2 Synthetic methods

Part (iii) Protecting groups

Alan C. Spivey* and David Leese

Department of Chemistry, Brook Hill, University of Sheffield, Sheffield, UK S3 7HF.
E-mail: a.c.spivey@sheffield.ac.uk; Fax: (0114) 2738673; Tel: (0114) 2229467

Protecting groups

Another excellent and comprehensive annual ‘update’ review of the 2000 literature relating to protecting group (PG) strategies in organic synthesis has appeared this year.1 The employment of PGs to direct ‘docking’ at oxidative enzyme active sites thereby controlling subsequent hydroxylation of unactivated carbon atoms has also been overviewed.2,3 Moreover, a summary of the use of microwave (MW) heating for accelerating various PG manipulations (acylation, alkylation, silylation, acetalisation, deacylation, desilylation and deacetalisation) with particular reference to carbohydrate manipulations has appeared.4 Two reviews focusing on orthogonal PG strategies for ribonucleic acid synthesis5 and solid phase peptide synthesis6, respectively, have also appeared.

Hydroxy protecting groups

The use of Williamson etherification conditions for the preparation of simple alkyl ethers often proceeds slowly and provides rather moderate yields under conventional conditions. MW heating, using a MW oven modified to allow introduction of a reflux condenser, has been reported to improve yields and reduce reaction times for the preparation of alkyl ethers of phenols (and also for the preparation of dioxolanes from aromatic aldehydes).7 The acid labile cyclopropylmethyl PG was introduced in 1995 for side-chain OH protection of serine and threonine during peptide synthesis but has not found widespread application. However, a more acid labile analogue of this PG, the 1-methyl-1cyclopropylmethyl (MCPM) group, has now been shown to be useful for soluble polymer-supported oligosaccharide synthesis.8 This PG is readily introduced using the corresponding trichloroacetimidate derivative. Features that make this PG attractive for oligosaccharide synthesis are: its small size, its electron donating character, its characteristic high field proton nuclear magnetic resonance (1H NMR) signals, its poor co-ordination to Lewis acids used in glycosylation reactions and the mild conditions needed for its removal using 10% trifluoroacetic acid (TFA) in CH2Cl2 at room temperature (rt) for 1 h.
A number of new protocols for the introduction and removal of acetal PGs have been advanced this year. For the introduction of tetrahydropyranyl (THP), tetrahydrofuranyl (THF) and 1-ethoxyethyl (EE) ethers, procedures employing tetrabutylammonium tribromide (TBATB, 10 mol%) in CH$_2$Cl$_2$ at rt,$^9$ and acetonyl-triphenylphosphonium bromide [ATPB (10 mol%), and its polymer-supported analogue] in CH$_2$Cl$_2$ at rt$^{10}$ have been reported. Both catalysts are also suitable for removal of these groups when employed in MeOH. The ATPB method is suitable for 1$^\circ$, 2$^\circ$ and 3$^\circ$ alcohols and phenols and has been shown to induce less elimination than pyridinium toluene-p-sulfonate (PPTS) when deployed for acid sensitive substrates such as 1-phenylethylhexan-1-ol. Four new procedures for the removal of acetal PGs are: CBr$_4$ (10 mol%) in refluxing MeOH for methoxymethyl (MOM) and methoxy-ethoxymethyl (MEM) ethers,$^{11}$ CeCl$_3$7H$_2$O (50 mol%) in refluxing MeCN for MEM ethers,$^{12}$ Sc(OTf)$_3$ (0.5-5 mol%) in MeOH at rt for THP ethers (and in propane-1,3-diol at rt for MOM ethers),$^{13}$ and Montmorillonite K-10 clay in anhydrous benzene for phenolic MOM, MEM and β-trimethylsilylthoxymethyl (SEM) ethers.$^{14}$ The method employing CeCl$_3$7H$_2$O is notable in that it is sufficiently mild to allow deprotection in the presence of other hydroxyl PGs including: benzyl (Bn), tert-butyldimethylsilyl (TBDMS), Me, p-methoxybenzyl (PMB), THP, MOM and benzyl-oxymethyl (BOM) ethers, acetyl (Ac) groups and benzylidene acetals. The method employing CBr$_4$ is believed to operate through the *in situ* generation of trace quantities of HBr and can be made chemoselective for the removal of 1$^\circ$ MEM ethers in the presence of 1$^\circ$ triisopropylsilyl (TIPS) or tert-butyldiphenylsilyl (TBDPS) ethers by employing the more bulky i-PrOH in place of MeOH as solvent. Removal of THP and EE but not MOM PGs has also been shown to be possible by employing Pd(0)-catalysed hydrogenolysis conditions [10% Pd/C, EtOH, H$_2$ (g) (1 atm), rt].$^{15}$ The deprotection is effected by trace amounts of HCl in the reaction mixture. The HCl is derived from residual PdCl$_2$ in the catalyst. The extent of this contamination varies from batch to batch and with manufacturer; Aldrich-sourced catalyst apparently being particularly contaminated. An alcoholic solvent, as expected, is essential for this acid catalysed acetal exchange process and the reaction can be completely suppressed by the addition of a small amount of pyridine.

A series of new substituted 1-(benzylxyloxy)ethyl acetal PGs has been examined for the protection of the 2$^\circ$-position during oligoribonucleotide synthesis by the 5$^\circ$-O-(4,4$'$-dimethoxytrityl) [5$^\circ$-O-DMT] phosphoramidite approach.$^{16}$ However, all simple derivatives were found to be partially labile towards the acidic conditions required to remove the DMT group [*i.e.* 1.3% dichloroacetic acid (DCA) in CH$_2$Cl$_2$] and therefore of no synthetic value. Consequently, a ‘safety-catch’ regime was adopted involving a [2-(4-nitrophenyl)ethoxy]carbonyl (NPEOC) carbonate derivative of an acetal having a phenolic hydroxyl at the 4-position. The resulting 1-[(4-((2-(4-nitrophenyl)ethoxy)-carbonyl)oxy)benzyl]oxo]ethyl (NEBE) acetal is removed by a two step procedure: the NPEOC group is removed by β-elimination using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in MeCN to reveal the ‘deprotected’ acetal which in turn is removed using 0.3–3% aqueous AcOH at rt within 2 h. Overall, this safety-catch approach is claimed to offer more straightforward work-up conditions relative to alternative protection regimes requiring fluoride deprotection (Scheme 1).

Four new procedures for the removal of trityl (Tr) groups have been described this year: Ce(OTf)$_4$ (10 mol%) in wet MeCN at rt,$^{17}$ elution through a silica gel flash
column (FC) prepared with 1% TFA in hexane,\textsuperscript{18} HgCl\textsubscript{2} (10 equiv.) and NaBH\textsubscript{4} (excess) in MeCN,\textsuperscript{19} and TFA (4 equiv.) with either triethylsilane (4 equiv.) or Me\textsubscript{3}N–BH\textsubscript{3} (1.3 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C.\textsuperscript{20} The Ce(OTf\textsubscript{4})\textsubscript{2}-based method is claimed to operate under essentially neutral conditions and to be efficient for 1° and 2° alcohol deprotection. Surprisingly, the FC-based method is effective even for some relatively acid-labile galactofuranoside substrates and has the attractive feature that the liberated Tr cation is not eluted from the column. The reductive demercuration conditions (using HgCl\textsubscript{2}–NaBH\textsubscript{4}) formed part of a detailed study of the selective deprotection of Tr-thioethers, Tr-amines and Tr-ethers from pertillylated substrates. Orthogonal conditions for deprotection of each derivative were established. The method employing TFA in the presence of a reductant was developed for the deprotection of certain N–Tr aziridines for which C–N bond ring cleavage is a problem under standard acidic conditions. A new Tr-related PG that has been investigated this year is the 4-monomethoxytritylthio (MMTrS) group.\textsuperscript{21} The ‘parent’ tritylthio (TrS) group has been used previously to protect amines as sulfenamide derivatives and alcohols as sulfenate esters. Introduction at the 5’-OH of 3’-O-tert-butylidemethylsilylthymidine was achieved following deprotonation using lithium hexamethyldisilazide (LHMDS) and quenching with MMTrSCl. The MMTrS group was stable to aqueous NH\textsubscript{3}–EtOH (3:1, 24 h, rt) and 1 M t-BuOOH–MeCN (20 min, rt) but was removed rapidly to give thymidine by treatment with 0.1M I\textsubscript{2}/MeCN–pyridine–H\textsubscript{2}O (10:9:1, 1 min) and was shown to be compatible with a phosphoramidite-based solid phase polythymidine synthesis.

Allyl ethers can be deprotected by oxidation to the corresponding allyl ester followed by hydrolysis. A new reagent for accomplishing the oxidation is tetra-n-butylammonium peroxydisulfate (1 equiv.) in MeCN at 8 °C.\textsuperscript{22} Acetal, triazoyl and glycosidic methyl groups are inert both to these conditions and the subsequent hydrolysis using NaOMe in MeOH at rt. A new one-pot alternative, which is also effective for removal of N-allyl groups, is treatment with OsO\textsubscript{4} (cat.), N-methylmorpholine N-oxide (NMO, 3 equiv.) and NaIO\textsubscript{4} (3 equiv.) in dioxane–H\textsubscript{2}O (1:1).\textsuperscript{23} Careful analysis of intermediates and by-products suggested that the reaction proceeds via dihydroxylation then oxidative C–C bond cleavage to give the ethanal derivative which itself enolises and is dihydroxylated. The resulting triol derivative undergoes a second oxidative C–C bond cleavage to give the formate ester which slowly hydrolyses under the reaction conditions, completing the deprotection (Scheme 2).

A selective method for the removal of 3,3-dimethylallyl [prenyl (Pre)] ethers in the presence of standard allyl and Bn ethers, TBDPS ethers and acetals (e.g. acetonides) is the use of I\textsubscript{2} in CH\textsubscript{2}Cl\textsubscript{2} with 3 Å MS at rt.\textsuperscript{24} The conditions are essentially neutral and the choice of solvent is crucial to the success of the reaction. Another protocol that is selective for the removal of substituted allyl ethers (e.g. Pre, crotyl, cinnamyl and

β-methallyl) over simple allyl ethers is treatment with CeCl₃·7H₂O (1.5 equiv.), NaI (1.5 equiv.) and propane-1,3-dithiol (1.5 equiv., as allyl iodide scavenger) in nitromethane at reflux in ~2 h. Unsubstituted allyl ethers are removed under these conditions but only after prolonged (>24 h) heating. These conditions were effective for the removal of cinnamyl ethers from monosaccharides containing Tr, allyl and TBDPS protected hydroxyl groups.

Some interesting studies probing the mechanism of BiBr₃-catalysed benzylation of 2º alkyl alcohols, by Bn alcohols, in CCl₄ at rt have been reported this year. The experiments focused on the preparation of 1-phenylethylethers from 1-phenylethanol and it was postulated on the basis of stereochemical correlation that the active species might be an octahedral hexacoordinate bismuth intermediate in which two molecules of the Bn alcohol occupy axial positions via η⁶ π–bonds and the ‘substrate’ alkyl alcohol an equatorial position (Scheme 3).

Further applications of the use of NaBrO₃–Na₂S₂O₄ in EtOAc–H₂O for the oxidative removal of Bn ethers from sugars have appeared this year. In particular, the method has been shown to be compatible with supported oligosaccharide synthesis on controlled pore glass. The sequential removal of PMB and 2-naphthyl (2-NAP) ethers in the presence of Bn ethers by oxidative cleavage has been demonstrated. Thus, ceric ammonium nitrate (CAN, 4 equiv.) in acetone:H₂O (9:1) at rt effects selective removal of the PMB in the presence of both 2-NAP and Bn ethers, while 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ, 4 equiv.) in CH₂Cl₂:MeOH (3:1) can then effect selective removal of the 2-NAP in the presence of the Bn ether. Two interesting benzyl-type PGs are the p-phenylbenzyl (PPB) and 2,6-dimethoxybenzyl (2,6-DMB) ethers. The PPB group is introduced using either PPBBr–NaH in THF or PPB-trichloroacetimidate [PPBOC(=NH)CCl₃] in CH₂Cl₂ and removed smoothly using DDQ (>1 equiv.) in CH₂Cl₂:H₂O (19:1) or DDQ (10 mol%), Mn(OAc)₃ (3 equiv.) in CH₂Cl₂. The oxidative cleavage could be achieved in the presence of standard Bn and benzhydryl ethers catalysed by trifluoromethanesulfonic acid (TfOH) and the group is stable towards 60% aqueous AcOH at 60 °C and TFA in CH₂Cl₂ at rt. The 2,6-DMB ether displays usefully high reactivity towards
CrCl₂-activated deprotection by LiI. The Cr(II) is believed to chelate between the benzylic ether oxygen and an o-methoxy oxygen, thereby activating the benzylic methylene to attack by iodide. In practice this means that selective deprotection is possible using CrCl₂ (3 equiv.), LiI (4 equiv.) in EtOAc:H₂O (1:1.005) at 75 °C in the presence of Bn ethers or 3,4-DMB ethers. Conversely, Bn ethers can be removed using Pd/C H₂ (1 atm) hydrogenolysis and 3,4-DMB ethers using DDQ in CH₂Cl₂:H₂O, both without affecting 2,6-DMB ethers. The Cr(II)-mediated deprotection of 2,6-DMB ethers can also be achieved without cleaving acetonides, THP acetics or TBDPS ethers and does not induce isomerisation of allylic alcohols or (Z)-alkenes although the rates of these reactions were retarded by amine functionality (Scheme 4).

In the area of ester protection of alcohols there have been some further advances in non-enzymatic kinetic resolution (KR) of 2° and 3° alcohols via acylation catalysed by chiral nucleophiles and Lewis acids. The most selective nucleophilic catalysts yet described for acylative KR of aryl alkyl carbinols [using (i-PrCO)₂O] are based on the selective phosphabicyclo[3.3.0]octane (PBO) skeleton. A short review detailing the evolution of these catalysts has been published, and their use for preparatively useful KR of certain classes of allylic alcohols demonstrated. Additionally, the use of these catalysts, in conjunction with a polymer-bound lipase, for an ingenious three-phase parallel KR (PKR) has been shown to give exceptional levels of selectivity and efficiency in the KR of 1-phenylethanol. A polymer-bound version of a prolinol-derived diamine nucleophilic catalyst has also been shown to effect efficient KR of aryl alkyl carbinols, albeit with slightly lower selectivities than the soluble parent. The utility of a chiral (4-dimethylamino)pyridine (DMAP) derivative as a nucleophilic catalyst for the acylative KR of cyclic cis-1,2-aminoalcohols has been reported. Probably the most significant advance in this area, however, has been the demonstration that certain short peptide sequences with defined secondary structure and having an appropriately situated N-methylhistidine residue act as efficient nucleophilic catalysts not only for the KR of 2°, but also 3° alcohols. The catalysis has been shown to be crucially dependent on the presence of a proximal amide carbonyl group which is postulated as having a hydrogen bonding role.

Scheme 4

screening methods for identifying the appropriate peptide for a specific synthetic application has also been demonstrated and applied to the asymmetric synthesis of a mitosane derivative which contains the core functionality of the anti-tumour natural product mitomycin C (Scheme 5).  

New achiral methods for the catalysed esterification of alcohols include: using a carboxylic acid and HfCl$_4$(THF)$_2$ (0.1–1.0 mol%) in toluene at reflux,$^{42}$ using Ac$_2$O, N-bromosuccinimide (NBS, 5–10 mol%) in CH$_2$Cl$_2$ at rt,$^{43}$ using Ac$_2$O, LiClO$_4$ (10 mol%) under solvent free conditions,$^{44}$ using isopropenylacetate, LiClO$_4$ (1 equiv.) and In(ClO$_4$)$_3$•8H$_2$O (1 mol%) in EtOAc at rt,$^{45}$ and using Ac$_2$O, Bi(OTf)$_3$•xH$_2$O (0.1 mol%) in MeCN at rt.$^{46}$ The method using HfCl$_4$(THF)$_2$, which is commercially available, is particularly significant in that it uses readily available carboxylic acids (1 equiv.) as acyl donors and is selective for esterification of 1° alcohols in the presence of 2° alcohols or phenols. A mini-review of the catalysis of esterification of alcohols using carboxylic acids has also appeared.$^{47}$ In contrast, the NBS- and LiClO$_4$-based methods are effective even for hindered 3° alcohols such as 1-methylcyclohexanol. The Bi(OTf)$_3$•xH$_2$O catalysed method is limited to 1°, 2° and phenolic alcohol esterification but is distinguished by the need for very low catalyst loadings, making it suitable for large scale work. Some intriguing results have also been reported for the regioselective benzoylation of the 1° alcohol residue in 1,2-diols by the use of a 5-fold excess of benzoyl chloride (BzCl) and Et$_3$N under carefully controlled MW heating conditions.$^{48}$ Three new methods for the deprotection of acetates have been disclosed this year. For aryl acetates the use of natural kaolinitic clay in MeOH at rt has been advocated.$^{49}$ Alkyl acetates and methyl esters are untouched under these conditions. Also selective for deprotection of aryl acetates and benzoates is the use of K$_2$CO$_3$ (2 equiv.) in N-methyl-2-pyrrolidinone (NMP) at 100 °C.$^{50}$ A particularly detailed study of the use of the neutral distannoxane catalyst [t-Bu$_3$SnOH(Cl)]$_2$ (5 mol%) in MeOH for deacetylation has appeared.$^{51}$ The mildness of the reaction allows many

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Scheme 5

[Chemical structure images]
FGs to be tolerated and for differentiation between $1^\circ$, $2^\circ$ and $3^\circ$ acetate esters, and between other esters under appropriate conditions. No racemisation occurs with chiral Ac esters and the crude products can be used for further reactions without purification. A closely related fluorous distannoxane catalyst has also been shown to mediate a very efficient transesterification between esters and alcohols (1:1) in a biphasic perfluorocarbon solvent system.\textsuperscript{52} A new condition for deprotection of $p$-nitrobenzoate (PNB) esters is treatment with Na$_3$N in MeOH.\textsuperscript{53} These conditions, being essentially neutral, are particularly useful for application to protected $\beta$-hydroxycarbonyl compounds which are prone to elimination. 9-Fluorenylmethoxy carbonyl (Fmoc) and TFA carbamates, Bz esters and ethyl esters remain unaffected.

Three new ester PGs are the ‘bisfluorous propanoyl’ (Bfp) group\textsuperscript{54} and the 3-fluoro- and 2,5-difluorobenzoyl groups.\textsuperscript{55} The Bfp group is a $\beta$-alanine derivative having two C$_8$F$_{17}$ linear hydrocarbon chains appended. The group displays the reactivity that would be expected of a standard alkyl ester residue but the fluorous chains render a protected derivative (e.g. a tetrasaccharide) highly soluble in fluorous solvents (e.g. FC72), thereby facilitating purification by extraction from a standard organic solvent. The two fluorinated Bz groups have been developed for use in glycopeptide synthesis in an attempt to combine the advantages of the Bz group in the formation of glycosidic bonds (i.e. high anomeric stereoselectivity and low levels of orthoester formation) with the ease of removal characteristic of the Ac group. When either the 3-fluoro- or 2,5-difluorobenzoyl groups were used for protection of each of two model glycopeptides (known to be unusually sensitive to $\beta$-elimination on base catalysed deacylation) the extent of $\beta$-elimination decreased from 80% to 10% and from 50% to 0%, respectively, as compared to when using the ordinary Bz group.

In the area of silyl protection of alcohols, various interesting observations have been made and new methods devised this year. For example, a cautionary note has been sounded regarding the introduction of TIPS groups using TIPSOTf.\textsuperscript{56} It reports that commercial TIPSOTf can contain significant amounts of disopropyl(n-propyl)-silyl triflate. Since this impurity couples more readily than the TIPSOTf under the standard introduction conditions, and the resulting silyl ether is extremely difficult to separate from the TIPS ether, the use of excess TIPSOTf during preparation should be avoided. The seldom used tribenzylsilyl group has been shown to be an even more effective steric diasterecontrol element than the TIPS group in the context of a photo-[4 + 4]- cycloaddition reaction.\textsuperscript{57} Two new methods for the introduction of silyl ethers are: using $O$-(trisubstituted silyl)benzamides (Si–BEZAs) (1.5 equiv.) with Py·TfOH (<20 mol%) in either THF or benzotrifluoride (BTF),\textsuperscript{58} and using trimethylsilylazide (TMSN$_3$, 1.5 equiv.) with tetrabutylammonium bromide (TBABr, <20 mol%) in the absence of solvent.\textsuperscript{59} Si–BEZAs are powerful silylation reagents that can be prepared for TMS, triethylsilyl (TES), TBDMS, TIPS and TBDPS groups by treatment of benzanilide with NaH (1.0 equiv.) and then the appropriate silyl chloride (1.0 equiv.) in MeCN. Silyl ether synthesis using these reagents is successful for aliphatic, allylic and phenolic hydroxyls and is particularly valuable for introduction of even sterically hindered silyl groups (e.g. TBDPS) onto 3° alcohols under mild conditions. The TMSN$_3$-based method is also reported to be successful for the introduction of TMS groups into hindered 3° alcohols, although under less forcing conditions selectivity can be achieved for 1° and 2° in the presence of 3° alcohols. For the deprotection of silyl ethers Br$_2$ in MeOH has been noted to give selectivity for TBDMS in

the presence of TBDPS ethers. Bismuth(III) salts are also effective Lewis acids for cleavage of silyl ethers. Various 1°, 2°, allylic and phenolic TMS ethers are removed very rapidly in MeOH at rt using BiCl3, Bi(OTFA)3, or Bi(OTf)3 (all <3 mol%), whereas TBDMS ethers are inert towards BiCl3 and Bi(OTFA)3 but are cleanly cleaved by Bi(OTf)3. Cleavage of TMS ethers with concomitant oxidation to the corresponding aldehyde or ketone is possible using a wide variety of oxidants and three new conditions described this year are: using zeolite HZSM-5 supported iron(III) nitrate (zeofen) with MW heating (900 W, 2 min) under solvent-free conditions, using benzyltriphenylphosphoniumperoxymonosulfate (BnPPh3HSO5, 1 equiv.) and BiCl3 (40 mol%) with MW heating (900 W) in CH2Cl2, and using NaBrO3 (1 equiv.) and NH4Cl (1.5 equiv.) in aqueous MeCN at 80 °C. BnPPh3HSO5 is a stable white powder prepared by the dropwise addition of an aqueous solution of BnPPh3Cl to an aqueous solution of Oxone® and the conditions of this deprotection are also appropriate for oxidative deprotection of THP acetals and for the deprotection of dioxolane-protected ketones and aldehydes. Two new photolabile silyl PGs, (E)-(2-hydroxystyryl)diisopropylsilyl (HSDIS) and (E)-[(2-hydroxy-3-naphthyl)vinyl]-diisopropylsilyl (HNVDS) have been disclosed this year. Quantitative deprotected is achieved by photolysis in MeOH in a Rayonet cabinet at 254 and 350 nm respectively. For both groups the basis of the deprotection is a photochemical (E) to (Z) alkene isomerisation followed by intramolecular 6-exo-trig silyl ether formation. The PGs are prepared by hydrosilylation of the appropriate o-ethynylarylacetate with chlorodiisopropylsilane to furnish the acetate protected chlorosilane which is reacted with the substrate alcohol in the presence of diisopropylethylamine (DIPEA). The acetate is then deprotected with a cyanide resin in MeOH. Although the stability of these PGs towards typical reaction conditions was not reported, and so their utility is difficult to gauge, it is clear that the phenolic hydroxyl group could be further protected to provide a ‘safety-catch’ system (Scheme 6).

Scheme 6

Carbonates are not widely employed as PGs for alcohols because generally they are significantly labile under mildly basic hydrolytic conditions. However, their use in specialist applications, particularly for masking the 5’-OH group during oligonucleotide synthesis, ensures that there is continuing development in this area. In particular, the use of photolabile carbonate groups has drawn significant attention in the post-genomic era for the preparation of deoxyribonucleic acid (DNA) microarrays by photolithography. This year a detailed photochemical study has been performed on the photolabile 5’-O-2-(2-nitrophenyl)ethyloxycarbonyl (o-NPEOC) derivative of
Flash photolysis was used to monitor the exact course of the photolytic deprotection under various conditions of solvent and pH. The closely related photo-labile 2-(2-nitrophenyl)propyloxycarbonyl (o-NPPOC) PG has also been further evaluated for reverse (5’ to 3’) DNA synthesis in a microarray format. A new photolabile carbonate PG is the anthraquinon-2-ylmethoxycarbonyl (Aqmoc) group. This group was the most efficient of a series of potentially photolabile carbonates examined and has quantum yield 0.10, molar absorptivity 1500 M^{-1} cm^{-1}, and rate constant ∼10^6 s^{-1} for removal from galactose in 50% THF–H_2O (100 µM) at 350 nm. Its utility was further demonstrated by the regeneration of adenosine from 5’-O-Aqmoc-adenosine by photolysis in 91% yield. The N-methyl-N-(o-nitrophenyl)carbamate has also been evaluated as a new photolabile PG which is introduced via the corresponding carbamoyl chloride and removed by photolysis between 248 and 365 nm in EtOH–H_2O. Traditional ribonucleic acid (RNA) synthesis by the phosphoramidite method employs fluoride-labile TBDMS ‘permanent’ protection for 2’-OHs and acid-labile DMT ‘temporary’ protection for 5’-OHs. More recently, in addition to interest in 5’-OH ‘temporary’ protection by photolabile groups, attention has focused on regimes in which the 2’-OHs are ‘permanently’ protected with various acid-labile acetals in combination with base-labile ‘temporary’ protection for the 5’-OHs. Substituted ethyl carbonates containing electron withdrawing groups (e.g. CN or 4-nitrophenyl) at the β-position are suitable base-labile PGs and a new series of these has been evaluated this year. The most useful appears to be the (1-phenyl-2-cyanoethoxy)carbonyl (1-PCEOC) group, which is removed with a half-life of 12 s using 0.1 M DBU in MeCN, making it compatible with ‘permanent’ protection of nucleobases using the NPEOC PG (which is base-labile but has a half-life of 94 min under these conditions). This year has also seen the development of indium powder in aqueous NH_4Cl–MeOH at reflux as a mild and selective method for the deprotection 2,2,2-trichloroethoxy-carbonyl (Troc) and trichloroacetyl alcohol PGs. Chiral substrates can be deprotected without racemisation, TBDMS ethers, TBDPS ethers, Bz groups, alkenes, alkynes, aryl chlorides, alkoxy groups, esters and amides are unaffected, and the method is applicable to highly hindered alcohols. A new carbonate PG is the p-chlorophenylcarbonate (CPC) which has been developed for oligosaccharide synthesis. This group is readily introduced via the corresponding chlorocarbonate and removed using LiOH–H_2O_2 in THF:H_2O (3:1) at 0 °C. Deprotection is possible in the presence of Bz and pivaloyl (Piv) esters, and the CPC group is stable to various Lewis acidic and protic conditions for glycosylation. Furthermore it yields solely β-linked glycosides when used as a C-2 participating group.

O-Sulfonilation is also a relatively rarely employed mode of OH protection but interesting chemoselectivity has been disclosed this year for the O-sulfonylation of myo-inositol-1,3,5-orthoester: the axial 4- and 6-OH groups react in preference to the equatorial 2-OH. The reaction was effective using a range of sulfonyl chlorides with NaH in N,N-dimethylformamide (DMF) but the regioselectivity was lost in THF or in the presence of 18-crown-6, suggesting a role for chelate formation. For the protection of 1,2-diols, the xanthen-9-ylidene and 2,7-dimethylxanthen-9-ylidene PGs have been developed as more acid-labile analogues of the commonly employed isopropylidene PG. Specifically, these groups have been developed as achiral acetals for protection of the 2′,3′-cis-diol systems of ribonucleosides. The respective half-lives of isopropylidene, xanthen-9-ylidene and 2,7-dimethylxanthen-9-
yridene derivatives of uridine towards TFA:H₂O:MeOH (1:2:7) are: 178 min, 31.7 min and 8.6 min at 30 °C. An alternative and rather unusual mode of deprotection, which avoids any chromatography and which is equally effective for both of these new PGs, is treatment with DCA (4 equiv.) and pyrrole (5 equiv.) in CH₂Cl₂ at rt followed by precipitation of the 9,9-di(pyrrrol-2-yl)xanthene by-product with excess FeCl₃ in Et₂O (Scheme 7).

![Scheme 7](image)

An interesting method for the rearrangement of benzylidene acetals of 1,2- and 1,3-diols to yield a Bz mono-ester via a radical redox process has been reported. The procedure involves refluxing in dry octane with 2,2-di-tert-butyldiroyxybutane (DBPB, 5 mol%), tert-dodecanethiol (TDT, 5 mol%) and collidine (10 mol%) for 3 h. This radical rearrangement results in preferential homolysis of the C–O bond bearing the most substituted carbon with concomitant conversion of the remaining alcohol to a Bz ester. The role of the thiol is as a protic ‘polarity-reversal catalyst’ for H-atom transfer from the methine group of the acetal to the 3° or 2° alkyl radical (Scheme 8).

![Scheme 8](image)

Various substituted bis-enol ethers of butane-2,3-dione have been shown to be efficient reagents for the protection of 1,2-diols as butane-1,2-diacetals. They react smoothly with a variety of 1,2-diols in the presence of Ph₃P·HBr in CH₂Cl₂ at rt to give diastereoisomeric mixtures of acetals which are directly equilibrated using BF₃·Et₂O (0.25 equiv.) to the corresponding thermodynamically most stable butane diacetal (BDA) products. Three different derivatives have been investigated, the bis-methyl, bis-Bn and bis-allyl enol ethers. The bis-methyl enol ether is prepared using butane-2,3-dione, HC(OMe)₃, and H₂SO₄ (cat.) in MeOH, whereas the Bn and allyl reagents are prepared by a four-step protocol from diethyltartrate. Deprotection of the methyl substituted BDAs requires aqueous TFA. Deprotection of the Bn substituted BDAs can be achieved using Pd/C, H₂ (1 atm) in EtOAc. Deprotection of the allyl substituted BDAs can be achieved using Ir(COD)(PPh₂Me)₂PF₆, then O₃ in CH₂Cl₂–MeOH, followed by hydrolysis with NaHCO₃ in THF–H₂O. The cyclic di-tert-butylsilylenediy (CDBS) ether is an effective PG for the 4- and 6-OHs of

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pyranosides during oligosaccharide synthesis. Introduction is by treatment with di-tert-butyldichlorosilane, 1-hydroxybenzotriazole (HOBt), and pyridine at 95 °C. The group is stable to acetylation, benzylation and glycosylation reactions and is readily removed by treatment with tetrabutylammonium fluoride (TBAF), THF, 0 °C, 24 h, or triethylamine–3HF complex, THF, 0–25 °C, 4 h.

Thiol protecting groups

The Fmoc PG is widely used for protection of amino and hydroxyl groups but it has not previously been used for thiol protection. However, protection of the sulphydryl group in N-tert-butoxycarbonyl (Boc)-cysteine methyl ester has now been accomplished in 98% yield under standard conditions: FmocCl, Et₃N, CH₂Cl₂. The product is a stable and easily handled white solid. Interestingly, an analogous reaction with FmocOSu (Su = succinimidyl) yields only the S-9-fluorenylmethyl (Fm) adduct in 92% yield with no trace of the S-Fmoc product. The conversion of the S-Fmoc adduct to the S-Fm adduct, with loss of CO₂ via elimination/addition, can be accomplished by treatment with stoichiometric Et₃N in CH₂Cl₂. Consequently, the difference between the two protection procedures can be attributed to the amount of unprotonated triethylamine present in solution [reflecting the relative acidity of HCl (pKₐ = −7) and SuOH (pKₐ 4)]. The S-Fmoc protected cysteine derivatives were shown to be useful in peptide synthesis and the PG can be removed selectively in the presence of N-Fmoc groups using Et₃N and I₂ to give disulfides. A new method for deprotection of thioesters is treatment with TiCl₄/Zn at 0–25 °C in CH₂Cl₂. This method is complementary to the more commonly used acid or base promoted hydrolysis and LiAlH₄ reduction. Importantly, deprotection can be accomplished in the presence of other carbonyl functional groups and PGs such as TMS and TBDMS ethers, methyl esters and N-benzyloxycarbonyl (Cbz) adducts.

Carboxy protecting groups

As highlighted previously in this article, there is considerable ongoing interest in the development of efficient catalysts for esterification using equimolar amounts of carboxylic acid and alcohol, and recent advances in this area have been highlighted this year. Additionally, a very simple method for the preparation of t-Bu esters by transesterification from methyl esters has been disclosed. t-Bu esters enjoy unique status among ester PGs because of their resistance to nucleophilic attack, simple ¹H NMR signal and ease of removal by mild acid. However, their preparation is often non-trivial by conventional means and so the finding that transesterification of methyl esters simply by treatment with KOt-Bu (1–1.2 equiv.) in Et₂O, driven by precipitation of potassium methoxide, at 0–20 °C within 30 min is significant. Freshly prepared KOt-Bu and absolutely anhydrous Et₂O are essential for success. 2-(Trimethylsilyl)ethyl (TMSE) esters are generally deprotected using TBAF or another source of fluoride ions. A new method of deprotection, which paves the way for the use of TMSE esters in conjunction with standard silicon-based OH PGs such as TMS and TBDMS ethers, and SEM acetals (all of which remain unaffected) is treatment with...
1–2 equiv. of NaH in DMF at rt.\textsuperscript{82} It is proposed that the reaction proceeds via formation of NaOH from adventitious H\textsubscript{2}O in DMF. For the selective deprotection of \textit{i}-Pr esters (and \textit{i}-Pr carbamates and carbonates) AlCl\textsubscript{3} (4 equiv.) in MeNO\textsubscript{2} at 0–50 °C has been found to be effective. \textit{t}-Bu and Bn esters are also removed under these conditions but \textit{i}-Pr esters are considerably more stable to protic acids than these derivatives. Some exciting advances in the area of photolabile ester PGs have been made this year. In particular, it has been shown that orthogonality between groups can be efficiently controlled by choice of wavelength of irradiation.\textsuperscript{83} For example, a 2-nitro-4,5-dimethoxybenzyl ester can be removed selectively in the presence of a 3,5-dimethoxybenzoin ester by irradiation at 420 nm in MeCN for 24 h, whereas the latter can be selectively removed in the presence of the former by irradiation at 254 nm in MeCN for 5 min (Scheme 9).

Two new classes of ester PG that have been developed this year are a family of fluorous-tagged \textit{t}-Bu-based esters\textsuperscript{84} and a family of (\textit{Z})-stilbene-based esters termed ‘precipitons’.\textsuperscript{85,86} The fluorous-tagged \textit{t}-Bu esters are based on fluorinated 3° alcohols and allow for efficient separation of medium-sized non-polar carboxylic acids into a fluorous solvent phase, but in other respects behave like standard \textit{t}-Bu esters. The precipiton concept is new and relies on the usually rather dramatic (>100 fold) difference in solubility between the (\textit{Z})- and (\textit{E})-isomers of methyl(4′-phenyl)-4-stilbenyl esters. This difference in solubility in common organic solvents such as EtOAc, THF, Et\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, CHCl\textsubscript{3} and toluene allows chemistry to be performed in solution on (\textit{Z})-ester derivatives prior to isolation by precipitation. Precipitation is induced by thermodynamically driven stilbene isomerisation either by addition of PhSSPh and heating (e.g. THF at reflux) or irradiation with a sun-lamp following addition of I\textsubscript{2} and BzOOH. The method was found to be useful for the preparation of a series of isoxazolines by 1,3-dipolar cycloaddition of various nitrile oxides to (\textit{Z})-methyl-(4′-phenyl)-4-stilbenyl acrylate esters.

The mild conditions under which secondary amides can be hydrolysed to the corresponding carboxylic acids has been powerfully demonstrated in a recent synthesis of teicoplanin aglycon.\textsuperscript{87} Late on in the synthesis of this complex glycopeptide antibiotic core, N\textsubscript{2}O\textsubscript{4} in DMF at 0 °C was employed to convert a methyl amide into the corresponding \textit{N}-nitroso derivative which was in turn hydrolysed (in the presence of six peptide bonds and a TFA carbamate) using 2:1 DMF:H\textsubscript{2}O at 60 °C for 7 h.
Phosphate protecting groups

Oligonucleotide synthesis on a solid support is generally carried out using the phosphoramidite method in which the phosphate is protected as a 2-cyanoethyl group and final deprotection is achieved with NH$_3$ via β-elimination. However, the by-product (acrylonitrile) is toxic, a potential carcinogen, and can alkylate nucleic bases. Consequently, particularly with a number of antisense drugs now being required on a kilogram scale, there is interest in alternative PGs without these drawbacks. A series of 2-benzamidoethyl groups has been screened as alternative PGs in this context. The most promising derivative was the 2-[N-isopropyl-N-(4-methoxybenzoyl)amino]ethyl, which can be introduced by reaction of the corresponding alcohol with the bis(di-i-Pr)amidite in the presence of 1H-tetrazole in CH$_2$Cl$_2$. This mode of protection was shown to be compatible with the synthesis of a 20-mer oligonucleotide. Deprotection was accomplished using concentrated NH$_4$OH within 25 min at 25 °C. In fact, various by-products were isolated following deprotection but these were shown not to be toxic or reactive towards nucleic bases.

Carbonyl protecting groups

A large number of new acidic and Lewis acidic conditions for acetal formation have again been described this year. These include: titanium cation-exchanged Montmorillonite clay in the absence of solvent, Pt–Mo modified ZrO$_2$ in toluene at reflux, phenylsulfonic acid functionalised mesoporous silica (MSU–X) in the absence of solvent, TiCl$_4$ (0.1–1 mol%) with Et$_3$N or NH$_3$, and various rather esoteric Ru, Rh and Ir complexes. For the preparation of mono-ketals of cyclic, acyclic, aromatic and aliphatic ketones with pentaerythritol [C(CH$_2$OH)$_4$], which is highly insoluble in most organic solvents, the use of a benzene:DMF (4:6) mixed solvent system in the presence of catalytic toluene-p-sulfonic acid (p-TSA) has been shown to give excellent results. A new 1,2-diol terminated polyethylene glycol polymer has also been shown to be useful for protection of certain ketones during synthesis, this being exemplified by the preparation of some natural insect pheromone spiroketals. Vanadyl(iv) acetate [VO(OAc)$_2$, ~30 mol%] has been shown to be a mild and efficient heterogeneous catalyst for the deprotection of acetals and ketals in dry MeCN at rt. New and more efficient conditions for the electroreductive deprotection of 4-(4′-nitrophenyl)-1,3-dioxolane and 7-nitro-1,3-benzodioxane PGs have been reported this year. The use of a Hg electrode in 0.15 M KOH in EtOH:H$_2$O (6:4) was found to be significantly better than the previously employed conditions using DMF.

Aldehydes can be cleanly and chemoselectively protected in the presence of ketones by treatment with TBDMS–Cl and imidazole. The resulting O-TBDMS-imidazoyl aminals are reasonably stable to mildly acidic conditions but can be quantitatively removed by treatment with 80% AcOH at 80 °C for 24 h. Deprotection of these adducts is also possible in 9:1 MeCN:49% HF at rt but surprisingly TBAF was not successful for their removal.

A new method for the conversion of aldehydes into gem-dicarboxylates (acylals) is treatment with acid anhydride (1 equiv.) in the presence of LiBF$_4$ (10 mol%).
Aromatic and aliphatic aldehydes including sterically hindered ones (e.g. pivalaldehyde) showed similar reactivity (i.e. no chemoselectivity was observed). Deprotection of gem-diacetates can be achieved by the use of CBr₄ (20 mol%) in refluxing MeCN; conditions which leave N-Boc and other acid-sensitive functional groups intact. The utility of gem-dicarboxylates as electrophiles in asymmetric synthesis as exemplified by the alkylation of “soft” (e.g. malonate) carbanions by allyl gem-diacetates has also been highlighted this year.

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**Amine protecting groups**

Despite the harsh hydrolytic conditions required for deprotection of simple amide PGs they remain useful in many applications. For example, Bz and isobutyryl amides have been used for purine base protection during solid phase peptide nucleic acid (PNA) synthesis on controlled pore glass (CPG) solid support. N-Boc groups are used for backbone protection of the PNA so that global deprotection [and cleavage of the phenylacetamidomethyl (PAM) linker to the CPG support] is achieved either by treatment with NH₃ (32% aqueous, 20 h at 60 °C) or with methylamine (40% aqueous, 4 h, rt). Chemoselective acylation of 1° and 2° aliphatic amines in the presence of other potentially acylable functionality (e.g. ROH, RSH, indoles, imidazoles and phenols) can be achieved by the use of 3-acyl-1,3-diaryltriazenes. These reagents are readily prepared by the reaction of 1,3-diaryltriazines (Ar = 4-NO₂-C₆H₄ or 4-NO₂-2-Cl–C₆H₃) with the appropriate acyl chloride in MeCN or acetone in the presence of Na₂CO₃ or Et₃N. The acylations are performed using 3-acyl-1,3-diaryltriazine (1.1 equiv.) in either MeOH or MeCN at rt, and work-up simply involves filtering off the deacylated triazine (80–95% recovery). An intriguing method for the acylation of 1° and 2° amines to form amides under completely neutral conditions is by acyl transfer from photoactivated N-acyl-5,7-dinitroindolines. This reaction was first described in the 1970s but has now been rendered more useful by the disclosure of improved conditions for the preparation of the key N-acyl-5,7-dinitroindolines by acylation of 5,7-dinitroindoline. The cleavage of 1° amide PGs under nucelophilic conditions is well known to be promoted by prior conversion to an N-carbamate derivative (e.g. N-Boc derivatisation), which renders the amide carbonyl significantly more electrophilic by virtue of reduced resonance stabilisation from the nitrogen lone pair. This principle has now been extended to electrochemical and reductive cleavage of 1° N-Bz derivatives and related heteroarylamides. Similar results have previously been reported for sulfonamides. Similarly, deprotection of N-Ts and N-Bz protected tryptophan and histidine side-chains is possible using either Mg in anhydrous MeOH or Hg-activated aluminium. The removal of a 2° N-Bz PG in the presence of an O-Bz ester has also been achieved in a neat two-step sequence in which the N-Bz group is first reduced to the corresponding N-Bn borane-amine adduct using BH₃·THF in THF and then subjected to hydrogenolysis using Pd/C in MeOH. The borane acts as the internal hydrogen transfer source for this second step (Scheme 10).
Aminals are not very commonly employed as amine PGs but the MOM group has now been shown to be a useful PG for 3-(2H)-pyridazinones.\(^{108}\) Introduction is achieved using MOM–Cl, DIPEA and DMAP in CH\(_2\)Cl\(_2\) at 0 °C for 1 h, and removal involves treatment with either BBr\(_3\) in CH\(_2\)Cl\(_2\) at −78 °C or AlCl\(_3\) in toluene at reflux. Protection in this manner was highly effective for allowing a series of Pd(0)-catalysed cross-coupling reactions of a bromide at the 5-position to be achieved successfully.

Allylic and benzylic PGs remain a popular choice for amine protection. This year has seen the development of a new method for deprotection of 3\(^{-}\)allylamines using Grubbs’ catalyst, Cl\(_2\)(Cy\(_3\)P)\(_2\)Ru=CPh (5 mol%) in toluene at reflux for 0.5–5 h.\(^{109}\) The mechanism is believed to occur through isomerisation to the corresponding enamine followed by hydrolysis on work-up. The conditions do not affect N-p-methoxyphenyl (PMP), N-Bn or isopropylidene groups. Further developments have also been reported in the orthogonal deprotection of dibenzyl protected chiral amines.\(^{110}\) Thus, following diastereoselective conjugate addition of lithiated-N-Bn-N-\(\alpha\)-methyl-4-methoxybenzylamide to \(\alpha,\beta\)-unsaturated esters, selective deprotection of the Bn PG can be achieved by treatment with aqueous CAN (2.1 equiv.), leaving the \(\alpha\)-methyl-4-methoxybenzylamine substituent intact. Removal of this group can however be achieved by further treatment with aqueous CAN (4.0 equiv.). The 2-nitrobenzyl PG, which is removed under photochemical irradiation, has been employed in a neat synthesis of the cytotoxic quinazolinone ent-fumiquinazoline G from the fungus *Aspergillus fumigatus*.\(^{111}\)

Schiff’s bases are also occasionally employed as PGs for both valencies of 1° amino groups, particularly when an electron-withdrawing PG must be avoided. This year has seen the development of the new \(N\)-2-hydroxyarylidene PG in this context.\(^{112}\) Introduction is by reaction of the 1° amine with salicylaldehyde in MeOH, and deprotection is possible under neutral conditions using MeONH\(_2\) (10 equiv.) in CHCl\(_3\)/MeOH (95:5) at rt for 1 h. Salicylaldehyde-\(O\)-methyl oxime is the side-product. The utility of this PG was highlighted by its use to allow the selective acylation of a secondary amino group in the presence of a primary one (Scheme 11).
Carbamates are probably the most widely used class of amine PGs both in and beyond peptide chemistry. This year has seen the development of another variation of three-component coupling for the preparation of carbamates from an amine, CO\(_2\) and an alkyl halide.\(^{113}\) The method employs the requisite alkyl bromide–chloride (3 equiv.), Cs\(_2\)CO\(_3\) (3 equiv.) and tetrabutylammonium iodide (TBAI, 3 equiv.) in DMF at rt while bubbling CO\(_2\) for ∼3 h. If BnCl is used then the method is suitable for the preparation of Cbz derivatives and is compatible with a range of alkyl, aromatic and heteroaromatic amines. Electron-deficient aryl amines, as expected due to their poor nucleophilicity, react sluggishly. A polymer-bound Fmoc-OSu (Su = succinimidyl) reagent has also been developed for the preparation of N-Fmoc derivatives.\(^{114}\) Related polymers, formed by ring-opening metathesis polymerisation (ROMP) of exo-N-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide using Grubbs’ catalyst, have been used previously as solid-supported acyl transfer reagents but this polymer is formed by reaction of commercially available styrene–maleic anhydride co-polymer with a 50% aqueous solution of hydroxylamine followed by reaction with Fmoc-Cl. Residual polymeric SuOH present after the protection reaction is separated by simple filtration. Two new carbamate PGs are the 9-xanthenylmethyloxycarbonyl\(^{115}\) and ‘fluorous Boc’ (\(^{19}\)Boc)\(^{116}\) groups. The 9-xanthenylmethyloxycarbonyl group is introduced by reaction of the amine with 9-xanthenylmethyl-p-nitrophenylcarbonate (1 equiv.) in DMF at 50 °C. Deprotection is accomplished by irradiation in MeCN using low-pressure Hg lamps (~300 nm) in a Rayonet photolysis chamber. The \(^{19}\)Boc group \([\text{C}_9\text{F}_7\text{CH}_2\text{CH}_2\text{CH}_3\text{CH}_3\text{CH}_2\text{CO}(\text{O})\text{O}]\) has been developed as an analogue of the standard Boc group, which incorporates a fluorous tag to allow separations of protected derivatives into fluorous organic solvents. An interesting study has been carried out on the unexpected migration of a Boc group [and Cbz and methoxycarbonyl (Moc) groups] from N to O in a protected pyroglutaminol on cleavage of a silyl ether (TBDMS or TBDPS) by TBAF.\(^{117}\) The involvement of an alkoxide formed by collapse of the Si–O bond from a hexacoordinate silicate intermediate is implicated. A survey has also been made of PGs/activating groups suitable for the synthesis of hydroxylamines using the Mitsunobu reaction and a number of N,O-dicarbamate derivatives were found to be suitable.\(^{118}\) A combination of N-Boc and N-triphenylphosphonium PGs has been shown to be very useful for the selective synthesis of substituted hydrazines.\(^{119}\) The triphenylphosphonium moiety simultaneously fulfils two functions: protection and activation of the attached amine towards deprotonation. Thus, BocNH–NHP\(^{+}\)PPh\(_3\)Br\(^{-}\), which is readily prepared from commercially available t-Bu carbazate and triphenylphosphine dibromide, undergoes deprotonation with n-BuLi to give the phosphinamine, which in turn is readily alkylated in situ. Removal of the phosphonium PG is accomplished by treatment with 2 M NaOH in CH\(_2\)Cl\(_2\) in <5 min (Scheme 12).

A number of methods for the deprotection of Boc carbamates have been published this year. A method that is selective for N-Boc deprotection even for substrates

\[\text{Reagents and conditions: (a) PPh}_3\text{Br}_2, \text{Et}_3\text{N, toluene, rt; (b) BuLi, THF, 0 °C; (c) R}^1\text{X; (d) 2M NaOH, CH}_2\text{Cl}_2, \text{rt; (e) R}^2\text{COX, Py, rt; (f) R}^3\text{X, NaOH, K}_2\text{CO}_3}\]

Scheme 12
immobilized on resins via the acid labile Wang linker is concentrated H$_2$SO$_4$ in 1,4-dioxane (1:9).\textsuperscript{120} In stark contrast, the use of 4 M HCl in CH$_2$Cl$_2$ resulted in complete cleavage of the Wang linker, with Boc groups remaining largely intact. Nitrolytic deprotection of N-Boc groups using HNO$_3$ (3.5 equiv.) in CH$_2$Cl$_2$ at 0 °C for 1 h has also been demonstrated.\textsuperscript{121} This is unsurprising given the previously disclosed effectiveness of these conditions for deprotection of t-Bu esters. Alanine, phenylalanine, serine and lysine derivatives were efficiently deprotected without racemization and without affecting N-Cbz or alkyl ester functions. Fast and efficient deprotection of N-Boc groups from amino acid derivatives and peptides in the presence of other t-Bu-based PGs (i.e. t-Bu esters and ethers including thio-t-Bu ethers but not phenolic t-Bu ethers) can be accomplished by the use of commercially available 4 M HCl in anhydrous 1,4-dioxane from 0 °C to rt within 30 min.\textsuperscript{122} An interesting set of conditions for accomplishing the reverse selectivity, i.e. the removal of a t-Bu ester from an N-Boc protected amino acid derivative is: NaI (1.3 equiv.) and CeCl$_3·7$H$_2$O (1.5 equiv.) in refluxing MeCN for 5 h.\textsuperscript{123} A highly efficient and rapid deprotection of the N-allyloxycarbonyl (Alloc) group uses Pd(PPh$_3$)$_4$ (10 mol%) in combination with DABCO (5 equiv.) as allyl scavenger in CH$_2$Cl$_2$.\textsuperscript{124} This protocol has been incorporated into a one-pot deprotection/peptide coupling protocol of Alloc-protected amino acids with activated N-Boc or N-Fmoc amino acids using a carbodiimide-based coupling reagent (EDC) and HOBt. Ammonium formate-based catalytic transfer hydrogenolysis using 10% Pd/C in MeOH at rt has been suggested to be a very efficient method for deprotection of halogenated analogues of the N-Cbz and N-Bn groups [e.g. N-2-Cl–Cbz, N-2,6-di-Cl–Cbz and N-4-Br–Cbz)].\textsuperscript{125} These groups are often employed in place of the standard PGs because of their improved acid stability but removal by hydrogenolysis under standard conditions is invariably sluggish.

The area of non-enzymatic, acylative KR of amines has lagged significantly behind its counterpart, the acylative KR of alcohols. Although some stoichiometric processes based on chiral acylating agents have been developed,\textsuperscript{126} catalysis has been elusive. The reason for this is undoubtedly the much greater reactivity of amines towards common acylating/carbamoylating agents, which can cause the uncatalysed reaction rate to be significant. In the light of this, a landmark publication has appeared this year detailing the use of a planar-chiral DMAP derivative for catalysis of the KR of aryl alkyl 1° amines by carbamate formation.\textsuperscript{127} Although the convenience of the method is currently severely compromised by the requirement for 10 mol% of what is a rather inaccessible chiral catalyst and a rather elaborate stoichiometric carbamoylating reagent, further advances in this area can be expected in the near future (Scheme 13).

In the last few years, 2-, 4- and 2,4-dinitrobenzenesulfonamides (N-Ns and N-DNs PGs) have become probably the most popular sulfonamide PGs for amines. This

Scheme 13
popularity arises from their ready deprotection, in stark contrast to the harsh conditions required for deprotection of most other sulfonamides, by nucleophilic aromatic substitution ($S_N$Ar with thiols under relatively mild conditions). This year a series of optimised removal conditions have been reported. These include the use of $\text{HSCH}_2\text{CH}_2\text{OH}$ (2 equiv.) and DBU (2 equiv.) in DMF at 0 °C for 30 min. Selective removal of a 2,4-DNs group in the presence of a 2-Ns group can be achieved by omitting the DBU from this procedure.

Finally, a couple of full papers describing the synthesis of complex lipidated peptides using a wide array of orthogonal PGs should be highlighted. In particular, the successful preparation of the N-terminal undetrigintapeptide of endothelial nitric oxide synthase (eNOS) was achieved by employing a combination of an enzyme-labile ($p$-phenylacetoxybenzyloxycarbonyl (PhAcOCbz)) N-terminal PG, a Pd(0)-labile allyl C-terminal PG, and acid-labile side-chain PGs in a solution-phase synthesis of S-palmitoylated building blocks under mild conditions with solid-phase techniques and solution-phase fragment condensations. This synthesis of this complex triply lipidated 29-mer powerfully demonstrates the exquisite selectivity now achievable using carefully designed orthogonal PG regimes.

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