl ether removal in extremely base sensitive situations where alternative fluoride sources fail.<sup>49</sup> This reagent has been used in DMF at 23 °C to successfully deprotect TBDMS and triethylsilyl (TES) ethers in complex natural product synthesis when tetrabutylammonium fluoride (TBAF) and HF-pyridine methods failed. Cerium(III) chloride heptahydrate (CeCl<sub>3</sub>·7H<sub>2</sub>O)-sodium iodide in CH<sub>3</sub>CN is also a useful reagent combination for nearly neutral deprotection of trialkylsilyl ethers in the presence of THP ethers.<sup>50</sup> The versatility of pyridinium toluene-*p*-sulfonate (PPTS) as a cheap, mild and selective acid catalyst has been highlighted by its use for primary TBDMS ether deprotection in the presence of primary *N*-Boc carbamates.<sup>51</sup> Silyl protecting groups are gaining popularity for protection of 5'-hydroxy positions during RNA synthesis using the phosphoramidite method. Traditionally this position is protected as an acid labile dimethoxytrityl (DMT) ether and the 2'-hydroxy by a fluoride-labile TBDMS group. The 'reversal' of this orthogonality by employing fluoride-labile 5'-protection and acid-labile 2'-protection appears to produce cleaner RNA. Both 5'-*O*-SIL-2'-*O*-ACE<sup>52</sup> and 5'-*O*-TES-2'-*O*-THP<sup>53</sup> ribonucleoside phosphoramidites (Scheme 4) have been advocated although the former presently appears superior since fluoridolytic cleavage of the TES group induces partial cleavage of the 2-cyanoethyl phosphoramidite group.

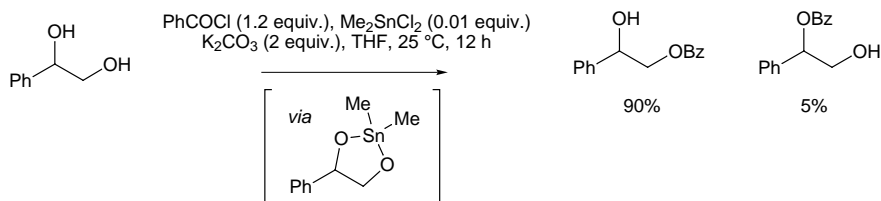
Oxidative cleavage of silyl ethers yields either aldehydes or ketones. DDQ is

probably one of the mildest methods available for this transformation and is useful for the preparation of labile  $\alpha,\beta$ -unsaturated aldehydes from allylic TBDMS ethers and benzaldehyde derivatives from benzylic TBDMS ethers.<sup>54</sup> A more vigorous procedure employs dinitrogen tetroxide complexes of iron(III) nitrate [ $\text{Fe}(\text{NO}_3)_3 \cdot \text{N}_2\text{O}_4$ ] and copper(II) nitrate [ $\text{Cu}(\text{NO}_3)_2 \cdot \text{N}_2\text{O}_4$ ] either neat, in  $\text{CH}_2\text{Cl}_2$ , or in  $\text{CCl}_4$  at 25 °C.<sup>55</sup> These conditions also effect oxidative cleavage of THP ethers, acetals and thioacetals to give aldehydes and ketones.

4,6-*O*-Phenylboronate diester protection of thioethylglycosyl donors during *N*-iodosuccinimide (NIS)–triflic acid (TfOH) mediated glycosylation appears to offer an interesting alternative to benzylidene acetal protection.<sup>56</sup> A particular advantage is the easy introduction of this grouping by refluxing with phenylboronic acid in benzene with a Dean–Stark trap and easy deprotection using the borate selective resin Amberlite-IRA-743 in dry  $\text{CH}_3\text{CN}$  at room temperature. The 1,1,3,3-tetraisopropyl-1,3-disiloxanediy group can also be used for this same 1,3-diol protection. The advantage of this mode of protection is the ability to effect partial ring-opening at the sterically less hindered 6-position using polyhydrogen fluoride. This, and the chemistry of this group in a broader setting have been reviewed.<sup>57</sup> A selective, one-pot protection of the secondary alcohol of 1,2-diols using BuLi then di-*tert*-butylchlorosilane to form a cyclic silyl ether followed by Si–O ring-opening with BuLi at –78 °C has been developed.<sup>58</sup> This affords 2-(butyldi-*tert*-butylsiloxy)alkan-1-ols with excellent regioselectivities and as such represents an interesting alternative to the more readily accomplished selective protection of the primary alcohol. Selective *mono*-protection of the primary (*i.e.* 1-) position of 1,2-diols can be achieved by trityl protection (by virtue of the steric bulk of this protecting group) or benzylative or benzoylative ring-opening of dibutylstannylene acetals. However, the large quantities of dibutyltin oxide required to form the stannylene acetals invariably present unwanted purification problems and so a new procedure employing just catalytic quantities of dimethyltin dichloride for the *in situ* formation of dimethylstannylenes during benzoylation should find wide utility in synthesis (Scheme 5).<sup>59</sup>

## 2 Carboxy protecting groups

TMS chloride catalyses the selective formation of aliphatic methyl esters from their corresponding acids in the presence of aromatic acids using 2,2-dimethoxypropane–MeOH at 25 °C.<sup>60</sup> As the reagents are cheap and all the by products are volatile this represents an attractive method. An intriguing new method for the synthesis of benzyl esters from their corresponding acids by simply heating in toluene with *O*-benzyl-*S*-propargyl xanthate (propargyl = prop-2-ynyl) has been described.<sup>61</sup> The conditions are essentially neutral making the procedure useful for sensitive substrates and also for benzylation of other suitably acidic ( $\text{p}K_{\text{a}}$  below  $\sim 8$ –10) functionality such as phenols and tetrazoles. Transesterification is another popular method for the preparation of esters and further mechanistic details of the alkali-metal alkoxide cluster catalysed procedure have appeared.<sup>62</sup> Titanium(IV) ethoxide has also been shown to be an effective catalyst for the preparation of hindered menthyl esters from ethyl or methyl ester precursors although the reaction fails for highly hindered *tert*-triphenylmethyl ester formation.<sup>63</sup> Cleavage of highly hindered *tert*-butyl esters is



**Scheme 5**

generally achieved using excess TFA either neat or in concentrated CH<sub>2</sub>Cl<sub>2</sub> or CH<sub>3</sub>CN solutions with cation scavengers such as anisole, MeOH or trialkylsilanes added. A new method employs just two equivalents of commercial 100% nitric acid in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C.<sup>64</sup> As the liberated *tert*-butyl cation is rapidly scavenged by nitrate as 1,2-dimethylethyl nitrate (*cf.* poor scavenging properties of trifluoroacetate) the addition of supplementary scavengers is unnecessary. Catalytic transfer hydrogenolysis of *p*-nitrobenzyl (PNB) esters using 10% Pd–C in MeOH with ammonium formate (or aqueous phosphinic acid) acting as hydrogen donor allows for clean deprotection in 3-cephems.<sup>65</sup> 3-Cephems are notoriously prone to alkene isomerisation (to give 2-cephems), which occurred in this case when employing alkali- or fluoride-mediated hydrolysis. Alkaline hydrolysis is also problematic for the deprotection of peptide methyl esters as very careful control of pH is required to minimise racemisation in most cases. Tetrabutylammonium hydroxide (40% aqueous) in DMF or THF at 0 °C now appears to be the method of choice for this application, particularly for poorly soluble, non-polar peptide esters.<sup>66</sup> These often hydrolyse very slowly and with unacceptable levels of epimerisation using alkali metal hydroxide hydrolysis.

### 3 Carbonyl protecting groups

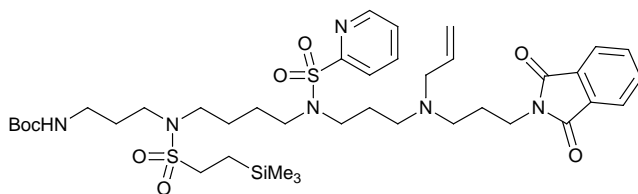
A new type of acetal protective group for aldehydes and ketones has been introduced: the methylenephénylsulfone appended ethylene acetal.<sup>67</sup> These are formed from 3-phenylsulfonylpropane-1,2-diol by refluxing in benzene with a catalytic quantity of PPTS and can be readily cleaved by β-elimination on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.2 equiv.) in CH<sub>2</sub>Cl<sub>2</sub>. Such deprotection is complementary to conventional acid or Hg salt mediated cleavage of the ‘parent’ ethylene acetals (1,3-dioxolanes) for which a new protocol employing copper(II) chloride dihydrate in CH<sub>3</sub>CN at 25 °C has been described.<sup>68</sup> Catalytic quantities of CuCl<sub>2</sub>·2H<sub>2</sub>O suffice but the conditions do appear to be substantially acidic, causing concomitant deprotection of TBDMS and THP ethers. A neutral and anhydrous alternative is the use of (trimethylsilyl)bis(fluorosulfonyl)imide [TMSN(SO<sub>2</sub>F)<sub>2</sub>, (1.1 equiv.)] in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C.<sup>69</sup> This reagent can also be used in catalytic quantities (5 mol%) for the deprotection of dimethyl acetals of aromatic carbonyl compounds at –78 °C and aliphatic counterparts at 0 °C. 1,1-Diacetates (acylals) are useful protective groups for aldehydes as they are particularly stable in basic media. Classical preparative procedures employ Ac<sub>2</sub>O in conjunction with Brønsted or Lewis acids. Scandium triflate (2 mol%) in nitromethane has now been shown to catalyse this reaction,<sup>70</sup> as has TMS iodide in CH<sub>3</sub>CN or CHCl<sub>3</sub> (generated *in situ* from TMS chloride and sodium

iodide),<sup>71</sup> and commercially available zeolite-Y in neat  $\text{Ac}_2\text{O}$ .<sup>72</sup> Aldehydes and ketones are occasionally protected as oximes during synthesis and furthermore the formation of an oxime from a carbonyl compound can often expedite its purification and characterisation. Mild methods for regeneration of the carbonyl function from its corresponding oxime are still being sought. This year two new methods have been described, one using silica-supported chromium trioxide ( $\text{SiO}_2\text{-CrO}_3$ )<sup>73</sup> and the other using the Dess–Martin periodinane<sup>74</sup> to effect oxidative cleavage of the C=N bond. The former method gives excellent yields and involves pre-adsorption of the oxime onto the derivatised silica, microwave (MW) irradiation for 45 s in a domestic 750 W MW oven, and elution from the silica. The latter method also gives excellent yields and employs 1.1 equiv. of the Dess–Martin oxidant in wet  $\text{CH}_2\text{Cl}_2$  at 25 °C for less than half an hour. It seems likely that the essentially neutral Dess–Martin reagent would be preferred in an acid sensitive molecule of some complexity for which pre-adsorption on silica would not be recommended.

#### 4 Amine protecting groups

In impressive studies directed towards the controlled synthesis of polyamine toxins isolated from the venom of spiders and wasps, an orthogonal set of five independently removable amine protecting groups has been developed.<sup>75</sup> The groups in question are: i) Boc, ii) *N*-(trimethylsilyl)ethanesulfonyl (SES), iii) *N*-allyl, iv) *N*-phthalimido (Phth), and v) *N*-pyridine-2-sulfonyl. The conditions for their selective removal are as follows: i)  $\text{TFA-CH}_2\text{Cl}_2$ , 25 °C, ii)  $\text{CsF-DMF}$ , 90 °C, iii)  $\text{Pd(PPh}_3)_4\text{-}N,N'$ -dimethylbarbituric acid (NDMBA)- $\text{CH}_2\text{Cl}_2$ , 30 °C, iv)  $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ , EtOH, reflux, and v) electrolysis, -1.83 mV (having previously removed the *N*-Phth group and reprotected as the trifluoroacetate using  $\text{TFA-Et}_3\text{N-CH}_2\text{Cl}_2$ , 0 °C). The trifluoroacetate group can also be selectively deprotected using potassium carbonate in MeOH at 25 °C (Scheme 6).

2-*N*-Ac Protection of  $\text{D-glucosamine (GlcNH}_2\text{)}$  derived glycosyl donors during the synthesis of  $\beta\text{-GlcNAc}$  and  $\beta\text{-GalNAc}$  containing glycoconjugates is unsatisfactory due to the poor reactivity and poor anomeric  $\alpha/\beta$ -stereocontrol this group imparts (due to neighbouring group participation to give a 1,3-oxazolium intermediate). Consequently, numerous alternative protecting groups for the primary 2-amino group have been investigated. *N*-Phth protection in this context is widespread because of the  $\beta$ -directing influence which the 2-*N*-Phth unit imparts to the glycosyl donor. However, deprotection by prolonged heating with  $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$  or ethylenediamine is often problematic in complex carbohydrates. The 4,4,5,5-tetrachlorophthaloyl (TCPht) and 4,5-dichlorophthaloyl (DCPhth) groups have been advocated as alternatives which retain the advantageous  $\beta$ -directing influence but allow cleavage under milder conditions. The DCPhth group is more stable towards basic conditions than the TCPht group and has now been shown to survive deacetylation, benzylation, benzylidenation, and Lewis acid-, silver salt-, and iodonium ion-promoted glycosylation.<sup>76</sup> The dimethylmaleoyl (DMM) group has also been touted for this role and appears to be an attractive choice in view of its good  $\beta$ -selectivity, stability during TMS-OTf mediated trichloroacetimidate glycosylation, and ease of removal by treatment with NaOH and then dilute HCl (pH 5).<sup>77</sup> The 2,5-dimethylpyrrole group has also been evaluated for use as a protecting group at this position and gives high yields



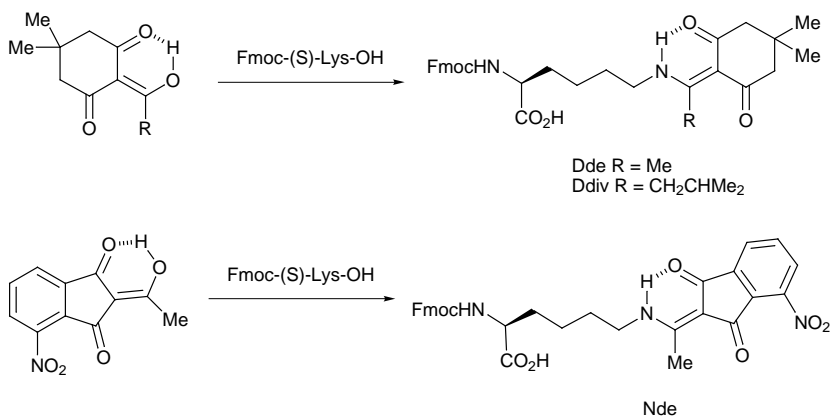
Scheme 6

and high  $\beta$ -selectivity in TMS-OTf promoted trichloroacetimidate glycosylation.<sup>78</sup> The group is readily introduced using hexane-2,5-dione–Et<sub>3</sub>N in MeOH, is removed using hydroxylamine hydrochloride and is significantly more base stable than Phth, DCPht, or TCPht groups. Interestingly, it is stable to conditions required for the removal of the *N*-Phth group. The enhanced stability towards basic conditions of the 2,5-dimethylpyrrole group relative to Phth type groups also make this the group of choice for protection of anilines during nucleophilic aromatic substitution (*e.g.* copper(I) chloride mediated methoxylation of iodoaniline derivatives).<sup>79</sup>

Efficient protection of the side-chain primary amino functionality of lysine and ornithine residues during automated solid-phase peptide synthesis (SPPS) in a manner which allows for mild cleavage is also a challenge for which the Phth group falls short and for which solutions are valuable given current interest in the synthesis of cyclic and branched peptides. Monomethoxytrityl (MMT) and dimethoxytrityl (DMT) groups have been suggested for this role when using Fmoc based procedures but are incompatible with Boc based procedures.<sup>80</sup> However, the 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde) group (the enamine of 2-acetyldimmedone) is a promising alternative. It is stable to the acid (TFA) and base (20% piperidine–DMF) conditions employed during Boc and Fmoc based SPPS strategies, but is readily removed with 2% *v/v* hydrazine in DMF. Furthermore, providing allyl alcohol is added as a sacrificial scavenger, this hydrazinolysis is compatible with *N*-allyloxycarbonyl (Alloc) protection too.<sup>81</sup> Two protecting groups closely related to Dde have been introduced this year: the enamine of 2-isovaleroyldimmedone (*N*-Ddiv),<sup>82</sup> and the enamine of 2-acetyl-4-nitroindane-1,3-dione (*N*-Nde).<sup>83</sup> The former displays slightly improved base stability and resistance to intramolecular N → N migration relative to Dde and the latter has the advantage over Dde that its removal is readily monitored visually. All three groups show exquisite selectivity for introduction onto primary amines due to the formation of a strong intramolecular hydrogen bond making them attractive groups also for the synthesis of complex polyamines (*e.g.* spermidine derivatives) (Scheme 7).

Another group which has been evaluated as a nitrogen protecting group which is orthogonal to Boc based peptide synthesis, for the synthesis of cyclic peptides, is the cyclohexyloxycarbonyl (Choc) group.<sup>84</sup> This group is stable under the 1 M TMS-OTf–thioanisole/TFA Boc cleavage conditions but is removable with anhydrous HF.

Selective *N*-benzylation of less hindered amines in the presence of more hindered amines is possible using 2-chloro-*N,N*-dibenzoylaniline.<sup>85</sup> The method is useful for discrimination between primary amines in sterically different environments, between primary amines and secondary amines, and between secondary amines in sterically different environments. The reagent, which is an air-stable solid, is readily prepared



**Scheme 7**

from 2-chloroaniline using BuLi–benzoic anhydride in THF at 25 °C.

A new and versatile method for the introduction of rigidifying constraints into amino acids and peptides is Ru-catalysed ring-closing metathesis. *N*-Allylation of amino acids and peptides is a relatively easy method for the introduction of the primary alkene functionality required for these reactions and has now been shown to be readily accomplished from *N*-Ts protected derivatives using allyl ethyl carbonate and 1 mol% allylpalladium chloride dimer.<sup>86</sup> Should deprotection be required then a new method employing Me<sub>3</sub>Al (3 equiv.) and (dppp)NiCl<sub>2</sub> (4 mol%) in toluene can be employed.<sup>87</sup> Diisobutylaluminium hydride (DIBAL, 1.5 equiv.)–(dppp)NiCl<sub>2</sub> (4 mol%) can be used for the analogous removal of *N*-allyl groups from primary or secondary amines. Deprotonated *N*-allyl-, *N*-benzyl-, and *N*-3,4-dimethoxybenzyl- $\alpha$ -methylbenzylamine are useful chiral ammonia equivalents for the synthesis of  $\beta$ -amino acids *via* conjugate addition to acrylates. Selective deprotection to leave just the *N*- $\alpha$ -methylbenzyl group from these derivatives can be achieved by palladium or rhodium catalysed deallylation, hydrogenolysis using Pearlman's catalyst [10% Pd(OH)<sub>2</sub> on carbon] in MeOH, and cerium(IV) ammonium nitrate (CAN) in CH<sub>3</sub>CN–H<sub>2</sub>O or DDQ in CH<sub>2</sub>Cl<sub>2</sub>–H<sub>2</sub>O respectively.<sup>88</sup> Further studies on the utility of the *o*-nitrobenzyl group as a photolabile benzyl protecting group have now established that this group can be efficiently introduced onto (*o*-nitrobenzyl bromide–NaH–DMF) and removed from (*h* $\nu$  300 nm) a number of indoles, benzimidazoles, and 6-chlorouracil.<sup>89</sup>

Carbamate protection remains one of the most valuable methods for the protection of amines both in natural product and peptide synthesis. Unsurprisingly, therefore, new methods for their introduction and removal continue to be developed. Of particular note is a new method for the introduction of common carbamate protecting groups simply by mixing the amine and appropriate chloroformate (ethyl, isopropyl and benzyl) in benzene at 25 °C in the presence of powdered zinc (1 equiv.).<sup>90</sup> Excellent yields are observed and reaction times are generally under 20 min, although electron deficient anilines can take up to 6 h. Alkyl esters and *tert*-butyldiphenylsilyl (TBDPS) ethers are tolerated and the zinc can apparently be recovered and re-used. Six new

methods for the deprotection of *N*-Boc groups have been reported. Two closely related methods involving MW irradiation involve either pre-adsorption onto silica<sup>91</sup> or pre-adsorption onto AlCl<sub>3</sub> doped neutral alumina.<sup>92</sup> Both methods are applicable to both *N*-Boc amines and amides although the latter method appears to tolerate a wider range of potentially acid- and base-sensitive functionality (*e.g.* TBDMS ethers and benzyl ethers). A related method involving pre-adsorption onto Yb(OTf)<sub>3</sub> doped silica followed by heating to 40 °C appears to be limited to the deprotection of *N*-Boc amides which can be deprotected in the presence of *N*-Cbz carbamates and acetonides.<sup>93</sup> Use of AlCl<sub>3</sub>-anisole in CH<sub>2</sub>Cl<sub>2</sub>-MeNO<sub>2</sub> (2: 1) has been reported to successfully deprotect immobilised *N*-Boc-5'-amino-2',5'-dideoxynucleosides (on controlled pore glass, CPG).<sup>94</sup> The use of TFA in this instance resulted in unacceptable depurination at the 5'-terminus. The use of TMS-OTf-2,6-lutidine in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C is also sufficiently mild to allow *N*-Boc deprotection of peptides immobilised to resins *via* the Rink amide method (which is a TFA cleavable linkage).<sup>95</sup> The strongly acidic ion-exchange resin Amberlyst-15 is also capable of deprotecting *N*-Boc amines and has the advantage that the released amino function becomes ionised and binds to the ion exchange resin thus allowing for separation and subsequent release from the resin by elution with ammonia-saturated methanol and evaporation.<sup>96</sup> A specialised procedure for the introduction of carbamate protection onto the guanidino function of arginine *via* a silylated intermediate has also been disclosed.<sup>97</sup>

A one-pot conversion of *N*-Fmoc amino acids and dipeptides linked to Wang resin into *N*-Boc derivatives can be achieved in high yields using KF-Et<sub>3</sub>N and either Boc<sub>2</sub>O or *S*-Boc-2-mercapto-4,6-dimethylpyrimidine in DMF.<sup>98</sup> This transformation is particularly valuable because unlike *N*-Fmoc derivatives, *N*-Boc derivatives can be cleaved intact from Wang resin using trimethyltin hydroxide. A direct comparison of the efficacy of the 2-(4-nitrophenylsulfonyl)ethoxycarbonyl (Nsc) group and the Fmoc group with respect to N( $\alpha$ )-amino protection during the automated SPPS of peptides on PEG-PS and Wang-PS using standard (benzotriazolyl)tris-(dimethylamino)phosphonium hexafluorophosphate (BOP)-diisopropylethylamine (DIEA) protocols has appeared.<sup>99</sup> There appears to be very little to choose between the groups which are both base labile (*via*  $\beta$ -elimination) although the Nsc protected peptides are substantially more polar than their Fmoc counterparts.

Sulfonamide deprotection has again come under the spotlight and in particular some limitations to the thiolate cleavage of *p*-nitrobenzenesulfonyl (*p*-NBS) groups have been highlighted.<sup>100</sup> Thus it has been found that deprotection (*via* S<sub>N</sub>Ar substitution *ipso* to the sulfonamide) using thiophenol-DIEA in DMF is accompanied by significant (up to *ca.* 11%) substitution *ipso* to the nitro group. This side reaction, which seems to be most severe for cyclic amines, generates 4-thiophenylbenzenesulfonyl protected amines which are essentially uncleavable. It was noted that the corresponding *o*-nitrobenzenesulfonyl (*o*-NBS) group did not suffer from this side reaction. The *o*-NBS group has also been examined as an alternative to Fmoc for SPPS.<sup>101</sup> Advantages are reported to include: i) deprotection liberates a yellow chromophore which allows visual or spectrophotometric confirmation/quantitation of deprotection, ii) the possibility of selective *N*-methylation of *N*-*o*-NBS protected nitrogen during peptide synthesis, iii) the *o*-NBS amino acid chlorides couple more efficiently to hindered amines than Fmoc ones, and iv) *o*-NBS chloride is ~10 times cheaper than Fmoc chloride. Furthermore, since *o*-NBS groups cannot form

oxazolone intermediates it is possible that racemisation levels may be reduced. However, it was noted that even for the automated synthesis of a hexapeptide a product of slightly lower purity relative to that prepared using Fmoc protection was obtained. Finally, there has been an extensive study of methods for the cleavage of *N*-*p*-tolylsulfonyle (N-Ts) from chiral aziridines (2-phenyl, 2-benzyl and 2-carboxy-).<sup>102</sup> Of the methods surveyed ( $M^{n+}$  in liq.  $NH_3$ , Mg in MeOH, aromatic radical anions,  $SmI_2$ , *hv*), lithium with a catalytic amount of di-*tert*-butylbiphenyl (DTBB) in THF at  $-78^\circ C$  and Mg in MeOH at  $25^\circ C$  with ultrasound were the best giving good yields of desulfonylated aziridines without detectable racemisation. Only the use of magnesium in MeOH was successful for the efficient deprotection of sensitive 2-phenylaziridines.

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