Linkers and Cleavage Strategies in Solid-Phase Organic Synthesis and Combinatorial Chemistry

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I. Introduction

The massive increase in the number of papers describing the use of polymeric supports in organic synthesis over the past decade is a vivid demonstration of its impact in the chemical community. Few other changes in synthetic chemistry methodology have displayed such a growing passion or had such a profound influence on the way synthetic chemistry

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Fabrice Guillier was born in 1968 in the city of Saint Denis, France. He received his diplome d'Ingénieur chimiste in 1992 from the National Institute of Applied Sciences (INSA Rouen) after studying chemical engineering and organic chemistry. In 1996 he completed his Ph.D. thesis on natural product synthesis using metalation and cross-coupling reactions in the laboratories of Professor Guy Quéguiner (URA1429-IRCOF–Rouen-France). These methodologies using palladium and lithium derivatives were suitable for the synthesis of polyheterocyclic marine alkaloids of the pyridoacridine family. He spent then one year as a postdoctoral fellow at Southampton University, working with Professor Jeremy Kilburn (Department of Chemistry, University of Southampton) studying the synthesis and supramolecular interactions of guanidinium-based tweezer receptors of C-terminal tripeptides. From 1997 to 1999 he joined the research group of Professor Mark Bradley at the University of Southampton, where he conducted research on the development of new methods for screening on solid supports and the synthesis of libraries of polyamines as inhibitors of *trypanothione reductase* and substituted pyrimidines for *kinases* inhibition. Currently he is developing new reactions for lead discovery using solution-phase parallel synthesis at Alanex Division of Agouron Pharmaceuticals (San Diego, CA) as a research fellow.

David Orain was born in 1971 in Rennes, France. He studied chemistry at the University of Rennes and received his DEA (Masters) degree in 1994 under the supervision of Dr. Paul Mosset at ENSCR (School of Chemistry at Rennes) where he studied the synthesis of α,α'-bifunctionnalized heterocycles. Then he moved downstairs at ENSCR and worked with Dr. J. C. Guillemin's group during his Ph.D. studies. His research involved the use of zirconium organometallic complexes for solution and support chemistries. He was awarded his Ph.D. degree in December 1998. In January 1999, he crossed the Channel and joined Professor Mark Bradley's group (Department Chemistry, Southampton University) as a postdoctoral researcher. His current research focuses on the development of a new safety-catch linker for amine release under biological conditions and new direct screening processes of a library of *trypanothione reductase* inhibitors.

is carried out. The advantages gained by this methodology are striking, with four main factors contributing to the popularity of the technique. (i) *The ease of chemistry*. Reactions can be accomplished in only three steps: addition of reagents, filtering, and

Mark Bradley was born in the United Kingdom in 1962. He received his first degree from the University of Oxford in 1986 and his DPhil degree from the same institution three years later under the supervision of Professor Sir Jack Baldwin in the area of Penicillin biosynthesis. In 1989 he moved to the United States to work with Professor Chris Walsh at Harvard Medical School. He then returned to the United Kingdom and to Southampton University in 1992 as a Royal Society University Research Fellow. In 1997 he was made a Professor of Combinatorial Chemistry and has published in excess of 50 papers in the combinatorial area. In January 2000 he became director of the Combinatorial Centre of Excellence now housed in Southampton. His research interests span across the whole area of combinatorial high-throughput synthesis, screening, and analysis from an academic viewpoint. This includes interests in solid-phase and small-molecule synthesis as well combinatorial activities in the area of catalysts, dendrimers, fluorophores, and polymers. He has interests in the area of enzyme inhibition including work in the area of proteases, antibacterial agents, and antiparastics.

washing the resin, thus allowing many simple automated procedures to be developed. (ii) *The elimination of purification steps en route*. For each step of a multiple-step synthesis, the only purification needed is a resin-washing step. Only the final product of cleavage needs to be purified. (iii) *In a solid-phase synthesis, high concentrations of reagents can be used to drive reactions to completion*. (iv) *The straightforward nature of parallel solid-phase synthesis*.

However, for a solid-phase synthesis to be practical, several important issues need to be addressed, including the correct choice of solid support and the mode of attachment and cleavage of materials from the resin matrix. Efficiency in anchoring and removing a small organic molecule from the polymeric resin relies on the correct choice of the linker group. This key fragment is crucial in planning a synthetic strategy. However, if the objective of a single or parallel solid-phase organic synthesis is to produce one or several defined products upon release, the correct choice of an adequate linker system can enable further goals to be attained. Multidetachable linkers allow the preparation of different products depending on the cleavage conditions selected. Partial release can be useful for monitoring reactions or screening mixtures for deconvolution. Structural elucidation of hits from mixtures of products is another application of linkers in combinatorial chemistry, allowing "tags" of a variety of forms to be incorporated and read.

II. Solid Supports for Organic Synthesis

Cross-linked polystyrene resin beads have been used for organic synthesis since 1963, when Merri-

field first used a chloromethylated-nitrated copolymer of styrene and divinylbenzene (DVB).[1] Resins now used in solid-phase organic synthesis have changed little since this time. These insoluble supports have a gel-type structure which readily allows penetration of reagents and solvents into the beads to sites where chemistry is taking place. A compromise has been found between moderately cross-linked resins (5% DVB) which are very stable but do not swell particularly well, thus reducing site access and low cross-linked resins where mechanical stability becomes an issue. A general consensus now seems to have been reached, and typical supports used for solid-phase synthesis consist of polystyrene with a 1−2% DVB cross-linking. The three dominant polystyrene supports currently in use are the following. (i) *Chloromethylpolystyrene*. Originally prepared by resin postderivatization using chloromethylmethyl ether and $SnCl_4$, it has been more recently prepared by copolymerization using chloromethylstyrene/styrene/DVB mixtures. This core resin is used widely for the attachment of linkers by ether formation. (ii) *Hydroxymethylpolystyrene*. Prepared from Merrifield resin by esterification with potassium acetate followed by saponification or reduction of the ester.[2] (iii) *Aminomethylpolystyrene*. Mitchell[3] prepared this resin either by potassium phthalimide substitution of the Merrifield resin followed by hydrazinolysis or by direct aminomethylation of the polystyrene resin. Aminomethyl resin allows a multitude of spacers/linkers to be appended to the resin by amide bonds, which are stable under strongly acidic conditions. This still provides one of the main workhorse resins of today.

A few other materials are used but polystyrene resin dominates; among the other materials used, TentaGel resin (TG) and ArgoGel (AG), both polystyrene/DVB−poly(ethylene glycol) graft copolymers (PS−PEG), developed by Bayer,[4] are the most favored. They have specific uses, such as when polar solvents are needed or when distancing from the resin core becomes necessary. Crowns/Pins (CP) are another kind of support used in solid-phase synthesis and consist of a radiation-grafted polyethylene/polypropylene support.[5] Kieselguhr/polyacrylamide-based resins (KPA)[6] and controlled-pore glass (CPG)[7] are used in continuous flow SPPS and oligonucleotide synthesis but are usually avoided by the synthetic chemist. PEGA,[8] a poly(ethylene glycol)/dimethylacrylamide copolymer, is a very polar material which confers unparalleled swelling properties in water and possesses a flexible interior enabling access for a variety of large macromolecules such as enzymes; however, low mechanical stability makes handling difficult and expense precludes large-scale use.

III. Linker and Linker Attachment

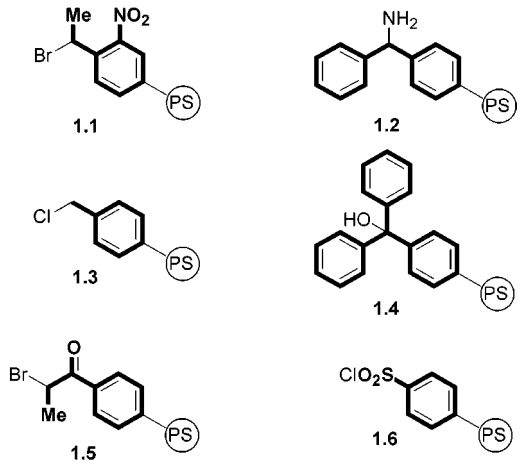
The attachment point of the linker to the solid support or spacer should be chemically stable during the synthesis and cleavage, and as for any solution-phase protecting group, yields for its loading and cleavage should be as quantitative as possible. In combination, the *Resin−(Spacer)−Linker* unit can thus be considered to be an insoluble, immobilizing protecting group for solid-phase synthesis. A great number of linkers (more than 200) have been developed over the past 15 years in order to allow many multistep organic syntheses to be performed and the use of a broad range of reagents, allowing cleavages in a very selective manner (see refs 9−15 for reviews). Although a linker should ideally enable a selective cleavage to take place under a defined set of conditions, these conditions are in reality not only dependent on the linker but also on the compound attached to the linker, the spacer, and importantly on the resin type, its loading, and bead size. Thus, smaller beads have a much greater efficiency of cleavage under photolysis conditions. Reduced cross-linking dramatically enhances the rate of cleavage from solid supports under acidic conditions.[16] Lack of resin preswelling in CH_2Cl_2 prior to cleavage with TFA can also cause reduction in yields.[16] Many different parameters are thus involved in the cleavage of compounds from the solid support and not just the linker needs to be considered.

A. Linker Types

In this review, to aid clarification and to avoid inaccuracies, there will be a clear distinction made between resins and linkers: Resins will be considered as an inert matrix, passive to chemistry. Linkers will be considered simply as immobilized protecting groups and will be classified into one of two types: (i) *Integral linkers* in which part of the solid support core forms part or all of the linker and (ii) *Nonintegral (or grafted) linkers* in which the linker is attached to the resin core. A linker which has been prepared in solution will be defined as a *unloaded linker*.

Many examples of integral linkers exist (Scheme 1), and certainly they were very popular in the early

Scheme 1



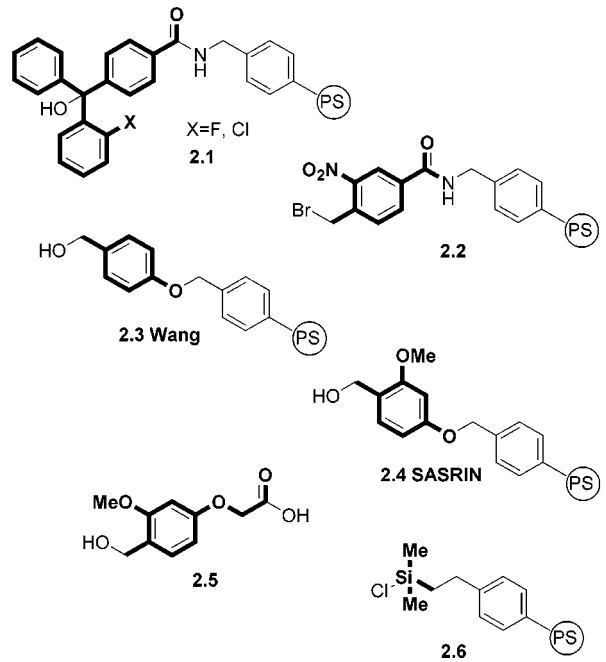
days of solid-phase synthesis. Thus, linkers such as the *o*-nitro-(α-methyl)bromobenzyl linker **1.1** prepared by Pillai[17] is a classic example of an integral linker. Its preparation was realized by functionalizing polystyrene/DVB resin with acetyl chloride/$AlCl_3$, reducing the resulting ketone and bromination of the resulting alcohol. The nitro group was then incorporated by nitration of the resin. Also included in this list are the benzhydrylamine (BHA) linker **1.2** pre-

pared by Friedel−Crafts acylation of polystyrene with benzoyl chloride.[18] The resulting benzophenone derivative was transformed into the desired product by either reduction of an oxime, ammonolysis of the bromo derivative, or reductive amination with ammonium formate. The original chloromethylated polystyrene resin **1.3** used by Merrifield can in many respects be considered as an integral linker. This allowed Merrifield to anchor *N*-protected amino acids onto solid supports by formation of immobilized benzyl esters. The trityl linker **1.4** was developed by Leznoff[19] by lithiation of polystyrene and reaction with benzophenone and by Fréchet[20,21] by treatment of benzophenone-based polystyrene with phenylmagnesium bromide. Another light-cleavable bromine-derivatized linker **1.5** was obtained by functionalization of 2% polystyrene/DVB with 2-bromopropionyl chloride/$AlCl_3$ under Friedel−Crafts conditions.[22] Two percent cross-linked benzene sulfonyl chloride **1.6** was prepared from Dowex 50W ion-exchange resin (−SO_3H).[23]

The disadvantage with any integral linker is the control of synthesis, taking place as it does directly on the resin, with the whole range of steric and electronic effects having an influence over the synthetic outcome. The exact degree of loading and functionalization can be hard to control.

The majority of linkers used in solid-phase synthesis are thus of the nonintegral type (Scheme 2).

Scheme 2

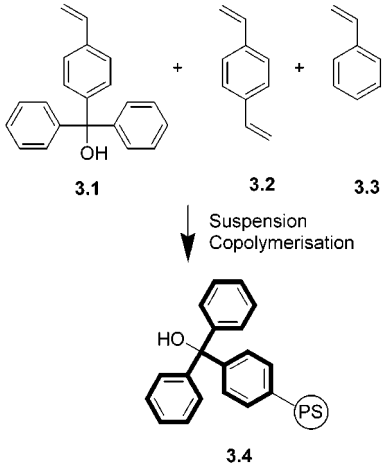


These can be loaded onto the resin and then derivatized or preloaded prior to attachment. This resin attachment is generally realized in one of three ways: (i) *Ethers*, (ii) *Amides*, and (iii) *C−C bonds*.

Thus, derivatives of the trityl linker **2.1** have been prepared in the nonintegral manner by attachment of 4-carboxy derivatives[24] through an amide bond. A light-cleavable linker *o*-nitrobenzyl (ONB) **2.2** was prepared[25] by coupling 3-nitro-4-bromomethylbenzoic acid onto an aminomethylpolystyrene resin, in clear contrast to the integral linkers described above. The *p*-alkoxybenzyl alcohol Wang linker **2.3** was initially prepared by reacting 4-hydroxybenzyl alcohol with Merrifield resin in the presence of sodium methoxide.[26] The Sasrin linker **2.4** was first described by Mergler[27,28] and was initially anchored onto the resin by etherification. Sheppard[29,30] prepared the unloaded linker **2.5**, allowing attachment to an aminomethylpolystyrene resin. Dimethylsilyl chloride groups have also been attached to the polystyrene core through an ethylene bridge to give **2.6** by hydrosilylation of (vinyl)polystyrene.[31] Here again the resin core is not an integral part of the linker.

Linkers that are copolymerized into resin beads can be either of the integral or nonintegral type. Those which are not part of the polymer core can be considered as nonintegral (or grafted) in nature. Scheme 3 shows the preparation of a trityl (integral) linker **3.4** by suspension copolymerization of monomer **3.1**, DVB **3.2**, and styrene **3.3**.[32]

Scheme 3

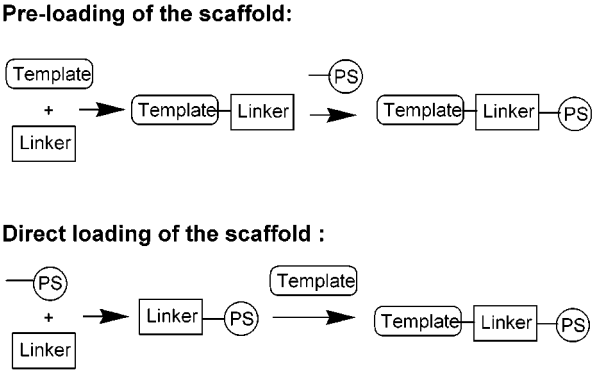


B. Scaffold Preloading and Direct Loading

The choice of which method, ***preloading*** or ***direct loading*** of the scaffold onto a nonintegral (or grafted) linker, is the most suitable for use in solid-phase synthesis is not clear-cut. The first method usually ensures much higher loading levels and that only purified materials are coupled onto the solid support and also reduces the number of solid-phase steps. The second method is usually less efficient since excess materials are often used in the coupling step, a problem if valuable scaffolds are being used, but is faster since no solution steps or purifications are needed (Scheme 4).

In addition, if all the derivatized sites on the loaded linker are not reacted, then undesirable side reactions can take place. There are certainly cases where linkers attached to resins have not been added cleanly and have given rise to numerous side reactions and impure products. Thus, the attachment of 4-hydroxybenzyl alcohol onto Merrifield resin to form the Wang linker using the original procedure described had to be improved in order to limit the side reactions which afforded more than five different byproducts as originally reported.[33]

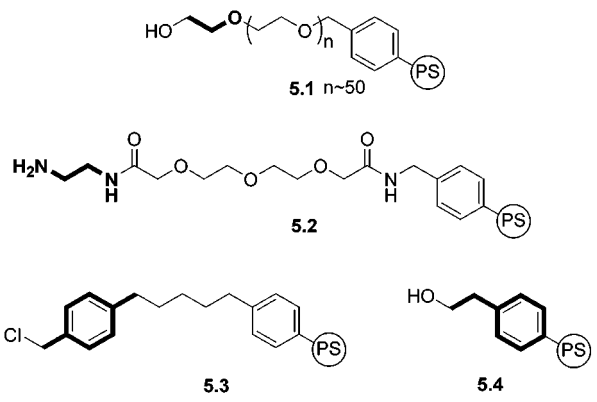
Scheme 4



C. Spacers

A group can be attached to the solid support to act as a spacer unit. The spacer has a number of roles. Principally, it acts to distance chemistry from the solid support and tailors the swelling properties of the resin materials to give more "solution-like" properties and better solvent compatibility. Typical examples of spacers are PEG chains (as in PS−PEG-based resins such as TentaGel **5.1** or resin **5.2**[34]) or alkyl chains as shown in **5.3**[35] (Scheme 5). Spacers

Scheme 5

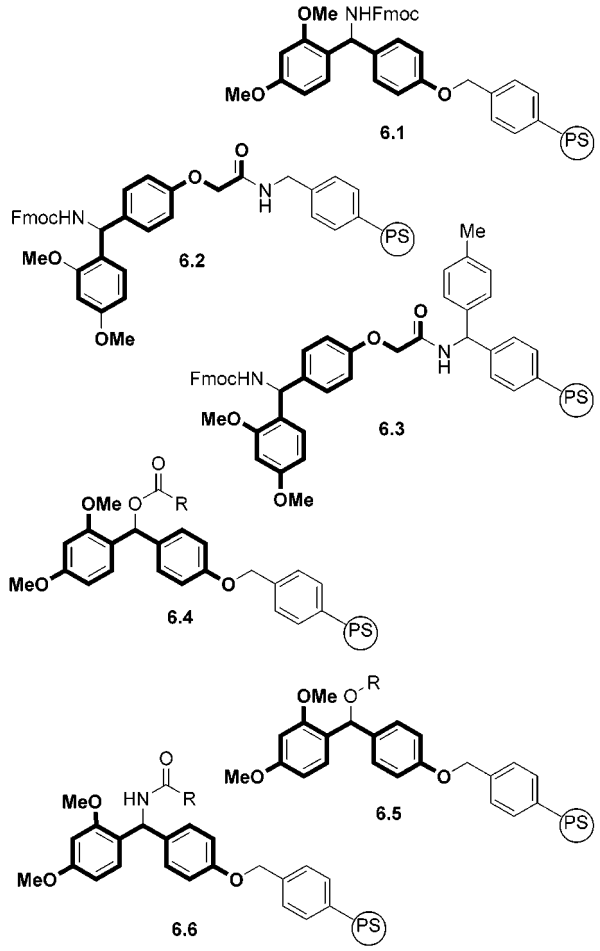


can therefore alter the cleavage properties of the linker, affecting resin swelling as well as complicating electronic effects. The extra methylene unit present in **5.4** compared to the classical hydroxymethylpolystyrene resin confers crucial properties such as acid stability,[36,37] although possibly sensitivity to β-elimination once loaded.

D. Linker Attachment

Although the core structure of the linker may remain unchanged, the group placed between the linker and the support can modify the cleavage conditions and also alter the degree of linker cleavage as well. An example has been illustrated with the Rink resin **6.1**.[38] High concentrations of TFA can sometimes cleave some of the Rink linker from the polystyrene support and introduce colored impurities into the cleaved product. The Rink amide AM **6.2** (RAM) and Rink amide MBHA **6.3** are much more stable to TFA (Scheme 6) (these constructs are made by coupling the so-called Knorr linker[39] to the resin through an amide bond).

Scheme 6



E. Leaving Groups and Scavengers

The Rink linker may be employed to attach a range of different functional groups to a common solid support, for example acids, amides, amines, etc. However, each functionality can be cleaved only under specific conditions. Thus, 0.1% TFA in CH_2Cl_2 will release acids[38] from linker **6.4** while 5% TFA in CH_2Cl_2 is needed to cleave alcohols from **6.5** and amides[40] from **6.6** (Scheme 6). Since the dimethoxybenzhydryl cation is generated in all of these cases, labilities must depend on the ease of protonation of the attached scaffold as well as its leaving ability. Thus, clearly, linkers are only one factor in determining "cleavability".

Another important factor, which can impede cleavage, is the reversibility of the reaction. This is certainly well-documented in solid-phase peptide synthesis (SPPS) where linker cation alkylation can be a serious problem, especially with peptides containing cysteines (thiols) or tryptophans (indoles), with the extent of alkylation being directly related to the proximity of specific residues to the linker. This is presumably also a problem in solid-phase organic synthesis (SPOS), although less well-documented with poor yields usually attributed to other factors. In the peptide area, scavengers are often used in order to trap the cationic linker species and prevent re-attachment. Usually scavengers such as ethanedithiol (EDT) or thiophenol are used, although ir-

reversible quenching using trialkylsilanes is common. Water is another very commonly used additive in cleavage solutions. Reagent K[41] (82.5% TFA, 5% phenol, 5% H_2O, 5% thioanisole, 2.5% EDT) is a cleavage mixture which has been found to be efficient (if smelly) and is now a fairly general cocktail for peptide chemistry. For multiple parallel solid-phase synthesis, much less complex scavenger mixes are desired/needed and often just water is used.

IV. Linkers and Cleavages in Organic Synthesis

In the following sections, classification of the linkers has been attempted across seven major classes of cleavage reaction; however; overlap between classes does occur: (A) Electrophilically cleaved linkers, (B) Nucleophilically cleaved linkers, (C) Photocleavable linkers, (D) Metal-assisted cleavage procedures, (E) Cleavage under reductive conditions, (F) Cleavage under oxidative conditions, and (G) Cycloaddition- and cycloreversion-based release.

Particular attention has been paid to linkers such as safety-catch linkers, which can achieve a higher degree of orthogonality by being uncleavable until activated. Purities and yields are considered throughout, and cyclorelease methodologies are exemplified in this respect. The common and appealing "*traceless cleavage*" terminology has been avoided as it lacks definition and is inaccurate.

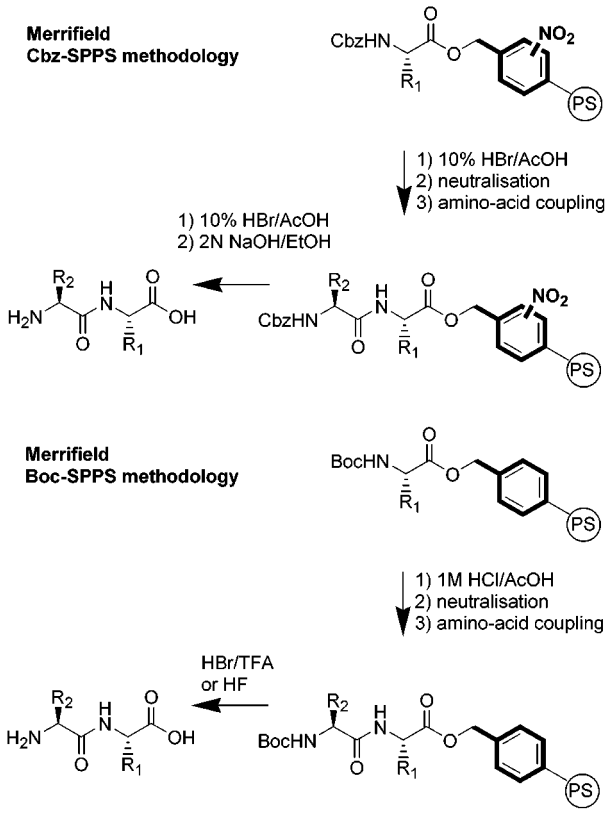
A. Electrophilically Cleaved Linkers

Two main modes of electrophilic cleavage are used: protons and halogens. The largest one by far involves proton sources. Large arrays of compounds have been cleaved, including acids, amides, alcohols, thiols, amidines, amines, sulfonamides, etc. Although the introduction of a halogen group is useful, the range of cleaved products in this area is at the present time somewhat restricted.

1. Strong Acid Cleavable Linkers

a. Merrifield Resin. Solid-phase methodology was initially developed for the preparation of peptides; the classical synthesis involved the anchoring of the free carboxylic acid of benzyloxycarbonyl (Cbz) *N*-protected amino acids onto a nitrated chloromethylpolystyrene resin (Scheme 7). Subsequent deprotection of the Cbz-amino-protecting group with hydrogen bromide in glacial acetic acid gave the amines ready for chain extension after neutralization. Under these Cbz-deprotection conditions (10% HBr), the ester bond linking the peptide to the resin was stable (with only 3.2% cleaved after 6 h).[1] Release of the peptide was carried out under basic conditions (principle of orthogonality) by saponification. In the synthesis of Bradykinin, Merrifield[42] used *tert*-butyloxycarbonyl (Boc) amino-protecting groups which could be deprotected with 1 M HCl without the loss of peptide from chloromethylpolystyrene resin (now known as Merrifield resin) (Scheme 7). Nitration of the resin was no longer necessary due to the reduction in acid strength used for amine deprotection (i.e., Boc vs Cbz). This alternative use of protecting groups also allowed the use of hydrogen fluoride for both resin and side-chain deprotection,[43] a cleavage method which has dominated Boc/Bn solid-phase peptide chemistry since its introduction in 1965.[44] The HF method gives products of high purity and in good yield with excess volatile HF being removed by evaporation.

Scheme 7

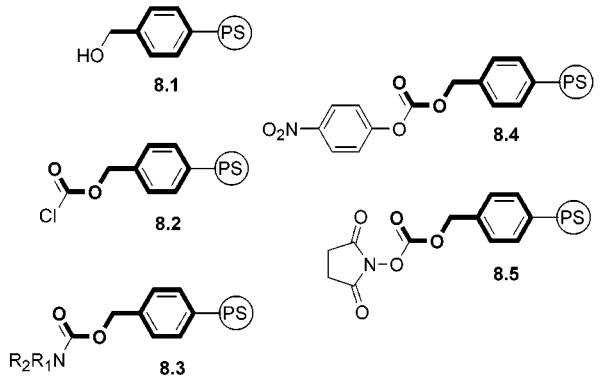


Nevertheless, low temperatures (0 °C) and short reaction times (30−60 min) are advised with HF in order to avoid side reactions.[45] Techniques such as Low−High HF cleavages, where temperature, reaction time, concentration, and the nature of the scavenger are varied, have been created, but in each case they are strongly dependent on the side-chain protecting groups that are present.[46] Using a low concentration of HF, the alkyl side chains are trapped by scavengers, preventing side-chain alkylation.[47,48] A higher HF concentration enables the cleavage of the clean product from the resin. Trifluoromethane sulfonic acid (TFMSA), an alternative to HF, was introduced in 1974.[49] Even though it is a very strong acid, it does not require special laboratory glassware. However, unlike HF, TFMSA is not volatile and can therefore be difficult to remove. Peptides must be precipitated from solution using dry solvents such as ether and are susceptible to salt and scavenger association. They need to be neutralized and desalted before further purification. As with HF, TFMSA can be used in a Low−High procedure.

Some benzyl-based linkers are presented in Schemes 8−11. Hydroxymethylpolystyrene resin **8.1** has been used in place of Merrifield resin to anchor carboxylic acids by a number of methods, including DIC/DMAP activation or Mitsunobu coupling. The sensitivity of the resulting ester to cleavage naturally remains unchanged.

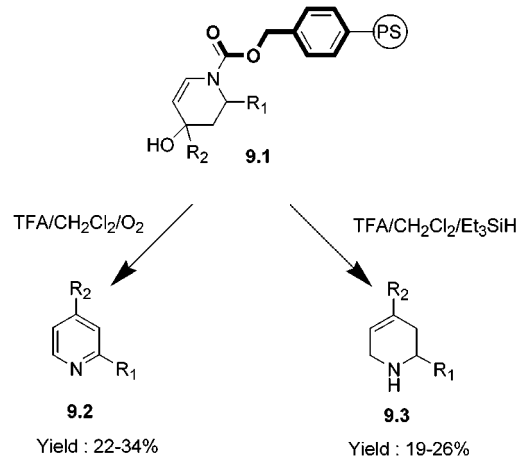
Amines can be easily loaded onto Merrifield resin, but their removal is nearly impossible. However, a very convenient way to release amines from benzylic supports is to use the carbamate linker **8.3**. In this case the amine can be liberated under acidic conditions with evolution of CO_2. Burdick[50] transformed hydroxymethyl resin into the chloroformate derivative **8.2** using phosgene[51,52] and then reacted this intermediate resin with anilines. Cleavage with HF and anisole provided the desired anilines. Leznoff also obtained carbamate **8.3** from *p*-nitrophenylcarbamate derivative **8.4** for the anchoring of symmetrical diamines. Cleavage was then achieved either using anhydrous HCl in benzene or TFA/TFAA/$CHCl_3$ (10:1:10).[53,54] A team from Organon recently used disuccinimidyl carbonate linker **8.5**[55] to prepare a library of 150 pyridine-based compounds obtained with purities of between 40% and 60% after cleavage with TFA/thioanisole[56] (9:1) for 4 h. Alcohols have also been anchored and released from Merrifield resin using dissucinimidyl carbonate **8.5**, Scheme 8.[57]

Scheme 8



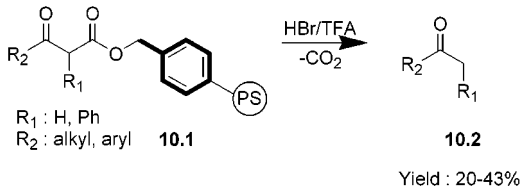
A particular example of nitrogen-based compound release from carbamate resin is shown with the cleavage of carbamate **9.1** under oxidative conditions (TFA/CH_2Cl_2 (2:1) and O_2 bubbling) or reductive conditions (TFA/CH_2Cl_2 (2:1) and 1 equiv of triethylsilane) leading to the formation of pyridines **9.2** or tetrahydropyridines **9.3**, respectively (Scheme 9).[58]

Scheme 9



Decarboxylation procedures can be used to afford products where the carboxyl group forms part of the linking group involved in attachment to the solid support. The interesting feature is that the generated compound "loses" its attachment point. In 1970 Patchornik[59] generated ketones **10.2** after treatment of a β-ketoester anchored onto a 2% cross-linked Merrifield resin using dry HBr in TFA (Scheme 10).

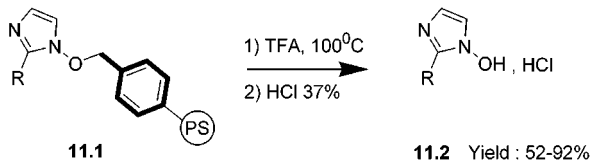
Scheme 10



More recently, supported 2-carboxylquinazolines have been involved in the synthesis of quinazolines by decarboxylative cleavage using TMSI as the Lewis acid source for 1−3 days at 75 °C. Postcleavage treatment with 1 M HCl in solution phase was carried out when decarboxylation was not spontaneous.[60]

The relative weakness of the N−O bond has been used in the cleavage of 1-hydroxyimidazole **11.2** from resin **11.1**.[61] However, heating at 100 °C for 20 h in TFA using a sealed tube was required followed by trituration with 37% aqueous HCl to form the hydrochloride salt (Scheme 11).

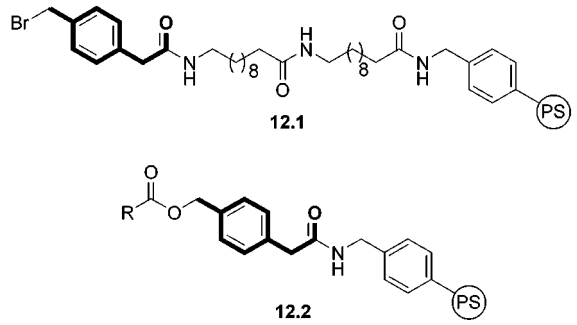
Scheme 11



b. PAM Linkers. The stability of the benzylic ester-based linkages (esterified chloro- or hydroxymethylpolystyrene resins) to TFA is not absolute.[62] Thus, when ribonuclease A was synthesized on this resin, an average of 1.4% of the growing peptide chain was lost after each deprotection step (using 50% TFA in CH_2Cl_2), which was disastrous for this 124mer peptide.[45] In 1976, Sparrow[63] decided to place a long "spacer" between the point of attachment of the first residue and the polystyrene support. Two important advantages were expected: Higher overall yields after HF cleavage and better homogeneity of the peptidic product. The author did not invoke the acidolysis problem but believed that uncompleted coupling at each step occurred due to the steric hindrance of the polystyrene backbone. He observed a 3-fold improvement in the overall yield of a 19-residue peptide using spacer/linker **12.1**. Merrifield[64] prepared the PAM linker **12.2** and suggested that, without this linker, loss of material at each cycle of peptide synthesis was in fact due more to a partial cleavage (using TFA 50% in CH_2Cl_2) rather than to uncompleted coupling. The presence of the electron-withdrawing phenylacetamidomethyl (PAM) linker was shown to increase the stability of the peptide ester 100-fold relative to the peptide ester obtained from chloro- or hydroxymethylpolystyrene resin when submitted to 50% TFA in CH_2Cl_2.[65] These PAM

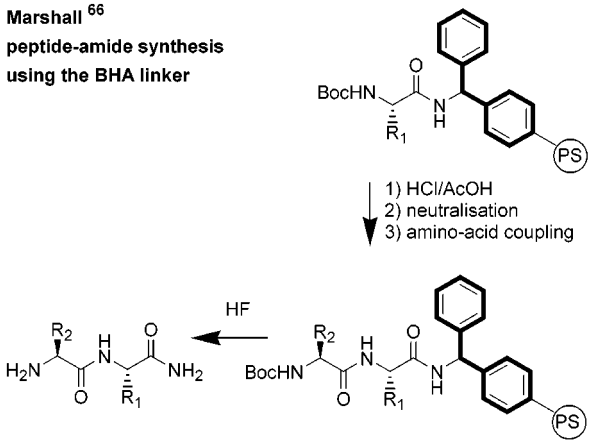
linkers (Scheme 12) thus constitute a more stable form of the conventional Merrifield benzyl ester linkage.

Scheme 12



c. Benzhydryl Linkers. Preparation of carboxamides through acidolysis became feasible using a benzhydrylamine (BHA) linker designed by Marshall (Scheme 13).[66] Selective cleavage of the N−C bond

Scheme 13

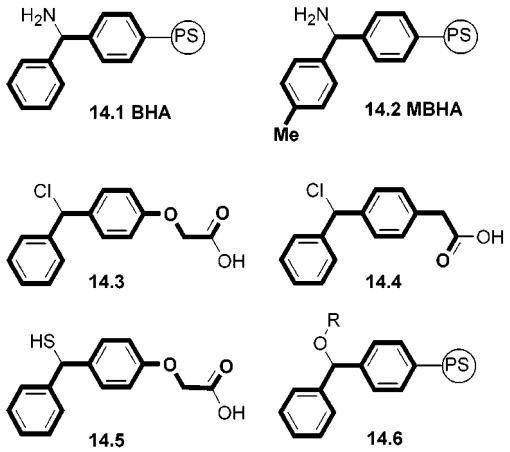


occurs, allowing the formation of the carboxamide. A charge-stabilizing group (phenyl) was added onto the benzylic carbon in order to increase the stability of the carbocation, enabling the equilibrium to be displaced toward the cleaved product.

Matsueda[67] described the preparation of the 4-methylbenzhydrylamine linker (MBHA) **14.2**. This linker is more easily cleaved than the BHA linker **14.1** due to the effect of the extra methyl group stabilizing the cation formed upon cleavage. However, HF was still required. In a comparative study of benzhydrylamine linkers (Scheme 14) and chloromethylated resins by Hruby,[68] the author points out that yields can be slightly improved if proper use of the cleavage mixture is made. TFMSA and HBF_4/thioanisole in TFA, a weaker acid than HBr in TFA, were also reported to cleave the MBHA linker.[69] Houghten, surprisingly, achieved the cleavage of some amines from MBHA **14.2** with HF/anisole.[70]

Li[71] preloaded thio acids on the phenylchloromethylphenoxy unloaded linker **14.3** before resin attachment. Earlier studies involved the use of a phenylchloromethylphenylcarboxymethyl group **14.4**.[72] Canne[73] described the preparation of the 4-(α-mercaptobenzyl)phenoxyacetic acid unloaded linker **14.5**. Preloading of an amino acid prior to resin attachment

Scheme 14

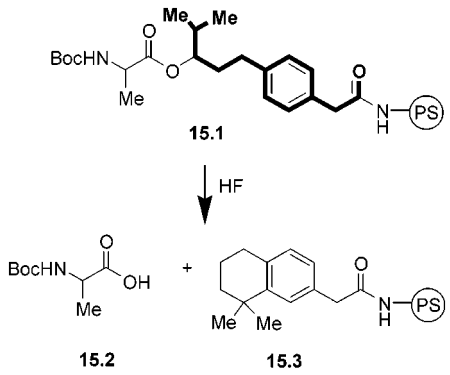


then further peptide elongation allowed the preparation of a C-terminal thio acid peptide upon HF cleavage. These linkers (Scheme 14) are particularly useful for the convergent synthesis of peptides by chemical ligation.

Benzhydryl resin **14.6** can also be used to release protected peptide alcohols using repetitive treatments (2−5 min each) of 1−2% TFA in CH_2Cl_2.[74] In this case, the mild acid lability is due to the alcohol leaving group.

d. Miscellaneous Strong Acid Cleavable Linkers. Undén[75] prepared OMPPA (4-(3-hydroxy-4-methoxypentyl)) phenylacetic acid linker **15.1** as a new linker for SPPS using Boc chemistry (Scheme 15). The author studied the stability to TFA of the

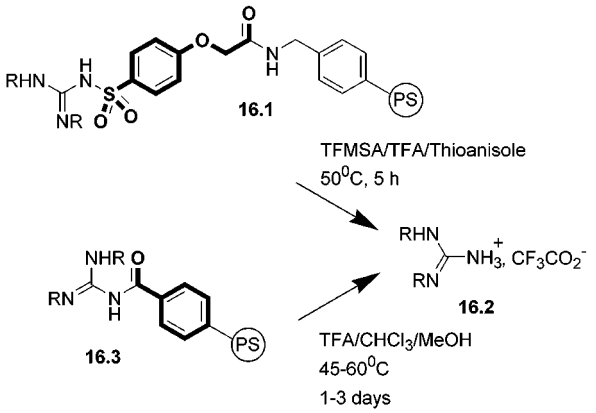
Scheme 15



linkage between the linker and the first residue and concluded that the bond was more stable than with the PAM linker and was very suitable for a low-TFMSA/high-HF procedure. During the cleavage, the initially formed secondary cation rearranges into a tertiary cation, which is trapped through an intramolecular cyclization to form **15.3**. This process prevents the reattachment of the cleaved peptide acid **15.2** onto the resin.

Kilburn[76] described the *p*-phenoxysulfoguanidine linker **16.1** which is cleavable using TFMSA and thioanisole (Scheme 16). Wilson[77] used a benzoyl immobilizing group **16.3** (Scheme 16) and found milder conditions for the release of guanidine **16.2**. The products were obtained in 38−74% overall yields (five-step synthesis) after cleavage with TFA/$CHCl_3$/

Scheme 16



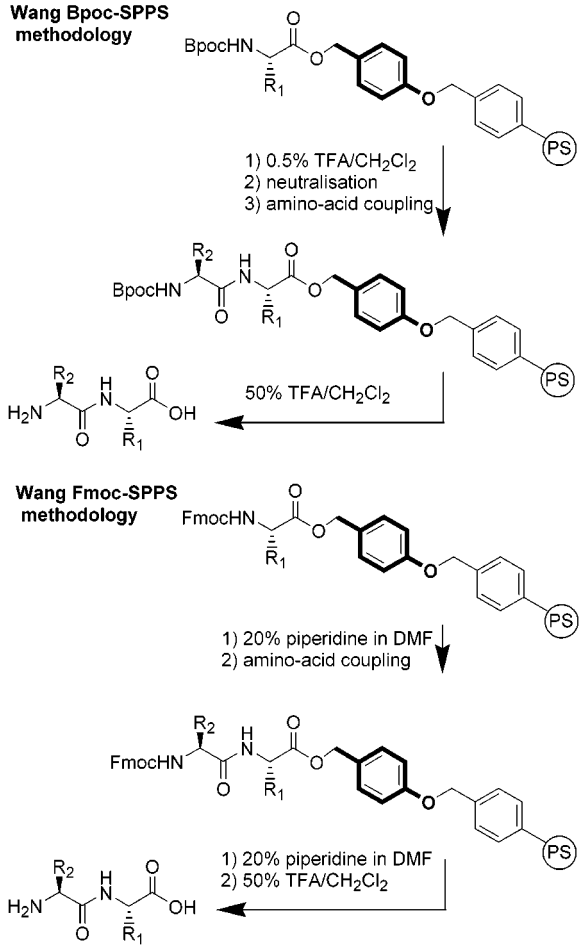
MeOH (1:1:1) at 45−60 °C for 1−3 days and HPLC purification.

2. Mild Acid Cleavable Linkers

HF and other strong acidolytic cleavage procedures suffer from a common drawback that limits their use: they are extremely hazardous and not generally applicable to multiple parallel synthesis (although some brave souls may disagree with these sentiments). Nevertheless, they received wide acceptance in the field of peptide research because of significant improvements in yield and purity over conventional methodologies used at the time. As the sensitivity of a linker toward acidic cleavage is related to the stability of the carbocation formed upon cleavage, addition of more electron-donating groups should decrease the acid strength needed to cleave the linker. We saw previously that addition of a phenyl or *p*-methylphenyl group onto aminomethylpolystyrene resin was sufficient to allow the cleavage of amides normally impossible on simple aminomethyl resins. However, in these cases, HF was still required. Two different approaches have been successfully attempted: the addition of extra methoxy or alkoxy functionalities, which leads to the Wang, Sasrin, and Rink linkers, and addition of extra phenyl groups, which gives rise to the Rink and trityl derivatives.

a. Wang Linker. In 1973, Wang[26] described the *p*-alkoxybenzyl alcohol linker which allowed the cleavage of peptide acids from solid supports using relatively mild acid conditions (at least compared to HF) (Scheme 17). The final peptide being cleaved with trifluoroacetic acid under conditions where side-chain protecting groups (Tos, Bn, NO_2) would be stable. Very acid-labile 2-(*p*-biphenyl)-2-propyloxycarbonyl (Bpoc) groups could then be used for amino protection (cleaved with 0.5% TFA in CH_2Cl_2), allowing the peptide to be cleaved from the linker at the end of the peptide synthesis using 50% TFA. Peptide chemistry evolved, with the base-sensitive 9-fluorenylmethyloxycarbonyl (Fmoc) group stategy (see ref 78 for reviews) which replaced the mild acid cleavage needed for the Bpoc groups. The Wang linker **18.1** is now the standard support for the synthesis of peptide acids using the base-labile Fmoc-amino protecting strategy (Scheme 17). Attached esters can be cleaved using 50% TFA in CH_2Cl_2 for 30 min. These mild and

Scheme 17

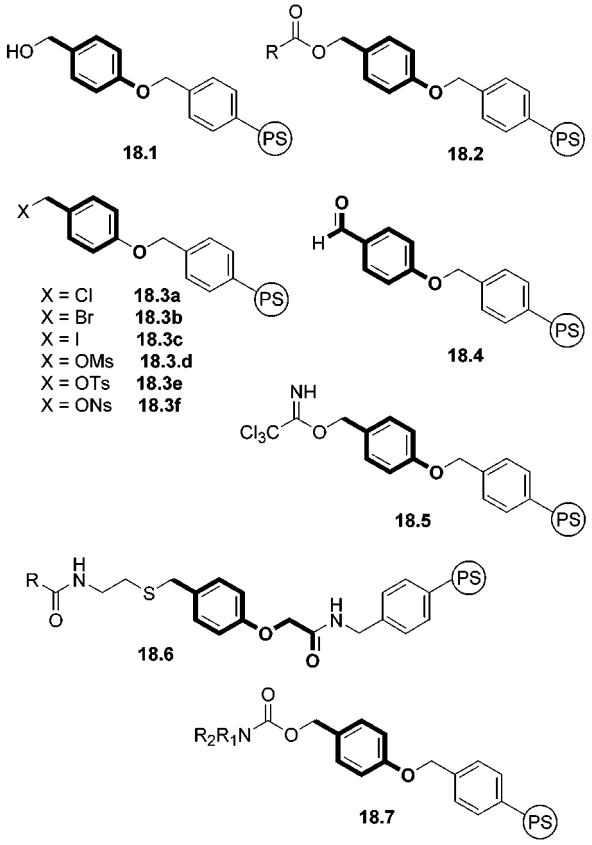


efficient cleavage conditions have made this linker popular and widely used in SPPS and SPOS.

Carboxylic acid groups are generally anchored onto the Wang linker using classical coupling agents such as DIC/DMAP, although Mitsunobu chemistry is also employed in some cases to form Wang ester **18.2**. The Wang linker can be simply converted into the chloro **18.3a**,[79−82] bromo **18.3b**,[82,83] or iodo **18.3c**[83] derivatives as well as mesyl **18.3d**,[81,83] tosyl **18.3e**,[83] or nosyl **18.3f** [83] derivatives, essentially giving a Merrifield variant (chloromethylpolystyrene resin) of the Wang linker, Scheme 18. In this manner the linker can be used to anchor amines.[83] Amines have also been anchored through the Wang aldehyde **18.4** by reductive amination affording an interesting method to produce secondary amides after acylation and cleavage.[84] Hanessian devised an alternative route for anchoring alcohols.[85] The author used the trichloroacetimidate-activated Wang linker **18.5** and reported the release of alcohols from the Wang linker using only 1−10% TFA in CH_2Cl_2.[85,86] Interestingly, the thioether linkage of **18.6** was found stable to neat TFA for 60 h.[87] HF/*p*-cresol (9:1) for 1 h at −5 °C was required to achieve the cleavage and obtain peptides containing the C-terminal thiol functionality, although the use of scavengers with TFA might have forced the equilibrium in favor of thiol release.

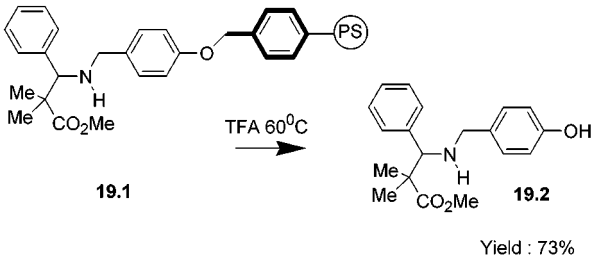
If the anchoring of amines is possible with derivatized resins **18.3** and **18.4**, transformation into the respective amides, ureas, carbamates, or sulfona-

Scheme 18



mides is necessary to achieve cleavage with TFA. Kobayashi observed that the cleavage occurred on the phenylbenzyl ether moiety when amine **19.1** was treated with strong acid such as TFMSA, TMSOTf, or TFA at 60 °C (Scheme 19).[88] Nevertheless, prepa-

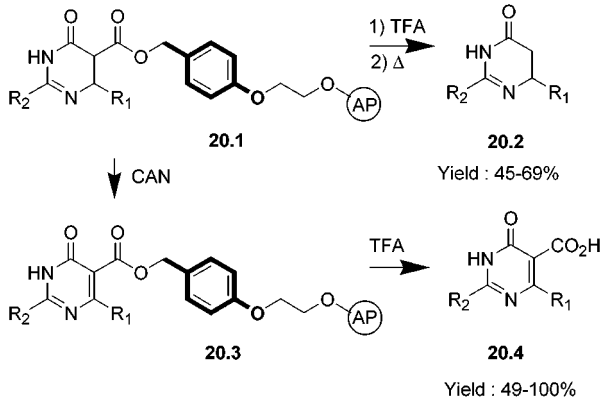
Scheme 19



ration of amines was achieved using carbamate linkers. Carbonylimidazole or *p*-nitrophenyl carbonate can be used as precursors of carbamate **18.7** for the preparation of various amines (Scheme 18).[89] The presence of the electron-donating *p*-alkoxy group enables the use of only dilute TFA in CH_2Cl_2 for cleavage.

When activated esters such as *β*-ketoesters or malonates were attached to the Wang linker and transformed into heterocycles, the resulting decarboxylation products were observed due to release of the acids in solution and subsequent decarboxylation. Thus, treatment of **20.1** with TFA and then concentration of the pyrimidinones and dihydropyrimidinones gave rise to the decarboxylation products **20.2**. The pyrimidinones **20.4** were found to be more stable and did not undergo decarboxylation (Scheme 20).[90]

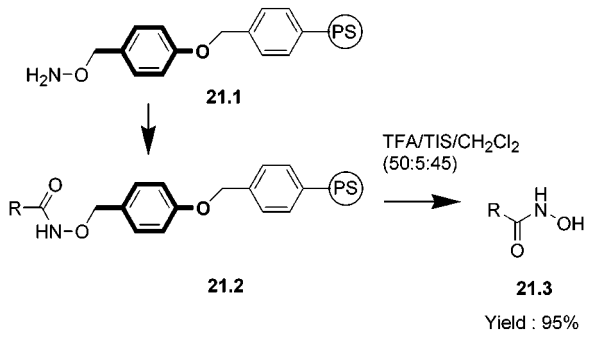
Scheme 20



Other examples of decarboxylation with the Wang linker have been described.[91−93]

The hydroxylamine resin **21.1** devised by Floyd,[94] useful for the solid-phase synthesis of hydroxamic acids **21.3** (Scheme 21), was prepared by conversion

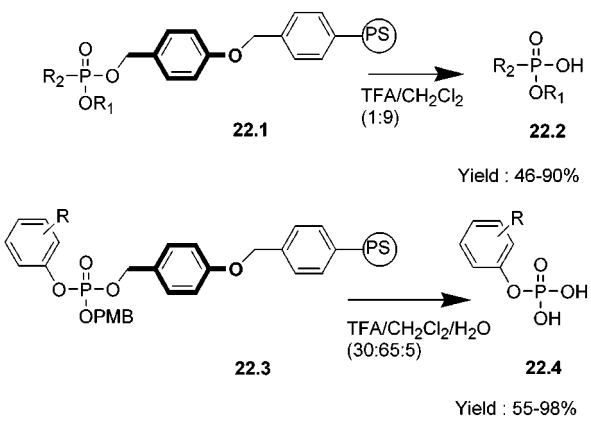
Scheme 21



of the Wang resin into the *N*-hydroxyphthalimide derivative using Mitsunobu conditions followed by hydrazine deprotection. Richter[95] found that TFA/iPr$_3$SiH/CH_2Cl_2 (50:5:45) and TFA/anisole (9:1) were efficient conditions for cleavage of linker **21.2** and noticed that water must be avoided as the hydroxamates can be hydrolyzed into their corresponding acids.

Polymer-bound phosphonates **22.1** were prepared on the Wang linker and used to synthesize various α-aminophosphonates and phosphonic acid derivatives **22.2** cleaved using 10% TFA in CH_2Cl_2 for 10 min. Preparative TLC gave the products in 46−90%

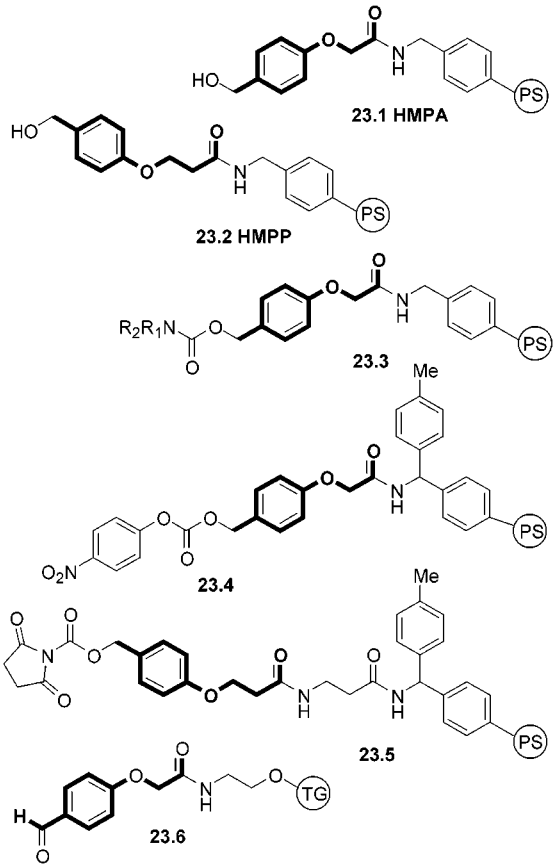
Scheme 22



overall yields.[96,97] After chemical modification, the phenyl phosphate **22.4** was released from protected linker **22.3** by treatment with a mixture of TFA/CH_2Cl_2/H_2O (30:65:5), Scheme 22.[98]

Hydroxymethylphenoxyacetic acid HMPA **23.1** and hydroxymethyphenoxypropionic acid HMPP **23.2** display similar acid labilities to the Wang linker, although the additional methylene unit in HMPP **23.2** changes the electronic parameters of the resultant *p*-alkoxybenzyl ester such that the rate of acidolytic cleavage is 2- to 3-fold increased compared to HMPA, Scheme 23. TFA (20%) in CH_2Cl_2 for 2 h was

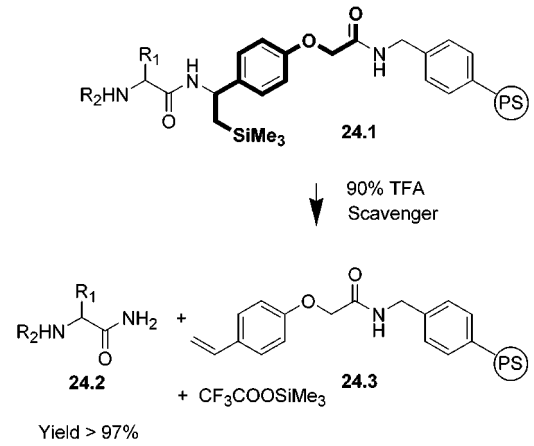
Scheme 23



sufficient to cleave 96% of a peptide ester against 42% with the HMPA linker.[99] Aqueous TFA (95%) was used to cleave polyamines from carbamate **23.3**.[100] In this case, the scaffold (polyamine) was bound to the linker prior to the resin attachment. *p*-Nitrophenyl carbonate derivative **23.4**[101] and succinimidyl carbonate **23.5** can also be employed to anchor amines directly onto the solid support.[102,103] An aldehyde version **23.6** enables loading of the amine by acylation to allow reductive amination and secondary amide synthesis.[104]

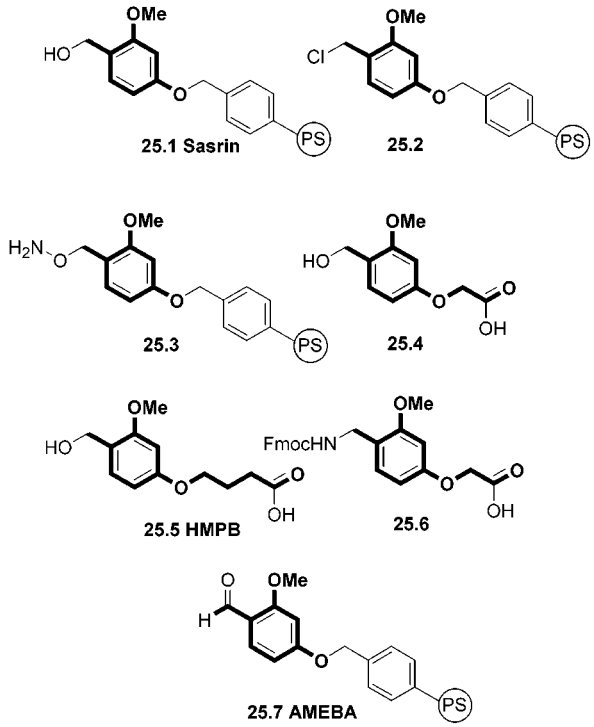
Chao[105] developed linker **24.1** based on the stabilization of a carbocation by a β-trialkylsilyl group (Scheme 24). β-Elimination neutralizes the transient cation to give a stable styrene derivative **24.3**. These so termed SAL linkers **24.1** (silyl amide linkers) gave improved yields of C-terminal tryptophan amides over conventional linkers, although scavengers were needed as the styrene moiety is sensitive to protonation.

Scheme 24



b. SASRIN Linker. The SASRIN linker **25.1** (superacid sensitive resin) linked to the solid support through an ether bond was first described by Mergler.[27,28] The addition of one or more methoxy groups onto the Wang linker makes these linkers more acid labile due to the enhanced stabilization of the cation during/upon cleavage. These 2,4-dialkoxybenzyl alcohol linkers (Scheme 25) are suitable for anchoring

Scheme 25



acids, which can be cleaved with 1% TFA. Preparation of the chloride derivative **25.2** has been reported.[79,81] Hydroxamic acids have been cleaved with 5% TFA/CH_2Cl_2 for 15 min using resin **25.3**.[106]

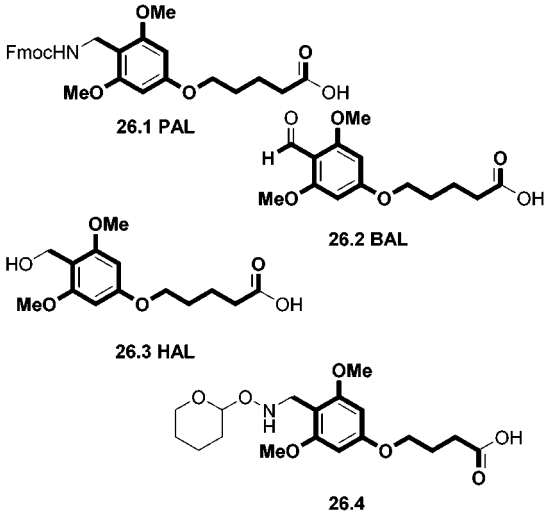
Work on *o*-methoxy-substituted Wang linker was in fact initiated by Sheppard,[29,30] who developed the unloaded linker **25.4** in order to cleave peptide acids still bearing Boc/*t*Bu protecting groups ready for a fragment condensation strategy. The addition of three methylene groups instead of a single methylene unit between the phenoxy group and the acid functionality gives the hydroxymethylmethoxyphenoxy-

butyric acid (HMPB) unloaded linker **25.5**, which has increased acid lability due to increasing electron donation by the oxygen atom.

In a full paper, Albericio[107] noticed that after Fmoc-deprotection and acylation of the unloaded linker **25.6**, treatment with TFA/CH_2Cl_2 (70:30) gave only 24% of the amide product and 80% with TFMSA/TFA/CH_2Cl_2 (1:9:10). However, secondary amide, sulfonamide, urea, and carbamate derivatives have been obtained very smoothly (5−30% TFA/CH_2Cl_2) using the acid-sensitive methoxy benzaldehyde linker (AMEBA) **25.7**. Here again, slight modifications on the phenol oxygen alkyl chain result in important shifts in cleavage sensitivity. Linker **25.7** was functionalized using reductive amination, allowing the attachment of various amines. Subsequent acylation/activation allows cleavage. Since cleavage is selective, purity is high as unreactive amines will stay on the resin.[108−110]

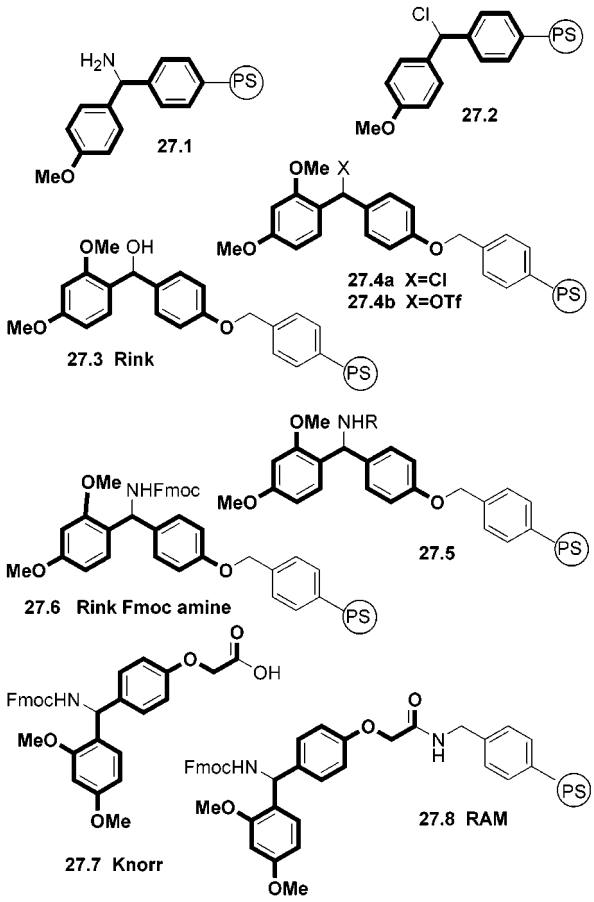
c. PAL Linker. The peptide amide-unloaded linker (PAL) **26.1** described by Albericio[107,111] essentially bears two methoxy groups in the ortho positions of the Wang linker and a Fmoc-protected benzylamine group in place of the hydroxymethyl function. The formyl derivative **26.2** named backbone amide linker (BAL)[112,113] affords the possibility of anchoring various amines by reductive amination onto the resin and furnishes amides after acylation/activation and cleavage. It also enables the synthesis of C-terminally modified peptides as well as cyclic peptides. Although primary alkylamines are not usually cleaved from the PAL linker, anilines were cleaved with TFA/H_2O/DMS (90:5:5).[114] The analogous peptide acid linker, called the hypersensitive acid-unloaded linker (HAL) **26.3**,[115] is cleaved with 0.05−0.1% TFA in CH_2Cl_2 with scavengers. A THP-protected hydroxylamine derivative **26.4** of the PAL linker was used by Patel[116] to generate hydroxamic acids after deprotection and cleavage with 50% TFA. However, these linkers (Scheme 26) can result in poor loadings and yields[113] due to the steric effects provided by the extra methoxy groups.

Scheme 26



d. Rink Linker. Introduction of alkoxy groups onto the benzhydryl system was first reported by Walter,[117] who used the *p*-methoxybenzhydrylamine linker **27.1** and observed that cleavage yields with HF were superior for C-terminal phenylalanine residues than with using BHA **13.1**. Brown[118] recently reported the same linker and termed it MAMP (α-methoxyphenyl linker) **27.2** and used it for the preparation of secondary amides after reacting various primary amines and anilines before acylation. The authors used dilute TFA (CH_2Cl_2/TFA/H_2O (75:23:2)) to cleave compounds from the support. More alkoxy groups lead to the famous Rink linker **27.3** introduced in 1987.[38] This 4-(2′,4′-dimethoxyphenylhydroxymethyl)phenoxymethyl polystyrene **27.3** allows the preparation of peptide acids under extremely mild cleavage conditions (10% AcOH in CH_2Cl_2 or 0.2% TFA in CH_2Cl_2). The author noted that such was the acid sensitivity that the use of coupling catalysts such as HOBt was not possible without buffering by DIPEA. In his initial work, Rink loaded the linker by trapping the intermediate cation (generated by protonation of the benzhydryl alcohol) with acids or amides, akin to the recent use of various halogen variants of the Rink linker such as Rink chloride **27.4a**[40] (Scheme 27). Rink chloride **27.4a**,

Scheme 27

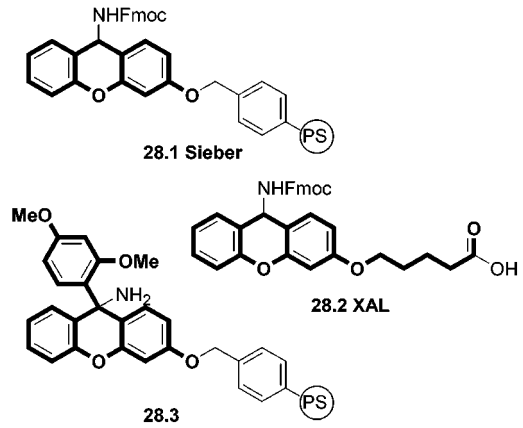


Rink triflate **27.4b**, or Rink Fmoc amine **27.6** has been used to anchor hydroxamic acids,[119] alcohols, phenols, amines, anilines, thiols, and thiophenols.[40,120,121] The amino derivative **27.5** was also useful for the preparation of secondary amides and could be obtained by reductive amination using either the Rink amine **27.6** or the benzophenone precur-

sor.[122] The Rink amine linker **27.6** has been widely used for the synthesis of peptide amides by SPPS using Fmoc chemistry, the final peptide being generally released with concentrations of TFA varying from 10% to 95% in CH_2Cl_2. Lower concentrations of TFA (10%) or addition of trialkylsilane scavengers are advised to avoid some problems with breakdown of the linkage bearing the benzyl ether moiety. The bifunctional Knorr unloaded linker **27.7** allows anchoring onto the solid support through an amide bond, making the linker less prone to degradation. However, higher concentrations of TFA are required for peptide amide cleavage (generally 95% in CH_2Cl_2). Bernatowicz[39] compared the reactivity of Rink amide AM or RAM **27.8** (obtained by coupling the unloaded linker Knorr **27.7** on aminomethyl polystyrene resin) and PAL **26.1** and found that the half-life of Fmoc-Val-NH_2 on the resin with TFA/phenol (95:5) was 9 and 4 min, respectively.

e. Sieber Linker. In 1987, Sieber[123] described the preparation of the xanthenyl linker **28.1** allowing the synthesis of amides under very mild cleavage conditions (TFA/DCE/EDT (2:98:0.1)). Albericio[124] made comparative studies between PAL **26.1** and XAL **28.2**. Different XAL's were prepared varying the length of the spacer and the position on the ring (meta or para to the aminobenzyl group). The author concluded that XAL can provide C-terminal peptide amides at TFA concentrations between 1% and 25%, which are lower than those required to effect cleavage on PAL. The best result was obtained for 3-XAL_4 **28.2**, which bears a butylene spacer in the para position. According to this classification, XAL linker **28.2** has a more superior acid sensitivity than PAL **26.1**, being itself comparable to Knorr **27.7**. Voelter[125] presented a new derivative **28.3** of the Sieber linker bearing a supplementary dimethoxyphenyl group on the benzylic carbon, Scheme 28. The author obtained

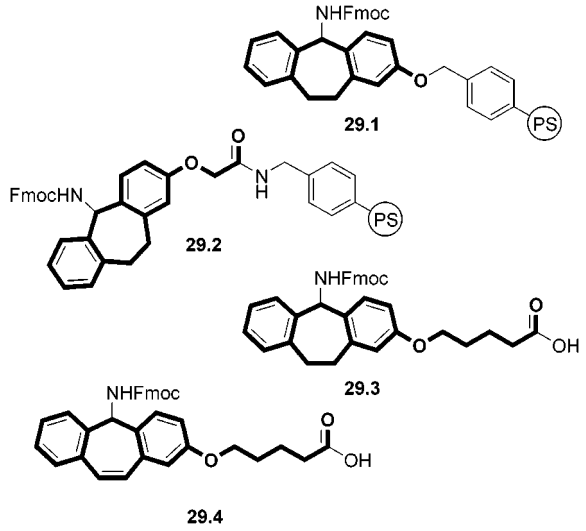
Scheme 28



a 90% yield for the cleavage step with 1% TFA in CH_2Cl_2 after 1 min. However, it should be noted that this linker is fairly close to the trityl linkers in structure and presumably steric hindrance now becomes an issue.

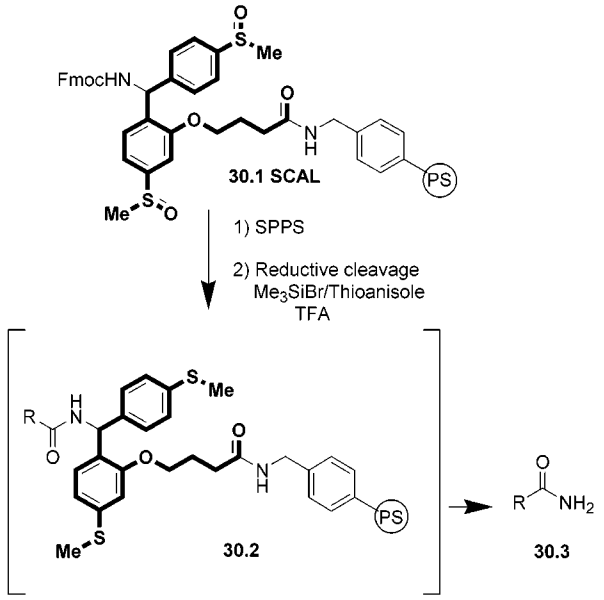
Ramage[126,127] described the preparation of linkers **29.1** and **29.2**, based on the dibenzocyclohepta-1,4-diene structure, for the preparation of C-terminal primary/secondary amides and hydrazide derivatives. Complete cleavage of peptide−amides is achieved with TFA/CH_2Cl_2 (3:97) in 30 min. Nokihara[128] compared linkers CHA **29.3** and CHE **29.4** with PAL **26.1** and Knorr **27.7** and obtained half-lives for cleavage with TFA/CH_2Cl_2/phenol (25:70:5) for CHE, CHA, PAL, and Knorr of <2 min, <4, 35, and 38 min respectively. Although **29.4** was more cleavable with lower TFA concentrations than **29.3**, its synthesis and the final yield of recovered product was less satisfactory than **29.3**. These linkers are not, however, in widespread use, Scheme 29.

Scheme 29



f. SCAL Linker. In 1991 Lebl[129] reported the preparation of a safety-catch acid-sensitive linker (SCAL) which extended the orthogonality of currently used systems for the synthesis of C-terminal peptide amides (Scheme 30). The Fmoc-protected 2-alkoxy-

Scheme 30

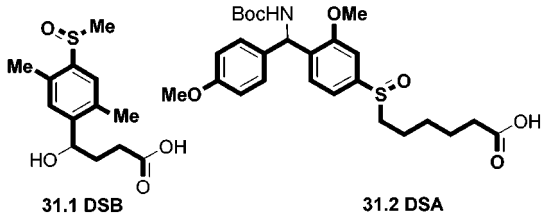


4,4′-bis(methylsulfinyl) benzhydrylamine deactivated linker **30.1** was used in SPPS with either a Fmoc or Boc strategy. (The sulfoxide derivative was stable to 50% TFA in CH_2Cl_2/anisole.) A one-pot reductive acidolysis with 1 M Me_3SiBr/thioanisole/TFA trans-

formed it into the activated bis-alkylthio **30.2** and enabled the preparation of peptide amides **30.3** in 95% purity after 2 h at 0 °C.

The 4-(2,5-dimethyl-4-methylsulfinylphenyl)-4-hydroxybutanoic acid (DSB) unloaded linker **31.1** described by Kiso[130] allowed him to synthesize a γ-endorphin of 17 residues using Boc chemistry in an overall yield of 62% (after FPLC purification) following cleavage with $SiCl_4$/thioanisole/anisole (100 equiv each) in TFA/CH_2Cl_2 (9:1). The 4-(4-methoxyphenyl-Boc-amino)methyl-3-methoxyphenylsulfinyl-6-hexanoic acid (DSA) unloaded linker **31.2** was suitable for the synthesis of peptide amides and displayed the same reactivity toward reductive acidolysis (Scheme 31).[131]

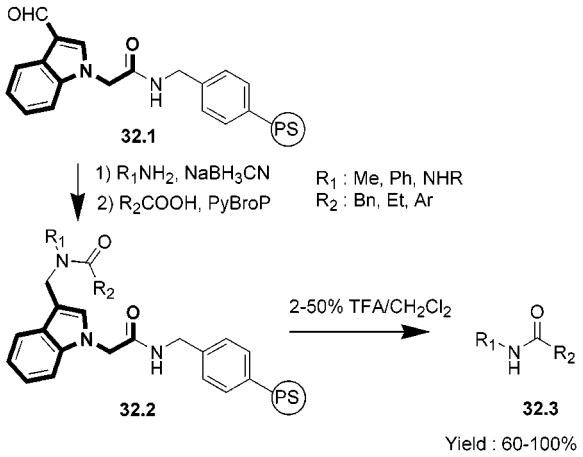
Scheme 31



31.1 DSB 31.2 DSA

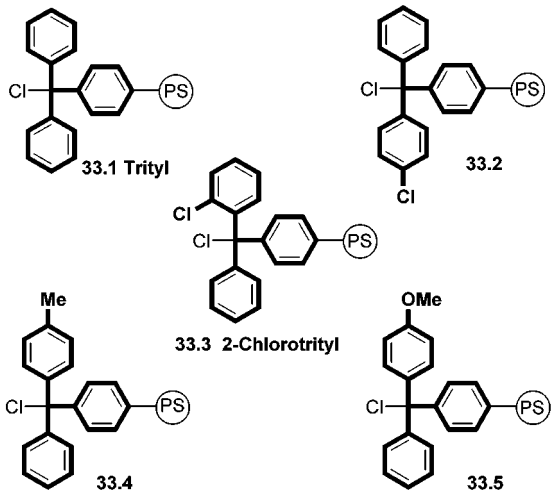
g. Indole Linker. Estep[132] designed the linker **32.1** based on readily available 3-formylindole. This allowed amines to be anchored by reductive alkylation, which could then be reacted with chloroformates, isocyanates, sulfonyl chlorides, or acids and subsequently released using TFA in CH_2Cl_2 (2−50%) (Scheme 32).

Scheme 32



h. Trityl Linkers. The trityl linkers (Scheme 33) were developed initially by Leznoff[19] and Fréchet.[20,21] Both authors focused on the use of this particular linker attached to polystyrene resin as an insoluble protecting group for monoprotection of symmetrical molecules. The trityl chloride **33.1** was used to anchor selectively one alcohol group of a diol, preferably primary alcohols. Cleavage was found to be straightforward, using anhydrous TFA or dry HBr.[21] More detailed studies indicated that 0.3 M anhydrous HCl in dioxane was sufficient for cleavage.[19] In 1988, Barlos[133] saw the use of these linkers for Fmoc-SPPS. The author employed trityl chloride **33.1** to immobilize amino acids and used *p*-TsOH in THF, 1 N

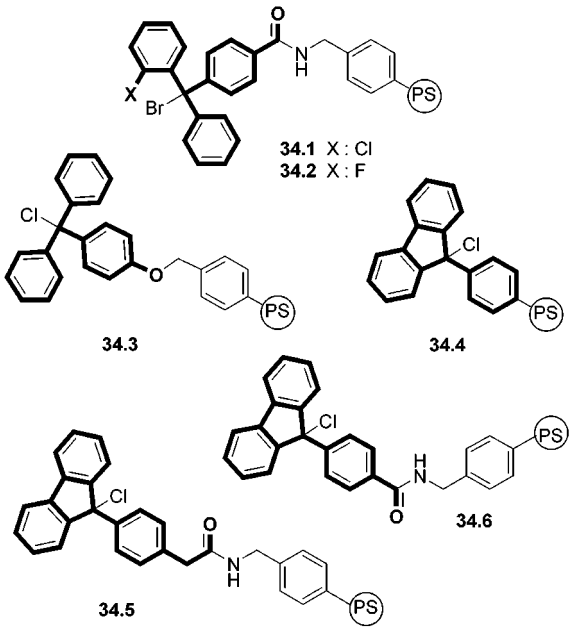
Scheme 33



HCl in THF, or 2% TFA to release the peptides in 75−95% yield. More interestingly, 1 year later the same group published the preparation of various substituted trityl linkers and the anchoring of amino acids by ester formation using only DIPEA.[134] The 4-chloro derivative **33.2** had little if any effect compared to **33.1**, while a chloro group in the 2 position (2-chlorotrityl linker **33.3**) stabilized the ester compared to **33.1**. Recently, Barlos[135] compared four different trityl linkers and confirmed that acid sensitivity increases in the order 2-chlorotrityl **33.3**, trityl **33.1**, 4-methyltrityl **33.4**, and 4-methoxytrityl **33.5**. A mixture of AcOH/TFE/CH_2Cl_2 (1:1:8) is sufficient to carry out the cleavage for all of these linkers, and hexafluoro-2-propanol[136] in CH_2Cl_2 (1:4) also was found to be efficient with 2-chlorotrityl **33.3**. On the other hand, esters bound to trityl **33.1** or 4-chlorotrityl linkers **33.2** are very sensitive to acid with cleavage being observed with HOBt. The addition of base during the coupling step is often necessary to avoid loss of the peptide chain. For these reasons, the 2-chlorotrityl linker **33.3** has emerged as the linker of choice for its stability during coupling[137] and is definitely the one to choose for releasing amines by acidic treatment. It is also often suitable for producing side-chain-protected peptides. TFA (1−50%) in CH_2Cl_2 with 5% TIS are the most often used cleavage conditions for releasing alcohols, hydroxamic acid,[138] amines, thiols, and acids.[12,15]

Various derivatives of the trityl linker have now been prepared (Scheme 34). The trityl linker can be obtained as an unloaded linker through its 4-carboxy derivative.[24] The 2-chloro **34.1** and 2-fluoro **34.2** proved to be as advantageous as the normal 2-chlorotrityl linker with cleavage being achieved with AcOH/TFE/CH_2Cl_2 (1:1:8) or 0.1% TFA in CH_2Cl_2.[24] Fukuyama used an ether link to attach his phenol derivative **34.3** onto Merrifield resin.[139] The 9-phenylfluoren-9-yl-based linkers **34.4** and **34.5** were found to be more acid stable than trityl **33.1**. TFA (20%) was required to cleave anilines and alcohols and 20−95% TFA for amines.[140] The 4-carboxylic analogue **34.6** was found to be totally resistant to TFA and required a mixture of TFMSA (30%) in TFA to achieve cleavage.[141]

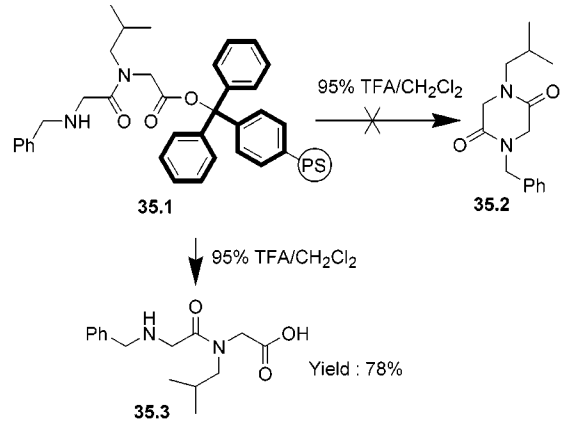
Scheme 34



Interestingly, cleavage of imidazolyl compounds from 2-chlorotrityl linkers **33.3** using 5% TFA was shown to be faster than cleavage using 65% TFA, indicating that imidazolyl reattacks the linker cation.[134] This is a general point. Cleavage is an equilibrium process and often needs to be forced by trapping out the linker cation. This can be very important when cleaving molecules with nucleophilic sites.

Trityl linkers have certain advantages in comparison to the alkoxybenzyl alcohol, especially in the area of peptide chemistry. First, the problem of racemization during the loading of the first amino acid (using DIPEA) is avoided with trityl linkers. Second, due to steric factors, no diketopiperazine (DKP) formation is observed. Thus, when preparing *N*-alkyl peptoids, Roques[142] did not observe formation of DKP **35.2** with the 2-chlorotrityl linker and obtained the peptoid **35.3** in 78% yield compared to 0% due to DKP formation with a classical Wang linker (Scheme 35).

Scheme 35

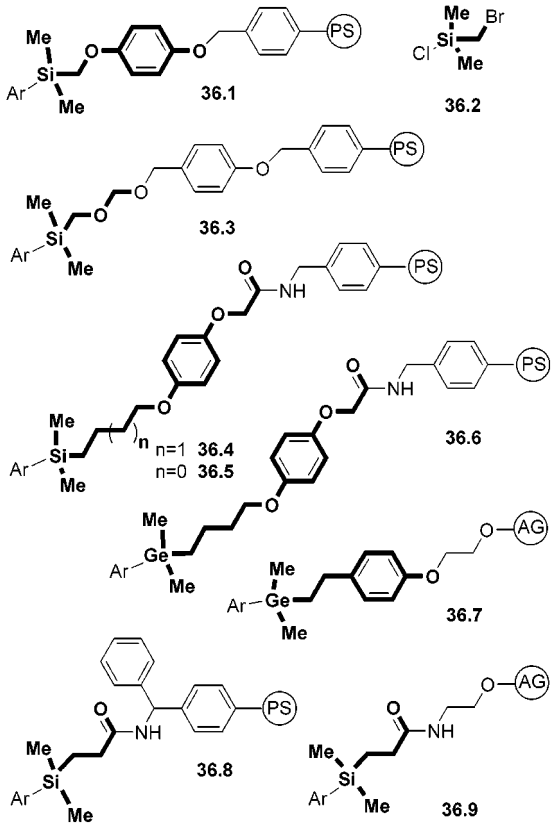


3. Silicon Linkers

a. Si−C Bond Rupture. Organosilyl groups have become one of the most widely used protecting groups in organic synthesis since their introduction in the early 1970s. Although silicon groups are mainly used for the protection of heteroatoms, they can also be situated on carbon. These protecting groups are compatible with many organic transformations, and orthogonality can be easily found as specific reagents are often used for removing the silicon group, such as acid or fluoride ions. In this section we will look only at the acid-labile Si-protecting groups.

Acidic removal of a silicon group provided one of the first approaches toward a linker used for cleavage of a C−Si bond. This linkage can be cleaved quantitatively and selectively, leaving behind a hydrogen in place of the silicon (in a similar way, cleavage of the Wang linker also leaves behind a hydrogen). Protiodesilylation is generally attempted on electron-rich aromatic rings (Scheme 36). Veber[143] used TFA

Scheme 36

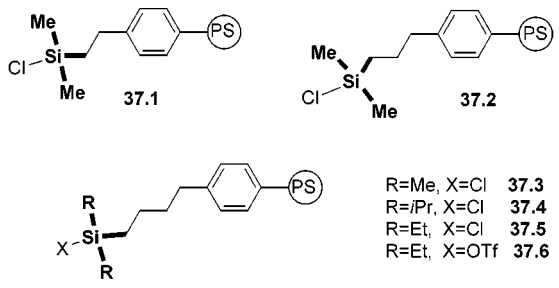


to cleave biaryl compounds anchored onto a dimethylphenoxymethylsilyl group **36.1**. Linker attachment was realized in two steps by reacting a lithiated aromatic species with a bromomethylchlorodimethylsilane **36.2** followed by substitution of the bromide by a polymer-supported phenol. Cleavage was evaluated under various conditions with nucleophilic fluoride or with HF or CsF. TFA was unsuccessful if the aromatic compound bore electron-withdrawing groups which prevented formation of the ipso-substituted intermediate necessary to generate a carbonium ion β to the silicon moiety. Halogens were introduced onto the aromatic ring by electrophilic ipso-substitution using linker **36.3**.[144] Good yields were obtained for the bromo and iodo derivatives after reaction with Br_2 and ICl, respectively. Ell-

man[145] prepared a library of 1,4-benzodiazepines with linker **36.4**. In this case, however, the silicon−aryl bond was found to be stable to TFA because of the electron-poor nature of the protonated benzodiazepine products. The aryl−silicon group was finally cleaved with HF. In addition, the author noticed that the use of a three-carbon **36.5** instead of a four-carbon spacer **36.4** led to byproducts containing silicon. Better results were obtained when Ellman[146] used another element of group IV, germanium, which allowed cleavage of these benzodiazepines from linker **36.6** with neat TFA at 60 °C instead of HF. It was postulated that cleavage arises under milder acidic conditions due to the more powerful β effect of germanium compared to silicon. With this linker, electrophilic cleavage with elemental bromine was complete in 5 min without over-bromination. Final products were purified by column chromatography and obtained in 47−59% for the bromo derivatives and 58−68% for hydrogen derivatives. Spivey[147] prepared a similar germanium-based linker **36.7**. Iodo- and bromoaryls were obtained by reaction with ICl and Br_2, respectively, and chloroaryls using NCS or chloramine-T in refluxing THF. Moore[148] described the preparation of linker **36.8** to generate electron-rich aromatics, following treatment with TFA. Nevertheless, cleavage was quite slow, and 40 h with neat TFA was required to obtain a nearly quantitative yield. The slow and constant rate for cleavage allowed the authors to suggest this as a possible method for controlled partial release for single bead screening.[149,150] Comparing Si-based linkers **36.8** and **36.1**, Hone[151] postulated that the more efficient cleavage was achieved for **36.8** through enhancement of the ipso-protonation step and that this may be facilitated by intramolecular delivery from the protonated amide carbonyl. Opportunities for such interactions are not present within ether-tethered linkers such as **36.1**. When Armstrong[152] used related linker **36.9**, 30% TFA for 10 min was sufficient to cleave biaryl derivatives. The author suggests this is an effect of the β amide, which allows a lower concentration of TFA for cleavage, although the ArgoGel resin and the biaryl group are also likely to be responsible.

The next generation of silicon linkers was based on an all-carbon anchoring spacer (Scheme 37).

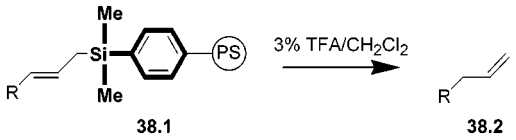
Scheme 37



Dimethylsilyl groups were thus attached, by hydrosilylation, to the polystyrene core through an ethylene spacer **37.1**,[31] propylene spacer **37.2**,[153] or butylene spacer **37.3**.[154] Porco[154] reported some modifications with diisopropyl **37.4** and diethyl derivatives **37.5**. The aromatic scaffolds are usually lithiated in order to be attached to these trialkylsilyl chloride resins. When cleavage was performed on diethylbutylsilyl linker **37.5** functionalized with electron-rich aromatics, TFA/CH_2Cl_2 (1:1) was sufficient to give 70−80% yields.

A β-elimination process is involved with the allylsilane-based linker **38.1** described by Blechert.[155] This linker could be cleaved with 3% TFA in CH_2Cl_2 (Scheme 38) and furnished some allyl derivatized products **38.2**.

Scheme 38



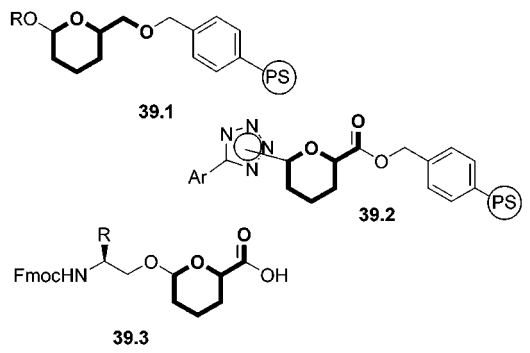
b. Si−O Bond Rupture. A number of silicon-based linkers have been employed to anchor alcohols. Cleavage generally is performed under nucleophilic conditions using fluoride, and only a few examples used an acidic cleavage step. Various alcohols have been loaded onto linker **37.5**, and cleavage of the corresponding silyl ether was achieved using AcOH/THF/H_2O (6:6:1) at 50 °C for 4−8 h for primary alcohols.[154] Silyl ethers of secondary alcohols required longer treatments (60−80 °C for 8−12 h). A mixture of AcOH/THF/H_2O (6:6:1) at 65 °C for 10 h allowed the deprotection of the primary alcohol of oligosaccharides from linker **37.5**.[156] The triflate-activated linker **37.6** was used to anchor α,β-unsaturated ketones to form the polymer-supported silyl enolether.[157] Various cyclohexanones were obtained after Diels−Alder reaction and treatment with 10% TFA in CH_2Cl_2.

4. Ketal Linkers for Alcohol Immobilization

Trityl, Wang, and Rink linkers have all been used to immobilize alcohols onto the solid phase, reactivity being based on the benzyl ether linkage modified by surrounding groups. Other linkers have also emerged directly from solution-phase protecting-group chemistry, in particular the 1,3 bis-heteroatom moieties commonly found in ketals, acetals, aminals, and 2-alkoxy tetrahydropyrans.

a. THP and other Ketal Linkers. The tetrahydropyran linker **39.1** was introduced by Ellman[158] in order to provide a linker allowing the protection of hindered secondary alcohols suitable for organic synthesis and stable to strong bases and nucleophiles. Cleavage could be realized either by employing TFA/H_2O (95:5) for 15 min or 2 equiv of *p*-TsOH in butanol/DCE (1:1) at 60 °C for 16 h. Yields between 66% and 95% were obtained for primary and secondary alcohols but only 10% for a tertiary alcohol. This THP linker (Scheme 39) has been used to anchor purine derivatives which were released with 12% TFA in CH_2Cl_2.[159] Cleavage of tetrazoles from **39.2** required 3% HCl in methanol for 24 h in 58% yield compared to 25% obtained with TFA/CH_2Cl_2 (1:1) for 1 h.[160] Linker **39.3** was used by Chen[161] to prepare an octapeptide bearing a C-terminal alcohol functionality. Cleavage involved TFA/thioanisole/EDT/

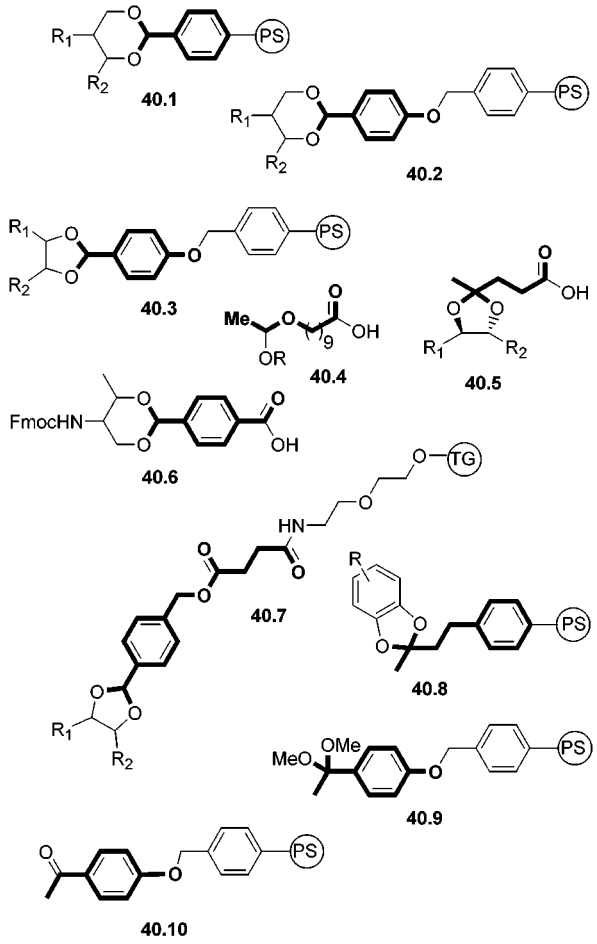
Scheme 39



H_2O (90:5:2.5:2.5), which allowed simultaneous deprotection of the side chains.

The ketal/acetal approach has been used to anchor diols (Scheme 40) onto a carbonyl linker or to anchor

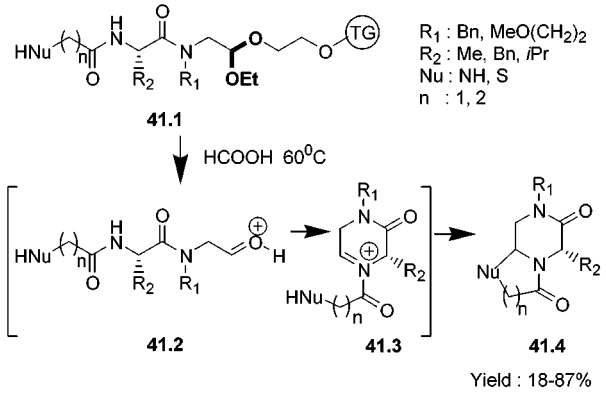
Scheme 40



a carbonyl group onto a diol-based linker. The first polymeric protecting group for diols was formyl polystyrene, but this has not been widely used apart for the protection of the 4,6-diol group in glycosides forming the dioxane linker **40.1**.[162,163] Hydrolysis of an acetal linkage was achieved in 70−92% yields using 10% TFA in CH_2Cl_2 with a trace amount of water or methanol for the dioxane linker **40.2** and dioxolane linker **40.3**.[164] Peptidomimetics possessing an alcohol or diol group have been synthesized on the solid phase using the diol moiety or the hydroxyl group as the attachment point.[165] 10-Vinyloxydecanoate and levulinic acid were preloaded with hydroxyl **40.4** and diol **40.5** moiety, respectively. Acetal linkages **40.4** in the alcohol series could be cleaved with 30% aqueous TFA for 3 h, but ketals **40.5** required much more drastic conditions. Best results were obtained with 95% TFA overnight, but significant amounts of contaminating compounds were observed. Final purity was estimated to be between 30% and 70% for alcohols and 20% and 50% for diols. In the later case, the long reaction time with TFA was the source of the problem. Chen[166] used linker **40.6** for the synthesis of a C-terminal threoninol octapeptide. Cleavage of the elongated peptide was carried out using 90% aqueous TFA containing thioanisole, ethylenediamine, and phenol. Preparative HPLC gave the desired compound in 75% yield. Wong[167] used the acetal linker **40.7** to anchor fucose derivatives. Cleavage was realized using 80% aqueous acetic acid (+2% TFA) for 20 h followed by chromatographic purification. Catechols have been released from linker **40.8** using 5 M HCl in dioxane/EtOH (1:1) 80 °C for 4 h.[168] A more reactive dimethylketal linker **40.9** compared to the ketone **40.10** was required for the anchoring of cyclohexene-1,2-diol under very mild conditions in order to avoid aromatization through water loss.[169] Diols were eventually released using 5% TFA in CH_2Cl_2 for 1.5 h.

Piperazine-containing heterocycles have been prepared from linker **41.1** (Scheme 41).[170] Cleavage

Scheme 41

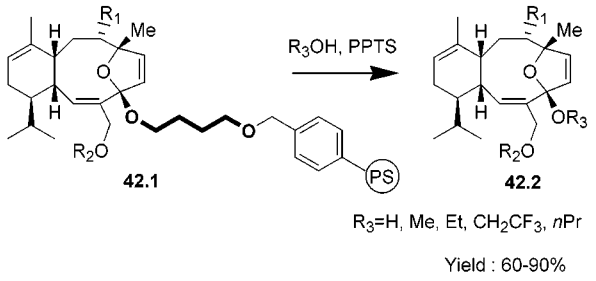


using formic acid generated an aldehyde which cyclized into the six-membered piperazine, followed by a second cyclization involving the acyliminium ion intermediate leading to the final bicyclic product. Eight compounds were prepared and isolated in yields ranging from 18% to 87%.

b. Transketalization-Based Linkers. For the modification of the sarcodictyin scaffold on solid support, Nicolaou[171] used a hydroxy-based resin to immobilize the hemiacetal moiety, thus forming the ketal-bound linker **42.1**. After derivatization of the scaffold, the release of sarcodictyin analogues **42.2** was achieved by transketalization in acidic medium (Scheme 42). Exposure to CSA in CH_2Cl_2/H_2O (2:1) yielded the hemiacetal and the acetate derivative if Ac_2O, Et_3N, and DMAP were added. PPTS in alcohol afforded the ketal depending on the alcohol (R_3OH) used, with overall yields of 60−90%.

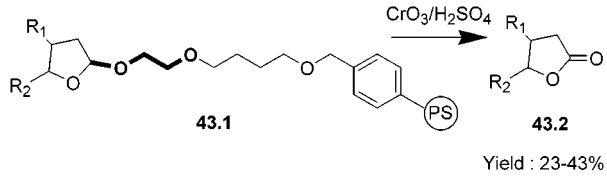
γ-Butyrolactones **43.2** have been prepared by Jones oxidation and acidic treatment of acetal-based tet-

Scheme 42



rahydrofurans anchored onto polyether modified Merrifield resin **43.1** (Scheme 43).[172] Final products

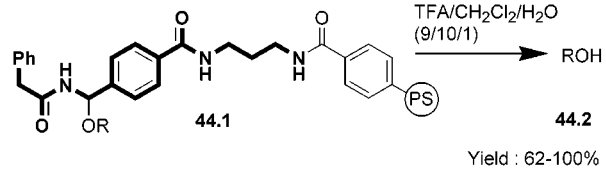
Scheme 43



were recovered after neutralization and extractive work up with yields of isolated compounds ranging between 23% and 43%.

c. Aminal Linkers. Aminals are known to be unstable and sensitive to hydrolysis. Turner[173] described linker **44.1** based on a phenylacetylaminal moiety. After treatment with TFA/CH_2Cl_2/H_2O (9:10:1), the phenylacetamide was cleaved, leading to the liberation of primary and secondary alcohols **44.2** (Scheme 44). In a reverse approach, argininal ami-

Scheme 44

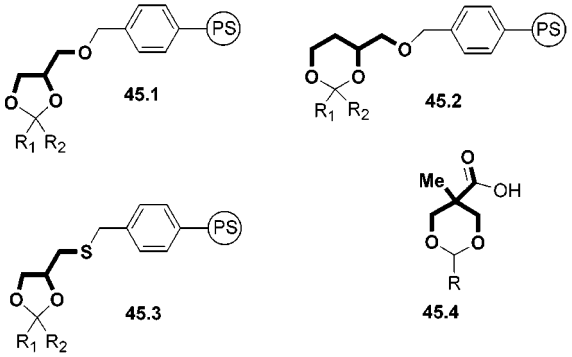


nals were released into solution when the hydroxyl group was attached onto the solid support.[174]

5. Linkers for Carbonyl Group Immobilization

a. Ketal Linkers. As acetals and ketals are the predominant protecting groups used to protect carbonyl functionalities in organic synthesis, their use as anchoring groups was studied very early on in the history of solid-phase synthesis (Scheme 45).

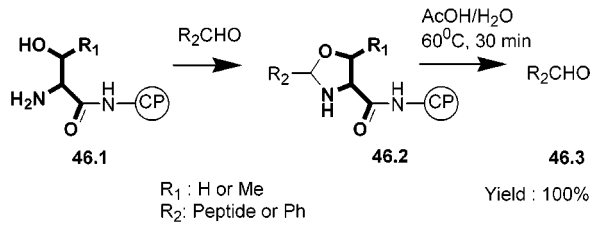
Scheme 45



Leznoff,[175] in 1973, used a dioxolane-substituted linker obtained from Merrifield resin (2% DVB) by substitution of the chloride by the sodium salt of 2,2-dimethyl-1,3-dioxolane-4-methanol. Subsequent hydrolysis of the acetonide and carbonyl immobilization afforded linker **45.1**. The main objective of the author was to protect symmetrical dialdehydes due to supposed site isolation of the polymer. Nevertheless, they encountered some difficulties with sterically hindered aldehydes. After the chemistry on the other part of the molecule occurred, a monoaldehyde was released using a mixture of 1 M HCl/dioxane (1:1) for 48 h. Benzaldehydes have been released from this linker with a mixture of 3 M HCl/dioxane (1:1) for 48 h at 80 °C.[176] The author found this cleavage method to be very reliable, although requiring prolonged reaction times. Good results were obtained for symmetrical ketones with linker **45.1**.[177] Different linkers were synthesized by Leznoff,[178] as it was well-known that 1,3-dioxanes were more suitable for ketones while 1,3-dioxolanes were better for aldehydes. However, poor results were obtained with ketal derivative **45.2** which precluded its use. In 1983, Hodge[179] used a 1,2-supported diol **45.3** obtained in one step from Merrifield resin by phase-transfer-catalyzed reaction with 3-mercaptopropane-1,2-diol. This linker was successfully used in a resin-capture approach and allowed the isolation of aldehydes or ketones from mixtures. It was able to discriminate a 3-oxosteroid from a 17- or 20-oxosteroid. Metz[180] employed advantageously the commercially available and inexpensive 2,2-bis(hydroxymethyl)propionic acid. Preloading of this diol with various aldehydes was made before anchoring the resulting unloaded linker **45.4** onto the resin. Aldehydes were recovered in 60−97% yield after cleavage with 95% aqueous TFA from a resin derived from TentaGel-S−NH_2 and **45.4**.

An oxazolidine linker **46.2** was used by Bray[181] to anchor aldehydes onto a solid support (Scheme 46),

Scheme 46

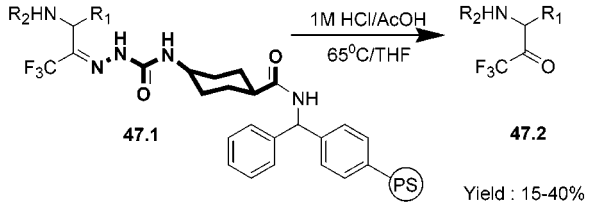


precursor **46.1** being composed of threonine (R_1 = Me) or serine (R_1 = H) residues bound to a crown/pin support. Benzaldehyde was cleaved with AcOH/water at 60 °C for 30 min. The authors noticed that acylated amines were not cleaved using TFA at room temperature (95% in water or 5% in CH_2Cl_2) and suggested a safety-catch approach by protecting the amine in **46.2** with a Boc group. A pretreatment with TFA thus activates the linker without loss of product.

b. Semicarbazone Linker. The semicarbazone linker was initially created to protect *C*-terminal peptide aldehydes.[182] Preloading of the scaffold was carried out in solution prior to the attachment onto a MBHA linker. After peptide elongation, the corresponding aldehyde was released using dilute aqueous

acid and formaldehyde. Later, trifluoromethyl ketones **47.2** were prepared using a similar linker **47.1** (Scheme 47).[183] Cleavage was achieved by refluxing

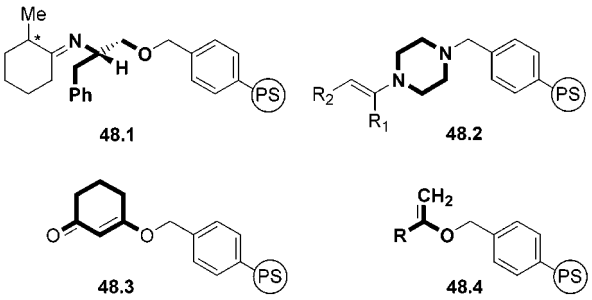
Scheme 47



the linker in THF containing aqueous HCl and acetic acid at 65 °C for 4 h. After 2 or 3 cleavage cycles the overall yields of the HPLC-purified products were in the range of 15−40%.

c. Imines, Enol Ethers, and Enamine Linkers. Chiral amines have been used to anchor ketones and allow enantioselective methylations on a solid support.[184] Cleavage of the supported imine **48.1** afforded the α-methyl ketone with a 94% enantiomeric excess (Scheme 48). Supported 2-aminobuta-1,3-dienes were

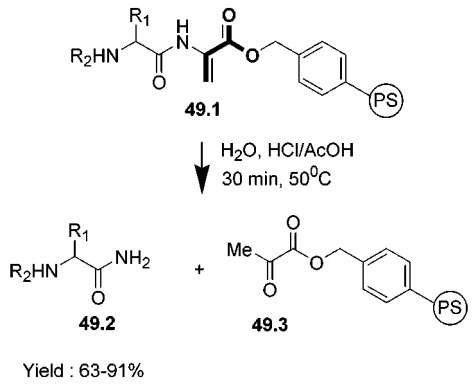
Scheme 48



prepared and used in Diels−Alder reactions. These enamines, **48.2** could be cleaved with 3% TFA in CH_2Cl_2, resulting in the synthesis of ketones[185] and cyclohexanones.[186] Rubino[187] reacted hydroxymethyl resin with 1,3-cyclohexanedione and CSA to produce linker-bound 2-cyclohexenone **48.3**. After addition of various Grignard or lithiated reagents onto the carbonyl group, the alcohol products were released and dehydrated with 3% TFA in CH_2Cl_2. Excellent purities were obtained as unreacted enone remained bound, the ketone having a deactivating effect on the enol hydrolysis. Barrett[188] reported the transformation of a linker-bound ester into an enol derivative **48.4** through the Tebbe reaction. This strategy relies on the safety-catch approach where the linker is activated just prior to the cleavage step. Cleavage, after reaction of the ester precursor with the Tebbe reagent, takes place with 1% TFA.

The mechanism of cleavage of the Dha linker **49.1** relies on an enamine-type hydrolysis due to the propensity of this particular residue to be hydrolyzed under acidic conditions. Nisula[189] anchored the *C*-terminal dehydroalanine peptide onto Merrifield resin; then after elongation of the peptide chain, he released the peptide amide by treatment with 1 equiv of water in 1 M HCl in glacial acetic acid for 30 min at 50 °C (Scheme 49).

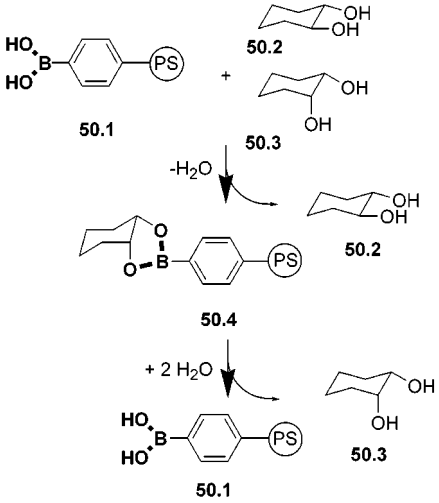
Scheme 49



6. Boronate Linkers

Polystyrylboronic acid linkers **50.1** have been used to protect various glycosides[190] and for the separation of a *cis*−*trans* diol mixture (Scheme 50).[191] Advan-

Scheme 50

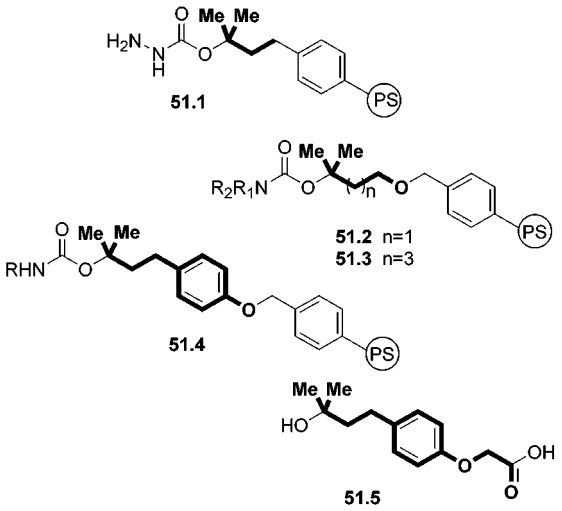


tages and disadvantages are linked. The boronate products are sensitive to water, and simple hydrolysis is sufficient for cleavage. Therefore, formation and further functionalization of the boronate requires dry conditions. Fréchet in early studies used specially designed reaction vessels to enable washing and manipulation of this linker without transfer or exposure to the atmosphere, preceding today's reaction vessels designed for inert solid-phase chemistry.[192]

7. tert-Alkoxycarbonyl-Based Linkers

Linkers based on the *tert*-butyloxycarbonyl (Boc) group have been used since 1969 (Scheme 51). Wang and Merrifield[193] prepared the hydrazide linker **51.1** which they used to synthesize a tetrapeptide hydrazide in 76% overall yield after cleavage with 50% TFA in CH_2Cl_2 for 30 min. This particular linker was found to be sufficiently stable to low concentrations of TFA (only 6% cleavage after 10 h exposure to 0.5% TFA) in order to perform OH or Bpoc-based SPPS. More recently, two activated *tert*-alkoxycarbonyl linkers have been used for the immobilization of amines. Hodges[194] developed linkers **51.2** and **51.3**, which could be used to release primary or secondary

Scheme 51



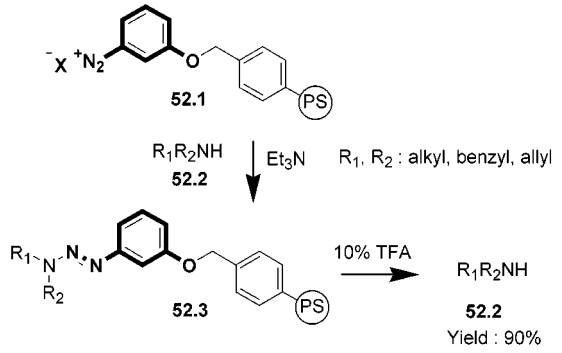
amines and anilines. The length of the chain was important, and longer TFA treatments were needed for the shorter chain ($n = 1$) than for the longer one ($n = 3$). A similar linker **51.4** was used to immobilize *N*-terminal peptides.[195]

The 4-(1′,1′-dimethyl-1′-hydroxypropyl)phenoxyacetyl (DHPP) linker **51.5** based on the *t*Bu ester protecting group allows the anchoring and release of acids (Scheme 51).[196] This linker has been used in SPPS, suppressing the loss of dipeptides by diketopiperazine formation in the same way as trityl-based linkers. Cleavage can be realized using either TFA/thioanisole[197] or 1 M HBF_4/thioanisole/TFA.[198] Blackburn[199] successfully employed this linker for the release of libraries of angiotensin converting enzyme inhibitors from TentaGel resin using TFA/H_2O (95:5).

8. Aryltriazene Linkers

Diazonium-based linkers **52.1** have been used to anchor primary and secondary amines **52.2**.[200] The resulting triazene moiety in linker **52.3** is stable to various chemistries (Scheme 52). Cleavage can be

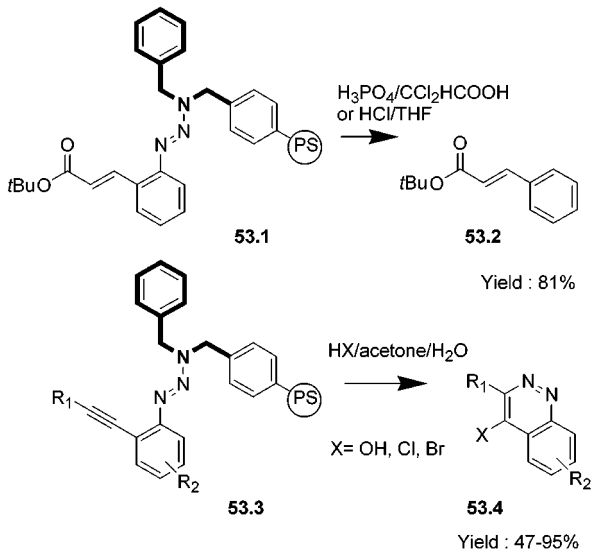
Scheme 52



realized with 10% TFA in 90% yield. When acetyl chloride was used to mediate cleavage, *N*,*N*-dialkylacetamides were observed. Cleavages conducted with tetrafluoroboric acid regenerated the aromatic diazonium-based linker **52.1**.

This methodology has been successfully employed in a reverse way with linker **53.1** (Scheme 53).[201]

Scheme 53

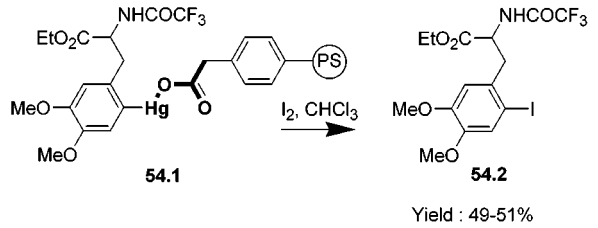


Aromatic diazonium salts reacted with supported secondary amines to form **53.1.** This linker could be cleaved reductively with H_3PO_2 in dichloroacetic acid for 8 h to produce aromatic compound **53.2**. The use of HCl/THF led, surprisingly, to the same aryl derivative instead of the aryl halide as observed in solution-phase tests, although no reducing agent was present. Modification of the aryl group by incorporation of an alkyne function afforded **53.3**, which underwent a Richter-type cleavage when submitted to haloacid in a mixture of acetone and water. Various 4-halo- and 4-hydroxycinnolines **53.4** were prepared in 47−95% yields.[202]

9. Organometallic-Supported Scaffold

Mercury attached to a solid support and bound to a DOPA precursor has been developed for the preparation of 6-halo-DOPA's **54.2** in order to avoid removal of unreacted mercury starting materials after reaction (Scheme 54).[203] Iododemercuration

Scheme 54



using I_2 in chloroform afforded the product in 49−51% yields, the major impurity being the protodemercuration product.

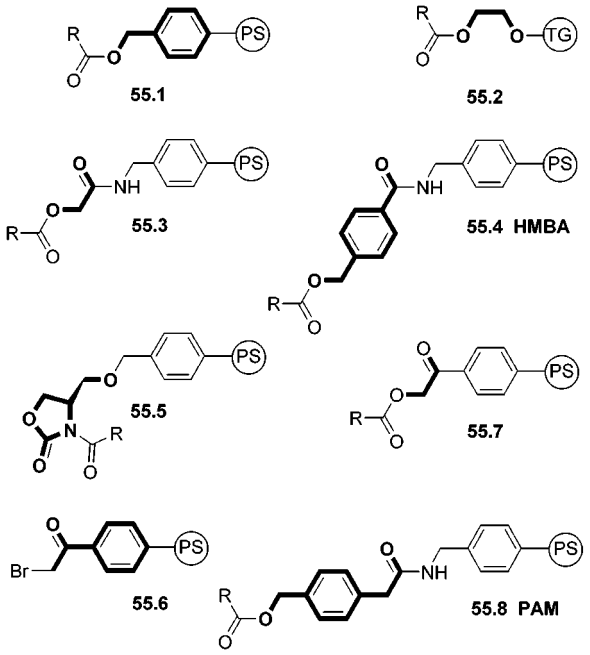
B. Nucleophilically Cleaved Linkers

1. Oxygen Nucleophiles

a. Saponification. Saponification and the release of peptide acids has been used since the introduction of solid-phase chemistry by Merrifield in 1963[1] (Scheme 7) and constitutes the classical preparation of peptide acids, the method being completely orthogonal to Boc and CBz chemistries. Despite the fact

that benzyl esters **55.1** are easily cleaved by 0.1 M NaOH, milder (nonracemizing) conditions such as 5 equiv of K_2CO_3 in methanol for 48 h at room temperature or tetrabutylammonium hydroxide in THF are often used. In one publication the author explained that although both methods were used initially, he preferred to use K_2CO_3 as it was simpler and resulted in fewer byproducts, although sometimes complete cleavage was achieved only with ammonium hydroxide.[204] Saponification of benzoic esters required considerable experimentation by Snieckus,[205] who finally employed a mixture of 5 equiv of LiOH (0.2 M) in H_2O/MeOH/THF (1:2:5) under reflux for 1−2 days in order to produce pure materials suitable for direct biological screening. Another recent example of cleavage of benzoic esters was to use a mixture of 70% 1 M aqueous NaOH in *i*PrOH followed by neutralization.[206] Moderate yields (40−70%) were obtained for a four-step synthesis carried out on TentaGel-S−OH resin **55.2**. Linkers play an important role in determining the ease of cleavage of esters. Electron-withdrawing groups can dramatically enhance the release. Scheme 55 displays

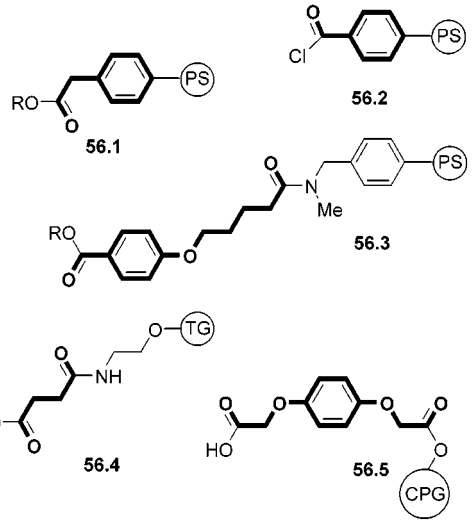
Scheme 55



some of the more usual linkers involved in nucleophilic release. The glycolamidic ester linkage **55.3** which displays complete stability to acids has been used in SPPS using a Fmoc/*t*Bu strategy and is quantitatively cleaved with 1 M NaOH.[207] Such stability is similar to that of the benzylic ester linkage derived from 4-hydroxymethylbenzoic acid (HMBA) **55.4**.[208] Polymer-supported "Evans" oxazolidinone **55.5** was alkylated by Allin,[209] and the α-alkylated carboxylic acid was released by lithium hydroxide monohydrate in THF/water (3:1) for 12 h. Hydrogen peroxide has also been used in conjunction with 1 M aqueous LiOH.[210] Sodium methoxide in THF at −20 °C[210] or lithium benzyloxide[211] have been used to generate the corresponding methyl or benzylesters from resin **55.5**. Mizoguchi[212,213] reported the preparation of the linker **55.6** bearing a haloacyl functionality which could be esterified to **55.7**. Basic aqueous dioxane, sodium thiophenoxide in DMF, methanolic ammonia, and hydrazine hydrate in methanol were all successful for the smooth cleavage of ester **55.7**. Merrifield[214] cleaved the phenacyl linker **55.7** using the 18-crown-6 complex of potassium cyanide, with cyanide displacing the peptide without affecting side-chain protecting groups. The yields were better than using thiolysis or saponification. Ueki[215] studied ester hydrolysis for the removal of peptide acids from PAM linker **55.8**, employing 0.05 M TBAF·3 H_2O in DMF for 30 min. Pentapeptides were obtained in yields of 46−61%.

Saponification of esters has been used to generate alcohols in the reverse approach using acid-derivatized linkers and hydroxy-based products (Scheme 56). In this case the nucleophiles do not have to be

Scheme 56



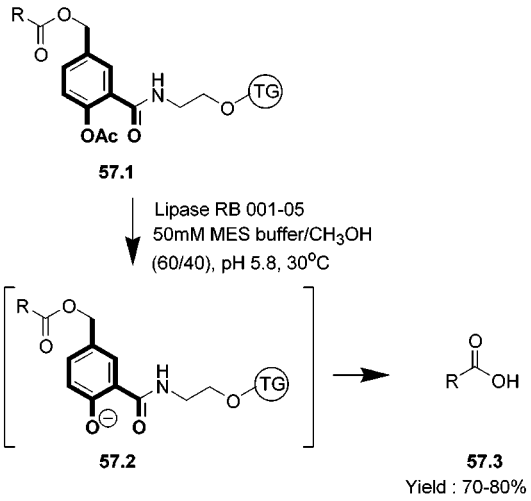
hydroxide ions, and more efficient cleavage reagents as hydrazine, ammonia, ethanolamine, or methylamine can be used.[216] Polymers containing acid chlorides were obtained from Merrifield resin by Leznoff[217] and used to generate the ester-based linkers **56.1** for the preparation of monoalkyl ethers of symmetrical diols. Release of the desired compound was achieved using 0.5 M NaOH in dioxane (1:1) or concentrated ammonia in dioxane. Classical extraction and silica purification were required. Phenyl acetyl linkers **56.1** have been used to anchor the 5′-hydroxyl group of thymidine for the synthesis of oligodeoxyribonucleotides.[218] Treatment with ammonia allowed cleavage. In the case of phenol derivatives, linker **56.1** was unsuccessful and polymer-bound benzoyl chloride **56.2** gave better results.[219] Various basic conditions can be used to release alcohols from resin **56.2** such as K_2CO_3 in MeOH/THF (1:2),[220] a mixture of tetrabutylammonium chloride, KOH, H_2O, THF at 80 °C for 48 h,[221] or MeONa, MeOH, THF for 4 h.[222]

The use of a specific carboxylated resin can be avoided if a dicarboxylic spacer is added. Linker **56.3** was used by De Mesmaeker[223] relying on the ease of benzoic ester hydrolysis with MeONa/MeOH/dioxane. More generally, succinyl spacers have been employed. Thus, in **56.4** the anhydride was placed between the

resin and the compound with the succinic spacer attached to the alcohol moiety prior to resin coupling.[224,225] Cleavage was effected using MeONa/MeOH/dioxane or concentrated aqueous ammonia. Hydroquinone-*O*,*O*-diacetic acid (QDA) **56.5** was found to be more labile than the succinic-acid-based linkers when used for oligonucleotide synthesis on CPG support.[226] The oxalyl linker was not considered suitable by this team as it is too base-sensitive.

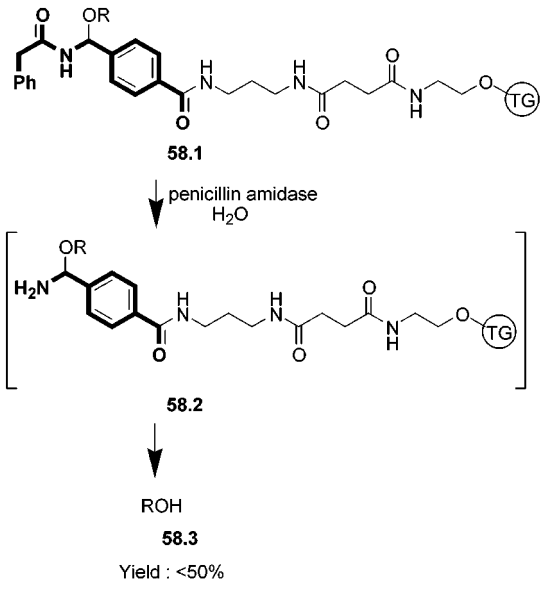
b. Enzyme Cleavable Linkers. An enzyme-labile linker has been developed by Waldmann.[227] The 4-acyloxybenzyloxy linker **57.1** was hydrolyzed with lipase RB 001−05 on TentaGel resin. Upon cleavage of the 4-acetyl group by the esterase (Scheme 57), various compounds have been released.

Scheme 57



Turner[173] has shown that a phenylacetamide-protected aminal **58.1** could be hydrolyzed using a penicillin amidase leading to an unstable hemiaminal **58.2** which releases the desired alcohol **58.3** (Scheme 58). Surprisingly, Waldmann and Turner obtained

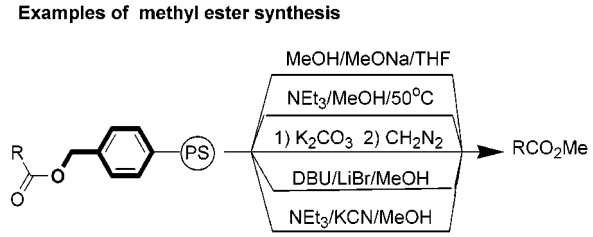
Scheme 58



good yields (70−80% and 50% yields, respectively) using TentaGel resin, although Lebl has demonstrated that only 1−2% of sites are accessible on TentaGel resin to a variety of proteases.[228]

c. Nucleophilic Transesterification. Esters instead of acids can be released by transesterification or by nucleophilic attack of an alkoxide. Good yields are generally obtained with primary alcohols (MeOH, EtOH, BnOH), in each case moisture has to be excluded. Esterification in solution by cleavage and subsequent treatment of the released acid with diazomethane was frequently used by Leznoff.[204,229,230] Costero[231] proposed another ester-interchange method by refluxing the polymer in a mixture of dimethylaminoethanol/DMF (1:1) for 20 h and then stirring the concentrated filtrate in methanol. Direct one-pot transesterification procedures are now preferred. A general scheme for ester preparation is described in Scheme 59. Beyerman[232] successfully employed dif-

Scheme 59

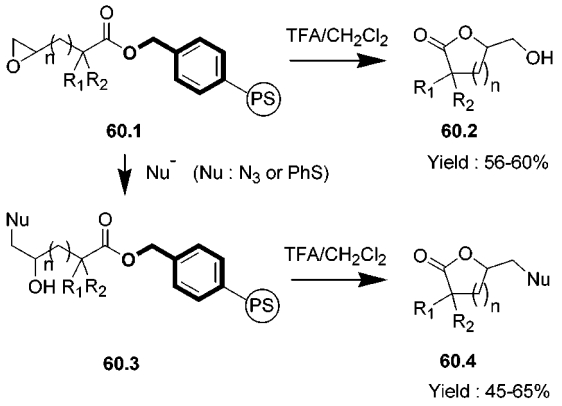


ferent tertiary amines and alcohols to affect nucleophilic transesterification. The author noticed that when the benzyl ester linkage was submitted to ethanolic ammonia, both the ester and amide were obtained. Similar observations were made with methanolic ammonia. Consequently, the best results were achieved with hindered bases (NMM and triethylamine) and methanol followed by simple evaporation. 4-Hydroxymethylbenzoic acid (HMBA) **55.4**, which is resistant to acid cleavage, was used by Hutchins[233] in a Fisher indole synthesis and was cleaved with MeOH/Et_3N (9:1) at 50 °C. Catalysts can be used ($ZnCl_2$ or TFA). Addition of KCN to Et_3N/ MeOH/ benzene (5:20:75) proved to be efficient for the preparation of nitrosoacetals.[234] DBU, LiBr in MeOH was chosen by Anslyn[235] for the preparation of oligomeric thioureas. This methodology has been used to cleave a tetrapeptide from the PAM linker **55.8** in 93% yield without epimerization and was slightly better than the method employing tetraethoxytitannate in ethanol (leading to the ethyl ester).[236] Sodium methoxide in refluxing THF[237] or in a mixture of MeOH/THF[238,239] is commonly used to release methyl esters.

d. Lactones via Cyclorelease. Lactones have been synthesized using a cyclorelease strategy by activation of the ester group and reaction with an internal alkoxy group. No specific linker is generally required for cleavage. The main advantage of cyclorelease is purity, as only the product should be released if the alcohol moiety is incorporated/unprotected in the last step of the supported synthesis. γ-Lactones and δ-lactones **60.4** have been prepared with the nucleophilic alcohol coming from an epoxide opening.[240] This opening has been performed by the attack of a number of nucleophiles (NaN_3, PhSNa), with lactonization realized by shaking for 2 h with

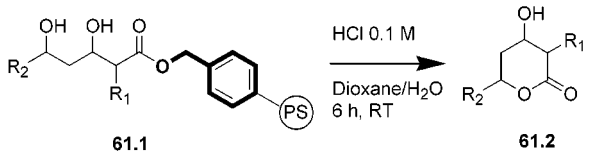
TFA/CH_2Cl_2 (1:1). Similar yields of product **60.2** (56−60%) were obtained by direct treatment of the epoxide **60.1** with TFA (Scheme 60).

Scheme 60



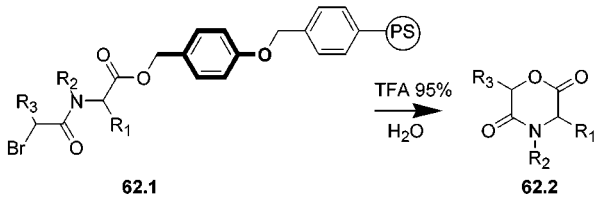
2*H*-Pyranones **61.2** have been obtained from derivatized hydroxymethylpolystyrene linker **61.1** by treatment with 0.1 M HCl in dioxane/water (1:1) for 6 h with sonication (Scheme 61).[168]

Scheme 61



Substituted 2,5-diketomorpholines were also prepared from ester **62.1** using 95% aqueous TFA for cleavage (Scheme 62).[241] Unfortunately, as the au-

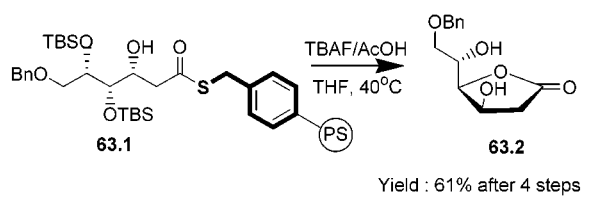
Scheme 62



thors used the acid-labile Wang linker, it is not clear if cyclization occurred during or after cleavage.

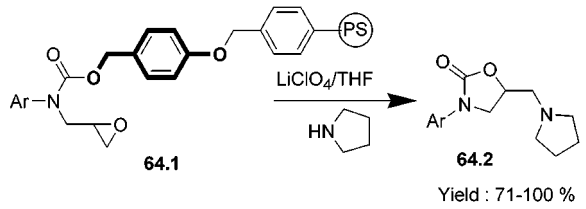
Kobayashi[242] used the thioester-based linker **63.1** to synthesize lactones **63.2** by cyclorelease after deprotection of a silyl group using TBAF in THF with or without acetic acid (Scheme 63).

Scheme 63



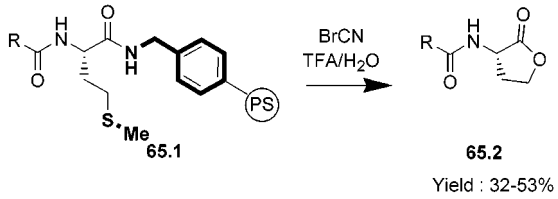
Treatment of **64.1** with lithium perchlorate and pyrrolidine achieved the opening of an internal epoxide, the alcohol of which cleaved the carbamate linker (Scheme 64). Pure products were obtained after aqueous workup.[243]

Scheme 64



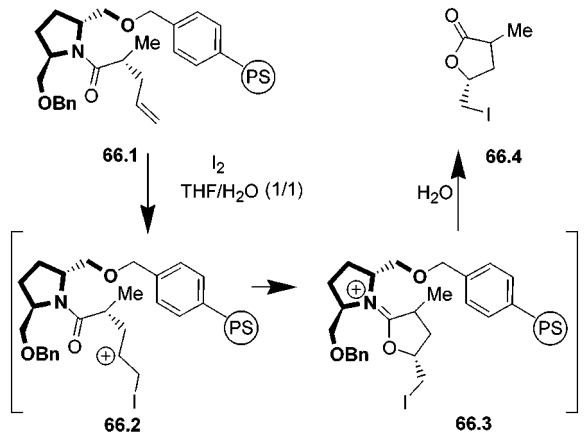
Peptides containing methionine residues can be cleaved with cyanogen bromide, giving rise to lactones.[244] C-Terminal methionine residues anchored onto aminomethyl polystyrene can thus be used as linkers **65.1**, cleaved by the action of cyanogen bromide in TFA (Scheme 65).[245]

Scheme 65



Amide bond rupture was also involved in the preparation of butyrolactone **66.4**. An alkenyl precursor was activated with iodine, allowing amide bond cleavage and subsequent release. The prolinol-based linker **66.1** was used to ensure a stereoselective synthesis of 3,5-disubstituted γ-butyrolactones (Scheme 66).[246,247]

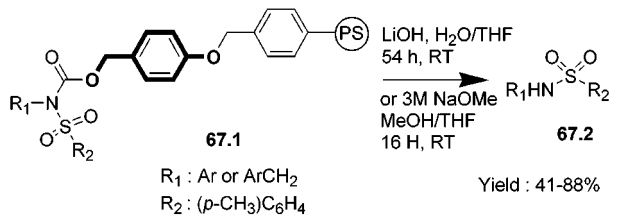
Scheme 66



The same group led by Kurth developed the solid-phase preparation of cyclic ethers.[248] Tetrahydrofuroisoxazolines were bound to an electron-donating support, and cyclization was realized by activation of the alkenyl moiety using ICl as previously described.

e. Nucleophilic Cleavage Involving Carbamates. Nonhindered carbamate linkers can be cleaved if the carbonyl functionality is sufficiently activated (i.e., nitrogen of sulfonamide group). Basic conditions such as MeONa in THF or LiOH in THF/water have been used to cleave the urethane linkage **67.1** attached to a Wang linker (Scheme 67).[249] The authors confirmed that when urethane and sulfonamide groups were attached to the same nitrogen atom,

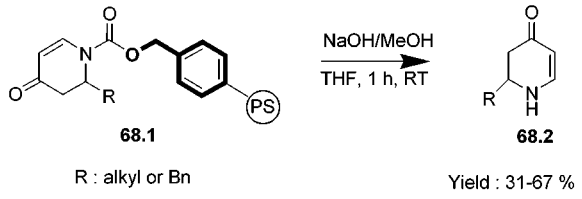
Scheme 67



cleavage under basic conditions occurred at the urethane rather than the sulfonamide. Sulfonamide **67.2** was thus obtained after decarboxylation. Cleavage with amines resulted in a mixture of desired aminosulfonyl ureas accompanied by sulfamamide byproducts.[250]

Dihydropyridones **68.2** anchored as their carbamate derivatives can be released using a catalytic to stoichiometric amount of NaOH in MeOH (Scheme 68).[251]

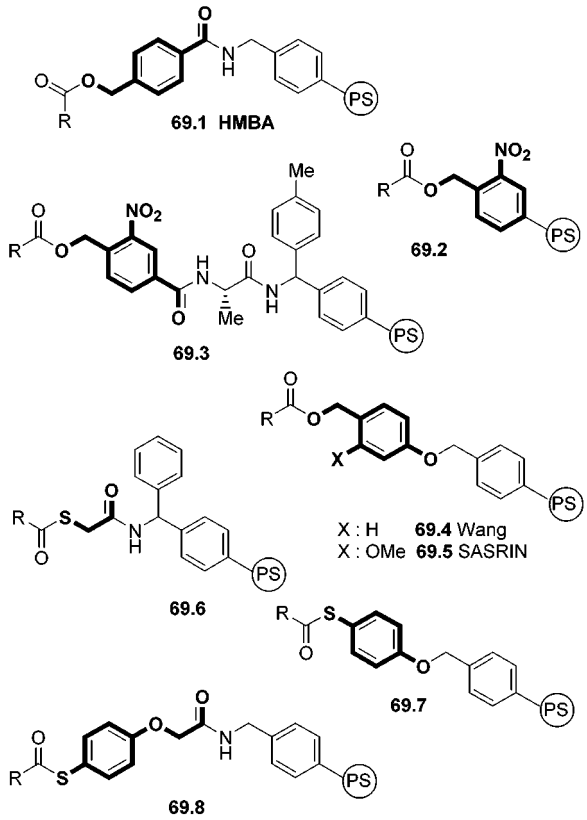
Scheme 68



2. Nitrogen Nucleophiles

a. Ammonolysis and Aminolysis. Displacement reactions involving nitrogen have generally been directed toward the preparation of amide from supported activated esters (Scheme 69).[252] During the preparation of carboxy amide derivatives of oxytocin, Beyerman observed that *C*-terminal amides could be obtained by ammonolysis and aminolysis of the benzylester-based linker with the aid of ammonia[253,254] or methylamine.[255] Linkers are important for these nucleophilic displacements, and electron-withdrawing groups present on the hydroxymethylbenzoic acid derivatized linker (HMBA) **69.1** or the 4-hydroxymethyl-3-nitrophenyl-based linker **69.2**[256] enhance aminolysis, whereas electron-donating groups decrease the rate. As usual, a compromise between stability and reactivity has to be found. Piperidine (20% in DMF) is not nucleophilic enough to cleave most ester bonds, and even esters of 4-hydroxymethylbenzoic-acid-based linkers **69.1** are stable to the Fmoc strategy. Primary peptide amides are usually prepared from linkers by ammonolysis using ammonia in 2-propanol rather than methanol to avoid the possibility of methyl ester formation.[257] Nucleophilic cleavage from the 3-nitrobenzamidobenzylester (Nbb) linker **69.3** (this linker was developed essentially for its photocleavable properties) has been studied by Albericio.[258] The author obtained yields ranging from 25% to 89% depending on the primary amine used for the cleavage and the first residue bound to the linker. This cleavage was sensitive to steric hindrance as piperidine and dimethylamine both gave low yields. In addition, this linker gave peptide acids in good yields using H_2O/TBAF as well as peptide methyl esters by reaction with MeOH/KCN or MeOH/DIPEA. Wang **69.4** or SASRIN **69.5** linkers, being much less labile toward nucleophiles, are versatile but cleavage becomes correspondingly more difficult. Better results (purer products) were obtained with SASRIN linker **69.5** by cleaving with neat amines under pressure (for gaseous amines such as ammonia, methylamine, and ethylamine) rather than by employing aqueous or alcoholic solutions.[259] Concerning liquid and solid amines, it was observed that the cleavage rate for this linker was sensitive to the bulk of the amine and the best yields are obtained with undiluted linear aliphatic amines. Excess amine has to be removed by evaporation under reduced pressure, and further workup by precipitation and chromatography depends on the solubility of the product. A particular problem was encountered with the crown/pin method. Ammonia and its solutions are not compatible with the open-well format of this technique, and anhydrous conditions are difficult to maintain. Nevertheless, using this multipin approach, a method employing gaseous NH_3 gave access to hundreds or thousands of discrete peptide amides in quantities (10−100 nmol) sufficient for biological evaluation.[260,261]

Scheme 69



Various primary amines have also been used to cleave linker **69.6**, but secondary amines required more reactive thioesters such as thiophenol-based linkers **69.7** and **69.8**. With these two linkers, yields of amides were in the region of 60−70% when proline methylester or phenylalanine methylester were used at 75 °C.[262]

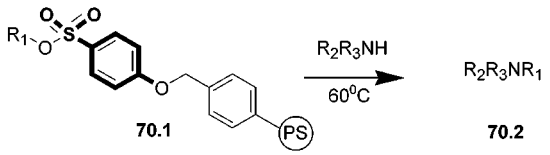
Hydrazinolysis performed with hydrazine hydrate in DMA or in methanol allows the preparation of peptide hydrazides.[255,263] This class of compounds is

especially interesting as they can constitute the precursors of protected peptide azides and can be generated and coupled in situ. This azide coupling method is known for preventing racemization in most cases.[264] Hydroxamic acids have been obtained by displacement of supported esters using aqueous hydroxylamine in THF[265] or in methanol.[255]

Ammonolysis is known to be catalyzed by ammonium salts, but the crude product has to be freed from adherent ammonium chloride after evaporating the ammonia. Methods using Lewis acids have also been employed to activate amidation reactions and are considered in section IV.D.3.b.

The main involvement of other nitrogen nucleophiles applies to the preparation of amines from sulfonate-bound material. Reitz[266,267] showed that arylsulfonates **70.1** could be displaced by various amines (secondary, volatile primary amines, imidazole) as well as thiolates yielding the corresponding alkylated compounds **70.2** (Scheme 70). These aryl-

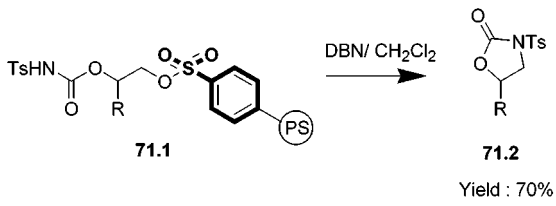
Scheme 70



sulfonate esters **70.1** were found to be stable when involved in Grignard addition, Wittig reactions, $NaBH_4$ reduction, reductive aminations, and Suzuki couplings.

A sulfonate-based polystyrene, Dowex 50X2−400 ion-exchange resin **71.1**, has been used for the preparation of oxazolidinones by a cyclorelease pathway.[23] Treatment with 3 equiv of DBN in CH_2Cl_2 promotes the internal substitution of the sulfonate by the nitrogen of the carbamate, affording the cycloelimination product **71.2** (Scheme 71). Purifica-

Scheme 71

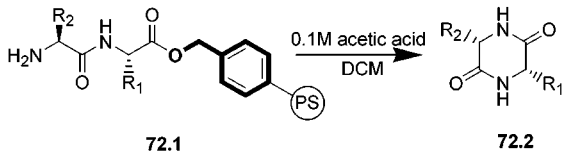


tion through a short plug of silica provided 1,3-oxazolidin-2-ones in 70% overall yield.

c. Lactam and Carbamate Formation by Cyclorelease. Amide bond formation has been used to generate small heterocyclic compounds by a number of cyclorelease approaches. The main advantage of this strategy is the fact that only the desired product should be released into solution. Mechanisms for the formation of these five- to seven-membered ring compounds is based on the activation of a carbonyl group (generally an ester function) and subsequent intramolecular nucleophilic attack by a nitrogen atom. In many cases no specific linker is required and the ester group is simply attached to Merrifield resin. A spacer is sometimes used[268] for enhanced resin swelling. Some syntheses of five- to six-membered heterocycles featuring a lactam or carbamate moiety are presented here as classical examples.

(i) Diketopiperazine. Merrifield[269] observed that acetic acid in CH_2Cl_2 was effective for the formation and the release of diketopiperazine (DKP) products, especially from *C*-terminal proline and glycine-anchored peptides (Scheme 72). Acetic acid was

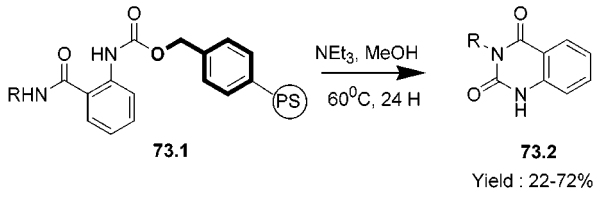
Scheme 72



preferred for cyclization as much stronger acids lead to a much higher proportion of nonnucleophilic protonated amines. For many years DKP formation was considered to be an unwanted side reaction. However, diketopiperazines **72.2** are now prepared due to their potential biological properties.[270,271] Yager[272] released some tetrahydro-β-carbolines derivatized DKP's, the displacement taking place on an acid-stable 4-hydroxythiophenol linker. Upon evaporation, only the pure product and a stoichiometric amount of $Et_3N\cdot$HCl were observed. Fmoc deprotection using 5% piperidine was also efficient in ensuring cleavage from hydroxyethyl-functionalized resin **5.4**.[273] Unsaturated DKP's have also been obtained by reacting α-ketoamides with ammonium acetate in acetic acid, cleavage occurring via the enamine.[274]

(ii) Pyrimidinediones. The amide nitrogen of **73.1** can be involved in the nucleophilic attack onto a carbamate functionality (Scheme 73). Quinazoline-

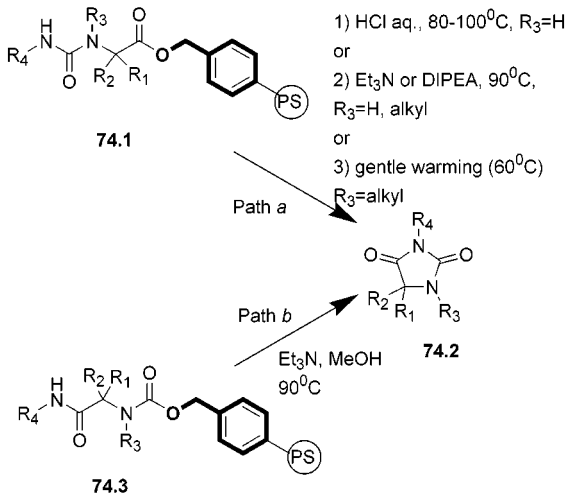
Scheme 73



2,4-diones **73.2** have been obtained in 20−70% yields in this manner using Et_3N, MeOH at 60 °C for 24 h with purities greater than 80%.[275]

(iii) Hydantoins. More conventionally, nucleophilic attack of a nitrogen (NH urea) has been used to prepare hydantoins **74.2** by cyclization and cleavage of an ester-anchoring group **74.1** (Scheme 74, path *a*). This approach, again, leads to high purities when the urea is selectively generated just prior to the cleavage step. Basic conditions are used such as Et_3N/dioxane (5:95) at 60 °C,[268] Et_3N/THF,[276] or neat diisopropylamine.[277] Acid activation has also been employed using 6 M aqueous HCl at 85−100 °C for 2 h followed by methanol extraction and concentration,[278] but this method is considered to provide lower yields than the base-promoted method.[279] The presence of a hydrazone moiety forced Wilson[280] to use neutral conditions and activation by silylation with bis(trimethylsilyl)trifluoroacetamide. Kurth[281] reported that release can be achieved upon gentle

Scheme 74

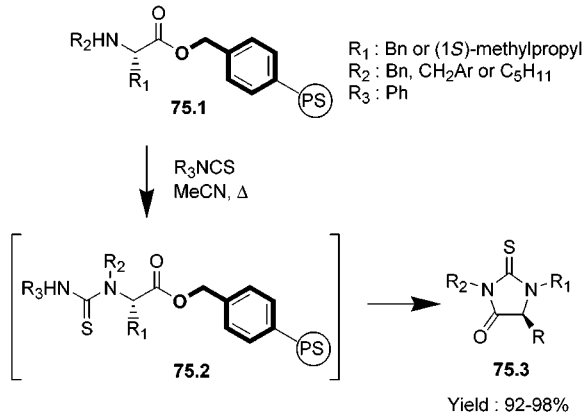


warming (60 °C) without any acid or base catalysis for *N*-3-alkylated hydantoins.

Another pathway to form hydantoins involves the attack of an amide nitrogen onto a carbamate linker **74.3**, and cleavage proceeds with Et_3N, MeOH, 55−90 °C (Scheme 74, path *b*).[282]

Thiohydantoins **75.3** have been obtained under neutral conditions as the thiourea intermediates **75.2** were found to cyclize upon standing in the absence of base (Scheme 75).[279] Optimum yields were found

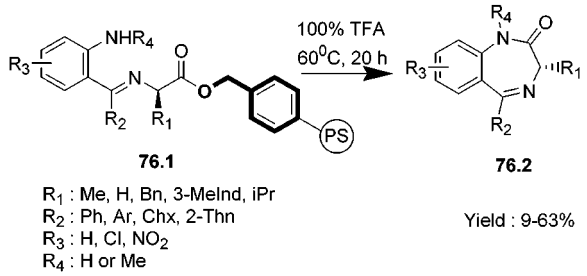
Scheme 75



after refluxing in acetonitrile. This spontaneous cyclization makes the removal of excess isothiocyanate, used to make the thiourea, difficult. Trapping the unreacted excess with supported scavenging amines is the most convenient option.

(iv) Benzodiazepinones. Synthesis of benzodiazepines **76.2** by cyclorelease has been realized follow-

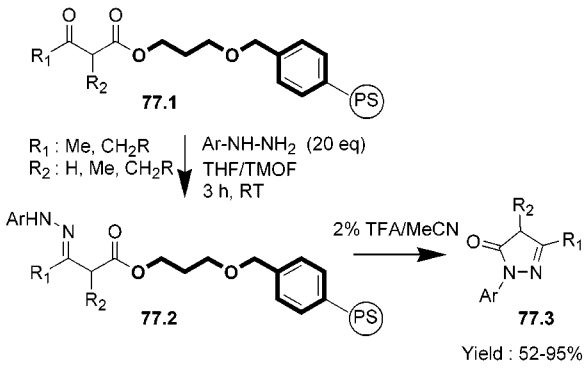
Scheme 76



ing ester activation using neat TFA at 60 °C for 24 h (Scheme 76).[278] There were 9−63% yields with purities above 90% obtained for 40 products after aqueous workup. However, basic procedures (*t*BuONa/THF 60 °C for 24 h) now seem to be preferred.[283]

(v) Pyrazolones. Pyrazolones have been prepared by reaction of the linker-bound *β*-ketoester **77.1** with hydrazine derivatives (Scheme 77). Spontaneous cy-

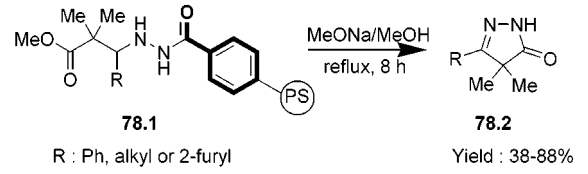
Scheme 77



clorelease of pyrazolones **77.3** occurs when hydrazine hydrate was used, but heating[284] or the use of 2% TFA in acetonitrile[285] was necessary for less nucleophilic hydrazines.

A recent example of the synthesis of pyrazolones involved the hydrazide linker **78.1** (Scheme 78).[286]

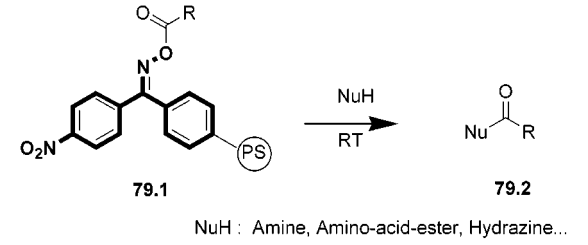
Scheme 78



Treatment with base (MeONa in refluxing MeOH, 8 h) furnished the corresponding pyrazolones **78.2** in 38−88% yields after preparative TLC purification.

d. Oxime Linker. Esters derivatized onto the oxime (Kaiser) linker **79.1**[287] are cleavable under much milder conditions of hydrazinolysis or aminolysis than standard esters (Scheme 79). Amino acid

Scheme 79



esters have also been used as a source of amines, allowing peptide fragments to be coupled together. Cyclic peptides are an important class of compounds that have been prepared using the Kaiser linker typically in 50−70% yields.[288] The 4-nitro group on the Kaiser linker reduces the linker's lability to TFA; less than 5% is lost when the resin is submitted to 25% TFA for 4 h, which corresponds to the total amount of exposure to TFA encountered in the

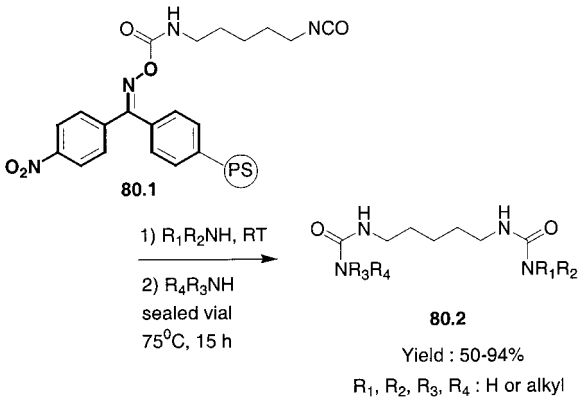
synthesis of a nonapeptide using the Boc/Bn strategy. Typical procedures involve the use of 1.1 equiv of amine in CH_2Cl_2 with overnight stirring. An aqueous workup and crystallization affords the products in 40−99% yields. A catalytic amount of AcOH is generally used to enhance aminolysis.[287] Various primary aliphatic and aromatic amines have been successfully used, although there are limitations with deactivated or sterically hindered amines.[289]

Recently, DeGrado developed a linker-to-linker transfer method and showed that oxime-based esters **79.1** could be cleaved using HOBt as the nucleophile at 50−70 °C.[290a] This work follows from classical earlier solid-phase studies.[290b] The released HOBt-ester could then be trapped by an amine-containing resin, allowing amide bond formation on another solid support.

Hydroxamic acid derivatives have also been prepared using the Kaiser linker with 5 equiv of *tert*-butyldimethylsilyl-*O*-hydroxylamine followed by silyl group deprotection in solution phase with TFA.[291] Aqueous workup and evaporation afforded products in 30−89% yields. Fully protected peptides have been released as peptide C-terminal thio acids by treatment with hexamethyldisilathiane ($Me_3Si-S-SiMe_3$) and tetrabutylammonium fluoride, with such peptides being useful for fragment couplings.[292]

Reacting bis-isocyanates with the Kaiser linker followed by reaction with an amine (R_1R_2NH) at room temperature allows the preparation of intermediate mono-ureas. Excess amine forms the terminal urea without affecting the oxime-derivatized carbamate function, the carbonyl function being sufficiently deactivated. However, it can be cleaved with another amine (R_3R_4NH) if the reaction is carried out in a sealed tube at 75 °C to form bis-urea **80.2** (Scheme 80).[293]

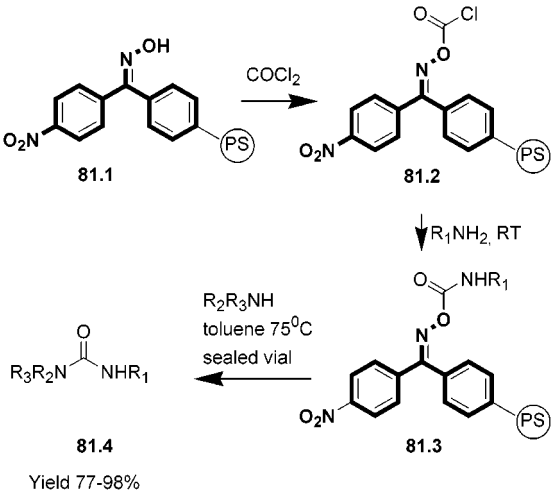
Scheme 80



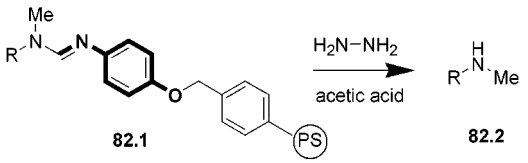
A more general approach to ureas is to use the "phoxime" linker **81.2**, made from oxime linker **81.1** by reaction with phosgene. Carbamates **81.3** derived from "phoxime" linkers undergo thermolytic isocyanate generation which can be trapped by an amine (4 equiv of amine in sealed tube at 75 °C) to form the corresponding urea **81.4** (Scheme 81).[290,294]

e. Hydrazine-Sensitive Linkers. Due to its high nucleophilicity, hydrazine has been used to cleave many linkers. Formamidine linker **82.1** is thus cleaved by heating in an ethanolic solution of hydrazine and acetic acid for the generation of secondary amines **82.2**.[295] Other reagents can be used to cleave the formamidine including $LiAlH_4$, KOH in MeOH, or $ZnCl_2$ in EtOH. Aqueous workup and HPLC purification is required (Scheme 82).

Scheme 81

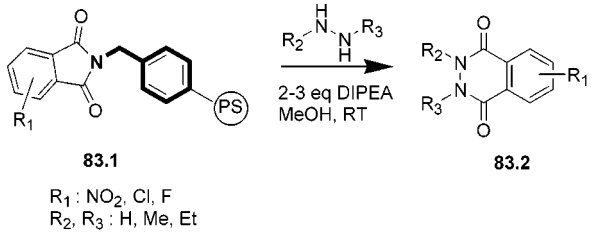


Scheme 82



In a reverse approach, phthalimide linkers **83.1** have been cleaved by various hydrazine derivatives, releasing into solution the corresponding phthalhydrazides **83.2** (Scheme 83).[296] The author observed

Scheme 83

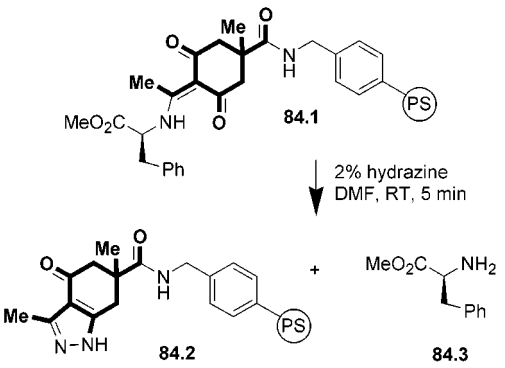


that aliphatic hydrazines reacted well whereas aromatic hydrazines were either very sluggish or did not react at all.

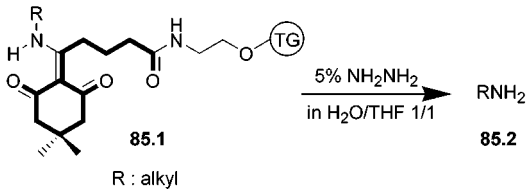
Bannwarth[297] devised the 4-acetyl-3,5-dioxo-1-methylcyclohexane carboxamide (ADCC) linker **84.1**. Phenylalanine methyl ester **84.3** was quantitatively recovered after shaking **84.1** in a 2% hydrazine hydrate solution in DMF for 5 min under argon even with the presence of a methyl ester group (Scheme 84). The author also claimed that this linker was stable to basic conditions (piperidine, DBU).

Another related linker **85.1**, based on the 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde) protecting group for amines, was described by Bycroft[298] 2 years later for the release of primary amines **85.2** upon treatment with 5% hydrazine hydrate or 10% *n*-propylamine in THF/H_2O (1:1) (Scheme 85).

Scheme 84



Scheme 85

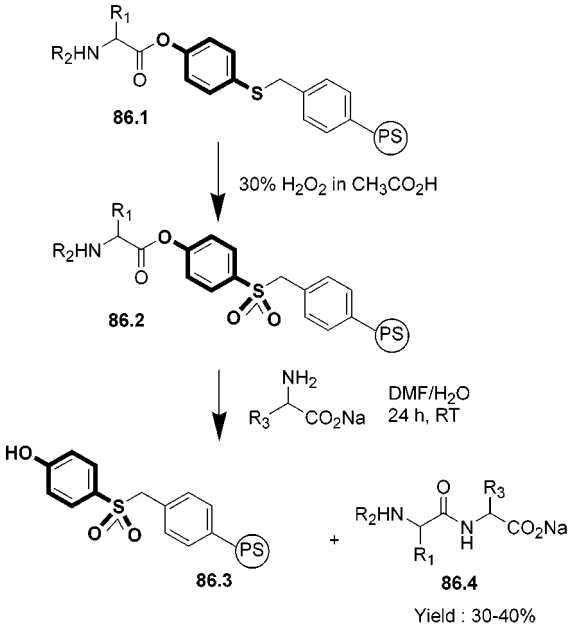


Linker **85.1** is stable to bases and orthogonal to Fmoc protection in peptide synthesis, although partial loss was observed (12% after 6 h contact with 20% piperidine). Preloading of amines can be carried out on the unloaded linker before its attachment onto the resin.[297−299]

3. Safety-Catch Linkers Sensitive to Nucleophiles upon Activation

a. Sulfide/Sulfone Safety-Catch Linkers. It is clear that nucleophilic displacement is facilitated if electron-withdrawing groups are placed in the 2- or 4-position of aromatic linkers. Marshall[300] devised a safety-catch linker based on a sulfide/sulfone transformation (Scheme 86). Amino acids were anchored

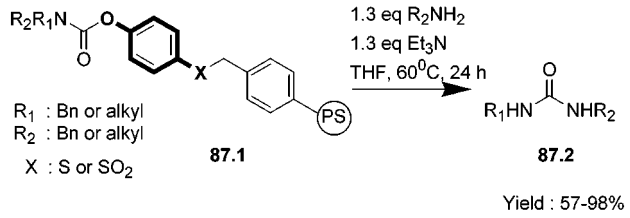
Scheme 86



onto the phenolsulfide linker to give **86.1**. Displacement of the ester with another amino acid residue was performed after oxidation of the sulfide with hydrogen peroxide, allowing amide bond formation. Dipeptides **86.4** were obtained in 30−40% yields after crystallization, precipitation, or chromatography.

Intramolecular cyclative cleavages of peptides were also obtained in moderate yields following the sequence: *m*CPBA-oxidation/Boc-deprotection/base-treatment.[301] More recently, Yager[272] prepared a library of 345 tetrahydro-*β*-carboline-3-carboxamides employing 23 different primary amines in the cleavage step. The amine was used as the limiting component (0.5 equiv) in order to avoid problems with its removal. Purity was in excess of 95% with quantitative yields (based on amine). The authors emphasized, surprisingly, that oxidation was not required for the displacement, which extends the type of chemistries that could be used. A comparative study was carried out by Dressman[302] who produced pure ureas by reaction with 0.1 equiv of amine and repeating the process with the same batch of linker **87.1** but a different amine (5 times). Even in the case of less electrophilic carbamate **87.1**, the author observed that oxidation was not necessary if triethylamine was added to the cleavage mixture (Scheme 87). Still without the oxidation−activation step, a

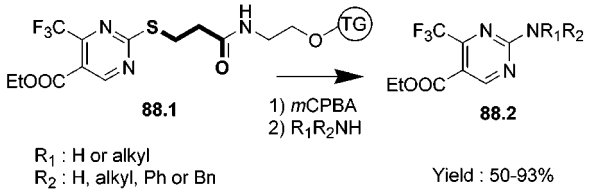
Scheme 87



team from Arris Pharmaceuticals[303] demonstrated that cleavage was more efficient in pyridine than DMF. An excess of amine was used to effect cleavage in good yield in less than 24 h.

Nucleophilic aromatic substitution of the sulfone group by amines allowed the synthesis of various 2-aminopyrimidines **88.2** (Scheme 88).[304] Ammonia

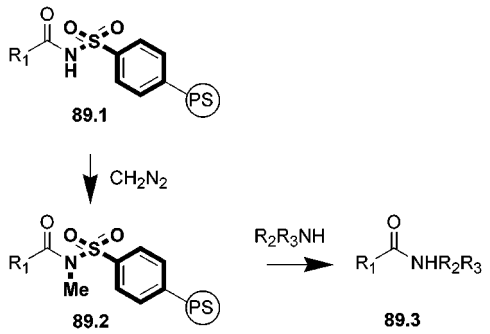
Scheme 88



and primary or secondary amines (slightly less than 1 equiv for nonvolatile amine) reacted easily, but anilines gave only 50% of the desired product. This procedure was also based on the safety-catch principle as the sulfone was generated only prior to the cleavage by *m*CPBA oxidation of linker **88.1**. Sodium azide has also been used as a nucleophile to liberate 2,4,5-trisubstituted pyrimidines in 70% yield from polystyrene resin.[305]

b. Kenner Safety-Catch Linker. The safety-catch principle has been used with the acylsulfonamide linker **89.1** devised by Kenner (Scheme 89).[306] Acylsulfonamide-derivatized linkers are resistant to

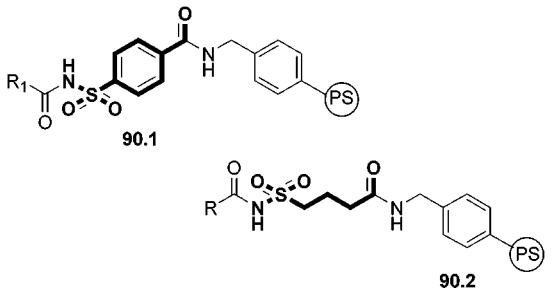
Scheme 89



the acidic conditions (TFA, HBr−AcOH) used for the removal of Boc-protecting groups, while alkaline conditions ionize the acidic NH group (pK_a 2.5), making the amide bond insensitive to attack by OH^- or other nucleophiles. Activation by alkylation using diazomethane makes the amide bond of **89.2** now susceptible to cleavage by amines, leading to the formation of amides **89.3**. Alkaline hydrolysis with 0.5 M NaOH dioxane leads to acids; ammonolysis with 0.5 M NH_3 in dioxane leads to primary amides; while hydrazinolysis with 3 equiv of methanolic hydrazine leads to the corresponding hydrazides.[306]

More reactive linkers **90.1** and **90.2** have been designed by Ellman, Scheme 90.[307−309] Cyanomethylation using ICH_2CN instead of methylation with diazomethane is used for **90.2** to provide a higher cleavage efficiency. Linker **90.2** has been used for peptide synthesis using either a Boc or Fmoc strategy. The resulting peptides were cleaved with various nucleophiles,[309] with an 84% yield being obtained with poor nucleophiles such as aniline when forcing conditions were used (dioxane, 90 °C).

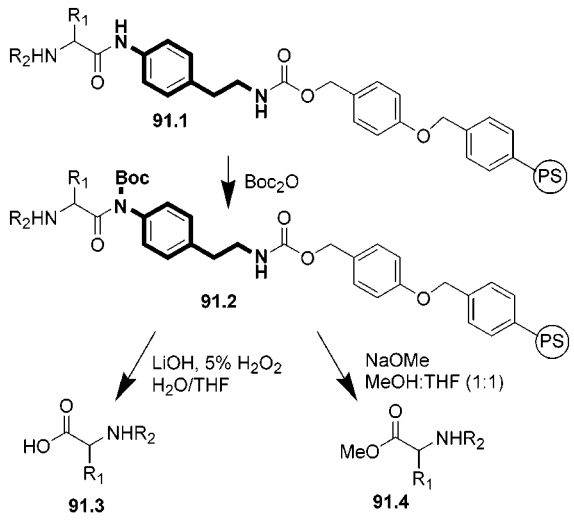
Scheme 90



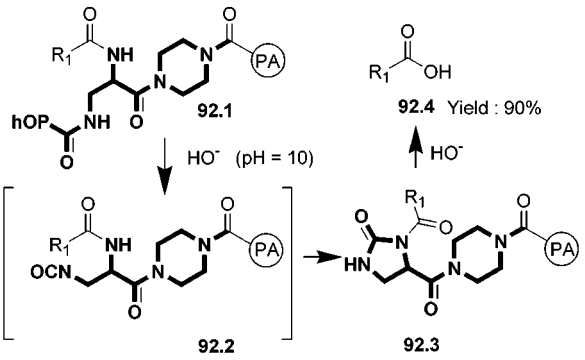
c. Boc-Benzamide Activation. A safety-catch approach was developed by Hulme[310] to cleave amide bonds. Activation of the inert benzamide carbonyl of **91.1** is realized by formation of the Boc carbamate **91.2**. The amide carbonyl thus becomes sensitive to hydrolysis by LiOH, 5% H_2O_2, or alcoholysis with MeONa/MeOH/THF (1:1), thus allowing a normally inert amine bond to be cleaved by mild basic hydrolysis (Scheme 91).

d. Dpr(Phoc) Linker. Because peptides anchored through an ester bond are not always stable under neutral or acidic conditions, Pascal[311] devised a new linker where the peptide was linked through a stable amide bond (Scheme 92). The 2-amino-3-*N*-phenoxycarbonylaminopropionic acid (Dpr(Phoc)) based linker **92.1** was obtained from Boc-asparagine by a Hofmann degradation of the side-chain amide followed by protection of the resulting β-amino group through the phenyloxycarbamate function. Pretreatment of **92.1** with mild alkaline conditions (dilute sodium hydroxide pH 10) afforded the isocyanate intermediate **92.2**, which was trapped by neighboring amide nitrogen, leading to the activated cyclic urea. Cleavage was carried out without isolation of this acylurea **92.3** by treatment with 2 equiv of 0.04 M NaOH in *i*PrOH/H_2O (7:3). A 90% yield was obtained for peptide acids **92.4** after usual workup (extraction and chromatography purification). The corresponding peptide amides were obtained using an aqueous buffer at pH 10 before ammonolysis (*i*PrOH saturated with NH_3, 24 h), giving yields between 60% and 80%.[312]

Scheme 91



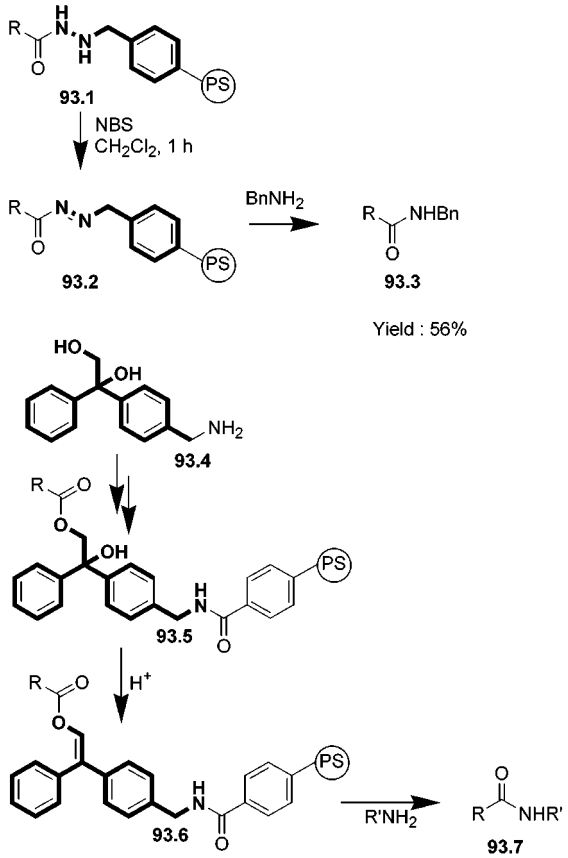
Scheme 92



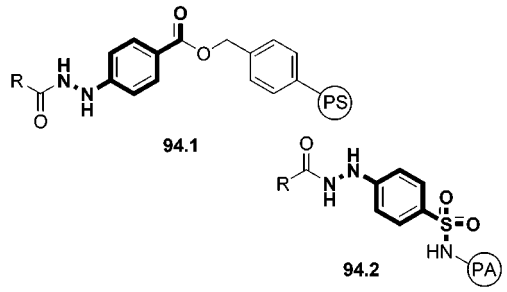
e. Wieland Safety-Catch Linker. Wieland[313a] developed a safety-catch linker based on the benzyl hydrazide functionality. Oxidation of hydrazide **93.1** produces reactive diazene **93.2**, which reacts with nucleophiles to liberate 4-methylpolystyrene, nitrogen, and functionalized acyl derivatives **93.3** (Scheme 93). This procedure was used for peptide synthesis directly by derivatizing Merrifield resin by reaction with hydrazine. Wieland[313b] developed as well the unloaded linker **93.4**. After activation, the activated ester **93.6** can be attacked by amines to release amides.

The 4-carboxyphenylhydrazide **94.1** (Scheme 94) was used to reduce side reactions due to the aliphatic azo group.[313] Activation by NBS oxidation in CH_2Cl_2 followed by reaction with benzylamine in CH_2Cl_2

Scheme 93



Scheme 94

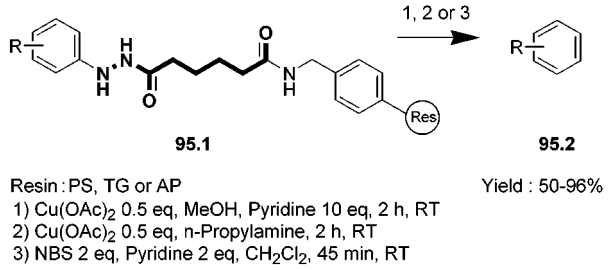


afforded the benzylamide product in 62% yield. Semenov[314] described the use of the phenylhydrazide linker **94.2** where the aryl group was attached to the resin through a sulfonamide group. Upon aerial oxidation in a mixture of DMF, pyridine, aqueous acetic acid, and $CuSO_4$, decomposition of the resulting phenylazo compound took place in situ. A protected tripeptide was obtained in 83% HPLC purity after 16 h.[314]

In a more versatile strategy, linker **95.1** was suggested by Lowe.[315] Attaching the hydrazide group to the resin through the acyl functionality, oxidation, followed by nucleophilic attack would lead to the release of aryl derivatives **95.2** into solution. Waldmann[316] realized this approach, the aromatic products being obtained after oxidation using NBS or $Cu(OAc)_2$ in the presence of a nucleophile (Scheme 95).

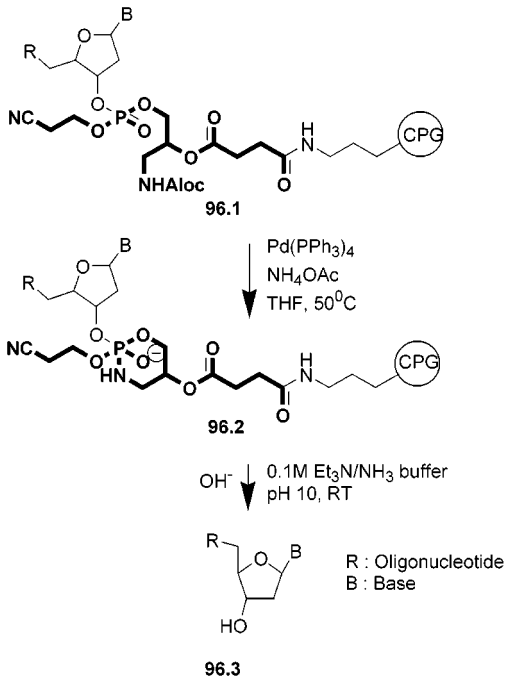
f. Lyttle Safety-Catch Linker. Lyttle[317] devised a safety-catch linker based on the 3-amino-1,2-dihydroxypropane group. After completion of the

Scheme 95



oligomeric synthesis on CPG support, a two-step cleavage procedure from linker **96.1** allows the generation of 3′-hydroxynucleotides **96.3**. Removal of the allyloxycarbonyl group is achieved using Pd(0) at 50 °C followed by treatment with aqueous Et_3N/NH_3 at pH 10, permitting the liberation of product **96.3** (Scheme 96).

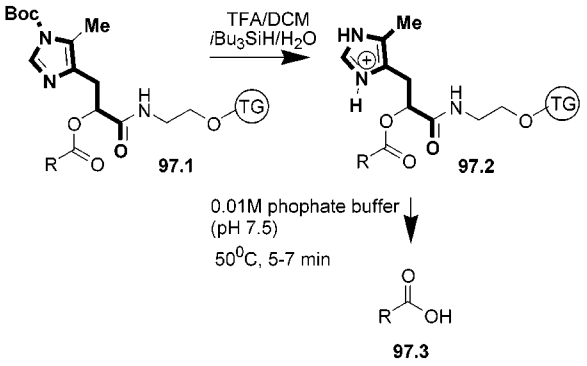
Scheme 96



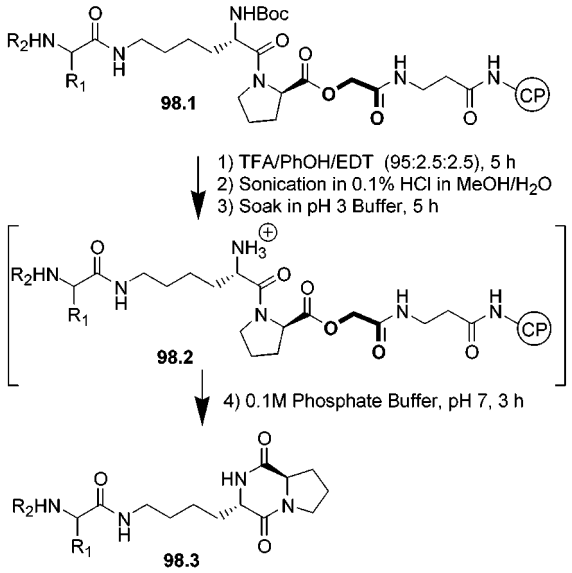
g. Frank Safety-Catch Linker. Intramolecular or general base catalysis of cleavage by an imidazoyl group has been used by Frank.[318] The author described the preparation of the safety-catch linker **97.1**, designed to anchor and release peptide acids **97.3**. Activation by TFA deprotection of the Boc group, followed by treatment with 10 mM phosphate buffer (pH 7.5) for 5−7 min at 50 °C, causes hydrolysis of the ester bond (Scheme 97). Volatile salts such as triethylammonium acetate can be used to allow the generation of peptide acids salt-free.

h. Safety-Catch Linkers Based on DKP Formation. The particular behavior of C-terminal anchored prolines led Geysen[319] to design a linker **98.1** based on DKP formation (Scheme 98). The second residue was lysine where the α-amine was protected with a Boc group and peptide synthesis carried out on the side-chain amine. Boc group removal by acidic treatment followed by neutral buffer (pH 7.5−8.30) generated the peptide **98.3** still bearing the C-terminal DKP moiety.

Scheme 97

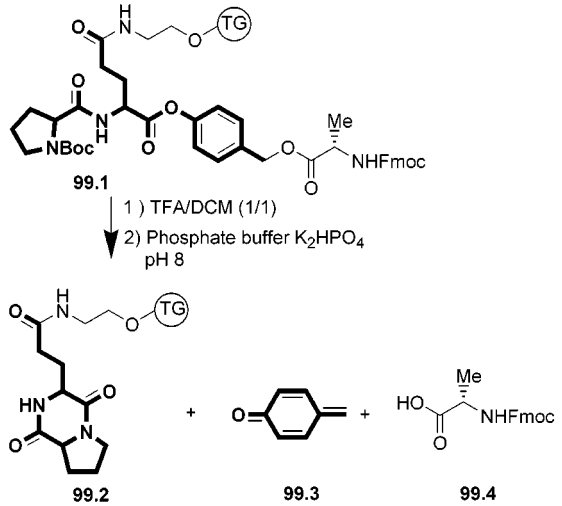


Scheme 98



To obtain the peptide free of this DKP group, Bradley[320] designed a linker **99.1** based on the release of a 4-hydroxyphenylmethyl ester which decomposes, leading to the liberation of the peptide acid **99.4** (although the quinone methide **99.3** is not ideal) (Scheme 99). This strategy allows the release of compounds in buffered aqueous solutions and into agarose gels (particularly suitable for zone diffusion assays and single bead screening).

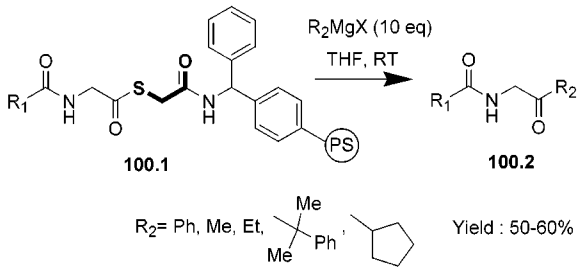
Scheme 99



4. Carbon Nucleophiles

Thioester linkers **100.1** have been cleaved with organometallic reagents to generate ketones (Scheme 100).[262] Reaction with 5−10 equiv of Grignard re-

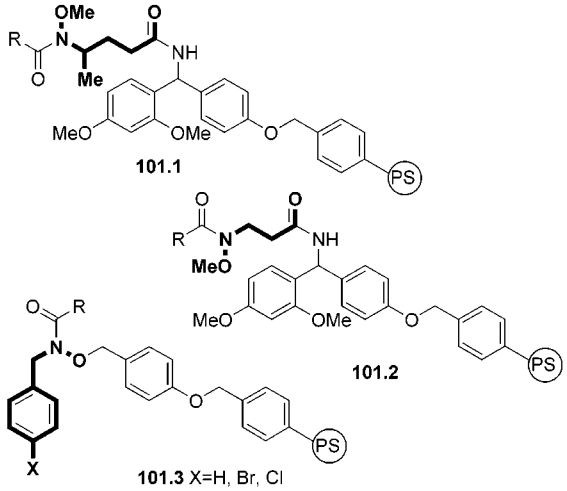
Scheme 100



agents selectively afforded the ketone **100.2**, the tetrahedral intermediate being isolable and washed prior to quenching with a proton source. Ketones were produced in yields of 50−60%.

Weinreb amide-based linkers (Scheme 101) have been developed in order to obtain aldehydes and

Scheme 101

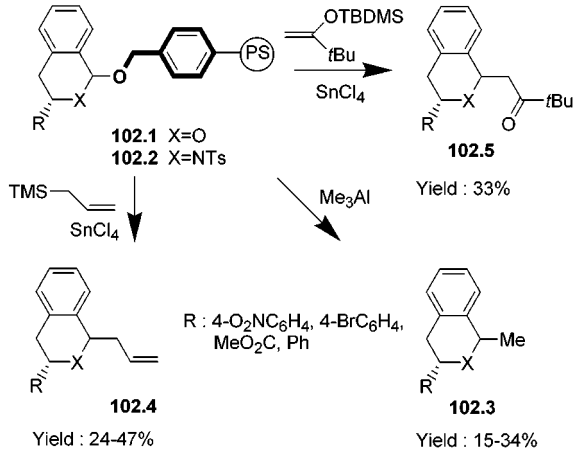


ketones (see section IV.E.4. for aldehyde preparation). However, when the alkyl group bearing the nitrogen is substituted as in linker **101.1**, problems can be encountered and the main products result from N−O cleavage.[321] The best yields were obtained for the nonhindered linker **101.2**, ranging from 16% to 78% for Grignard reagent addition. Salvino[322] described the preparation and reactivity of the Weinreb amide linkers **101.3**. Reaction with EtMgBr afforded ketones in yields of 68% with 97% purity (X = Br).

Acetal **102.1** and aminal **102.2** based linkers have been cleaved with a number of organometallic reagents.[323] For example, 1.5 equiv of $AlMe_3$ was used to introduce a methyl group in 15−34% yield after aqueous workup. Allylsilane/$SnCl_4$ (2.5 equiv) allowed the introduction of allyl groups in 24−47% yields. Ketone **102.5** was obtained by reaction with 2.5 equiv of silylenolether/$SnCl_4$ in 33% yield (Scheme 102).

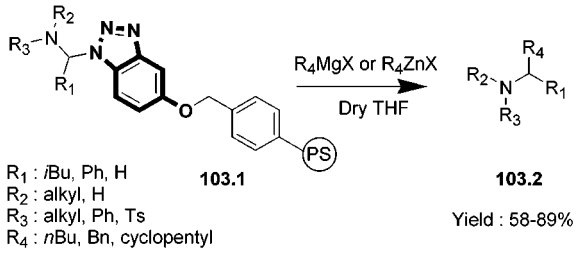
Katritzky[324] and Showalter[325] prepared tertiary amines using a polymer-bound benzotriazole leaving

Scheme 102



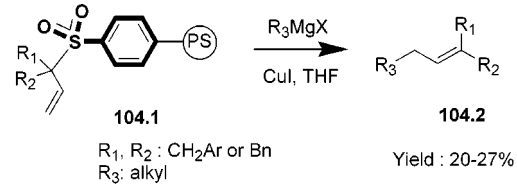
group. Cleavage from resin **103.1** was performed with Grignard reagents in 63−89% yield (*n*BuMgBr, cyclopentylMgCl) or with organozinc reagents (BnZnBr) in 58% yield (Scheme 103).[324]

Scheme 103



Linker **104.1** was devised by Kurth[326] (Scheme 104) to react with cuprate reagents for the release of the

Scheme 104

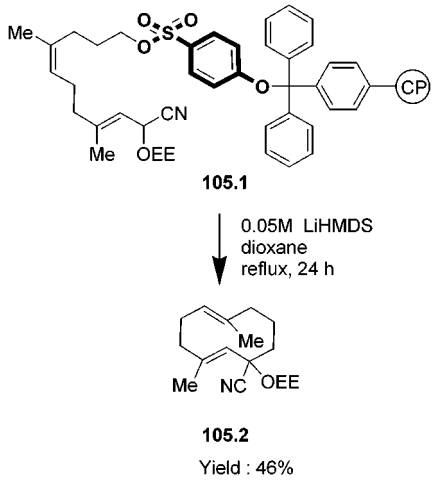


substituted allylic products **104.2** in solution via a S_N2' mechanism. An aqueous workup followed by chromatography was necessary to obtain the products in poor yields (20−27%).

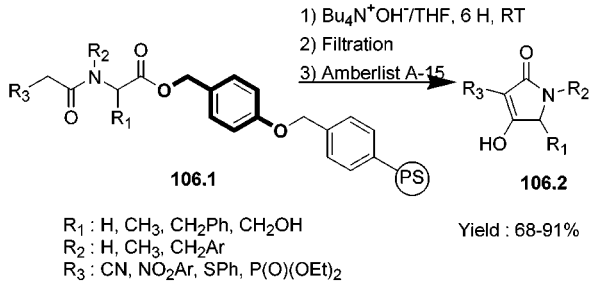
Muscone synthesis has been realized using cyclorelease from sulfonate resin **105.1** (Scheme 105).[327] The nucleophilic carbanion involved in the displacement was obtained by deprotonation of the ethoxyethyl ether-protected cyanohydrin by the action of LiHMDS in dioxane. The compound was then transformed in solution into the corresponding ketone.

Tetramic acids **106.2** are an important class of compounds which can be generated by cyclorelease. This has been achieved by nucleophilic attack of a carbanion α to the amide carbonyl. Bases such *t*BuOK and lithium hexamethyldisilazane (LiHMDS) have been used, but tetrabutylammonium hydroxide was preferred due to its ease of removal (Amberlyst A-15) (Scheme 106).[328] EtONa (0.1 M) has been employed, allowing formation of the corresponding

Scheme 105



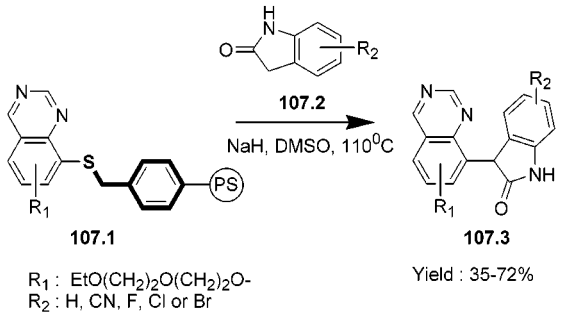
Scheme 106



sodium enolate. A carboxylic acid ion-exchange resin afforded conversion of excess sodium ethoxide into ethanol and protonation of the sodium salt of the tetramic acids.[329]

A polymer-bound arylthio group in linker **107.1** has been successfully displaced by the sodium anion of oxoindoles **107.2**, preformed by reaction with NaH in DMSO (Scheme 107).[330] As precipitation and

Scheme 107

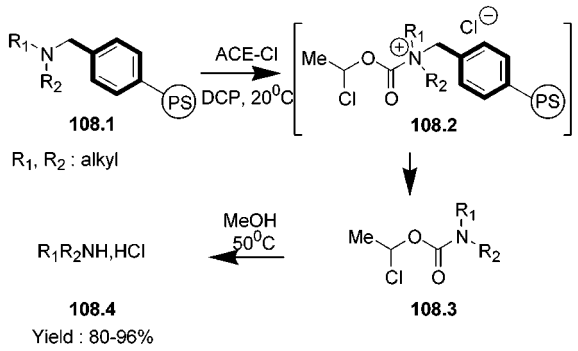


chromatography were not satisfactory, oxoindoloquinazolines **107.3** were finally purified by SPE and obtained in 35−72% yields.

5. Halogen Nucleophiles

Halides have been used to cleave materials from solid supports. For example, chloride ions cleave immobilized *N*-benzyl tertiary amines **108.1** following treatment with α-chloroethylchloroformate (ACE-Cl) and subsequent methanolysis in solution to yield various secondary amines **108.4** (Scheme 108).[331] The secondary amines were obtained as their HCl salts

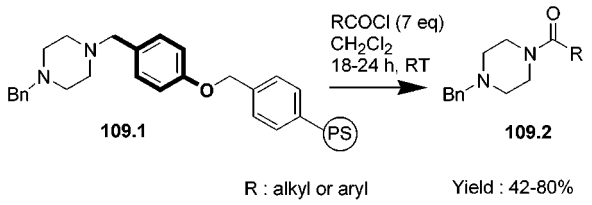
Scheme 108



after simple evaporation in 70−96% yields with purities greater than 80%. This standard solution procedure was quite useful as secondary amines can be easily anchored onto Merrifield resin, thus creating the reactive and labile benzyl tertiary amines **108.1**.

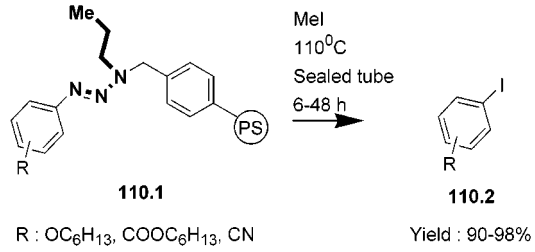
Instead of using ACE-Cl, acetylation can be carried out with acid chlorides to allow the formation of amides.[332] Since reaction with acid chlorides was reported to be quite slow, the author chose to use a linker with an electron-donating group in the para position of the benzylic moiety. After anchoring secondary amines onto the bromo derivative of the Wang linker, cleavage of **109.2** was achieved in 42−80% yields (Scheme 109).

Scheme 109



Methyliodide has been used to activate 1-aryl-3,3′-dialkyltriazenes **110.1** in order to release aryliodides **110.2** (Scheme 110).[333] Severe conditions (neat methyl iodide at 110 °C in sealed tube for 24 h) were required to promote the cleavage.

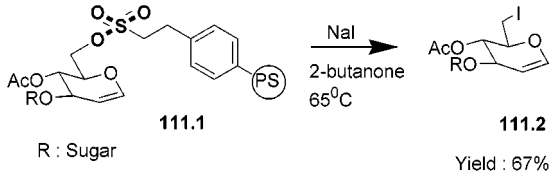
Scheme 110



Nucleophilic displacement by sodium iodide of sulfonate groups allows the preparation of 6-iodosaccharides **111.2** (Scheme 111).[327,334] Other nucleophiles ranging from AcO^- to N_3^- were suitable for the substitution reaction.

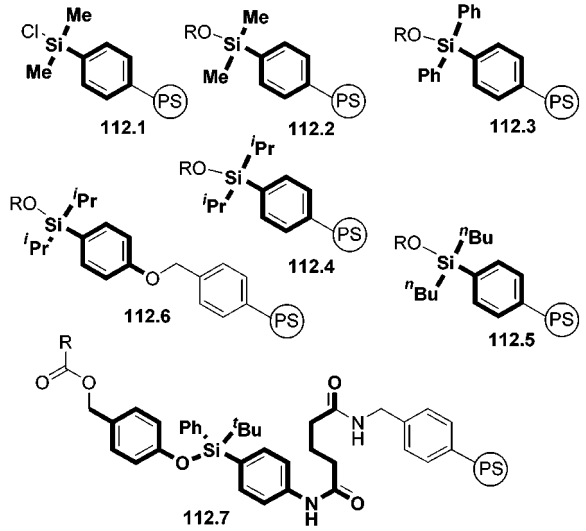
The high thermodynamic affinity of fluorine for silicon allows mild deprotection conditions using fluorine sources such as tetra-*n*-butylammonium fluoride (TBAF) in THF or HF in acetonitrile which are compatible with a wide range of functional groups.

Scheme 111



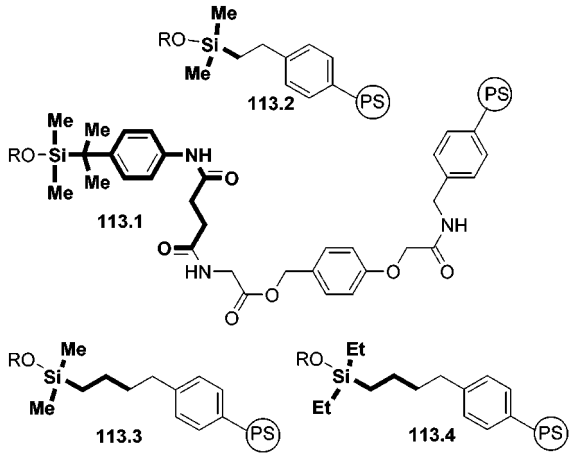
(i) Alkylarylsilyl and Trialkylsilyl Linkers for Alcohol Protection. The chloro precursor **112.1** of protected silyl alcohols was initially prepared by Fréchet[335] by direct lithiation of polystyrene resin and reaction with dichlorodialkylsilane. Polymer-anchored organosilyls were first used as protecting groups by Chan in 1985.[336] The author compared the reactivity of the dimethyl **112.2** and diphenyl **112.3** silyloxy derivatives and found the diphenyl variant was readily cleaved with TBAF in CH_2Cl_2. Danishefsky[337,338] obtained increased yields using the diisopropyl-functionalized polymer **112.4** due to the superior stability of this linkage. Di-*n*-butylsilyl linker **112.5** was preferred[339] for the synthesis of prostaglandin derivatives as the author observed that alcohols linked through the diisopropylsilyl linker did not cleave easily in dilute (17.5%) HF/pyridine, a cleavage reagent compatible with *β*-hydroxyketone derivatives. Preparation of polyketides was realized using the diisopropylsilyl linker **112.6** and cleaved using TBAF, AcOH, and THF at 40 °C for 14 h.[340] Linker **112.7** described by Barany[341] allows the anchoring of Fmoc-amino acids onto aminomethyl resin. One equivalent of TBAF in DMF permitted the cleavage of protected gastrin fragment Fmoc-Glu(O*t*Bu)-Ala-Tyr(*t*Bu)-Gly-OH in 93% yield. A general selection of dialkylarylsilyl linkers is given in Scheme 112.

Scheme 112



Trialkylsilyl linkers can also be cleaved by fluoride to generate the corresponding alcohol in solution (Scheme 113). Anchoring of serine or threonine residues has been achieved onto a dimethyl-*tert*-butylsilyl derivative **113.1** through their hydroxyl

Scheme 113



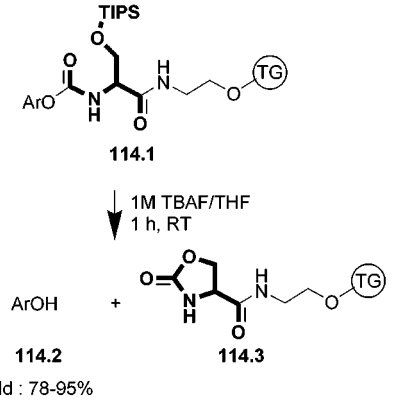
side-chain groups.[342] Cleavage with 50 mM CsF, 50 mM 18-crown-6, and 0.25 M AcOH in THF and purification by chromatography afforded the peptidoglycan product in 73% yield. Dimethylethylpolystyrylsilyl linker **113.2** was found to be reusable and allowed selective anchoring of primary over secondary or secondary over tertiary alcohols.[31] Cleavage was then achieved with $HF/H_2O/CH_3CN$ and resin regenerated by treatment with BCl_3 in CH_2Cl_2. The authors observed that TBAF induced cleavage much more slowly than HF (18 h vs 30min) and suggested that the bulky and ionic nature of the former reagent hindered its penetration into the hydrophobic polymeric matrix. The diethylbutylpolystyrylsilyl linker **113.3** allows deprotection of alcohols with 0.4 M HF/pyridine for 2 h for primary alcohols and 8−12 h at 60−80 °C for secondary alcohols.[154] Electron-deficient aromatic rings were cleaved with 1 M TBAF/THF in 58% (3-quinolinyl) to 80% yields (phenyl). Linker **113.4** can be generated by hydrosilylation from an immobilized silane precursor with Wilkinson catalyst and various aldehydes.[343] The resulting silyl ether **113.4** can be successfully cleaved with 0.4 M HF/pyridine in THF. Excess HF may be scavenged using methoxytrimethylsilane ($MeOSiMe_3$), leading to volatile trimethylsilyl fluoride and methanol.

The serine-based linker **114.1** was reported by Mohan[344] and was used to release phenol derivatives **114.2**. The cleavage of the triisopropylsilyl-protected alcohol was achieved using 1 M TBAF in THF, giving rise to the supported oxazolidinone **114.3** and release of the phenol **114.2** (Scheme 114). Products were obtained in 78−95% yields with purities above 90%, although requiring TBAF removal.

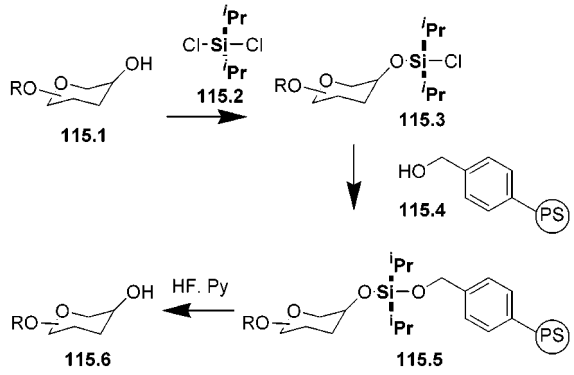
More recently, Danishefsky's team[345] developed another approach involving the preloading of carbohydrate derivatives **115.1** on dialkyldihalosilane **115.2** (Scheme 115). This strategy appears particularly useful for hindered hydroxyl-bearing systems. HF·pyridine and anisole in THF at 0 °C for 3 h or TBAF for a few minutes allowed the release of the glycan derivative **115.6** from bis-etherdialkylsilyl linker **115.5**.

(ii) Fluoridolysis Methods for Release of Aromatic Compounds. Several trialkylsilyl linkers have been employed to release aromatic compounds from solid supports (Scheme 116). Veber[143] successfully cleaved

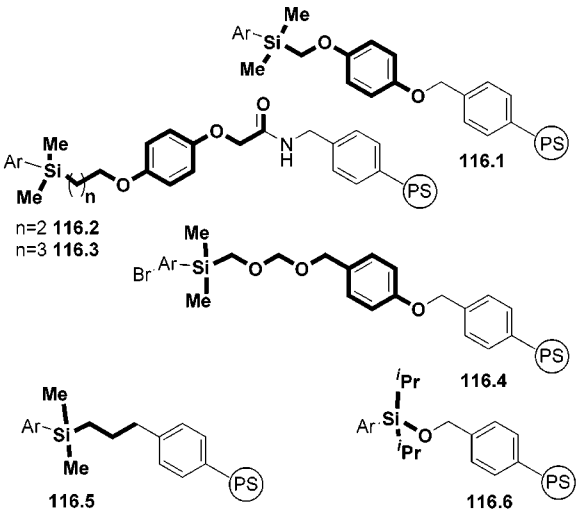
Scheme 114



Scheme 115



Scheme 116



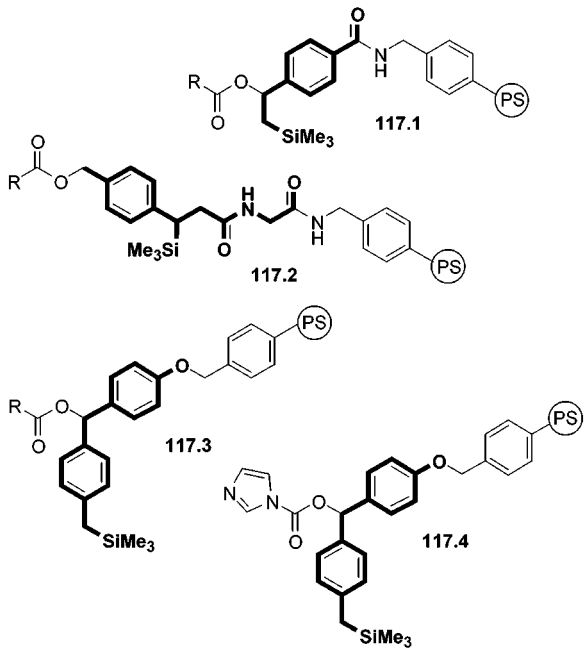
aryl silane linker **116.1** using fluoride. Fluoride proved to be the solution for electron-poor systems when protiodesilylation failed. TBAF or neutral conditions (CsF in DMF/water (4:1) at 110 °C) were found to be satisfactory, whereas HF resulted in undesired cleavages. Linker **116.2**, described by Ellman[145] for the formation of benzodiazepines, was cleaved with anhydrous HF but was found to be stable to TFA. The formation of silicon-containing benzodiazepines was observed for the 3-methylene unit spacer **116.3**.[146] Han[144] observed that bromo derivative **116.4** was resistant to 10 equiv of KF in a refluxing mixture of dimethoxyethane/H_2O containing 18-crown-6. A very electron-poor system could be released with TBAF in THF for 2 h as exemplified

by the preparation of pyridobenzodiazepines obtained in 48−65% overall yields from linker **116.5**.[153]

Arylsilyl ethers **116.6** were cleaved using Stork's conditions[346] of fluoride-induced hydrodesilylation of a siloxane (TBAF in DMF at 60 °C) (Scheme 116).[347] Using this method, both O−Si and C−Si bonds are disrupted. Benzofurans were obtained in 40−57% overall yields (7 steps) following an aqueous workup and filtration through a plug of basic Al_2O_3.

(iii) Silicon Linkers Based on the Trimethylsilylethyl Ester Protecting Group. Particular linkers have been designed to be cleaved by a β-elimination mechanism based on the 2-(trimethylsilyl)ethyl ester protecting group (TMSE) (Scheme 117). Chao[348]

Scheme 117

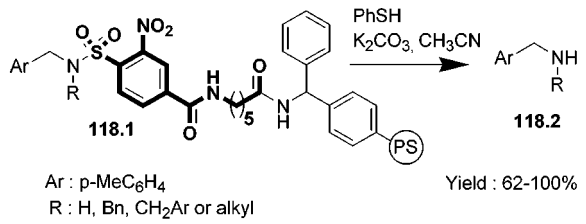


devised the linker **117.1** enabling the preparation of protected peptide fragments using either fluoridolysis or dilute acid cleavage. C-Terminal tryptophans or prolines could be successfully anchored with this linker, and no undesired alkylation or diketopiperazine formation was observed upon cleavage. Various fluoride sources ($LiBF_4$, KBF_4, KF/hexamethylphosphorus triamide, $PhCH_2NMe_3F$ (BTAF) and $PhCH_2NMe_3F$, HF (BTAHF)) were studied. Ramage[349,350] described linker **117.2** and generated a hexapeptide in 62% overall yield after cleavage with 2 equiv of TBAF in DMF, followed by purification by RP-HPLC. Linker **117.3** described by Routledge[351] gave 78% cleavage using either TBAF or CsF. The resin-bound acyl imidazole **117.4** was used to anchor and release amines and alcohol. The best yields of release by fluoridolysis were 88% and 68%, respectively.

6. Thiol Nucleophiles

Linker **118.1** is based on Fukuyama's orthonitrobenzene sulfonamide and has been used to protect amines. Sulfur dioxide and amine **118.2** are generated after treatment with thiophenol (Scheme 118).[352] Thiophenol (2 equiv) is required to achieve good yields (62−100%). A basic extractive workup was

Scheme 118

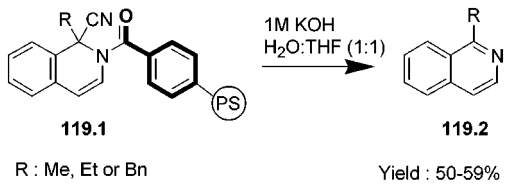


thus needed to remove excess of reagent. A mixture of β-mercaptoethanol and DBU have also been used to cleave this linker.[299]

7. Base-Promoted Cleavage

a. Reissert-Reaction-Based Release. The Reissert reaction provides an elegant way to functionalize pyridine and isoquinoline ring systems by alkylation in the 2-position. The unsubstituted pyridine is activated in two steps by *N*-acylation using an acid-chloride-based resin followed by cyanide addition onto the resulting imminium species. After alkylation using various electrophiles in the presence of base, the hydrolysis of the corresponding Reissert amide complex **119.1** can be carried out with aqueous 1 M KOH in THF/H_2O (2:1). Release of the functionalized isoquinoline ring **119.2** was achieved in 50−59% yields with 95% alkylation after aqueous workup and extraction (Scheme 119).[353]

Scheme 119



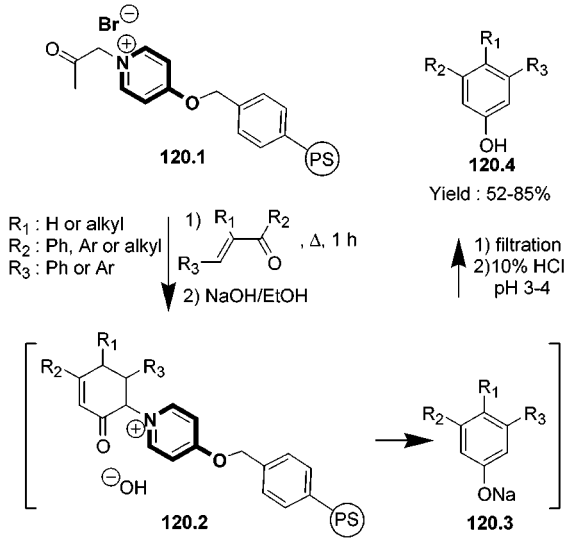
b. Base-Promoted Aromatization. Katritsky[354] developed the preparation of substituted phenols by reacting various α,β-unsaturated ketones and acetonyl groups anchored onto polymer-bound pyridine. The one-pot reaction involves a combination of Michael-addition/annulation reactions followed by elimination and rearrangement into the corresponding phenolates **120.3**, which are filtered from the support and acidified to furnish the phenols **120.4** (Scheme 120).

c. Wittig- and Wittig−Horner-Based Release. Horner−Wadsworth−Emmons reactions using a phosphonoester linked onto TentaGel resin **121.1** can be achieved under basic conditions ($LiBr/Et_3N$) to generate alkenes **121.2** in 45−76% yields (Scheme 121).[355]

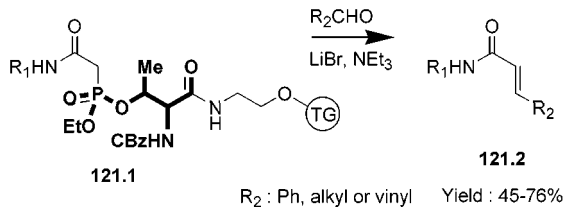
Cyclorelease of macrocycles from the ketophosphonate/aldehyde **122.1** allowed the preparation of muscone precursors **122.2** using K_2CO_3, 18-crown-6 in benzene at 65 °C in 35−65% yields (Scheme 122).[356]

Benzylphosphonium derivatives **123.1** were prepared from commercially available polymer-bound triphenylphosphine. Cleavage could be obtained with sodium methoxide and excess aldehyde in methanol affording the olefinic product **123.2** as a 3:1 *E*/*Z* mixture in 82% yield.[357] Removal of the excess

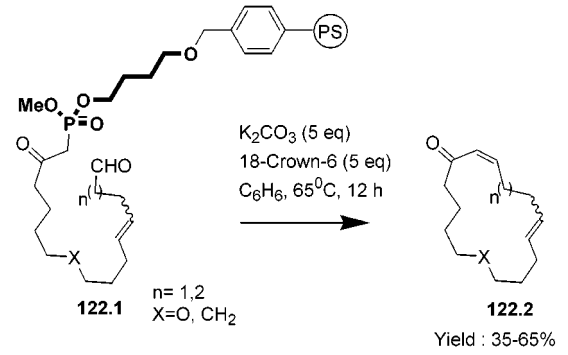
Scheme 120



Scheme 121



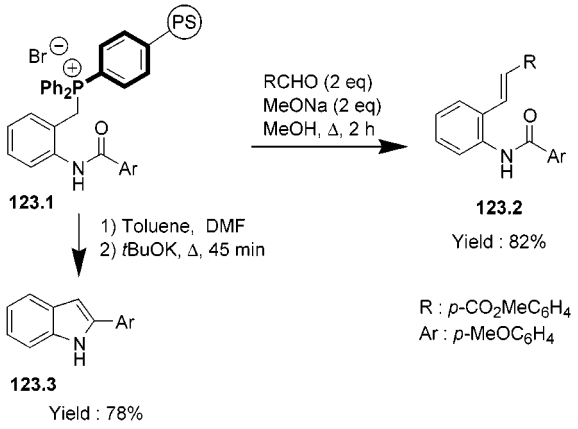
Scheme 122



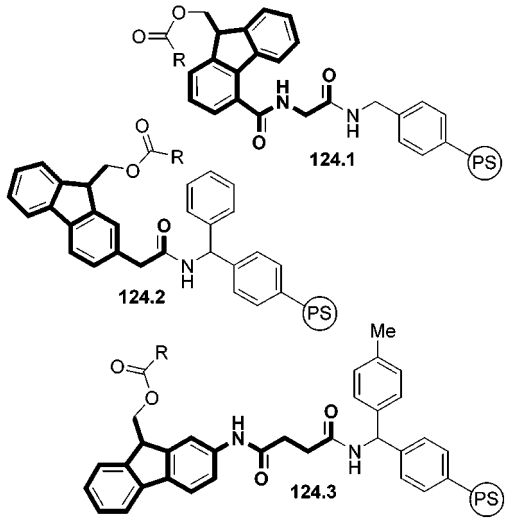
aldehyde was achieved through formation of an insoluble imine with aminomethyl resin. The toluene derivative was obtained in 81% yield when the hydrolytic cleavage was performed in the absence of any aldehyde. Cyclorelease of **123.3** by means of an intramolecular Wittig reaction involving the relatively unreactive amide carbonyl was achieved under anhydrous conditions using *t*BuOK as the base (Scheme 123).

d. Release Based on *β*-Elimination. A fluorene-based linker **124.1** (Scheme 124) was developed by Mutter[358] for the solid-phase synthesis of protected peptides. This linker exhibits properties comparable to the well-known Fmoc-protecting group. It has been found to be completely stable in 1 M HCl/AcOH, TFA/DCM (1:1), neat TFA, and 30% HBr/AcOH and cleavable in 15% piperidine, Et_2NH, morpholine, or Et_3N in DMF. The main drawback is that this linker was sensitive to DIPEA, which was required for neutralization after acidic deprotection during Boc-SPPS (9% cleavage after 3 h treatment with 10%

Scheme 123



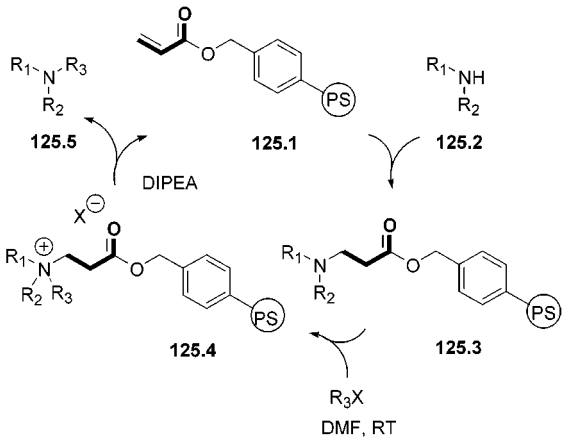
Scheme 124



DIPEA in DMF). The stability of linker **124.2** (Scheme 124) was found to be better.[359] Albericio[360,361] claimed some improvements with linker **124.3** (Scheme 124), the electron-donating *N*-acylamido group being crucial to the increased stability. Quantitative cleavage by *β*-elimination was achieved with 20% morpholine in DMF or 10% piperidine in DMF.

The REM (regenerated resin and Michael addition) linker **125.1** was designed to generate tertiary amines using a Hofmann-elimination reaction (Scheme 125).[362] Michael addition of a secondary amine onto an

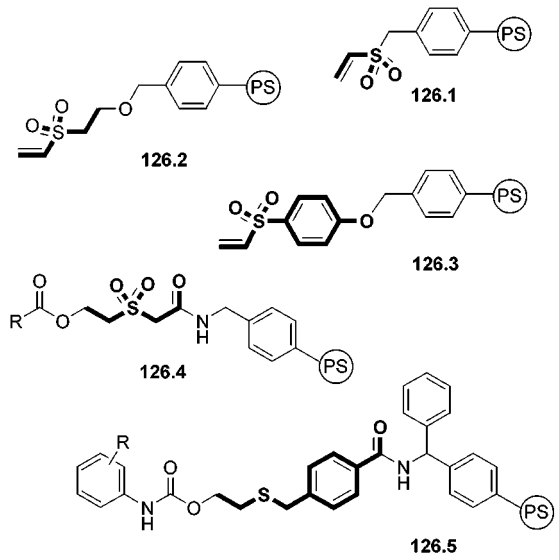
Scheme 125



acrylate resin gives a resin-bound secondary amine which can be quaternarized by a limited number of reactive halides such as methyl, allyl, or benzyl bromides or iodides. DIPEA allows elimination and regeneration of the resin. This resin can be used several times, although it would be wise to only do this for a common compound. The nature of the chemistry ensures that the purity is high (>95%), but SPE purification is often performed.[363] A two-resin system was used by Murphy[364] to achieve cleavage and trap salts. In this case, simple filtration and evaporation provided pure products without the need of an aqueous workup. Amberlyte basic ion-exchange resin or deprotected Rink amide resin were equally efficient. Ethylpiperazine-based resin could be used in a similar manner.[365]

Vinyl sulfones **126.1**[366] and **126.2**[367] (Scheme 126) were employed as alternative REM linkers by two

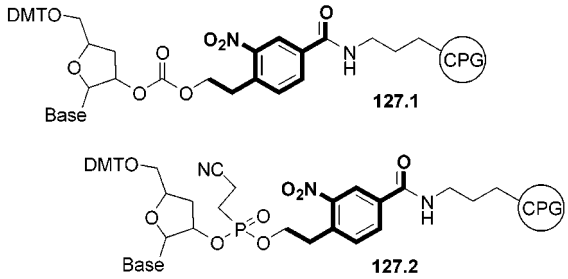
Scheme 126



different groups. Linker **126.3** affords, in theory, a wider range of chemistries than the REM benzyl ester system since the aryl sulfone derivatives do not have acidic benzylic protons or a labile ester which could be involved in side reactions. Vinyl sulfone linker **126.4** was created in order to release peptide acids with the first residue anchored prior to attachment to the solid support.[368] After completion of the synthesis, Leu-enkephalin was generated in 54% or 60% overall yields using either Boc or Fmoc chemistries. Cleavage was achieved using dioxane/MeOH/4 M NaOH for 30 min followed by re-acidification, extraction, and crystallization. Echeverria[369] developed linker **126.5** based on the safety-catch principle. A 2-mercaptoethanol-derivatized resin allowed the anchoring of phenylisocyanate by carbamate formation. Activation of the resin by treatment with *m*CPBA followed by elimination with 10% aqueous ammonia promoted elimination of anilines.

β-Elimination was also found with 2-(2-nitrophenyl)ethyl (NPE) linkers (Scheme 127). Release of 3′-hydroxyoligonucleotides and 3′-phosphateoligonucleotide from CPG support was achieved through carbonate or phosphate linkers **127.1** and **127.2**, respectively.[370] The conditions used were either 0.5 M DBU in

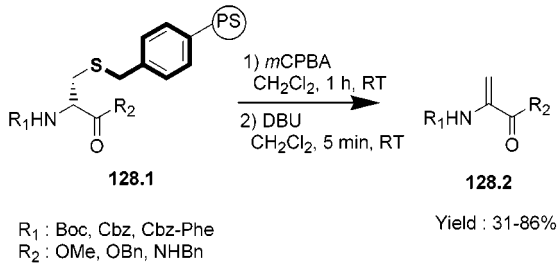
Scheme 127



dioxane, pyridine for 1 h, and ammonia for 5 h at 55 °C or 20% piperidine in DMF for 3 h. Fortunately the linkage was found to be resistant to 40% Et_3N in pyridine for 16 h, conditions commonly used to remove the 2-cyanoethyl phosphate protecting group.

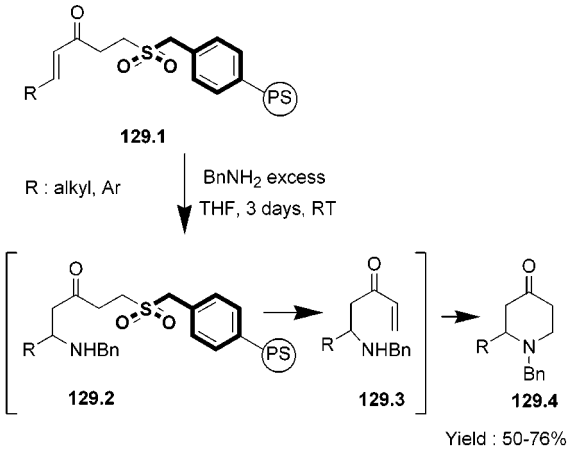
Dehydroalanine derivatives have been synthesized using this methodology.[371] Cysteine anchored onto Merrifield resin through the side chain gave the sulfide **128.1**. After modification of both C- and N-termini, *m*CPBA oxidation and β-elimination promoted by DBU furnish the dehydroalanine derivatives **128.2**. Aqueous workup and concentration yielded the compound in 31−86% yields with purities above 95% (Scheme 128).

Scheme 128



Polymer-bound sulfones **129.1** have also been involved in heterocyclization chemistry (Scheme 129).[372] Benzylamine acts both as a nucleophile and

Scheme 129



as a base promoting a Michael addition in **129.1**, inducing elimination of the sulfone group followed by a second Michael addition on **129.3**. Filtration, evaporation, and chromatography lead to formation of 2-substituted-*N*-benzylpiperidin-4-ones **129.4** in 50−76% overall yields.

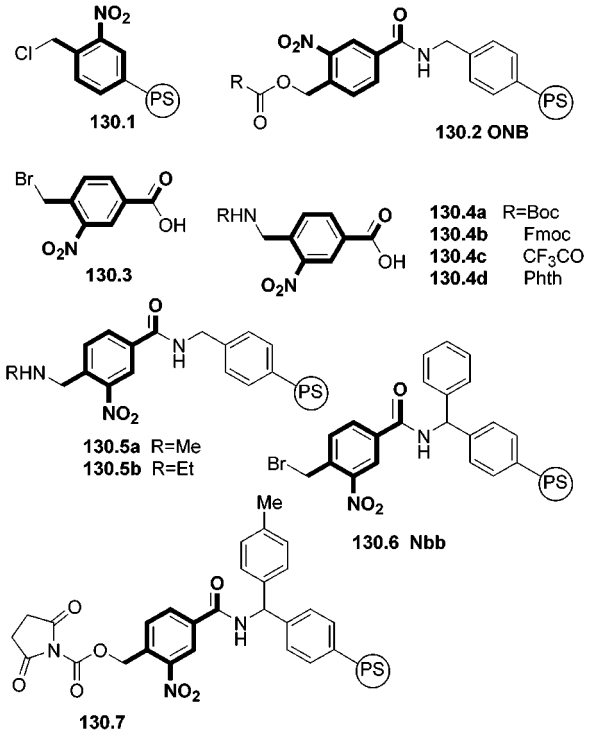
C. Photocleavable Linkers

Photolysis offers a mild and potentially orthogonal method of cleavage that takes place under neutral conditions. Photocleavable protecting groups have been used widely in carbohydrate chemistry, nucleotide and peptide synthesis. Their application and generalization toward nonoligomeric syntheses has been limited by the fact that many small organics absorb light or are sensitive to the irradiation needed to cleave the linker, as well as concerns about the rates of photolysis and the yields. The light used should only be absorbed by the linking group and should not affect other groups if possible. The main problem is how to achieve good yields for cleavage. Nevertheless, important work has been done and continues with these integral or nonintegral linkers.

1. o-Nitrobenzyl-Based Linkers

a. ONB Linkers. Rich[373] first used light-cleavable linkers preparing an *o*-nitrobenzyl (ONB) linker **130.1** by nitration of 1% cross-linked chloromethylated polystyrene resin. Unfortunately, as a result of over nitration, moderate yields (62%) were obtained for a tripeptide due to the poor swelling properties of the resin in low-polarity solvents. Another *o*-nitrobenzyl-based linker **130.2** was prepared by coupling 3-nitro-4-bromomethylbenzoic acid **130.3** (Scheme 130) onto an aminomethylpolystyrene resin

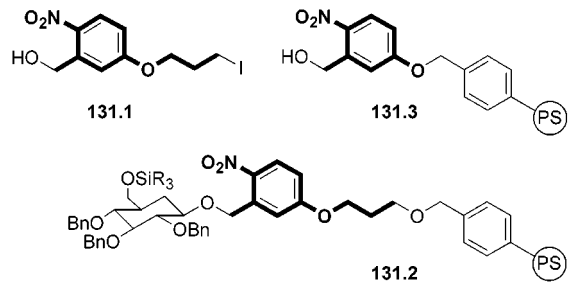
Scheme 130



followed by esterification.[25] This linker was found to be suitable for the synthesis of Boc-protected peptides with release by irradiation at 350 nm. These conditions were orthogonal to acid protecting groups and did not decompose aromatic amino acids. After 18−24 h of photolysis in methanol in a flask surrounded by a jacket containing a 40% $CuSO_4$ solution (used to filter out wavelengths below 320 nm), a protected decapeptide was purified by gel filtration and crystallization and obtained in 64% overall yield. The corresponding Boc-amino derivative **130.4a**[374] (Scheme 130) was prepared in order to generate peptide amides upon photolysis as well as Fmoc **130.4b**, trifluoroacetamido **130.4c**, and phthaloyl **130.4d** derivatives (Scheme 130).[375] *N*-Methyl- and *N*-ethylamide terminal peptides were generated from linkers **130.5a,b** using Boc-amino acids.[376,377] Albericio[9,378] extensively used the Nbb linker **130.6** made from 4-bromomethyl-3-nitrobenzoic acid **130.3** attached to a BHA linker (Scheme 130) for the anchoring and release of peptide acids. The author noticed that for this particular linker, cleavage employing sonication and the right choice of solvent (best results obtained with a mixture of CH_2Cl_2/trifluoroethanol) leads to better yields. The structure of the first amino acid seemed to be more important than the length of the peptide for improved photocleavage yields. Succinimidyl derivative **130.7** was used for anchoring alcohols or phenols.[57]

Replacement of the carboxamide group situated in the 3-position by an alkoxy group in the 4-position affords the unloaded linker **131.1**.[379] Glycosidation then attachment to hydroxymethylpolystyrene resin provided the first steps for a general solid-phase synthesis of oligosaccharides using a photocleavable linker **131.2**. After irradiation in THF at 25 °C, 95% yields were obtained. An analogous phenol linker was attached directly onto Merrifield resin to afford linker **131.3** (Scheme 131).[380]

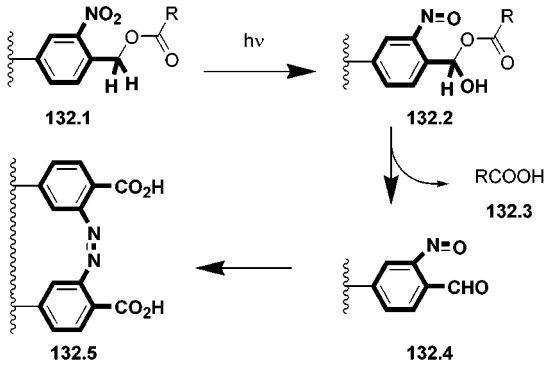
Scheme 131



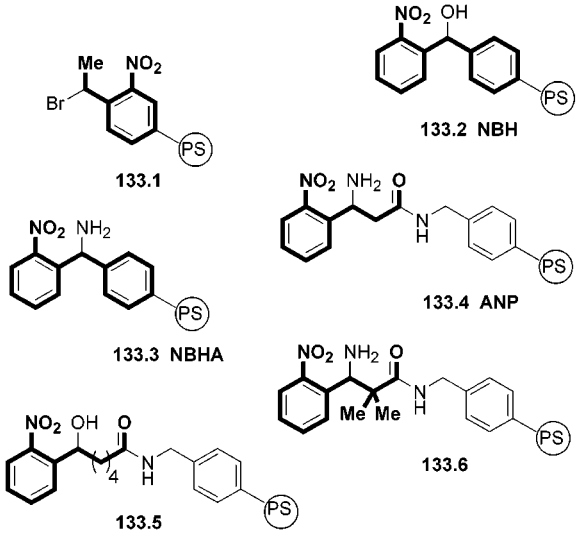
b. α-Substituted ONB Linkers. A new class of nitrobenzyl linkers has been sought after to increase the yield of the photocleavage reactions. The mechanism of photocleavage involves the conversion of the nitro into a nitroso group and insertion of an oxygen atom into the C−H bond located at the benzylic position. The released product **132.3** is accompanied by the *o*-nitrosobenzaldehyde photoproduct **132.4**, which is then further transformed, through cross-linking, into the azobenzene-2,2′-dicarboxylic acid **132.5** which, having a deep red color, acts as an internal light filter, thereby reducing cleavage yields as well as cross-linking the resin and preventing compound diffusion (Scheme 132). The aldehyde can also trap out the amine product.

This dimerization reaction can be reduced/eliminated by using α-substituted *o*-nitrobenzyl groups.[381,382] Pillai[17] prepared the *o*-nitro-(α-methyl)-bromobenzyl linker **133.1** (Scheme 133) by functionalizing polystyrene resin with acetyl chloride/$AlCl_3$, reducing the resulting ketone, and bromination of the

Scheme 132



Scheme 133

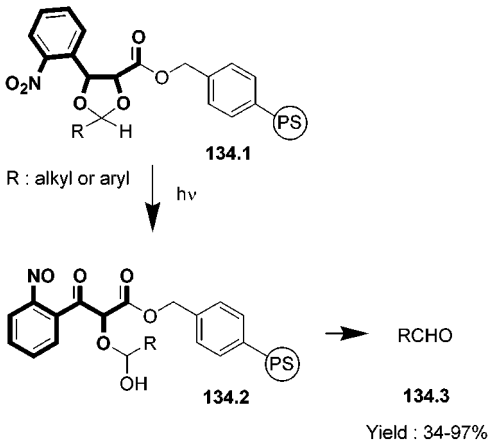


resulting alcohol. The nitro group was incorporated by nitration of the linker. However, overloading of the nitro groups caused swelling difficulties, which caused problems to be encountered during synthesis. Pentapeptides were obtained in modest yields (40−50%).

Nitrobenzhydryl linker **133.2** (NBH) and nitrobenzhydrylamine linker **133.3** (NBHA) (Scheme 133) can be seen as *o*-nitro-α-phenyl-substituted benzyl linkers and are useful for the synthesis of protected peptide acids[383] and amides.[384] Higher yields are obtained due to better photocleavage efficiency compared to *o*-nitrobenzylamino linkers. Another possibility is the 3-amino-3-(2-nitrophenyl)propionyl (ANP) linker **133.4** (Scheme 133).[385] Peptide amides were obtained in 80% yield with this linker compared to 40% with the *o*-nitrobenzylamine linkers **130.4**−**130.5** after cleavage in water/methanol (4:1) at 365 nm for 20 h. The alcohol-derivatized linker **133.5** (Scheme 133) permits the synthesis of peptide acids and sugars upon photolysis in THF/water at 365 nm.[386] The authors compared their linker **133.5** with the amide-releasing ANP **133.4** and obtained similar cleavage rates. In a comparison study for the release of Fmoc-Arg(Ts)-OH, these two linkers were found to be better than the α-methyl-*o*-nitroveratyl-based linker **135.3** and far better than the classical *o*-nitrobenzyl linker (ONB) **130.2** used for peptide acid synthesis. In addition, ANP **133.4** is sensitive to *β*-elimination side reactions which led to the premature release of the carboxamide, giving a low final yield. Stability was much improved using linker **133.5** bearing a four methylene chain spacer or for the dimethyl-substituted linker **133.6** (Scheme 133).[387]

c. Photocleavable Linker for Aldehydes. Nitrophenylethyleneglycol-based linkers **134.1** were developed from the linkers described earlier for the release of aldehydes (Scheme 134).[388] They are cleaved

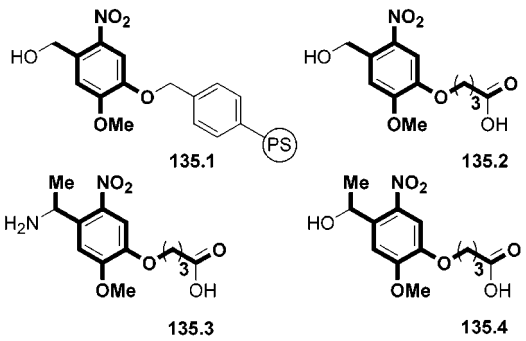
Scheme 134



in an analogous manner, leading to the 2-nitroso hemiacetals **134.2** which undergo spontaneous cleavage to give the carbonyl products **134.3** and resin-bound α-hydroxy-2-nitrosoacetophenone. Irradiation of polystyrene-supported nitroaryldioxolanes **134.1** for 7 h in benzene with a mercury lamp afforded aliphatic aldehydes in quantitative yield and aromatic aldehydes in 34−63% yields.

d. Nitroveratryl Linkers. 6-Nitroveratryl alcohol-based linker **135.1** (Scheme 135) incorporates ad-

Scheme 135

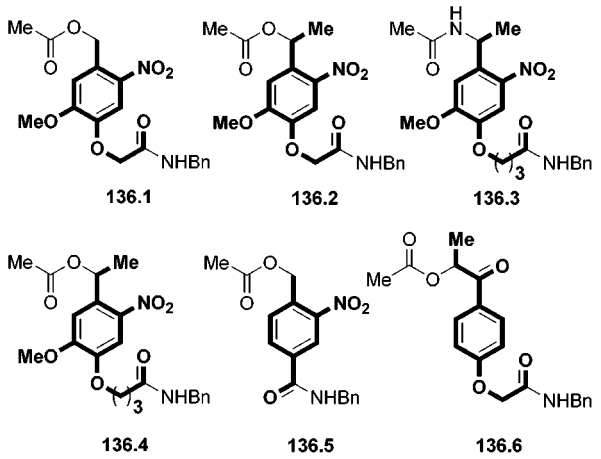


ditional alkoxy groups onto the benzene ring, which serves to enhance the cleavage rate. Although it constitutes one of the first examples of light-sensitive linkers and was described by Zehavi,[389] it became fashionable only later on when stability problems where solved by addition of the methyl group in the α-position. Zehavi[389] attached 6-nitrovanilin to a 2% cross-linked Merrifield resin through an ether bond and performed oligosaccharide synthesis after reduction of the aldehyde group. In this way the alcohol-based linker **135.1** was produced (Scheme 135). Irradiation at wavelengths above 320 nm allowed the release of product. Final cleavage yields were reported to be 10−30%, and release was found to be

much slower compared to a solution model. Photolytic release of oligonucleotides was achieved in 92% yield using unloaded linker **135.2** attached to CPG.[390,391] Following the example of Pillai, Holmes[392] incorporated a methyl group into the benzylic carbon and formed the amine-unloaded linker **135.3** (Scheme 135), which was used to release 4-thiazolidinones in 95% purity and more than 90% yield by irradiating for 3 h at 360 nm. *N*-Unsubstituted *β*-lactams were prepared using an Fmoc derivative of unloaded linker **135.3** on TentaGel resin.[393] Gennari[394] obtained better yields (77−86%) and no byproducts using this linker for the synthesis of vinylogous sulfonamidopeptides compared to the *o*-nitrobenzylamine linker **130.4a**. Both syntheses were carried out on TentaGel resin, and cleavage required 1−4 days in methanol and irradiation at 354 nm. The corresponding hydroxy-unloaded linker **135.4** (Scheme 135) was successively prepared by Teague,[395] Holmes,[396] and Austin.[397]

Holmes[396] compared and examined the kinetics of photolytic cleavage of acetic acid at 365 nm using solution models of phenacyl, *o*-nitroveratryl, and *o*-nitrobenzyl photolabile derivatives (Scheme 136).

Scheme 136

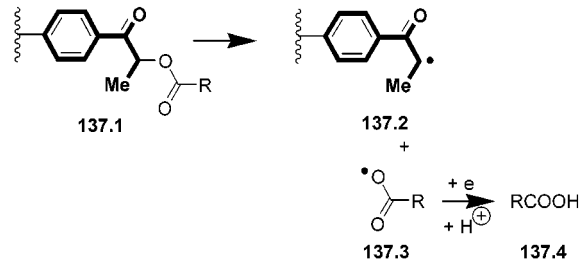


o-Nitroveratryl models **136.1**−**136.4** were found to be superior to the ONB analogue **136.5**. Good results were seen with the α-methyl-*o*-nitroveratryl alcohol-based compound **136.2**, and introduction of the additional benzylic methyl group increased the rate of cleavage by 5- to 7-fold compared to model **136.1**. It was found that the amide model **136.3** cleaved 3−7 times faster than the ester **136.4**, although unfortunately the real cleavage efficiency, as measured by acetic acid release, was not determined. Using linker **135.4** on the solid phase, the author noticed that support-bound photolysis was considerably slower than that in solution due to light scattering, shielding, and shadowing effects from the linker as well as solvation and swelling effects of the support. Water or organic solvent could be used, and amine-based scavengers also improved the yield. In addition, Holmes compared these models with the phenacyl **136.6** and found it to be less efficient even compared to the ONB **136.5**. Half-lives of compounds **136.6, 136.5**, **136.1**, **136.4**, **136.2**, and **136.3** are, respectively, 348, 14, 13, 2.9, 1.7, and 0.7 min in phosphate-buffered saline (PBS) pH 7.4.

2. Phenacyl Linkers

Wang[22] claimed an increase in photolysis yield for the α-methylphenacyl linker **137.1** (Scheme 137)

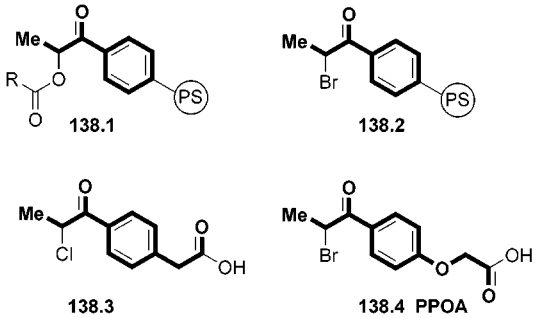
Scheme 137



compared to the ONB linker **130.2**. The phenacyl group has low-energy excited states which make the phenacyl ester photolytically labile. The mechanism has been established to be a simple radical scission of the carbon−oxygen bond. The presence of a methoxy group in the para position and α-substituents increase cleavage rates.[398,399]

The bromine- derivatized precursor **138.2** can be obtained simply by functionalization of 2% polystyrene resin with 2-bromopropionyl chloride/$AlCl_3$ under Friedel−Crafts conditions. This linker **138.1** has been used in many peptide applications. A 2- to 5-fold increase in cleavage rate was found for the release of CBz-Lys(CBz)-Phe-Phe-Gly-OH tetrapeptide (half-life of approximately 5 h) compared to the polymer-bound *o*-nitrobenzylester **130.2** under similar conditions.[22] The cleavage of a fully protected hexapeptide by irradiation at 350 nm in DMF was realized in 84% yield after 3 days and purification by gel filtration on Sephadex LH-60.[400] In the case of photolabile linkers, photolysis reactions and radical pathways are often solvent dependent and water and alcohol, which are sometimes chosen, require the use of appropriate resin.[377] Tjoeng[401] gave a preparation of the chloro derivative **138.3** (Scheme 138). In 1985,

Scheme 138



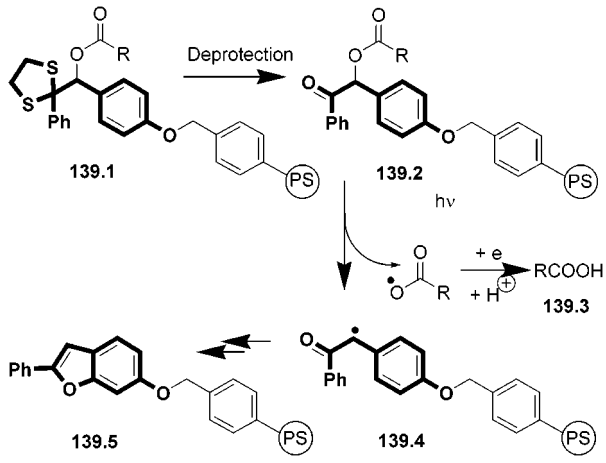
Mutter[402] prepared the PPOA-unloaded linker (4-(2-bromopropionyl)phenoxyacetic acid) **138.4** (Scheme 138). The author invoked increased lability toward photolytic conditions due to the bathochromic shift due to phenoxy substitution. A pentapeptide was cleaved off the support by irradiation at 350 nm in 71% overall yield. Gauthier[403] coupled this unloaded linker **138.4** onto a BHA-derivatized resin and prepared octapeptides on a 10−40 mmol scale. Irradia-

tion was performed at 350 nm in DMF/ethanol for 18 h. Yields of 85% with HPLC purities greater than 95% were found after filtration, concentration of the filtrate, and precipitation. Nevertheless, phenacyl linkers suffer some drawbacks as the carbonyl group is quite reactive and can participate in undesired cyclizations as well as being sensitive to mild nucleophilic reagents. Surprisingly, they did not perform particularly well in the comparative study made by Holmes.[396]

3. Alkoxybenzoin Linkers

These essentially form an extension of the previous section with the replacement of the methyl group by a phenyl group. Benzoin esters **139.2** can be photochemically cleaved to give the 2-phenylbenzofurans **139.5** and acids **139.3**, respectively (Scheme 139). The

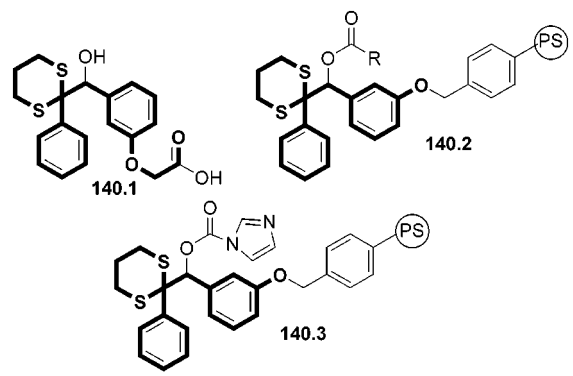
Scheme 139



formation of the furan ring is facilitated by the presence of alkoxy groups.[404] Such compounds have been found to be very sensitive to standard laboratory lighting and a protected form is required. The use of the Corey−Seebach dithiane leads to the synthesis of dithiane-protected benzoins **139.1** in one step from the aldehyde precursors and constitutes a safety-catch approach as the group is activated only after dithiane deprotection (Scheme 139).

Chan[405] developed the benzoin-ester-unloaded linker **140.1**, allowing the release of peptide acids (Scheme 140). Removal of the dithiane was realized using bis(trifluoroacetoxy)iodobenzene in acetonitrile/water (9:1). Similar 3-alkoxy-protected benzoin linkers **140.2**

Scheme 140

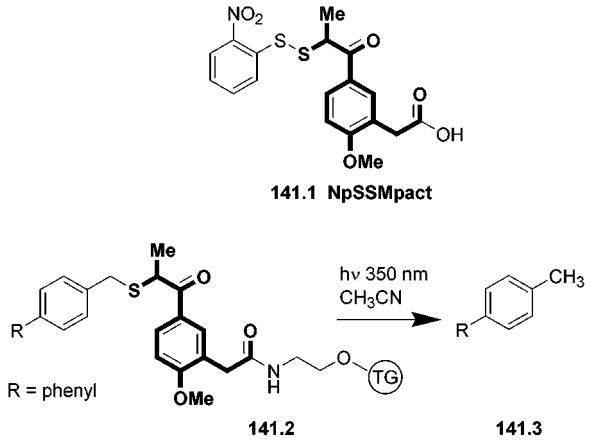


and **140.3** (Scheme 140) were prepared by Balasubramanian[406] for the release of acids and alcohols, respectively. Deprotection of the carbonyl function was attempted on solid support with various oxidizing agents. Treatment with mercury perchlorate proved to be slightly superior to periodic acid or bis(trifluoroacetoxy)iodobenzene, and exposure to irradiation at 350 nm in THF/methanol (3:1) allowed the release of the acid. A recent full paper[407] indicated that the linker matrix does not influence the photochemical reaction as similar half-lives were obtained using polystyrene or TentaGel resins. Linker loading proved to be important. A decrease in loading from 0.59 to 0.26 mmol/g improved the rate of cleavage (half-lives of 6.7−2.6 min). Attempts to functionalize the linker with either electron-donating groups or electron-withdrawing groups on both phenyl groups surprisingly failed to improve the cleavage efficiency compared to the 3-alkoxybenzoin linker **140.3**. In addition, the authors showed that the dithiane group could be removed by alkylation using methyltriflate.

4. NpSSMpact Linker

The homolytic photochemical cleavage of supported benzylthioethers allows the generation in solution of the tolyl derivatives. Sucholeiki[408,409] designed the unloaded linker **141.1** (NpSSMpact) (Scheme 141)

Scheme 141

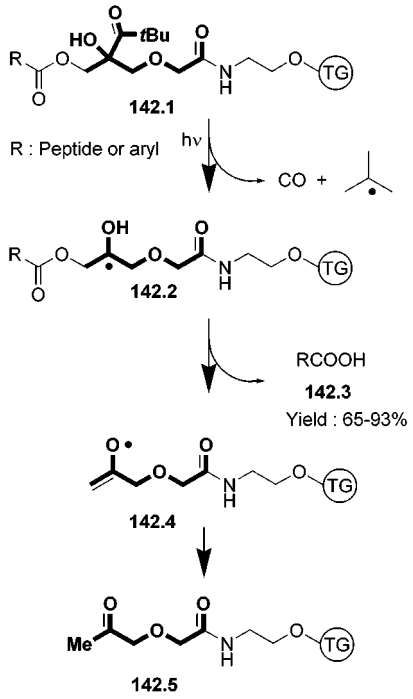


which could be anchored onto the resin and deprotected by reduction to generate the free thiol. This thiol group could undergo functionalization by alkylation with various benzylbromides, leading to **141.2** (Scheme 141). Upon irradiation, tolyl formation can take place. However, this linker suffers from major drawbacks, as release seems to be restricted to *p*-phenyltolyl products, giving them in 33−58% yields after irradiation at 350 nm in acetonitrile. In addition, some benzaldehyde byproducts could also be found when deoxygenation of the cleavage solvent was not performed.

5. Pivaloylglycol Linker

Giese[410] devised an original linker **142.1** (Scheme 142) based upon the radical-induced β-C,O bond cleavage of a pivaloylglycol group. Upon irradiation, an α-hydroxyalkyl radical **142.2** is generated via a Norrish type I reaction with release of carbon mon-

Scheme 142

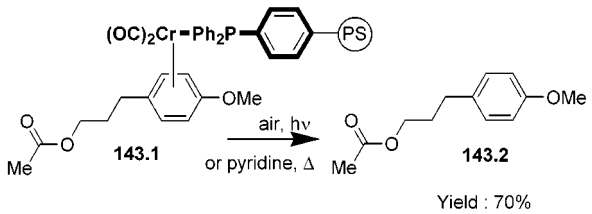


oxide and a *tert*-butyl radical which leads to isobutylene. Elimination then takes place where the glycerol radical is converted into an enolate radical **142.4** and a carboxylic acid **142.3** is released. (Scheme 142). The authors investigated different reaction parameters and found that the reaction was not solvent-dependent, while selection of wavelength was crucial. Aromatic carboxylic acids and peptides were obtained in yields of 65−93%. Comparison with the *o*-nitroveratryl-based linker **135.4** showed that photolysis of the pivaloyl linker was 3−4 times faster.

6. Miscellaneous Photolytic Protocols

Chromium arene complexes have been attached to polymer-supported triphenylphosphine through π-complexation.[411] Oxidation by air under irradiation conditions allows the release of aryl **143.2** in 70% yield (Scheme 143) in a truly traceless manner. Heating in pyridine can also be employed to cleave this linker.

Scheme 143



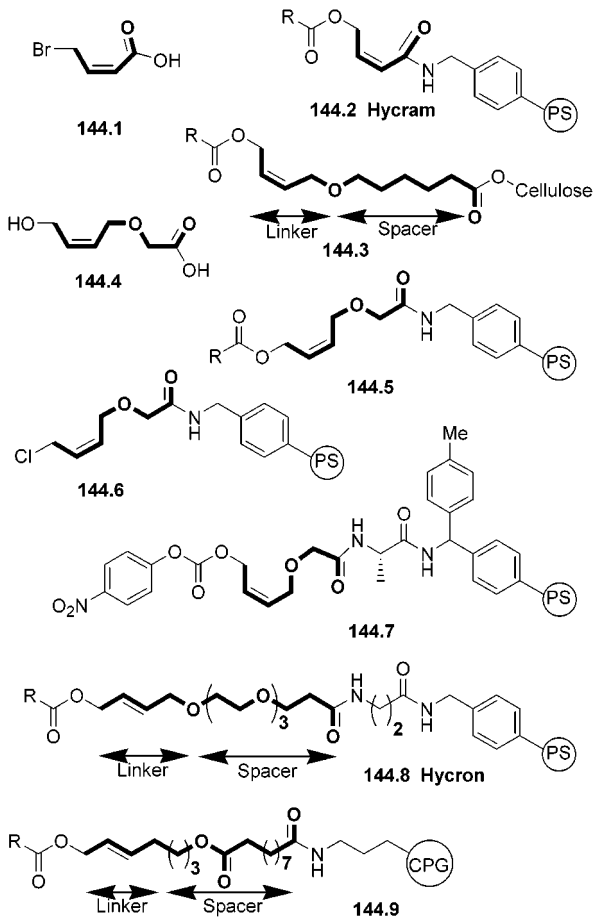
D. Metal-Assisted Cleavage Procedures

Two distinct approaches have been based on metal-assisted solid-phase cleavage reactions either through the activation of olefins by transition metals or activation/polarization of carbon−heteroatom bonds by Lewis acids, often softening the cleavage conditions. The main drawback is that these methods are invasive and result in "pollution" by metallic species, which even in catalytic amounts and despite the power of SPE techniques, with the remaining metallic traces as low as ppb, may not be without consequences for pharmaceutical screening.

1. Palladium Deblocking of Allyloxycarbonyl Group

Palladium(0)-catalyzed transfer of the allyl group onto a nucleophile,[412] which acts as an allyl scavenger, can be used to perform cleavage of allylic linkers. Kunz[413] published, in 1988, the use of the bromocrotonic-acid-unloaded linker **144.1** (Scheme 144) which

Scheme 144

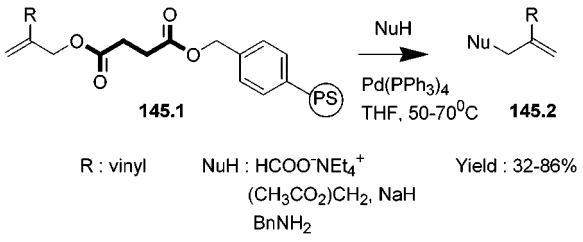


was attached to an aminomethyl resin. Functionalization by displacement of the reactive bromide with the cesium salt of some C-terminal peptide acids furnished the derivatized Hycram linkers **144.2** (Scheme 144). Boc and Fmoc synthesis were then performed, and detachment of peptides and glycopeptides was achieved using 8% tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) in a mixture of morpholine/THF (1:10) for 2−12 h, giving yields of 48−98% after chromatographic purification. Different nucleophiles can be used, but HOBt was preferred by Frank[414] over morpholine during the cleavage of Fmoc-protected peptide fragments in order to avoid *N*-terminal deprotection. The author cleaved linker **144.3** (Scheme 144) using 2 equiv of $Pd(PPh_3)_4$ and 3 equiv of HOBt. Guibé[415] used the unloaded linker **144.4** to functionalize an aminomethylpolystyrene resin. Either, preloading or direct loading of the first amino acid can be realized, forming in both cases **144.5** (Scheme 144). The chloro derivative **144.6**

(Scheme 144) was also prepared allowing anchoring by carboxylate substitution. The cleavage can be carried out in two steps by palladium-catalyzed hydrostannolytic cleavage and then conversion of the resulting tin carboxylate into the carboxylic acid with DMF/1N HCl (1:1). Undén[416] attached the unloaded linker **144.4** onto an alanine-substituted MBHA-derivatized resin. Reaction with 4-nitrophenylchloroformate led to carbonate **144.7** (Scheme 144), allowing the author to anchor and then release amino compounds after chemical modification (5% $Pd(PPh_3)_2Cl_2$, 3 equiv of TFA, 2 equiv of nBu_3SnH as the nucleophile in CH_2Cl_2/DMSO (1:1)). This linker was stable to 20% piperidine in DMF for 24 or 12 h treatment with 50% TFA in CH_2Cl_2. Albericio[417] investigated the use of two allylic linkers (**144.1** and **144.4**) and found that a proton source was required in order to obtain the free peptide carboxylic acid after release. Optimized conditions employed DMSO/THF/0.5 M HCl (2:2:1) for 18 h under argon with 50 equiv of morpholine as the nucleophile. Use of 1 equiv of palladium was preferable, but lower yields were obtained with palladium(II) catalysts such as $PdCl_2$ and $Pd(PPh_3)_2Cl_2$ compared to $Pd(PPh_3)_4$. The author pointed out that oxygen must be rigorously excluded and that the correct balance between the solvents used must be achieved. Finally, no striking difference was found between the linkers. Improvements were brought about with the Hycron linker **144.8** (Scheme 144) which bears a flexible, polar spacer able to reduce steric hindrance and association with the polystyrene matrix.[418] *N*-Methylaniline, not basic enough to be a problem in Fmoc chemistry, was used as a scavenger. In other studies, this linker has been derivatized prior to resin attachment.[419] Oligonucleotide synthesis and mechanistic studies have been undertaken by Greenberg,[420] who used 4 equiv of Pd_2dba_3 and DIPHOS as a ligand in wet chloroform for 1 h at 55 °C for cleaving linker **144.9**. Not only carboxylic acids were obtained, but 3′-hydroxy-terminated products were released when a carbonate derivative was employed.

Blechert[421] used substituted allylesters **145.1** (Scheme 145) in a reverse approach and released

Scheme 145



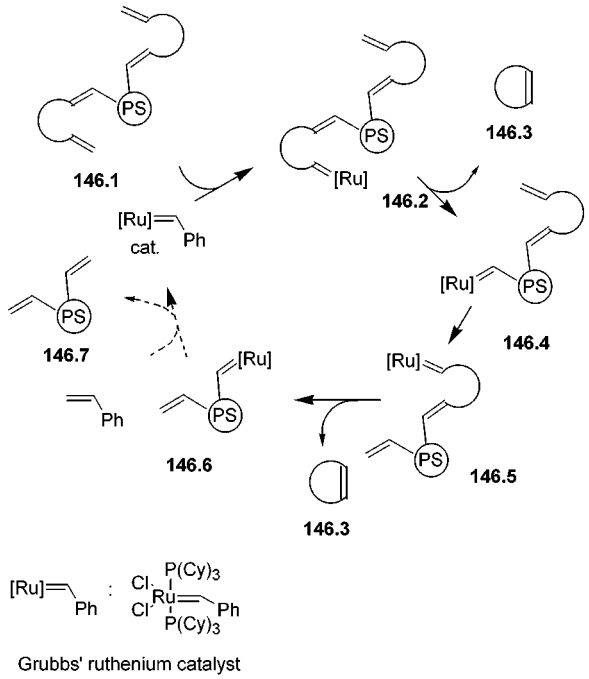
allyl-functionalized compounds into solution upon activation with palladium(0) and reaction with nucleophiles. Amines were used, but malonate derivatives and hydrides generated from ammonium formate are also applicable. Polysubstituted olefins were prepared in 32−86% yields after purification by column chromatography. This approach has been used recently for the formation of pyrrolidines by cyclorelease when the scavenger was an internal homoallylic amine.[422]

2. Metal-Catalyzed Release by C–C Bond Formation

a. RCM-Based Release. Blechert[423] first showed that ring-closing metathesis (RCM) was feasible on solid supports (TentaGel, tritylpolystyrene) and demonstrated the preparation of five- and six-membered heterocyles still bound to the resin. These studies used 10−15 mol % of ruthenium catalyst at 25−35 °C in CH_2Cl_2 for several days. After cleavage from the support, yields of 70−91% were obtained. Release using ring-closing metathesis has now been extensively investigated on the solid-phase as it has several advantages. First, cyclorelease means that high purities are expected (except for contamination by the catalyst) for the detached product, second, it generates an olefin functionality, and, third, the cleavage conditions are mild and the catalyst tolerates a variety of functionalities (carboxylic acids, anydrides, amides, aldehydes, ketones, alcohols, ...).

Seven-membered cycloolefins have been generated from immobilized dienes on polystyrene resins using the precursor **147.1** (Scheme 147).[424] Modest yields (54%) were obtained using bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (Grubbs' ruthenium catalyst) in stoichiometric amounts at 50 °C for 16 h in toluene. To improve the yield, the author added ethylene as a cofactor in order to release the immobilized catalyst in **146.6** (Scheme 146).[424] A more detailed study by Rutjes[425] used

Scheme 146

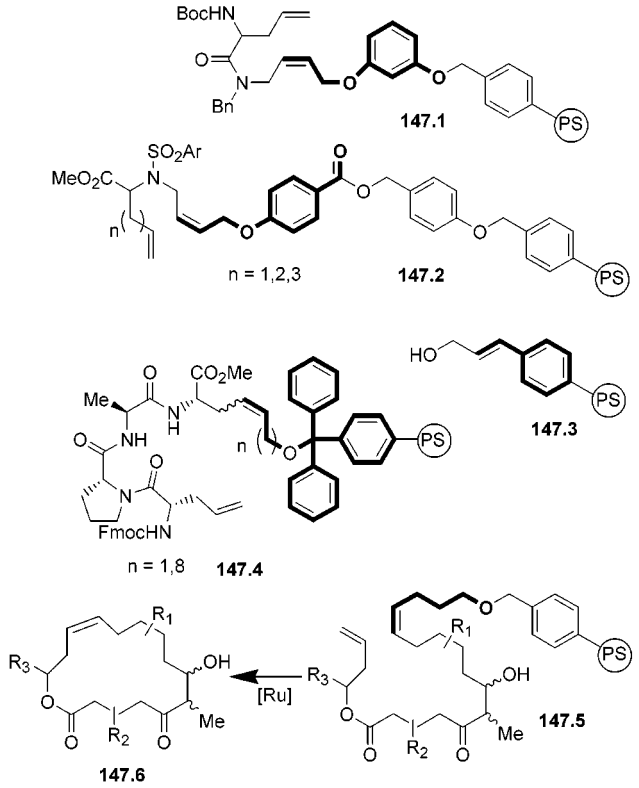


precursor **147.2**. Large-membered rings are often difficult to cyclize, and Rutjes obtained decreasing yields of 80%, 59%, and 12% for six-, seven-, or eight-membered unsaturated rings. The author noted that in the last case the reaction failed in solution, emphasing the role of the solid support for the pseudodilution effect. Investigating the mechanism of this pseudocatalyzed reaction on solid support (Scheme 146), he suggested that the catalyst could be regenerated by chain transfer from **146.4** to **146.5**.

However, addition of an olefin (styrene) significantly improved the yield of released product **146.3** by helping to regenerate the catalyst in solution (86% with 5% Grubbs' ruthenium catalyst, 1 equiv of styrene 18 h at 50 °C in toluene compared to 56% without styrene).[425] Piscopio[426] demonstrated that resin-bound ruthenium alkylidene complexes **146.4** could efficiently re-enter the catalytic cycle; hence, cofactors were not required except in a catalytic amount. Assuming sufficient flexibility, transfer of the metal complex within the polymer should enable further catalytic cleavage cycles.

A 71% yield was obtained for 2-phenyldihydropyran after reacting with 5% Grubbs' ruthenium catalyst in CH_2Cl_2 for 16 h at room temperature.[426] Other tetrahydropyridines and seven-membered ring lactams were obtained in various yields (16−62%) from precursor **147.3** (Scheme 147).[427,428] Blechert[429] took

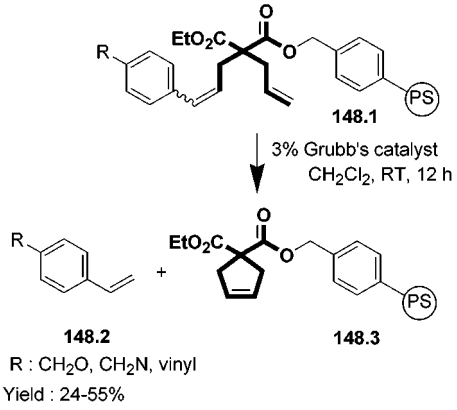
Scheme 147



advantage of macrocyclization on the solid supports for large-ring synthesis to limit the formation of polymeric compounds. Even with a loading of 0.5 mmol/g, the cyclization−release occurred more rapidly than the interchain reaction of two terminal olefins. In addition, the author showed that the reaction rate depended strongly on spacer length and, thus, mobility of the polymer-supported intermediates. The best results were obtained with an eight-methylene chain spacer **147.4** (Scheme 147) with yields of 70% compared to 30% for the single methylene unit. A library of 44 16-membered ring epothilone precursors **147.6** were prepared from linker **147.5** and purified by preparative TLC.[430]

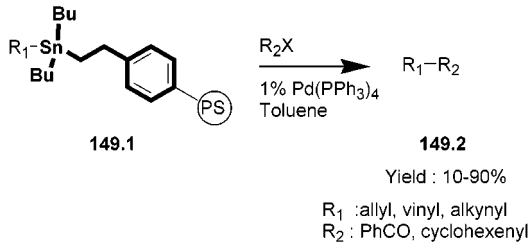
Metathesis is not only a tool for the release of cyclic compounds. This reaction has been successfully used to remove acyclic olefins from solid supports. Blechert[431] used bisallyl-derivatized malonate linker **148.1**. After functional modification, two to three exposures to 3% Grubbs' ruthenium catalyst in CH_2Cl_2 for 12 h released the styrene products **148.2** (Scheme 148).

Scheme 148



b. Palladium-Catalyzed Cross-Coupling Release. Cross-coupling reactions involving palladium as a catalyst (Suzuki, Stille, Heck, Sonogashira) are far more widely used in organic synthesis than RCM, but their application in SPOS for releasing material is inhibited by the complex preparation of a suitable linker. Since 1994, Kuhn[432] has used polymer-supported organotin reagents for Stille reactions. The main advantage is that the organotin byproduct remains attached to the support and the organic target molecule is virtually free of toxic organotin materials. Various alkenyl and alkynyl products **149.2** were prepared after exposure of linker **149.1** to 1 equiv of alkenyliodide or benzoyl chloride and 1−2% $Pd(PPh_3)_4$ in toluene at 40−80 °C for 1−3 days, Scheme 149. The linker **149.1** was easily prepared

Scheme 149

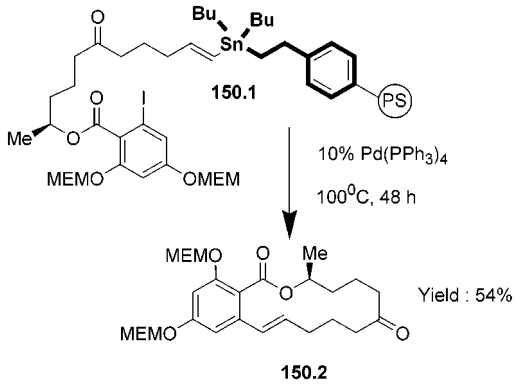


either via Grignard reaction onto a supported tin chloride or via hydrostannation reaction between a supported tin hydride and an alkyne reagent.

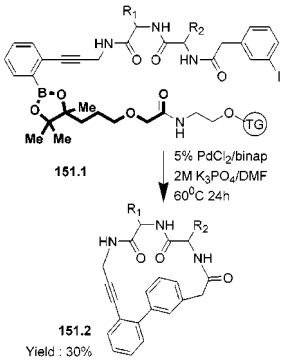
Cyclorelease has been performed by Nicolaou[433] for the synthesis of a precursor of (s)-zearalenone **150.2**. A 54% yield was obtained for the intramolecular Stille reaction using linker **150.1** and 10% $Pd(PPh_3)_4$ for 48 h in toluene at 100 °C (Scheme 150).

A similar strategy was employed by Burgess[434] to produce the β-turn mimic **151.2** via Suzuki cross-coupling. The pinacol linker intermediate was reacted with the aryl boronic species and subsequently anchored onto an aminomethyl resin (MBHA or TentaGel) to form linker **151.1** (Scheme 151). Cyclization was achieved in 30% yield using 5% $PdCl_2$/binap and 2 M K_3PO_4 in DMF at 60 °C for 24 h.

Scheme 150

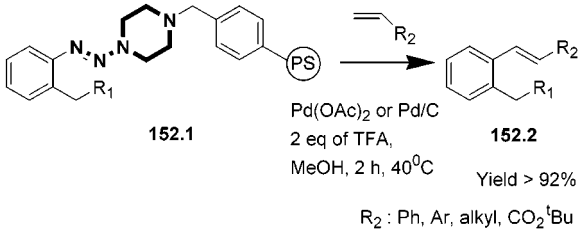


Scheme 151



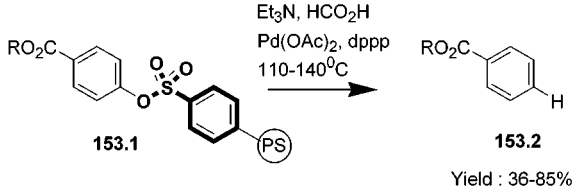
Bräse has shown that the triazene resin **152.1** can be cleaved under cross-coupling conditions, allowing the formation of a range of lipophilic products **152.2** (Scheme 152).[435]

Scheme 152



An example of a Pd(0)-catalyzed reductive cleavage of a linker-bound arylsulfonate was described by Wustrow (Scheme 153).[436] Arylsulfonates **153.1** were

Scheme 153

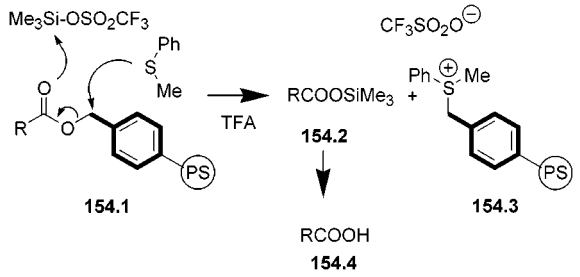


prepared from a 2% cross-linked benzenesulfonyl chloride polystyrene resin (Dowex 50W ion-exchange resin). The aromatic products **153.2** were liberated by employing $Pd(OAc)_2$/dppp, triethylamine, and formic acid for 12 h at 110−140 °C. The author demonstrated that electron-withdrawing groups must be present on the aryl moiety to achieve cleavage.

3. Metal and Nonmetal Lewis-Acid-Assisted Cleavage.

a. Lewis Acids in Ester and Ether Cleavage. Lewis acids such as TMSOTf and TMSBr have been used by Yajima[437] to replace TFMSA for the cleavage of benzylic esters on polystyrene resins **154.1** (Scheme 154). These silyl compounds act as hard acids and

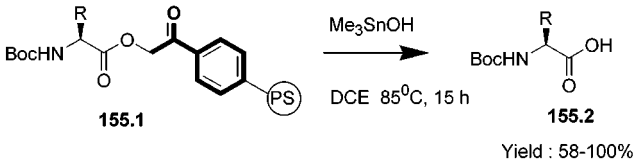
Scheme 154



are employed in conjunction with a soft base (thioanisole for example) according to the hard and soft acids and bases theory developed by Pearson.[438] A simple hydrolysis step is sufficient to generate the product **154.4** from the silyl intermediate **154.2**. MBHA linker was cleaved using TMSBr/thioanisole/TFA to release peptide amides.[439]

Other Lewis acids have been used such as trimethyltin hydroxide or bis(tributyltin) oxide to cleave the phenacyl ester linker **155.1** (Scheme 155).[440] The

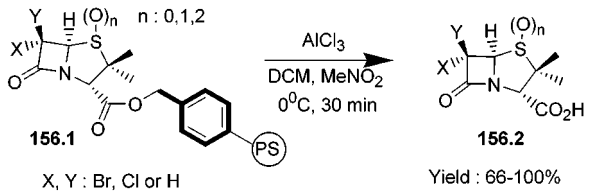
Scheme 155



author achieved the cleavage in more than 58% yield after 15 h at 85 °C in DCE using 2 equiv of Me_3SnOH. Purification was realized with a simple aqueous workup as the reacted tin was bound to the resin while the unreacted tin was soluble in water. This methodology has been used to release some Boc-protected compounds from Merrifield resin, as well as from PAM **10.2** or Wang **15.1** linkers; however, Fmoc- or Cbz-protecting groups are not suitable under these conditions.[441]

Aluminum chloride has been used to cleave penicillin derivatives **156.2** (Scheme 156) from Merrifield

Scheme 156

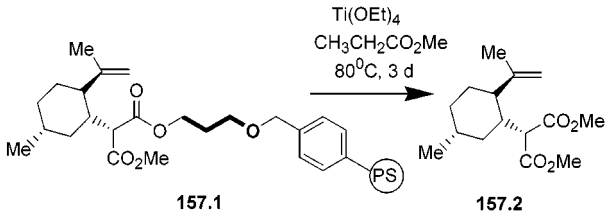


esters **156.1** by Mata.[442] The author wanted to use the Merrifield resin to allow a broader range of reaction conditions due to its acid stability but was reluctant to employ strong acid such as HF in order to keep the β-lactam ring intact. The sulfide, sulfoxide, or sulfone derivatives were all released from

either Merrifield resin or Wang linker in excellent yields (mainly higher than 80%) after reacting with 4 equiv of $AlCl_3$ in nitromethane for 30 min at 0 °C followed by an aqueous acid workup.

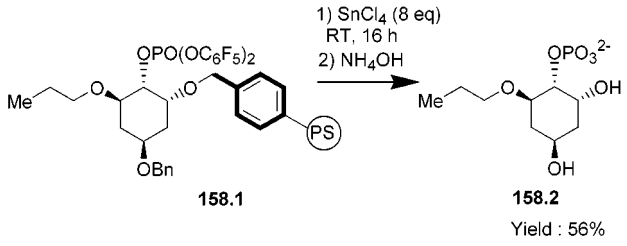
Transesterification in dry methyl propionate in the presence of 1 equiv of titanium(IV) ethoxide for 3 days at 80 °C afforded **157.2** from anchored ester **157.1** (Scheme 157).[443]

Scheme 157



Benzyl ethers are known to be sensitive to Lewis-acid cleavages. Gani[444] used $SnCl_4$ to selectively cleave benzyl Merrifield ethers **158.1**, affording the required alcohol **158.2** in 56% overall yield after purification through a cellulose phosphate ion exchange column (Scheme 158). Further studies showed

Scheme 158

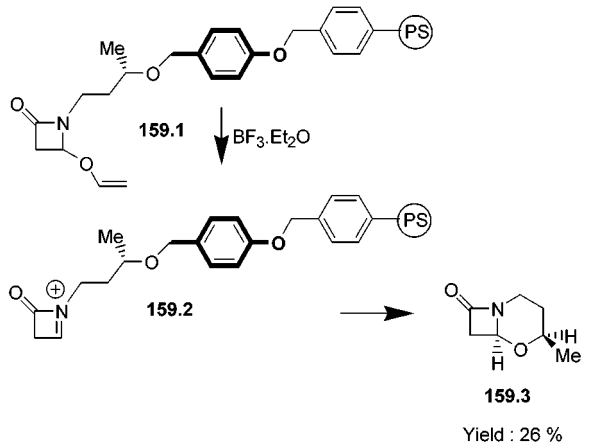


that treatment of primary and secondary alcohols and phenols attached to Merrifield resin with 10 equiv of stannic chloride for a few hours at 30 °C followed by aqueous workup and extraction into CH_2Cl_2 gave the expected products in 70−95% yields. However, tertiary alcohols resulted in elimination products. The authors noticed that $TiCl_4$ was also useful in cleaving Merrifield ethers. Kobayashi[88] cleaved some phenol derivatives from Merrifield resin using TMSOTf in 59−98% yields.

The benzylic oxygen of a Wang linker **159.1** can be used to trap a stabilized cation **159.2** and hence initiate cleavage from the resin under Lewis-acid conditions (1 equiv of $BF_3{\cdot}Et_2O$ in CH_2Cl_2). Oxacepham **159.3** was prepared in 26−30% yields over 6 steps (Scheme 159).[445,446]

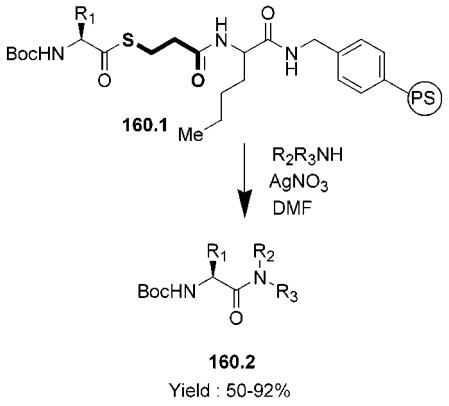
b. Lewis-Acid-Assisted Aminolysis. Metals have been used to accelerate amidation reactions by multiple coordination between the oxygen of the carbonyl and the amino group. Aminolysis reactions on the Wang linker or TentaGel-PHB resin (Wang-derivatized TentaGel resin) have been achieved with various Lewis acids.[447] $AlCl_3$ and $ZrCl_4$ have been selected as the reagents of choice.[448] Various peptide-amides were obtained in yields ranging between 11% and 74% with amines such as dimethylaminoethylamine, cyclohexylamine, *N*-methylpiperazine, and *N*-methylbenzylamine. Purification was achieved following quenching with 1 M potassium carbonate, filtration, and SPE. Some recent examples carried out on the

Scheme 159



Wang linker utilized benzylamine−dimethylaluminum complexes, but the reaction was poor.[449] Tam[450,451] with a mercaptopropionamide-substituted polystyrene resin **160.1** used silver ions to form a ternary complex of the silver-cation/amine/thioester (Scheme 160). Good to excellent yields were obtained for

Scheme 160



cleavage−amidation of C-terminal peptides employing weakly nucleophilic arylamines or hindered secondary amines. Cyclization could also be achieved using the free amino group on the peptide chain, allowing the release of several cyclic pentapeptides.

E. Cleavage under Reductive Conditions

Besides acidic, basic, nucleophilic, and photolytic cleavages, reduction represents an important class of cleavage reactions and is orthogonal to many other methodologies. However, reduction is far less widespread in solid-phase synthesis than in solution, and only four types of reductive cleavages have been used to date, as far as we are aware, to release products from solid supports: (i) *Catalytic hydrogenation*, (ii) *Disulfide reduction*, (iii) *Desulfurization*, and (iv) *Nucleophilic attack by hydride or hydrogen radicals*.

Despite many studies of catalytic hydrogenation on solid phase during the late 1970s and early 1980s, this technique no longer appears to be favored, which may be due to a report by Merrifield[452] describing unsuccessful attempts to hydrogenolyze a resin-based benzyl ester using a variety of catalysts. Desulfurization and disulfide reduction methods have been

employed only in particular cases, and it is too early to predict a potential for linkers based on this strategy. The only remaining reduction method which is proving to be fairly general is the use of hydrides. However, major concerns relate to the low yields obtained and the necessary workup following the cleavage.

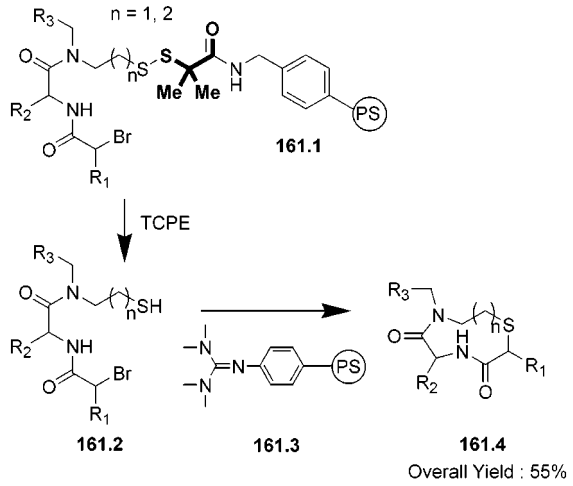
1. Catalytic Hydrogenation

Despite being a mild method to deprotect compounds, there was no report of catalytic hydrogenation on solid supports until 1977. The basic and obvious reason is that the catalyst has to enter into the resin. A team from Searle Laboratories[453,454] dissolved palladium(II) acetate in DMF and removed a pentapeptide from Merrifield resin by reduction of the benzylic ester. Different parameters were investigated, and the best conditions were found to be 40 °C at 4 atm for 24 h. After two cycles, the resin was removed by filtration and the DMF was distilled off under high vacuum. Purification gave the product in 71% yield. The authors tried different catalysts and found that $Pd(PPh_3)_2Cl_2$ and $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst) totally failed despite being soluble in DMF. Cyclohexene as a source of hydrogen has been used for the preparation of a protected peptide by hydrogenolysis at atmospheric pressure, 70 °C, for 4 h in the presence of palladium black generated in situ from palladium acetate.[455] The octapeptide bradykinin was obtained in 20% overall yield after purification. Protecting groups such as Cbz, Bn, and NO_2 were removed simultaneously, but Boc was stable during the cleavage step. Cyclohexadiene was also used as a source of hydrogen by Colombo[456,457] for the cleavage of various peptides and Boc-protected amino acids. A 28mer was obtained by this route from a modified 4-nitrobenzhydrylamine linker in 22% yield after purification.[456] Short reaction times were also found with ammonium formate catalytic transfer hydrogenation for the synthesis of the pentapeptide Leu-enkephalin anchored to standard Merrifield resin via a benzylester linkage.[458] There was 70% removal observed after 10 min at room temperature and atmospheric pressure and >95% after 120 min. Folkers[459] showed that the influence of the peptide on hydrogenation was crucial. He also obtained lower yields with ammonium formate and cyclohexene methods compared to hydrogen gas.

2. Reduction of Disulfide Bonds

Despite the fact that disulfide bonds can be cleaved under very mild conditions, few linkers have been based on this strategy. Reduction (thiolysis) by DTT[460] allowed the release of a mercaptoamide peptide, while the reduction with tris(2-carboxyethyl)phosphine[461] (TCEP) was used for the preparation of meracaptoamide phosphonopeptides. Both syntheses were performed on polyacrylic polymers (Expansin). This method was used recently on polystyrene resin by Ellman[462,463] for the preparation of β-turn mimetics. After synthesis of the turn mimetic, treatment of linker **161.1** with 4.0 mM TCEP in dioxane/water (9:1) allowed its release into solution (Scheme 161). Upon filtration, the filtrate was reacted with a supported guanidine **161.3** which acted as both a scavenging resin for removing the TCEP oxide and excess TCEP as well as a supported base. High levels of purity (>90%) and overall yields of 55% were obtained for **161.4**. Cyclic dimers or oligomers were not observed upon cyclization at 1 mM concentrations.

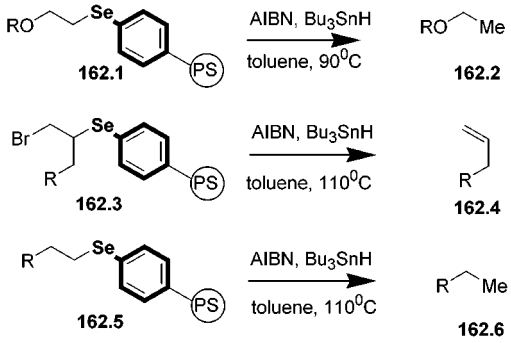
Scheme 161



3. Reductive Desulfurization and Deselenization Techniques

Linkers have been extensively studied in order to furnish C−H bonds upon release. Ruhland[464] furnished the first example of a reductive desulfurization/deselenization on polystyrene resin. The author developed a selenide-based resin **162.1** (Scheme 162).

Scheme 162

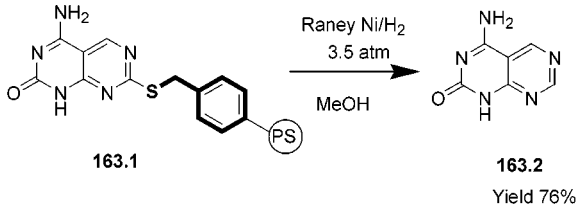


Homolyses of the selenides are considered to proceed faster than for the corresponding sulfides. The selenide resin was cleaved with tributylstannane and AIBN in toluene for 12 h at 90 °C in a sealed tube (Scheme 162). Due to the high selectivity for the cleavage of the bond between selenium and an aliphatic carbon compared to an aromatic carbon, the selenium remained immobilized on the resin. Alkyl aryl ethers were obtained in 57−83% yields and 78−88% purities after purification by SPE. Nicolaou[465] anchored aliphatic compounds using solid-supported selenium resins **162.3** and **162.5** (Scheme 162). Aliphatic and ethylenic products were finally released using 2 equiv of tributylstannane and a catalytic amount of AIBN in toluene for 6 h at 110 °C.

Desulfurization using Raney Ni/H_2, MeOH at 3.5 atm for 12 h reportedly allows the release of py-

rimido[4,5-*d*]pyrimidines **163.2** in 74−80% yields with purities above 90%, although the manner of access for the Raney Nickel into the resin was not discussed.[466] The pyrimidine unit was bound to the Merrifield resin through a thioether, which was the cleavage point (Scheme 163).

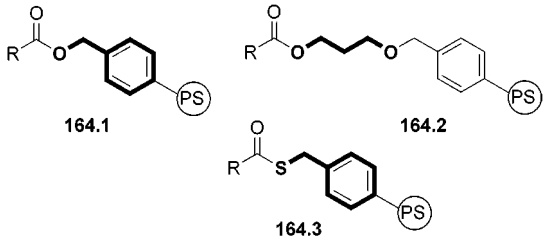
Scheme 163



4. Hydride Nucleophiles

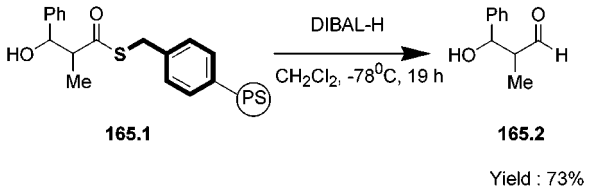
Alcohols can be obtained by direct reduction of esters anchored onto Merrifield resin without the need of a particular linker. Yields of alcohols obtained by DIBAL-H reduction have generally been poor (20−50% for reduction of esters **164.1**[467] and **164.2**[468]) (Scheme 164). Better results were obtained by Kobayashi[469,470] with lithium borohydride on thioester **164.3** with yields ranging from 55% to 80% (Scheme 164).

Scheme 164



DIBAL-H has also been used for generating aldehydes **165.2** from thioester-based resin **165.1** (Scheme 165) when the temperature was kept at −78 °C.[469]

Scheme 165

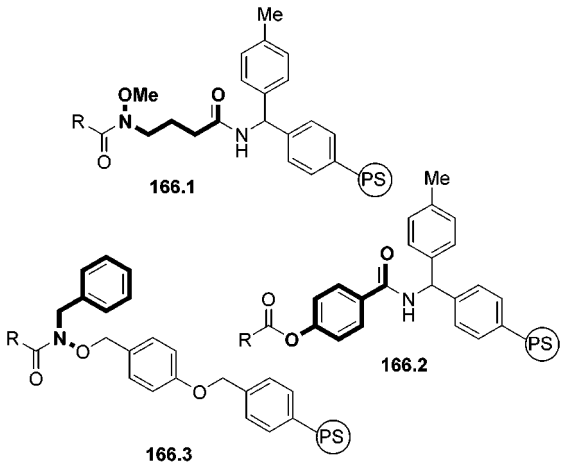


Good yields (73%) were obtained after aqueous workup and chromatography.

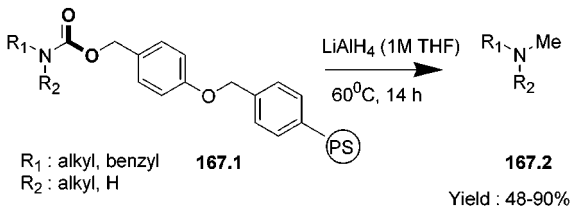
Various Weinreib amide-based linkers have been developed in order to produce C-terminal peptide aldehydes (Scheme 166). Reduction of linker **166.1** with $LiAlH_4$ affords the aldehyde in 40% yield after aqueous workup and chromatography.[471] The author compared this resin advantageously with the phenylester resin **166.2**.[471] Salvino[322] has described the preparation and reactivity of the Weinreb amide linker **166.3**. In this case, yields were between 0% and 54% for $LiAlH_4$ reduction with purities between 85% and 97%.

Carbamate **167.1** was cleaved with lithium aluminum hydride at 60 °C to give *N*-methylamine products **167.2** (Scheme 167).[472] Secondary and tertiary amines were obtained in 48−90% yields with purities

Scheme 166



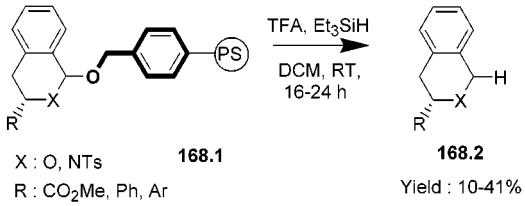
Scheme 167



above 84% after quenching with aqueous NaOH and then RP−SPE for removal of salts. Substituted *N*-methylpyrrolidines were prepared in 70% yield according to this procedure.[473]

Craig[323] devised a reductive release of benzodihydropyrans and tetrahydroisoquinolines by transformation of the corresponding acetal- or aminal-bound compounds **168.1** into cyclic ethers or amines **168.2** (Scheme 168). Ten equivalents of triethylsilane and

Scheme 168

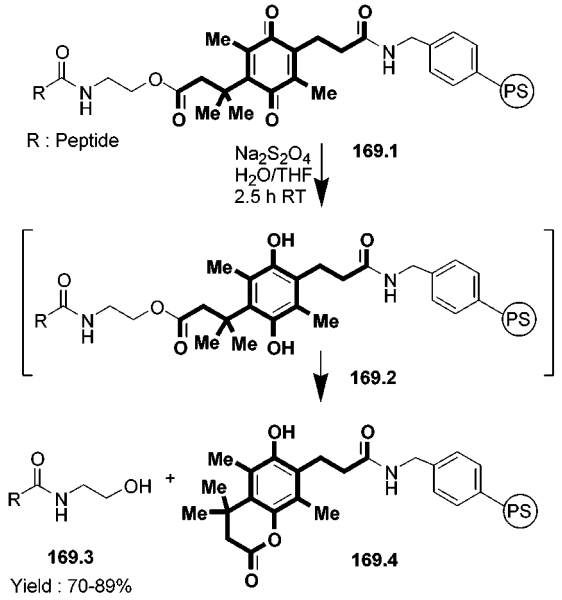


5 equiv of TFA were used for the reduction−cleavage protocol. However, poor yields were obtained (10−41%).

5. Miscellaneous Reductive Protocols

A redox-sensitive linker **169.1** was prepared by Wang[474] for the synthesis of C-terminally modified peptides (Scheme 169). Upon reduction, a quinone group **169.1** was transformed into the corresponding hydroquinone **169.2**, which underwent a facile lactonization reaction due to the "trimethyl-lock" effect. Mild reductive conditions (sodium hydrosulfite ($Na_2S_2O_4$ in water/THF)) were employed. Reaction progress was determined by IR and the disappearance of the yellow color of the quinone motif. An aqueous workup was required, and after extraction into ethyl acetate

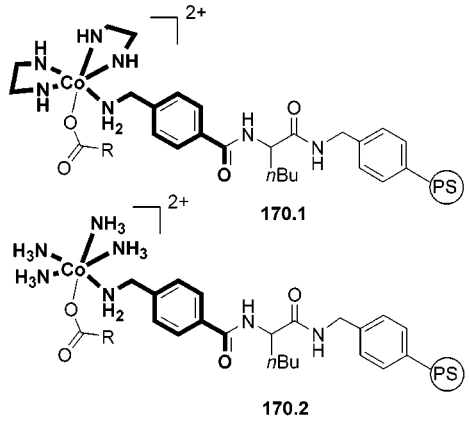
Scheme 169



the product was purified by silica gel column chromatography yielding a tri-, tetra-, or pentapeptide in 89%, 83%, or 70% yield, respectively. However, this strategy is limited to the preparation of *N*-(2-hydroxyethyl)peptide-amides **169.3**.

Reduction of a Co(III)-based linker has also been reported with DTT.[475] This allowed the preparation of protected C-terminal peptide acids using both Boc and Fmoc strategies from linkers **170.1** and **170.2** (Scheme 170). The first residue was covalently bound

Scheme 170



through an ester bond, forming the cationic cobalt-(III)-complex-based resin. Purified Leu-enkephalin was obtained in 67−69% overall yields.

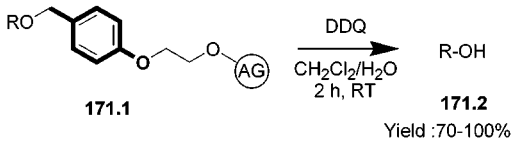
F. Cleavage under Oxidative Conditions

Oxidation represents an orthogonal strategy to many existing conditions. Up until now, two different approaches have been attempted either by creating a linker sensitive to oxidation (ozonolysis of alkene, oxidation of sulfur- or selenium-based linker) or by using the properties of existing linkers. Oxidation strategies are obviously not compatible with the presence of sensitive groups on the molecule which can be modified by the utilization of oxidizing agents such as CAN, DDQ, or mCPBA.

1. Oxidation of p-Alkoxybenzyl Groups

p-Methoxybenzyl ether (PMB) protecting groups can undergo electron transfer to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to generate an oxonium ion, which can be captured by water leading to the hemiacetal, generating the alcohol product **171.2** and 4-methoxybenzaldehyde resin. Thus, Porco,[476] interested in finding an alternative to TFA acidic cleavage of alcohols attached to Wang-ArgoGel, used a DDQ cleavage. His rationale was to reduce the formation of trifluoroacetate ester byproducts, although the use of HCl would have been an alternative. A mixed-bed ion-exchange scavenger resin enabled scavenging of DDQH from the cleavage solution (Scheme 171). Another important fact is that the

Scheme 171

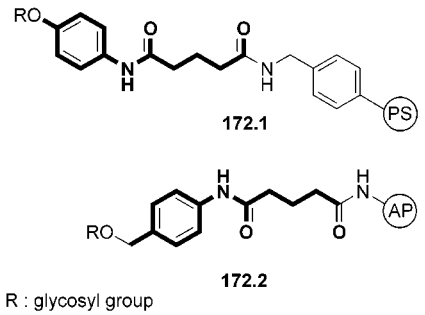


yield of cleavage is correlated with the amount of DDQ used. One equivalent of DDQ was necessary for complete cleavage, thus providing a potential way for a controlled release of aliquots of product from the resin. Isoxazoles[477] and amines[88] have been released using this method.

This method should be amenable to the cleavage of other widely used linkers. We observed that the Rink linker was sensitive to *m*CPBA.[478] *m*CPBA was also responsible for degrading the Wang linker as reported by Rotella.[479] It should also be noted that both DDQ and *m*CPBA lead to acidic byproducts and an eventual acidic-based mechanism for the cleavage is possible.

Acid-stable *p*-acylaminophenyl **172.1** and *p*-acylaminobenzyl **172.2** linkers (Scheme 172) have been

Scheme 172



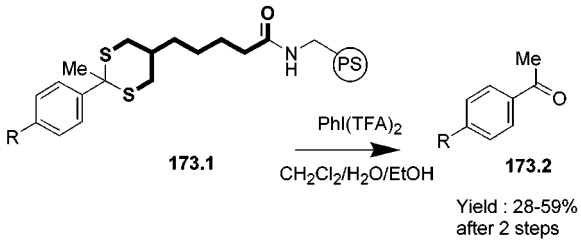
found to be suitable for anchoring glycoside groups using an appropriate spacer on polystyrene and ArgoPore resins, respectively. Cleavage was achieved using 5 equiv of CAN in CH_3CN/H_2O (10:1) in 70% yield for **172.1**[480] and 1.2 equiv of DDQ in CH_2Cl_2/H_2O (5:1) in 91% yield for **172.2**.[481]

2. Oxidation of Sulfur and Selenium Linkers

S,S and O,S acetals possess properties distinct to those of their O,O analogues; for example, they are

far less susceptible to acidic cleavage. The main routes to achieve cleavage involve activation of the sulfur group by metal coordination, alkylation, or oxidation, with oxidation often being the method of choice. A 1,3-dithiane linker **173.1** has been prepared, by Huwe, onto aminomethyl polystyrene resin, and the scaffold was preloaded.[482] Cleavage and release of methylaryl ketones **173.2** was realized using 2.5 equiv of (bis(trifluoroacetoxy)iodo)benzene (PhI(O-$COCF_3)_2$) in CH_2Cl_2/EtOH/H_2O (9:9:2) for 30 min (Scheme 173). After chromatographic purification,

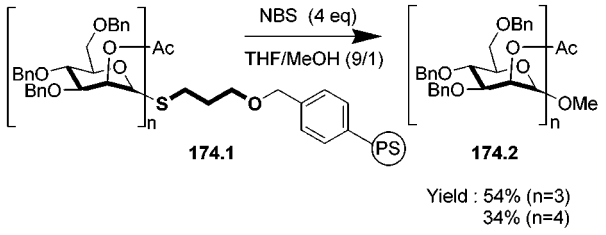
Scheme 173



products were obtained in 28−59% overall yields. The authors noted that this oxidation method afforded less side products than anhydrous H_5IO_6.

Thiol-based linker **174.1** (Scheme 174) was used to anchor glycosides at the anomeric position.[483] After

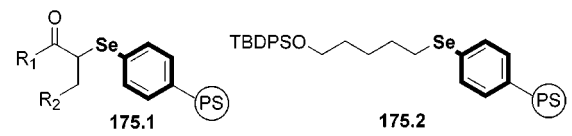
Scheme 174



chemical modification, cleavage was performed using 4 equiv of NBS in a mixture of THF/MeOH, leading to the methylglycosides **174.2** in 54% and 34% overall yields for the tri- and tetrasaccharides, respectively. Yields were lower when other oxidants such as *m*CPBA or iodonium reagents were used.

Twenty-five years ago, Heitz[484] prepared a polymer-supported selenophenol by copolymerization of DVB and 4-vinylselenophenol. Transformation into the selenenyl chloride or sodium selenide allowed anchoring of scaffolds to form resin **175.1**, which was treated with 30% hydrogen peroxide for 2 h at 30 °C (Scheme 175). Spontaneous oxidation−elimination

Scheme 175

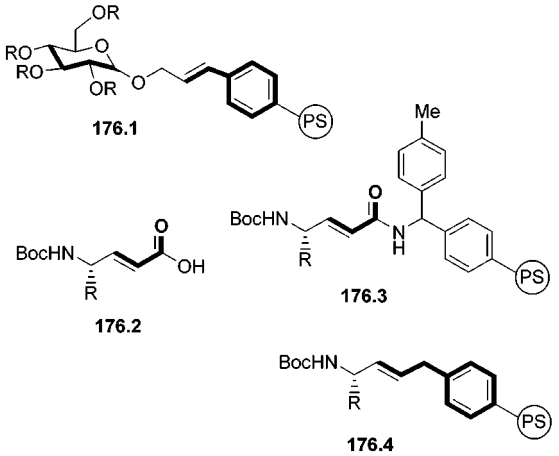


resulted in the release of the corresponding α,β-unsaturated ketone at room temperature. A different preparation, starting from polystyrene resin and grafting selenium by metalation, was reported by Nicolaou,[465] who generated alkenes using resin **175.2** and 1 equiv of H_2O_2 (30%) in THF for 12 h in 78% overall yield.

3. Ozonolysis of Polymeric Olefins

Some preliminary experiments to release aldehyde-derivatized oligosaccharides by ozonolysis from resin **176.1** (Scheme 176) were carried out by Fréchet[485]

Scheme 176

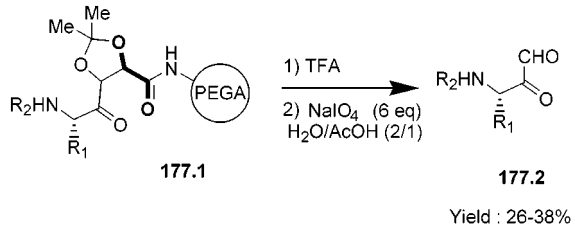


in 1971. Mioskowski[486] investigated the stability of polystyrene resin to ozonolysis, in studies directed toward the preparation of peptide aldehydes. This class of compounds is very important due to the inhibitory properties exhibited toward many classes of proteases. Peptide aldehydes represent a challenge to chemists, as these compounds are very prone to epimerization, especially during the purification process. Martinez[487] attached ethylenic precursors **176.2** (Scheme 176) to the solid support in order to prepare peptide aldehydes by treatment with ozone in CH_2Cl_2 at −80 °C for 5 min (quenched with thiourea) giving tri- and tetrapeptide aldehydes in 30−83% yields. Later on, the same team attached amino-aldehydes directly onto a phosphine- or phosphonate-based resin through a Wittig or Wittig−Horner reaction to form resin **176.3** (Scheme 176). In this way, the author avoids the time-consuming preparation of all the different preloaded linkers **176.2**. Unfortunately, although yields and HPLC purities were good, some epimerization was observed.[488] Simultaneously Hall[489] developed the same chemistry and elaborated linker **176.4** from polymer-supported triphenylphosphonium bromide. After tripeptide synthesis, ozonolysis, and reductive workup with dimethyl sulfide, the tripeptide aldehydes were obtained as single diastereoisomers with purities above 90%.

4. Miscellaneous Oxidative Protocols

A tartaric-acid-based linker **177.1** has been created for the synthesis of C-terminal α-oxo-aldehyde.[490] The glyoxilic product **177.2** was released from the support by periodic oxidation in 26−38% yields after RP-HPLC purification (Scheme 177). This can be considered as a safety-catch linker as a TFA pretreatment is required to deprotect the diol functionality.

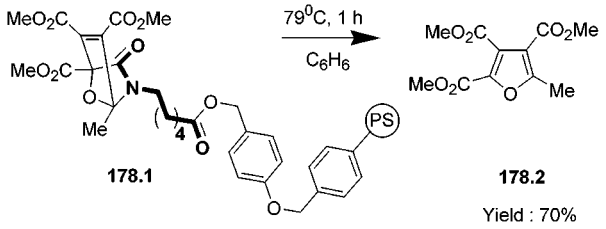
Scheme 177



G. Cycloaddition- and Cycloreversion-Based Release

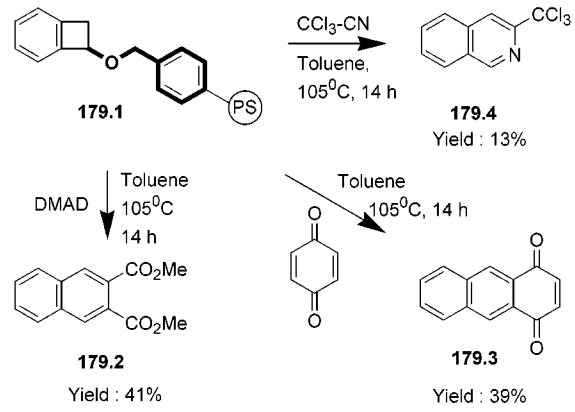
Only a few examples of Diels−Alder cycloadditions or cycloreversions are described in the literature concerning the release of supported compounds. Resin-bound cycloadduct **178.1** was obtained by a 1,3-dipolar cycloaddition of an α-diazoketone anchored onto a Wang linker, with rhodium(II) catalyst and dimethyl acetylenedicarboxylate (DMAD). Cleavage, by heating at 79 °C in benzene for 1 h, cleanly liberated the tetrasubstituted furans **178.2**, by thermolytic cycloreversion in 70% yield and 98% purity (Scheme 178).[491,492]

Scheme 178



Linker **179.1** composed of *o*-quinodimethane attached to hydroxypolystyrene resin was used as a diene precursor in a Diels−Alder reaction.[323] Reaction with DMAD, benzoquinone, and trichloroacetonitrile as dienophiles gave, respectively, substituted naphthalenes **179.2**, **179.3** and isoquinolines **179.4** in 41%, 39%, and 13% yields (in toluene at 105 °C for 14 h). Unfortunately, larger amounts of dienophile did not improve the yield and led to problems of purification (Scheme 179).

Scheme 179



V. Guide for Functional Groups Release

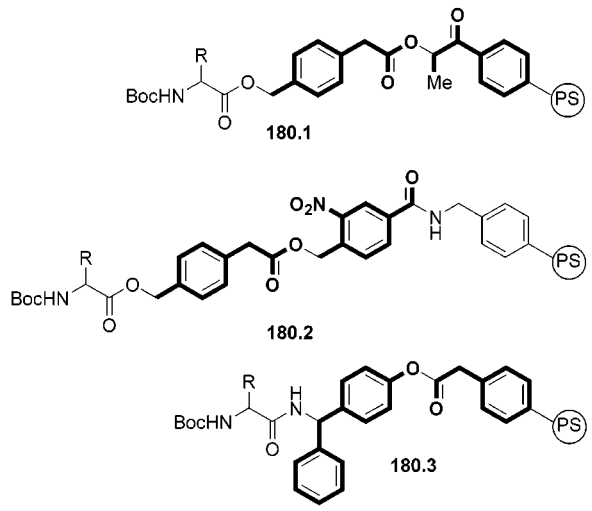
To illustrate the wide applicability of some described linkers, a short list of released functional groups is reported. Only the most reliable reactions have been considered (used by several different groups). This list is deliberately nonexhaustive, and selection of the best conditions would be more appropriate using the excellent review by James[14] devoted to this purpose. This list has been created only to emphasize the large number of products already available after cleavage. Despite this, only a few linkers are commonly used (Merrifield ester, Wang, Rink, trityl, ...). Constant improvements are being made to achieve cleavage under different conditions for different products, but in each case the large array of possible linkers has to be considered to choose the most suitable, Table 1.

VI. Multidetachable Linkers (In-Line Linkers)

Multidetachable linkers (two in-line linkers) have been used to generate different products depending on the cleavage conditions selected from a single solid support. This strategy offers the possibility of varying the terminus on the released compound, thereby potentially increasing diversity as different compounds are obtained but also allowing activation or analysis probe to be added to the compound interested. However, orthogonality of the synthesis becomes more difficult to achieve, as the attached compound is sensitive to several cleavage conditions throughout the synthesis.

Merrifield[498a] introduced this concept in 1980. The basic idea was to construct a peptide on solid phase with a resin containing two consecutive linkers with independent release conditions Boc-Peptide−LinkerB−LinkerA−Resin. Two multidetachable constructs were designed by Merrifield: Boc-aminoacyl-2-[4(oxymethyl)phenylacetoxy]propionyl resin **180.1** and Boc-aminoacyl-4-[4-(oxymethyl)phenylacetoxymethyl]-3-nitrobenzamidomethyl resin **180.2**. In both cases, acidolysis or hydrogenolysis could cleave the benzyl ester functionality of the PAM moiety whereas the other ester linkage could be selectively cleaved using either photolysis or thiols as nucleophiles. Another example **180.3** including a benzhydryl linker was reported by Tam[498b] in 1985 (Scheme 180).

Scheme 180



In the functioning of the cleavage conditions, different peptide residues can be obtained such as

Table 1. Published Studies Using Linkers for Release of Organic Compounds

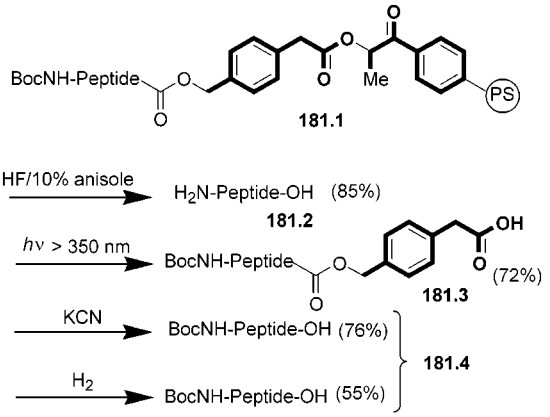
product	linker type	cleavage condition	ref
alcohol	2-chlorotrityl **33.3**	1−50% TFA/CH_2Cl_2 + 5%TIS	12, 46
	trityl **33.1**	AcOH/THF	538
	THP **39.1**	95% TFA/H_2O	158
	Wang **18.1**	3−50% TFA/CH_2Cl_2	85
	Rink chloride **27.4**	5% TFA/CH_2Cl_2	40
	benzoic ester **56.2**	K_2CO_3/MeOH/THF	219
	ONB **130.7**	*hν* 350 nm/TFE/CH_2Cl_2	57
	Wang **171.1**	DDQ/CH_2Cl_2/H_2O	476
	thioester **164.3**	$LiBH_4$/Et_2O	469
	silyl **112.4**	TBAF/AcOH/THF	338
aldehyde	acetal **45.1**	3 M HCl/dioxane 80 °C	176
	alkene **176.2**	O_3/CH_2Cl_2	487
	Weinreib **166.3**	$LiAlH_4$/THF	322
allyl	allyl **145.1**	Pd(0)/THF	421
amide 1° ($RCONH_2$)	Rink amide **27.6**	95% TFA/CH_2Cl_2	38
	Sieber **28.1**	2% TFA/DCE	123
	PAL **26.1**	90% TFA/CH_2Cl_2	111
	HMBA **55.4**	NH_3/*i*PrOH	257
	nitoveratryl **135.3**	*hν* 365 nm/H_2O/DMSO	392
amide 2° (R^1CONHR^2)	Rink amide **27.6**	5% TFA/CH_2Cl_2/H_2O	122
	AMEBA **25.7**	30% TFA/CH_2Cl_2	109
	Wang **18.3**	95% TFA/H_2O	82
	SASRIN **69.5**	R^2NH_2/pressure (diversification)	259
	Marshall **86.2**	R^2NH_2/CH_2Cl_2 (diversification)	272
	oxime **79.1**	R^2NH_2/$CHCl_3$ (diversification)	289
amide 3° ($R^1CONR^2R^3$)	Wang **18.3**	R^2R^3NH/$AlCl_3$/CH_2Cl_2 (diversification)	447
	Oxime **79.1**	R^2R^3NH/$CHCl_3$/AcOH (diversification)	289
amidine	HMP **23.3**	50% TFA/CH_2Cl_2/H_2O	493
amine 1° (RNH_2)	Rink chloride **27.4**	5% TFA/CH_2Cl_2	40
	2-chlorotrityl **33.3**	1−50% TFA/CH_2Cl_2 + 5%TIS	12, 46
	trityl **33.1**	5% TFA/CH_2Cl_2	539
	Wang **18.7**	50% TFA/CH_2Cl_2	89
	Fukayama **118.1**	PhSH/K_2CO_3/CH_3CN	352
	Dde **85.1**	NH_2NH_2/H_2O/THF	298
amine 2° (R^1R^2NH)	HMPA **23.3**	95% TFA/H_2O	100
	Merrifield **108.1**	ACE-Cl/DCP then MeOH 50 °C	331
	2-chlorotrityl **33.3**	50% TFA/CH_2Cl_2	541
amine 3° ($R^1R^2R^3N$)	REM **125.1**	R^3X/DMF then DIPEA (diversification)	363
	Wang **167.1**	$LiAlH_4$/THF 60 °C (R^3 = Me)	472
	sulfonate **70.1**	R^2R^3NH/CH_3CN 60 °C (diversification)	266
aniline	Rink chloride **27.4**	5% TFA/CH_2Cl_2	40
	BAL **26.2**	90% TFA/H_2O/DMS	114
aryl	silyl **37.5**	50% TFA (electron-rich Ar)	154
	triazene **53.1**	H_3PO_4/CCl_2HCO_2H	201
benzodiazepine-2-one	Merrifield **76.1**	TFA 60 °C (cyclorelease)	278
	Wang **18.1**	NaOtBu/THF 60 °C (cyclorelease)	283
	silyl **36.4**	HF	145
carbamate	AMEBA **25.7**	5% TFA/CH_2Cl_2	108
carboxylic acid	Rink **27.3**	10% AcOH/CH_2Cl_2	38
	2-chlorotrityl **33.3**	10% AcOH/TFE/CH_2Cl_2	135
	Wang 18.1	50% TFA/CH_2Cl_2	26
	SASRIN **25.1**	1% TFA/CH_2Cl_2	27
	Merrifield **55.1**	0.2 M LiOH/H_2O/MeOH/THF	205
	phenacyl **55.7**	1 M NaOH/dioxane/H_2O	213
	nitroveratryl **135.4**	*hν* 354 nm	397
	Hycron **144.8**	Pd(0)/morpholine/DMF/DMSO	418
cyclic peptide	Merrifield **72.1**	0.1 M AcOH/CH_2Cl_2 (cyclorelease)	269
	BAL **26.2**	95% TFA/TIS/H_2O	112
	Wang **18.1**	90% TFA/H_2O	494
	oxime **79.1**	DIPEA/AcOH/CH_2Cl_2 (cyclorelease)	495
diol	Wang aldehyde **40.3**	10% TFA/CH_2Cl_2	164
ester	Merrifield **55.1**	MeONa/MeOH/THF	239
	HMBA **55.4**	MeOH/NEt_3 50 °C	233
	PAM **55.8**	MeOH/DBU/LiBr	235
hydantoin	Merrifield **74.1**	Et_3N/THF 60 °C	276
	Merrifield **74.1**	6 M HCl 100 °C	278
hydrazide	Merrifield **55.1**	NH_2NH_2/MeOH	255
hydroxamic acid	Wang **21.1**	50% TFA/CH_2Cl_2/TIS	95
	PAL **26.4**	50% TFA/CH_2Cl_2	116
	Rink chloride **27.4**	90% TFA/TIS/DTE/H_2O	119
	Merrifield **55.1**	NH_2OH/MeOH	255
ketone	semicarbazone **47.1**	1 M HCl/AcOH/THF 65 °C	183
	enamine **48.2**	3% TFA/CH_2Cl_2	185
	thioester **100.1**	RMgX/THF (diversification)	262
	Wienreb **101.3**	EtMgBr/THF	322

Table 1 (Continued)

product	linker type	cleavage condition	ref
olefin	phosphonium **123.1**	RCHO/MeONa/MeOH (diversification)	357
	allyl **147.3**	Grubbs' Ru/DCE 80 °C (cyclorelease)	427
phenol	Wang **18.1**	50% TFA/CH_2Cl_2	496
	2-chlorotrityl **33.3**	20% TFA/CH_2Cl_2/MeOH	540
	Rink chloride **27.4**	5% TFA/CH_2Cl_2	40
pyridine	silyl **37.5**	TBAF/THF (electron-poor Ar)	154
sulfonamide	Rink amide **27.6**	20% TFA/CH_2Cl_2	497
	Wang **18.3**	95% TFA	83
	AMEBA **25.7**	5% TFA/CH_2Cl_2	108
thiocarboxylic acid	benzhydryl **14.4**	HF/anisole	72
thiol	Rink chloride **27.4**	5% TFA/CH_2Cl_2	40
	2-chlorotrityl **33.3**	1−50% TFA/CH_2Cl_2+5%TIS	46
urea	phoxime **81.3**	RNH_2/toluene 70 °C (diversification)	290
	Wang aldehyde **18.4**	95% TFA/Et_3SiH	84
	AMEBA **25.7**	5% TFA/CH_2Cl_2	108
	Marshall **87.1**	RNH_2/Et_3N/THF 60 °C (diversification)	302

the free peptide, the Boc-protected peptide, or the peptide containing a linker part (Scheme 181). These different fragments can be used for analysis or reattached onto a resin (**181.3**).

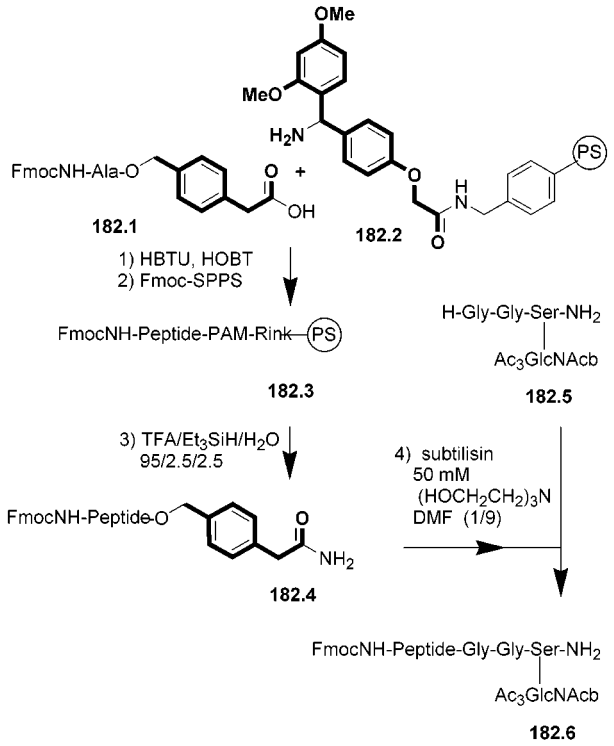
Scheme 181



One advantage of these two resins **180.1** and **180.2** relies on the prevention of side reactions often associated with the phenacyl linkers. The photolytic fragment is obtained in a high yield because the cleavable bond is not adjacent to the C-terminal amino acid. In addition, the photolytic fragment is obtained in a fully protected form and can be easily purified. The constructs **180.1** and **180.2** were used in the synthesis of Leu-enkephalin and angiotensin II, which were obtained in relatively good yields and good purities. The author also applied this strategy to peptide fragment condensation synthesis.

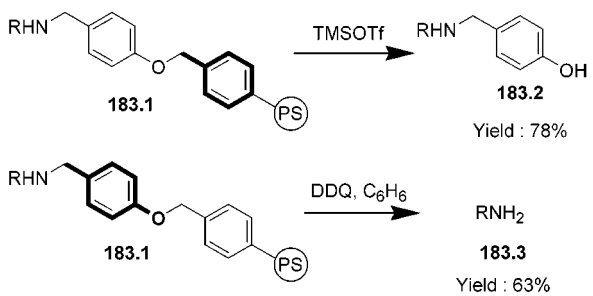
Wong[499] prepared some glycopeptides **182.6** using this methodology (Scheme 182). A Fmoc-protected alanine residue attached to the phenylacetamidomethyl (PAM) linker **182.1** was coupled to a Rink amide AM resin **182.2**. After peptide elongation, TFA cleavage conditions removed all acid-labile protecting groups from the side chains and detached the Fmoc-protected peptide PAM ester **182.4** from the solid support. This benzyl ester was used since it was found to be a good leaving group for subsequent peptide ligation. Accordingly, the segment condensation of the PAM peptide **182.4** with the *N*-terminally unprotected glycotripeptide **182.5** was catalyzed by protease subtilisin to give a glycopentadecapeptide in 84% yield.

Scheme 182



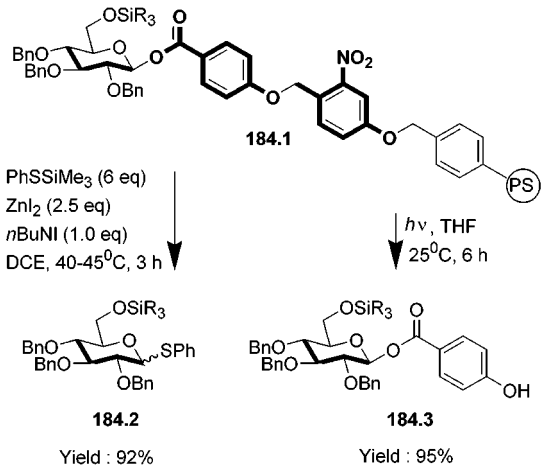
Kobayashi[88] used different conditions to release products from the amino-derivatized Wang resin **183.1**. Under strong acidic conditions (TMSOTf or TFA, 60 °C), the phenol **183.2** was dissociated from the Merrifield resin, and under oxidative conditions (DDQ in benzene), the amine product **183.3** was cleaved from the Wang linker in 63% yield (Scheme 183).

Scheme 183



Nicolaou[380] used a strategy based on multidetachable linkers in the synthesis of a dodecasaccharide. Under photolytic conditions, the cleavage of **184.1** afforded a phenolic ester **184.3** with a safe β-stereochemistry at the anomeric center, suitable for analysis. A cleavage/activation step using $PhSSiMe_3$ allows the preparation of thioglycoside **184.2**, which could be used, in a reiterative preparation of oligomers (Scheme 184).

Scheme 184



VII. Utilization of Linkers To Monitor Solid-Phase Organic Reactions

Monitoring of reactions in solid-phase synthesis is less accessible than in conventional solution-phase synthesis due to the presence of the support. Many analytical techniques available (colorimetric tests, HPLC, IR, or MS) are destructive and give only partial indications of the structure of the product. To solve this problem, special cleavage conditions with an appropriate linker can be used in order to release the information required for the monitoring.

1. Single-Bead Direct Analysis

Release from a single bead[500] can afford enough information to monitor a reaction on a solid support by mass spectroscopy, since this analytical method is extremely powerful and can be operated directly on the bead.

Bradley[501] showed that the utilization of MALDI-TOF MS analysis could be used for direct monitoring when submitting to TFA vapor a bead containing the product attached to the Rink linker. Others linkers such as Wang, HMPB, base labile, photolabile, or trityl linkers are also suitable for this technique.[502] The solid-phase synthesis of analogues of lysobactin and the katanosins were monitored using this procedure.[503] Laser photolysis has also been used to release products from photolabile phenacyl linkers for direct MALDI MS analysis.[504]

2. Controlled Partial Release

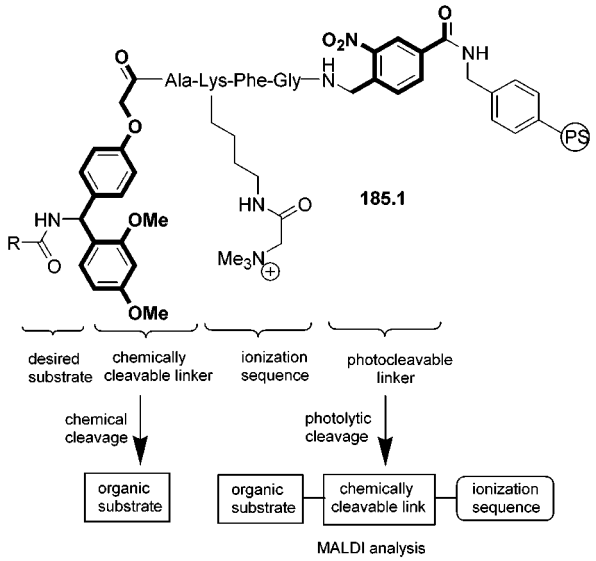
An alternative analytical method is to release only a small amount of product from the resin. Lerner[149] reported the utilization of gaseous TFA for partial release using MBHA linker. After Fmoc-SPPS of a peptide on a MBHA-derivatized resin, a dry-state severing method was used to release peptides from their solid supports. The MBHA linker was chosen for its slow release kinetics in the presence of gaseous TFA. This experiment involved TFA gas-phase cleavage followed by neutralization with gaseous NH_3/H_2O, allowing the released peptide to remain absorbed in the bead. The author showed that only 5% of the peptide was cleaved after 10 h with gaseous TFA. Gaseous TFA was also used for partial cleavage on Rink linker[505] or on a silyl linker.[148]

In this respect, photolabile linkers, in theory, provide a good solution due to their slow cleavage kinetics upon irradiation, ensuring that only a minimal amount of material is cleaved for analysis.

3. Monitoring with Multidetachable Linkers

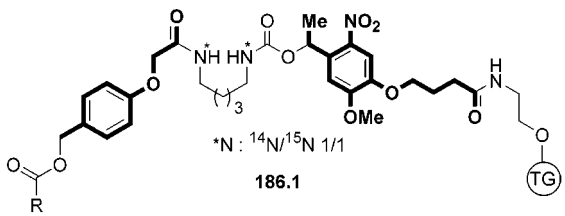
The previously described technique of multidetachable linkers[498] has also been applied for direct monitoring of organic reactions on solid support. The approach developed by Carrasco[506] with construct **185.1** involves a photocleavable linker, an ionization sequence to ensure a good detection by mass spectroscopy, and then a chemically cleavable linker (Rink) allowing the release of the product free of the linker sequence (Scheme 185).

Scheme 185



A dual-linker approach was also developed by McKeown[507] based on the photolabile carbamate **186.1** (Scheme 186). The MS sensitizing diamine

Scheme 186



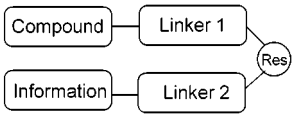
contains isotopically labeled atoms (a 1:1 mixture of $^{14}N_2$-diamine and doubly labeled $^{15}N_2$). Upon photolysis, all MS signals derived from this construct are

characteristic doublets, distinguishing them from extraneous and background noise. The same group recently reported a new construction with a hydrazine-sensitive linker (Dde **85.1**) and a thiol-sensitive linker (2-nitrophenylsulfonamide **118.1**) for analytical release and mass sensitization.[299]

VIII. Utilization of Linkers for Structural Elucidation of "Hits" in Combinatorial Chemistry

If the common role of linkers is to allow the efficient release of the organic product from the solid support, they can also be used to reveal information regarding the structure of the compound. In parallel synthesis, each compound is synthesized in a separate reaction vessel, for example in a 96-well plate. After cleavage from the solid support, one vessel gives one compound. These compounds are individually screened, and if one is active, the structure of a compound at a particular location is known and can be simply confirmed by analytical methods. For split/mix methods, even if one bead bears only one compound, many beads are usually being screened at the same time. To identify the structure of a hit, one solution is to code onto each bead some "information" to identify one bead from another. This "information" will enable the structure of the compound on the bead to be determined. In many cases a two-linker system is employed, one for the organic product and the other for the information or code (Scheme 187).

Scheme 187



A. Encoding Strategies

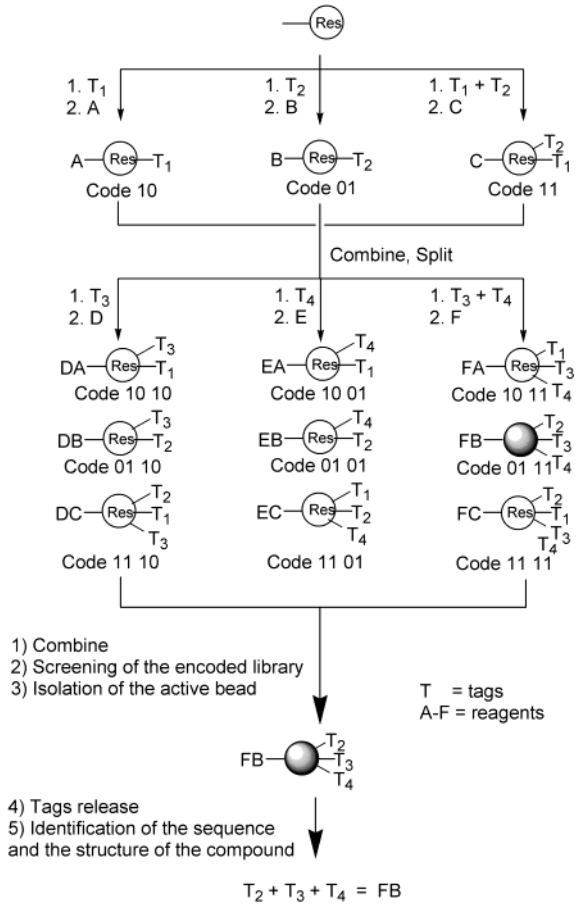
The basic idea behind encoding techniques is to record directly on the bead all the synthetic steps by introduction of a specific code for each step. After completion of the synthesis and detection of the active bead, the codes are read from or on the bead, enabling the identification of the "history" of this active bead. In this way, the different chemical steps are known and the structure of the compound can be proposed.[508−511]

1. Haloaromatic Tags for Binary Encoding Strategy

In this approach, chemical tags recording the reaction sequence are attached to the resin bead concurrently with the synthesis of the compound on the bead. The encoding sequence is based on a binary approach. At the end of the synthesis, each bead will have its own collection of tags (Scheme 188). Only a small proportion of the resin needs to be functionalized with the tags, but these must be highly stable, inert to the majority of reaction conditions, and easily detectable.

Still[514] used this binary encoding strategy, preparing haloaromatic molecules by alkylation of commercially available halophenols with ω-bromo-1-alkanols. These tags could be detected at levels of less than 0.1 pmol using electron-capture GC; so only

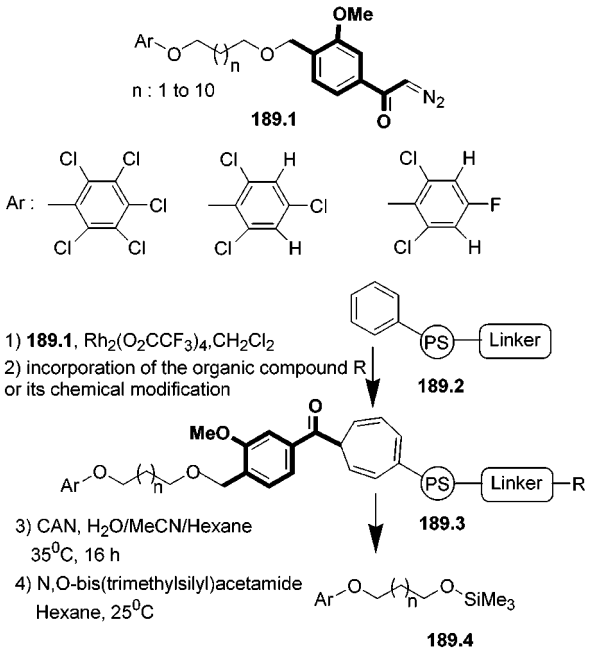
Scheme 188



1% levels of molecular tags per building blocks were needed for encoding. This minimizes the problems in library evaluation resulting from tag−receptor interactions when support-bound assays were used.[512,513]

Two different attachment strategies to bind the tags to the resin were successively used. In initial work, the tag was previously preloaded to a photocleavable linker in solution before attachment onto an amino-based resin through an amide bond.[514,515] At each step, only 1% of the free amino groups belonging to the growing product was devoted for tagging. After completion of the synthesis and identification of the active beads, the tag alcohols were released by irradiation at 366 nm and trapped by addition of bis(trimethylsilyl)acetamide to give the trimethylsilylated tag aryl ethers **189.4**. The resulting solution of tags could be analyzed directly by electron-capture capillary gas chromatography. The problem of this approach was the need to generate a free amino function at each step of the synthesis in order to perform tag attachment. A recent approach led to the attachment of the tags to the resin beads by rhodium-catalyzed acylcarbene insertion from a diazoketone function of the linker containing the tag **189.1** onto a phenyl group of the polystyrene matrix **189.2**.[516−518] The release of tags was then realized under an oxidative process by addition of ceric ammonium nitrate. After subjection of the liberated alcohols to bis(trimethylsilyl)acetamide, detection of the silylated tags **189.4** was accomplished as previously reported (Scheme 189).

Scheme 189



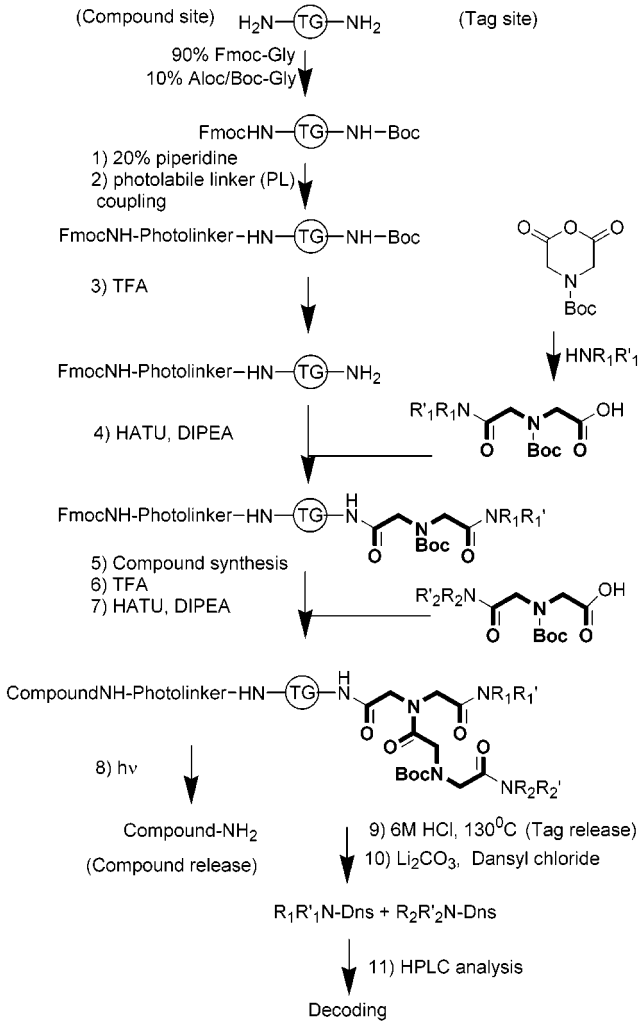
2. Secondary Amine Tags

An Affymax team led by Gallop[519] developed an encoding strategy based on the use of chemically robust secondary amines. These tags were incorporated as part of a polyamide backbone. This secondary amine-coding scheme uses an amine-based resin that is differentially functionalized with sites for ligand synthesis and sites for tag addition. These sites are defined by orthogonal protecting groups that permit the chemistry to be addressed unambiguously at either the compound (90% level) or tagging entities (10%) (Scheme 190).

At each step of a "split/pool" combinatorial synthesis, the addition or modification of the scaffold (R) is recorded by coupling the appropriate mixture of tag. Upon screening, after isolation of the active beads, individual beads are treated with HCl (6 N) in capillary tubes to release the secondary amines from the support. The liberated secondary amines are then reacted with dansyl chloride (Dns) and analyzed using HPLC fitted with a microbore column and a fluorescence detector (the detection threshold for these dansyl sulfonamides is typically 20−30 fmol).[520] An application of this technique using amino tags has been made in the synthesis of an encoded combinatorial library against plasmepsin II and cathepsin D.[521] Affymax has recently published a new set of amino tags and the optimization of analysis conditions.[522]

Amino tags have also been used by Powers[523] to encode olefin polymerization catalyst libraries. A bromomethyl polystyrene resin was used as the starting material, and 30% of the sites were capped with a secondary amine (tag) (one amine per member of the library). The other sites were used for the library construction. After identification of the active catalyst, the tag was released by treatment of the resin with ACE-Cl and then MeOH at 50 °C to give the corresponding amine, which was dansylated before HPLC analysis.

Scheme 190



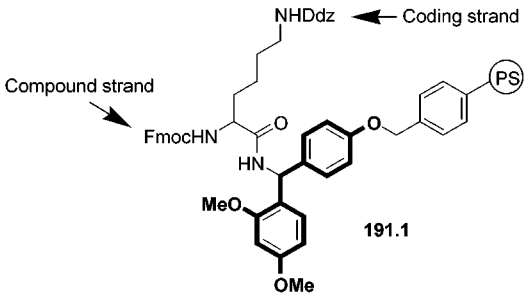
3. DNA-Encoding Strategy

The principle of a DNA encoding strategy, suggested by Brenner[524] in 1992 following an earlier patent by Affymax, is to code each building block by a determined sequence of oligonucleotides. An orthogonal protecting-group strategy was used to differentiate the DNA tag and the synthesized compound. On the DNA arm, a PCR primer is first introduced. This PCR primer plays the role of the linker between the solid matrix and the coding strand. Then, a split/mix synthesis of the compound is realized with concomitant incorporation of new nucleotide at each step on the coding strand. After concluding the synthesis, another PCR primer is added to the DNA side chain. After identification of the active bead, the appropriate enzyme is used to release the coding sequence, and this one is amplified by PCR affording the "history" of the bead.

4. Amino-Acid-Encoding Strategy

Zuckermann[525] developed an alternative method for the coding of building blocks by replacing the oligonuceotide sequence by a sequence of amino acids. Instead of defining a small proportion of the sites for the coding strand, a bifunctional linker **191.1** was used (Scheme 191). A lysine residue was first anchored onto a Rink amide linker. This lysine bore a base-labile Fmoc group on the α-amine devoted to the compound strand and a mildly acid-labile (5% TFA)

Scheme 191



Ddz group on the ϵ-amine for the "coding" strand (Scheme 191). In his paper, Zuckermann used four amino acids (Phe, Ala, Leu, and Gly) to code each building block by a sequence of three amino acids: for example, Phe-Ala-Leu for one building block, Gly-Leu-Phe for another one (64 coding possibilities). At the end of the synthesis, a *N*-terminal phenylalanine is added to the coding strand to serve as an internal standard for Edman sequencing. After identification of the active beads, subsequent Edman degradation of the coding strand provides the compound sequence. The authors noted that no significant interference of the coding strand in the biological evaluation of the compound was observed. Thus, the IC_{50} values of the compound/coding adduct were similar to that of the compound alone.

A similarly strategy was employed by Nikolaiev.[526] Fmoc protection was used for the coding strand and Boc protection for the compound strand. This time, the screening assay was carried out in solution where the compound was released, the coding strand still being on the resin. To enable the decoding, this procedure required that the solution containing the compound be spatially addressable to the bead from which it was originated.

Vagner[228] developed another approach of producing a peptide-encoded peptide library. The basic principle was to physically differentiate a screening area and a coding area. For this purpose, he used an enzyme shaving method to attribute the interior of the bead to the coding area and the surface to the screening area. The author dedicated Boc chemistry for the internal sites and Fmoc chemistry for the external sites. So, each amino acid added on the screening area was coded by another amino acid inside the bead. After selection of the active bead, the interior sequence was determined by Edman degradation from which the peptide sequence was deduced.

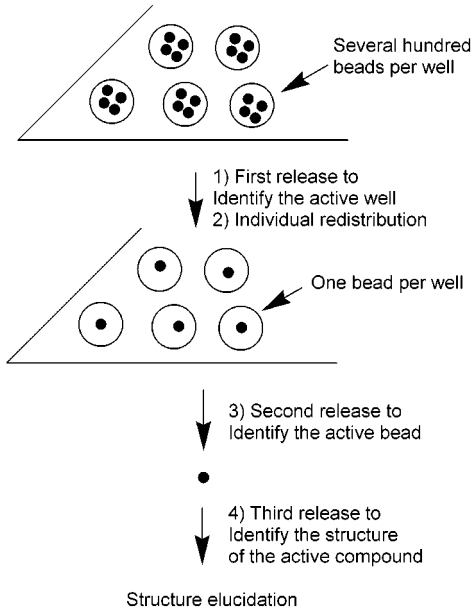
More recently, Camarero[527] described a novel technique called "encoded amino acid scanning". A defined sequence of *N*-Boc amino acids containing one cysteine residue Fmoc-protected on the thiol is attached onto a PAM-derivatized resin. Then a dodecapeptide library was synthesized with modification for two residues. When a modification occurred at one position, the thiol of the cysteine was deprotected and encoded with an appropriate amino acid. After completion of the synthesis, the dodecapeptides bearings the amino acid tags on the cysteine position were cleaved from the resin by addition of HF. Upon selection of the active peptides, the tags were removed from the cysteine by treatment with $Hg(OAc)_2$, revealing the modification effected on the peptide.

B. Multiple-Release

In this approach the compound is directly released from the support for biological screening. However, the release is only partial. A fraction of the compound is still on the bead to allow identification of the structure. A combination of linkers with different cleavage sensitivities is therefore required. This technique is therefore different from the controlled partial release where the cleavage resulted in a function of time of exposure to the cleavage conditions.

An example of a screening process using this method is shown in Scheme 192. The bead-based

Scheme 192

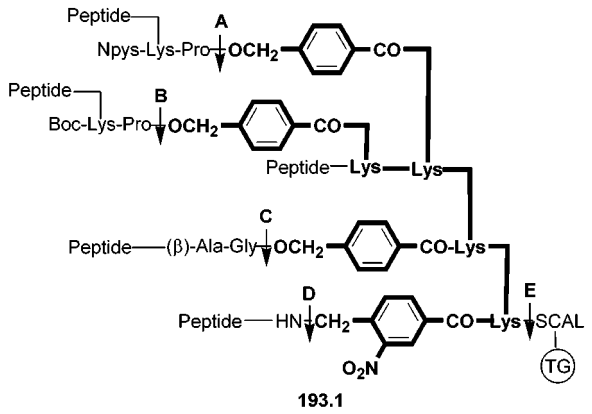


library is distributed into a standard 96-well microtiter plate with several hundred beads per well. A compound is partially released, liberating only a fraction of the loaded compounds per well. After screening, the beads belonging to the active well are redistributed individually. A second release is effected to allow the selection of the active bead, then the determination of its structure is made possible by a third release.

Lebl[528] developed multiple-cleavable linkers for Selectide. The first designed linker (**193.1**) could provide five independent releases (Scheme 193). However, the problem of this particular system was that the released products (peptides) bore different C-terminal moieties depending on the release performed and this could affect their activity. In further studies, an alternative attachment of the peptide was designed with two independent releases (NaOH saponification and TFA-promoted DKP formation), final identification being realized by Edman sequencing on a third strand of peptide still attached on the bead.[150]

The same group designed another new generation of double-cleavable linkers using iminodiacetic acid (Ida) as the key component.[529,530] After completion of the synthesis, the first release was realized at pH 8.5 after TFA activation (DKP formation). Then the

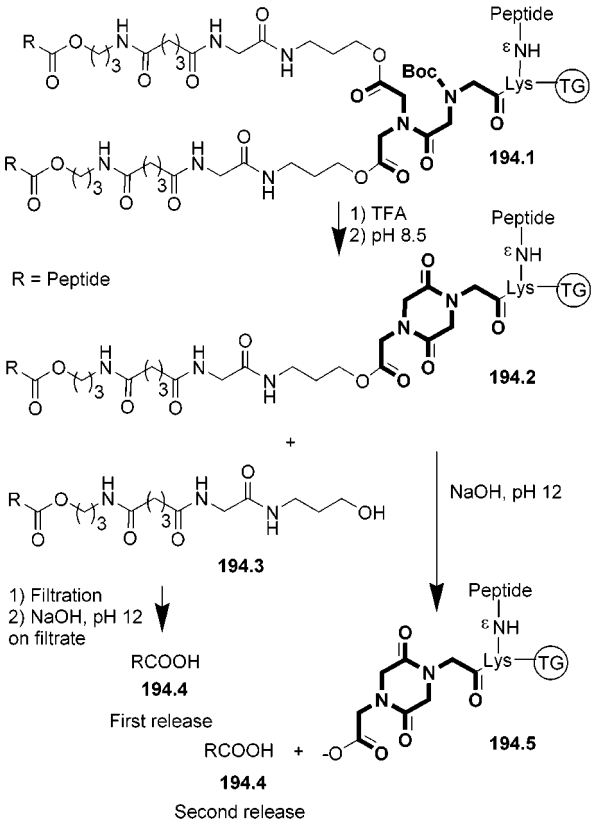
Scheme 193



Release A : 0.1M PPh_3/TsOH/DMF via DKP formation
Release B : 50% TFA via DKP formation
Release C : NaOH
Release D : Photolysis
Release E : 1M Me_3SiBr/thioanisole/TFA
SCAL : Safety Catch Acid Linker

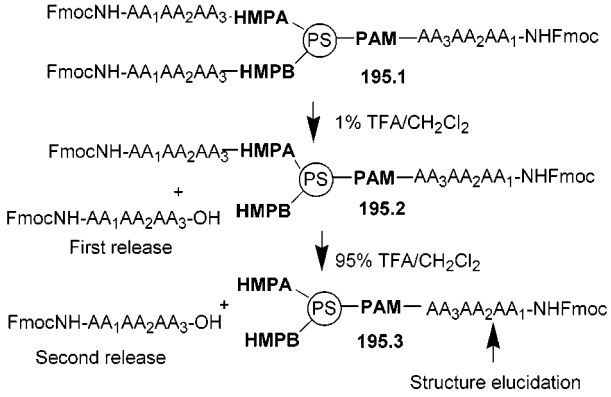
same compound (peptide **194.4**) was released a second time by treatment of the resin to NaOH (pH 12) (Scheme 194).

Scheme 194



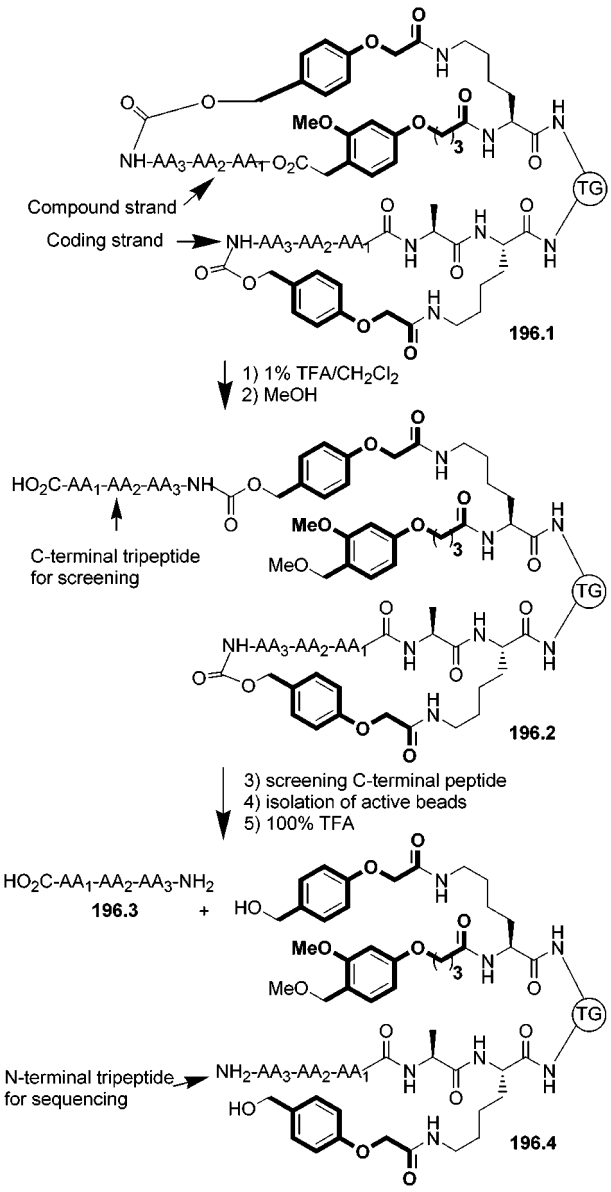
Bradley[531] developed an alternative approach using a combination of different linkers. A mixture of three different linkers was added in a ratio of 1:1:1 onto an aminomethyl resin. After Fmoc SPPS, the first release from the HMPB linker **195.1** was realized by treatment of the resin using 1% TFA in CH_2Cl_2. TFA (95%) treatment provides the second release from the HMPA linker **195.2**, and finally Edman degradation was accomplished on the last strand of **195.3** in order to identify the peptidic sequence (Scheme 195).

Scheme 195



Edman sequencing for the active bead after screening of an inverted C-terminal peptide library was made possible by Bradley[532,533] using a two-linker system (Scheme 196). An HMPB linker **196.1** was

Scheme 196

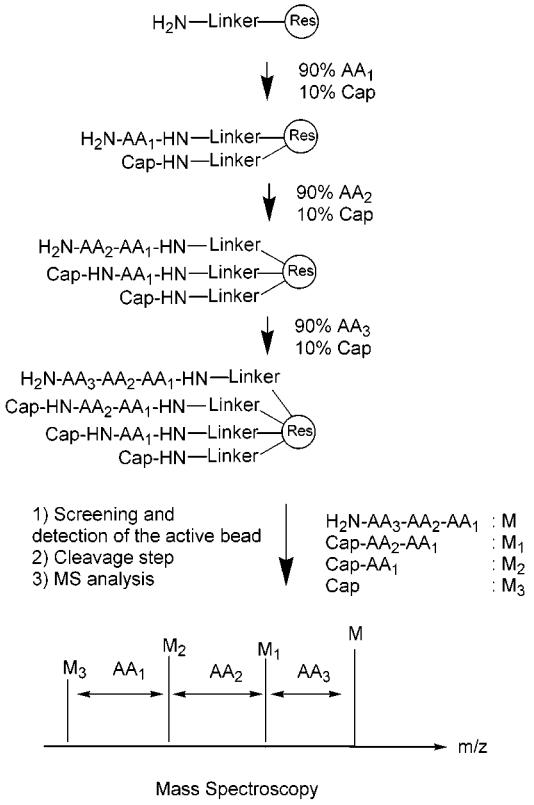


cleaved using 1% TFA, allowing the screening of an inverted C-terminal peptide library. More severe conditions (100% TFA) were applied on the other linker (HMPA) **196.2** to reveal, finally, the corresponding code in a way suitable for Edman sequencing (*N*-terminal peptide). This strategy relies both on encoding and multiple-cleavable linkers.

C. Ladder Scanning Strategy

The ladder strategy is a method for direct determination of peptide sequence by mass spectroscopy. For this strategy, at each step of the synthesis, a small part of the peptide is capped to block the synthesis. After selection of the active bead upon screening, the bead is removed and submitted to cleavage, which furnishes a series of truncated products: the final compound and the family of its capped precursors. Identification of the structure, especially its sequence, is realized by mass spectroscopy as each building block is designated by the mass difference in the mass spectrum (Scheme 197). This

Scheme 197

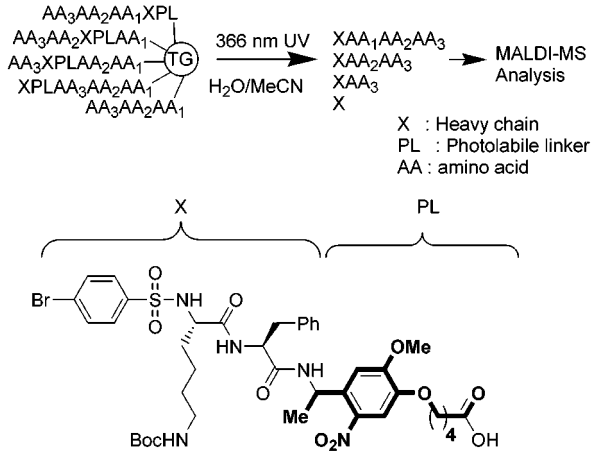


method can be compared to the sequencing of peptides by enzymatic degradation.

Youngquist[534] started this technique for the sequencing of peptides on solid support. The resin-bound H_2N-β-Ala-Pro-Pro-Pro-Arg-Met-O−Resin was prepared on an aminomethyl-derivatized TentaGel support and served as a linker and a mass sensitizer. After completion of the peptide synthesis, the release of the peptides was carried out by cyanogen bromide digestion (the methionine will be converted into the homoserine lactone) releasing the different peptide-β-Ala-Pro-Pro-Pro-Arg-homoserine lactone. The linker therefore increases the molecular mass of the released compounds and ensures that each member of the peptide ladder has a mass greater than the chemical noise produced by desorption of the UV-absorbing matrix. The MALDI-TOF mass spectroscopy technique used proved to be powerful as only 1% of the material from a single bead was required to give good sequencing data. The author applied this technique in the identification of peptide ligands of streptavidin and against a HIV-1 monoclonal antibody.

Burguess[535] employed a modified approach for the synthesis of a library of tetrapeptides on TentaGel resin. This time the truncation was not realized through partial capping but by insertion of a photolabile linker (PL) **198.1** on 5% of the amino sites. At the end of the synthesis, photolytic cleavage produces a mixture of different fragments, which were analyzed by MALDI-MS enabling determination of the sequence of the active bead. Again a "heavy" spacer (X) was used to generate relatively heavy fragments (larger than 550 Da) to facilitate detection (Scheme 198).

Scheme 198

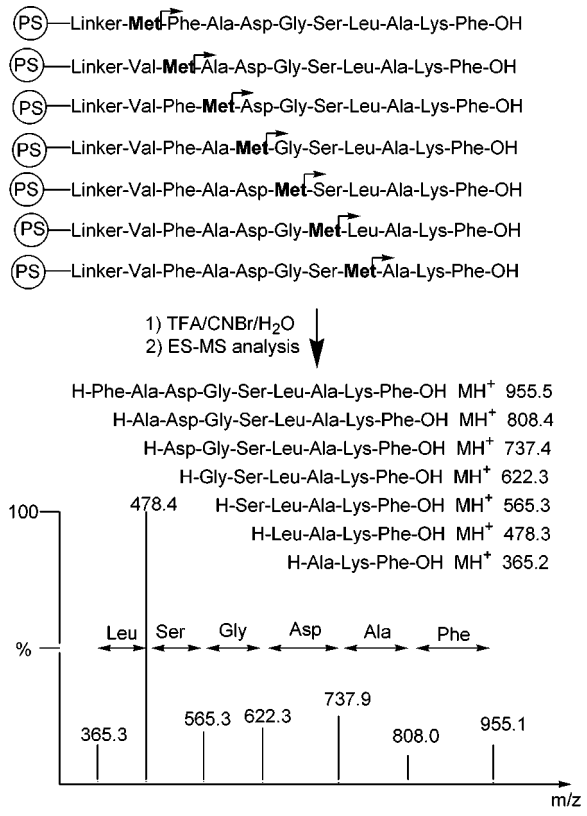


Bradley[244] reported a method of ladder identification based on the incorporation of a small amount of Fmoc-methionine (5−10%) with each amino acid during the synthesis of the peptide library. Thus, the inverted decapeptide H_2N−Val-Phe-Ala-Asp-Gly-Ser-Leu-Ala-Lys-Phe-OH was prepared with 10% methionine incorporated at positions from Val to Leu, giving the parent peptide and a family of seven "methionine scanned" daughters. Treatment with BrCN in TFA/H_2O for 24 h resulted in cleavage of this mixture of peptides of different sizes. The correct sequence of the peptide was finally determined from this mixture by MS-ES analysis, after cleavage was realized on a single bead (Scheme 199).

A cleavable thioester backbone (a Gly-S-β-Ala unit) was used by Dawson[536] to build his ladder library. Release was effected by addition of a solution of 1 M NaOH and structure determination performed by MALDI-MS.

Meldal[537] developed this strategy for the preparation of glycopeptide libraries. The Fmoc-SPPS synthesis was carried out with a photolabile linker with simultaneous capping effected by using a mixture of

Scheme 199



9:1 Fmoc and Boc residues. To identify the structure and to distinguish glycans of identical mass, the glycosyl amino building blocks incorporated in the library were "encoded" with simple carboxylic acids as capping group labels. Release was achieved by direct radiation of the beads by the MALDI N_2 laser.

IX. Conclusion

This comprehensive review demonstrates the vast literature, both old and modern, associated with linker chemistries. As Figure 1 shows, linker chemistry is experiencing a rebirth not seen since the days of Merrifield, only much greater in its magnitude and impact.

The number of different linkers used in the last 16 months is vast, although the mild acid-cleavable linkers dominate with Wang, Rink, and trityl linkers (Figures 2 and 3) being strong favorites. Nucleophilic cleavage is also very popular with 26% of the papers in this period using this method. Silicon-based linkers

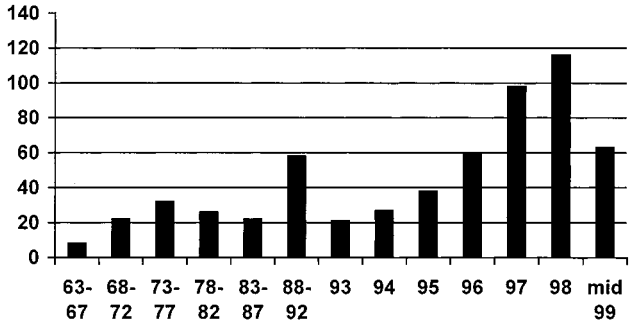


Figure 1. Number of publications dedicated to new or novel utilization of linkers. (Data from the review).

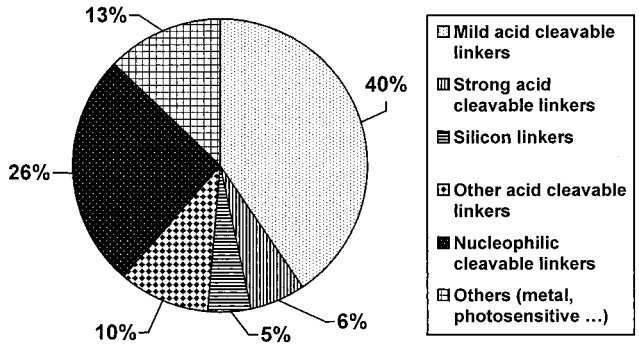


Figure 2. Percentage of the different types of linkers referenced in the literature over the last 16 months.

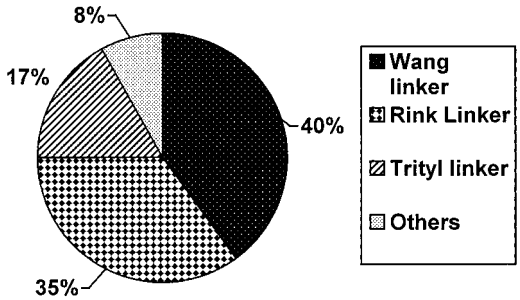


Figure 3. Proportion of the different mild acid cleavable linkers referenced.

are now making quite an impact (5%), a trend that will undoubtedly continue as modern linkers evolve from the peptide linkers of the past.

In summary, we have shown the broad range of cleavage conditions available to the solid-phase chemist. Undoubtedly, much more remains to be done, and the next few years will see many and new exciting cleavage strategies unveiled.

X. Abbreviations

1. Resins

AG	ArgoGel
AP	ArgoPore
CP	Crown/Pin
CPG	controlled pore glass
KPA	Kieselguhr/polyacrylamide
MP	macroreticular polystyrene (macroporous resin)
PA	polyacrylamide
PEG	poly(ethylene glycol)
PEGA	poly(ethylene glycol) dimethylacrylamide
PS	polystyrene
Res	Resin
TG	TentaGel

2. Linkers

ADCC	4-acetyl-3,5-dioxo-1-methylcyclohexane carboxamide
AMEBA	acid-sensitive methoxy benzaldehyde
ANP	3-amino-3-(2-nitrophenyl)propionyl
BAL	backbone amide linker
BHA	benzhydrylamine
CHA	5-((5-[Fmoc-amino]-10,11-dihydrodibenzo[a,d]-cyclohepten-2yl)oxy)valeric acid
HE	5-((5-[Fmoc-amino]-10,11-dibenzo[*a,d*]cyclohepten-2yl)oxy)valeric acid
DHPP	4-(1′,1′-dimethyl-1′-hydroxypropyl)phenoxyacetyl
Dpr(Phoc)	2-amino-3-*N*-phenoxycarbonylaminopropionic acid

DSA	4-(4-methoxyphenyl-Boc-amino)methyl-3-methoxyphenylsulfinyl-6-hexanoic acid
DSB	4-(2,5-dimethyl-4-methylsulfinylphenyl)-4-hydroxybutanoic acid
HAL	hypersensitive acide linker
HMBA	4-hydroxymethylbenzoic acid
HMPB	hydroxymethylmethoxyphenoxybutyric acid
HMPA	hydroxymethylphenoxyacetic acid
HMPP	hydroxymethylphenoxypropionic acid
MAMP	Merrifield, α-methoxyphenyl
MBHA	methylbenzhydrylamine
Nbb	3-nitrobenzamidobenzyl
NBH	2′-nitrobenzhydryl
NBHA	2′-nitrobenzhydrylamine
NPE	2-(2-nitrophenyl)ethyl
NpSSMpact	2-methoxy-5-(2-((2-nitrophenyl)dithio)-1-oxopropyl)phenylacetic acid
OMPA	4-(3-hydroxy-4-methoxypentyl)phenylacetic acid
ONB	*o*-nitrobenzyl
PAM	phenylacetamidomethyl
PAL	peptide amide linker
PL	photolabile linker
Pon	Boc-aminoacyl-4-[4-(oxymethyl)phenylacetoxymethyl]-3-nitrobenzamidomethyl resin
Pop	Boc-aminoacyl-2-[4(oxymethyl)phenylacetoxy]-propionyl resin
PPOA	4-(2-bromopropionyl)phenoxyacetic acid
QDA	hydroquinone-*O*,*O*-diacetic acid
RAM	Rink amide aminomethyl resin
REM	regenerated resin and Michael addition
SAL	silyl amide linker
SASRIN	superacid sensitive resin
SCAL	safety-catch acid sensitive linker
XAL	xanthenyl acid labile linker

3. Various

AA	amino acid
Ac	acetyl
ACE-Cl	α-chloroethylchloroformate
AIBN	azobis(isobutyronitrile)
Ar	aryl
Atm	atmosphere
binap	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Boc	*tert*-butyloxycarbonyl
Bpoc	2-(*p*-biphenyl)-2-propyloxycarbonyl
Bn	benzyl
BTAF	benzyltrimethylammonium fluoride
BTAHF	benzyltrimethylammonium hydrogen difluoride
CAN	ammonium cerium (IV) nitrate
Cbz	benzyloxycarbonyl
CSA	camphor sulfonic acid
Cy	cyclohexyl
dba	dibenzylidene acetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCP	1,3-dichloropropane
Dde	1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl
Ddz	*N*-((2-(3,5-dimethoxyphenyl)prop-2-yl)oxy)carbonyl
DTT	dithiothreitol
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
Dha	dehydroalanine
DIBAL-H	diisobutylaluminum hydride
DIC	*N*,*N*-diisopropylcarbodiimide
DIPEA	*N*,*N*-diisopropylethylamine
DIPHOS	1,2-bis(diphenylphosphino)ethane
DKP	diketopiperazine
DMA	dimethyacetamide
DMAD	dimethylacetylenedicarboxylate
DMAP	4-*N*,*N*-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DMT	4,4′-dimethoxytrityl
Dns	dansyl
DOPA	3,4-dihydroxyphenylalanine
dppp	1,3-bis(diphenylphosphino)propane
dppe	1,3-bis(diphenylphosphino)ethane
DVB	divinylbenzene
EDT	ethanedithiol
EE	2-ethoxyethyl
Et	ethyl
Fmoc	9-fluorenylmethyloxycarbonyl
FPLC	fast-phase liquid chromatography
GC	gas chromatography
HATU	2-(1*H*-7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt	*N*-hydroxybenzotriazole
HPLC	high-pressure liquid chromatography
Ida	iminodiacetic acid
*i*Pr	isopropyl
IR	infrared
LHMDS	lithium hexamethyldisilazane
*m*CPBA	3-chloroperoxybenzoic acid
MALDI	matrix-assisted laser desorbtion ionization
Me	methyl
MES	morpholinoethane sulfonic acid
Ms	mesyl
MS	mass spectroscopy
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
Ns	nosyl
OEE	*o*-ethoxyethylether
PBS	phosphate-buffered saline
Phth	phthaloyl
PMB	paramethoxybenzyl
ppb	parts per billion
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
RCM	ring-closing metathesis
RP	reverse-phase
RT	room temperature
SPE	solid-phase extraction
SPOS	solid-phase organic synthesis
SPPS	solid-phase peptide synthesis
*t*Bu	*tert*-butyl
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCE	trichloroethane
TCEP	tris(2-carboxyethyl)phosphine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	trifluoroethanol
TFMSA	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TIS	triisopropylsilane
TLC	thin-layer chromatography
TMOF	trimethylorthoformate
TMS	trimethylsilyl
TMSE	2-(trimethylsilyl)ethyl

TOF	time-of-flight
Ts	tosyl
UV	ultraviolet

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