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Linkers for Solid Phase Organic Synthesis

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1. INTRODUCTION

Solid phase chemistry has been used for the synthesis of molecules for over 30 years, first for peptide,[1,2] and then nucleotide[3] synthesis. In the seventies, the synthesis of small organic molecules on the solid phase was investigated by a number of groups.[4,5] However, the wide range of chemical reactions that needed to be

optimized on the solid phase greatly reduced any advantage gained using this approach for the synthesis of the small number of molecules required. The advent of combinatorial techniques, first for peptides and nucleotides[6,7] then for small molecules,[8,9] has brought about a major revival in the study of solid phase organic synthesis. Large numbers of reactions have been translated from solution phase to solid phase[10-12] and more continue to be developed.

Critical to this process is the attachment of the molecule to the solid phase. This is achieved through a cleavable linker.[13,14] A linker has been described as a bifunctional protecting group (Figure 1) - it is attached to the molecule being synthesized through a bond labile to the cleavage conditions (e.g. silyl ethers, esters, carbamates, etc.) and is attached to the solid phase polymer through a more stable bond (alkyl ethers, amides, or alkanes). This definition gives a clear picture for many of the linkers used, and is readily visualized by synthetic chemists familiar with protecting group methods used in standard synthetic approaches. Indeed, linkers perform similar functions to protecting groups and many of the linkers developed in recent years are based on protecting groups frequently used in solution phase synthesis. There are, however, many linkers that are not based on common protecting group methods, such as the increasing range of traceless linkers, and those that rely on β-cleavage or cyclization. These fall into the broader definition of a linker as a connection between the molecule being synthesized and the solid phase polymer that is cleaved to release the desired molecule. This cleavage may involve a range of techniques and give a range of functional groups. The functional group obtained may be dependent not only on the linker, but also on the method of cleavage.

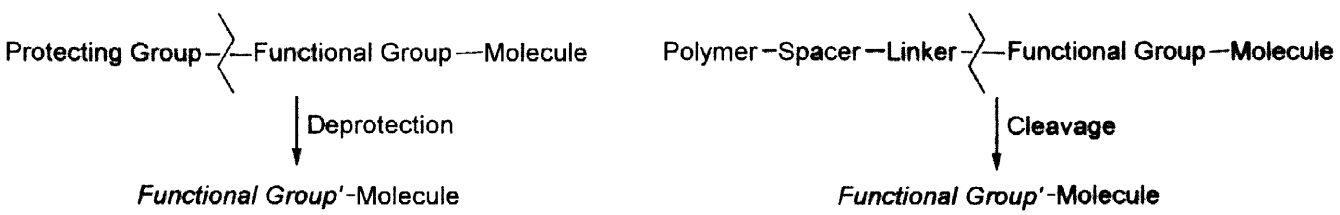


Figure 1. Linkers can perform a similar function to traditional protecting groups.

The ideal linker would fulfill a number of important criteria.

- It would be cheap and readily available.
- The attachment of starting material would be readily achieved in high yield.
- The linker would be stable to the chemistry used in the synthesis.
- Cleavage would be efficient under conditions that do not damage the final product(s).

Given that linkers are often applied to the synthesis of large libraries of compounds, a further important criterion for the ideal linker is:

- The cleavage method should be easily worked up in large numbers and should not introduce impurities that are difficult to remove.

Many linkers do not achieve all of these criteria. The attachment process may be problematic, although attachment via solution phase (Section 4) may be a valid approach. All linkers must survive the synthesis, although the choice of synthetic route may determine the choice of linker, and vice versa. Cleavage conditions are often harsh, for example TFA, and not all molecules will survive these conditions. It is important to assess this when planning a library synthesis.

The last point is probably open to the greatest contention. Many work up procedures add to the number of post-cleavage manipulations. Most cleavage methods use excess reagents to ensure complete cleavage. Many use reagents that are volatile, and excess reagent is removed by evaporation. Other methods use reagents that may be removed by lyopholization, for example, NH_4OH. A number of cleavage methods, though, use reagents that are not readily removed by these simple methods, for example cleavage using lithium aluminum hydride. Until recently, there were very few methods suitable for purifying the cleaved products in high numbers. However, new techniques of high throughput purification,[15] the use of disposable short columns[16] and solid phase reagents to remove impurities[17-19] may make the introduction of impurities in the cleavage step less problematic than it was only a few years ago.

It is important to consider how these extra manipulations may be performed in the numbers required for a library. The use of solid phase reagents to remove impurities is limited to cases where solid phase reagents suitable for the purification step are available. However, the process is easily performed in large numbers, requiring only a filtration step to separate the solid phase purification reagent from the purified product. Other methods, such as the use of short Solid Phase Extraction columns and high throughput HPLC are useful for small to medium numbers of compounds, but can be very time consuming if large numbers are being prepared. Aqueous work up can be automated with modern robotics, though these can typically handle up to only a few hundred compounds at a time. With these factors in mind, the selection of linker and cleavage method is not only based on the compounds being prepared but also on the size of library.

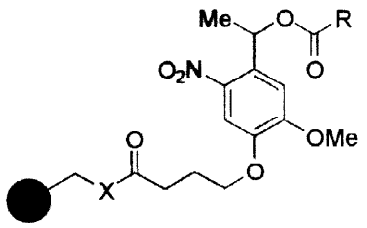
It is not surprising that a wide range of linkers have been reported in recent years given the range of reactions that a linker may have to survive during the synthesis of a molecule, the different types of molecules and functional groups that may have to survive the cleavage conditions, and the wide range of functional groups through which a substrate may be attached to the solid phase.

This review covers papers published up to August 1998. It will focus on the use of linkers for the synthesis of small organic molecules. Linkers that were initially developed for peptide synthesis and later used for the small molecule synthesis are also described. After a brief discussion on the general design and use of linkers, the emphasis of this review is on the functional group obtained after cleavage.

2. LINKER DESIGN

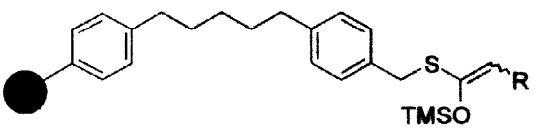
The choice of base polymer, spacer (any atoms between the polymer and the linker) and linker requires careful consideration when planning a reaction sequence on the solid phase. Polymer considerations are outside the realm of this review, but include such issues as solvation (poor solvation may hinder the release of the product molecule) and the presence of functional groups that may interfere with the chemistry. Similarly, spacers are not emphasized in this review, but the presence of problematic functional groups within the spacer has been reported. The method of attachment of the linker to the solid phase may also present problems to the subsequent synthesis on the solid phase. For example, the amide bond used to attach a photolabile carboxylic acid linker **1b** was believed to interfere with subsequent chemistry.[20] Replacement of the amide with an ester bond **1a** resulted in successful synthesis. Unnecessary heteroatoms were removed from the spacer of linker **2** so as to improve the overall performance when using a lanthanide catalyst.[21] Although preparation of the new spacer/linker combination required some synthetic effort, the workers were rewarded with significant improvements in the yields.

To cover this area in depth would require a separate review. However, it is important to consider the polymer, spacer and linker, as they may affect the outcome of a synthesis.



1

(a) X = O avoids the acidic amide proton present when (b) X = NH



2

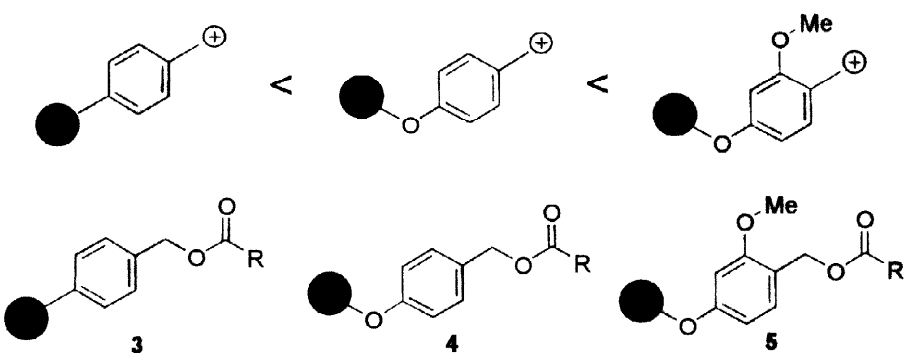
Gives superior yields for $Sc(OTf)_3$ chemistry than Wang or chloromethylpolystyrene derived linker

3. TYPES OF LINKER

In this section a brief description is given for each of the most commonly used types of linkers, which are categorized according to the method of cleavage. Linkers that rely on less common types of cleavage methods, such as oxidation and reduction, are discussed in Section 7.

3.1. Acid Labile

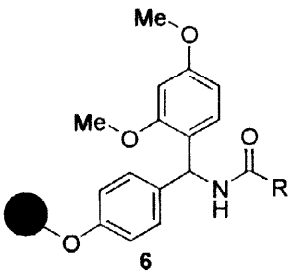
Strong acid is one of the most common cleavage conditions used in solid phase synthesis. Volatile acids, such as HF or much more commonly TFA, allow easy removal of excess cleavage reagent by evaporation. The lability of an acid labile linker is dependent on the relative stability of the protonated linker versus the cation formed upon cleavage. Therefore within a series of linkers, the more stable the cation formed, the more labile the linker is to acid. This is best illustrated using ester linkers. The stability of the illustrated cations increases from left to right as the number of electron donating groups increases, hence it is not surprising that the same trend is observed when comparing the ester linker **3**, derived from hydroxymethylpolystyrene linker (frequently call the Merrifield linker), which requires HF for cleavage, the Wang linker **4**, 50% TFA/DCM, and the Sasrin linker **5**, 1-3% TFA/DCM (Figure 2).



3 4 5

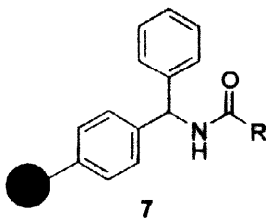
Figure 2

Similar trends are observed for amide linkers, with the Rink linker **6** (TFA cleavage) being significantly more acid labile than the benzhydryl linker **7** (HF cleavage).



6

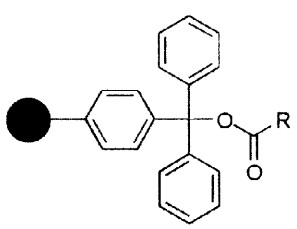
Rink Linker



7

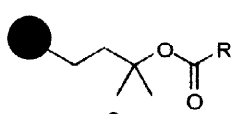
Benzhydryl linker

As is mentioned below, linkers based on ester bonds, such as **3**, **4**, and **5**, may also be cleaved by nucleophilic attack, e.g. with NaOMe to give the methyl ester. Hence, the acid labile linkers for carboxylic acids may also be cleaved, by these nucleophilic conditions. This is more of a problem with the Wang linker than it is for the Sasrin linker, primarily because of steric factors. Lability towards nucleophiles can be reduced by using sterically congested linkers. For example, both the trityl linker **8** and the hindered handle **9** are significantly hindered such that cleavage by even reactive and unhindered nucleophiles is limited.



8

Trityl linker

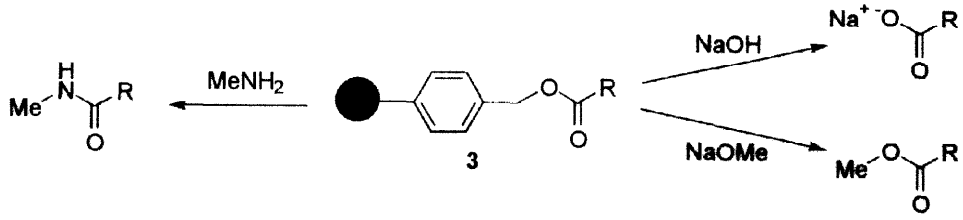


9

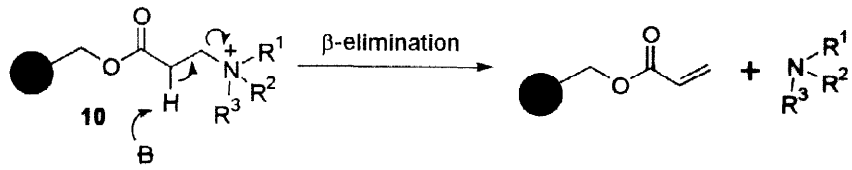
Hindered handle

3.2. Base Labile

Although the term 'base labile' is used, two types of cleavage are included under this heading. The more common type actually involves nucleophilic addition/elimination, usually on an ester, whereas the less common type involves a base catalyzed reaction, such as elimination or cyclization. The nucleophilic labile linker is typified by the ester linker derived from hydroxymethylpolystyrene **3**, already discussed above as an HF labile linker. Treatment with NaOH solution leads to the cleavage as the salt of the carboxylic acid (Scheme 1). Cleavage may also be achieved using NaOMe in MeOH to give the methyl carboxylic ester, or by an unhindered amine such as methylamine to give the amide. All of these cleavage reagents are bases, although the reactivity is determined primarily by their nucleophilicity. The true base labile linker is demonstrated by the tertiary amine linker **10** (Scheme 2). Cleavage occurs by Hofmann elimination of the ammonium salt and hence reactivity is determined by the basicity of the cleavage reagent.[22-25]

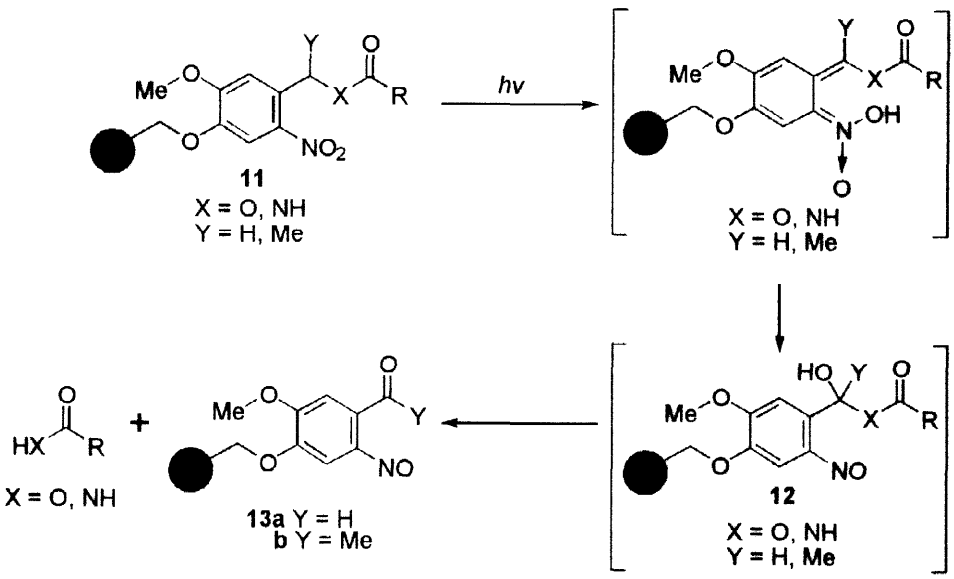


Scheme 1



Scheme 2

3.3. Photolabile



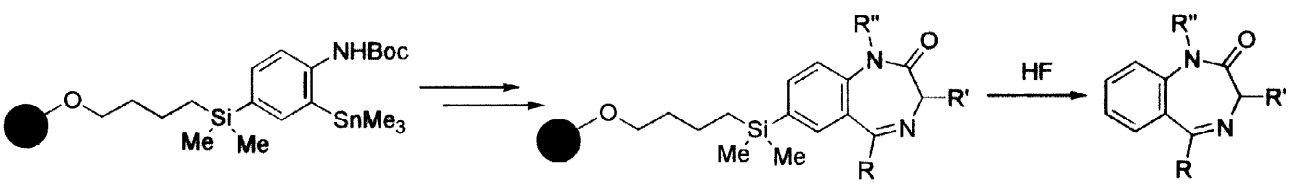
Scheme 3

Photolabile linkers are not as commonly used as either the acid labile or base labile linkers. The most common type is based on the nitrobenzyl moiety.[26,27] On irradiation of **11**, a 1,5-hydrogen abstraction occurs (Scheme 3). Further rearrangement leads to the formation of the acetal **12**, which then undergoes elimination releasing the product.[28] Generally, it has been found that, for the example illustrated, having an alpha-methyl group, which leads to formation of a ketone **13b** rather than an aldehyde **13a**, gives superior yields. This is due to two factors: the ketone is a superior chromophore than the aldehdye; and the product, once cleaved, can reattach to the solid phase through the aldehyde group. Electron donating alkoxy substitutions on the aryl group also generally improve yields.[29] Photolytic reactions take significantly longer for polymer bound substrates than they do for compounds in solution, because of shadowing by the polymer present. This prolonged treatment may be damaging to some compounds. One of the key challenges in this field is to improve cleavage rates and yields

whilst ensuring that cleavage does not occur inadvertently under ambient laboratory lighting. With the potential of developing a linker that will be stable to a large range of chemistries, then cleave under relatively neutral conditions, there continues to be significant research into photolabile linkers, and further improvements should be expected over the next few years.

3.4. Traceless Linkers

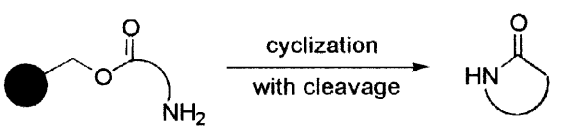
Most linkers leave a residue attached to the cleaved molecule; that is the functional group (or a derivative thereof) used to attach the molecule to the linker, i.e. a carboxylic acid, an amide or an alcohol. This is not always desirable for a library. For this reason, a number of groups have investigated linkers that leave no obvious residue on the cleaved molecule, *traceless linkers*. For the purpose of this review, a traceless linker is defined as one where a new carbon-hydrogen or carbon-carbon bond is formed at the linkage site of the cleaved molecule. This definition includes rearrangements such as retrocycloadditions. By far the most common form are the aryl silyl linkers that are used to attach aromatic molecules and cleave forming a new carbon-hydrogen bond (e.g. Scheme 4).[30,31] These are discussed in detail below (Section 8.1), but they usually rely on cleavage by strong acid such as HF, or TFA. Other strong electrophiles may be used for cleavage, such as I^+, but that application does not fall into the above definition of a traceless linker.



Scheme 4

3.5. Cyclative Cleavage

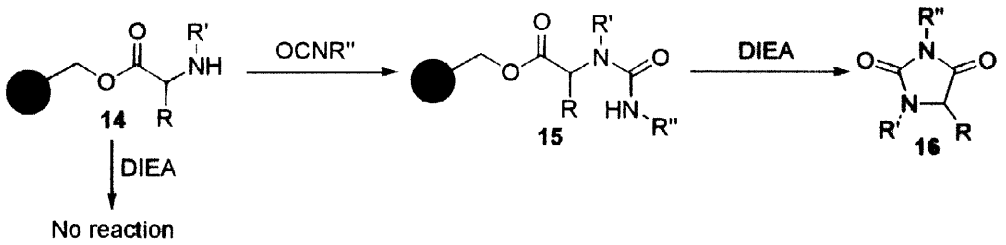
If the bond being broken in an intramolecular reaction is involved in attaching the molecule to the solid phase (i.e. part of the linker) then it is possible to achieve both cyclization and cleavage in the one step, i.e. cyclative cleavage. This is best illustrated by attack of a nucleophile, such as an amine, onto an ester derived linker (Scheme 5) to release a lactam. Rates of cyclization are dependant on the side-chains present on the cycle being formed, and hence vary from compound to compound. This can lead to variable yields.



Scheme 5

One of the ideals of solid phase chemistry, especially when used for preparing libraries, is to obtain products in high purity on cleavage from the solid phase, avoiding the need for purification. Using cyclative cleavage, only molecules containing the nucleophile will undergo cleavage, hence even if the synthetic step(s) which introduced the nuclephile into the molecule went in poor conversion, mainly the desired product will be obtained after cleavage. This method results in high purity, but at the cost of potentially reduced yields. For example, treatment of an amino acid attached to hydroxymethylpolystyrene **14** with an isocyanate gives the urea

15 (Scheme 6).[32] Treatment of 15 with base leads to nucleophilic attack on the ester and cleavage of the product as the hydantoin 16. Only the urea 15 will undergo cleavage under these conditions, any unreacted amino acid 14 will remain on the solid phase. The yields can vary widely, although the purity is generally high.

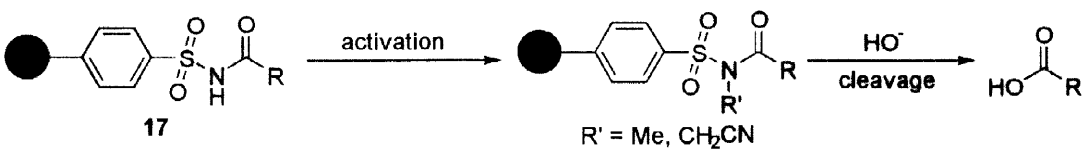


Scheme 6

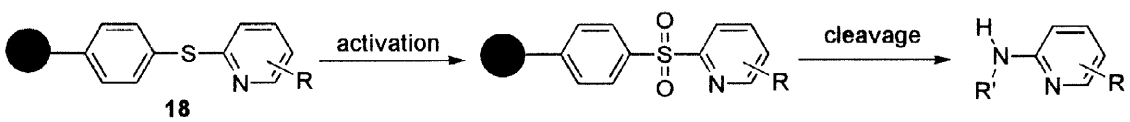
3.6. Safety Catch Linkers

Safety catch linkers are those that rely on a two step cleavage process.[33] The first step involves activation of the linker, the second step involves the actual cleavage. This is illustrated using two examples. Kenner's safety catch linker 17[34-37] is stable to both acidic and basic conditions until the nitrogen is alkylated either with diazomethane or iodoacetonitrile (Scheme 7). Once activated by alkylation, cleavage proceeds under nucleophilic conditions. A second example is the pyrimidyl linker 18 (Scheme 8).[38] The thiol linkage is stable to a range of conditions, but once activated by oxidization, cleavage is achieved by aromatic nucleophilic substitution with an amine.

The view is held by many that these linkers are advantageous as they are stable to a range of conditions, cleavage occurs under mild conditions. In contrast, the conditions for the activation steps are often harsh. The main advantage of these linkers is that if there is a need to use conditions similar to the cleavage conditions during the synthesis, this can be accommodated as the linker is stable until activated. However, the product being cleaved must be stable to both the activation and the cleavage conditions. For example, using Kenner's safety catch linker, the target molecule must be stable to the strong alkylation conditions, as well as the basic conditions of cleavage. Similarly, for the pyridyl linker, the target molecule must be stable to both the oxidation conditions, as well as the nucleophilic conditions. These stability issues must be considered when planning the application of these linkers.



Scheme 7



Scheme 8

4. ATTACHMENT METHODS

Usually, the starting compound is attached to the support-bound linker. This method is acceptable when the attachment process is achievable in good yield. However, for some linkers, this attachment of the starting material is problematic. This may be for a number of reasons. It may be that the reaction is disfavoured on steric or electronic grounds, leading to low loading on the solid phase. It is possible that an unstable intermediate is formed on the solid phase that leads to unwanted by-products, which are released on cleavage and contaminate the final product. Either way, this will lead to unsatisfactory results. One way of circumventing this problem is to attach the starting material to the linker in solution (Figure 3). The combined linker-starting substrate conjugate can be purified using conventional techniques, then attached to the solid phase using an efficient method, such as amide bond formation. Throughout the review, this method is called *attachment via solution phase*. It has the advantage that high loading of pure material can be achieved, however, the disadvantage is that the solution phase syntheses may require multiple steps and may not be amenable to high throughput. If only a limited variety of starting materials is used, this is acceptable, but if significant diversity is planned at the stage of the starting materials, then production of the library may be greatly retarded using this method.

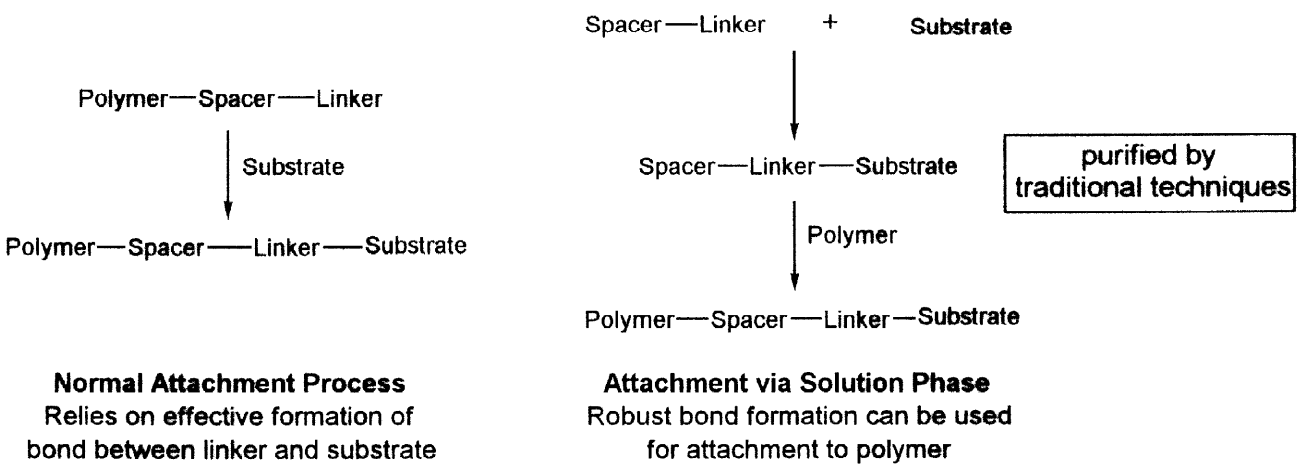


Figure 3

5. SCAVENGERS

During acidic cleavage, a carbocation is typically formed on the solid phase. This carbocation may react with nucleophilic species. If the nucleophilic species is part of the product molecule being cleaved, then the molecule may reattach to the solid phase by a non-cleavable bond, resulting in lower yields of cleaved product. This has erroneously been interpreted as failure to cleave, when in fact it is due to successful cleavage followed by undesired reattachment. Adopting harsher cleavage conditions would not markedly improve the yield, instead, it is necessary to quench the cation prior to its reaction with the cleaved product. This is achieved by scavengers.[39] The selection of scavengers is based on a number of factors:

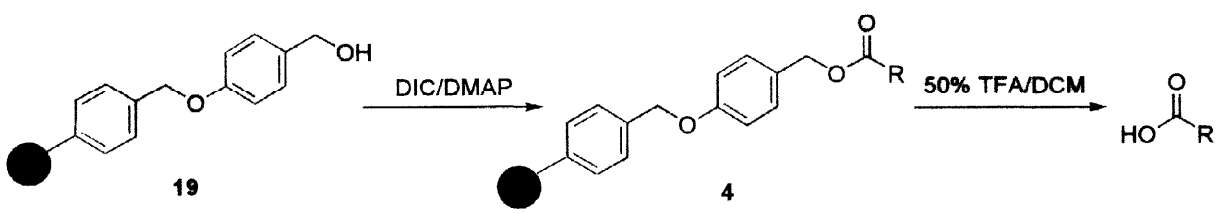
- The type of linker.
- The type of molecule being cleaved. The presence of nucleophilic sites in the template or side-chains needs to be noted.
- The scavenger itself may interfere with the template or side-chains of the cleaved molecule.

In many cases, no scavenger is required, and a large number of cases quoted below use a TFA/DCM mixture for cleavage. By far the most common scavenger reagent used for solid phase organic synthesis is water. It is frequently used at 5-10% and is suitable for a wide range of molecules, however, if more reactive moieties such thiols, thioethers, and electron rich aromatic systems, are present in the cleaved molecule, then more effective scavengers may be required. Possible scavengers include dimethylsulfide,[40] ethanedithiol (EDT),[41,42] anisole,[43,44] thioanisole,[45,46] and *p*-cresol.[47] Triethylsilane (TES) and triisopropylsilane (TIPS)[48] have also been found to be effective scavenger agents. There are disadvantages to each of the scavengers. Water, apart from not being sufficient for all systems, may hydrolyze the desired product, for example hydroxamic acids to carboxylic acids. Anisole and thioanisole are not volatile and need extractive removal from the cleaved product. For peptides, this is usually done by trituation from the precipitated peptide with ether/petrol. This is not suitable for many non-polar organic molecules, hence alternative purification methods would need to be used. EDT is very effective, but requires extractive work up and it does have the problem of stench. TES is attractive in that it does not have the stench problem and is volatile, however, it does partake in a number of side reactions, including addition to indoles and reduction of double bonds. TIPS is similar to TES but side reactions are less problematic because of its bulk. The selection of scavenger agents is often based on experience. Many groups use a cleavage mixture out of habit, only varying it when problems occur. As is seen by looking through the references, scavengers are often not used, however, investigation into which scavenger mixture is best for a specific system may result in significantly improved yields and allow for the preparation of more diverse libraries.

6. WANG AND RINK LINKERS

Two of the most widely used linkers in solid phase organic synthesis are the Wang and Rink linkers. They were designed for use in peptide synthesis giving carboxylic acids and primary amides respectively. Their scope has been greatly broadened in recent years such that they are now used to attach a broad range of functionalities.

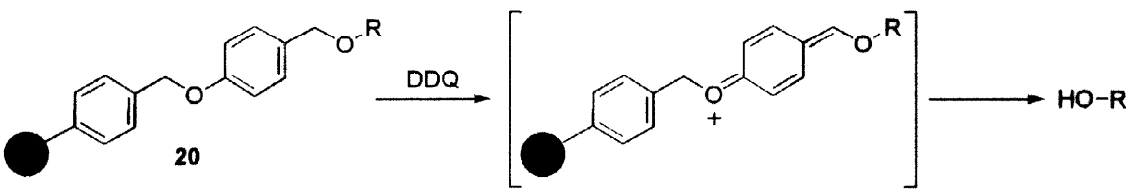
6.1. Wang Linker



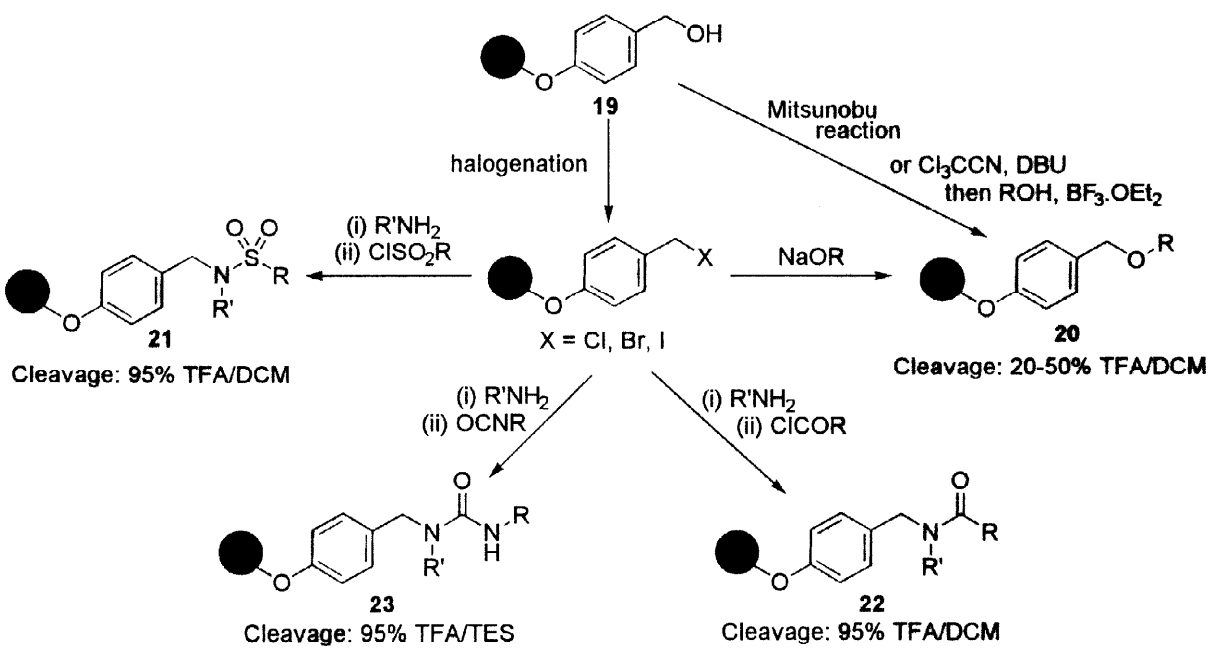
Scheme 9

The monoalkoxy benzyl, or Wang linker[49] was developed for the attachment of carboxylic acids (Scheme 9). Attachment to **19** can be achieved using a range of coupling methods, but the most common is DIC/DMAP. Cleavage can be achieved using 50% TFA/DCM. As discussed above, it is more stable than the dialkoxy benzyl

linker that requires only 1% TFA/DCM for cleavage,[50] but less stable then the hydroxymethylpolystyrene derived linker that requires HF.[51,52] The acid is attached through an ester bond, which is susceptible to nucleophilic attack, hence the linker may also be considered base labile. For example **4** can be cleaved with NaOMe[53] or TEA/MeOH/KCN[54] to give the methyl ester. The electron rich benzylic position is also susceptible to oxidative cleavage.[55,56] DDQ has been used cleave the ether of the Wang linker **20** (Scheme 10).[57,58] It has been reported that *m*CPBA may have caused some cleavage of the Wang linker.[59] In this example the linker was used to attach amines, via the carbamate, but the cleavage would probably also occur if it was being used to attach acids. It is unlikely that the cleavage is due to the acidity of *m*CPBA or its reduced form, as the solution was buffered with $NaHCO_3$.



Scheme 10

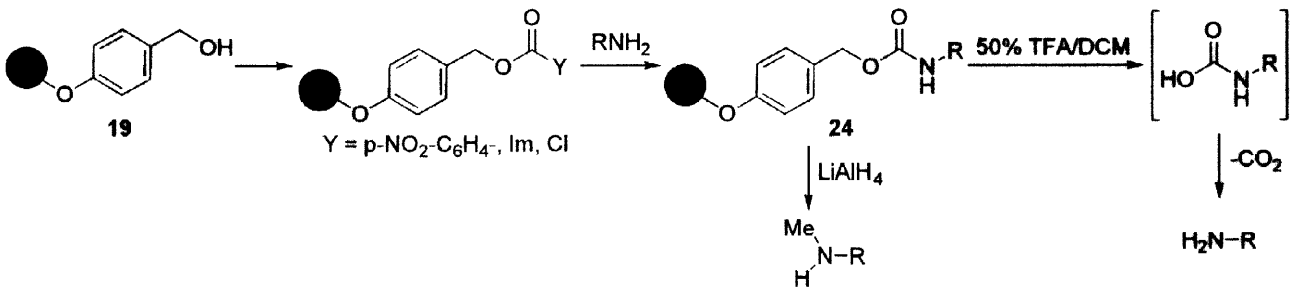


Scheme 11

The Wang linker has been used to attach a range of functionalities (Scheme 11). It can be converted to the chloride,[60,61] bromide,[61,62] iodide,[62] or trichloroacetimidate,[63] any of which can be further derivatized with a range of nucleophiles. For example, displacement with an amine, then sulfonylation gives a sulfonamide linker **21** that is cleaved with 95% TFA,[62] whereas acylation of the amine gives an amide linker **22** that cleaves under similar conditions. Acid labile urea linkers **23** also have been developed from Wang amines.[64] The ether **20** can be cleaved using 20% TFA/DCM,[57] although the TFA ester was observed as a major by-product (20-30%).

Phenols have been attached using Mitsunobu chemistry.[65] The Mitsunobu attachment, though, can be problematic and use of the trichloroacetimidate[63] or attachment via solution phase has been used to avoid this.[66,67] The Wang phenol linker is cleaved using 50% TFA/DCM.

Amines attached directly to the Wang linker are not readily cleaved with TFA, although, as has already been mentioned, the amides, sulfonamides, and ureas derived from them are cleaved. To use the Wang linker for amines, the amine is attached in the form of the carbamate **24** (Scheme 12).[68-70] Treatment with 50% TFA/DCM cleaves the linker to give the amine after *in situ* decarboxylation. The carbamate can be cleaved by reduction with $LiAlH_4$ to give the methyl amine.[71] Application of the carbonate of Wang, as a potential alcohol linker, failed because of poor stability.[72]

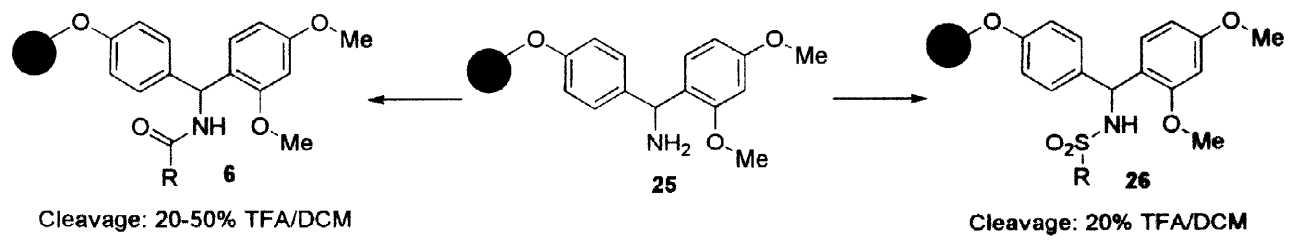


Scheme 12

The usage of the Wang linker has been extended to include aminosulfonylureas,[73] amidines,[74] sugars,[75] and phosphonates.[76] Tertiary amides have been achieved by treatment of the Wang ester linker with a secondary amine and $AlCl_3$ or $ZrCl_4$.[77] The Wang linker can also be used for cyclative cleavage[78,79] as is discussed in detail in Section 9.1.

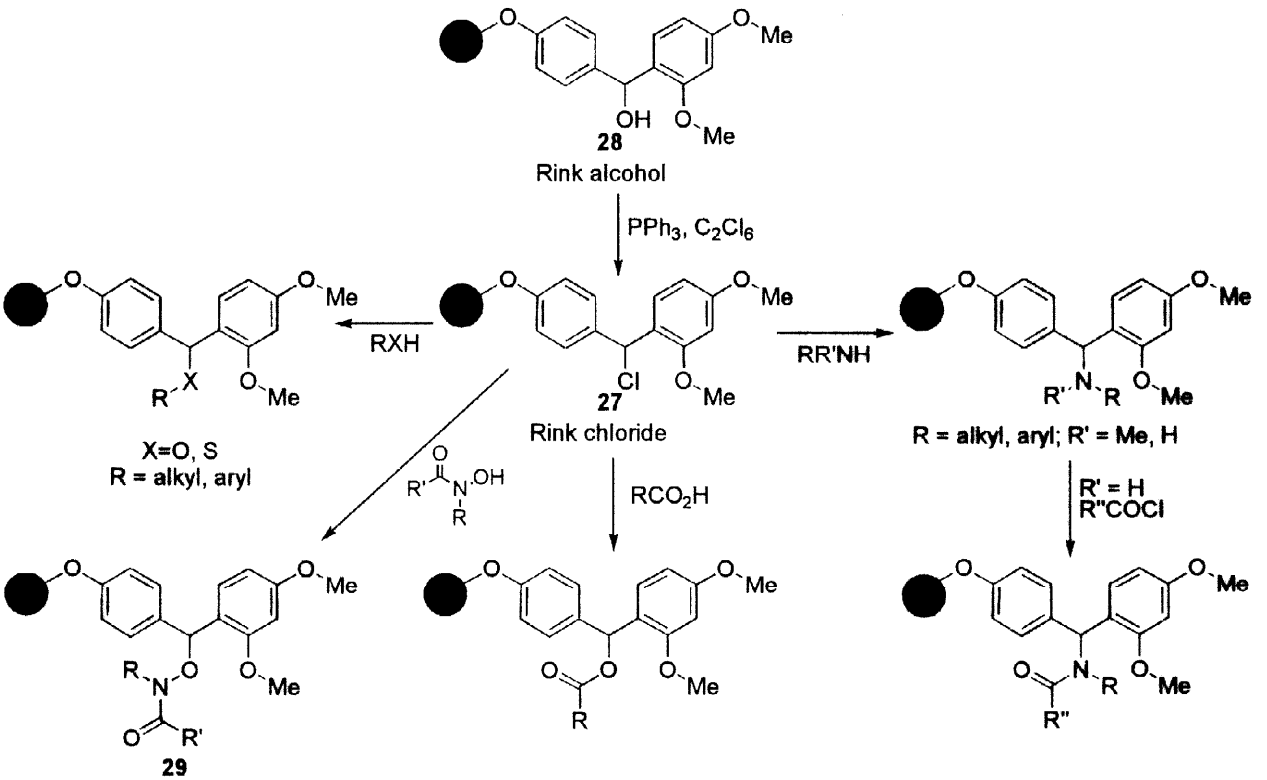
6.2. Rink Linker

The Rink linker[80,81] is widely used in solid phase organic chemistry. The three electron donating alkoxy groups greatly stabilize the cation formed on cleavage. Indeed, the solid phase turns a deep red colour on treatment with TFA, because of the stabilized cation. The amine nitrogen **25** can be acylated with a range of reagents and cleavage is achieved with typically 20-50% TFA/DCM (Scheme 13).[80,82] The sulfonamide linker **26** can also be prepared, with 20% TFA/DCM being used to achieve cleavage.[83]



Scheme 13

The use of this linker has been expanded by the development of the Rink chloride **27** (Scheme 14).[84] This is prepared from the Rink alcohol **28** using PPh_3/C_2Cl_6 or 1% HCl in DCM/THF.[85] Treatment with a nucleophile then allows the linker to be used to attach a range of functionalities, including primary and secondary amines, anilines, alcohols, phenols, thiols, thiophenols as well as acids. Cleavage is achieved using 5-10% TFA/DCM.[80] An *N*-substituted hydroxamic acid linker **29** has been prepared from the Rink chloride with cleavage achieved using 90% TFA.[85] It has also been reported that the cation formed by treatment of the Rink linker with TFA may be reacted directly with nucleophiles such as alcohols, amines, anilines and phenols, thereby avoiding the need to prepare the chloride.[80,86]



Scheme 14

The linker has been used to prepare secondary amides, although its bulkiness may lead to problems in some cases. The Rink amine has been reductively alkylated with a range of benzyl aldehydes and ketones to give secondary amines.[87] Amination of the Rink chloride has also been used to prepare secondary amines.[84] Acylation of the secondary amines is typically achieved using the highly reactive acid chlorides[84] or anhydrides[87] and cleavage to give the secondary amide is achieved with 5%TFA in DCM.

Unlike the Wang linker, which usually involves an ester or carbamate bond, the Rink linker is not highly susceptible to nucleophile attack, because of both steric hindrance and increased electron density. Therefore, when used to attach carboxylic acids, it is relatively stable to nucleophilic conditions. The highly electron rich benzylic position is prone to oxidation though, as has been observed for electron rich benzylic protecting groups.[55,56] Unpublished work within the laboratories of Chiron Technologies in Australia has shown that treatment with *m*CPBA or DDQ can cleave the Rink linker.

From these two examples it can be seen how a linker, developed initially to give a carboxylic acid or an amide, can be expanded for a range of functionalities. Many of the linkers discussed below are based on the same principles as those described above. They are extensions of linkers initially developed for peptide synthesis. These have proved very useful, although it should be recognized that organic chemistry uses a much wider range of reaction conditions than those used in peptide chemistry. This may invalidate a number of peptide derived linkers and provide challenges for the development of new linkers.

7. FUNCTIONAL GROUPS ACHIEVED BY CLEAVAGE FROM A LINKER

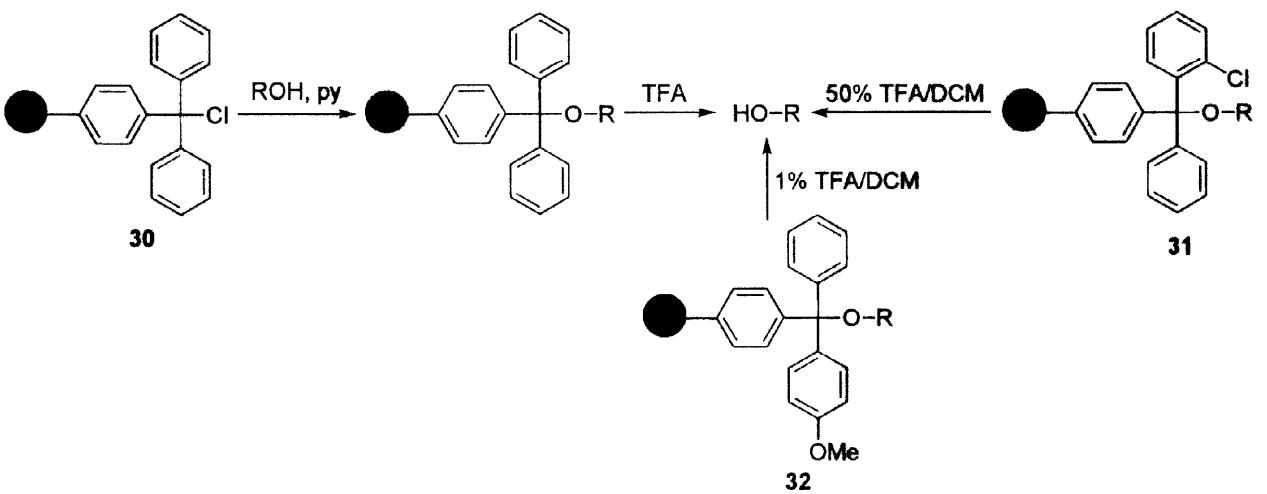
7.1. Alcohol

7.1.1. Acid Labile

Trityl: Attachment of the alcohol to trityl chloride **30** on the solid phase may be achieved using pyridine as the solvent (Scheme 15).[88] Cleavage can be achieved using <5% TFA/DCM[89] though the use of concentrations as high as 100% TFA[88] as well as TFA vapour[90] has been reported. The trifluoroacetate ester is a potential by-product when using these conditions, although it can be hydrolyzed by treatment of the crude product with sodium carbonate. Alternatively, 0.3M HCl in dioxane has been used for cleavage.[91-94] Dry HBr also gives cleavage,[88,95] though bromination is a potential side reaction.

Also used are the 2-chlorotrityl linker **31**, which is cleaved with 50% TFA/DCM,[96] and the 4-methoxytrityl linker **32**, which is cleaved with 1% TFA/DCM.[97]

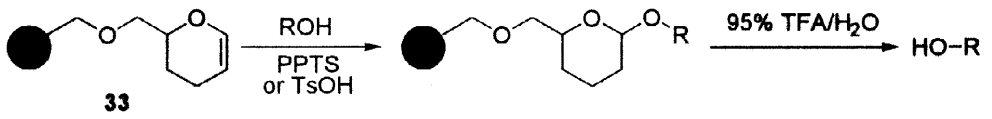
Trityl synthesis examples: perhydro-1,4-diazepine-2,5-diones.[90]



Scheme 15

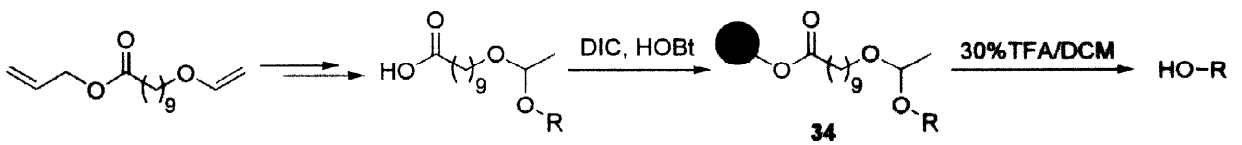
DHP Linker: The DHP linker **33** is an example of the development of a new linker based on a common solution phase protecting group. Attachment of an alcohol is catalyzed with PPTS in DCE at 80°C or *p*TsOH at 0°C (Scheme 16).[98] Cleavage is achieved with 95% TFA in water. This method has been used a number of times,[99-101] but the loading is dependent on the substrate and has been reported to be poor for highly hindered systems.[102] Phenols have also been attached using this linker.[103]

Synthesis examples: pyrrolidines[103] and tropanes.[104]



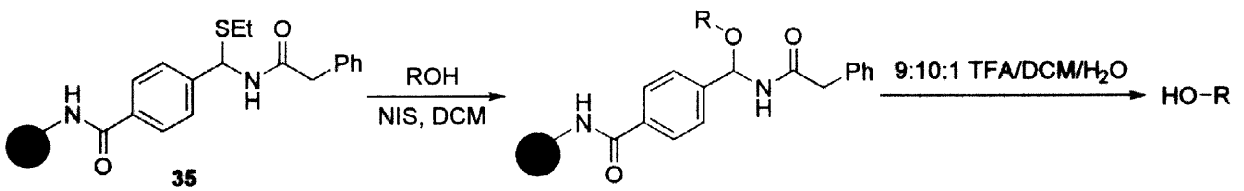
Scheme 16

Vinyloxy Linker: An acetal linker **34** may be prepared from the vinyloxy linker (Scheme 17).[102] The acetal is formed in solution then attached to the solid phase, i.e. attachment via solution phase. Cleavage is achieved with 30% TFA in DCM. Although less hindered than the DHP linker, use of this linker has not been widely reported.



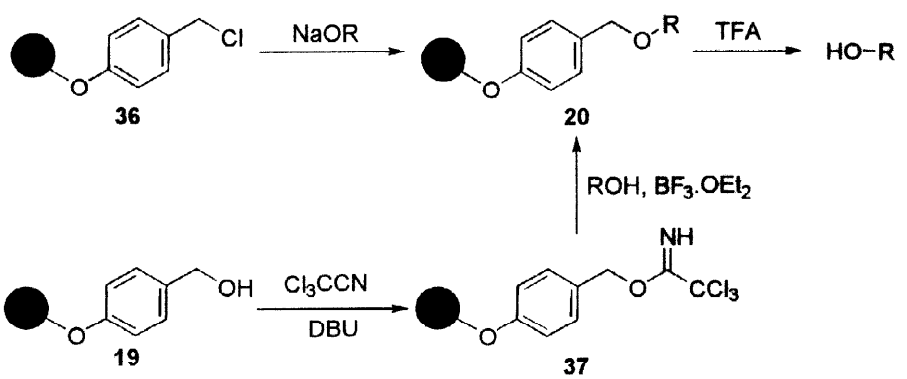
Scheme 17

Aminals: Alcohols can be coupled to **35** using NIS in DCM,[105] with 9:10:1 TFA/DCM/H_2O being used for cleavage (Scheme 18).



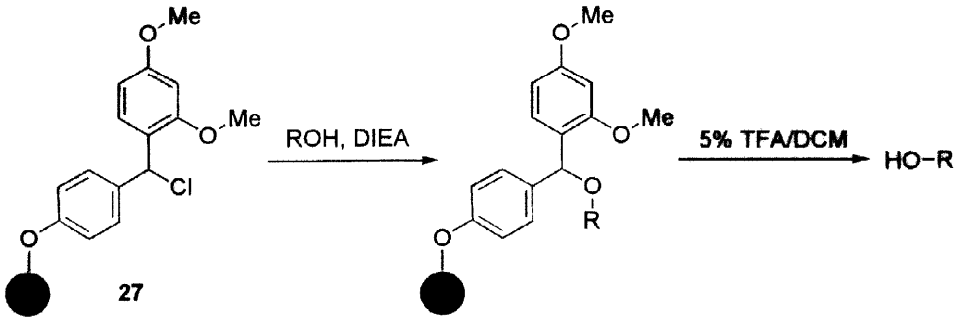
Scheme 18

Wang Linker: As discussed above in Section 6.1, cleavage of the alcohol attached via an ether bond to a Wang derived linker, **20**, using 10-50% TFA has been reported.[57] TFA ester formation was found to be a common side reaction during cleavage. The alcohol can be attached either by treatment of the Wang chloride **36** with sodium alkoxide[57] or by conversion of the Wang alcohol **19** to the trichloroacetimidate **37** then treatment with the alcohol and boron trifluoride etherate (Scheme 19).[63]



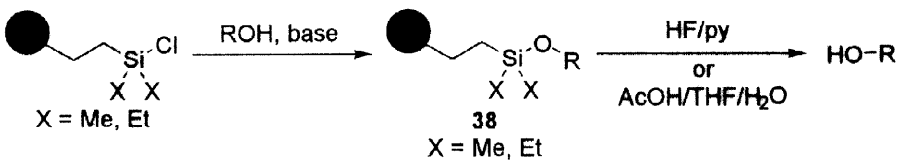
Scheme 19

Rink linker: The Rink linker has been derivatized as the chloride **27** for the attachment of alcohols (Scheme 20).[84] Cleavage is achieved with 5% TFA/DCM.



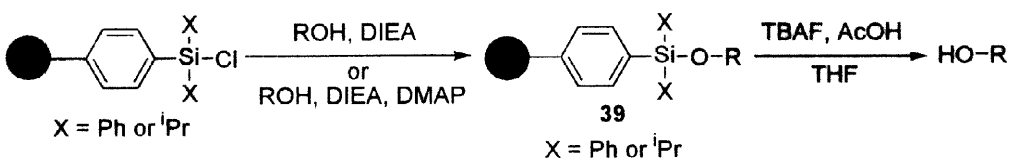
Scheme 20

Siloxy linkers: The trialkyl silyl ether **38** is acid labile (Scheme 21).[106,107] The attachment, using pyridine (R = Me) or imidazole (R = Et, Bu), is selective for primary over secondary alcohols and secondary over tertiary alcohols. Cleavage is successfully achieved using HF (R = Et), HF/py (R = Me,[106] Bu)[108] or 6:6:1 AcOH/THF/H_2O for primary alcohols (R = Me),[106] whereas cleavage with TBAF was found to be sluggish.[107] Although the early reports claim the solid phase bound silyl chloride to be relatively stable,[109] recent papers have discussed ways of masking the silyl chloride in a stable form such as the silane[106,110] or an electron rich aryl silane.[111]



Scheme 21

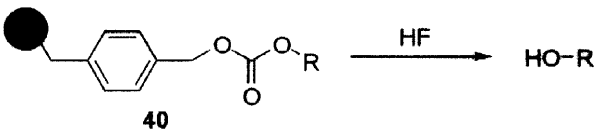
Triaryl siloxy ethers **39**, which are discussed below as base labile linkers, are also cleaved under acidic fluoride conditions (Scheme 22). Cleavage conditions include HF.pyridine with an anisole scavenger,[112] or TBAF and AcOH in THF.[113,114] The diisopropylaryl siloxy ethers have been reported to be superior to the triarylsilanes.[115] The alcohol is attached using DMAP catalysis with cleavage achieved using TBAF/AcOH in THF.[116-118]



Scheme 22

Carbonate linker: Similar to the attachment of amines via a carbamate (Section 7.8), alcohols have also been attached to 4-hydroxymethylpolystyrene via a carbonate **40** (Scheme 23).[72] The carbonate was formed by reaction with DSC/DMAP then the alcohol/DMAP. The relatively electron poor benzylic systems required HF

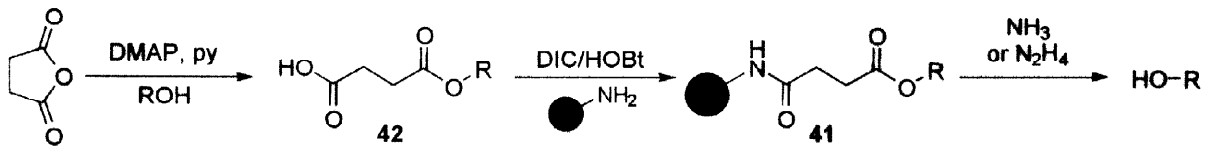
treatment for cleavage. It would be expected that the carbonate would be unstable to strongly nucleophilic conditions although it is stable to basic conditions such as 5% DIEA treatment.



Scheme 23

7.1.2. Base Labile

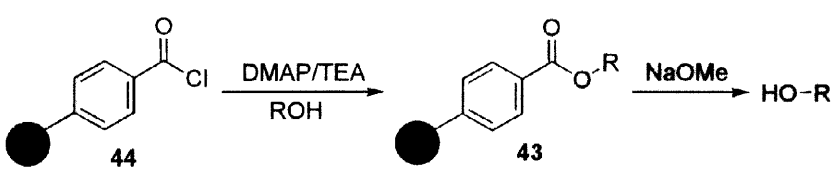
Ester Linker: Hydrolysis of an ester can be used to cleave alcohols from the solid phase. The succinate linker **41** has been utilized in this manner by a number of groups (Scheme 24). The alcohol is attached via solution phase [119] with the succinate **42** attached to the solid phase as the amide. Hydrolysis of the ester to release the alcohol is achieved using ammonia in MeOH or hydrazine in DMF. Oligosaccharides have been prepared using a succinamide linker at the C-2, C-3[120] and C-6[121] positions. Cleavage was achieved using concentrated aqueous ammonium hydroxide or NaOMe in MeOH/dioxane.



Scheme 24

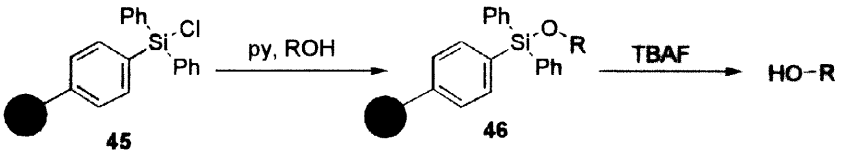
The benzylic ester **43** has frequently been used to attach alcohols. The alcohol is attached to the solid phase bound acid chloride **44** using DMAP, TEA[122] or pyridine (Scheme 25).[123,124] A wide range of cleavage conditions have been developed including: NaOMe in THF/MeOH(4:1)[123,125] or dioxane,[126-128] NaOH in H_2O/EtOH/dioxane,[129] NH_4OH in H_2O/dioxane,[130,131] K_2CO_3 in 1:2 MeOH/THF,[122,132] or Bu_4NCl, KOH in H_2O/THF.[124]

Synthesis examples: isoxazoles,[125] isoxazolines[125] and polyisoxazolines,[123] cyclopentenones via the Pauson–Khand reaction.[124]



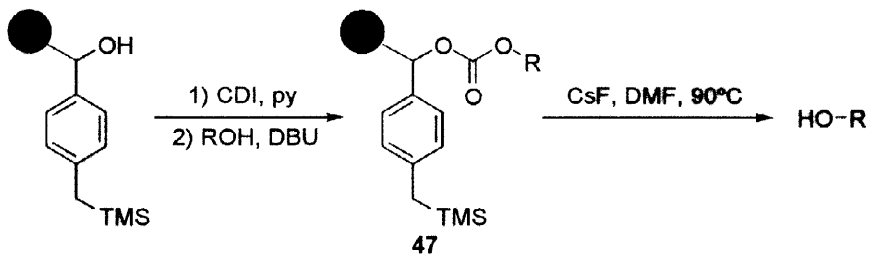
Scheme 25

Silyl Linker: Triaryl siloxy ether linkers described above are not only acid labile but also base labile.[109] The silyl chloride **45** was formed on the solid phase and the alcohol attached as the siloxy ether **46** using DIEA or pyridine as the base (Scheme 26). Primary alcohols are attached in preference to secondary alcohols. After synthesis, the alcohol is cleaved using TBAF. Further manipulation (in this case flash chromatography) is necessary to remove the fluoride salts.



Scheme 26

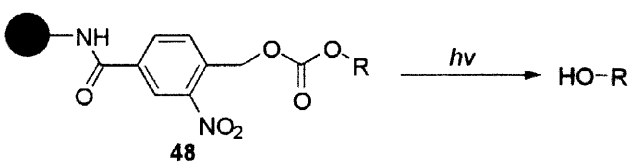
Carbonate: A fluoride labile carbonate linker **47** has been developed.[133] It is formed via the imidazolide carbamate, which is subsequently treated with the alcohol and DBU. CsF in DMF at 90°C is used for cleavage (Scheme 27).



Scheme 27

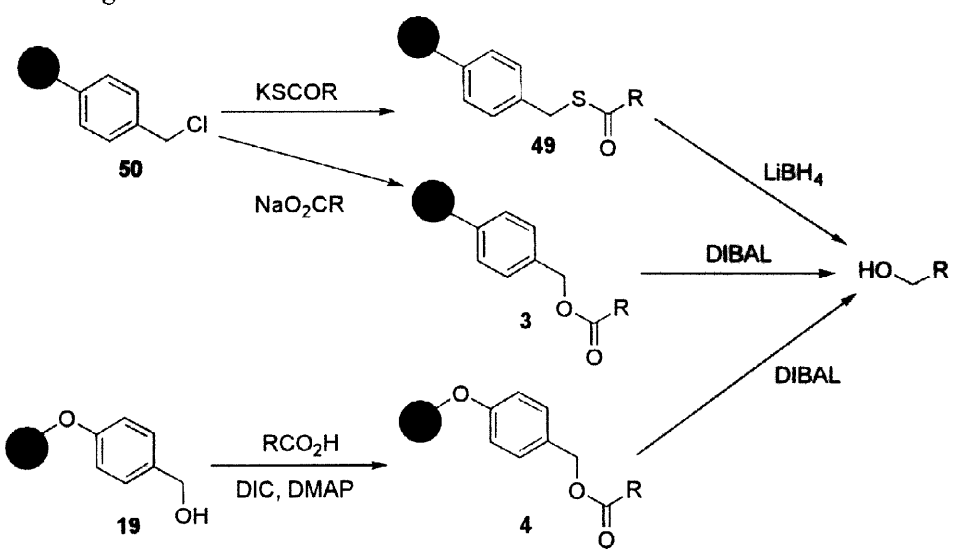
7.1.3. Photolabile

The carbonate **48** has been used for the preparation of alcohols.[72] Attachment is as described for the acid labile carbonate linker and cleavage is achieved by photolysis at 350nm (Scheme 28).



Scheme 28

7.1.4. Reductive Cleavage

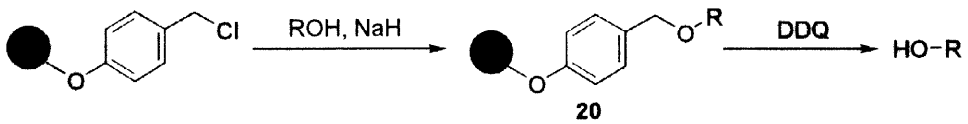


Scheme 29

Thioesters **49** may be used as reductively labile alcohol linkers.[21,134,135] The salt of the thioacid was used to attach the linker to Merrifield resin **50**, with cleavage then achieved using $LiBH_4$ (Scheme 29). The Wang esters **4**,[136] benzylic esters **3**,[137] and alkyl esters[138,139] also have been reductively cleaved with DIBAL to give the alcohol. For all of these examples, purification would be required to remove the excess reductant from the cleavage solution prior to screening of the products.

7.1.5. Oxidative Cleavage

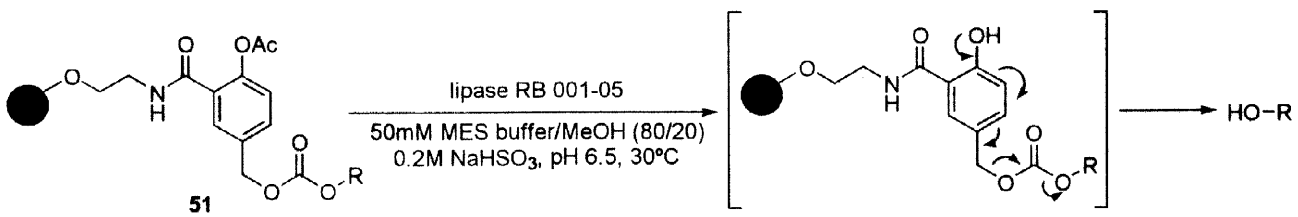
Wang Linker: As already stated, alcohols have been attached directly to the Wang linker via an ether **20**.[57] These can be cleaved with TFA, however, the TFA ester was found to be a common impurity (20-30%). To avoid this side reaction, cleavage can be achieved oxidatively using DDQ in 20:1 DCM/H_2O (Scheme 30).[57] Excess DDQ and DDQH is removed using an ion exchange resin added directly to the resin/cleavage mixture. It was reported that no DDQ derived residues were observed by HPLC analysis of the samples resulting from this approach.



Scheme 30

7.1.6. Enzymatic Cleavage

As an interesting addition to the range of methods available, enzymatic cleavage has recently been reported. The carbonate linker **51** can be cleaved to release the alcohol using lipase RB 001-05 in 50mM MES buffer/methanol (80/20) with 0.2M $NaHSO_3$ at pH 6.5 at 30°C (Scheme 31).[140] This actually involves enzymatic hydrolysis of the acetate followed by elimination of the carbonate then decarboxylation.[141] The alcohol would need to be isolated from the cleavage solution using purification techniques, although separation should be relatively straight forward. This method has been demonstrated for a range of functional groups and these are reported in the relevant sections. It should be noted that this cleavage method has been performed on a relatively hydrophilic polymer, polyethyleneglycol grafted polystyrene.

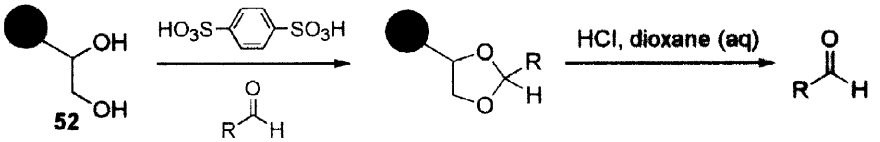


Scheme 31

7.2. Aldehyde

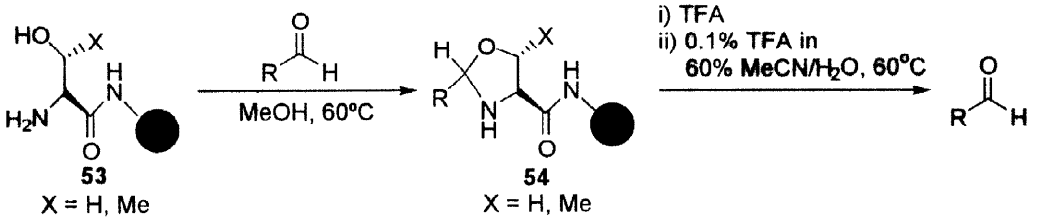
7.2.1. Acid Labile

1,2-Diols **52** have been used to attach aldehydes to the solid phase.[142-146] The aldehyde is attached using *p*-benzenedisulfonic acid in dioxane or *p*TsOH in benzene, with azeotropic removal of the water released during the reaction (Scheme 32). Cleavage is achieved by acid hydrolysis using HCl or *p*TsOH in aqueous dioxane. The 1,3-diol has also been used an aldehyde linker.[147] Attachment via solution phase is used and cleavage is achieved with 90% TFA.



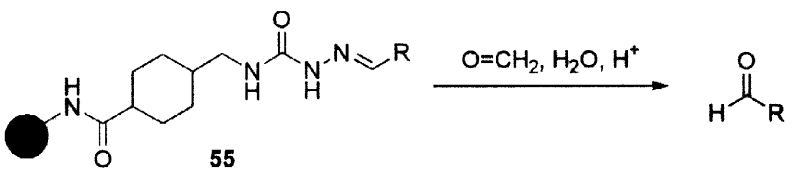
Scheme 32

A recent alternative to the acetal linkers involves the use of threonine or serine on the solid phase **53** to form an oxazolidine linker **54** when reacted with an aldehyde (Scheme 33).[148] The linker is stable to both basic and strongly acid conditions, but it is cleaved in mild aqueous acid. Therefore, acid labile protecting groups may be removed with neat TFA then the product cleaved with 0.1% TFA in 60% MeCN/H_2O.



Scheme 33

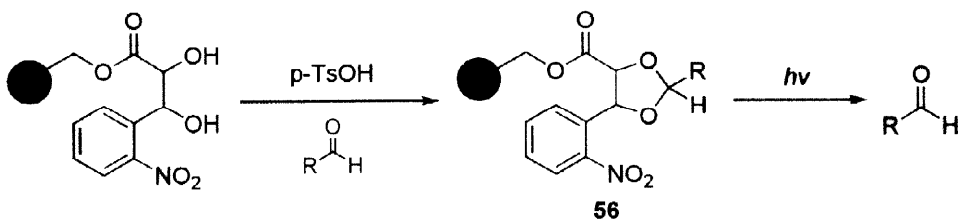
Semicarbazones **55** have also been used (Scheme 34).[149] The aldehyde is attached to the linker via solution phase and cleavage of the final product is achieved using formaldehyde in dilute aqueous acid.



Scheme 34

7.2.2. Photolabile

Nitroaryldioxalanes **56** have been used as photolabile aldehyde linkers.[150] Formation of the acetal is catalyzed with *p*TsOH in benzene (Scheme 35). Cleavage is achieved with visible light (Pyrex filtered Hg lamp) in typically 34 - 97% yield after 7 hours.

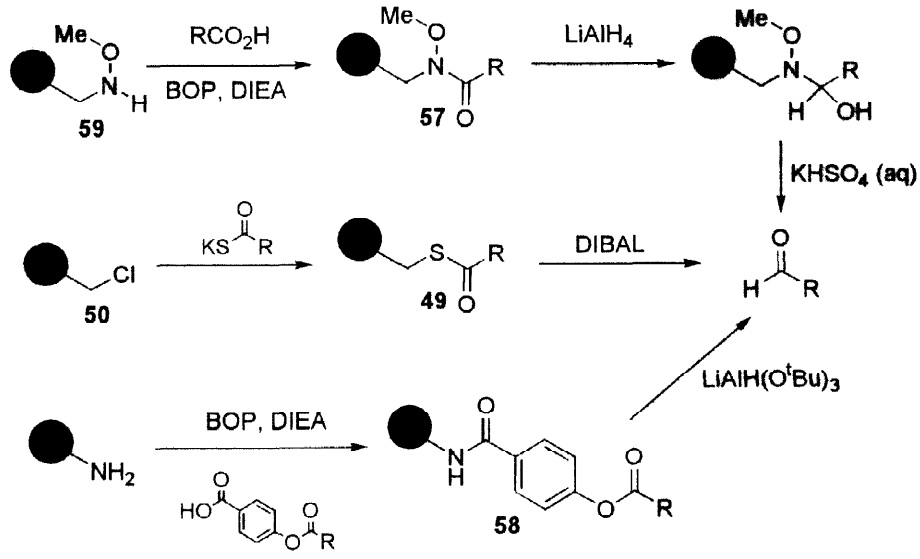


Scheme 35

7.2.3. Reductive

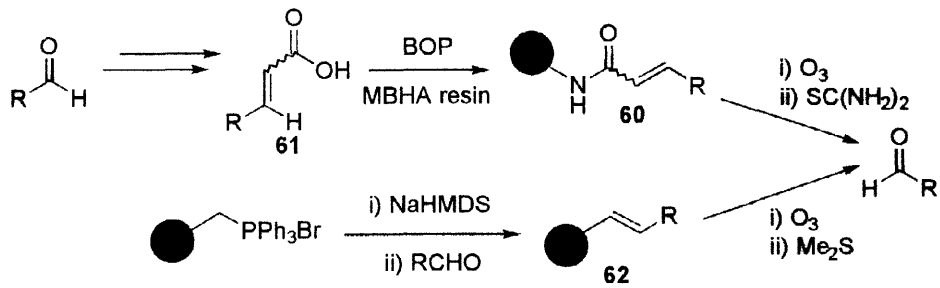
Reductive cleavage of solid phase bound Weinreb amides **57**, thioesters **49** and phenacyl esters **58** has been used to yield aldehydes (Scheme 36). The Weinreb amide **57** is prepared by coupling the carboxylic acid to the solid phase bound methoxyamine **59**.[151,152] At the end of the synthesis, it is cleaved with $LiAlH_4$ to give, after collapse of the tetrahedral intermediate, the aldehyde in solution. This procedure requires the use of an aqueous

solution to collapse the intermediate. This may lead to solvation problems with hydrophobic polystyrene and hence potential reduction in yields. DIBAL reduction of thioesters **49**[153] and $LiAlH(O^tBu)_3$ reduction of phenacyl esters **58**[152] have also been used to yield aldehydes. Over-reduction to the alcohol was reported as a side reaction for the phenacyl derived linker. For all approaches, it is necessary to remove the aluminum salts after the cleavage to achieve clean samples. This adds to the complexity of post cleavage manipulations.



Scheme 36

7.2.4. Oxidative

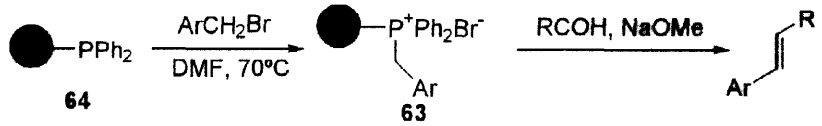


Scheme 37

Alkenes on the solid phase may be cleaved oxidatively to give aldehydes (Scheme 37).[154] The alkene **60** can be prepared in solution by first forming the α,β-unsaturated acid **61** then coupling this to the solid phase.[155] Ozonolysis of **60** gives the free aldehyde. The resulting solution requires aqueous workup to remove the excess thiourea. Alternatively, the alkene **62** can be prepared directly on the solid phase using Wittig chemistry.[156] In this case, the ozonide is treated with Me_2S to produce the aldehyde. The cleavage reagent is volatile hence removing the need for any aqueous work up, which may be problematic for simultaneous cleavage of large numbers of samples.

7.3. Alkene

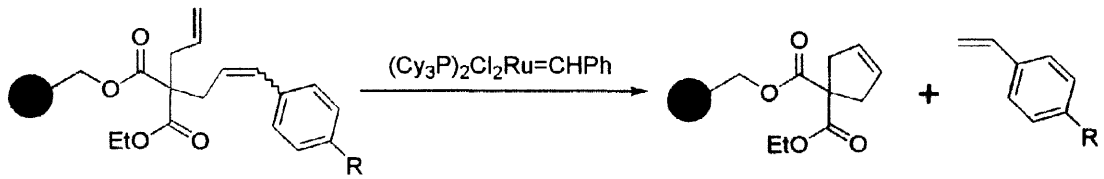
The Wittig reaction can be used to cleave solid phase bound phosphonium salts.[157] The phosphonium salt **63** is prepared by treatment of solid phase bound triaryl phosphine **64** with a benzyl halide (Scheme 38). Treatment with base (NaOMe) and aldehyde results in cleavage of the product as the alkene. Excess aldehyde is removed by either derivatization as a water soluble hydrazone and aqueous work up, or formation of the imine with aminomethylpolystyrene. The latter is a simple method, which, if successful, may be performed relatively easily in large numbers.



64 **63**

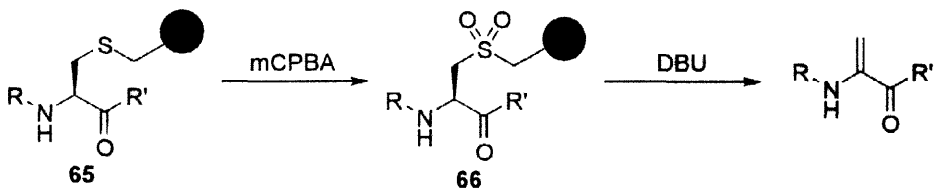
Scheme 38

Ring closing metathesis reaction has been used to cleave alkenes.[158] Attachment via solution phase is used, then treatment with Grubb's reagent forms the cyclic alkene on the solid phase and releases the desired alkene into solution (Scheme 39).



Scheme 39

β-Elimination of a cysteine-derived linker **65** has been used to prepare dehydroalanines.[159] The sulfide is oxidized to the sulfone **66** with *m*CPBA, then elimination and release of the product is achieved using DBU in DCM (Scheme 40).



65 **66**

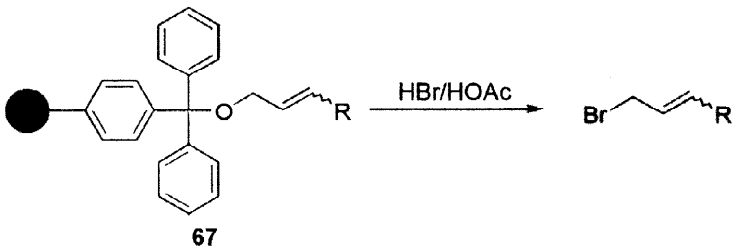
Scheme 40

7.4. Allyl

For linkers that cleave to give an allyl functionality, see Section 8.3.

7.5. Allyl Bromide

7.5.1. Acid Labile



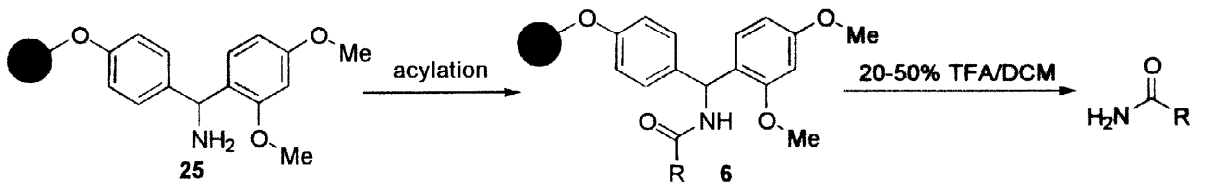
Scheme 41

Treatment of an allyl alcohol attached to trityl resin **67** with anhydrous HBr in AcOH results in release of the product as the bromide (Scheme 41).[88] Note that this is not a clean reaction, as removal of the acetate by-product is required.

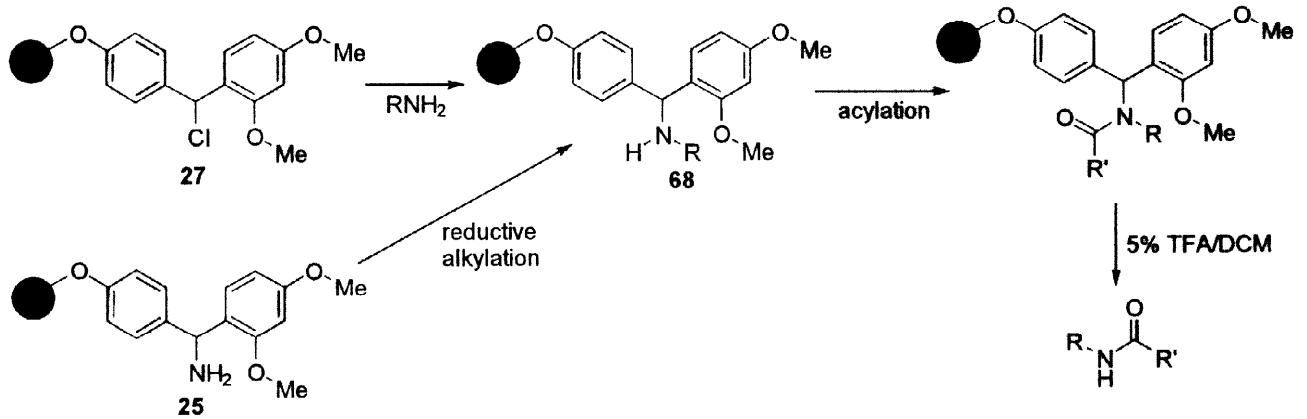
7.6. Amide

7.6.1. Acid Labile

Rink: One of the most common linkers used to access primary amides is the Rink linker.[80,81] The nitrogen of **25** can be acylated by a carboxylic acid using a range of acylating reagents such as DIC/DMAP or HOBt/BOP, although more forcing conditions may be required to prepare bulky amides. Cleavage is typically achieved with 50% TFA/DCM, although lower concentrations of TFA may be used, e.g. 20%TFA/DCM (Scheme 42).[82]



Scheme 42

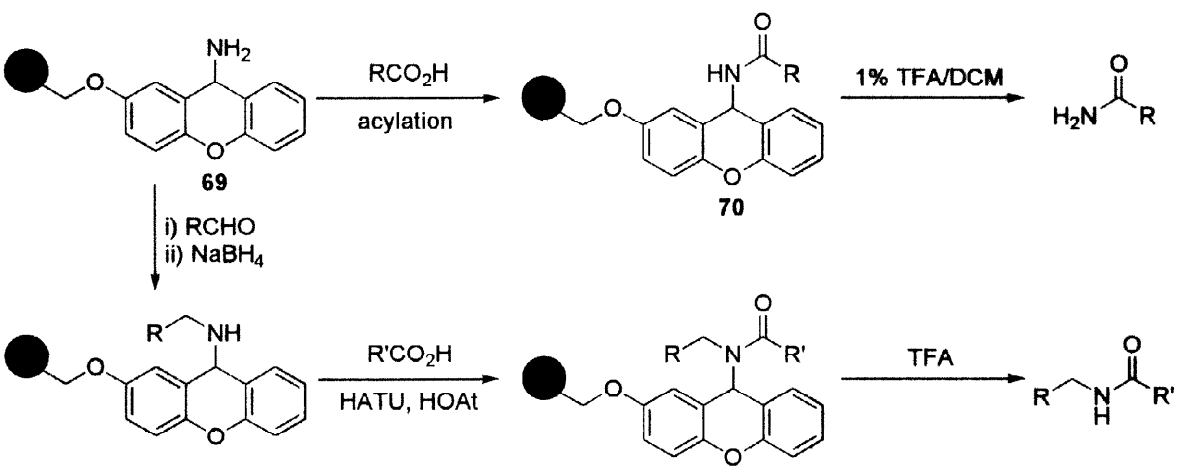


Scheme 43

The secondary amine derivative of the Rink linker **68** can be prepared either by amination of Rink chloride **27**[84] or reductive alkylation of the Rink amine **25** (Scheme 43).[87,160] Reactive reagents, such as the acid chlorides, are required for the acylation and the product is cleaved by 5%TFA/DCM to give the secondary amide.

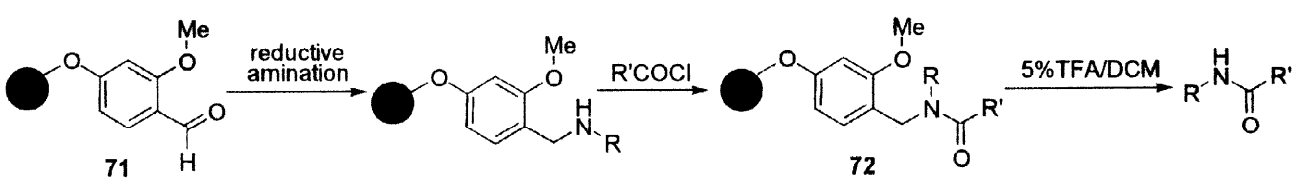
Synthesis examples for Rink amide linker: benzimidazoles,[161] 1,4-benzodiazepine-2,5-diones,[162] benzofurans,[163] benzofurans via SmI_2 radical cyclization,[164] dihydropyrimidines,[82] imidiazo[1,2-a]azines,[165] 2-imidazolidones,[166] indoles,[163,167] isoxazoles,[168,169] isoxazolidines,[170] isoxazolines,[169] 2-oxindoles,[171] 2-oxopiperidines,[172] pyrazoles,[82,168,173] pyrazolines,[174] pyridinium salts,[175] pyrimidines,[82] pyridines,[82] pyrroles,[176] tetrahydroimidazopyridines,[177] tetrahydroisoquinolines,[177] quinolines,[178] and 1,2,3,4-tetrahydroquinoxalin-2-ones.[179]

Sieber: The amine of the Sieber linker **69** is not as hindered as that of the Rink linker and is readily acylated (Scheme 44).[180] The amide **70** is very acid labile, cleaving in 1% TFA/DCM.[181] The linker can also be used to prepare secondary amides.[182] The amine is reductively alkylated then acylated by a carboxylic acid using HATU/HOAt. Although 90% TFA was used for cleavage in this example, this was primarily to ensure complete removal of protecting groups and a significantly weaker acid such as 1-2% TFA should be sufficient.



Scheme 44

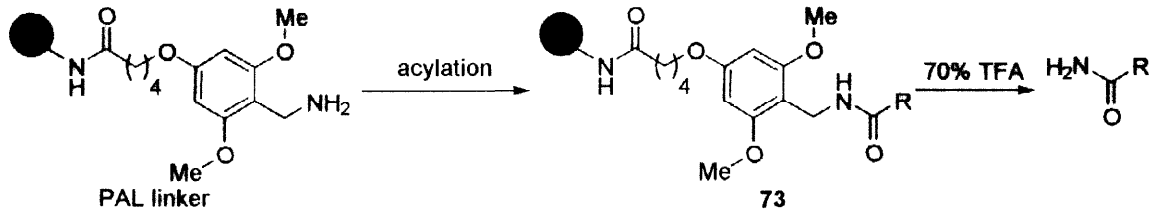
Sasrin: The dialkoxy Sasrin linker has been modified to attach secondary amides.[183-185] The aldehyde **71** is reductively aminated with a primary amine, then acylation with either symmetrical anhydrides or acid chlorides gives the amide **72** (Scheme 45). Cleavage is achieved with 30% TFA/DCM. This approach also has been used to link sulfonamides, ureas and carbamates.[183] The amine itself does not cleave in TFA, hence even if incomplete acylation (sulfonylation etc) occurs, only the desired amide (sulfonamide etc.) will be cleaved from the solid phase. Thus, the purity should remain high, although the yield may vary.



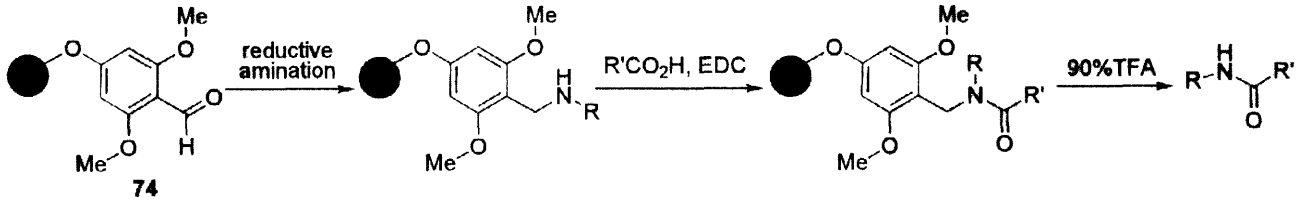
Scheme 45

PAL: The trialkoxy PAL linker[186,187] can be used to generate primary amides **73** and is cleaved in 70%TFA/DCM (Scheme 46). The related secondary amide linker has been developed by reductive amination of the aldehyde **74** then acylation (Scheme 47).[188,189] Cleavage of the secondary amide is achieved with 90% TFA.

Synthetic examples: 1,4-benzodiazepine-2,5-diones[189] and diketopiperazine.[190]

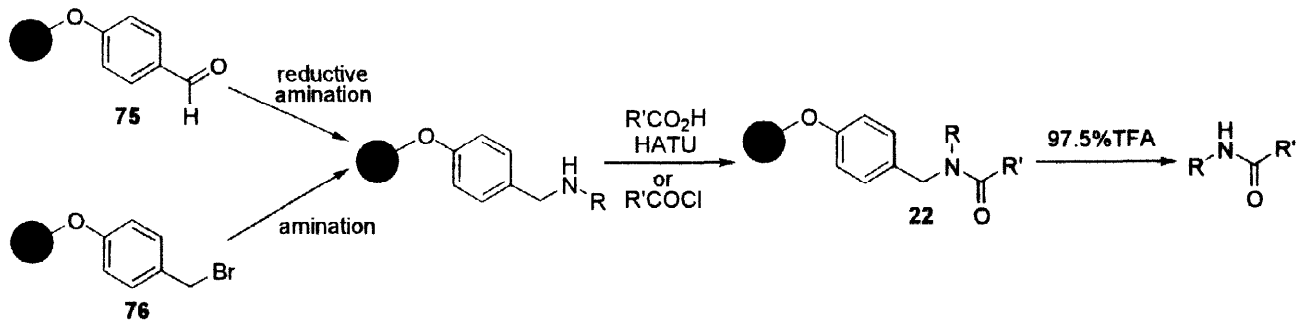


Scheme 46



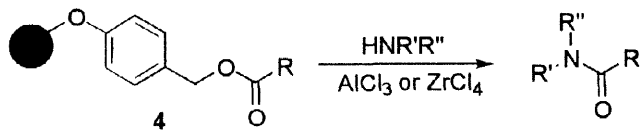
Scheme 47

Wang: The Wang linker has been used for preparation of secondary amides.[191] Preparation of the amide **22** from the aldehyde **75** is similar to that described above (Scheme 48). Cleavage is achieved using 97.5% TFA/TES. Alternatively, the Wang bromide **76** can be aminated then acylated with acid chlorides to give **22**.[61] Cleavage is achieved using 95%TFA/H_2O.



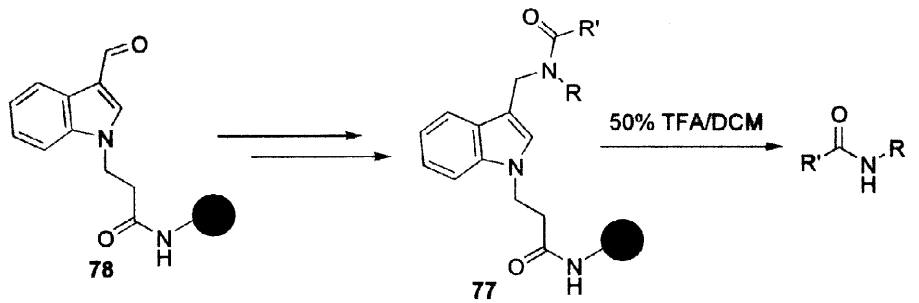
Scheme 48

Lewis acid ($AlCl_3$ or $ZrCl_4$) catalyzed aminolysis of the Wang linker **4** with a secondary amine has been used to cleave secondary amide products (Scheme 49).[77] Solid phase extraction was necessary to remove the aluminum or zirconium residues.



Scheme 49

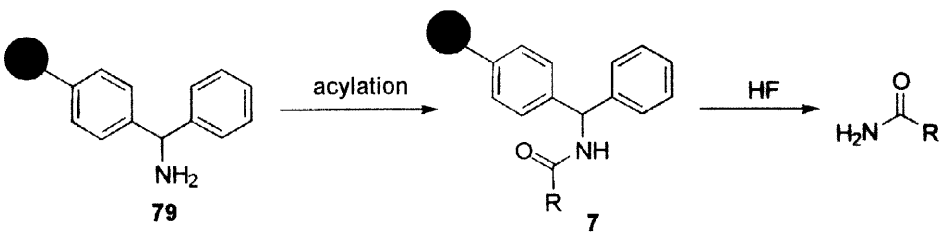
Indole: An indole derived linker 77 can also be used for secondary amides.[192] The aldehyde **78** is reductively aminated then acylated (Scheme 50). Cleavage is achieved with 50% TFA/DCM, with the cation formed on the solid phase stabilized by the indole group.



Scheme 50

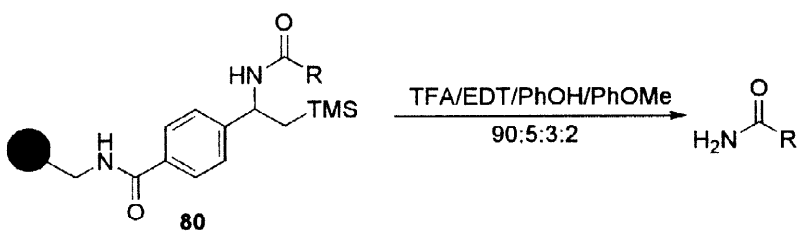
Benzhydryl: The benzhydryl amine **79** and related *p*-methylbenzhydryl amine linkers are also used for the preparation of primary amides. Being significantly less electron rich than the alkoxy substituted linkers such as Rink and PAL, the strong acid HF is required for cleavage (Scheme 51).[193,194]

Synthetic examples: cyclic ureas,[193] 3,4-dihydro-2(1*H*)-quinolinones,[195] perhydro-1,4-diazepine-2,5-diones,[194] and thiomorpholinones.[196]



Scheme 51

β-Silyl Linker:

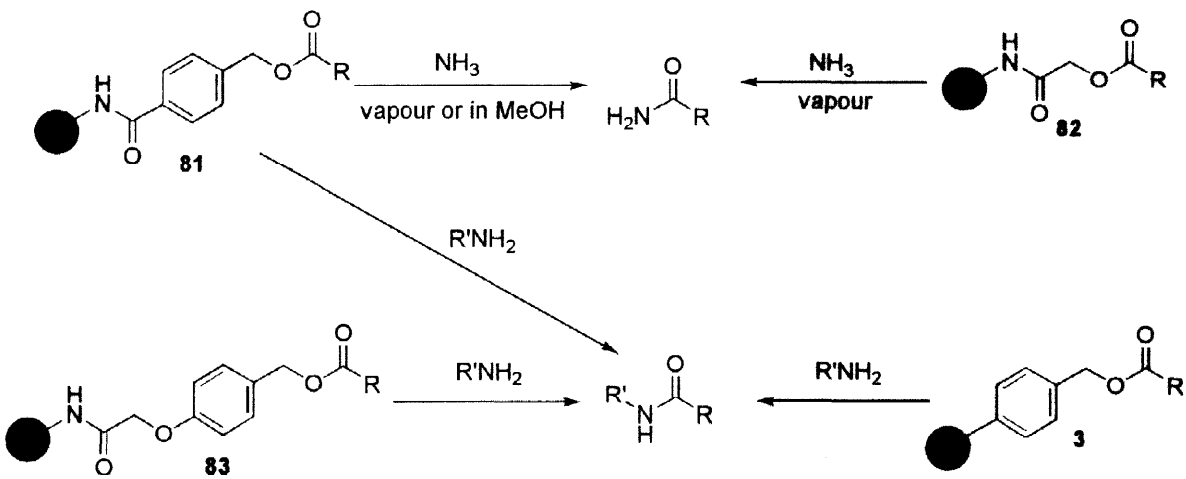


Scheme 52

As mentioned in Section 5, the carbocation formed on the solid phase may react with the molecule being cleaved. To reduce this, the β-silyl linker **80** was prepared (Scheme 52), with β-elimination of the trimethylsilyl group acting as an internal scavenger.[197] With an indole present in the molecule (tryptophan), the linker gave improved results over both the Sasrin and Rink linkers, although scavengers such as EDT, phenol and anisole were found to improve the yield of cleaved material greatly.

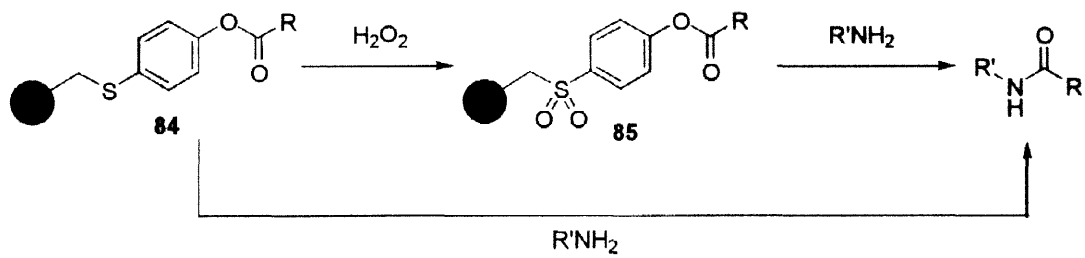
7.6.2. Base Labile

Ester Linker: The benzylic ester linker can be treated with an unhindered amine to cleave the product as an amide incorporating the amine used for cleavage (Scheme 53). Primary amides can be prepared by the aminolysis of the HMB **81**[198] and glycolamido **82**[199,200] linkers with the glycolamido linker being preferable for hindered compounds.[199] Similarly, treatment with a primary amine has been used to achieve secondary amides. Examples using the PAC ester **83**[201], the HMB ester **81**,[202] and the Merrifield ester[203,204] have also been reported. Typically an excess of amine is required, therefore the use of less volatile amines may introduce the need for a purification step.



Scheme 53

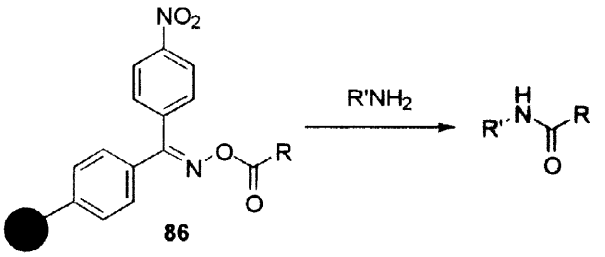
The thioether **84** was prepared as a safety catch linker, and activation by hydrogen peroxide oxidation of the thioether to the sulfone **85** followed by cleavage with a primary amine gives the amide (Scheme 54).[205,206] Recent studies though have shown that oxidation of the thioether is not necessary for effective cleavage even when using limiting amounts of the amine.[207] Excess amine in pyridine may be used to achieve more rapid cleavage, although solid phase extraction of the cleavage reagent is then required.[16]



Scheme 54

Kaiser Linker: Kaiser's oxime linker **86** has been used to couple carboxylic acids, which then may be cleaved with nucleophiles. For example, treatment with ammonia gives primary amides[208,209] or with primary amines and anilines gives secondary amides (Scheme 55).[210] As above, the excess amine needs to removed from the cleaved product, which may be problematic if the amine is not volatile.

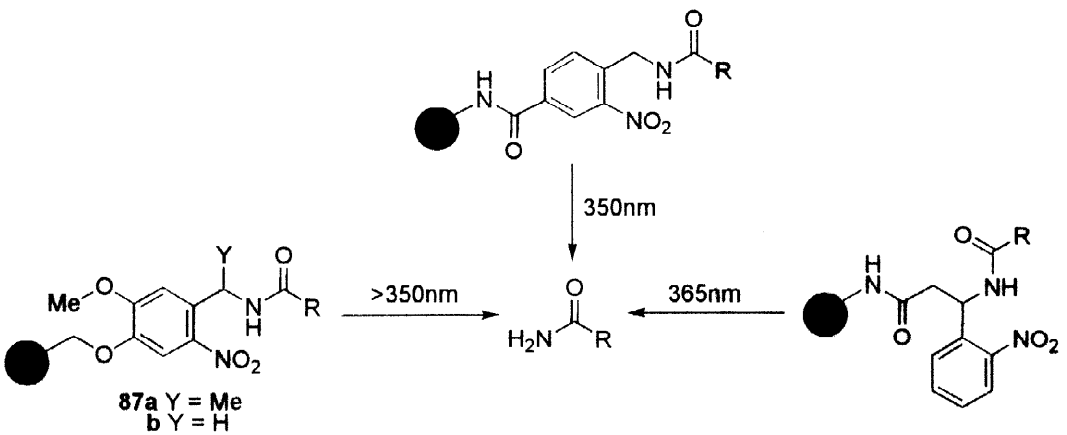
Synthesis example: 1,2,3,4-tetrahydro-β-carbolines[211]



Scheme 55

7.6.3. Photolabile

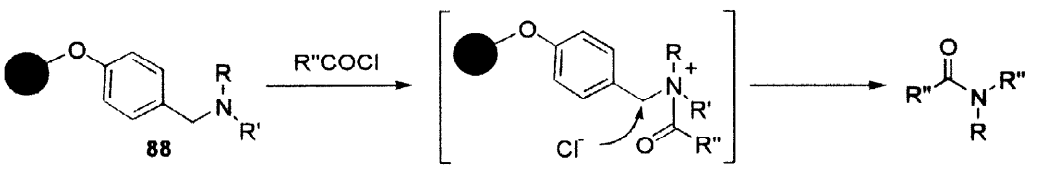
2-Nitrobenzyl amide linkers have been used as photolabile amide linkers (Scheme 56). As discussed in Section 3.3, the α-methyl derivative **87a** gives superior cleavage kinetics compared with the non-methylated linker **87b**.[29,212] Although alkoxy substitution on the aromatic ring usually improves the cleavage step, linkers without the electron donating groups on the aromatic ring have been used successfully for both primary[27,213,214] and secondary[215] amides. Cleavage is typically achieved using a 350 - 365nm light source.



Scheme 56

7.6.4. Other

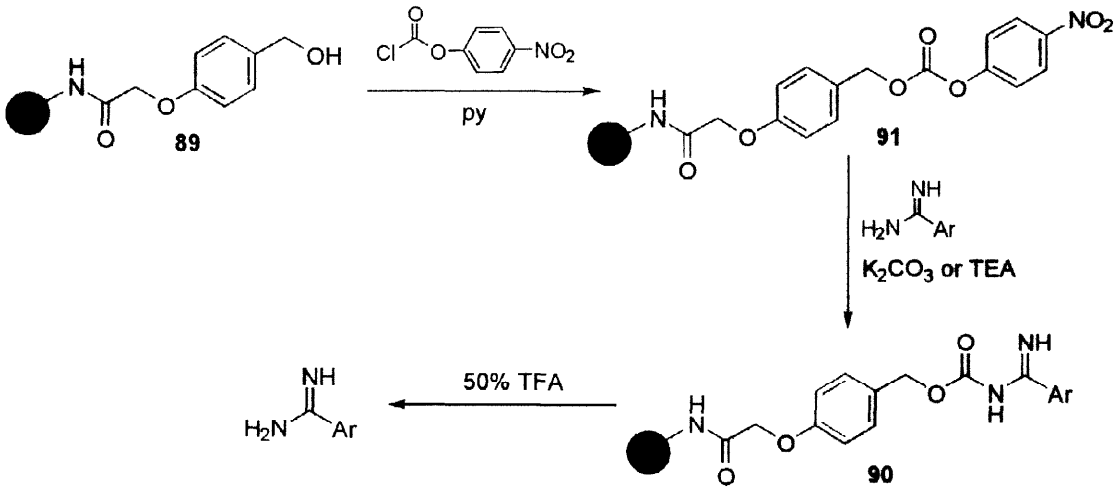
A linker has been developed to give tertiary amides upon cleavage (Scheme 57).[216] A secondary amine is attached to the Wang linker. Treatment with an acid chloride acylates the tertiary amine **88** which is cleaved from the solid phase to give the tertiary amide, probably via a mechanism involving the chloride ion. The excess acylating agent is removed using aminomethyl polystyrene.



Scheme 57

7.7. Amidine

The PAC linker **89** has been converted to the amidoxime **90** via the *p*-nitrophenylcarbonate **91** (Scheme 58).[74,217] Cleavage is achieved with either 50%TFA and 5%H_2O in DCM or 95%TFA/H_2O.

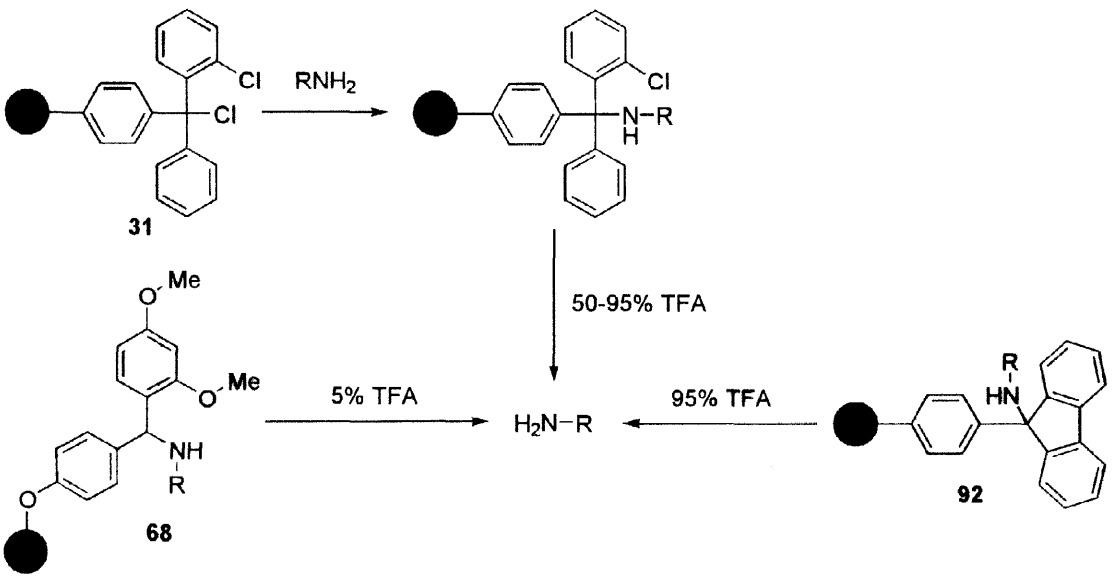


Scheme 58

7.8. Amine

7.8.1. Acid Labile

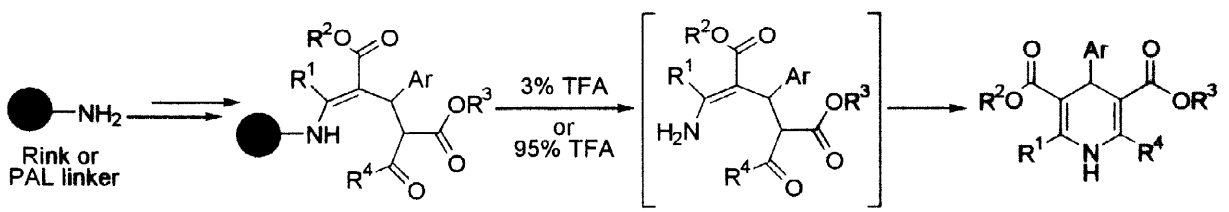
There are two main routes to attach an amine to solid phase so that it may be cleaved using acid. The first involves attachment directly to a linker, such as the 2-chlorotrityl or Rink derived linker, which can be cleaved with TFA. The second involves attachment of the amine through a carbamate to linkers originally developed to attach carboxylic acid. The linker is cleaved using similar conditions to those used to cleave the carboxylic acid. When TFA is used in the cleavage reaction, the products are generally isolated as the TFA salts.



Scheme 59

Direct Attachment: Amines are attached to the 2-chlorotrityl linker **31** either using only a slight excess of the amine with DIEA in DMF,[218] or by using a large excess of the amine and no other base (Scheme 59).[219,220] Cleavage is achieved with 50-95%TFA/DCM. As has already been illustrated in the preparation of secondary amides, the Rink linker has been derivatized as an amine linker **68** either by amination of the Rink chloride[84] or by reductive alkylation of the Rink amine. The linker is cleaved with 5% TFA/DCM. The PhFl linker **92**, based on the 9-phenylfluoren-9-yl protecting group, has recently reported.[221,222] This linker is more acid stable than either the 2-chlorotrityl or Rink derived linkers, requiring 95% TFA/H_2O for cleavage.

Amines have been directly attached to the PAL and Rink linkers in the synthesis of 1,4-dihydropyridines (Scheme 60).[223] Cleavage is achieved with 95% TFA/DCM for the PAL linker and 3% TFA/DCM for the Rink linker. These amines are in conjugation with an ester and this may render them more acid labile than unconjugated amines.

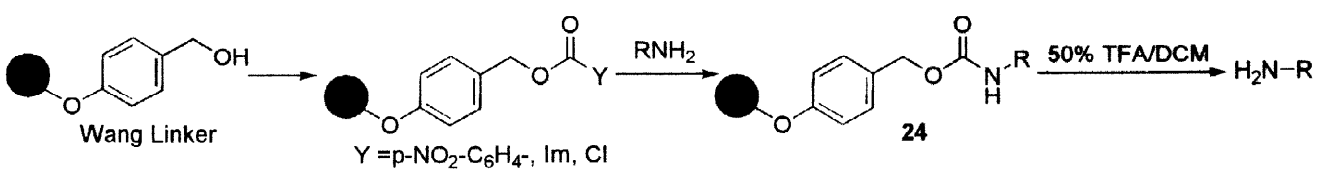


Scheme 60

Carbamate Attachment: A number of linkers initially used to attach carboxylic acids have been adapted to attach amines in the form of a carbamate. Cleavage involves initial release of the *N*-substituted carbamate then decarboxylation. The conditions for cleavage of the carbamate amine linker are usually similar to those used to release the carboxylic acid.

The carbamate of the Wang linker, **24**, is formed via either the chloroformate,[68] the imidazolide carbamate,[68] or the *p*-nitrophenylcarbonate (Scheme 61).[69,224-226] Typically, cleavage to give the amine is achieved with 50% TFA/DCM. Treatment with $LiAlH_4$ will also cleave the linker to give the methyl amine.[71] Successful use of *m*CPBA has been reported when using the Wang linker,[227] although in another instance unwanted cleavage was reported using similar conditions.[59]

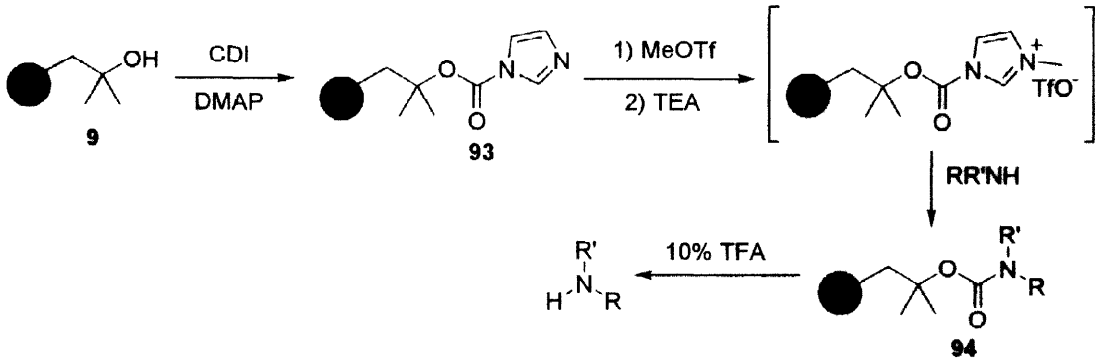
Synthesis examples: benzoxazoles,[228] 2,3-dihydrothiazoles,[229] thiofurans,[230] thiophenes,[229] and triazoles.[231]



Scheme 61

The PAC linker has been similarly derivatized for the attachment of amines.[232,233] Cleavage is achieved using 75-92% TFA with scavengers. Hydroxymethylpolystyrene has also been adapted for the attachment of anilines[234] with HF being required for cleavage.

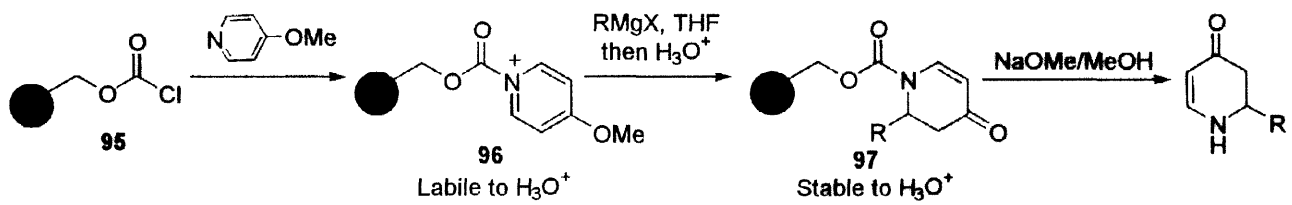
Derivatization of the hindered handle **9** has also been used.[235,236] The linker is prepared via either the *p*-nitrophenylcarbonate[236] or the imidazolide carbamate **93**, which requires alkylation with methyl triflate prior to treatment with an amine for efficient formation of the carbamate **94** (Scheme 62).[235] 10-20% TFA/DCM is required for cleavage. The steric hindrance of the dimethyl substituent would reduce the probability of nucleophilic attack on the carbamate that leads to undesired cleavage.



Scheme 62

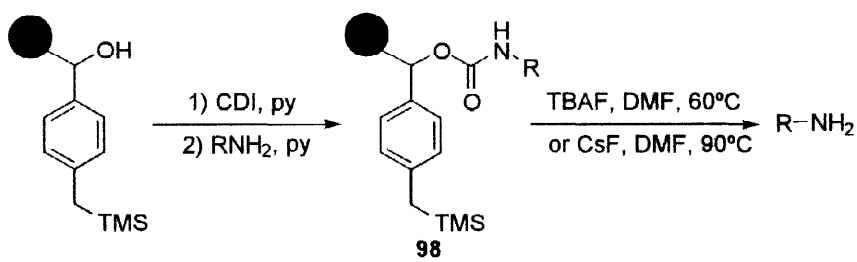
7.8.2. Base Labile

Carbamate Attachment: The carbamate linker approach has also been applied to hydroxymethylpolystyrene to prepare pyridyl derivatives (Scheme 63).[237,238] The chloroformate **95** is treated with pyridine to form the reactive acylium complex **96**, which is immediately treated with a Grignard reagent. If any of the acylium complex does not react in the second step, it is cleaved from the product in the acidic work up used, leaving only the cyclic amine attached to the solid phase **97**. The linker itself is cleaved with NaOMe in MeOH, although it would also be labile to HF treatment as described above.



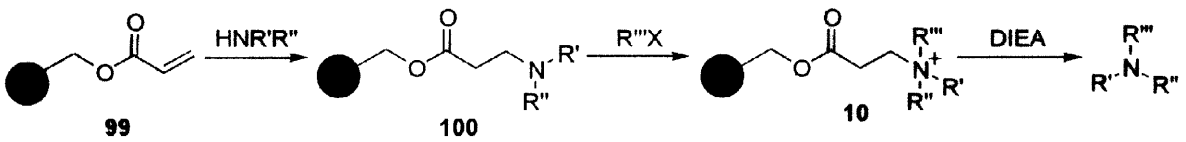
Scheme 63

The carbamate linker **98** has been developed and it is fluoride labile (Scheme 64).[133] Either TBAF in DMF at 60°C or CsF in DMF at 90°C can be used for cleavage.



Scheme 64

Hofmann Elimination Linkers: A suite of amine linkers has been developed based around Michael addition and Hofmann elimination. Michael addition of a secondary amine to an acrylate ester **99** on the solid phase is used as the attachment process (Scheme 65).[22,23] The cleavage involves a 2 step process. The tertiary amine **100** is treated with an active alkyl halide (e.g. benzyl or allyl bromide) to form the quaternary ammonium salt **10**, which is then eliminated using DIEA in either DMF or DCM. This Hofmann elimination releases the tertiary amine and reforms the acrylate ester on the solid phase, which may be recycled. Aqueous work up is used to help purify the products. Alternatively, the cleavage may be performed using either Amberlite IRA-95 ion exchange resin or Rink resin in DMF.[239] The basic resin is sufficient to achieve cleavage and avoids the need for aqueous work up. This surprising two resin result may be explained by thermal elimination of the amine as the hydrobromide salt. The basic resin then frees the amine to catalyze the β-elimination. Alternatively, it may also be due to trace base, either present in the solid phase from previous steps, or as trace dimethylamine in the DMF.

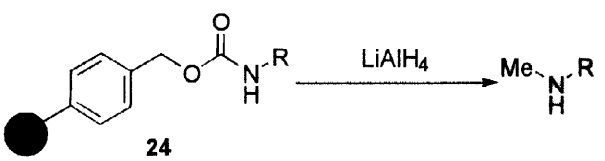


Scheme 65

The sulfone derivative has also been explored[24,25] with similar attachment and cleavage methods being used. It has been reported to be much more stable than the acrylate derivative to nucleophiles such as PhMgBr.

7.8.3. Reductive Cleavage

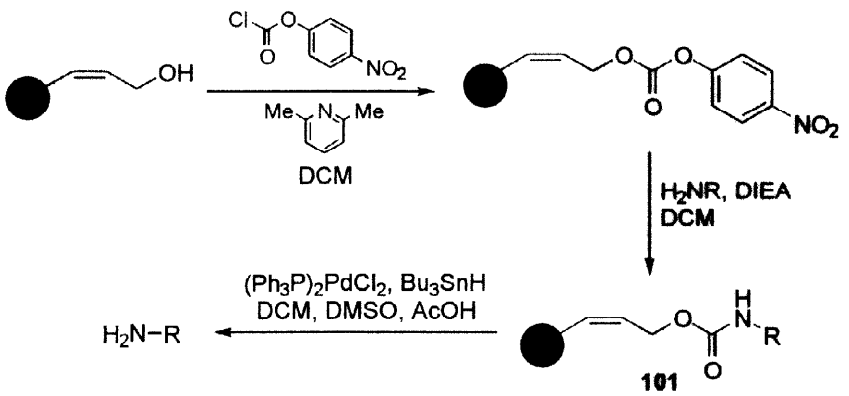
The Wang derived carbamate linker **24** may be reduced with $LiAlH_4$ in refluxing THF to form the methyl amines (Scheme 66).[71] Aqueous workup and solid phase extraction are used to remove aluminum salts.



Scheme 66

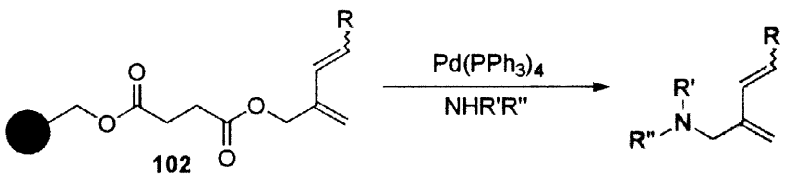
7.8.4. Pd Catalyzed Cleavage

Carbamate methodology has also been used to attach amines to an allyl linker.[70] The carbamate **101** is formed using the *p*-nitrophenylcarbonate method, and cleavage is achieved using palladium-catalyzed allyl transfer (Scheme 67). Purification is necessary to remove the cleavage reagents.



Scheme 67

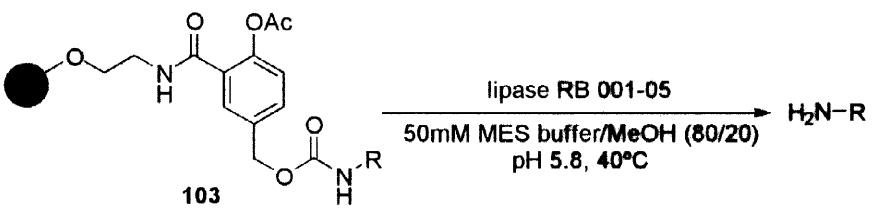
Conversely, solid phase bound allyl esters **102** may be cleaved as the allyl amine (Scheme 68).[240] Both secondary and tertiary amines have been prepared this way.



Scheme 68

7.8.5. Enzymatic Cleavage

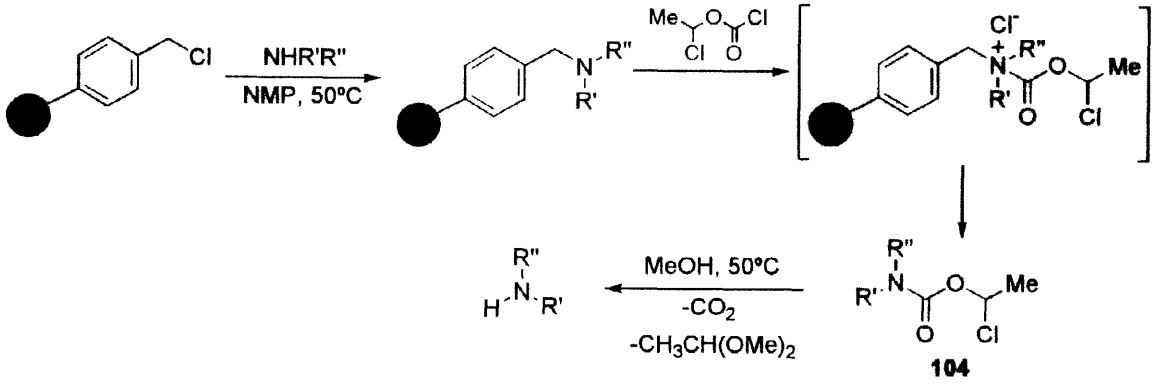
The carbamate linker **103** can be cleaved using lipase RB 001-05 in 50mM MES buffer/methanol (80/20) at pH 5.8 at 40°C to release the amine (Scheme 69).[140] (See also Section 7.1.6.)



Scheme 69

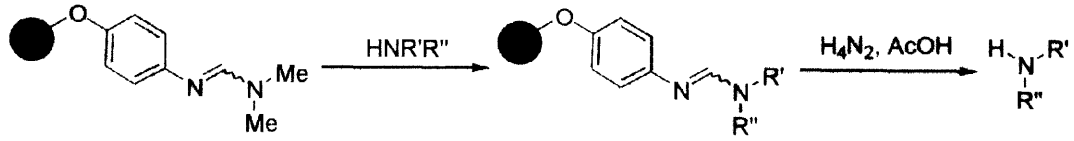
7.8.6. Others

Merrifield Amine: Secondary amines have been cleaved from Merrifield resin as the HCl salts using α-chloroethyl chloroformate (Scheme 70).[241] Heating in MeOH is required to decompose the carbamate intermediate **104** that is the initial cleavage product. All of the by-products are volatile, so high purity products can be achieved after evaporation. The use of heating, though achievable, does increase the complexity of the cleavage step if large numbers of individual compounds are being prepared.



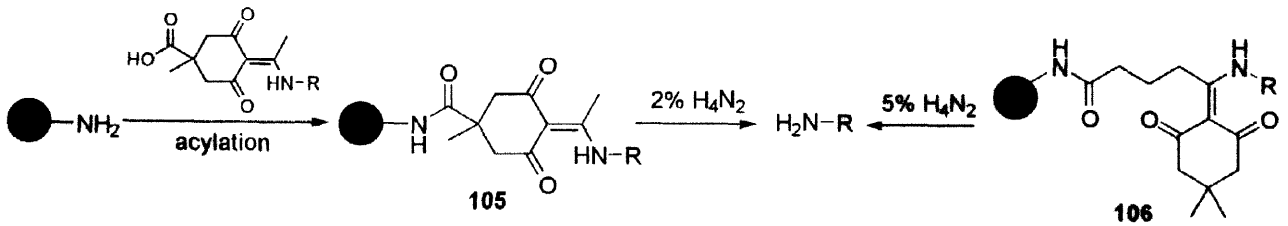
Scheme 70

Formamidine Linker: Transamination can be used to attach secondary amines to formamidines on the solid phase (Scheme 71).[242,243] Cleavage is achieved using hydrazine and acetic acid in ethanol at 60°C. Aqueous work up is used to remove excess cleavage reagents. As above, the use of heat during the cleavage step adds to its complexity. $LiAlH_4$, KOH in MeOH or $ZnCl_2$ in EtOH are also reported as cleavage reagents.



Scheme 71

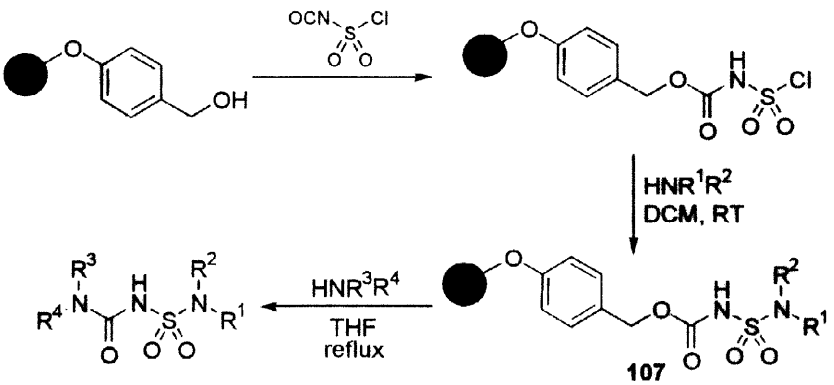
Dimedone Linker: Attachment via solution phase is used to attach amines to a linker derived from acetyldimedone (Scheme 72).[244] The linker **105** is stable to bases such as piperidine and DBU and to acidic conditions, however, it is cleaved rapidly with 2% hydrazine in DMF. The related linker **106** is prepared in a similar manner and cleaved with 5% hydrazine in 50% THF/H_2O.[245]



Scheme 72

7.9. Aminosulfonylurea

Attachment to the Wang linker using the carbamate method used to attach amines has also been used for the aminosulfonyl moiety (Scheme 73).[73] The linker **107** would probably be acid labile giving the aminosulfonamide after decarboxylation, but in the reported example it is used to prepare the aminosulfonylurea by treatment with a primary or secondary amine in refluxing THF. The amine used for cleavage is the limiting reagent and is mostly consumed in the reaction, hence giving high purity products following evaporation of the cleavage solution(s).

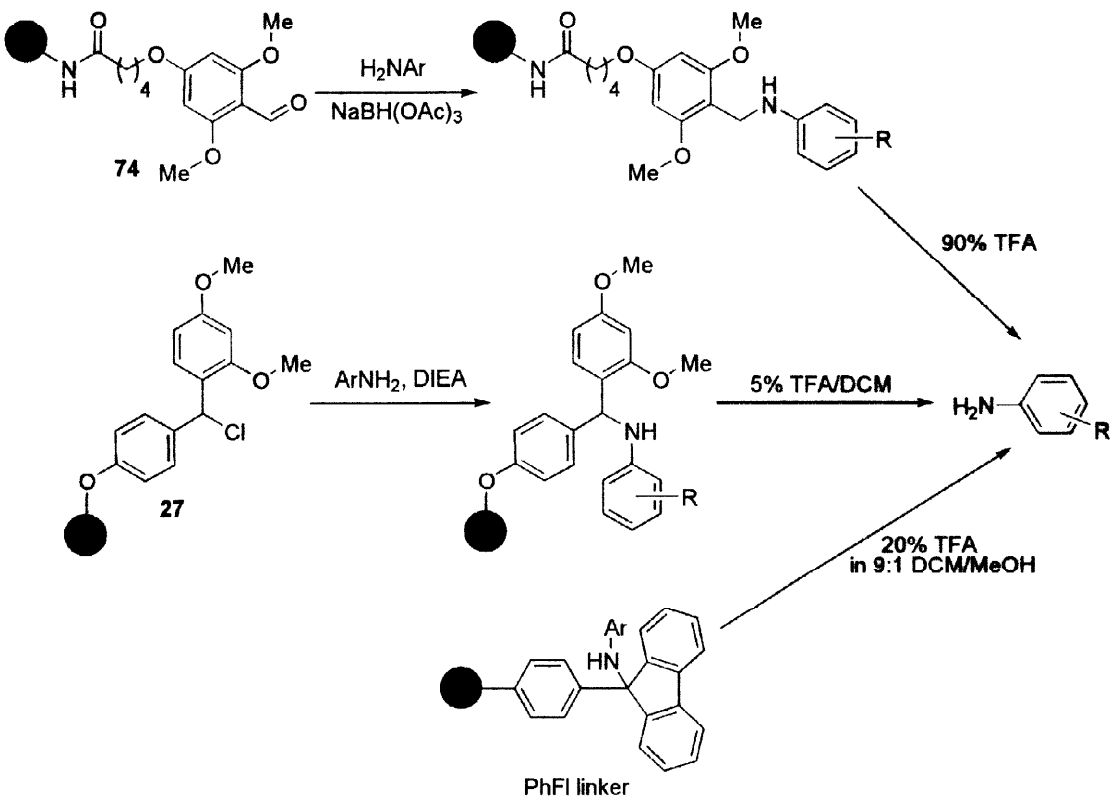


Scheme 73

7.10. Aniline

7.10.1. Acid Labile

A derivative of the PAL linker has been used to attach anilines to the solid phase.[246] The aniline is attached by reductive amination of the aldehyde **74** and cleavage is achieved with 90%TFA/5%Me_2S/5%H_2O (Scheme 74). The chloride **27** has been used as a means of attaching anilines to the Rink[84] and PhFl linkers.[221,222] Cleavage is achieved using 5% TFA/DCM and 20% TFA in 9:1 DCM/MeOH respectively.

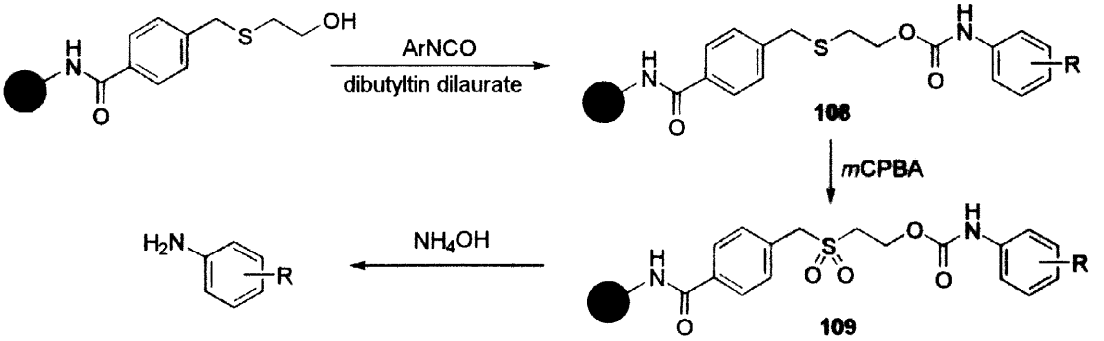


Scheme 74

Hydroxymethylpolystyrene has been adapted for the attachment of anilines using the carbamate method.[234] The carbamate is prepared via the chloroformate and HF is used for cleavage.

7.10.2. Base Labile

A safety catch version of the carbamate linker has been used to attach anilines.[247] The linker **108** is activated by oxidation of the thioether to the sulfone, **109**, with *m*CPBA (Scheme 75). Treatment with NH_4OH cleaves the product either by β–elimination and decarboxylation or by direct attack of the hydroxide on the carbamate.



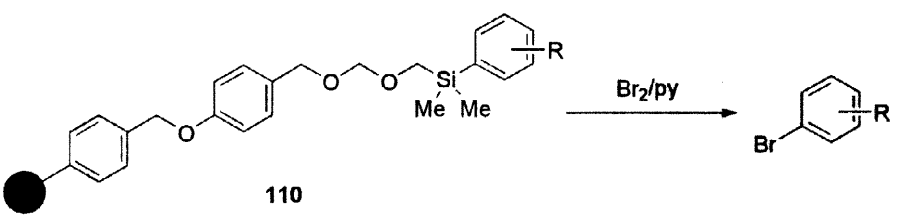
Scheme 75

7.11. Aromatic Group

A number of traceless linkers have been designed which give aromatic groups on cleavage. See Section 8.1.

7.12. Aryl Bromide

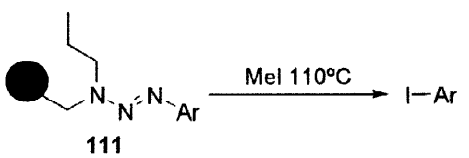
Electrophilic bromination with Br_2/pyridine may be used to cleave the aryl silane linker **110**, which was developed as a traceless aromatic linker. The product is the aryl bromide (Scheme 76).[248] Aryl germanium linkers may also be cleaved to give the aryl bromide.[30]



Scheme 76

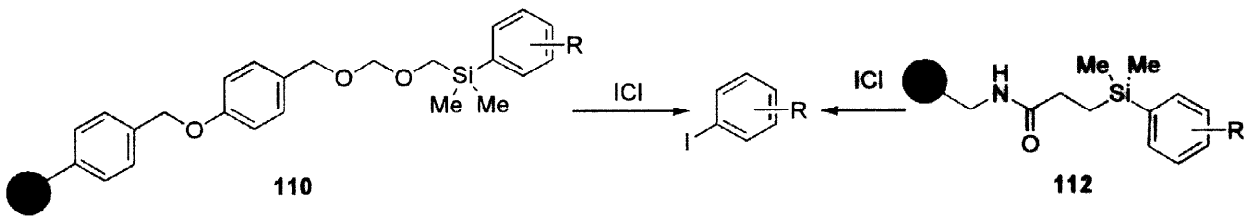
7.13. Aryl Iodide

Aryl triazines **111** have been cleaved with MeI at 110°C to form the aryl iodide (Scheme 77).[249,250] The excess alkylating agent would have to be removed prior to screening.



Scheme 77

The aryl silane linkers **110**, **112**, developed as traceless aromatic linkers, may be cleaved by electrophilic iodination using ICl to obtain the aryl iodide (Scheme 78).[248,251]

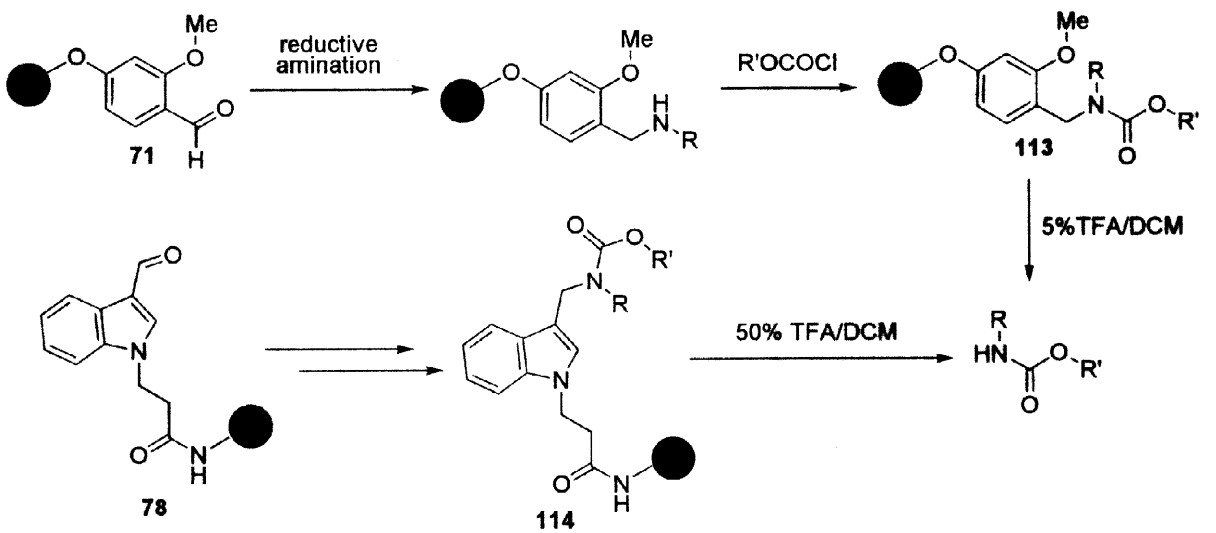


Scheme 78

7.14. Carbamate

7.14.1. Acid Labile

The Sasrin linker[183] and the indole linker[192] have been modified for the preparation of carbamates. For both, the solid phase aldehyde is reductively aminated, and treated with a chloroformate to form the carbamate (Scheme 79). Cleavage from the Sasrin linker **113** is achieved with 5% TFA/DCM, whereas 50% TFA/DCM is required for cleavage from the indole linker **114**.



Scheme 79

7.15. Carboxylic Acid

7.15.1. Acid Labile

The carboxylic acid group of a given alkoxybenzyl linker is more acid labile than the corresponding amide derivative. For example, cleavage of a carboxylic acid from the Rink linker is reported to require as low as 10% AcOH/DCM whereas 5-50% TFA/DCM typically is used for an amide.[80] The monoalkoxy benzyl linker, the Wang linker **4**,[49] which is cleaved with 50% TFA/DCM, is more frequently used than the Rink linker for carboxylic acids. Other acid labile linkers used to attach carboxylic acids are the PAC ester **83**, cleaved with 95% TFA,[198,252] the dialkoxy benzyl Sasrin linker **5**,[253-255] and **115**[50] both of which are cleaved with 1-3%

TFA/DCM (Figure 4). The trialkoxy benzyl HAL linker **116** requires only 0.05-0.1% TFA or 10% AcOH.[256] The benzylic ester with no alkoxy group **3**, usually derived from chloromethyl- or hydroxymethylpolystyrene, and frequently referred to as the Merrifield linker, is significantly more acid stabile. It can withstand high concentrations of TFA and requires the use of HF,[51,52] HBr/AcOH/TFA,[257] or HBr/TFA[258,259] to cleave the desired compound. $AlCl_3$ in DCM/$MeNO_2$[260] may also be used, although removal of the aluminum salts is not as simple as removal of the other cleavage reagents which are removed by evaporation. The PAM linker **114** is slightly more stable to acid than the Merrifield linker **3** but is also readily cleaved with HF.[261] In all cases, ester formation to attach the carboxylic acid is typically achieved with DIC/DMAP, or using the acid chloride and base, although the other methods described below for the base labile linkers may also be used. As with all esters, these linkers are not only acid labile, but may also be cleaved by nucleophilic attack on the ester, hence undesired cleavage may occur if unhindered nucleophiles for example, NaOMe,[53] are used in the synthesis. Prolonged treatment with $(Bu_3Sn)_2O$ has been reported to cleave the Wang and PAM linkers to release the acids.[262] The PAM linker is also labile to TBAF.$3H_2O$.[263]

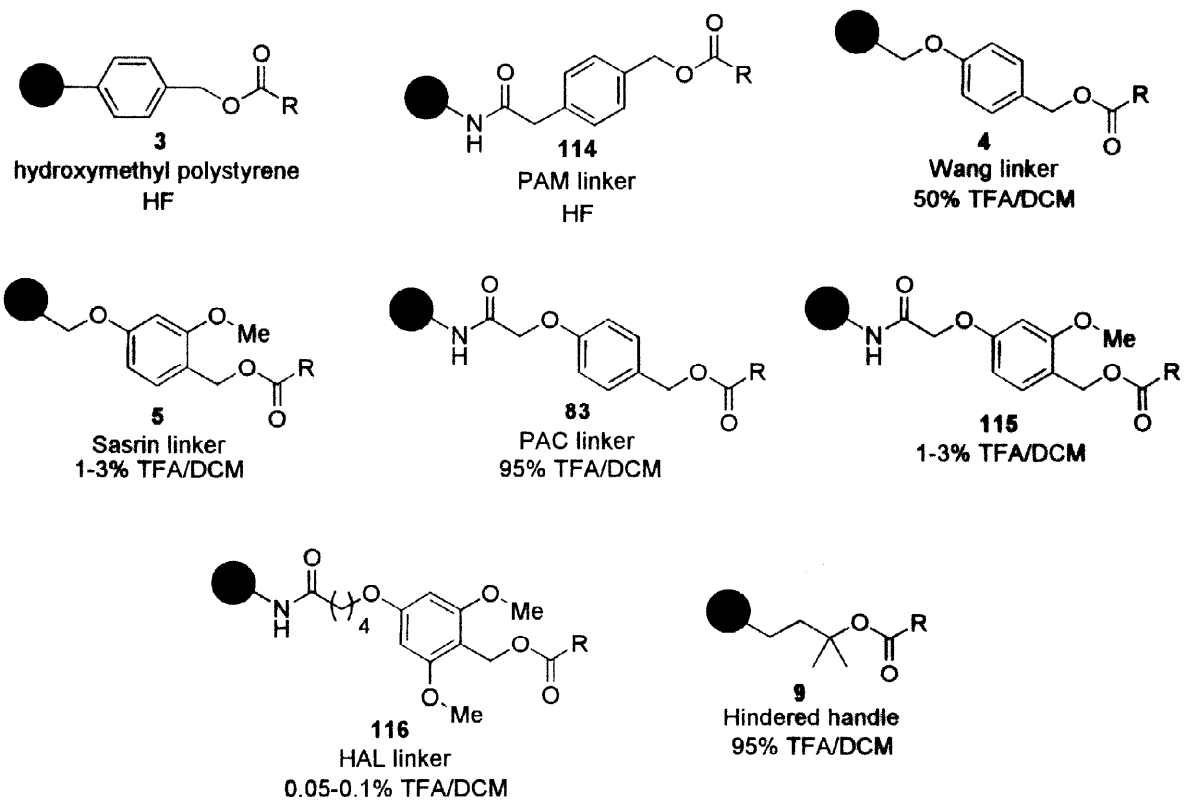
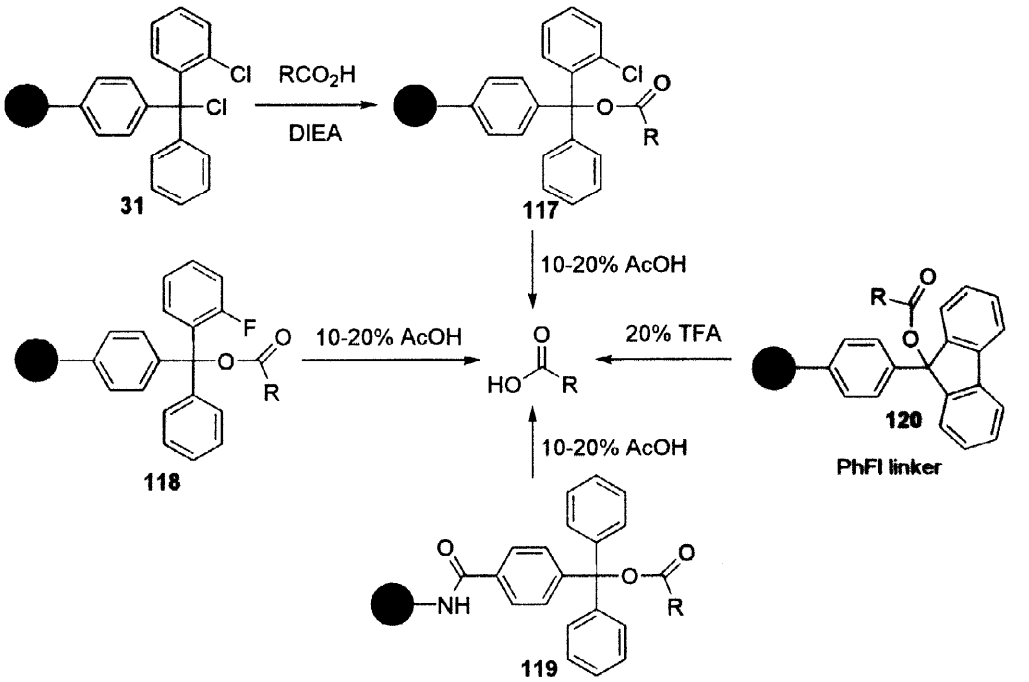


Figure 4

The *t*-butyl based hindered handle **9**[264] is cleaved by 95% TFA, but it is sterically hindered and hence resistant to nucleophilic attack and unwanted cleavage. The esterification to attach the first residue requires forcing conditions, such as the use of the acid chloride.



Scheme 80

When using trityl linkers to attach carboxylic acids, the 2-chlorotrityl linker **117** is used instead of the unsubstituted trityl linker as the latter is generally too labile. Attachment is performed using DIEA and cleavage is achieved using 1:1:8 AcOH/trifluoroethanol/DCM,[265-268] 5% TFA/DCM,[269] or 2:1:7 AcOH/TFA/DCM (Scheme 80).[270] The chloride of the 2-chlorotrityl linker **31** is highly reactive and, unlike most linkers where excess of the acid being attached is used, effective loading can be achieved even when limited amounts of the acid are used. This technique has been used in the synthesis of Taxol™ derivatives to limit the use of the expensive baccatin-III derivative.[270] The 2-fluorotrityl **118**[271] and the 4-(carboxamide)trityl **119** linkers[272] can be used in a similar manner to the 2-chlorotrityl linker. The PhFl linker **120**, based on the 9-phenylfluoren-9-yl protecting group, is more stable than the 2-chlorotrityl linker.[221,222] It is stable to AcOH, but it is cleaved with 20% TFA in 9:1 DCM/MeOH.

Synthetic examples using the Wang linker: benzimidazolones,[273] benzopiperazinones,[274] 1,3-benzoaxazine-2-ones,[275] coumarins,[276] cyclopentenones,[277] cyclopropanes,[278] dihydropyrimidines,[279] 3,4-dihydroquinazolines,[280] imidazoles,[281,282] indoles,[283] isoxazolines,[284] pyridines,[254] pyridopyrimidines,[254] quinazolinones,[285] quinolones,[286] tetrahydro-β-carbolines,[287] and tetrahydroquinolines.[288,289]

Hydroxymethylpolystyrene derived (Merrifield) linker: dihydro- and tetrahydro-β-carbolines[51] and indazoles.[257]

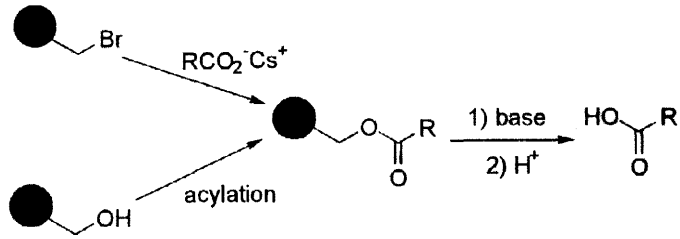
Sasrin linker: β-lactams,[290,291] pyrrolidines,[292] pyridines,[254] pyridopyrimidines,[254] quinazoline-2,4-diones,[293] and β-sultams.[294]

PAC linker: pyrazoles[295] and tropanes.[296]

2-Chlorotrityl linker: isoxazolidines[170]

7.15.2. Base Labile

Solid phase bound esters may be cleaved by hydrolysis to give carboxylic acids. The acid can be attached to the solid phase bound alcohol using Mitsunobu conditions,[297,298] or by means of the acid chloride[299] or anhydride (Scheme 81).[198] An alternative method for the attachment is displacement of the solid phase alkyl bromide or chloride with the cesium salt of the acid.[300] A range of esters have been used as base labile carboxylic acid linkers, including (with cleavage conditions in brackets): the ester of hydroxymethylpolystyrene or Merrifield linker **3** (0.85M Bu_4NOH in THF,[299,301] LiOH in 5:2:1 THF/MeOH/H_2O,[302] K_2CO_3 in MeOH[301,303]), the hydroxymethylbenzylamide or HMB linker **81** (0.1M aqueous NaOH),[201] the glycolamido linker **82** (NaOH in 70% ^{i}PrOH/water),[300] and **121** (3% 1M aqueous NaOH/^{i}PrOH at 50°C) (Figure 5).[297,298] The carboxylic acid is released as the salt and can be neutralized by treatment with a volatile acid.



Scheme 81

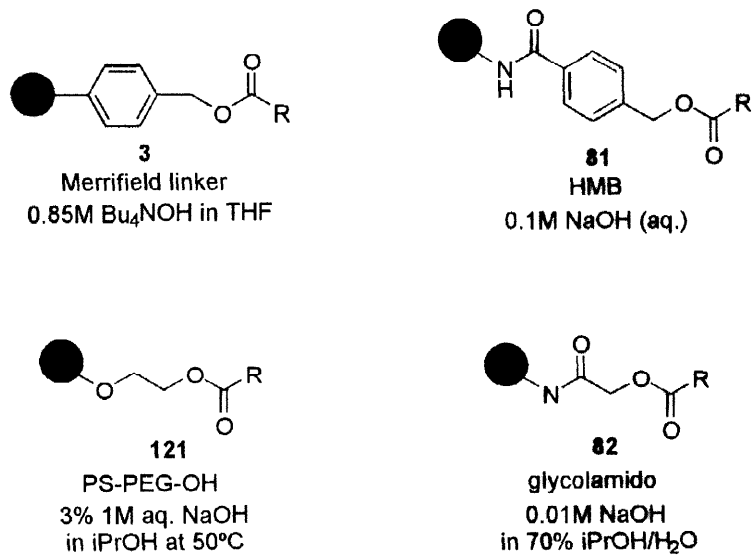
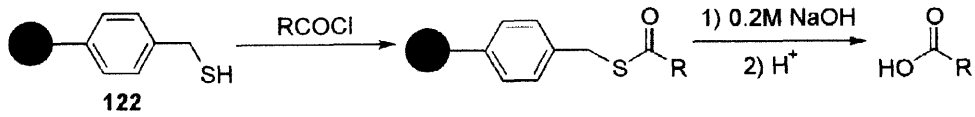


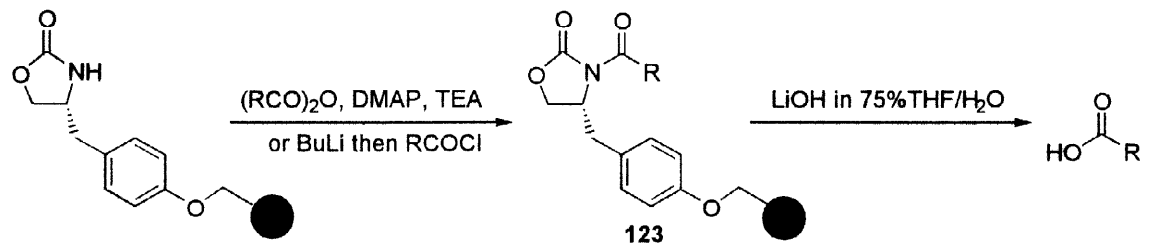
Figure 5

Thioesters can be prepared on the solid phase by acylation of the thiol **122** with the acid chloride (Scheme 82).[153] Treatment with 20% 1M aqueous NaOH in dioxane releases the product acid.



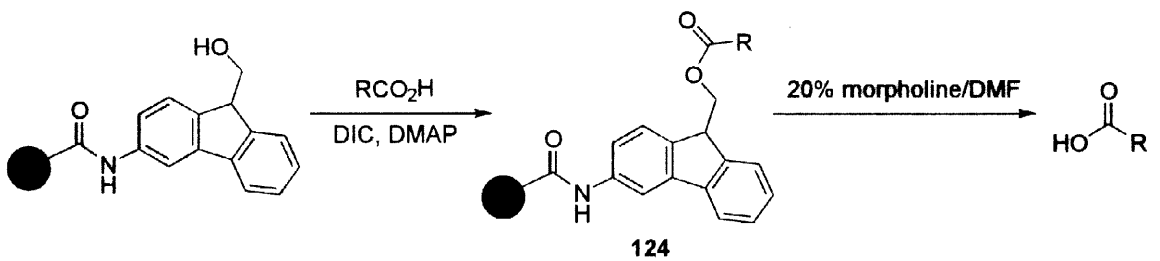
Scheme 82

N-Acylated chiral oxazolidinones **123** have been used as a base labile acid linkers.[304-307] The acid is attached using either the anhydride[304,307] or the acid chloride (Scheme 83).[305,306] On completion of the synthesis, the acid is cleaved from the solid phase by treatment with LiOH in 75% THF/H_2O. This process also regenerates the chiral auxiliary/linker.



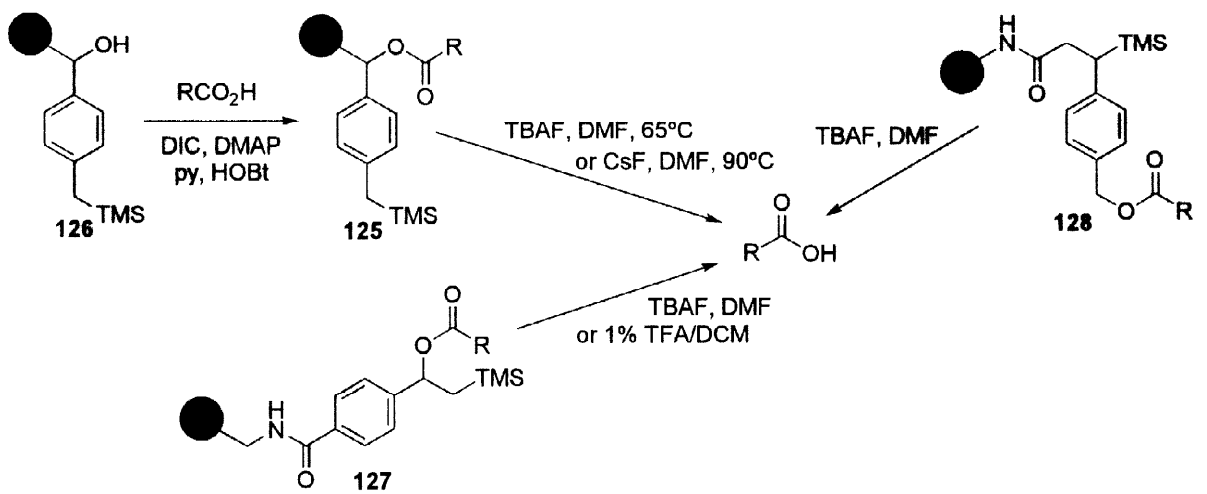
Scheme 83

A fluorene derived linker **124** has been developed with cleavage achieved by morpholine or piperdine in DMF (Scheme 84).[308,309]



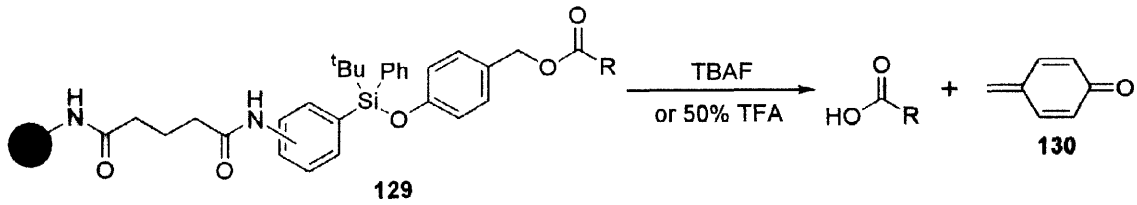
Scheme 84

A fluoride labile, silicon derived linker **126** has been developed.[133] Carboxylic acids are coupled to the alcohol **126** with DIC/DMAP (Scheme 85). Cleavage is achieved via 1,6-elimination using either TBAF in DMF at 65°C or CsF in DMF at 90°C. Further work up would be required after cleavage to remove the fluoride salts. The related linkers **127**[310] and **128**[311] have also been reported. Attachment of the acid is via solution phase and cleavage is achieved with TBAF in DMF. Linker **127** is also labile to 1% TFA/DCM.



Scheme 85

Carboxylic acids are attached to silyl linker **129** via solution phase.[312] The linker is labile to both 50% TFA in DCM and TBAF (Scheme 86). Apart from the desired carboxylic acid, this linker also releases the quinone methide **130**, which is scavenged by thiophenol in the cleavage solution. The final product has to be purified from this by-product.

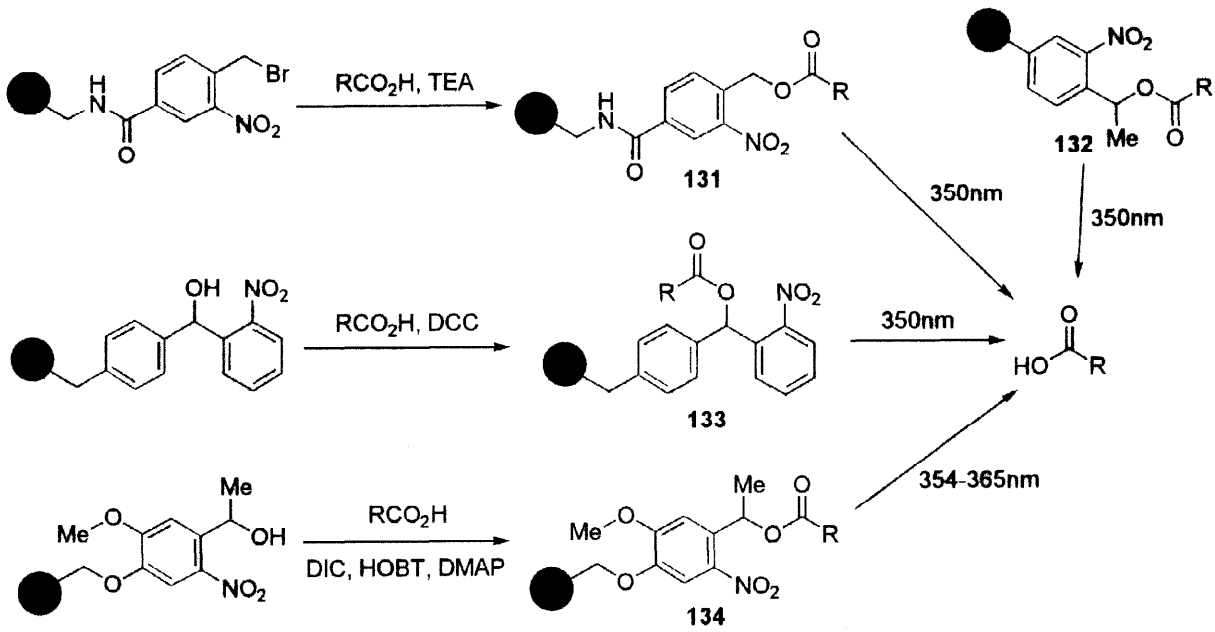


Scheme 86

7.15.3. Photolabile

The 2-nitrobenzyl **131**,[26,313] α-methyl-nitrobenzyl **132**,[314] 2-nitrobenzhydryl **133**,[315] and 4,5-dialkoxy-2-nitrobenzyl **134**[20,29,316] photolabile linkers have all been used to attach carboxylic acids (Scheme 87). Cleavage is performed by irradiation at 350-365nm.

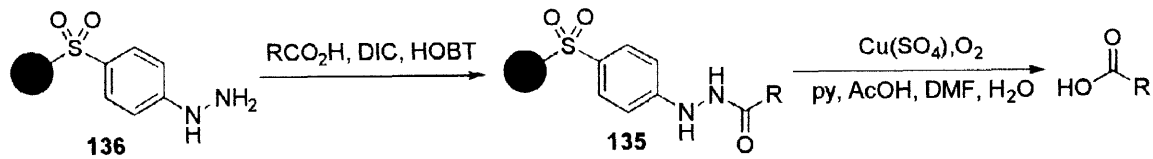
Synthesis examples: β-lactams[291] and β-sultams.[294]



Scheme 87

7.15.4. Oxidative Cleavage

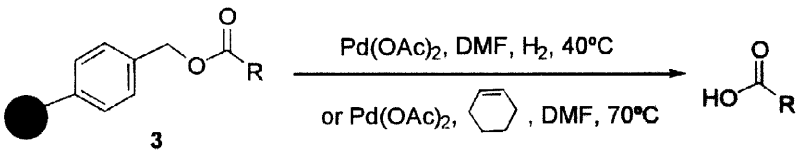
The phenyl hydrazide **135** has been used as an oxidatively labile linker for carboxylic acids.[317] The acid is coupled to the hydrazine **136** using DIC/HOBt (Scheme 88). Cleavage is achieved using copper(II) and oxygen.



Scheme 88

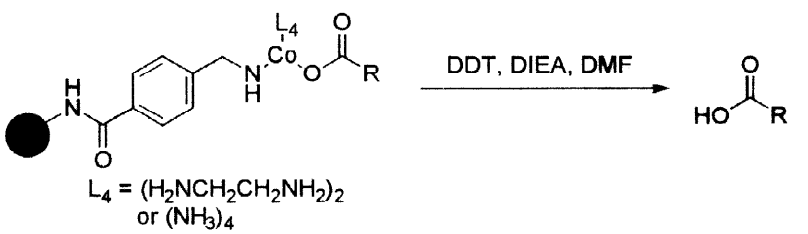
7.15.5. Reductive Cleavage

Esters attached to hydroxymethylpolystyrene may be cleaved by palladium catalyzed hydrogenation (Scheme 89).[318,319] Treatment with $Pd(OAc)_2$ in DMF at 40°C under 4 atmospheres of hydrogen may be used.[318,319] Alternatively cyclohexene may be used as the hydrogen source with the cleavage performed at 70°C.[320]



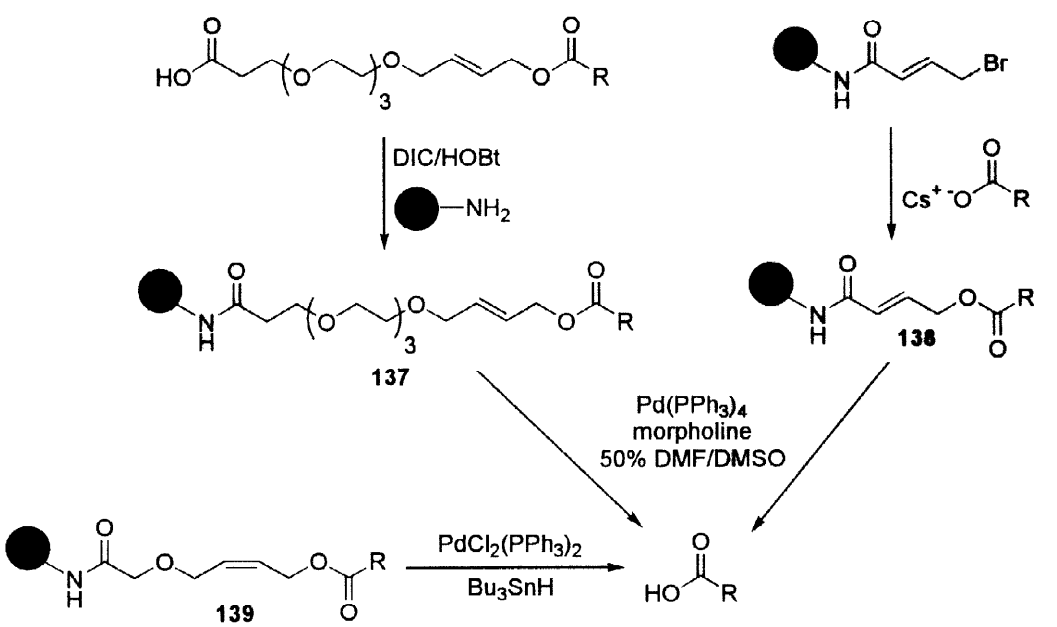
Scheme 89

One of the few linkers based on metal complexes involves the use of the cobalt(III) to attach acids (Scheme 90).[321] The complex with either bis(ethylene diamine) or tetraammonia ligands and the carboxylic acid is prepared in solution then attached to the solid phase. Cleavage is achieved using DDT and DIEA in DMF. The cobalt-sulfide by-product is removed by precipitation and the excess DDT is removed by extraction.



Scheme 90

7.15.6. Pd Catalyzed Cleavage

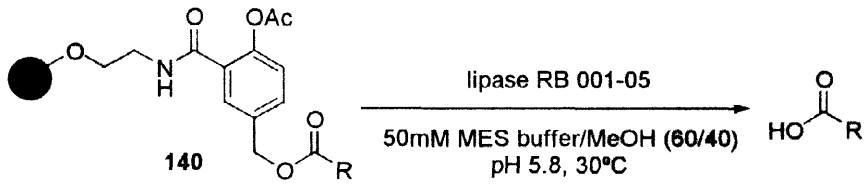


Scheme 91

Linkers based on palladium catalyzed allyl transfer have been used to attach carboxylic acids (Scheme 91).[322-324] Attachment of the carboxylic acid to give **137** is performed in solution phase and cleavage is achieved using $Pd(PPh_3)_4$ and morpholine in 50% DMF/DMSO. Purification is required to separate the desired product from the palladium catalyst. This ethylene glycol linker was found to be more stable to nucleophilic conditions such as secondary amines than the initially developed crotonyl derived linker **138**.[325] Using a similar approach, linker **139** is cleaved with $PdCl_2(PPh_2)_2$ and Bu_3SnH,[326] or $Pd(PPh_3)_4$ and morpholine in 2:2:1 THF/DMSO/0.5M HCl.[327]

7.15.7. Enzymatic Cleavage

The ester linker **140** can be cleaved using lipase RB 001-05 in 50mM MES buffer/methanol (60/40) at pH 5.8 at 30°C to release the acid (Scheme 92).[140] Tetrahydro-β-carbolines have been prepared using this linker. (See also Section 7.1.6.)



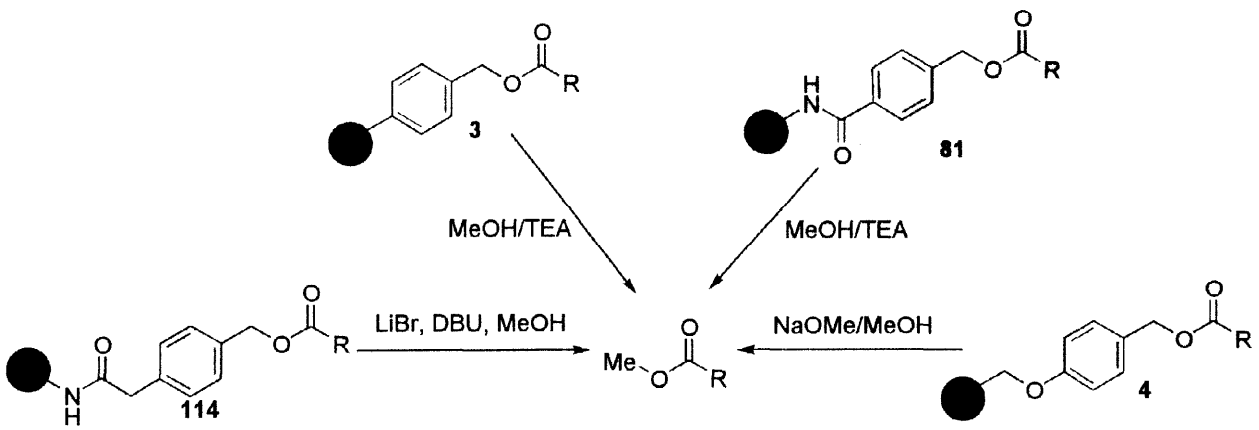
Scheme 92

7.16. Carboxylic Ester

7.16.1. Base Labile

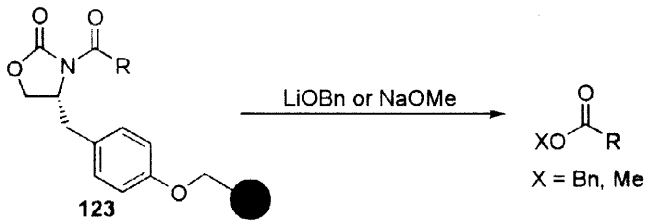
The ester based linkers used to attach carboxylic acids to the solid phase may be cleaved by saponification with an alkoxide to release the product as the ester (Scheme 93). Published examples of this reaction are mainly restricted to formation of the methyl ester. The Merrifield linker **3** is cleaved with MeOH and TEA or NMM[204,328] or with NaOMe in THF at reflux.[329,330] The HMB linker **81** is cleaved with 90% MeOH/TEA at 50°C[331,332] and the Wang linker **4** with NaOMe,[53] TEA/MeOH/KCN,[54] or LiBr/DBU/MeOH.[333] The PAM linker **114** is also cleaved with LiBr/DBU/MeOH.[333,334]

Synthesis examples: dihydropyrans[329] indoles,[331,332] and tetrahydro-1,4-benzodiazepine-2-ones.[53]



Scheme 93

A solid phase bound *N*-acylated chiral oxazolidinone **123** has been used as a base labile carboxylic ester linker (Scheme 94).[305,307] Cleavage with NaOMe/THF[305] or lithium benzyloxide generates the methyl ester or the benzyl ester respectively. This process regenerates the chiral auxiliary/linker.

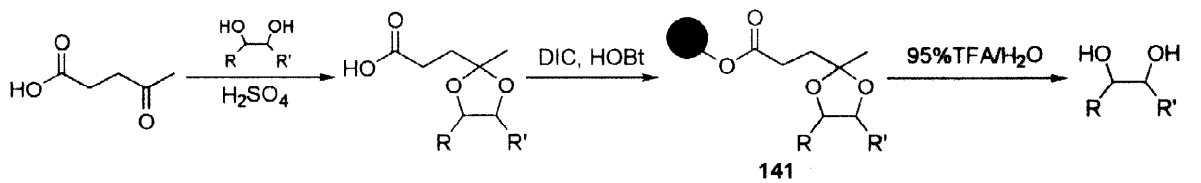


Scheme 94

7.17. Diol

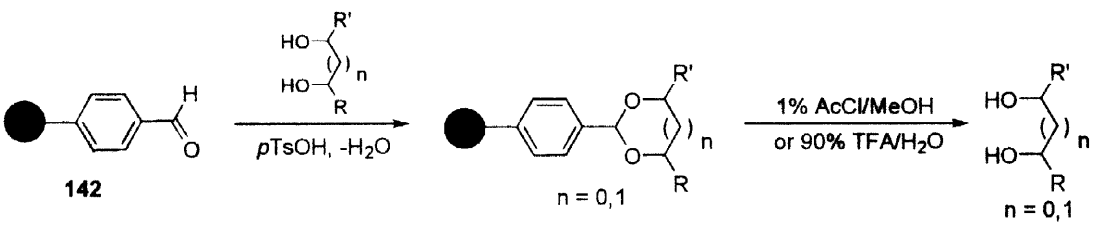
7.17.1. Acid Labile

The 5-membered cyclic ketal **141** has been used as a linker for 1,2-diols. Attachment via solution phase can be used and cleavage achieved using 95% TFA/water (Scheme 94).[102]



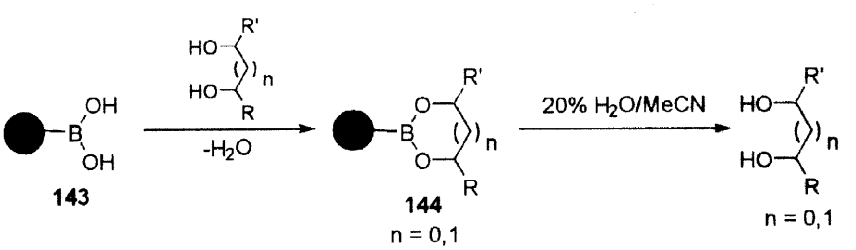
Scheme 95

Alternatively, 1,2-[335,336] and 1,3-diols[337] can be attached using *p*TsOH directly to a solid phase bound benzaldehyde **142** (Scheme 96). The 1,2-diols are cleaved with 1% AcCl/MeOH or 1% TFA in 80% AcOH/H_2O whereas the 1,3-diols required 90% TFA/water.



Scheme 96

Solid phase bound boronic acids **143** can also be used to attach 1,2- and 1,3-diols[338] using azeotropic removal of the water (Scheme 97). The linker **144** is water sensitive and cleavage is achieved using 20% H_2O/MeCN.



Scheme 97

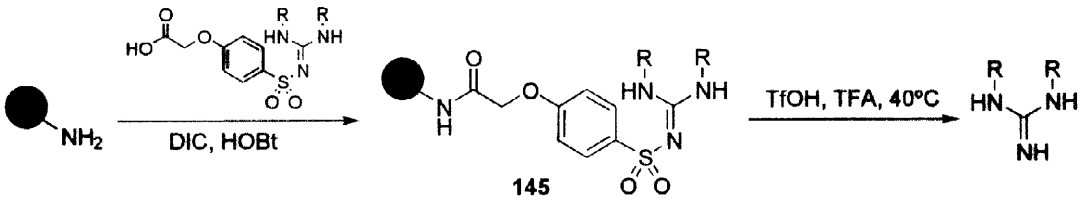
7.18. Furan

For a linker which cleaves to give a furan, see Section 8.6.

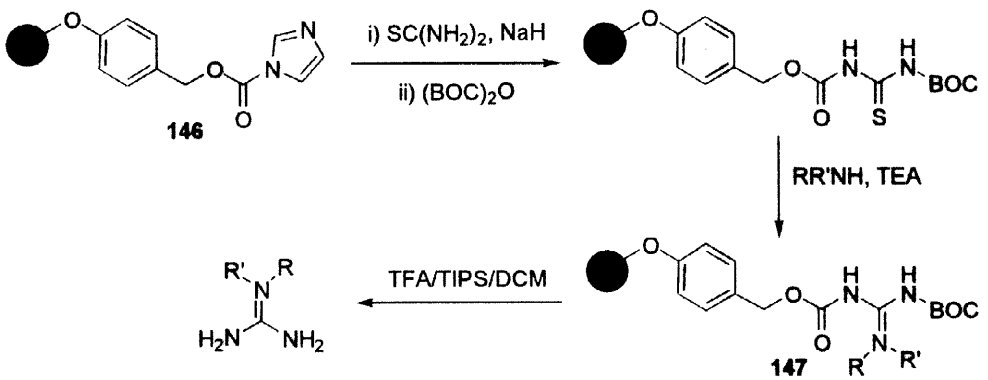
7.19. Guanidine

7.19.1. Acid Labile

The acid labile guanidine linker **145** is prepared using the attachment via solution method (Scheme 98).[339] The linker is stable to at least 20% TFA in DCM, but is cleaved by triflic acid in TFA at 40°C. The Wang linker has also been modified to attach guanidines (Scheme 99).[340] The imidazole carbamate **146**, derived from the Wang linker, is converted to the thiourea derivative **147**, which is then protected and treated with an amine to form the solid phase bound guanidine. Cleavage using 49% TFA in DCM gives the unprotected guanidine.

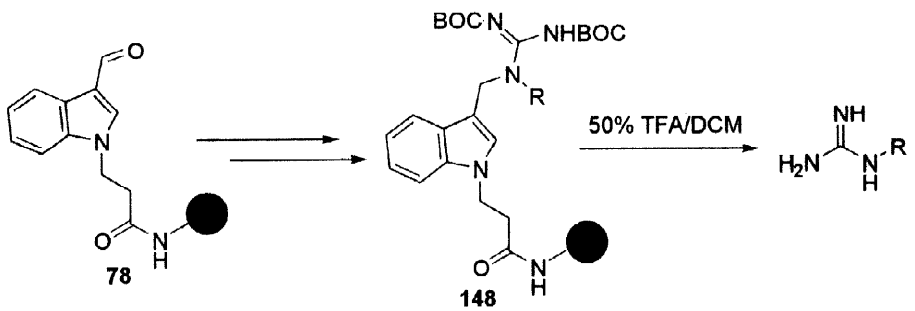


Scheme 98



Scheme 99

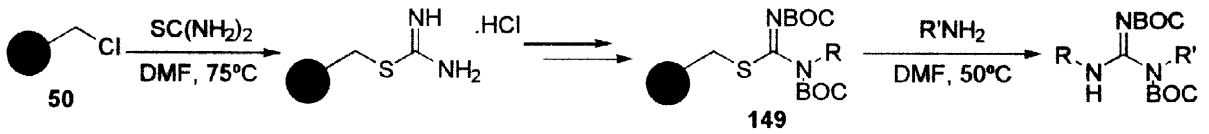
An indole derived linker **148** has also been used for guanidines.[192] The aldehyde **78** is reductively aminated then treated with BOC protected thiourea (Scheme 100). Cleavage to give the unprotected guanidine is achieved with 50% TFA/DCM.



Scheme 100

7.19.2. Base Labile

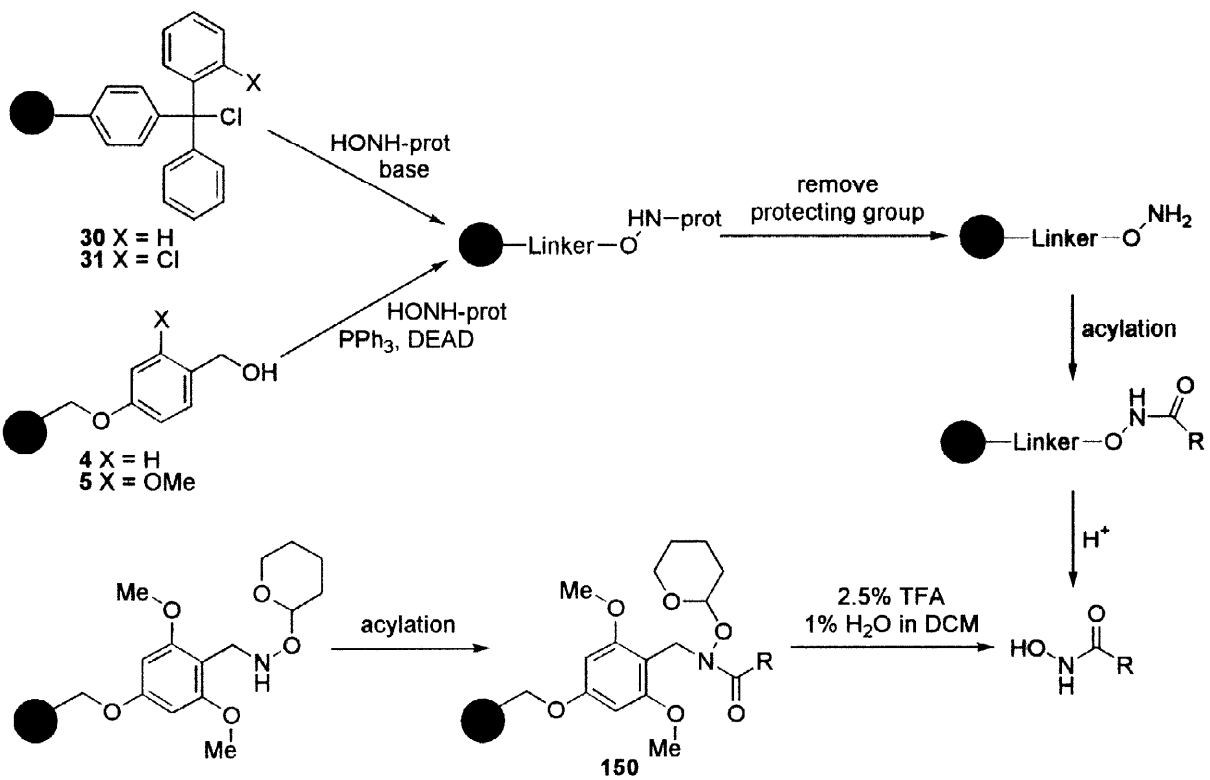
The thiopseudourea **149** has been used as a base labile guanidine linker.[341] It is prepared from chloromethylpolystyrene using thiourea, protected with $(BOC)_2O$ then alkylated using Mitsunobu chemistry (Scheme 101). Cleavage is achieved using a primary amine in DMF at 50°C. The BOC protecting groups can be removed after cleavage by treatment with TFA.



Scheme 101

7.20. Hydroxamic Acid

7.20.1. Acid Labile



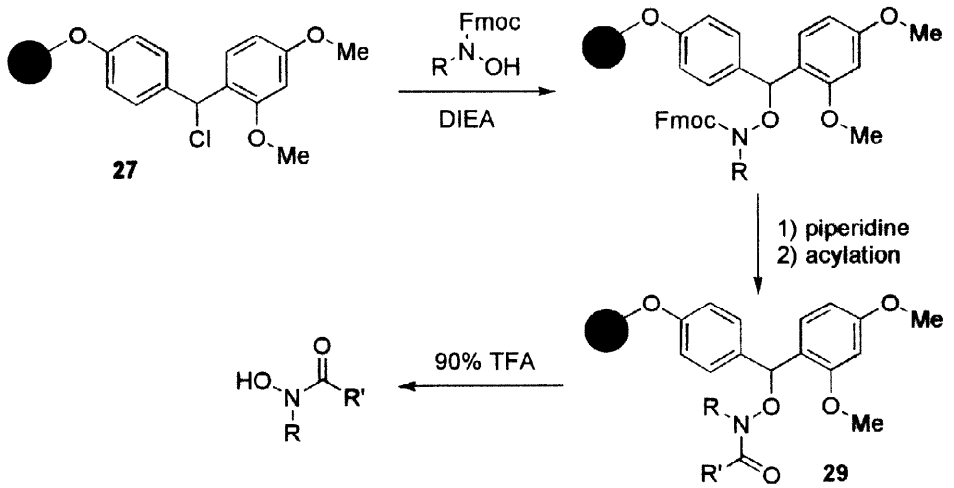
Scheme 102

A range of acid labile hydroxamic acid linkers have recently been published. Typically, the nitrogen of hydroxylamine is protected with either the Fmoc group[342] or as the phthalimide.[293,343-345] The protected hydroxylamine can be attached through the oxygen to the trityl **30**[344] or 2-chlorotrityl **31** linkers[342] by displacement of the halide or mesylate, or to the Sasrin **5**[293] or Wang **4**[343,345] linkers using the Mitsunobu reaction (Scheme 102). The protecting group is removed either with piperdine for the Fmoc group, or hydrazine for the phthalimide, and the nitrogen acylated with standard conditions, e.g. DIC, HOBt. The linkers are cleaved with acid: trityl, 25% formic acid; 2-chlorotrityl, 5% TFA/DCM; Sasrin, 1% TFA/DCM; and Wang,

70%TFA/DCM. The nitrogen of the hydroxymate is very nucleophilic and, for relatively unhindered linkers such as that derived from Sasrin, may participate in side-reactions. The bulk of the trityl group can hinder the reactive nitrogen, reducing these unwanted reactions.

An alternative approach involves the trialkoxy benzyl PAL linker.[346] The hydroxylamine is *O*-protected with a THP group and attached through the nitrogen (Scheme 102). The nitrogen is then acylated with either the acid chloride or the symmetrical anhydride. The tertiary nitrogen formed in **150** is unlikely to be involved in side-reactions. The THP protecting group is removed during cleavage with 2.5% TFA and 1% H_2O in DCM releasing the deprotected hydroxamic acid.

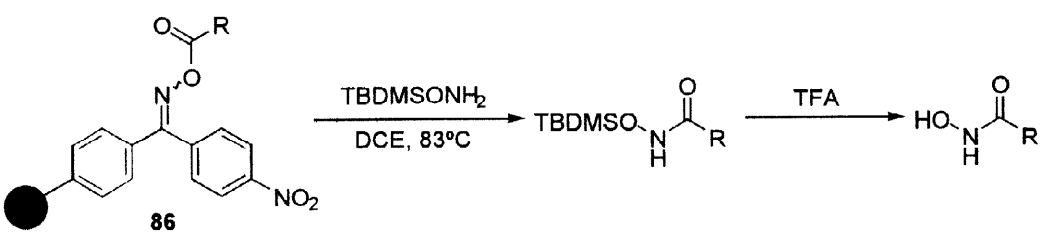
The Rink linker has been used to prepare *N*-substituted hydroxamic acids. Rink chloride **27** is treated with *N*-Fmoc-*N*-alkyl hydroxylamine and DIEA, deprotected then acylated with an acid (Scheme 103). On the completion of synthesis, cleavage is achieved with 90%TFA at 30°C.[85]



Scheme 103

7.20.2. Base Labile

Treatment of Kaiser's base labile oxime linker **86** with *tert*-butyldimethylsilyl *O*-protected hydroxylamine in DCE cleaves the product as the protected hydroxamic acid (Scheme 104).[347] The protecting group can be removed by treatment with TFA.

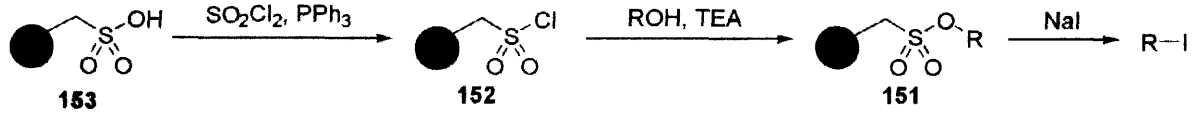


Scheme 104

7.21. Iodide

The sulfonate ester **151** has been used to attach compounds through an alcohol resulting in the iodide after cleavage.[348] The solid phase sulfonyl chloride **152** is prepared from the sulfonic acid **153** using SO_2Cl_2 then the alcohol is attached using TEA as the base (Scheme 105).[349] Alternatively, attachment via solution phase can be

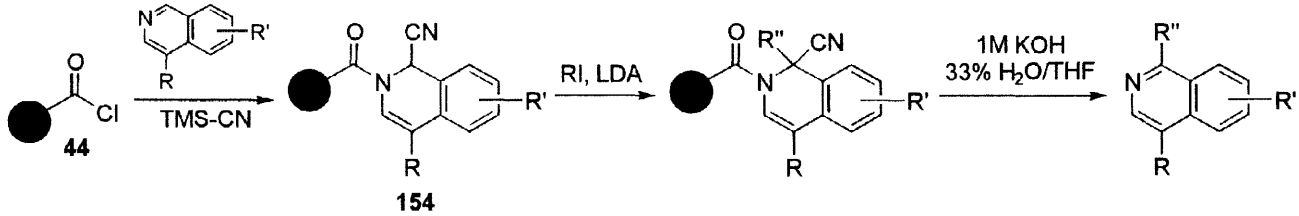
used.[348] Cleavage to give the iodide is achieved via nucleophilic displacement using NaI. This linker could be used to give other functionalities if treated with suitable nucleophiles, such as NaOAc or NaN_3. It has also been used as a traceless linker using intramolecular attack by a carbon nucleophile.[348]



Scheme 105

7.22. Isoquinoline

An isoquinoline linker has been developed based on Reissert compounds.[350,351] Treatment of resin bound benzoyl chloride **44** with isoquinoline and TMS-CN results in the Reissert linker **154** attached via the acyl group at the 2-position (Scheme 106). The 1-postion was then alkylated using LDA as base. Cleavage to release the isoquinoline is achieved by heating with KOH in 33% H_2O/THF. Aqueous work up is required after cleavage.

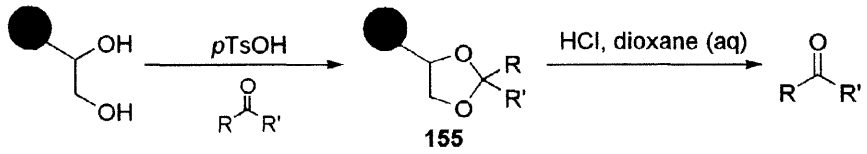


Scheme 106

7.23. Ketone

7.23.1. Acid Labile

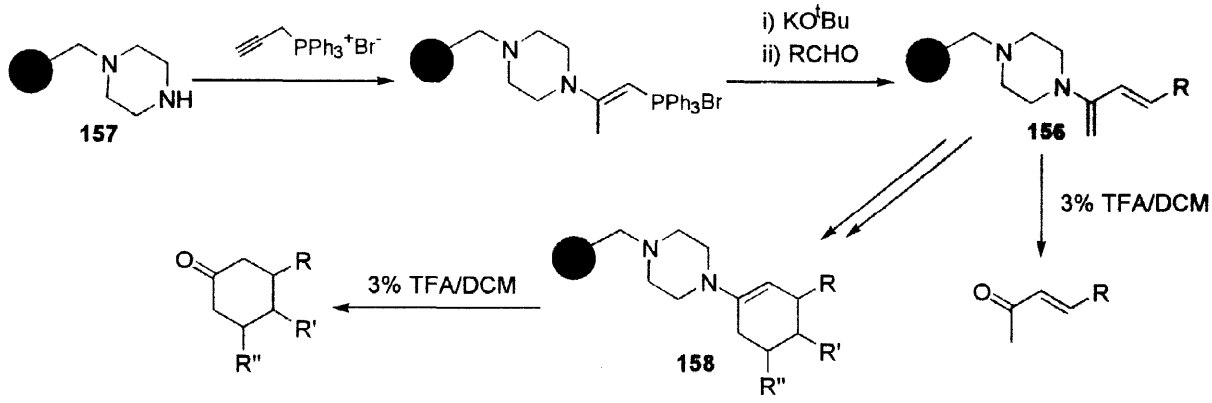
Ketals: In similar manner to the attachment of aldehydes, ketones have been attached to the solid phase as the 5-membered cyclic ketal **155**.[144,352] Attachment of the ketone is performed using *p*TsOH and cleavage is achieved using 2M HCl in 50% dioxane/water[352] or *p*TsOH in 20% dioxane/water (Scheme 107).[144]



Scheme 107

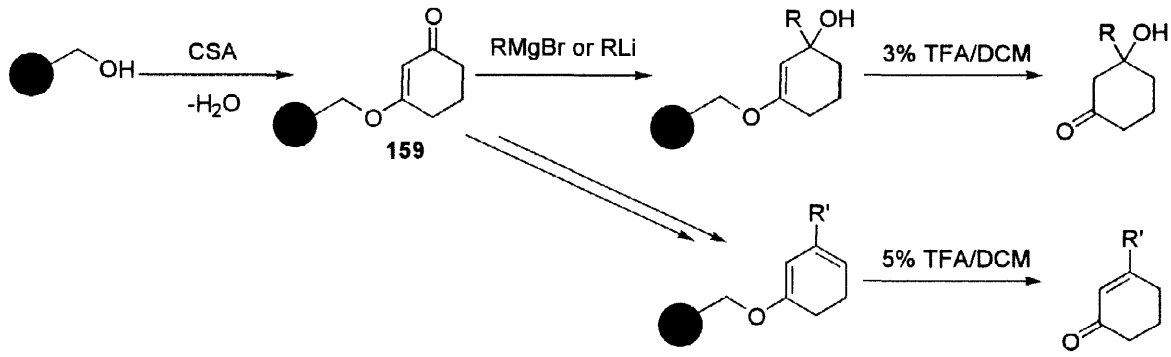
Enamines:

2-Aminobutadiene derivatives have been used to give α,β-unsaturated ketones. The diene **156** is formed by treatment of secondary amine **157** with propargyl triphenylphospine bromide followed by a Wittig reaction (Scheme 108). Treatment with 3%TFA/DCM cleaves the product as the ketone.[353,354] The diene can be further reacted resulting in an enamine linker **158**, which also cleaves in 3% TFA/DCM to give the ketone.[354]



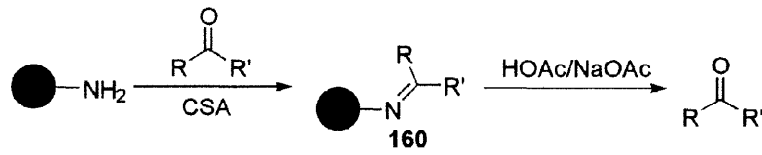
Scheme 108

Enol Ethers: 1,3-Diones have been attached to hydroxymethylpolystyrene as the enol ether **159**.[355] The ketone moiety not involved in binding to the solid phase can be transformed using various reactions. The linking ketone is released by treatment with 3-5%TFA (Scheme 109).



Scheme 109

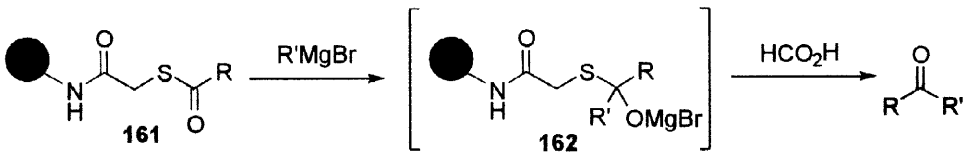
Imines: Ketones have been attached to amines on the solid phase as the imine **160** with cleavage achieved using the mild conditions of buffered aqueous acetic acid (Scheme 110).[356,357]



Scheme 110

7.23.2 Others

Treatment of a thioester linker **161** with a Grignard reagent leads to the formation of the tetrahedral intermediate **162** (Scheme 111). This can be washed with dry THF to remove the excess Grignard reagent then release of the product from the solid phase as the ketone is achieved by treatment with a proton donor such as formic acid.[358] Filtration is used to remove the magnesium salts. No tertiary alcohol products were reported as by-products in the cleaved samples.



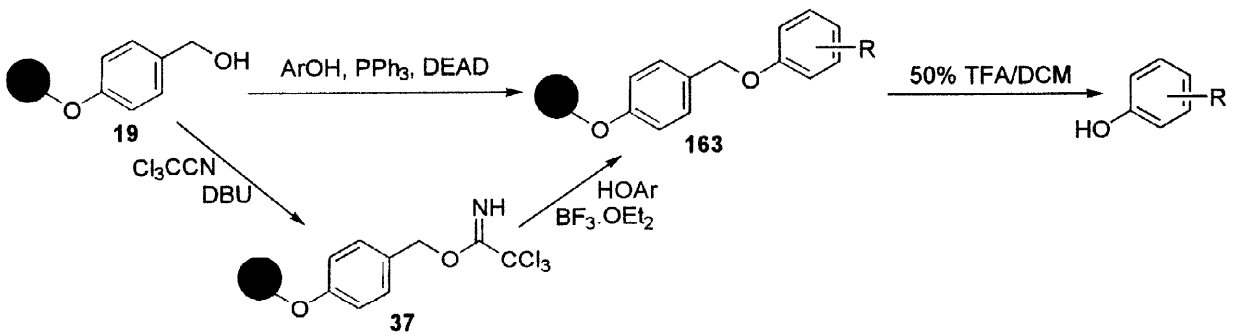
Scheme 111

7.24. Phenol

7.24.1. Acid Labile

The phenol group may be attached to the Wang Linker **19** using Mitsunobu chemistry (Scheme 112).[65] Cleavage of **163** is achieved with 10-50% TFA in DCM. This method can be problematic with the loading being highly dependent on the substrate. Also, hydrazinodicarboxamide derivatives have been reported as impurities in the cleaved product when using this method of attachment.[359] An alternative method for preparing **163** involves first treating the Wang linker **19** with trichloroacetonitrile and DBU to form the trichloroacetimidate **37**. This is then treated with the phenol and boron trifluoride etherate.[63]

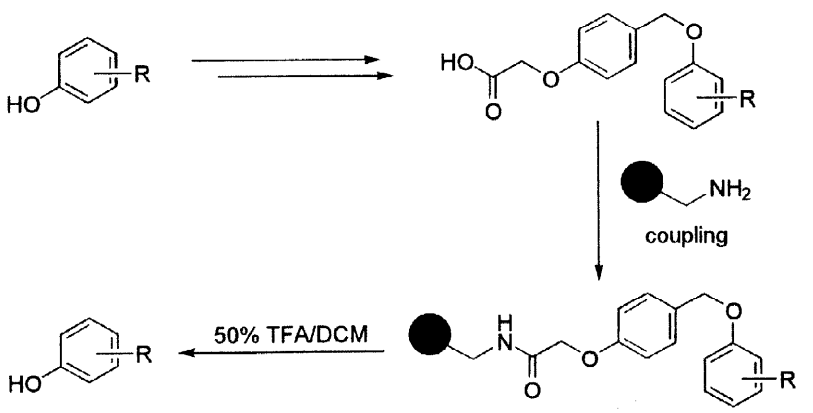
Synthesis examples: 2,3-dihydro-4-pyridones[360] and imidazoles.[282]



Scheme 112

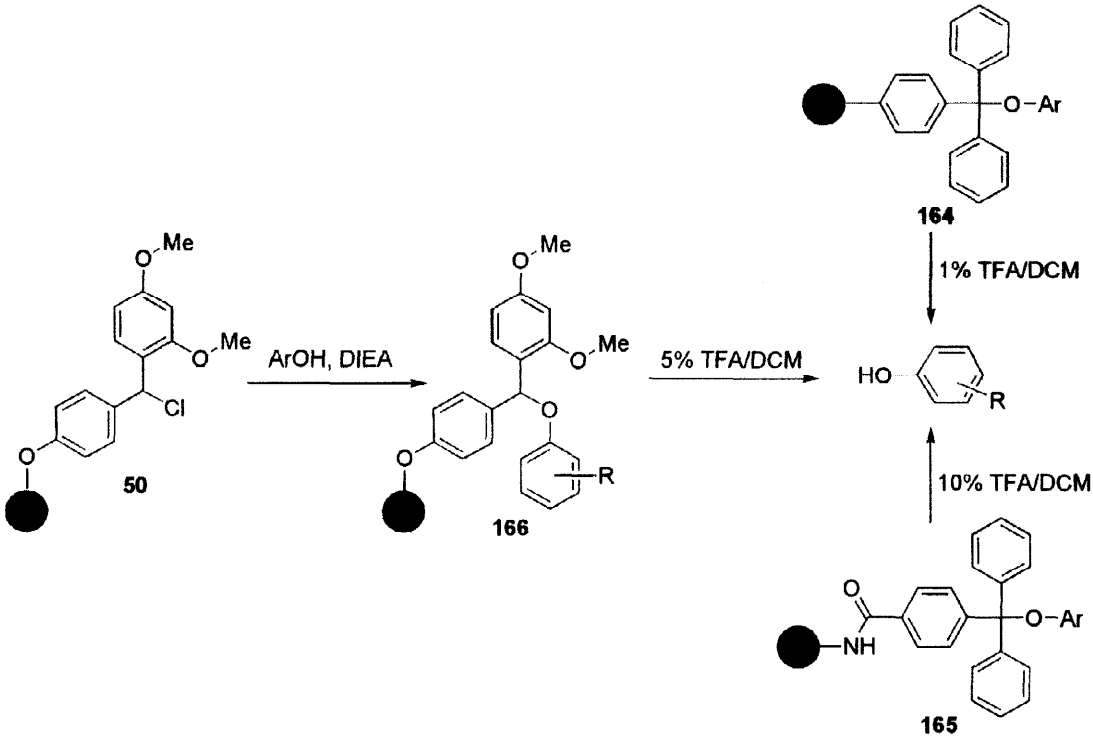
The monoalkoxy benzyl PAC linker also can be used as a phenol linker (Scheme 113). Usually the phenol is attached via solution phase,[31,67] hence removing the problem of variable loading and impurities that can be encountered when using Mitsunobu chemistry to attach to the linker. Cleavage is achieved using 95% TFA/H_2O.

Synthesis examples: benzimidalones,[66] 1,4-benzodiazepines,[361] indoles[362] and quinazoline-2,4-diones.[67]



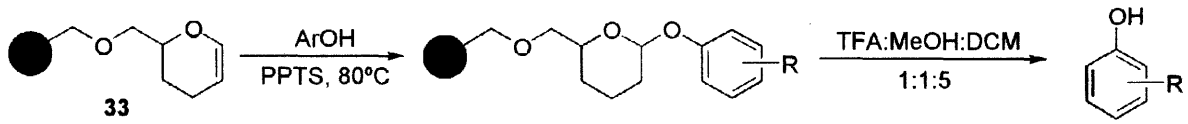
Scheme 113

Phenols can be attached to the Rink (**166**),[84] trityl (**164**),[363] and 4-carboxamidetrityl (**165**) linkers (Scheme 114).[364] The Rink linker is cleaved with 5% TFA/DCM and the trityl linkers are cleaved with 1 and 10% TFA/DCM respectively.



Scheme 114

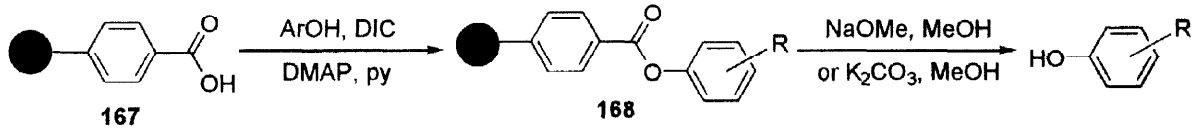
The DHP linker **33** has been used as a phenol linker using similar attachment and cleavage procedure to those used for alcohols (Scheme 115).[103]



Scheme 115

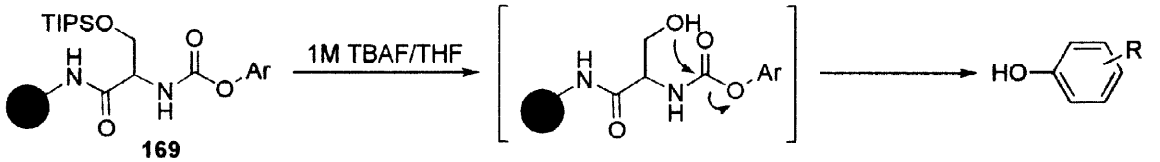
7.24.2. Base Labile

Phenols have been attached to a solid phase benzoic acid **167** as the ester **168** (Scheme 116).[365] After completion of chemistry, the ester bond is cleaved by hydrolysis with NaOH in dioxane,[366,367] NaOMe/MeOH/THF[365] or K_2CO_3 in MeOH.[365] Salts can be removed by filtration from organic solvent.



Scheme 116

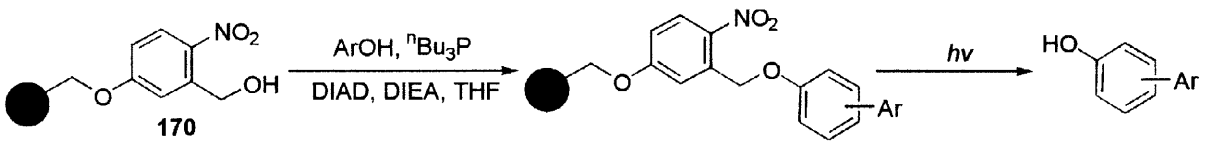
The phenols can be attached to the fluoride labile linker **169** via solution phase.[368] Treatment with 1M TBAF in THF deprotects the alcohol of the linker, which then cyclizes to form the solid phase bound oxazolidinone and releases the phenol (Scheme 117). Aqueous work up is used to remove the fluoride salts.



Scheme 117

7.24.3. Photolabile

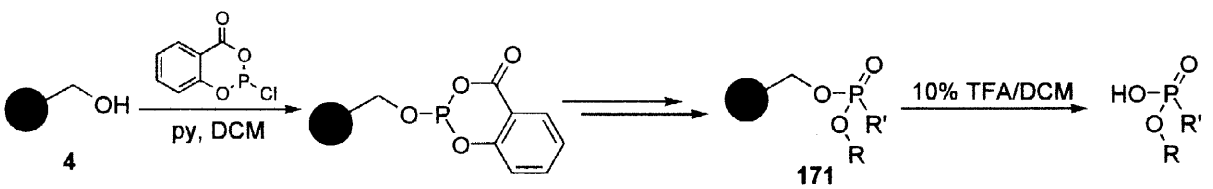
Photolabile cleavage has been used for phenols.[369] The phenol is attached to the **170** using Mitsunobu chemistry then cleaved using standard photolysis conditions (Scheme 118).



Scheme 118

7.25. Phosphonate

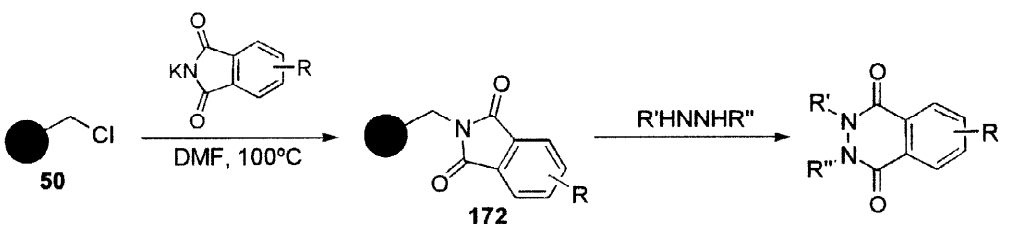
The Wang linker has been used to attach phosphonates.[76,370] The phosphorus is attached using 2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one (Scheme 119). It is further manipulated to form the solid phase bound phosphonate **171** which is cleaved with 10% TFA/DCM.



Scheme 119

7.26. Phthalhydrazide

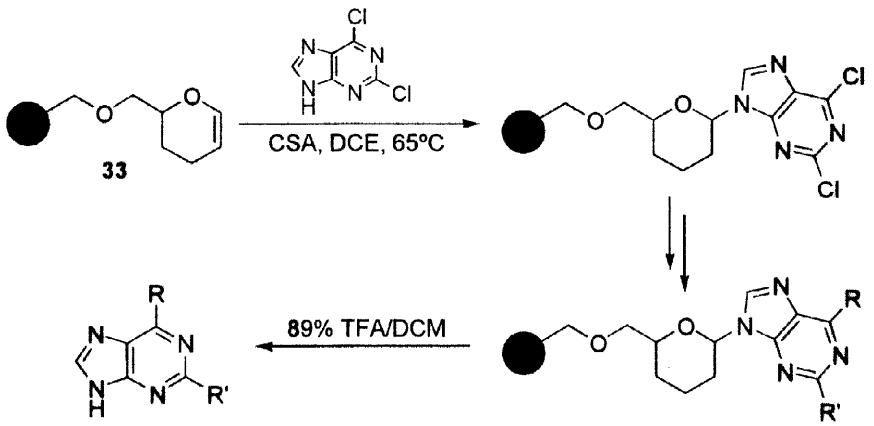
Phthalamides can be attached to chloromethylpolystyrene **50** using the potassium salt (Scheme 120).[371] Treatment of the attached phthalamide **172** with aliphatic hydrazines releases the product as the phthalhydrazide.[372]



Scheme 120

7.27. Purine

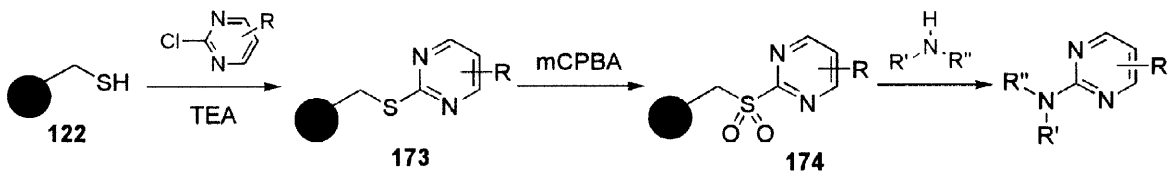
The purine group has been attached through the 9-position to the solid phase using the DHP linker **33**.[373] Attachment is catalyzed by CSA and the linker cleaved using 89% TFA/DCM (Scheme 121).



Scheme 121

7.28. Pyrimidine

Aromatic nucleophilic substitution by a solid phase bound thiol onto a 2-chloropyrimidine has been used to attach pyrimidines to the solid phase (Scheme 122).[38] On the completion of the synthesis this safety catch linker **173** is activated by oxidation of the aromatic thioether with *m*CPBA to the sulfone **174** then cleaved by aromatic substitution by an amine to release the pyrimidine as the 2-amino derivative. A limiting amount of the amine (i.e. no excess reagent) is used so no impurities are introduced from the cleavage step. Most primary and secondary amines are reported to give generally acceptable yields (>80%) whereas anilines are not as successful (~50%).

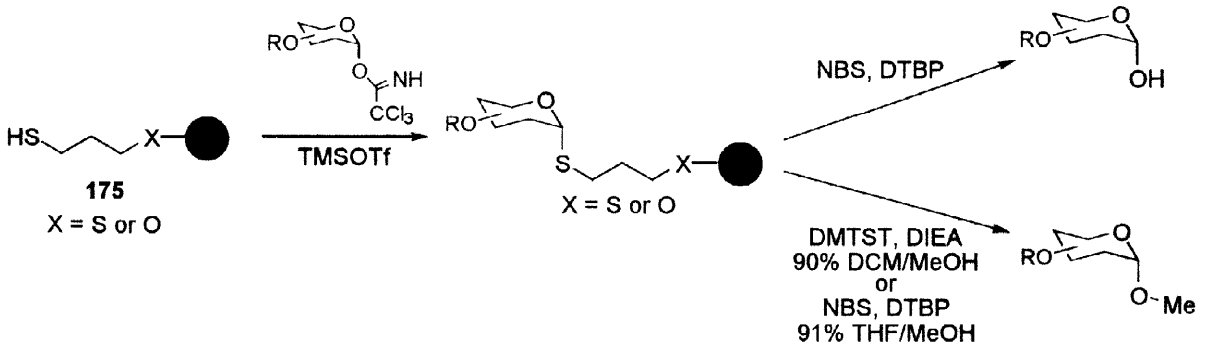


Scheme 122

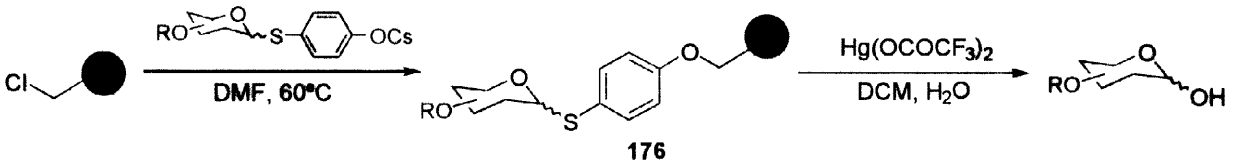
7.29. Saccharide

A number of linkers have been developed to link saccharides through the anomeric centre. Linkers used to attach saccharides through hydroxyls at other positions are included with the alcohol linkers (Section 7.1).

Thioether Linker: By attaching through the anomeric centre, sugars can be attached to the alkylthiol **175** using the trichloroactamide as an activating group.[374-376] The methyl ether at the anomeric centre is obtained by cleaving using either dimethylthiosulfonium triflate in DCM/MeOH[375] or NBS in THF/MeOH (Scheme 123).[376] Using NBS in acetone/H_2O for cleavage, the anomeric alcohol can be obtained.[376] The phenyl thioether **176** has also been used.[377] Attachment via solution phase is used, and mercuric trifluoroacetate is used for cleavage (Scheme 124). Post-cleavage purification is required to remove the mercury salts.

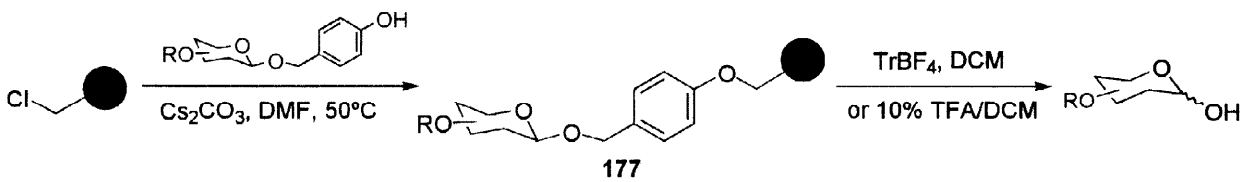


Scheme 123



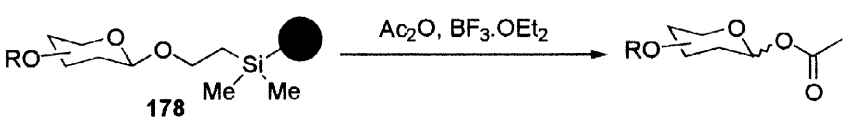
Scheme 124

Wang Linker: The Wang linker **177** has been used to attach sugars through the anomeric center.[75,378] The first sugar is attached to the linker in solution then the combined linker-sugar attached to the solid phase (Scheme 125). Cleavage is achieved using $TrBF_4$[75] or 10%TFA/DCM.[378]



Scheme 125

β-Silyl Ethyl Linker: The β-silyl ether linker **178** may be used to attach saccharides via solution phase.[379] Treatment with $BF_3.OEt_2$ and acetic anhydride in toluene releases the saccharide as the acetate (Scheme 126).

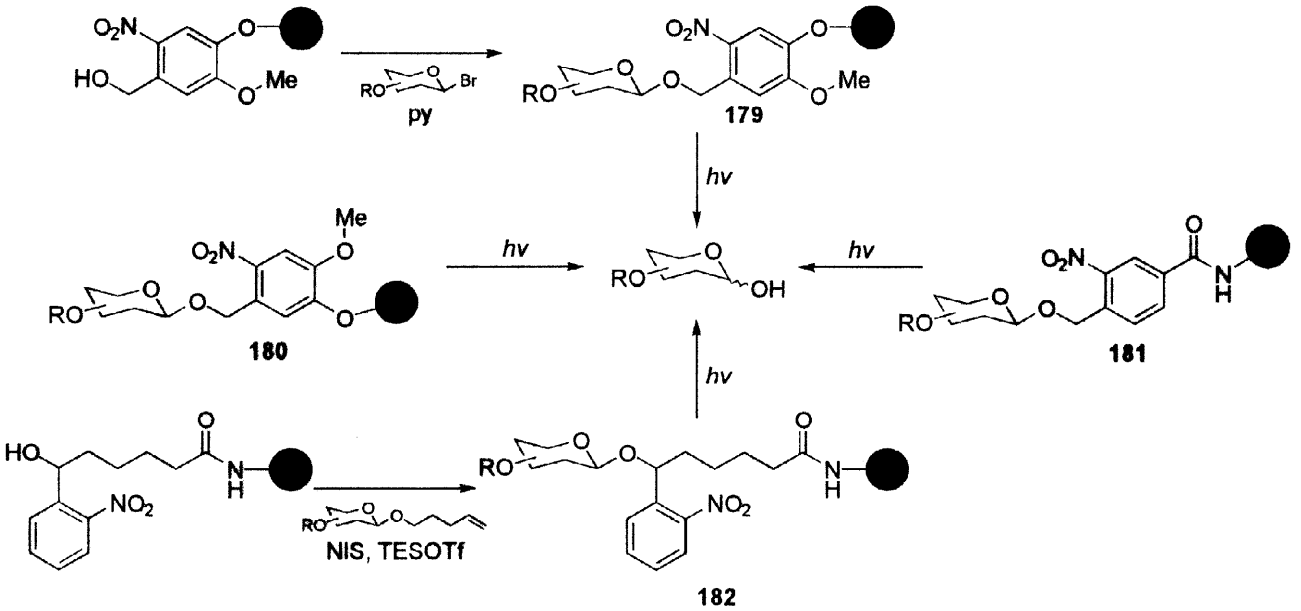


Scheme 126

7.29.1. Photolabile

Saccharides have been attached to the solid phase through the anomeric oxygen using a number of photolabile linkers **179**,[380] **180**,[381] **181**,[382] **182**[383] with cleavage generally being performed using irradiation at 350nm for 12 - 15h (Scheme 127). Both solution phase synthesis[381] and direct coupling of the saccharide to the linker already on the solid phase[380,383] have been used to attach the saccharide. Although a number of linkers are reported, surprisingly, the α-substituted version, such as in **182**,[383] generally has not been utilized. This is

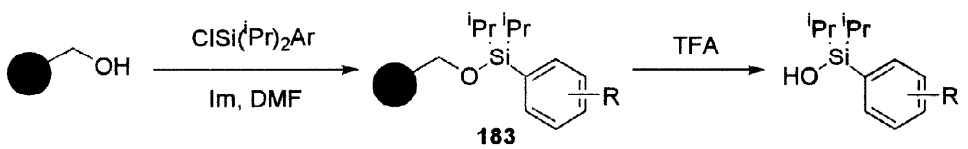
despite this being reported as being beneficial for the cleavage of amides and carboxylic acids from photolabile linkers.[29,212]



Scheme 127

7.30. Silanol

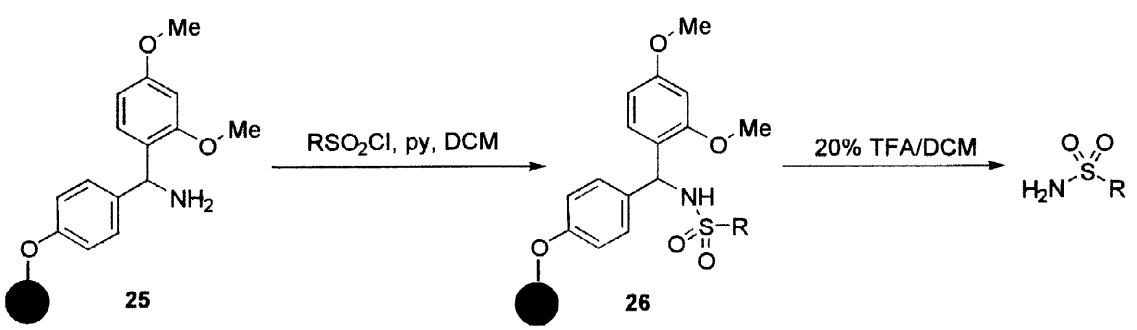
The siloxy linker **183**, used as a traceless linker for aromatic groups,[384] (Section 8.1.2) can be cleaved with TFA to give the silanol (Scheme 128).



Scheme 128

7.31. Sulfonamide

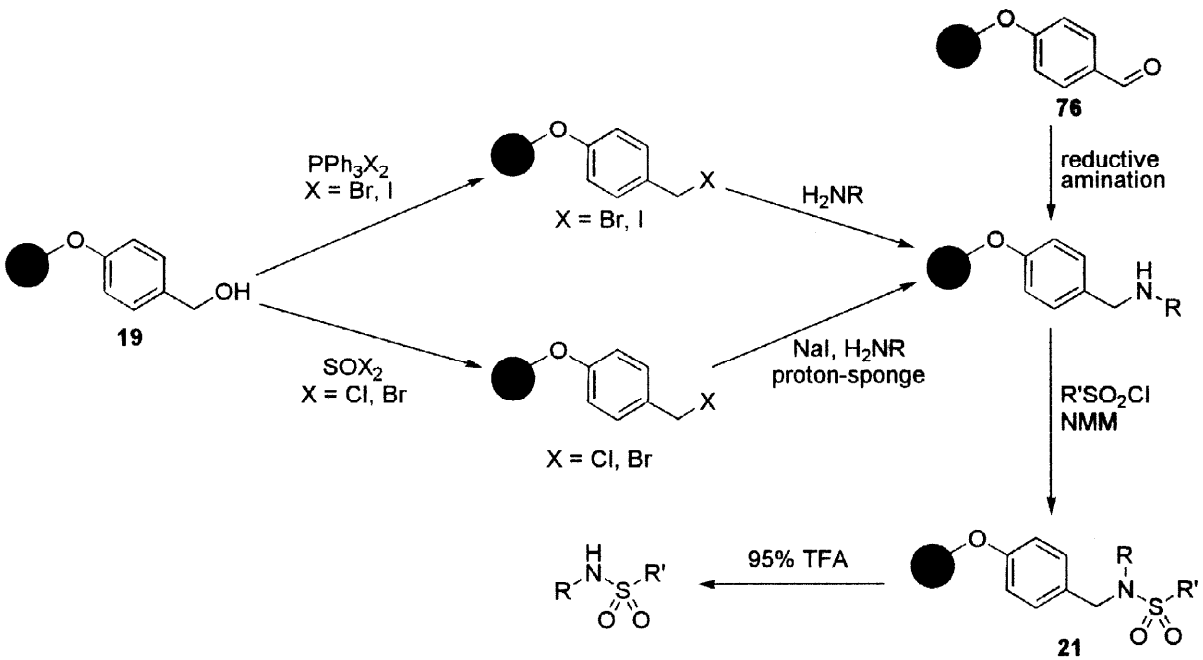
7.31.1. Acid Labile



Scheme 129

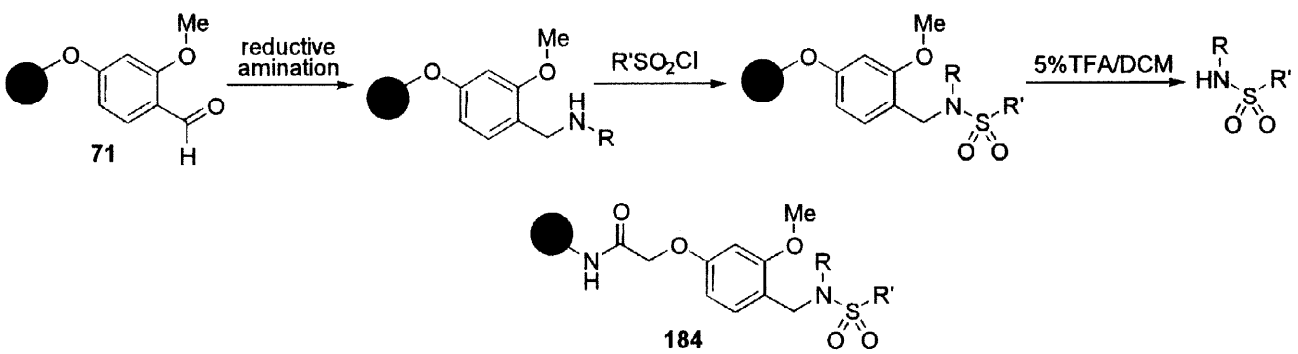
The Rink linker **25** may be treated with sulfonyl chlorides to form the sulfonamide **26** (Scheme 129).[83] The linker is stable to 50% AcOH/DCM but is cleaved in 20% TFA/DCM to give the primary sulfonamide.

The Wang linker has been used as a linker for secondary sulfonamides.[61,62] The alcohol **19** is converted to the halide (chloride, bromide or iodide), then treated with a suitable primary amine and finally a sulfonyl chloride to form the attached sulfonamide **21** (Scheme 130). Cleavage is achieved with 95% TFA. Reductive amination of the solid phase aldehyde **76** then sulfonylation has also been used to prepare the Wang derived secondary sulfonamide linker.[191] It was reported that the sulfonamide but not the amine is cleaved, so high purity is generally achieved even if the sulfonylation does not go to completion.



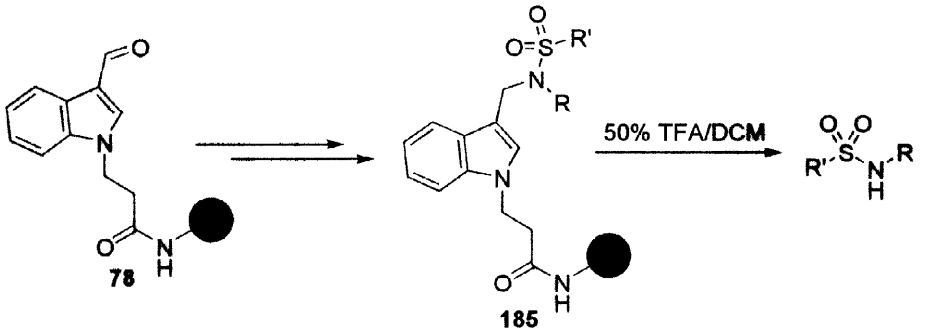
Scheme 130

The Sasrin linker also has been modified for use as a secondary sulfonamide linker.[183] Attachment is via reductive amination then sulfonylation and cleavage is achieved with 5% TFA (Scheme 131). Note, though, that a similar linker **184** was reported to give slightly inferior yields to its Wang equivalent.[61]



Scheme 131

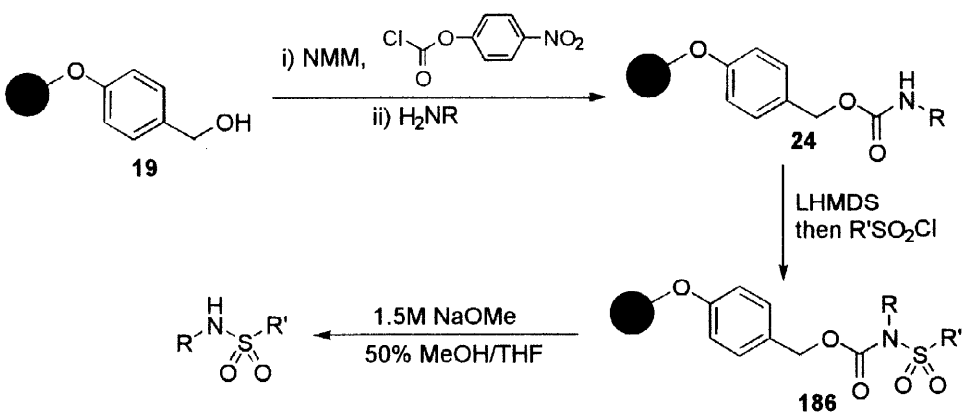
Reductive amination then sulfonylation is also used to prepare the indole derived sulfonamide linker **185** (Scheme 132).[192] Cleavage is achieved with 50% TFA/DCM.



Scheme 132

7.31.2. Base Labile

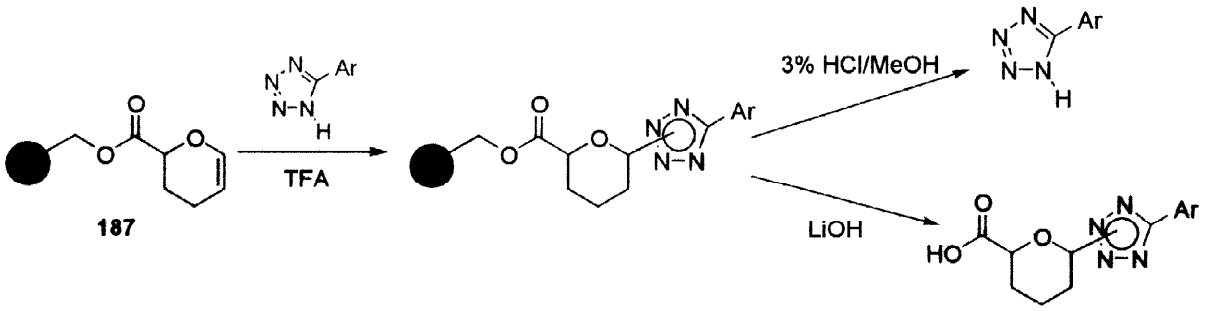
An alternative use of the Wang linker to attach sulfonamides is via the carbamate.[385] The carbamate **24** is formed via the *p*-nitrophenylcarbonate (Scheme 133). Deprotonation of the carbamate and treatment with a sulfonyl chloride forms the sulfonamide **186**, which can be cleaved with NaOMe in 50% MeOH/THF. Aqueous work up is used to remove the salts. Being derived from the Wang linker, cleavage may also occur under acidic conditions, although a hydroxymethylpolystyrene (Merrifield resin) version of this carbamate derived linker that would avoid this problem is also described.[385]



Scheme 133

7.32. Tetrazole

Tetrazoles can be attached to a DHP linker **187** using 1 equivalent of TFA (Scheme 134).[386] Cleavage is best achieved using 3%HCl in MeOH for 24h. The ester bond used to attach the linker to the solid phase allows the compound to be removed from the solid phase by LiOH in THF/H_2O to give a protected tetrazole.

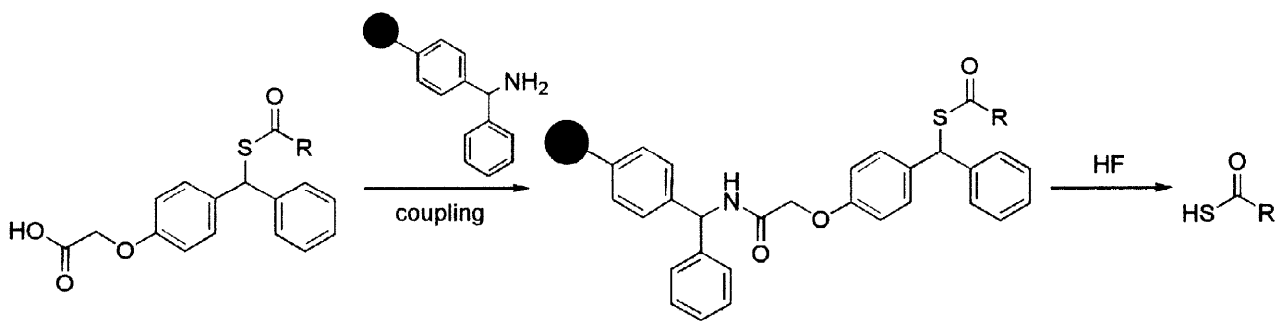


Scheme 134

7.33. Thioacid

7.33.1. Acid Labile

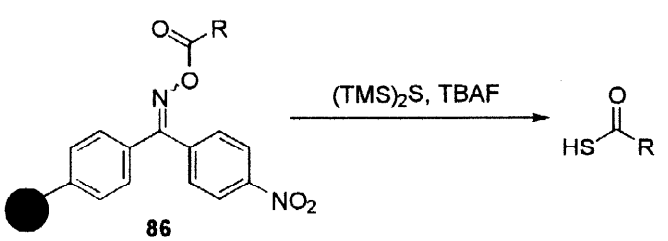
A benzhydryl linker has been used to attach thioesters.[387] Attachment via solution phase is used with cleavage on the completion of synthesis being achieved using HF (Scheme 135).



Scheme 135

7.33.2. Base Labile

Treatment of the base labile oxime linker **86**, initially developed as a carboxylic acid linker,[208,388] with $Me_3Si\text{-}S\text{-}SiMe_3$/TBAF (an H_2S equivalent) results in the cleavage of the product as the thioacid (Scheme 136).[389] Aqueous work up is used to remove the salts.

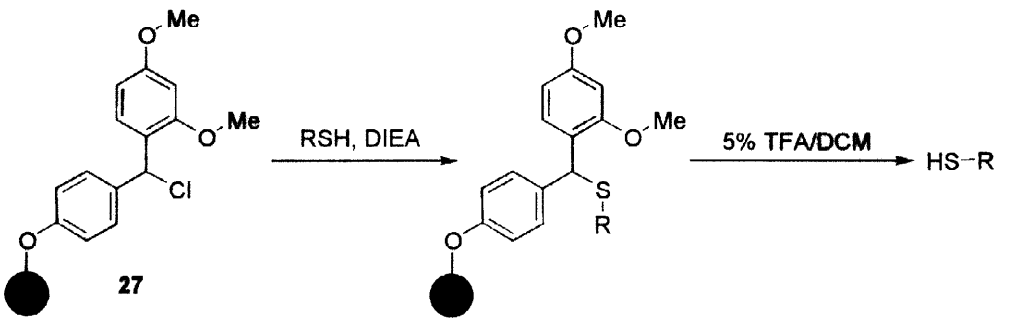


Scheme 136

7.34. Thiol

7.34.1. Acid Labile

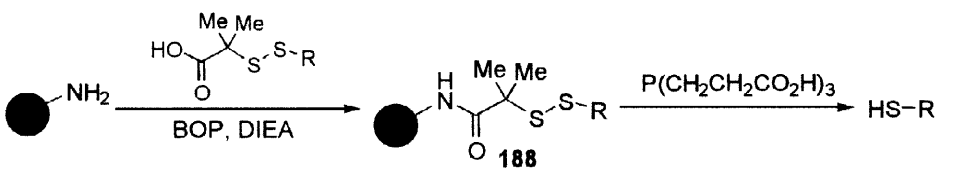
Thiols may be attached to Rink chloride 27 using DIEA (Scheme 137).[84] Cleavage is achieved with 5% TFA/DCM.



Scheme 137

7.34.2. Reductive Cleavage

The reductively labile dithiane linker **188** is prepared in solution and attached to the solid phase with the starting material attached (Scheme 138).[390,391] After synthesis, the product is cleaved using tris(2-carboxyethyl)phosphine to give the thiol. Purification is required to remove the phosphorus impurities.

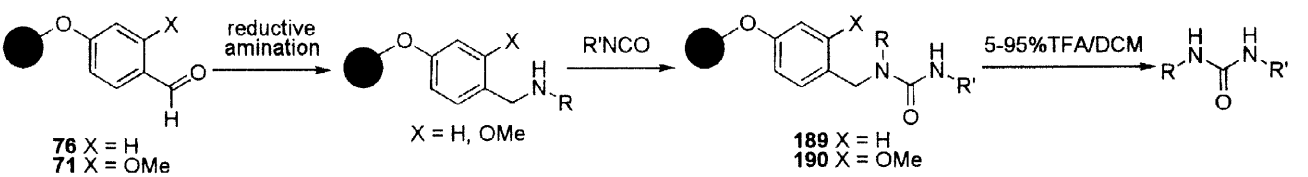


Scheme 138

7.35. Urea

7.35.1. Acid Labile

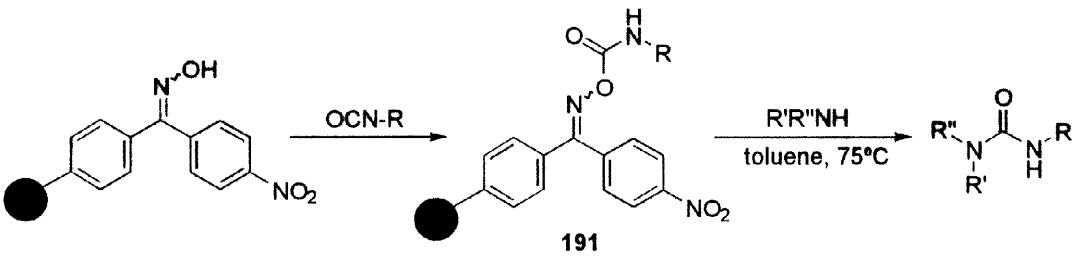
A modification of a Wang-aldehyde has been used to attach ureas.[64] The aldehyde **76** is reductively aminated with a primary amine (Scheme 139). Treatment with an isocyanate forms the urea **189**, which can be cleaved from the solid phase with 95%TFA/TES. A similar approach has been reported using the Sasrin derived linker **190**, with cleavage being achieved using only 5% TFA/DCM.[183]



Scheme 139

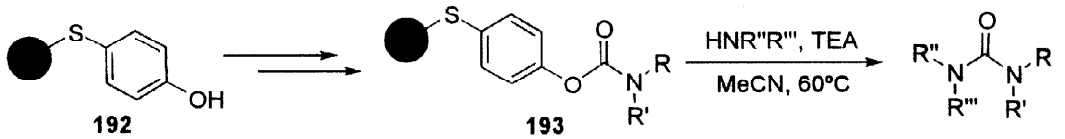
7.35.2. Base Labile

Isocyanates are used to form ureas on Kaiser's oxime linker.[392,393] The linker **191** is stable to treatment with amines at room temperature but cleaved with amines in toluene at 75°C (Scheme 140). One equivalent of amine can be used to ensure reasonable purity of cleaved compounds.



Scheme 140

The phenol **192** can be converted to the carbamate **193** via the *p*-nitrophenylcarbonate.[18] Treatment with TEA and an amine results in cleavage of the product as the urea (Scheme 141), possibly by release as an isocyanate, which reacts with an amine present to form the urea, or by direct reaction of the amine with the carbamate as above. Excess amine is removed by treatment with an isocyanate resin.[18]



Scheme 141

8. TRACELESS LINKERS

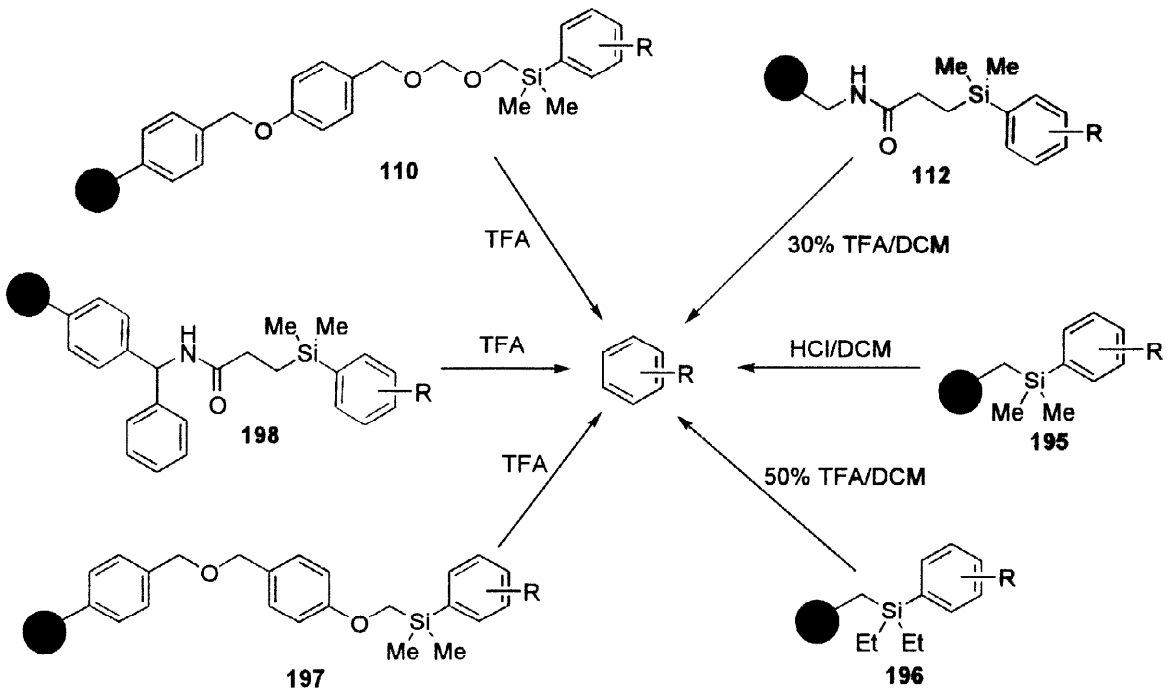
The key definition of a traceless linker is a linker whereby a new C-H or C-C bond is formed during cleavage. This has been expanded to include linkers that cleave give an aromatic, alkyl, alkene or alkyne group without a heteroatomic linker site, hence including other reactions such as retro cycloadditions. Other examples sometimes described as traceless linkers, such as those involving S_NAr with amines[38] or tertiary amine linkers cleaved by Hofmann elimination,[22,23] are omitted from this section but are included in the relevant sections above.

8.1. Aromatic

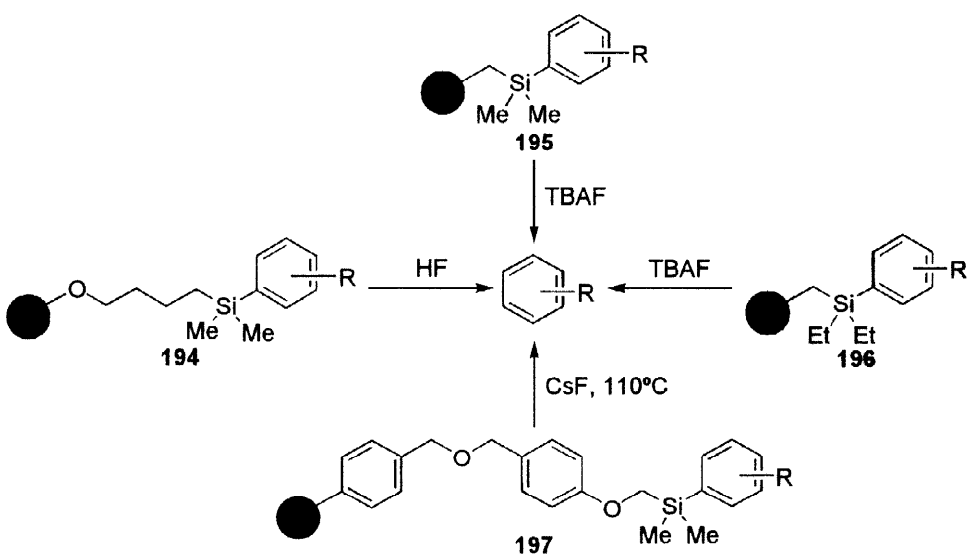
8.1.1. Trialkylsilane

Trialkylsilanes have been used as traceless linkers for aryl groups with cleavage by electrophilic *ipso*-substitution.[30,31,248,251] The acid required for cleavage is highly dependant on both the chemical nature of the linker and the electronic nature of the aromatic group (Schemes 142, 143). Fluoride cleavage may also be used, though extractive removal of the fluoride salts is required when using this method. A range of linkers has been developed. Linker **194** requires HF treatment to cleave the electron poor systems studied,[30,31] whereas CsF treatment at 100°C failed. For more electron rich systems, weaker acidic treatment would probably suffice. HCl

in DCM is sufficient to cleave electron rich systems from linker **195**[111] and 50% TFA/DCM will cleave them from linker **196**,[106] whereas for electron poor systems, TBAF achieves cleavage.



Scheme 142: Cleavage of Electron Neutral to Rich Aromatic Systems



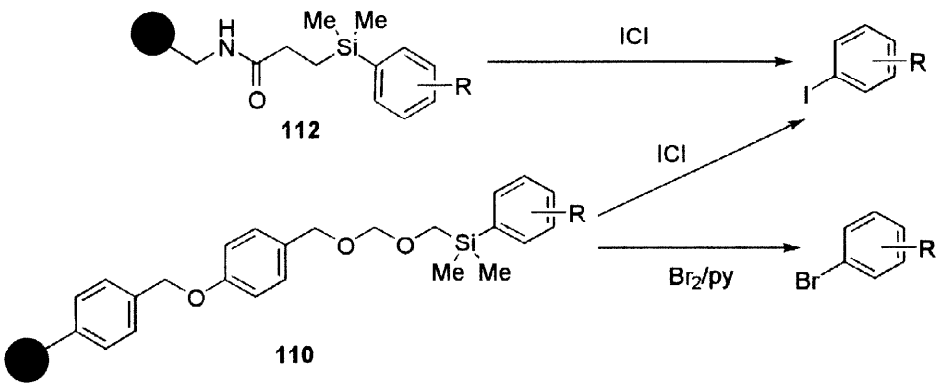
Scheme 143 Cleavage of Electron Poor Aromatic Systems

TFA is used for cleavage of electron rich systems from the α-alkoxy linker **197**[394] as well as **110**.[248] TFA cleavage of **197** fails for electron poor systems, for which CsF treatment at 110°C can be used.[394]

An amazing rate enhancement is observed when a β-amide (relative to the silyl group) is introduced.[251,395] Treatment with 30% TFA/DCM for only 10 minutes is required for cleavage of aromatic systems that are only slightly electron rich (**112**), as opposed to the hours of treatment with stronger cleavage reagents required for

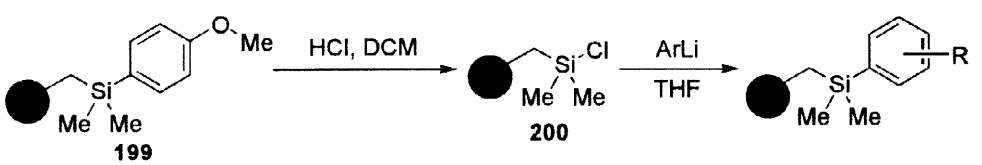
the other traceless linkers mentioned above. It has been suggested that this rate enhancement is due to either intramolecular delivery of the proton from the protonated amide, or carbonyl coordination to the mildly Lewis acidic silane, hence weakening the silane-aromatic carbon bond to attack by the proton. Interestingly, the related linker **198** does not show this rate enhancement, requiring TFA treatment for 40h for complete cleavage (Scheme 142),[396] possibly due to hindrance of the amide by the benzhydryl group preventing the β-amide assistance.

Electrophiles other than protons may be used so as to introduce further diversity. ICl may be used to obtain the aryl iodide from either **110** or **112** (Scheme 144).[248,251] The aryl bromide may be obtained from **110** using Br_2/pyridine.[248]

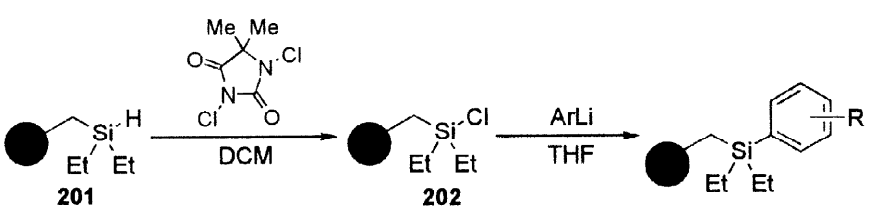


Scheme 144

The silyl chloride used to attach the aromatic group to the linker is quite unstable, so attachment via solution phase is usually used. A couple of ways of avoiding this have recently been reported. The linker can be attached as the anisyl silane **199**, which is stable to storage.[111] The silyl chloride **200** is formed by brief exposure to HCl in DCM, which removes the anisole group (Scheme 145). Alternatively, the linker can be stored as the silane **201**.[106] Conversion to the silyl chloride **202** is achieved by treatment with 1,3-dichloro-5,5-dimethylhydantoin (Scheme 146). In both cases, the silyl chloride is then treated with an aryl lithium species to attach the aryl group of interest.



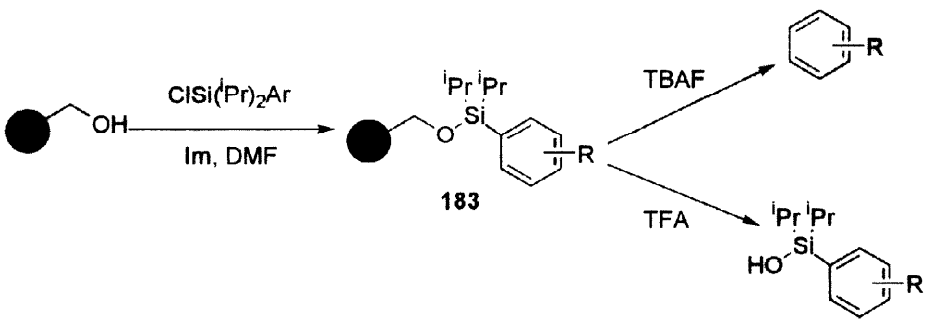
Scheme 145



Scheme 146

8.1.2. Dialkylsiloxy

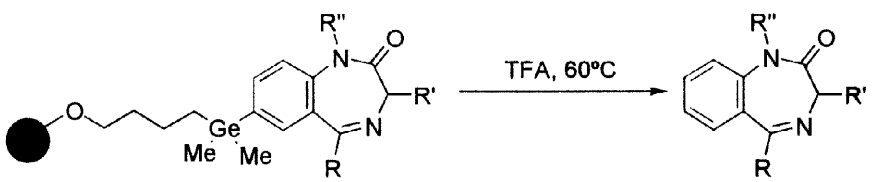
The siloxy group also has been utilized as an aromatic traceless linker.[384] The chlorosilane with the aromatic residue was formed in solution then coupled to hydroxymethylpolystyrene as the siloxy ether **183** (Scheme 147). After synthesis the aromatic group is cleaved with TBAF at 65°C. Aqueous work up and filtration is required to remove excess cleavage reagent. TFA can be used to release the product as an dialkylarylsilanol.



Scheme 147

8.1.3. Trialkylgermane

The more labile germanium analogue of the trialkylsilane linker has been used.[30] The germanium-carbon bond is significantly labile, such that TFA at 60°C is sufficient for cleavage of even electron poor aromatic systems (Scheme 148).



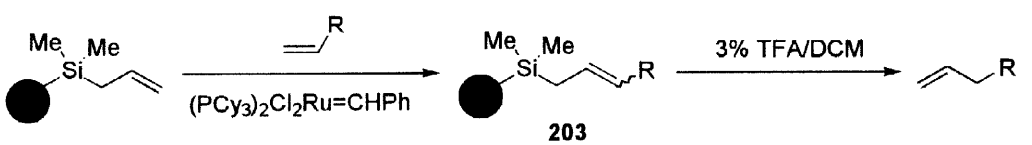
Scheme 148

8.2. Alkyl

Intramolecular attack of a carbon nucleophile onto the alkylsulfonate linker resulting in cyclative cleavage (Section 9.4) is a form of traceless linkage that leads to an alkyl group.

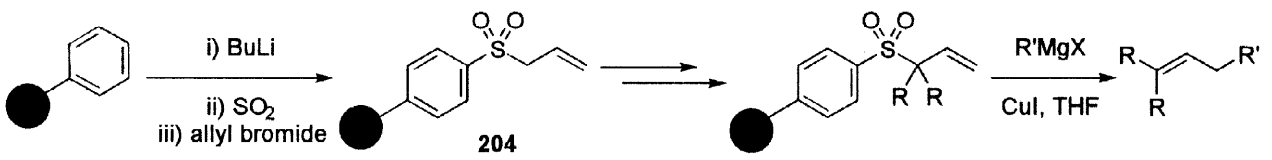
8.3. Allyl

The allyl silane linker **203** may be prepared using the metathesis reaction (Scheme 149).[397] It is cleaved with 3% TFA/DCM to release the allylic product.



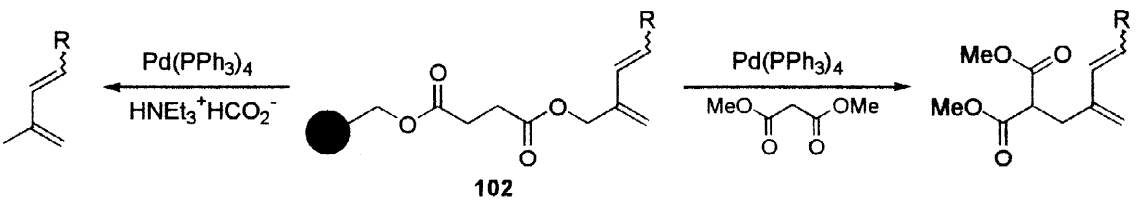
Scheme 149

Alternatively, allylic groups may be attached to the solid phase through a sulfone **204**.[398] This is prepared by lithiation of polystyrene then sequential treatment with sulfur dioxide and an allyl bromide (Scheme 150). Treatment with Grignard reagents in the presence of copper iodide results in S_N2' alkylation, cleaving the allyl group. The product must be purified from excess cleavage reagents.



Scheme 150

The allyl ester **102** may be cleaved with palladium and a nucleophile. If a carbon nucleophile, such as dimethyl malonate, is used then this acts as a traceless linker (Scheme 151).[240] Ammonium formate may be used as a hydride source for reductive cleavage of the product.



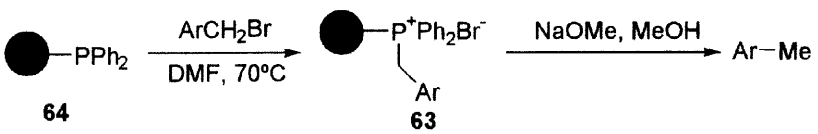
Scheme 151

8.4. Alkene

The alkene linkers described in Section 7.3 may all be considered traceless. Similarly, metathesis cyclization to release the product as the cyclic alkene (Section 9.5.1) also may be considered a form of traceless linker.

8.5. Benzyl

The benzyl phosphonium salt **63** when treated with NaOMe in refluxing MeOH cleaves from the solid phase as the toluene derivative (Scheme 152).[157]

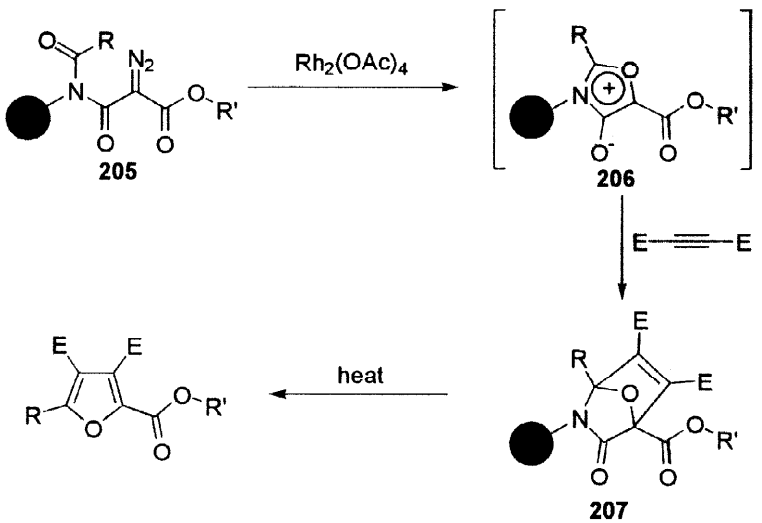


Scheme 152

8.6. Furan

An interesting form of traceless linker based on a retrocycloaddition has been used for the preparation of furans.[399,400] Treatment of the diazo carbonyl **205** with $Rh_2(OAc)_4$ or $Rh_2(pfbm)_4$ at 80°C leads to the formation of the isomünchone intermediate **206**, which reacts with an electron poor alkyne to form the bicyclic intermediate **207** (Scheme 153). This then undergoes retrocycloaddition releasing the furan. The catalyst and excess alkyne have to be removed from the products. The cleavage, however, can be performed in two steps by

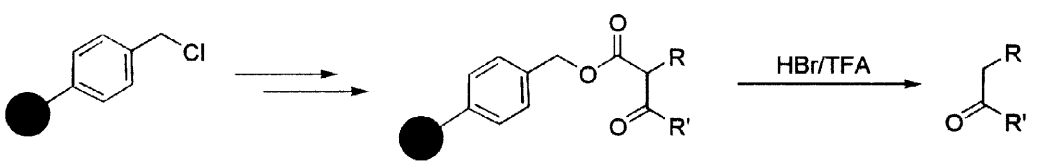
treating with $Rh_2(OAc)_4$ and acetylene at room temperature to form the bicyclic intermediate **207**. The solid phase can then be washed to remove the catalyst and the retrocycloaddition with cleavage achieved by heating at 80°C.



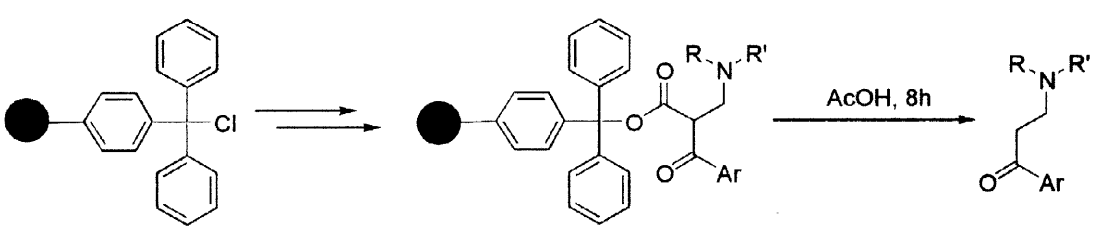
Scheme 153

8.7. Active Methylene Groups

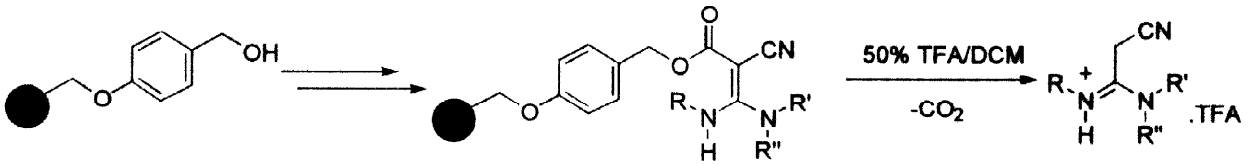
Under acidic conditions, carboxylic acids of activated methylene groups may undergo decarboxylation. Originally, ketones were prepared on hydroxymethylpolystyrene with cleavage and decarboxylation being achieved using HBr/TFA (Scheme 154).[401] More recently they have been prepared on the trityl linker, with prolonged treatment with AcOH used to achieve cleavage and decarboxylation (Scheme 155).[402] Similarly, cyanoacetamidines (Scheme 156),[403,404] and β-cyanoketones (Scheme 157)[401,402] were prepared using the Wang linker, with cleavage and decarboxylation being achieved using 50% and 70% TFA/DCM respectively.



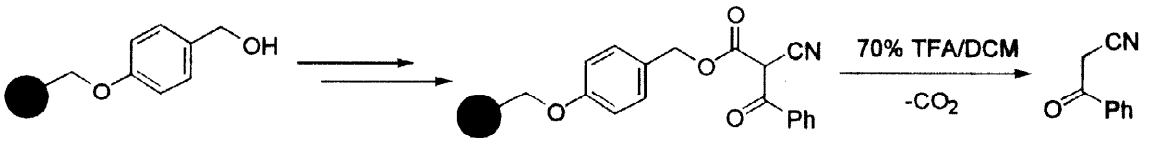
Scheme 154



Scheme 155



Scheme 156



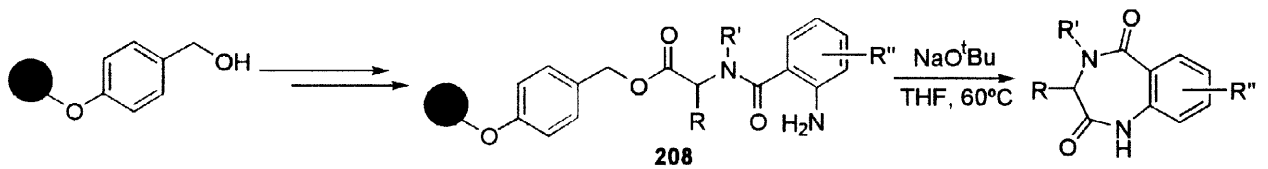
Scheme 157

9. CYCLATIVE CLEAVAGE

9.1. Cyclization onto Esters

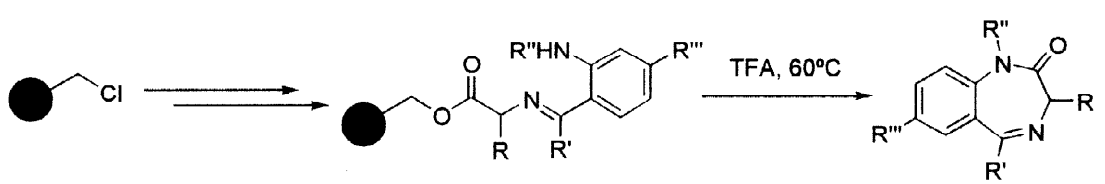
Both acid and base catalyzed cleavage of esters involving the intramolecular attack of nucleophiles have been used to cleave products. As discussed earlier, if the nucleophile is incorporated late in the synthesis in a manner that is reliant on the success of previous steps, then generally the desired product can be obtained in high purity, although the yield may vary.

1,4-Benzodiazepine-2,5-diones: Cyclization of the aniline nitrogen onto the Wang linker ester of **208**, forms the desired product and cleaves it from the solid phase (Scheme 158).[405] The cyclization is achieved using NaO^tBu in THF at 60°C. Yields are moderate to good (50-80%) and purity is generally good to excellent (81-98%).



Scheme 158

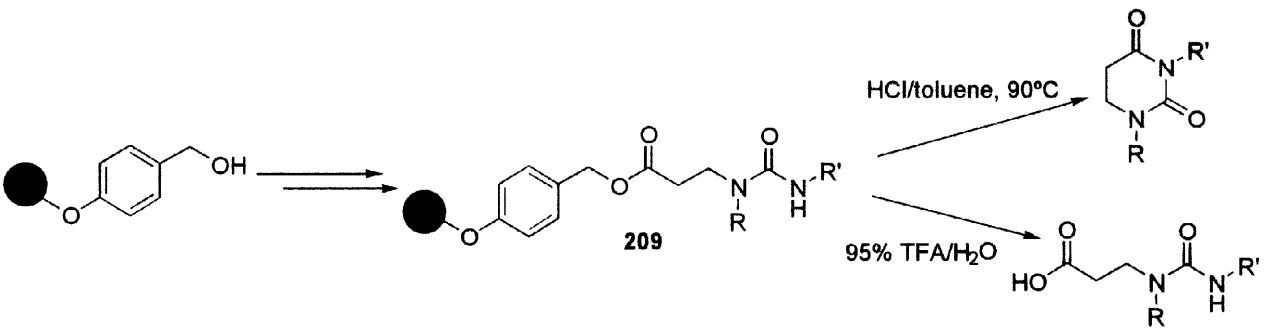
Benzodiazepinones: Intramolecular amide formation has been used to prepare benzodiazepinones using cyclative cleavage.[32] Chloromethylpolystyrene was used for the synthesis and the final cyclization was performed using TFA at 60°C (Scheme 159).



Scheme 159

Dihydropyrimidine-2,4-diones: Urea cyclization onto the Wang ester of **209** has been used to cleave 5,6-dihydropyrimidine-2,4-diones.[406] The cyclative cleavage is achieved using saturated HCl/toluene at 95°C

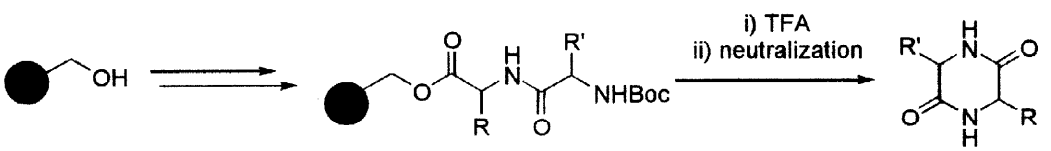
(Scheme 160). These conditions would probably cleave the Wang linker first, with cyclization occurring after cleavage. Heat is needed to obtain good yields of the cyclic product, as the uncyclized product is obtained by treatment with 95%TFA/H_2O at room temperature.



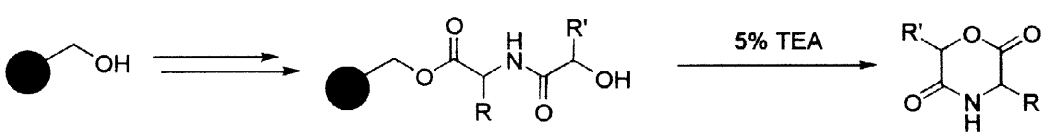
Scheme 160

Diketopiperizines (DKP): DKP formation is a side reaction in peptide synthesis and can occur after deprotection of the second residue, or during the attachment of the third residue, resulting in low yields. Many techniques have been developed to avoid this yield reducing process. It can, however, be used to prepare libraries of low molecular weight molecules. The first amino acid is attached through an ester. The second amino acid is attached with BOC protection on the α-nitrogen. To cleave the DKP, the BOC group is removed with TFA. The TFA salt is neutralized with 0.1M NH_4HCO_3 in 40% MeCN/H_2O[407] or 0.1M sodium phosphate buffer,[408,409] and cyclization occurs *in situ* at room temperature (Scheme 161). Sonication can aid the cleavage when using NH_4HCO_3.[407] The TFA salt also can be neutralized with DIEA, with the cyclative cleavage being subsequently induced using either 1%AcOH or 4% TEA in 1:1 toluene/EtOH.[410] Purity, using any of these methods, is generally >90%, as product will only cleave if the dipeptide is formed. Though the yields are highly dependent on the side-chains present. Substitution on the amide nitrogen generally aids the cyclative process. If an Fmoc amino acid is used for the second coupling, then cyclization with cleavage will occur *in situ* with Fmoc deprotection using piperidine.[411]

Replacement of the second amino acid with an α-hydroxyacid realizes the diketomorpholines after cyclative cleavage in 5%TEA/DCM (Scheme 162).[410]

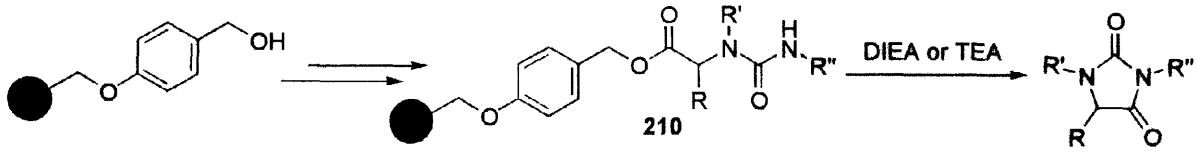


Scheme 161



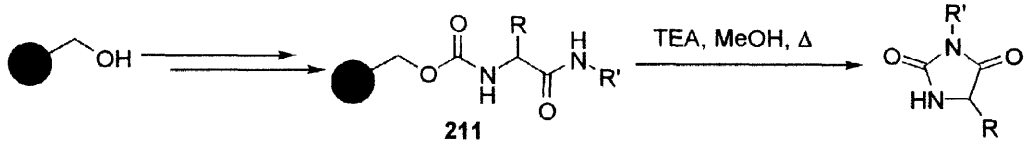
Scheme 162

Hydantoins: Hydroxymethylpolystyrene resin has been used to prepare hydantoins via cyclization of the urea using 6N HCl,[32] KO^{t}Bu,[412] or bis(trimethylsilyl)trifluoroacetamide at 83°C.[413] Cyclization of the urea onto the Wang ester of **210** using DIEA or TEA also has been used (Scheme 163).[78,79] Similar conditions are used to cleave an alkyl ester linkage.[414] In all these cases, cleavage only occurs if the urea has been formed, so again, products are generally obtained in high purity but variable yields.



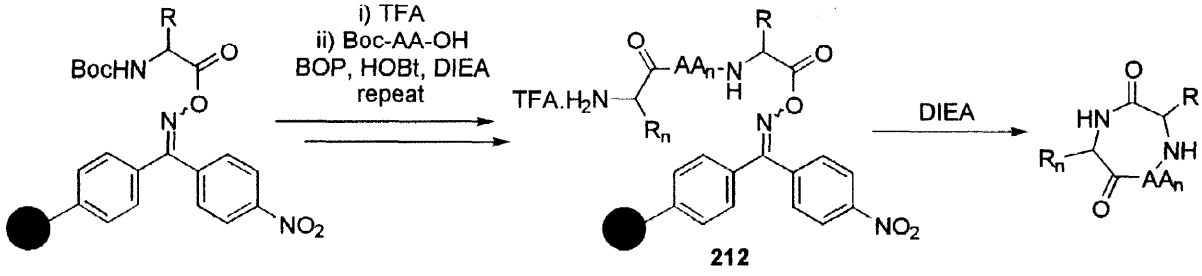
Scheme 163

Alternatively, cyclization of the amide onto the carbamate **211** can be used. The cyclization is catalyzed by TEA in MeOH at 55-90°C (Scheme 164).[415] Again mass recovery is variable but purity is generally good.



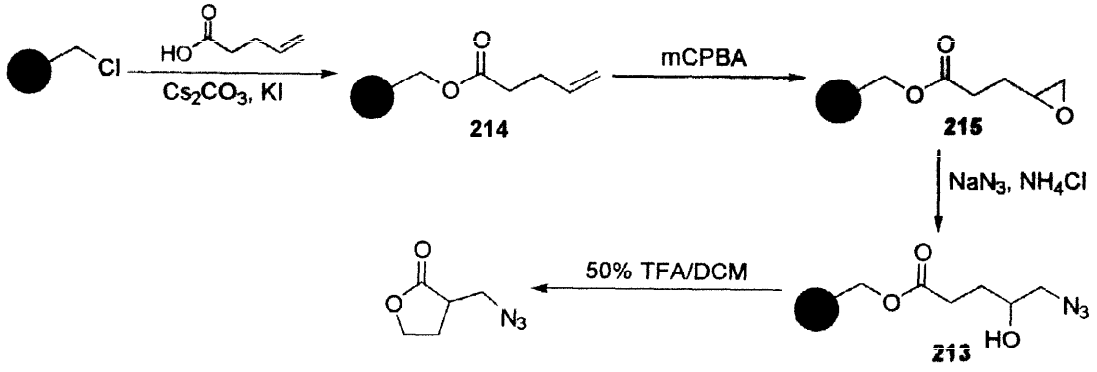
Scheme 164

Lactams: Kaiser's oxime linker has been used to form cyclic peptides. The peptide is prepared using BOC chemistry: TFA to remove protecting groups (amine remains as a TFA salt), then coupling with *in situ* neutralization. This process limits the presence of the nucleophilic free amine. To achieve cyclative cleavage, the deprotected peptide **212** is treated with DIEA (Scheme 165). A range of sizes of cyclic peptides have been prepared including 5-mers[416] and 10-mers.[417]



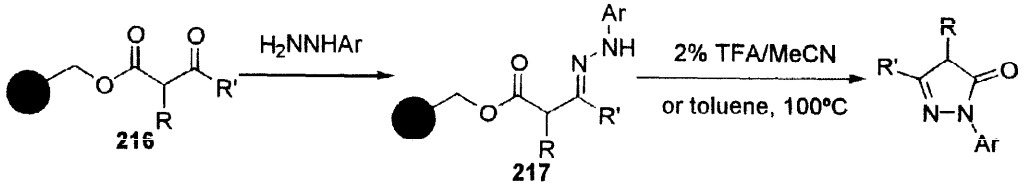
Scheme 165

Lactones: Lactone formation is demonstrated by the cyclative cleavage of alcohols using **213**.[418] The alkene **214** is oxidized with *m*CPBA. The resulting epoxide **215** is opened with a nucleophile (e.g. N_3^-), forming the alcohol **213**. Treatment with TFA cleaves the desired product as the lactone. The ester **214** is not labile with TFA, so if the oxidation failed, no product would be released. Although the purity of the products was generally high, 75-95%, the yields were only moderate, 45 - 67%.



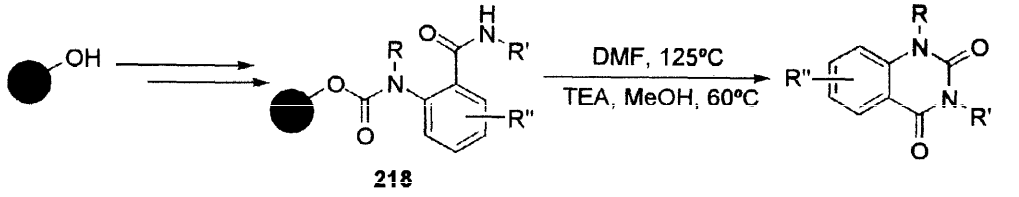
Scheme 166

Pyrazolones: Treatment of β-ketoesters **216** with primary hydrazines produces the hydrazones **217** which then cyclize on treatment with 2% TFA/MeCN to release pyrazolones (Scheme 167).[419] Heating at 100°C in toluene also causes cyclative cleavage although this method is not as amenable to parallel synthesis.[420]



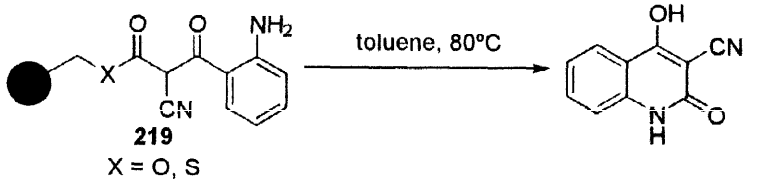
Scheme 167

2,4(1*H*,3*H*)-Quinazolinediones: The cyclization of an amide onto the carbamate linkage **218** has been used to prepare 2,4(1*H*,3*H*)-quinazolinediones. Cleavage is achieved by heating at 125°C in DMF,[421] or by using TEA/MeOH at 60°C (Scheme 168).[422] Purities are good although the yields vary significantly.



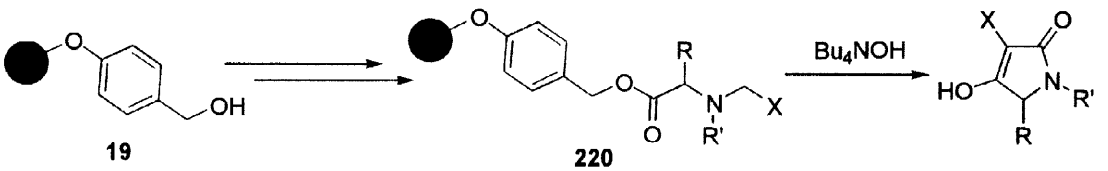
Scheme 168

Quinolin-2-ones: The aniline nitrogen of **219** can cyclize onto the Wang ester or thioester linker releasing the product as the quinolin-2-one (Scheme 169). This is achieved by heating in toluene at 80°C.[423]



Scheme 169

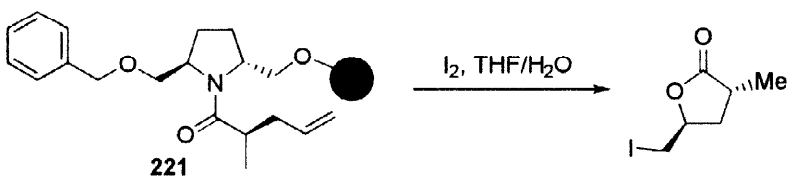
Tetramic Acids: Deprotonation of the activated methylene of **220** results in cyclization onto the Wang ester with cleavage to form the tetramic acid (Scheme 170).[19,424] Both tetrabutylammonium hydroxide and sodium ethoxide have been used as the base, with excess cleavage reagent removed by treatment with acidic ion exchange resin.



Scheme 170

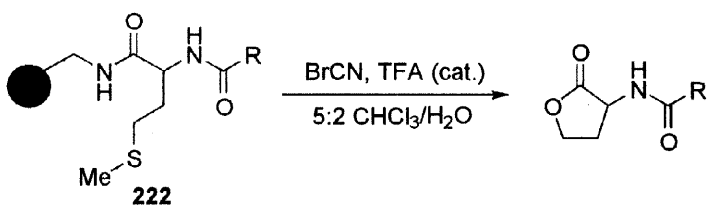
9.2. Cyclization onto Amides

Lactones: Iodolactonization onto an amide linker **221** using iodine in THF/H_2O releases the product as the lactone (Scheme 171).[425,426] This process regenerates the chiral linker.



Scheme 171

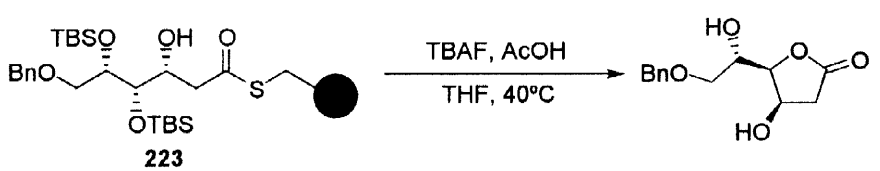
Lactones have also been prepared from the methionine derived linker **222**.[220,427] Cyanogen bromide is used to cleave the product as the homoserine lactone (Scheme 172).



Scheme 172

9.3. Cyclization onto Thioesters

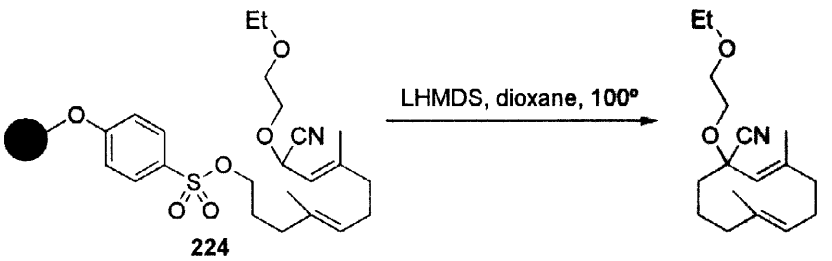
Lactones: Removal of the silyl protecting groups from **223** with TBAF in AcOH and THF at 40°C causes cyclative cleavage via attack on the thioester linker to form the 5-membered lactone (Scheme 173).[428]



Scheme 173

9.4. Displacement of Sulfonates

Alkanes: Removal of the acidic proton of **224** with LHMDS results in intramolecular displacement of the sulfonate releasing the product as the cyclic dialkene (Scheme 174).[348]



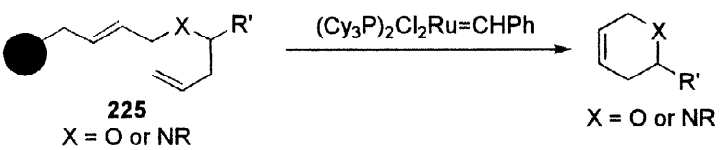
224

Scheme 174

9.5. Other Cyclizations

9.5.1. Metathesis

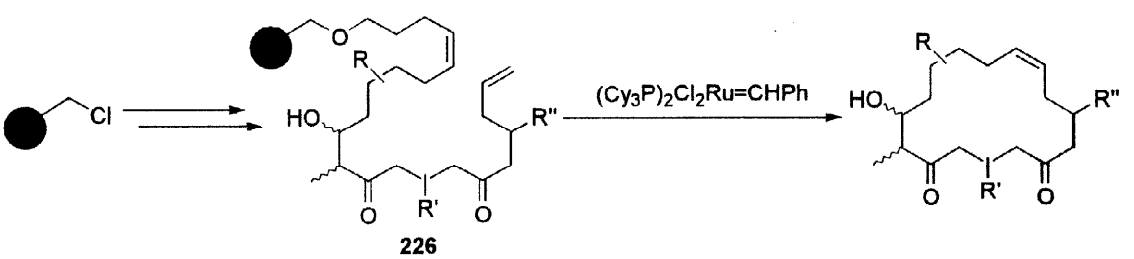
A suitable diene on the solid phase, e.g. **225**, and **226**, may be treated with a metathesis catalyst (usually Grubb's reagent, $Cl_2(PCy_3)_2Ru{=}CHPh$), so as to undergo intramolecular metathesis releasing the product as a cyclic alkene. This has been used for the formation of 6-membered dihydropyrans and tetrahydropyridines (Scheme 175), as well as 7-membered lactams[429,430] and to form 14-membered tripeptide derived macrocycles.[431] Purification is required to remove the ruthenium catalyst and this may reduce this method's applicability to large libraries. It has been used, though, in an impressive solid phase synthesis of 16-membered cyclic epithilone derivatives (Scheme 176).[432,433]



225
X = O or NR

X = O or NR

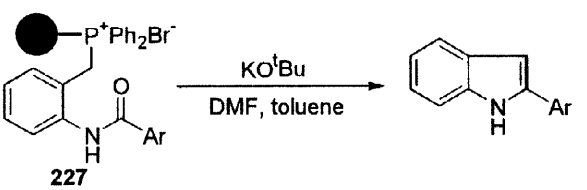
Scheme 175



226

Scheme 176

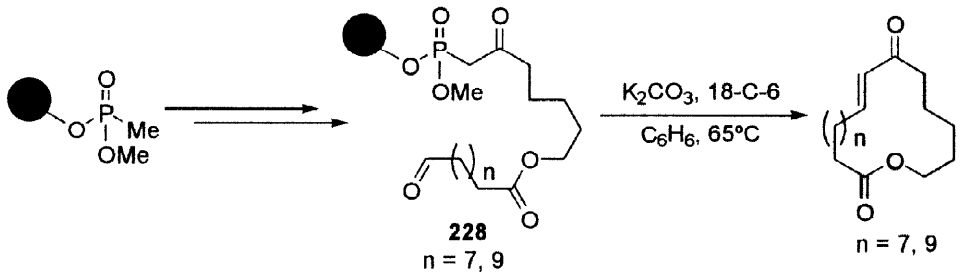
9.5.2. Wittig/Horner–Emmons Reaction



227

Scheme 177

Intramolecular Wittig reaction of the phosphonium salt linker **227** with an amide leads to formation of indoles (Scheme 177).[157] KO^{t}Bu is used as the base and strictly anhydrous conditions are required to avoid hydrolysis of the phosphonium salt. The intramolecular Horner–Emmons reaction can be used with a phosphonate ester linker **228** to give the cyclic alkene (Scheme 178).[434] K_2CO_3 and 18-crown-6 in benzene at 65°C are used to achieve the cyclative cleavage.

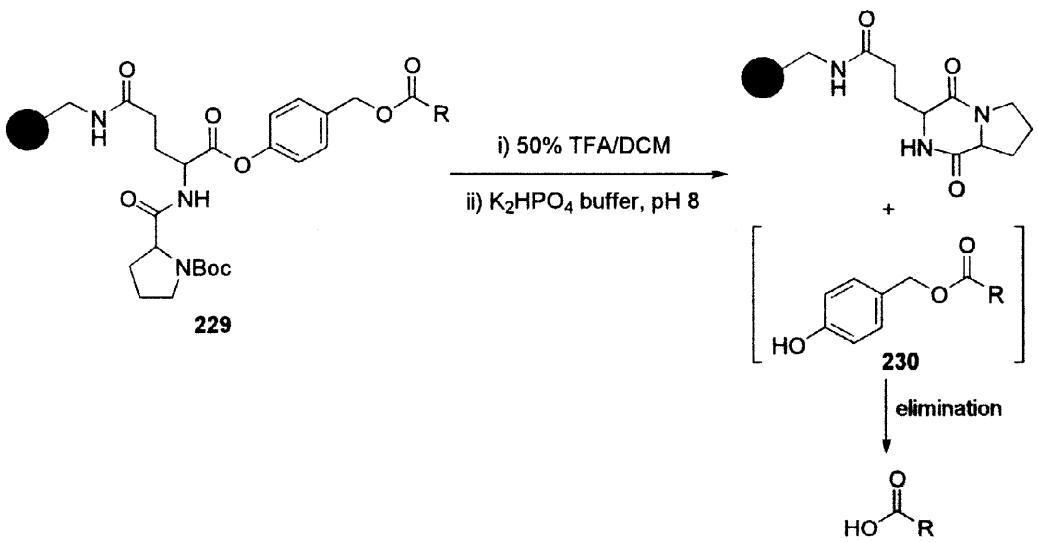


Scheme 178

10. SAFETY CATCH LINKERS

The previous sections have been categorised according to the products. This section is divided according to the chemistry involved in the activation and cleavage steps of safety catch linkers. Many of these potentially could be used to attach functional groups other than those mentioned here.

10.1. DKP Formation



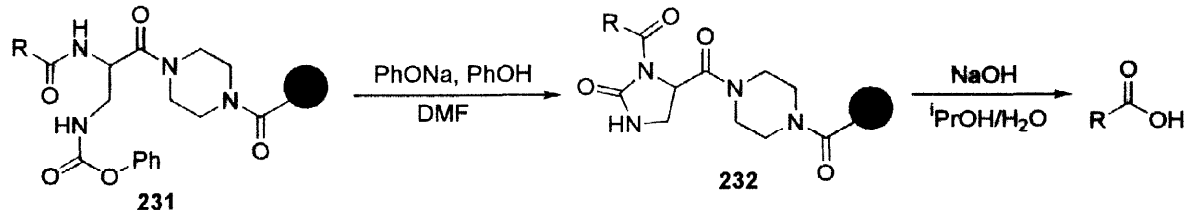
Scheme 179

Utilizing the same principles as the DKP synthesis discussed above (which can also be described a safety catch method) a linker has been designed so that the DKP formed remains on the solid phase with the desired product cleaving into solution.[435] Activation of **229** is achieved by removing the BOC protecting group with TFA then cleavage is achieved by neutralization at pH 7-8 (K_2HPO_4) to release the phenol **230**, which then

undergoes elimination to give the acid (Scheme 179). A similar approach has been used with BOC protected imidazoles, which then cyclize cleaving the ester bond after deprotection then neutralization.[436]

10.2. Cyclic Urea Formation

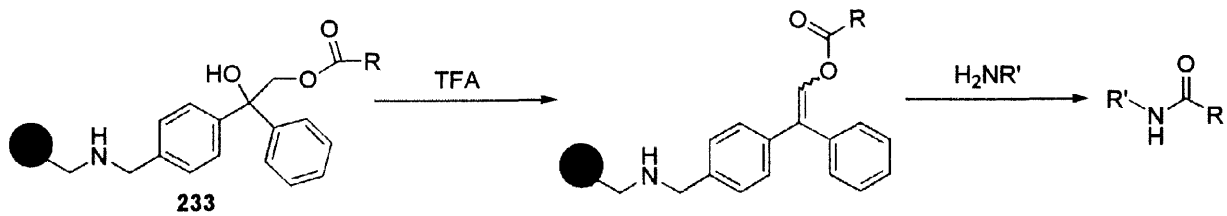
Linker **231** is stable to acidic and neutral conditions.[437,438] It is activated by treatment with sodium phenoxide and forms the cyclic urea **232** via the isocyanate (Scheme 180). The linker is then labile to nucleophiles and can be cleaved with NaOH in 70% ^{i}PrOH in water.



Scheme 180

10.3. Dehydration

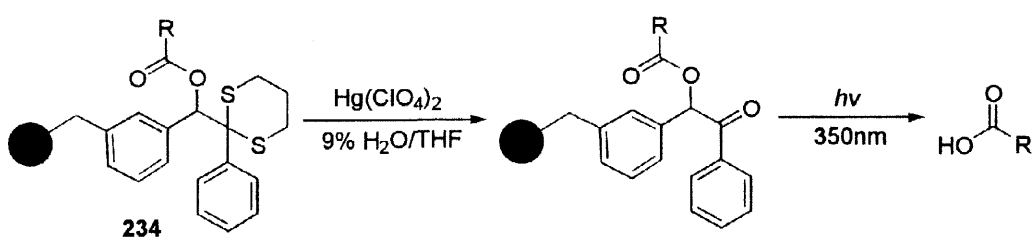
Linker **233** is activated by dehydration using TFA (Scheme 181).[439] Treatment with a primary amine releases the product as the amide.



Scheme 181

10.4. Dithioacetal Protection of Ketone

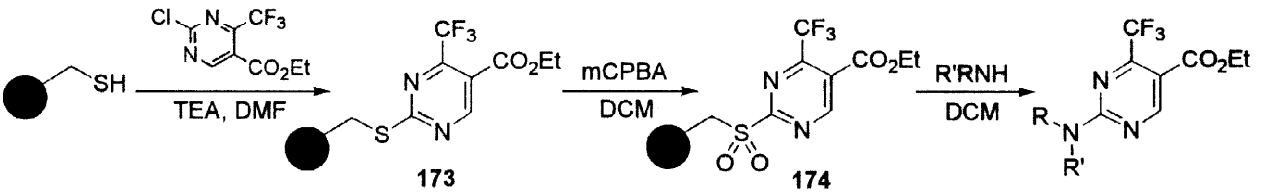
A photolabile linker has been converted into a safety catch linker by protection of the ketone as the dithioacetal **234**.[440] Activation involves removal of the dithioacetal using mercury(II) perchlorate and cleavage of the linker is achieved by irradiation at 350nm (Scheme 182). No discussion is given on ensuring complete removal of the toxic mercury residues, although bis[(trifluoroactoxy)iodo]benzene or periodic acid may be used in the activation step instead of the mercury salt. The linker can be used for attaching carboxylic acid via the ester linkage, or alcohols via the carbonate.



Scheme 182

10.5. Oxidation of Thioether

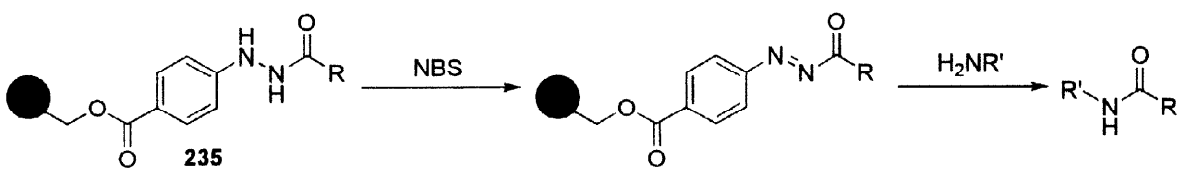
A sulfide linker **173** has been used for pyrimidines.[38] It is stable to both acidic and basic conditions, however, once oxidized to the sulfone **174** with *m*CPBA, it can be cleaved by nucleophilic aromatic substitution by amines (Scheme 183).



Scheme 183

10.6. Oxidation of Hydrazide

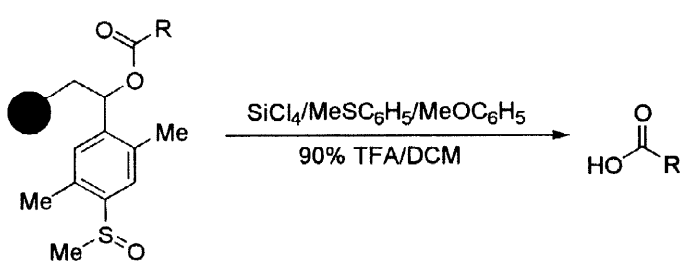
The diphenylhydrazide linker **235** is activated by oxidation with NBS (Scheme 184).[441] It is then base labile, being cleaved by treatment with an amine to release the product as an amide. The process can be performed in one step, using copper(II) acetate in the presence of the nucleophile and base.[442]



Scheme 184

10.7. Reduction of Sulfoxide

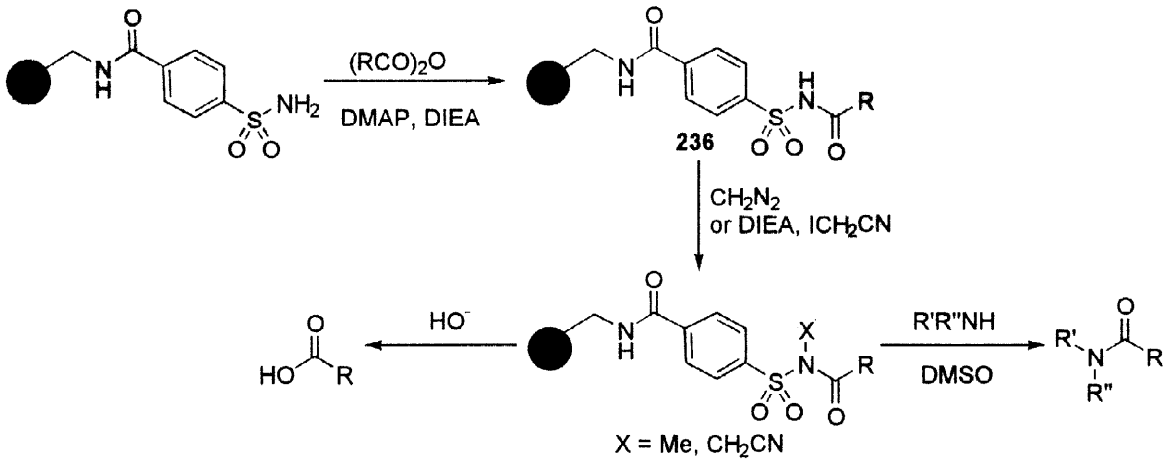
Electron rich benzylic linkers, which normally contain methoxy substituents, can be protected by exchanging one or more of the methoxy groups for a sulfoxide. The linker is stable to acid whilst in the oxidized state. Reduction of the sulfoxide(s) to the thioether(s) with $SiCl_4$/thioanisole/anisole results in a more electron rich benzylic linker, hence cleavage is achieved with TFA (Scheme 174). The reduction of the sulfoxide(s) is typically performed under acidic conditions so the two processes actually occur in the one step. This methodology has been used for linking carboxylic acids[443] and amides.[444]



Scheme 185

10.8. Kenner's Safety Catch Linker

The acyl sulfonamide developed by Kenner[34] is stable to both acid and base prior to activation. Under basic conditions the acidic acyl sulfonamide proton of **236** is removed protecting the acyl group from nucleophilic cleavage. To activate the linker for cleavage the nitrogen is alkylated with either diazomethane[34,35] or iodoacetonitrile (Scheme 185).[36,37] It is then cleaved using nucleophiles, such as hydroxide to give the carboxylic acid,[34,35] or amines to give the corresponding amides.[34-37]



Scheme 186

11. CONCLUSION

As the field of solid phase organic synthesis expands, so does the demand for new and novel linkers. Many of the linkers used were first developed for peptide synthesis. These have performed admirably and the synthesis of a large range of molecules has been achieved. They also have limitations though. The range of functionalities is limited and many are not stable to a wide range of organic reactions. Conversely, some require cleavage conditions that are too harsh for certain functional groups. In recent years, many protecting groups developed for solution phase synthesis have been translated for use as linkers for solid phase organic synthesis. These have greatly expanded the functionalities available for linkage and have a wide range of chemical stabilities and cleavage conditions. One of the key challenges in this area is to utilize cleavage reagents that are readily removed from the cleaved product. This is especially the case when preparing the large numbers of compounds required in combinatorial chemistry. Volatile reagents are ideal for this, although recently developed high throughput purification techniques such as solid phase purification reagents have increased the scope of this process. The area of cleavage techniques and methods of purification of the large numbers of compounds created by combinatorial chemistry will be one of great development over the coming years. The safety catch approach may prove useful here, using selective conditions for activation, then conditions for the cleavage which are easily worked up. The area of traceless linkers provides one of the biggest challenges as this is not based on common protecting group techniques. Already, great advances have been made with the silyl linkers for attaching aromatic groups. It will be interesting to see if these last the test of time, or if new, more labile linkers are developed. Although the universal linker, one which may be applied to any molecule, is an admirable goal, much

work needs to be performed before this will be possible, if indeed it is possible. Methods that are useful in specific cases, i.e. non-universal, will continue to be developed, and successfully applied. What is important is to understand fully the capabilities and short-comings of both current and new linkers. This can only be achieved by the open reporting of conditions that work, but also those that do not, or result in premature cleavage.

As in all areas of solid phase and combinatorial chemistry, the area of linkers is rapidly developing, and although many of the linkers reported here may not end up finding wide spread use, they will lay the foundation for new, more effective, linkers to be developed in the future.

12. ABBREVIATIONS

BOC, *tert*-butoxycarbonyl; BOP, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexfluorophosphate; CDI, 1,1′-carbonyldiimidazole; *m*CPBA, 3-chloroperoxybenzoic acid; CSA, 10-camphorsulfonic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, 1,3-dicylcohexycarbodiimide; DCE, 1,2-dichloroethane; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DDQH, 2,3-dichloro-5,6-dicyano-1,4-hydroquinone; DDT, dithiothreitol; DEAD, diethyl azodicarboxylate; DIBAL, diisobutylaluminium hydride; DIC, 1,3-diisopropylcarbodiimide; DIEA, *N,N*-diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; DMSO, dimethylsulfoxide; DMTST, dimethylthiosulfonium triflate; DSC, *N, N′*-disuccinimidyl carbonate; DTBP, di-*tert*-butylpyridine; EDT, 1,2-ethanedithiol; Fmoc, 9-fluorenylmethoxycarbonyl; Im, imidazole; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazol[4,5-b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HBTU, *O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophasphate; HOAt, 1-hydroxy-7-azabenzotriazole; HOBt, 1-hydroxybenzotriazole, LDA, lithium diisopropylamide; LHMDS, lithium bis(trimethylsilyl)amide; MES, 4-morpholineethanesulfonic acid; NBS, *N*-bromosuccinimide; NIS, *N*-iodosuccinimide; NMM, 4-methylmorpholine; NMP, 1-methyl-2-pyrrolidinone, pfbm, perfluorobutyramide; PPTS, pyridinium *p*-toluenesulfonate; *p*TsOH, *p*-toluenesulfonic acid; py, pyridine; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TEA, triethylamine; TES, triethylsilane; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, tetrahydropyran; TIPS, triisopropylsilane; TMS, trimethylsilyl; Tr, trityl.

13. ACKNOWLEDGEMENTS

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14. REFERENCES

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Biographical sketch

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