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Diversity Linker Units for Solid-Phase Organic Synthesis

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In recent years an ever-increasing number of traditional solution-phase reactions have been adapted for solid-phase organic synthesis (SPOS) because of the ease of application of solid-phase techniques to combinatorial chemistry and high-throughput screening. To accommodate the growing number of reactions being attempted on solid supports, new linker units continue to be reported in the literature. Linker units are typically grouped according to the functionality left at the "cleavage site" in the target molecule, and are normally classified as traditional (polar functionality remains following cleavage) or traceless (hydrogen residue left after cleavage) linkers. As the field continues to expand, however, more advanced linker units have been reported, which utilise the cleavage step in SPOS to incorporate additional diversity into target libraries. These linker units have been termed "diversity" or "multifunctional" linker units, and in this microreview we introduce this aspect of the field, giving representative examples indicating key stages of development including the linker units recently designed in our laboratory.

Contents

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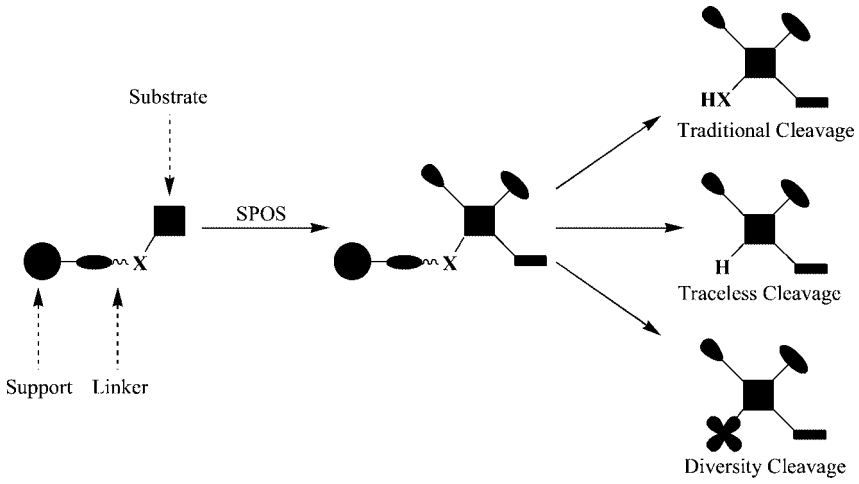
1 General Introduction

In the last few decades, automated combinatorial chemistry and high-throughput screening methods have revol-

Dr. Peter Scott (left) received his BSc in medicinal and pharmaceutical chemistry from Loughborough University in 2001 following research into peptide nucleic acids under the guidance of Prof. Raymond Jones. He then undertook doctoral research, designing novel diversity perfluoroalkanesulfonyl linker units for use in solid-phase synthesis, with Dr. Patrick Steel at the University of Durham and was awarded his Ph.D. in 2005. Dr. Scott is currently carrying out postdoctoral research in the field of rhodium carbenoid chemistry among a lot of snow at the University of Buffalo, the State University of New York, with Prof. Huw Davies. His research involves the adaptation of traditional rhodium catalysts for use in solid-phase synthesis and their application towards the synthesis of novel drugs for the treatment of depression and cocaine addiction.
Dr. Patrick Steel (right) studied chemistry at the University of Oxford where he obtained first his BA, and subsequently, in 1988, his Ph.D., working with Prof. Jim Thomas on the total synthesis of members of the milbemycin family of natural products. Following a period as a NATO-SERC postdoctoral fellow in the group of Prof. Gilbert Stork at Columbia University, NY, he returned to the UK to a lectureship at the University of Durham. In 1996 he received a Glaxo-Wellcome award for innovative Organic Chemistry and in 2000/01 held a Royal Society Industrial Fellowship working at the GlaxoSmithKline research centre in Stevenage. He is currently a Senior Lecturer in Chemistry where his research interests include new organosilicon chemistry, the development of novel synthetic methodology for both classical and solid-phase synthesis and projects at the chemistry–biology interface.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 1.

utionised organic chemistry and the processes by which novel compounds are synthesised and screened for biological activity. Underlying this advance has been the use of solid-phase synthesis and other related approaches for the preparation of compound libraries. Originally developed by Merrifield for peptide synthesis,[1] solid-phase organic synthesis is a simple and attractive synthetic technique in which the substrate is immobilised on an insoluble polymer support, most commonly a polystyrene bead, by a suitable linker unit (Scheme 1).[2,3] Reactions can then be driven to completion in solid-phase organic synthesis (SPOS), providing high yields, through the use of large excesses of reagents. Purification is then a simple process of collecting the solid-supported species by filtration and washing away unreacted reagents and any by-products. At the end of the synthetic sequence, the target compound is detached from the linker unit in a final cleavage step. (For abbreviations see Table 1).

The simplicity and ability to automate such a sequence has resulted in SPOS becoming much more common and no longer limited to peptide and oligonucleotide chemistry. In particular, owing to the boom in diversity-oriented synthesis (DOS) and chemical genetics, the desire to generate diverse compound libraries has become a major synthetic objective in its own right.[4,5] Reflecting this driving force, a wide range of standard solution-phase reactions have now been adapted for solid-supported synthesis, and these have been the subject of some excellent reviews.[2,6–8] To accommodate the growing number of reactions carried out on solid-supported substrates, large numbers of sophisticated linker units have been developed and are now routinely employed in solid-phase synthesis. Typically, linker units are conveniently grouped according to the functionality left at the "cleavage site" in the target molecule (Scheme 1), and can be classified as traditional/classical (the site of attachment to the resin remains following cleavage), traceless (hydrogen residue left after cleavage) or diversity linkers. Whilst the first two groups of linkers use a common cleavage cocktail for all members of a library, this microreview will focus on the last set, which maximises diversity by using the final cleavage step to incorporate further structural variation into the product library. A brief overview of

Table 1. Abbreviations.

Ac	acetate	DMSO	dimethyl sulfoxide
Acac	acetylacetonyl	DOS	diversity-oriented synthesis
AIBN	azo-bis-*iso*butyronitrile	*ee*	enantiomeric excess
AG	ArgoGel™	Fmoc	9-fluorenylmethyloxycarbonyl
Binap	2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl	*m*-CPBA	*meta*-chloroperbenzoic acid
Bn	benzyl	MEMO	methoxyethoxymethyl ether
Boc	*tert*-butyloxycarbonyl	Mpc	2-(4-methylphenyl)isopropyl carbamate
Bpoc	[(2-(4-biphenyl)isopropyl)oxyl]carbonyl	NCS	*N*-chlorosuccinimide
18-C-6	18-crown-6	PS	polystyrene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	Py	pyridine
DCM	dichloromethane	SPOS	solid-phase organic synthesis
Dppb	1,4-bis(diphenylphosphanyl)butane	TBAF	tetra-*n*-butylammonium fluoride
Dppf	1,1′-bis(diphenylphosphanyl)ferrocene	TBDPS	*tert*-butyldiphenylsilyl
Dppp	1,3-bis(diphenylphosphanyl)propane	TFA	trifluoroacetic acid
DIPEA	*N*,*N*′-diisopropylethylamine	TfO	triflate, trifluoromethanesulfonate
DMAD	dimethyl acetylenedicarboxylate	THF	tetrahydrofuran
DME	ethylene glycol dimethyl ether	TG	Tentagel®
DMF	dimethylformamide	TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone	Tr	trityl

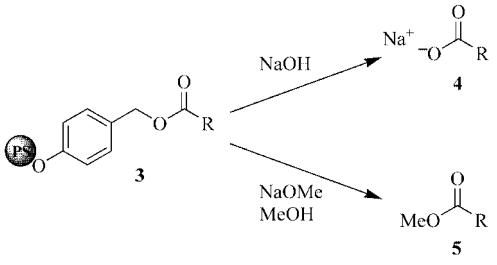
linker technology is presented below, tracing the evolution from traditional examples through to the more elaborate linker units in use today.

2 Linker Cleavage Strategies: An Overview

The purpose of the linker unit in solid-phase organic synthesis is twofold. Firstly, linkers possess a functional group that is used to attach reactive substrates to solid supports and that releases them at a later date under specific cleavage conditions. With this in mind, linker units can be viewed as polymer-supported protecting groups. Secondly, linker units tend to be "long" molecules, which serve to hold reactive substrates away from the support matrix in order to improve the reactivity. The ideal linker unit needs to be cheap, easily synthesised and coupled to the support, stable to a wide range of reaction conditions, and needs to give quantitative yields for the attachment and cleavage of substrates under mild and specific conditions. Because many linker units do not fulfil all of these criteria and, as the chemistry attempted on solid-supported substrates becomes ever more ambitious and diverse, more linker units are being developed all the time. Reflecting this, over 200 linkers have been developed in the last 20 years. These have been the subject of several extensive reviews. This section will not attempt to replicate these, but rather illustrate the evolution of the concept of the diversity linker unit.[2,3,9–17]

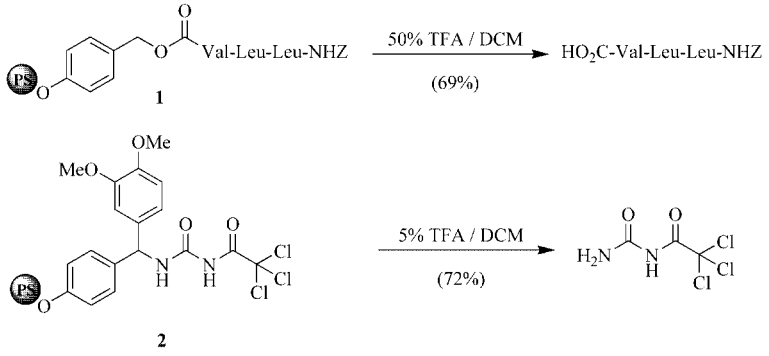
Reflecting their genesis in solid-phase peptide and oligonucleotide synthesis, early linker units typically possessed a polar functional group (e.g. OH, NH_2, CO_2H, etc.) that was used to attach substrates to the solid support. These may be classified according to whether acidic or basic conditions are required for cleavage of substrates, and many of these linker units are still employed regularly in solid-phase synthesis. Two of the most commonly used acid-cleavable linker units are the hydroxymethylphenyl linker developed by Wang[18] (**1**) and the aminomethylphenyl derivative **2**, which is stabilised by a further anisole unit as reported by Rink.[19] The *para*-oxygen atom in the Wang linker stabilises the resulting cation so that cleavage can be achieved using 50% TFA in DCM (Scheme 2). In comparison, a greater stabilisation of the intermediate carbocation is provided by the *ortho*- and *para*-methoxy groups of the Rink linker, enabling cleavage to be carried out under much milder conditions (e.g. 5–50% TFA/DCM). For example, Gütschow was recently able to cleave trichloroacetylurea using only 5% TFA in DCM.[20]

If acid cleavage of substrates was unsuitable, then the alternative strategy in early SPOS was to employ a base-cleavable linker unit (Scheme 3). For example, in Merrifield's original work, cleavage of the tetrapeptide product from the hydroxymethylpolystyrene **3** was achieved with sodium hydroxide to leave the salt of the carboxylic acid **4**.[1] Alternatively, the cleavage with sodium methoxide gives the corresponding methyl ester **5**, and this resembles a very simple and trivial example of diversity cleavage.[13]

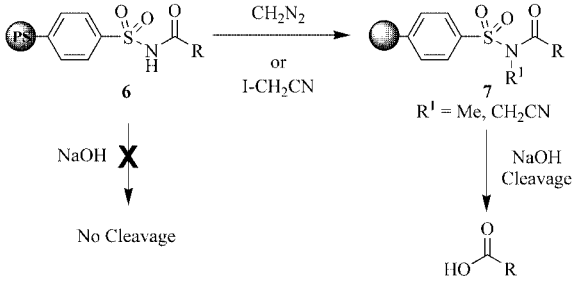


Scheme 3.

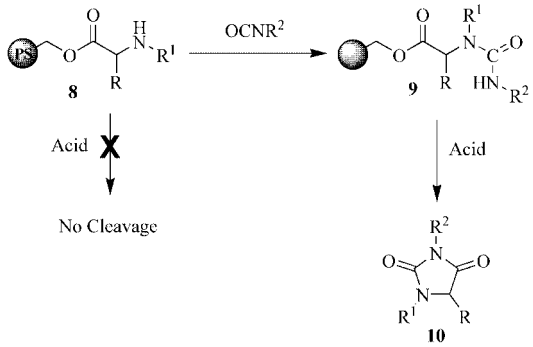
The main advantage of these early linker units is the ease with which cleavage of the substrates can be carried out under mild conditions. Target compounds can often be isolated in sufficient purity by simple evaporation of the cleavage reagents. One limitation associated with these simple linkers is that the use of nucleophiles in the synthetic sequence can lead to unwanted cleavage, particularly with ester-linked substrates. The solution to this problem is the safety-catch linker. In such linkers, the latent bond requires specific activation immediately prior to cleavage.[2,9,12] This allows for the use of reagents similar to those employed in the cleavage step during the synthesis. The first example was a sulfonamide linker introduced by Kenner in 1971.[21] The sulfonamide **6** is stable to both acidic and basic conditions, which is synthetically very useful. However, on alkylation of the nitrogen with diazomethane or iodoacetonitrile to give **7**, the substrates can be cleaved under nucleophilic conditions (Scheme 4).



Scheme 2.



Scheme 4.



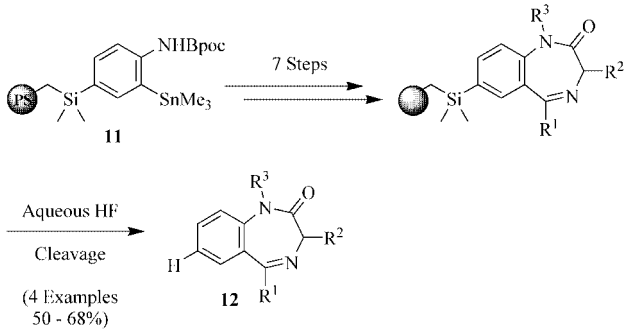
Scheme 5.

However, a significant drawback, which has limited the use of these traditional linker units in more general organic synthesis, remains. This is the common polar functional group that is introduced into every target molecule in a compound library upon cleavage. Whilst this may be an integral part of the desired structure, in many cases it is not, and the presence of such functionality can greatly affect the desired (biological) activity and must be removed. This is frequently a non-trivial undertaking and considerable research has been devoted to providing linker units that avoid this problem.

The first solution proposed involved the use of cyclo-release linker units. In this case, an intramolecular cyclisation of the resin-bound substrate takes place, and because the bond being broken in the intramolecular reaction is involved in attaching the substrate to the solid support, cleavage occurs simultaneously. Consequently, the polar functionality behaves as a leaving group and remains bound to the solid support following cleavage. The principle advantage of cyclo-release linker units is that only molecules containing the nucleophile will undergo cyclo-release.[2,9,12] Therefore, if, despite the use of excess reagents, some synthetic steps have not gone to completion, only the target molecule will be cleaved. This gives rise to products of high purity, which is especially important in solid-phase library synthesis where parallel purification of diverse structures can be challenging. A simple example of the cyclo-release linker concept is that reported by Pavia in 1993.[22] Treatment of the hydroxymethylpolystyrene-immobilised *N*-modified amino acid **8** with acid does not result in cleavage (Scheme 5). However, the reaction with an isocyanate generates the urea **9**, which on treatment with 6 M hydrochloric acid cyclises to form the hydantoin **10** and simultaneously cleaves the carbon–oxygen bond to release the product. Any amino acid that did not react with the isocyanate remains bound to the solid support, resulting in products of high purity.

The main advantage of cyclo-release linkers is that substrates can be coupled to the support using a chemistry similar to that of classical linkers, but the polar functional groups remain attached to the support, rather than to the target molecule, following cleavage. However, the use of cyclo-release linker units is limited by the substrate scope. In particular, many target compounds either are not cyclic or do not have a suitable ring size to work efficiently. In these cases, alternative approaches to avoid the unwanted common linking group are required, and this has led to the introduction of traceless and, more recently, diversity linker units.

Traceless linker units were pioneered by Ellman with the introduction of his ground breaking silicon-based linker unit **11**.[23] While there is a certain amount of ambiguity surrounding the term, in this review traceless linker units are exclusively those which leave a hydrogen residue upon cleavage. However, it should be noted that many traceless linker units can also function as diversity linker units by varying the cleavage conditions, as will become apparent in Section 3. Ellman made use of *ipso* substitution at silicon to leave a hydrogen residue in the substrates following acid cleavage (Scheme 6). The concept was demonstrated in the synthesis of benzodiazepines **12** and paved the way for the development of numerous traceless linker units.



Scheme 6.

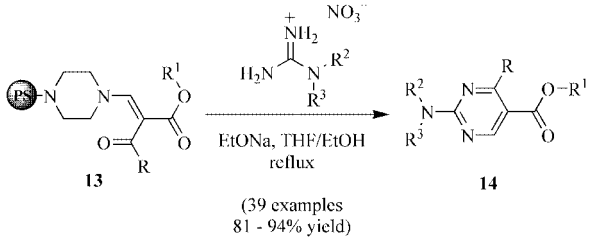
The drawback with traceless linker units is that, whilst the hydrogen residue that remains after traceless cleavage is biologically inert and therefore often preferential to an unwanted polar functional group, synthetically they are a dead-end. Consequently, traceless linker units have evolved into diversity or multifunctional linker units, which utilise the cleavage step in solid-phase synthesis for the incorporation of further diversity into target molecules and compound libraries. In recent years a considerable number of diversity linker units have been developed, and cleavage steps are becoming evermore elaborate. Section 3 surveys diversity cleavage strategies, illustrating these with selected examples from the literature.

3 Diversity Cleavage

The cleavage process in SPOS can be designed to produce diversity in a number of ways. In this review we have classified diversity linker units as those where diversity is introduced from a range of nucleophiles (Section 3.1) and those in which diversity originates in the electrophilic component (Section 3.2). In both cases, the reactions used in the cleavage step have evolved from more traditional SPOS cleavage reactions to transition-metal-catalysed cross-coupling reactions. More recently, diversity linker units that use other modes of cleavage, such as radical reactions or ring-closing metathesis, have also been developed. These alternative modes of cleavage are discussed in Section 3.3.

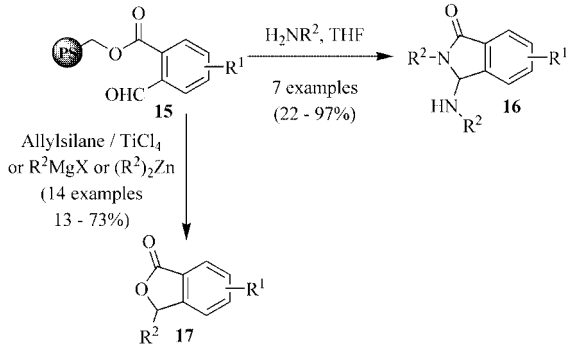
3.1 Diversity through a Nucleophilic Component

In its simplest form, nucleophilic cleavage can be considered as an extension of the base-mediated cleavage employed by Merrifield (Scheme 3). One can envisage the use of many classical linkers combined with a broad range of nucleophiles to introduce diversity at the cleavage site. For example, a number of amide libraries have been prepared from ester-linked substrates by cleaving with arrays of amines.[24,25] It can be argued that most of the linkers used in this fashion are not specifically diversity-generating and this approach will not be considered further. However, it is worth noting that more elaborate variations on this theme are possible in which the nucleophilic cleavage step is the first component of a heterocycle synthesis such as in the work of Porcheddu[26] and Clapham.[27] For example, Porcheddu reported the synthesis of a library of 2,4,5-substituted pyrimidines **14**, containing 4 points of diversity, from resin-bound β-enaminone **13** and guanidine (Scheme 7).[26]



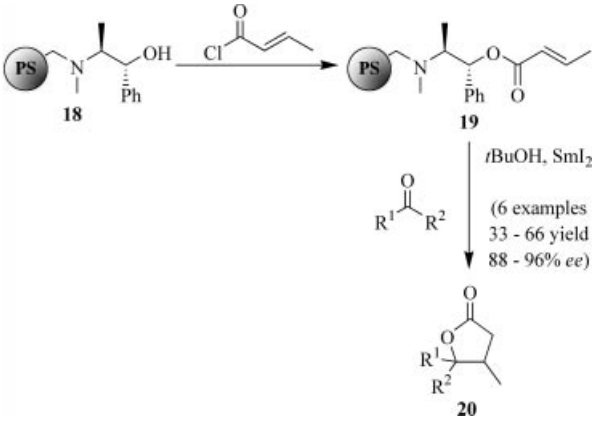
Scheme 7.

In a similar fashion, cyclo-release strategies can be rendered diversity-generating when the cleavage step is activated by addition of the diversity-introducing reagent. This approach has been employed by Bräse in the synthesis of isoindoles and phthalides, as both families of compounds were accessible from resin-bound aldehyde **15**.[28] Treatment with a range of amines gave a family of isoindoles **16**, whilst treatment with Grignard reagents, organozinc reagents or allylsilanes in the presence of a Lewis acid all resulted in phthalides **17** (Scheme 8).



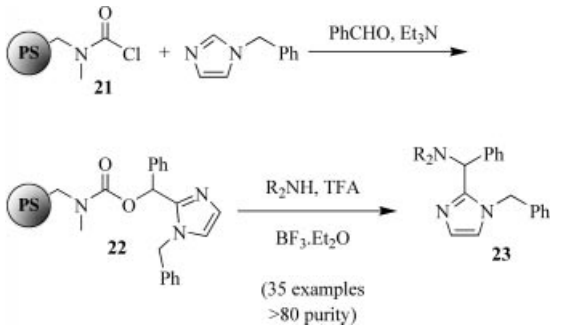
Scheme 8.

A second particularly attractive example of this approach is described by Procter and is used in the synthesis of γ-butyrolactones.[29] Ephedrine resin **18** was used to capture crotonyl chloride to give crotonate resin **19**. Reaction of this with the ketyl radical, generated from a range of aldehydes and ketones in the presence of samarium iodide, resulted in conjugate addition and concomitant cyclo-release to give γ-butyrolactones **20** with good control of enantioselectivity (Scheme 9). An additional advantage of this linker unit is that cleavage also regenerates the starting resin allowing for economic recycling.



Scheme 9.

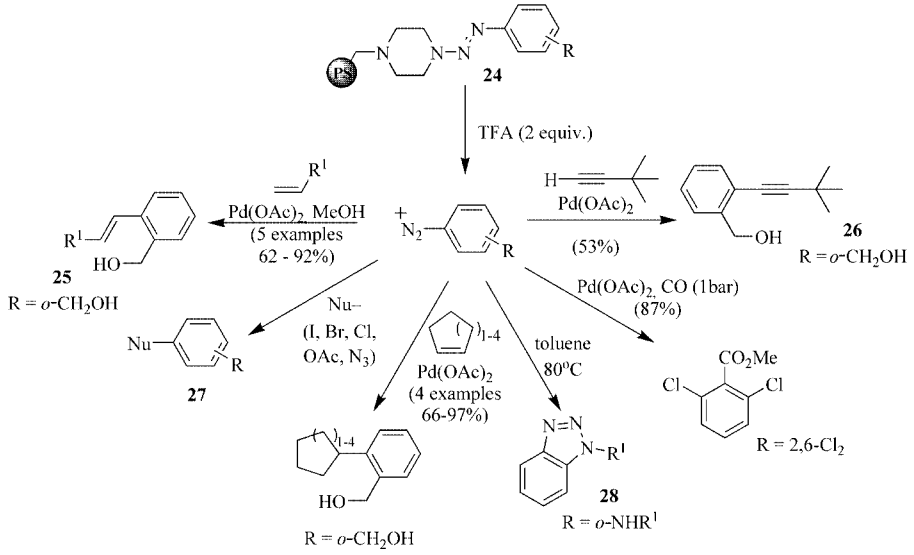
A further distinction can be made between linkers in which the cleavage agent is actually the diversity element and those in which cleavage releases a reactive entity that can be trapped by a structurally diverse set of reagents. An example of this second approach is the carbamyl chloride linker unit **21** described by Hlasta for the preparation of 2-substituted imidazoles.[30] The linker unit **21** was prepared from *N*-(methylaminomethyl)polystyrene and phosgene. A one-pot reaction with benzaldehyde and 1-benzylimidazole then gave the resin-bound 2-substituted imidazole **22**. Diversity cleavage was initiated by treatment with TFA, which generated a stabilised carbonium ion that could be trapped with a range of amines to afford a library of imidazoles **23** that contains three points of diversity introduced from the heterocycle, the aldehyde and the nucleophile used in the cleavage process (Scheme 10).



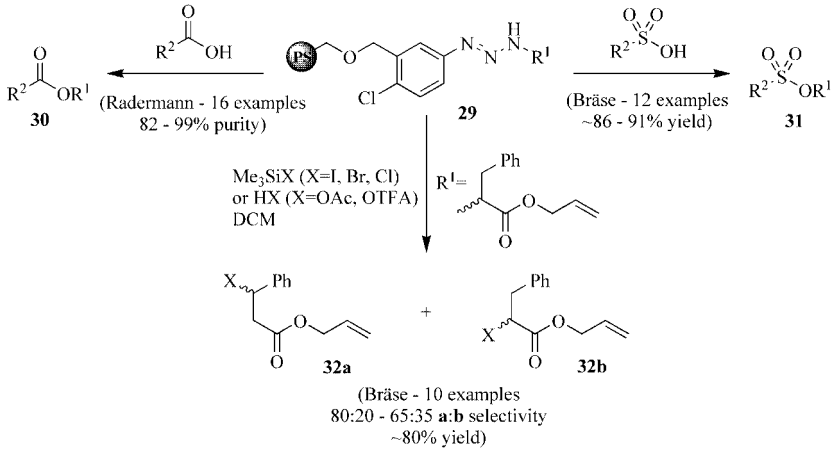
Scheme 10.

Other examples of this approach are found in the T1 and T2 triazene linker units developed by Bräse.[31] The T1 triazene linker unit **24** originally found use as a traceless linker, and treatment of T1-resin-bound substrates with TFA released the aryldiazonium salts. Enders demonstrated that by heating these diazonium salts nitrogen was liberated to leave a hydrogen at the cleavage site, and he used the T1 linker in the synthesis of β-lactams.[32] However, following the discovery that aryldiazonium salts are viable electrophilic components for cross-coupling reactions,[33] diversity cleavage strategies for the T1 linker unit **24** have also been extensively developed by Bräse (Scheme 11).[34,35] Cleavage strategies range from substitution with nucleophiles, thought to proceed via a radical pathway, to transition-metal-catalysed cross-coupling reactions. For example, the released aryldiazonium salts can undergo Heck or Sonogashira reactions to introduce alkenes **25** and alkynes **26** at the cleavage site, respectively, whilst reaction with a nucleophile gave access to the aryl halides, acetates and azides **27**. Bräse has also shown that the diazonium group, in addition to functioning as a leaving group, can be incorporated into the target molecule to give rise to heterocycles such as the benzotriazoles **28**.

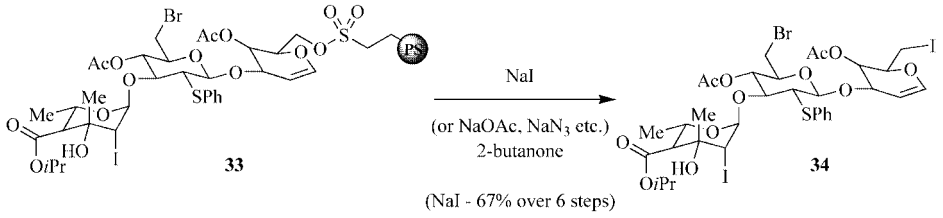
More recently, Bräse has also introduced the T2 triazene linker unit **29**. T2 linkers are resin-bound diazonium salts used for the immobilization of amines and other nitrogenous compounds.[36,37] Diversity cleavage has been demonstrated by using a range of "traditional" reactions to derivatise target molecules (Scheme 12). For example, reaction



Scheme 11.



Scheme 12.

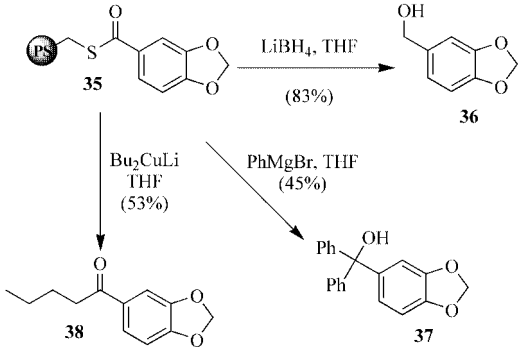


Scheme 13.

with carboxylic acids has been shown to give the simple esters **30**,[38] whereas cleavage with sulfonic acids provides the sulfonate esters **31**[39] and cleavage with trimethylsilyl halides or simple acids gives the corresponding alkyl halides, acetates and trifluoroacetates **32**.[40] Given the potential for both electrophilic and nucleophilic modes for diversity cleavage, these triazene linkers are truly versatile linker units that continue to find many applications in solid-phase organic synthesis.

Owing to the ability of a sulfur atom to function as a good leaving group, a number of different sulfur-based linker units that use nucleophilic cleavage to introduce diversity into target molecules have been developed in the last 10 years and are the subject of an extensive review by Procter.[17] The nucleophilic displacement of alkylsulfonate groups such as mesylates and tosylates are classical reactions in organic synthesis. The concept has been adapted for solid-phase synthesis, and Roush has used it in the preparation of oligosaccharides.[41] Oligosaccharides were bound to the resin through a sulfonate ester linkage (**33**) and nucleophilic cleavage of the target molecules using sodium iodide, sodium acetate or sodium azide gave the iodo-, acetoxy- and azido-substituted sugars **34**, respectively (Scheme 13).

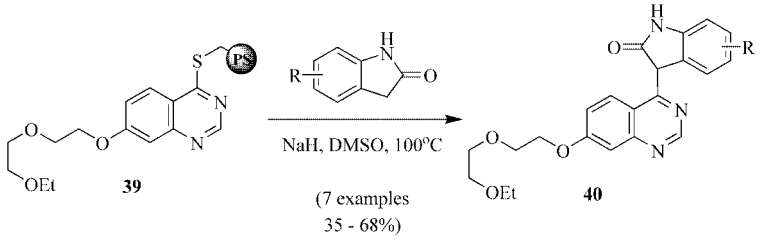
Another simple example of a sulfur-based linker unit is the thioester linker **35**, introduced by Bradley.[42] Diversity cleavage was achieved to leave a variety of functional groups at the cleavage site of the molecule, which is dependent upon the nucleophile used in the cleavage step. For example, cleavage using lithium borohydride gave the primary alcohols **36**, reaction with Grignard reagents produced the tertiary alcohols **37**, whilst the ketones **38** were released if a softer organometallic reagent such as an organocuprate was used (Scheme 14).



Scheme 14.

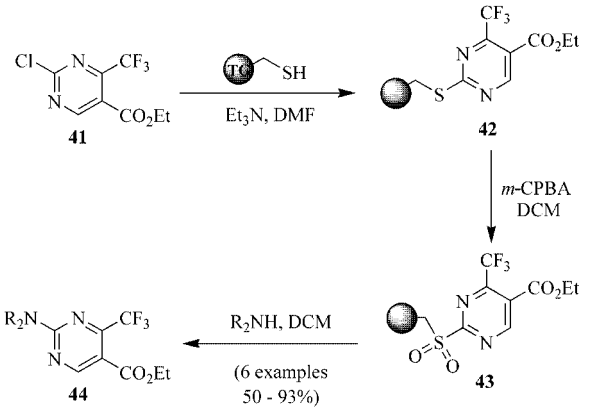
Somewhat related to this approach is the thiol-based diversity linker strategy originally used by Crosby in the simple sodium iodide mediated nucleophilic cleavage of alkyl thioethers to give the corresponding alkyl iodides.[43] Building on this concept, more sophisticated uses of this strategy continue to be reported. For example, Hennequin demonstrated the cleavage of resin-bound quinazolines **39** with the sodium anions of oxindoles to synthesize a library of oxindole quinazolines **40** (Scheme 15).[44]

With less reactive nucleophiles, the efficiency of this process is often poor but can be enhanced by conversion of the sulfide into a sulfone.[45] This ability to enhance the leaving-group ability of a thioether by oxidation has been much exploited in safety-catch linkers. This strategy has been widely employed in a diversity approach, and an early representative example is the safety-catch linker introduced by Gayo and Suto and used in the synthesis of functionalised pyrimidines **44**.[46] Pyrimidine **41** was loaded onto TentaGel® thiol resin to yield the resin-bound thioether **42**. Oxidation to the corresponding sulfone **43**, necessary to acti-



Scheme 15.

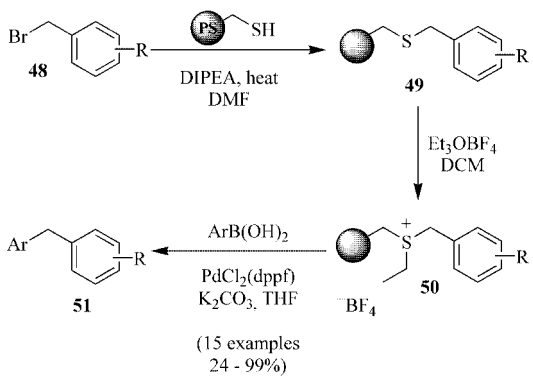
vate the safety-catch linker for cleavage, was achieved with *m*-CPBA. Cleavage through the nucleophilic aromatic substitution with primary and secondary amines afforded the functionalised pyrimidines **44** possessing a diverse range of amine functionalities at the site of attachment to the resin (Scheme 16).



Scheme 16.

Other sulfones are also amenable to nucleophile-mediated diversity cleavage. For example, Kurth demonstrated that allyl sulfone resins **45** can be cleaved with a range of organocuprates in an S_N2' process, albeit with low levels of efficiency when compared to the analogous solution-phase reactions.[47] To enhance this process, Kurth developed an alternative, more efficient strategy exploiting the allylic system **46** in a palladium-catalysed process. This is much more versatile than the original organocuprate approach as diversity can be introduced with a much broader range of general nucleophiles. Subsequently, similar palladium-mediated cleavage processes have been described by Blechert[48] and Brown[49] with the ester-linked substrates. For example, Blechert demonstrated diversity cleavage by treating ester **47** with dimethyl malonate in the presence of palladium (Scheme 17).

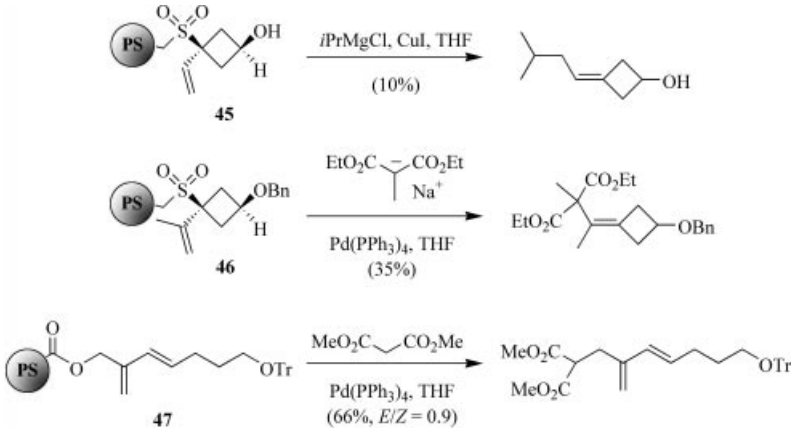
Rather than oxidation to facilitate cleavage, Wagner showed that activation of a benzyl thioether by quaternisation enables diversity cleavage through palladium-mediated cross-coupling with boronic acids (Scheme 18).[50] Analogues of the benzyl bromide derivatives **48** were loaded onto the polystyrene thiol resin to give the resin-bound thioethers **49**, which on treatment with triethyloxonium tetrafluoroborate afforded the solid-supported benzylsulfonium salts **50**. Nucleophilic diversity cleavage with a range of boronic acids in a palladium-catalysed Suzuki reaction then afforded a library of biarylmethanes **51**.



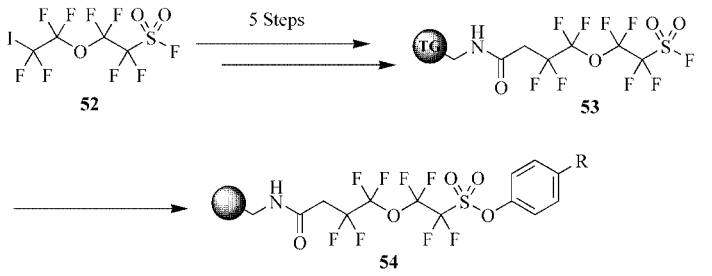
Scheme 18.

Given the wide range of coupling partners, such transition-metal-catalysed transformations are highly attractive for a diversity cleavage strategy. Amongst possible leaving groups, the triflate is recognised as being one of the most versatile. Aryl triflates exhibit high intrinsic stability, but when activated by metal salts show high activity towards nucleophiles. Perfluoroalkanesulfonyl linkers that are based on this concept were first reported by Pan and Holmes in 2001.[51,52] Perfluoroalkanesulfonyl linker **53** was derived in five steps from the commercially available iodosulfonyl fluoride **52**, and phenols were loaded using potassium carbonate to give the resin-bound perfluoroalkanesulfonate esters **54** (Scheme 19).

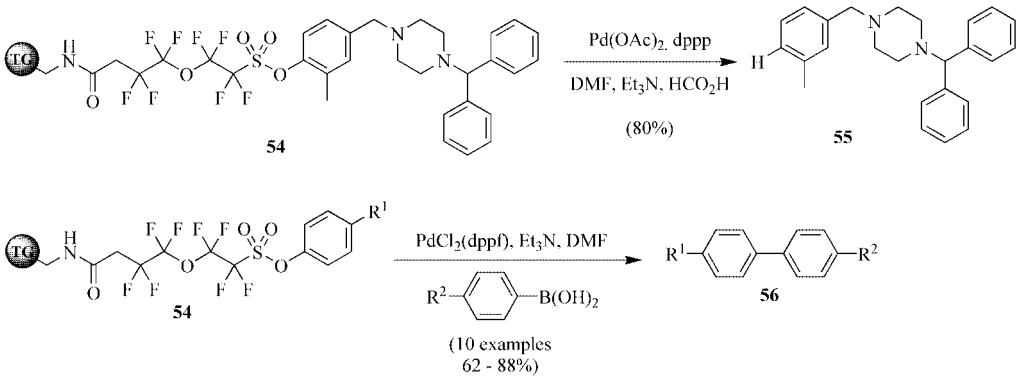
Traceless cleavage was demonstrated in the solid-supported synthesis of meclizine **55** with a palladium-catalysed transfer hydrogenation to leave a hydrogen residue at the cleavage site.[51] In further applications, diversity cleavage was also developed by using Suzuki reactions to release the desired target molecules as biphenyls **56** (Scheme 20).[52]



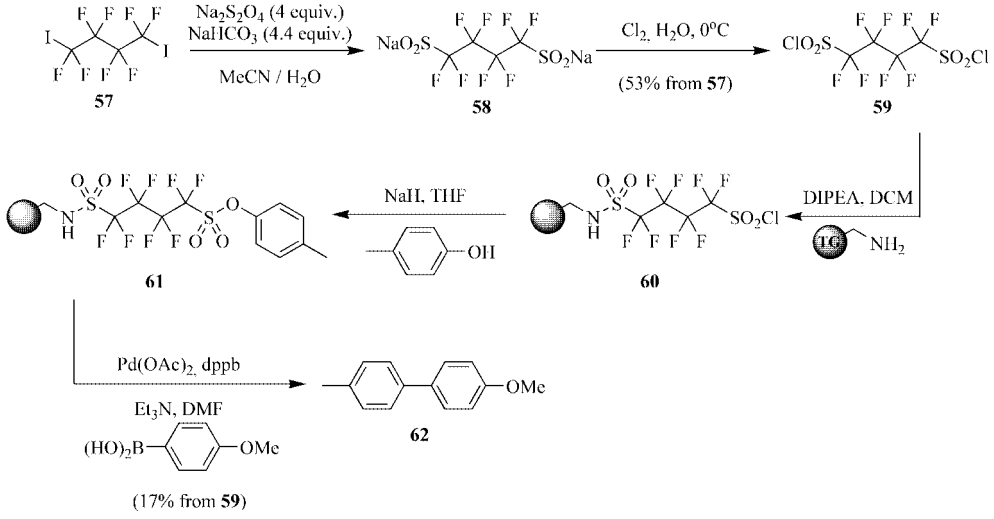
Scheme 17.



Scheme 19.



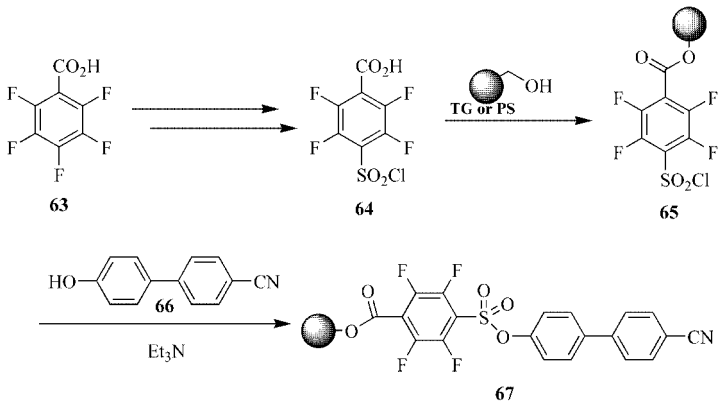
Scheme 20.



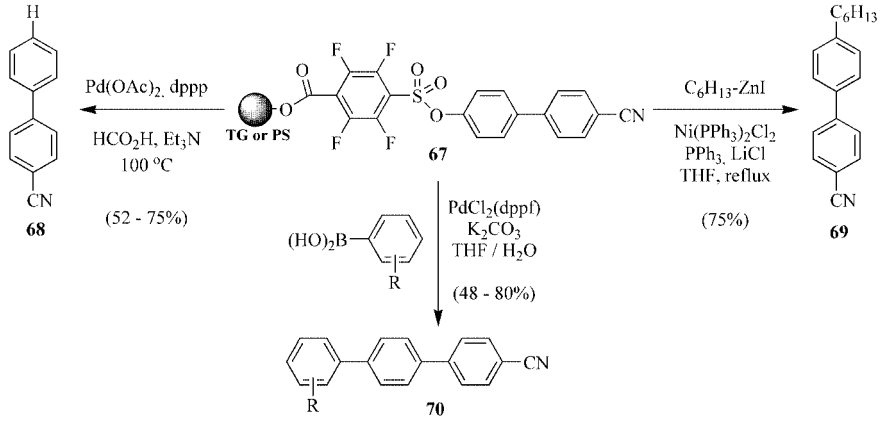
Scheme 21.

Concurrently with the efforts of Pan and Holmes, a perfluoroalkanesulfonyl linker unit has also been developed in our group starting from 1,4-diiodooctafluorobutane (**57**).[53] Radical addition of sodium dithionite to 1,4-diiodooctafluorobutane gave the bis(sodium) sulfinate salt **58**, and subsequent treatment with molecular chlorine yielded the bis(sulfonyl) chloride **59**. This bis(sulfonyl) chloride was loaded onto amino TentaGel® and gave the solid-supported perfluoroalkanesulfonyl chloride **60** (Scheme 21). Phenols were loaded onto this linker unit to give resin-bound analogues of the aryl triflates **61**, and cleavage of the substrates to give the biphenyls **62** was demonstrated using Suzuki cross-coupling reactions.

While the Pan and Holmes linker functioned efficiently, the method for its preparation is not trivial, and consequently it has seen limited use. A simpler alternative to these perfluoroalkanesulfonyl linker units is the fluoroarylsulfonate linker **65**, reported independently by both Cammidge[54] and Ganesan in 2004.[55] The sulfonyl chloride **64** was prepared from pentafluorobenzoic acid (**63**) and loaded onto hydroxymethyl TentaGel® to give the resin-bound sulfonyl chloride **65** (Scheme 22). Traceless and diversity cleav-



Scheme 22.

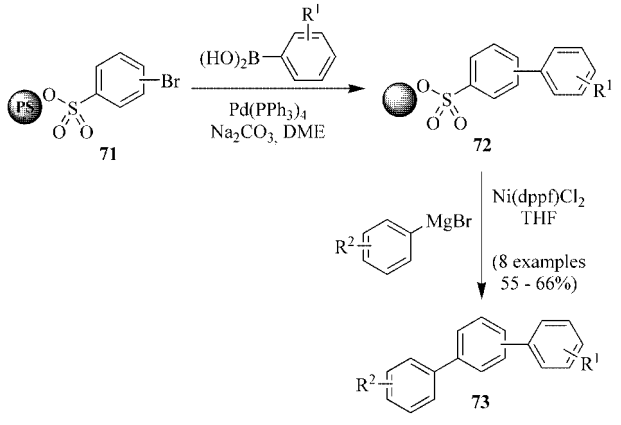


Scheme 23.

age was demonstrated by both groups by using several different strategies. For example, Cammidge loaded 4-hydroxybiphenyl-4′-carbonitrile (**66**) to give the resin-bound sulfonate ester **67**.

Traceless cleavage was demonstrated using formic acid to leave a hydrogen residue at the cleavage site of **68**. Alternatively, the diversity cleavage was efficiently achieved using Negishi and Suzuki reactions to leave alkyl groups and aryl groups at the cleavage site of the molecule in **69** and **70**, respectively (Scheme 23). This is a powerful diversity linker unit, which should see considerable exploitation in future SPOS.

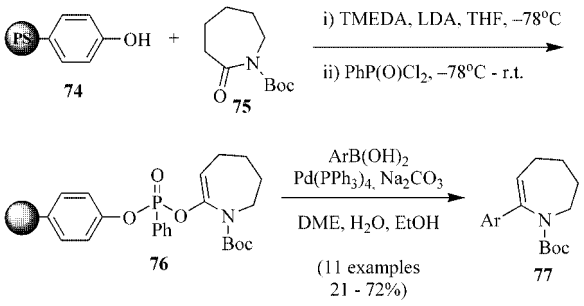
One restriction to these immobilised triflate analogues is the cost of the fluorinated precursors. In a related approach Park has recently described resin-bound arenesulfonates **71** as cheap and easily accessible alternatives (Scheme 24).[56] Reflecting the increased stability of arenesulfonates relative to their arylperfluoroalkanesulfonate counterparts, the arenesulfonate linker could be modified by using palladium-catalysed cross-coupling reactions to give the supported biphenyls **72**. Finally, cleavage with aryl Grignard reagents was demonstrated by using more active nickel-based catalysts to afford the terphenyls **73**.



Scheme 24.

Building on the reported use of phosphates as convenient more stable alternatives to enol triflates,[57] a phosphorus-based linker unit has been developed in our laboratory, which utilises transition-metal-catalysed cross-coupling reactions to achieve diversity cleavage.[58] The linker unit is a resin-bound phosphonate **76**, which is prepared in a one-pot procedure from phenol on polystyrene (**74**), the Boc-

protected ε-caprolactam (**75**) and phenylphosphonic dichloride. This polymer-supported enolate derivative is a stable entity, which can be stored for several months with no loss in activity. Diversity cleavage has been demonstrated by using palladium-catalysed Suzuki reactions with a range of boronic acids to leave aryl groups at the cleavage site in the target compounds **77** (Scheme 25).

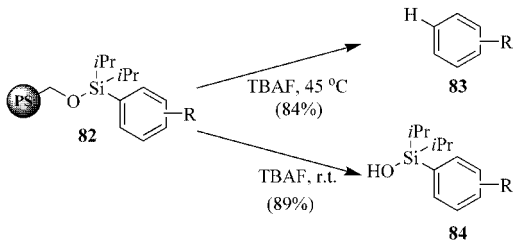


Scheme 25.

3.2 Diversity through an Electrophilic Component

The second class of diversity linker unit introduces diversity through electrophilic cleavage. This is generally achieved by an intrinsically electrophile-labile bond in the linker, the generation of a reactive species by using either a base or electron-transfer reagents, or activation by a transition-metal catalyst. In its simplest form, electrophilic cleavage is realised by simple protonation, and the early examples of diversity cleavage were derived from the traceless cleavage of the arylsilane unit. The first example was Ellman's germanium linker **78** (Scheme 26).[59] As with the silicon linker **11** discussed above (Scheme 6), the conventional cleavage of substrates from the germanium linker with TFA leaves a hydrogen residue at the cleavage site of the molecule **80**. However, organogermanium species are more reactive than their organosilicon counterparts, and in the case of the germanium linker **79**, Ellman was also able to cleave the carbon–germanium bond with bromine to release benzodiazepines as the corresponding aryl bromides **81**. The generation of additional diversity can be envisaged by further reaction of the resulting aryl bromide through, for example, palladium-catalysed cross-coupling reactions.

Enhanced reactivity, compared with Ellman's simple arylsilane, is also seen with the silyl ether based linker unit **82** described by Showalter.[60] Traceless cleavage occurs on treatment with cesium fluoride or TBAF at 45 °C, which leaves aryl groups with a hydrogen residue at the cleavage site of **83**. However, the oxygen atom also permits alternative modes of cleavage allowing applications as a diversity linker unit. For example, treatment with TBAF at room temperature cleaves the aryl group to give the dialkylarylsilanol **84** (Scheme 27).

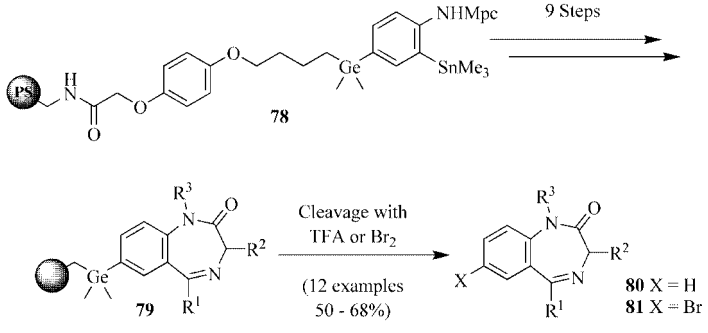


Scheme 27.

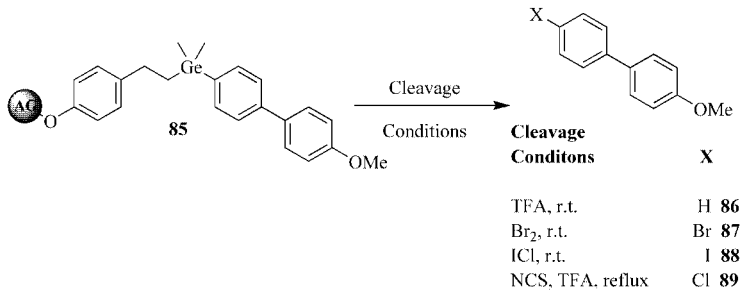
The germanium-based diversity linker approach has been refined and extended by Spivey[61] who described the preparation and application of the linker unit **85**. Treatment of this with TFA, bromine, iodine monochloride or *N*-chlorosuccinimide afforded the arene (traceless cleavage) **86**, aryl bromide **87**, iodide **88** and chloride **89**, respectively (Scheme 28).

These cleavage reactions are facilitated by the ability of the silicon or germanium to undergo *ipso* substitution via β-silicon- or β-germanium-stabilised carbocations. Allylsilanes can be combined with a range of electrophiles to produce a similar silicon-stabilised carbocation, which fragments to regenerate the alkene. This too has been exploited in traceless and diversity cleavage strategies. The first approach was initially described by Blechert who generated a range of immobilized allylsilanes **91** by a cross-metathesis reaction with **90**.[62] Treatment with 3% TFA/DCM cleaved the target molecule **92** with a terminal allyl group at the cleavage site (Scheme 29), whilst diversity cleavage can be realised through the use of other electrophiles, notably acetals to give **93**.

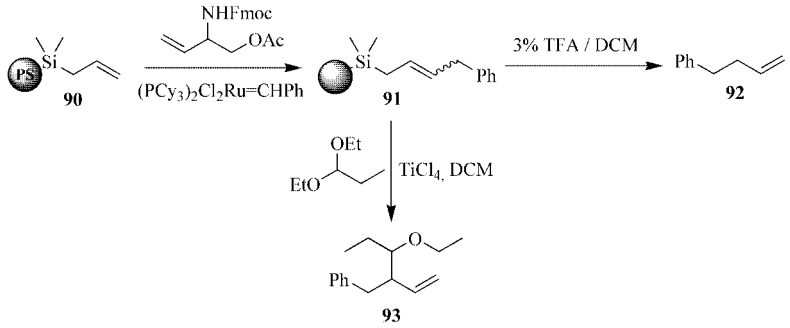
Suginome and Ito extended this concept when they introduced the chiral allylsilane scaffolds **94** and **96** as diversity linker units.[63] Diversity was introduced by cleavage



Scheme 26.

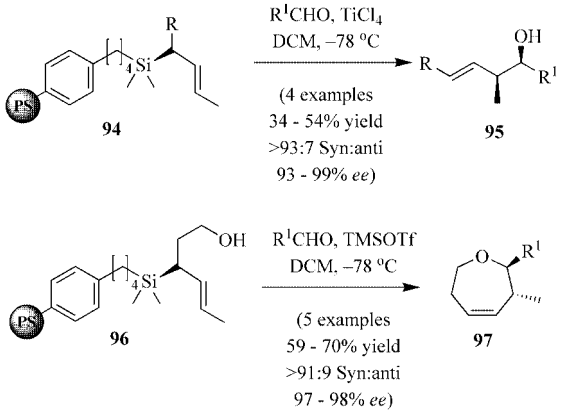


Scheme 28.



Scheme 29.

through reaction with a range of aldehydes mediated by a Lewis acid and was utilized in the preparation of the chiral alcohols **95** and cycloheptenes **97** (Scheme 30). Importantly, cleavage proceeded with efficient asymmetric transfer to provide both high enantioselectivity and good levels of diastereocontrol. Furthermore, it is worth highlighting that in neither case were by-products arising from the resin or the aldehydes observed in the crude products.



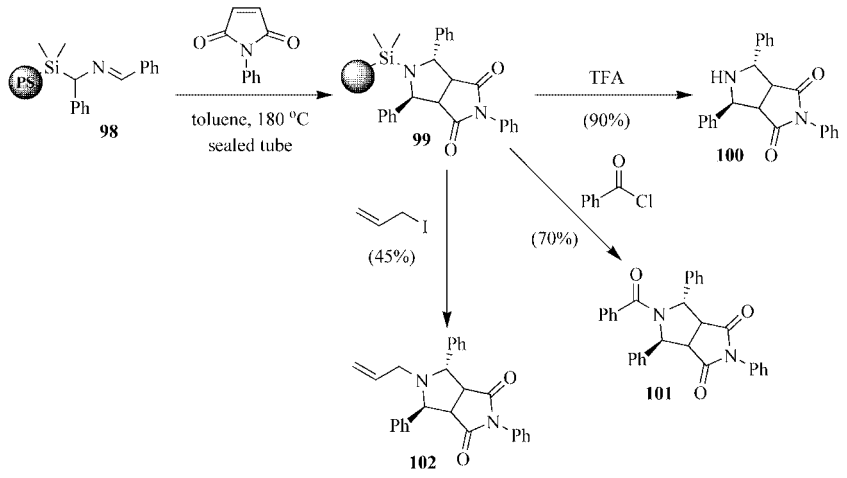
Scheme 30.

Silicon–nitrogen bonds are also labile in the presence of electrophiles, and this feature has been utilised by Komatsu in the application of the supported silylimine linker unit **98**.[64] Following silatropic ylide generation, a [3+2] cycloaddition reaction afforded a series of pyrrolidine derivatives **99** (Scheme 31). Cleavage was achieved with a range of electrophiles. For example, treatment with an acid left a hydrogen residue at the point of attachment (traceless cleavage, **100**), whereas the benzoyl (as in **101**) and allyl (as in **102**) groups were introduced through reaction with benzoyl chloride and allyl iodide, respectively.

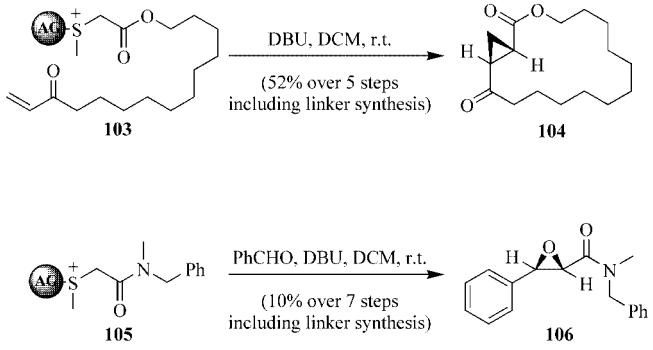
An alternative approach to diversity is to use the cleavage process to generate a reactive nucleophilic component, which can then be trapped with a set of electrophiles. Although diversity is also introduced from a range of electrophiles as for the linkers described above, the approach is subtly different because an active nucleophilic species is generated first. This can be achieved either by base activation or through the activation by organometallic reagents; both classes will be discussed in turn.

Structural diversity generated by enolate alkylation is common in solution-phase synthetic chemistry. However, the challenge in SPOS is to combine such nucleophilic reactions with a cleavage process. Commonly this involves an addition–elimination process. For example, Gennari reported a linker unit that makes use of sulfur ylide chemistry in the cleavage step.[65] Generation of ylide **103** led to an intramolecular cyclopropanation reaction by a Michael reaction and subsequent elimination, which simultaneously cleaved the carbon–sulfur bond. This left the thiol functionality bound to the solid support and provided the macrocycle **104** exclusively as the *trans* isomer (Scheme 32). In this case, the linker also functions as a cyclo-release diversity linker unit. However, diversity can also be introduced through an intermolecular reaction. If ylide **105** is treated with an aldehyde, then substrates can be cleaved from the resin as epoxides **106** – this clearly highlights the difference between cyclo-release and true diversity linkers.

A second group of base-activated diversity linkers are the phosphorus-based linker units that use Wittig-type chemis-



Scheme 31.

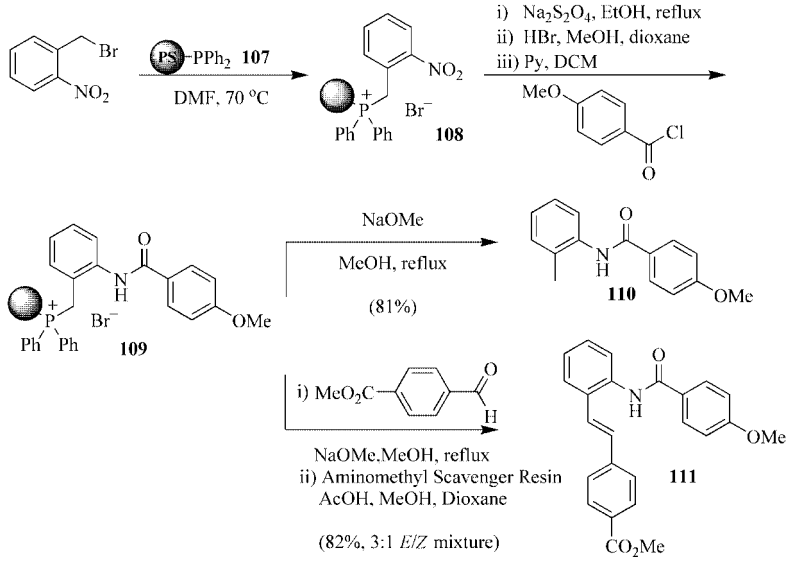


Scheme 32.

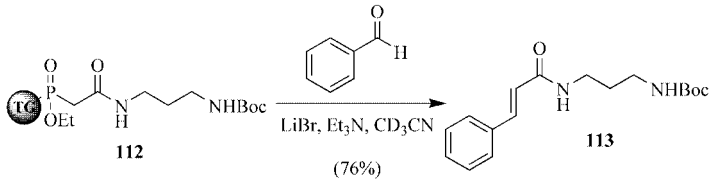
try to achieve cleavage. Whilst supported ylides have been known for a considerable time and allow for greatly simplified purification when compared to their solution-phase counterparts, their application in a true diversity approach remains less well-documented.[66] As with the sulfur ylides described above, in general, these linkers can function as both traceless linkers and diversity linkers, depending upon the actual substrate and cleavage conditions employed (Scheme 33). For example, Hughes described the application of the solid-supported phosphonium salt **108**.[67] Generated from the commercially available polystyrene-bound analogue of triphenylphosphane **107**, it was then reduced to the aniline and further functionalised to give **109**. Traceless cleavage was achieved with sodium methoxide in methanol to release the tolyl derivative **110**. Alternatively, diversity cleavage of substrates as 3:1 mixtures of the corresponding *E*/*Z* alkenes **111** was carried out by using simple Wittig chemistry.

In a similar fashion, the Horner–Wadsworth–Emmons reaction has been used to provide a phosphorus-based diversity linker strategy. For example, Johnson and Zhang described the release of substrates from the linker unit **112** by reacting with aldehydes under mild conditions to give the alkenes **113** with exclusively *E* geometry (Scheme 34).[68]

This approach has also been used by Nicolaou in the development of a cyclo-release linker unit.[69] Resin-bound

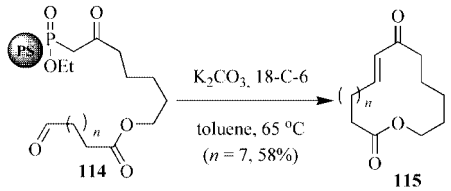


Scheme 33.



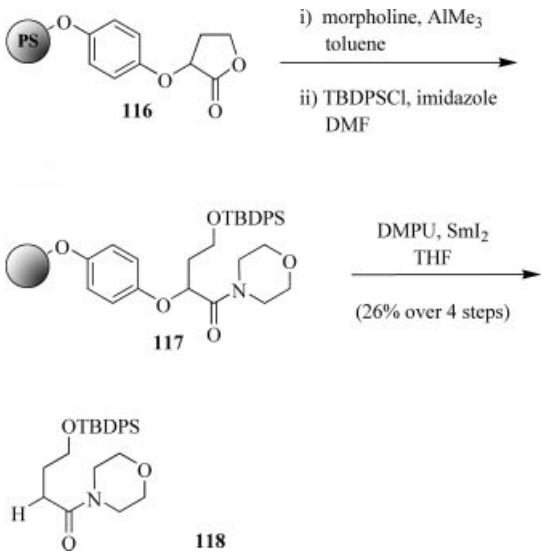
Scheme 34.

aldehyde **114** underwent a Horner–Wadsworth–Emmons reaction on treatment with potassium carbonate to cyclise and simultaneously cleave the target macrocyclic lactone **115** (Scheme 35).



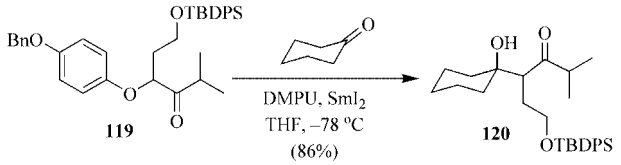
Scheme 35.

The second approach involving the generation of a nucleophilic species that can then be trapped by electrophiles is achieved by using electron-transfer reagents. For example, samarium(II) iodide is known to reduce α-alkoxycarbonyl compounds to produce a samarium enolate, which can then be trapped with a variety of electrophiles. Procter has exploited this approach to develop a new traceless linker strategy that is based upon a *para*-hydroxyphenol unit (**116**).[70] For example, α-bromo-γ-butyrolactone was loaded and then treated with morpholine to give the polymer-supported amide **117**. The resin-bound substrates could then be modified further and subsequently cleaved on treatment with samarium(II) iodide to leave a hydrogen residue at the cleavage site (as in **118**, Scheme 36).



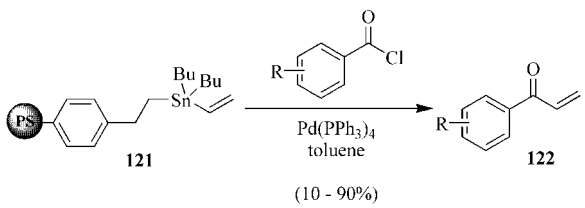
Scheme 36.

Whilst true diversity cleavage has not yet been realised, Procter has demonstrated the concept in model solution-phase studies, and the linker should find future applications in diversity-oriented SPOS. For example, the samarium(II) iodide mediated reaction of the benzyloxyphenol derivative **119** with cyclohexanone in THF gave the alcohol **120** (Scheme 37).

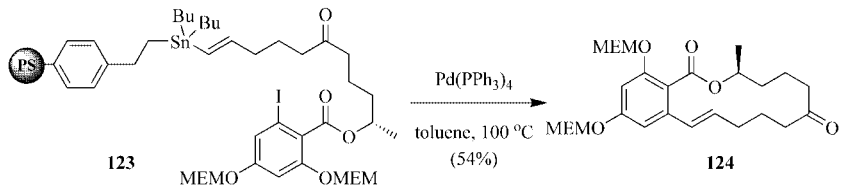


Scheme 37.

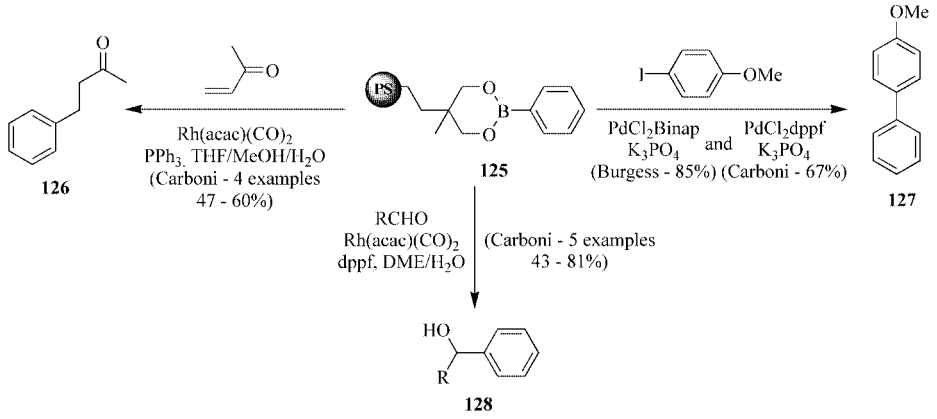
The concept of introducing diversity into compound libraries through transition-metal-mediated cleavage was introduced in Section 3.1 in the context of resin-bound electrophiles that can be cleaved with a range of nucleophiles. The converse is also true, and the transition-metal-promoted release of substrates from resin-bound pro-nucleophilic components is also possible with a range of electrophiles. One approach that is particularly amenable to solid-phase synthesis is the use of resin-bound organostannanes. Polymer-supported organotin compounds were introduced by Kuhn in 1994 and are particularly attractive reagents for synthetic chemists.[71] The main advantage of using a polymer-bound organotin reagent is that, following the Stille cleavage reaction, all tin by-products remain attached to the polymer. This allows for their simple and efficient removal by filtration and overcomes purification problems that have traditionally limited the use of organotin species in synthesis. Linker unit **121** was prepared by addition of a vinyl Grignard reagent to solid-supported tin chloride. Diversity cleavage of substrates was carried out using Stille-type cross-coupling reactions to leave, for example, a benzoyl group at the cleavage site of the molecule (**122**, Scheme 38).



Scheme 38.



Scheme 39.



Scheme 40.

The potential of such polymer-supported tin reagents has been shown by Nicolaou in the synthesis of the natural product (*S*)-zearalenone (**124**, Scheme 39).[72] In this case, the organotin linker unit **123** is bifunctional. Because the Stille cleavage reaction is intramolecular, the stannane unit functions as a cyclo-release traceless linker unit, but the opportunity for diversity cleavage also exists.

Despite the advantages of resin-bound organotin species, the toxicity of tin compounds creates a general reluctance to use Stille reactions when alternative methods are available. In particular, the availability of less toxic organoboronates has led to the Suzuki reaction becoming the method of choice for such transition-metal-catalysed cross-coupling reactions. The immobilised boron-based linker **125** was first prepared by Burgess through standard peptide coupling techniques, and cleavage of aromatic groups using Suzuki chemistry afforded biphenyls **127** (Scheme 40).[73] An advantage of this approach is that the pseudo-high-dilution conditions of solid-phase chemistry minimise the homo-coupling of the boronic acid that is commonly observed in solution-phase Suzuki reactions. Moreover, given the increasing role of boronic acids in synthesis, it is not surprising that other cleavage strategies are also possible. For example, Carboni reported a similar linker unit and showed cleavage by rhodium-catalysed nucleophilic addition to enones to give **126** and to aldehydes to give **128** as alternative ways of introducing diversity into target molecules.[74]

3.3 Other Diversity Linker Units

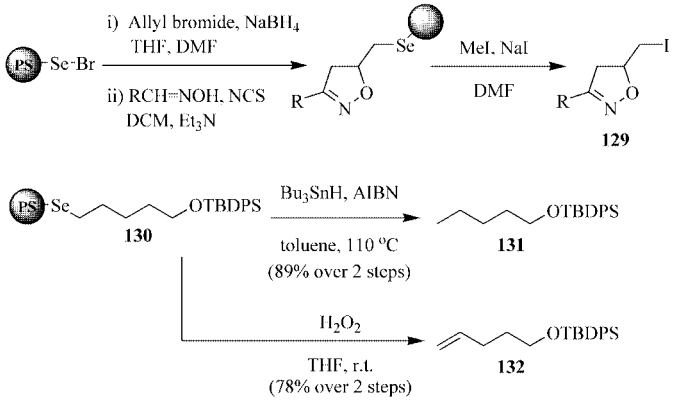
In Sections 3.1 and 3.2 we have shown a large number of linker units that use conventional ionic reactions to achieve diversity cleavage by a range of either nucleophiles or electrophiles. However, there are other linker units for which cleavage does not clearly fall into either category and these are discussed below.

3.3.1 Cleavage by a Radical Reaction

Building on the many applications of sulfur (thioether) linkers, both selenium and tellurium linkers have been reported, although there appears to be no significant advantages to the use of the latter.[75] These selenium linkers are extensively discussed in Procter's review and have been shown to be amenable to a number of different cleavage protocols.[17] Whilst simple nucleophilic cleavage with iodide is possible following quaternisation with MeI to give the iodo derivatives **129**,[76] the lability of an sp^3 C–Se bond to radical reduction (cf. Aryl C–Se bond) permits radical-mediated cleavage to be undertaken. The first selenium linker unit to exploit this observation was a traceless linker developed by Ruhland, in which the reaction with Bu_3SnH and AIBN afforded an unsubstituted alkyl group at the point of attachment.[77] This approach was simultaneously exploited by Nicolaou with the selenium diversity linker **130**.[78] The protected selenopolystyrene-bound alcohol **130** underwent radical cleavage to leave a hydrogen residue at the cleavage site (**131**). Alternatively, oxidation of **130** gave the corresponding selenium oxide, which underwent spontaneous elimination at room temperature to give the alkene **132** (Scheme 41).

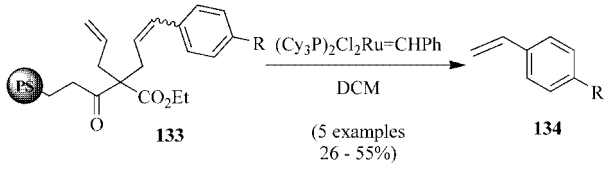
3.3.2 Cleavage by Ring-Closing Metathesis

Ring-closing metathesis has been recognised as an exceptionally mild process, tolerant of a broad range of functionality. Consequently, it has found wide use in various library



Scheme 41.

synthetic strategies, including cleavage processes. In 1997, Peters and Blechert introduced a cyclo-release diversity linker unit **133**, which utilises ring-closing metathesis to leave an alkene at the cleavage site of the molecule.[79] Cleavage was demonstrated by a ring-closing-metathesis reaction with Grubbs' catalyst to leave an alkene at the cleavage site in **134** (Scheme 42).



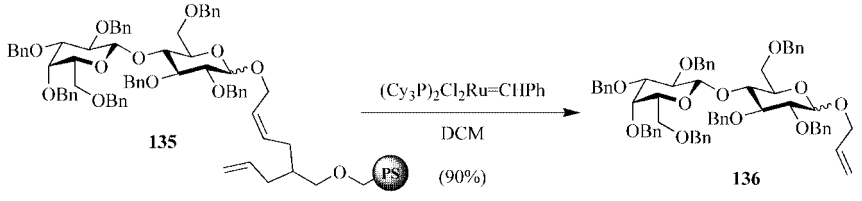
Scheme 42.

This linker unit has found widespread use in solid-phase synthesis and has recently been utilised by Knerr and Schmidt in the synthesis of oligosaccharides (Scheme 43).[80] The polymer-bound sugar **135** was cleaved by means of Grubbs' catalyst to leave an allyl group at the cleavage site in the target molecule **136**.

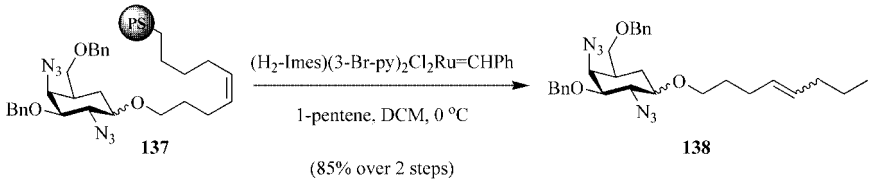
More recently, Seeberger has expanded on this concept and cleaved sugars from solid supports using cross-metathesis.[81] For example, the resin-bound sugar **137** was cleaved by an olefin cross-metathesis reaction to leave an unsaturated alkyl chain at the cleavage site ready for oligosaccharide synthesis (see **138**, Scheme 44). This is a useful development in metathesis-cleavable linker units as it demonstrates that diversity can be introduced by using a range of alkenes in an intermolecular reaction rather than limiting it to a cyclo-release process. Given the potential of cross-metathesis, many further examples of this chemistry can be expected in the future.

3.3.3 Cleavage by Diels–Alder Reactions

The use of [4+2] cycloaddition reactions with concomitant aromatisation as a means of introducing diversity during cleavage has been reported by Craig.[82] The polymer-bound *o*-quinodimethane precursor **139** can be considered as a resin-bound masked diene and a substrate for Diels–Alder type cycloaddition reactions. Diversity cleavage was demonstrated by treating **139** with a number of dienophiles to give a range of cycloaddition products (Scheme 45). For example, reaction with trichloroacetonitrile, benzoquinone and dimethylacetylene dicarboxylate gave 3-(trichloromethyl)isoquinoline (**140**), 2,3-naphthoquinone (**141**) and dimethyl naphthalene-2,3-dicarboxylate (**142**), respectively. This range of products highlights the potential for this linker unit to be used in the preparation of a library of structurally diverse products from a common polymer-

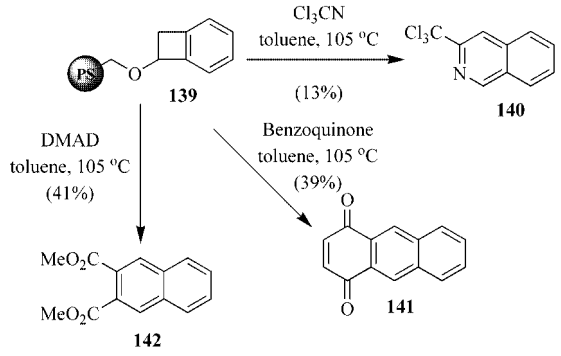


Scheme 43.



Scheme 44.

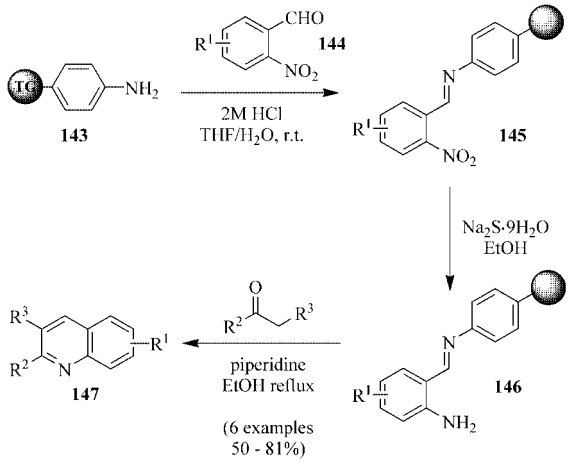
bound intermediate. Given the simplicity of the approach, such a strategy can be expected to find a number of applications in the future.



Scheme 45.

3.3.4 Cleavage by Friedländer Reactions

Levacher has adapted the Friedländer condensation used for the preparation of quinolines to solid-phase synthesis.[83] Initially the nitrobenzaldehydes **144** were condensed onto the resin-bound aniline **143** to give the polymer-supported imines **145**. The nitro group was then reduced to the corresponding aniline **146**, and Friedländer condensation with a range of ketones provided easy access to a set of quinolines **147** that contain 3 points of diversity. Considering the ease with which diversity can be introduced to the quinoline scaffold when using this approach, it has potential application in the construction of large libraries of quinoline and other azaheterocycles (Scheme 46).



Scheme 46.

4 Conclusions

In summary, the last few years have seen enormous creativity applied to the development of a large range of diversity linker units for use in solid-phase organic synthesis. These units enhance the process of library synthesis, enabling a quicker and more effective exploration of compound space. As a result of this, diversity linker units are already proving to be powerful tools in the arsenal of the solid-phase organic chemist and will continue to have an exciting future in the preparation of compound libraries. However, whilst many of the linkers described above are effective, in many cases they exhibit considerable substrate dependence, and consequently, there is an ongoing need for new and more versatile examples to be developed. The recent developments in the application of cross-metathesis and other transition-metal-mediated diversity cleavage strategies will play a prominent part in this process.

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