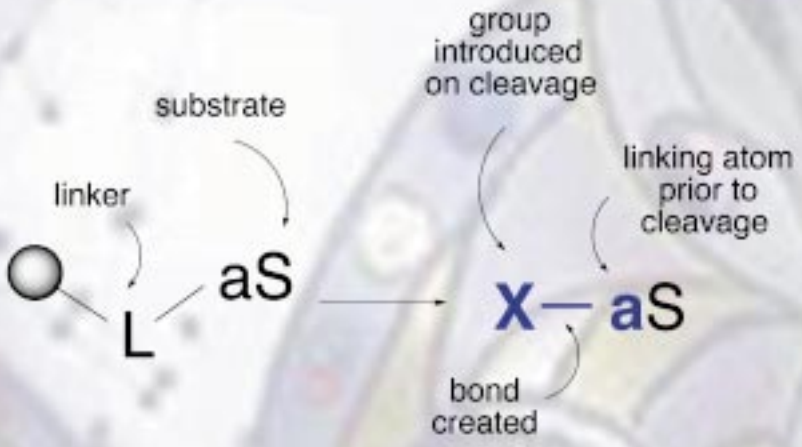
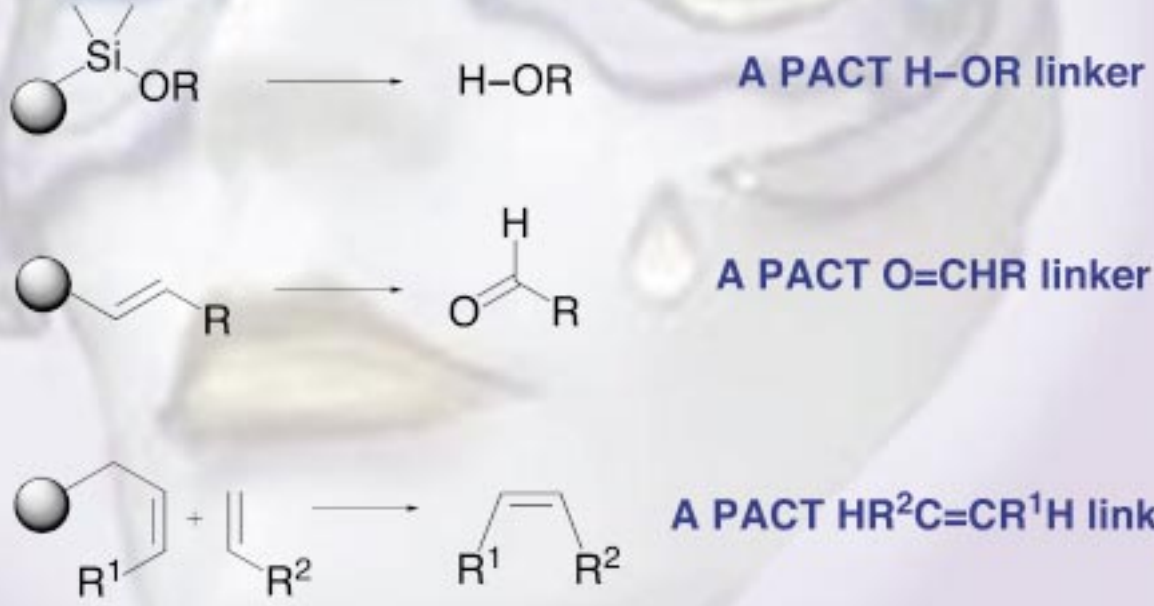
# A Venetian Carnival in Solid-Phase Synthesis? Traceless Linkers Remain Incognito!

## The Nomenclature Explained




The **P**oint of **A**ttachment of the substrate S is **C**onverted **T**o X-a:

**PACT X-a**

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# Tracelessness Unmasked: A General Linker Nomenclature

**Alex C. Comely* and Susan E. Gibson* (née Thomas)**

Nowadays it is rare to find an issue of a major chemistry journal without at least one article on solid-phase synthesis. This is hardly surprising: the technique promises an end to arduous work-up procedures and the ability to facilitate the creation of vast libraries of compounds using combinatorial techniques. No longer is the technique only of interest to those involved in peptide synthesis: an enormous variety of product classes have now been prepared on and isolated from the solid phase. It is the "linker" which is the focus of this article. The linker's ultimate function is to release a product from the support into solution: it does this, without exception, with a chemical change to the product at the former linkage site. Some linkers, apparently, are "traceless". But what, in fact, is "tracelessness"? Twenty years ago, in a climate where cleavage of a linker resulted in formation of a polar carboxylic acid as the vestige of the support, the concept was attractive. Today the chemist is faced with a myriad of novel linkers which have the ability to release products bearing most major functionalities at the former linkage site and we will argue here that the term "traceless", although currently in widespread use, is meaningless. Instead, we propose a new categorization of linkers based on the functionality they release upon cleavage, and suggest a nomenclature to underpin this categorization. We anticipate that the article will also serve to highlight areas of linker technology in need of further research.

**Keywords:** combinatorial chemistry · solid-phase synthesis · traceless linkers

## 1. Introduction

The seeds of Merrifield's pioneering solid-phase peptide synthesis have found fertile soil both in the academic world and the pharmaceutical industry.[1] Indeed, the years since its invention have seen wide-ranging developments: for example, vast peptide libraries have been prepared and screened using the concept of combinatorial chemistry[1a–h] and the "mix and split method". These processes have been enormously facilitated by the advent of automation and progress in reaction monitoring. The preparation of other oligomers such as peptides, oligosaccharides, oligocarbamates, and peptide nucleic acids has been equally successful.

As drugs, however, peptides pose certain problems. Ready hydrolysis and low bioavailability limit their value, and the translation of a peptidic lead structure into a non-peptidic analogue is far from trivial. The chemical focus of research has hence diverged to accommodate the solid-phase synthesis of "small organic molecules" and therefore, inevitably, the greater demands imposed by general organic chemistry.[1i–o]

In terms of the chemistry performed on the polymer-bound substrate there can now be few reaction classes not at the chemist's disposal and the excellent reviews compiled annually by researchers at Organon[1p–r] are categorized with this in mind. Any solid-phase methodology, however, necessarily has one constraint: that the polymer–product adduct be unstable to a set of conditions which effect the product's cleavage and isolation.

This constraint leads us to, perhaps, the most recent arena of research. The linker, the structural motif which temporarily joins the polymeric support and the substrate under manipulation, is of crucial importance.[1s–z] Not only must it tolerate the conditions used to elaborate the substrate, it must cleave under conditions mild enough not to affect the product's integrity. Unfortunately, such a proviso rules out a universal linker, namely, one suitable to every application, such that a catalogue of possible linkers is required containing one suitable for any synthetic sequence.

The linker clearly prescribes the revealed functionality at the former linkage site (the vestigial functionality) of the product as it is liberated. A legacy of solid-phase peptide synthesis is the release of carboxylic acids or amides from an ester- or amide-bound substrate. While entirely appropriate in peptide synthesis, this polar functionality is not always

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desirable in a more general arena. Efforts to address this problem have, in recent years, stimulated the evolution of so-called "traceless linkers".

*Traceless Linkers*

A survey of the literature in this area will quickly betray a confusion, however. What, in fact, is "tracelessness"? The term refers to some quality of a liberated product, but opinion clearly differs and three quite distinct definitions are in current use. These can be illustrated using the classification of linker types depicted schematically in Figure 1. The first definition of a traceless linker (Type A), and that primarily cited by the chemical community, refers to the introduction of a hydrogen atom at the former linkage site, be this onto an alkyl- or aryl-bound scaffold. In the face of the ubiquity of this C–H "functionality" the definition is, perhaps, justified. However, slow and incremental deviation from this conceptual "ideal" leads us to the quagmire of what "tracelessness" is to most authors in the field. The conceptual "hydrogen" definition is now so dilated as to embrace the formation of alkenes, amines, heteroarenes, ethers, alcohols, aldehydes, ketones, and even the carboxylic acid derivatives that the new technologies originally intended to avoid. Perhaps in the sense that the former linkage site now bears no resemblance to the linker prior to cleavage it is "traceless", but it is not easy to see how the term "traceless" remains meaningful or even valid.

A second definition of tracelessness has been attributed to linkers which belong to Type B in Figure 1, whereby cleavage results, usually from an aromatization or amine quaternization process, in what may be perceived as an overall reduction in the level of functionalization. For linkers that result in a chemical or connectivity change at the linkage site, this is arguably the strongest contender for the "traceless" title.

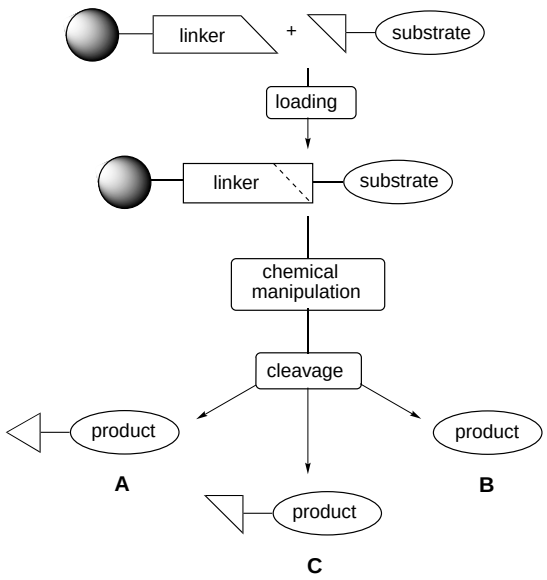


Figure 1. A schematic representation of the three linker types. Type A: Different functionality is incorporated on cleavage. Type B: The product has a reduced level of functionalization relative to the substrate prior to cleavage. Type C: The functionality released on cleavage is the same as the functionality loaded onto support.

Protecting group linkers, namely those which operate without overall chemical change at the linkage site, constitute a third category defined in the literature as "traceless": these belong to Type C linkers in Figure 1 and are "traceless" in that the substrate linkage site before and after immobilization is identical.

"Tracelessness" has also been defined on occasions in terms of ubiquity: if, for example, cleavage creates an aromatic C–H bond on a monosubstituted arene product, the linker is

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"traceless" in the sense that the new C–H bond is indistinguishable from the four already present.

Confronted by such an amorphous definition, it is of no surprise that authors can so easily hoist the "traceless" flag over novel linker technologies. Nomenclature is essential to the efficient communication of ideas and a more rigid and comprehensible terminology will clear the mists from a rather cloudy aspect of this very important field.

*A Solution…*

The ultimate function of the linker is to allow cleavage from the support. Regardless of the mechanism of release or the sequence history it will always be possible to define a linker according to the vestigial functionality of the liberated product. A categorization of linkers based on this assertion, where the spotlight falls only on the product functionality created on release from a support, will allow an author simply and precisely to define a linker. Moreover, such a classification should facilitate application to a specific chemical target: a linker may be chosen in light of the desired (or, indeed, tolerable) vestigial functionality—not an easy undertaking at present.

In this article we present such a categorization and, in addition, propose a nomenclature to facilitate its use. The following example is given to illustrate this.

*…And a New Nomenclature*

In the general transformation depicted in Scheme 1, the linker is cleaved to liberate an alkyl product bearing a hydrogen atom at the former linkage site (marked by an asterisk as it will be throughout this article). The *P*oint of *A*ttachment is *C*onverted *T*o (PACT) an H–Csp$^3$ bond. Hence, the linker illustrated can be described as a PACT H–Csp$^3$ linker or a PACT H–CR$^1$R$^2$R$^3$ linker.


PACT H-Csp$^3$ linker
PACT H-CR$^1$R$^2$R$^3$ linker

PACT H-Csp$^3$ vestige
PACT H-CR$^1$R$^2$R$^3$ vestige

Scheme 1. An illustration of the nomenclature for a general cleavage transformation where the point of attachment is converted to an alkyl C–H bond: the "PACT H–Csp$^3$" or "PACT H–CR$^1$R$^2$R$^3$" linker.

Either or both of these descriptors can be used where appropriate; indeed, any expression which accurately describes the molecular structure involved might be used. Central to our approach, however, is the dash representing the bond (–), which indicates the new bond formed to the linking atom or atoms. To the right of the bond is the substrate atom at the former linkage site and to its left is the atom introduced to the substrate at this site.

In terms of the released product, the linker can be accurately defined by the functionalities connected by this new bond. Furthermore, from the complexity or length of this term (which will represent the structural changes incurred on cleavage and any functionality required for cleavage), a broad assessment of the linker's generality can be made. By using the same nomenclature the product can be defined in terms of the linker from which it was released by reference to a PACT H–Csp$^3$ vestige or PACT H–CR$^1$R$^2$R$^3$ vestige.

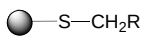
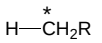
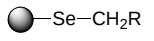
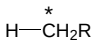
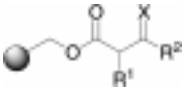
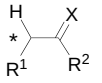
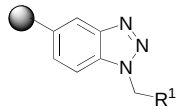
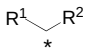
## 2. Alkane Formation

### 2.1. Aliphatic C–H Bond Formation

*PACT H–CR$_3$ or PACT H–Csp$^3$ Linkers*

The introduction of an aliphatic hydrogen atom on cleavage from the polymeric support offers arguably the most benign and general vestige: a small, ubiquitous atom, whose influence on biological or chemical activity is minimal. In addition, the linking system expends only one site of molecular diversity. Reports of linkers of this kind which may be classified as PACT H–Csp$^3$ or H–CR$_3$ linkers are summarized in Table 1, entries 1–3.

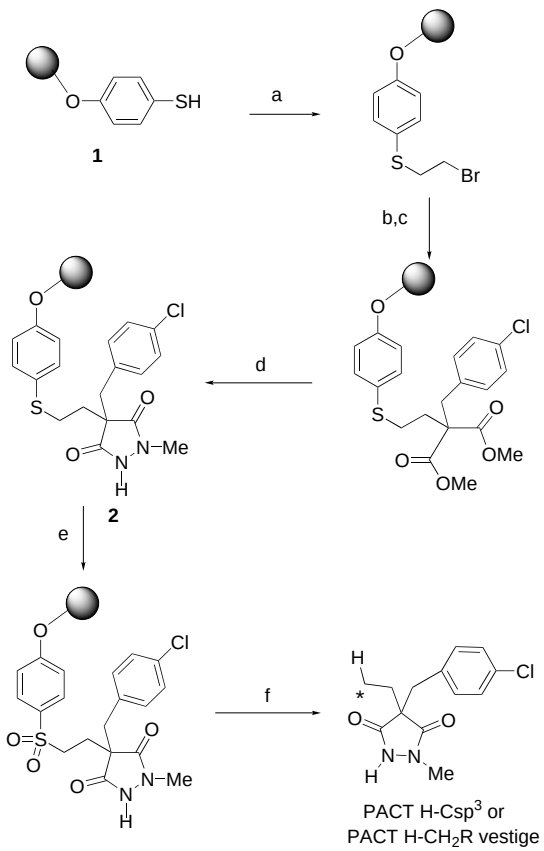
Table 1. Aliphatic C–H and C–C bond formation: PACT H–Csp$^3$ and PACT Csp$^3$–Csp$^3$ linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [2a–h] |
| 2 |  |  | [3a,b] |
| 3 |  |  | [4a–e] |
| 4 |  |  | [5] |

An example of a linker of this type (Table 1, entry 1)[2a–c] is the sulfide system devised by Janda and co-workers (Scheme 2). In an application directed towards the synthesis of a class of heterocycles used in the treatment of rheumatoid arthritis and other diseases thiophenol **1** was alkylated with symmetrical alkyl dihalides. Dialkylation of dimethyl malonate with the polymeric halide and a benzylic halide sets the stage for ester hydrolysis and heterocycle formation with methyl hydrazine to deliver the polymer-bound product **2**. Chemoselective sulfide oxidation with $KHSO_5$ was followed by reductive release (Na/Hg) of the methyl-bearing product from the PACT H–$CH_2$R linker.

This approach is not limited to methyl formation (PACT H–$CH_2$R), but also extends to the mid-chain methylene unit (PACT H–$CHR_2$).[2d] Earlier systems from the same research group obviate the thioether oxidation step,[2e,f] but the Raney nickel hydrogenative cleavage used is clearly incompatible with reduction-sensitive groups such as alkenes, alkynes, or epoxides. Analogous chemistry is reported by Sucholeiki and Forman[2g,h] in which formation of a benzylic C–H bond accompanies photolytic release.

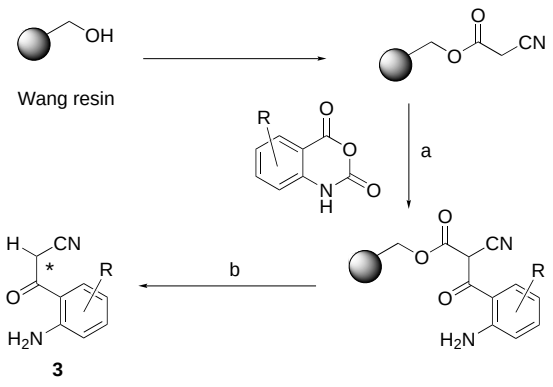
A selenium equivalent is described both by Ruhland et al.[3a] and Nicolaou et al.[3b] (Table 1, entry 2) in which a




Scheme 2. PACT H–$CH_2R$ or PACT H–$Csp^3$ linker. Synthesis of 3,5-pyrazolidinediones on polyethylene glycol (PEG) demonstrating polymer cleavage by reductive desulfonylation with sodium amalgam.[2a–c] a) $BrCH_2CH_2Br$, $Cs_2CO_3$; b) $CH_2(CO_2Me)_2$, $Cs_2CO_3$; c) *p*-$Cl(C_6H_4)CH_2Cl$, $Cs_2CO_3$; d) NaOH, $MeNHNH_2$; e) $KHSO_5$; f) Na/Hg, $Na_2HPO_4$.

haloalkane is directly loaded onto a tethered $SeB(OEt)_3^-Na^+$[3a] or SeLi[3b] species. Ruhland et al illustrate the linker's use with the construction of a small library by means of the Mitsunobu reaction. Homolytic cleavage of the Se–C bond was brought about with tributylstannane/azobisisobutyronitrile (AIBN).

Decarboxylative aliphatic C–H bond formation (Table 1, entry 3) can be attributed to Patchornik and Kraus,[4a] who in 1970 disclosed the monoacylation of tethered esters and decarboxylative release from the support. Ganesan and coworkers have recently demonstrated the principle (Scheme 3)




Scheme 3. PACT H–$CHR_2$ or PACT H–$Csp^3$ linker. Synthesis of $\beta$-ketonitrile displaying a decarboxylative release.[4b] a) $NEt_3$; b) 70% TFA.

with a synthesis of $\beta$-ketonitriles **3**.[4b,c] C-Acylation of the active methylene group precedes a trifluoroacetic acid promoted release and concomitant loss of $CO_2$.

### 2.2. Aliphatic C–C Bond Formation

*PACT $R_3C$–$CR_3$ or PACT $Csp^3$–$Csp^3$ Linkers*

An alternative approach to the release of aliphatic systems is the formation of a C–C bond. Schiemann and Showalter described the displacement of products from a benzotriazole linker using Grignard reagents as the carbon nucleophiles (Table 1, entry 4).[5]

## 3. Alkene Formation

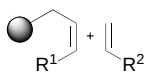
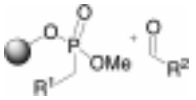
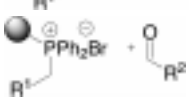
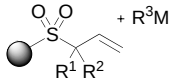
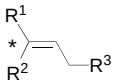
### 3.1. Mid-Chain Alkene Formation

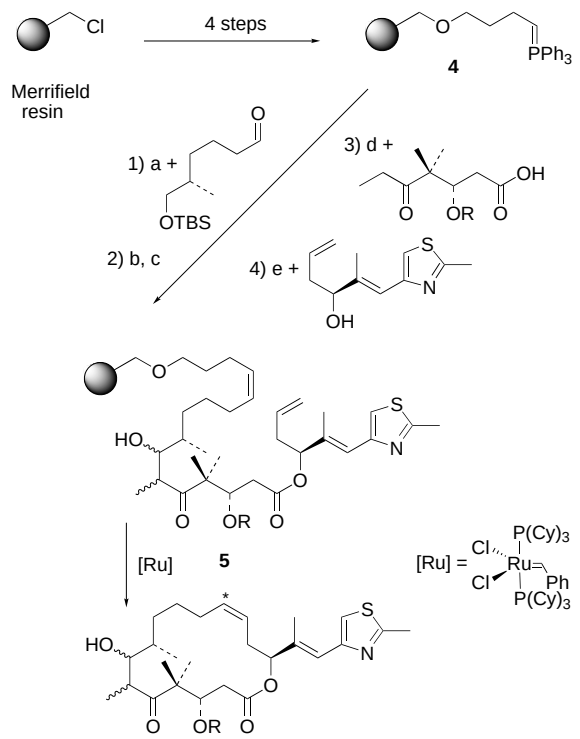
*PACT $R_2C$=$CR_2$ or PACT $Csp^2$=$Csp^2$(alkene) Linkers*

There exists numerous linking methods to achieve a carbon–carbon double bond upon cleavage should this motif be required or tolerable in a product. To date, however, the systems with this capacity are generally more structurally complicated than those described hitherto; between two and four sites of molecular diversity are expended, depending on the process employed. From a different perspective, of course, release can be said to be accompanied by an increase in molecular diversity. The "double" dash in the descriptor for these linkers, PACT $R_2C$=$CR_2$, indicates the formation of the double bond in the new alkene.

In a strategy for the solid-phase synthesis of epothilone A Nicoloau et al. described a ring-closing metathesis (RCM) approach[6a] to carbon–carbon double-bond generation on product release (Table 2, entry 1). The structural requirements for RCM, namely two alkene units, are incorporated in a five-step process from the ylide **4** (Scheme 4). Exposure of diene **5** to Grubbs' ruthenium catalyst effects product release and alkene formation. Nicoloau et al., in fact, proceeded to epoxidize this functionality, and a substantial library of epothilone analogues has been prepared following this final solution-phase reaction.[6b] Similar thinking is to be found

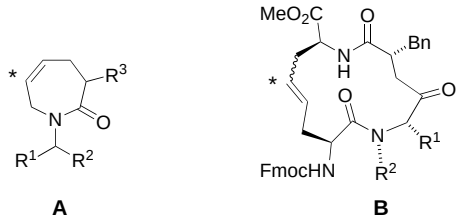
Table 2. Alkene formation: PACT $R_2C$=$CR_2$ or PACT $Csp^2$=$Csp^2$(alkene) linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [6a–f] |
| 2 |  |  | [7a,b] |
| 3 |  |  | [8a–f] |
| 4 |  |  | [9a,b] |



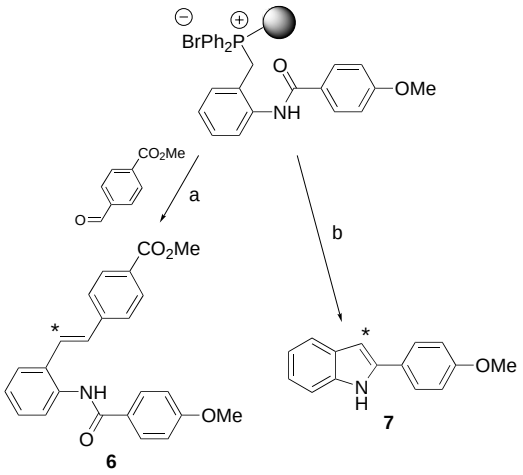

Scheme 4. PACT C=C or PACT $Csp^2$=$Csp^2$ linker. Synthesis of epothilone A demonstrating a ring-closing metathesis strategy.[6a] a) THF; b) HF · Py; c) $(COCl)_2$, DMSO, $NEt_3$; d) lithium diisopropylamide (LDA), $ZnCl_2$; e) *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP). [Ru] = Grubbs' catalyst.

behind the preparation of Freidinger lactams (**A**) by Piscopio et al.[6c,d] and van Maarseveen et al.[6e] Blechert and co-workers have also used the process to generate the tetrapeptide-derived macrocycle **B** through a PACT C=C or PACT $Csp^2$=$Csp^2$ linker by ring-closing metathesis.[6f]




Entries 2 and 3 of Table 2 represent the Horner–Wadsworth–Emmons[7a,b] and Wittig reactions,[8a–f] respectively. Nicoloau et al., for example, have recently reported an intramolecular ketophosphonate reaction which generates macrocyclic lactones and the precursors to a (DL)-muscone library.[7a] Hughes' phosphonium salt system[8a] (Scheme 5) is readily available from polymer-bound triphenylphosphane and a benzyl bromide. An intermolecular Wittig reaction affords stilbenes such as **6** whereas intramolecular cleavage to generate indoles of type **7** can be induced under anhydrous conditions.

An allylic sulfone linker created by Kurth and co-workers (Table 2, entry 4) results in the generation of trisubstituted alkenes and cyclobutylidenes.[9] Nucleophilic displacement of




Scheme 5. PACT C=C or PACT $Csp^2$=$Csp^2$ linker. Application of the Wittig reaction to product cleavage and alkene formation.[8a] a) NaOMe; b) KO*t*Bu.

the products was effected by allylic alkylation with Grignard reagents[9a] or under milder and more general palladium catalysis[9b] (PACT $RH_2CHCsp^2$=$Csp^2R_2$).

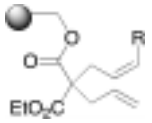
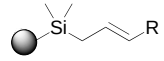
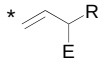
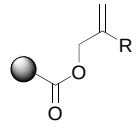
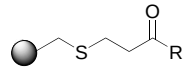
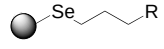
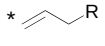
### 3.2. Formation of Terminal Alkenes

*PACT $H_2C$=C or $H_2Csp^2$=$Csp^2$ and PACT C=$CH_2$ or $Csp^2$=$Csp^2H_2$ Linkers*

Products possessing a terminal alkene functionality are accessible through several linking systems. Not unlike those in the previous section, these also require a high degree of structural complexity for cleavage to occur; unless the structural configurations summarized in Table 3 are specifically sought, these linkers are perhaps less useful than, for example, the PACT H–$CR_3$ ones.

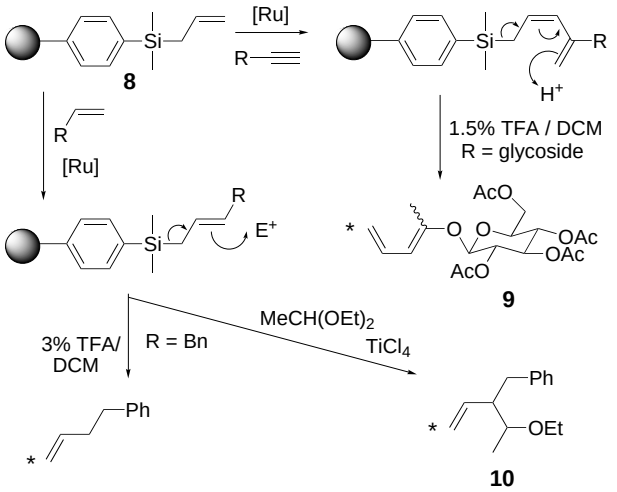
Complementary to RCM cleavage is a system shown in Table 3, entry 1. The product is released bearing the mono-

Table 3. Terminal alkene formation: PACT $H_2C$=C or $H_2Csp^2$=$Csp^2$ and PACT C=$CH_2$ or $sp^2$=$Csp^2H_2$ linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [10a,b] |
| 2 |  |  | [11a,b] |
| 3 |  |  | [12a,b] |
| 4 |  |  | [13a,b] |
| 5 |  |  | [3b] |

substituted alkene (PACT $H_2C{=}C$) while the product resulting from ring closing remains tethered to the support: Peters and Blechert have thus produced an array of styrene derivatives[10a] and Knerr and Schmidt have used the linker for the release of oligosaccharides in the form of their 1-*O*-allyl derivatives.[10b]

Blechert and co-workers have also developed a novel allylsilyl linker strategy that is suitable for electrophilic cleavage (Table 3, entry 2). The allyldimethylsilylpolystyrene resin **8** (Scheme 6) is prepared by the addition of allyldimethylsilyl chloride to lithiated polystyrene and undergoes cross-metathesis using Grubbs' ruthenium catalyst with both

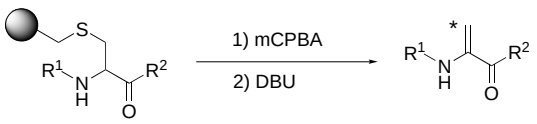



Scheme 6. PACT $C{=}CH_2$ or PACT $Csp^2{=}Csp^2H_2$ linker. An allylsilyl system which undergoes electrophilic cleavage to produce terminal alkenes[11b] and dienes.[11a] [Ru] = Grubbs' catalyst; DCM = dichloromethane.

alkynes[11a] and alkenes.[11b] For the former, protodesilylation under extremely mild conditions affords terminal 1,3-dienes such as the glycoside derivative **9**. Formation of a further C–C bond on product release is also viable: cross-metathesis of **8** with an alkene followed by addition of the electrophile derived from 1,1-diethoxyethane and $TiCl_4$ delivers **10**.[11b]

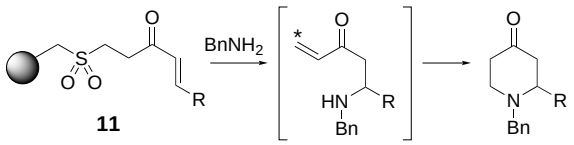
In a third approach proposed by the same research group (Table 3, entry 3) the vestigial functionality after cleavage is also the functionality required for cleavage to take place. Further structural diversity is introduced during a palladium(0)-catalyzed nucleophilic cleavage.[12a] The reaction with both carbon and nitrogen nucleophiles has been demonstrated: Brown and Fisher, in fact, have generated pyrrolidines through cyclization with a pendant secondary amine as the nucleophile.[12b]

*β*-Elimination of a sulfone prepared by oxidation of a sulfide tether (Table 3, entry 4) can also afford a terminal alkene. Yamada et al. have applied this technology to a synthesis of dehydroalanine derivatives (Scheme 7).[13a] Both the N- and C-termini of the tethered cysteine residue remain open for modification, and the intermediate sulfide linker is robust to most reaction conditions; oxidation, of course, provides the sulfone which readily undergoes elimination in the presence of a base.




Scheme 7. PACT $C{=}CH_2$ or PACT $Csp^2{=}Csp^2H_2$ linker. Sulfone elimination delivers dehydroalanine derivatives.[13a] mCPBA = *m*-chloroperbenzoic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

A series of substituted piperidin-4-ones was similarly prepared by Barco et al.[13b] whose enones **11** (Scheme 8) undergo a Michael addition with benzylamine. The resultant tethered secondary amine induces elimination and release,




Scheme 8. PACT $C{=}CH_2$ or PACT $Csp^2{=}Csp^2H_2$ linker. Synthesis of piperidine-4-ones: benzylamine effects sulfone elimination and a tandem aza-Michael addition.[13b]

and the desired product is isolated after a second, solution phase, Michael addition to the liberated enone. Although not implicit in the isolated piperidinone product, the specific linker depicted in Scheme 8 is most practicably described in terms of the alkene it releases into solution (PACT $C{=}CH_2$). That the alkene is an intermediate which participates in a further solution-phase transformation reflects the imagination of the authors and not the general chemistry of the linker.

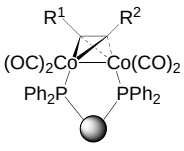
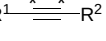
The selenium linker described by Nicolaou et al. in Section 2.1 has also been applied, under different cleavage conditions (hydrogen peroxide solution), to the oxidative release of terminal alkenes (Table 3, entry 5).[3b]

## 4. Alkyne Formation

*PACT Csp≡Csp or PACT RC≡CR Linker*

Until recently there existed no linking technology with the capacity to release alkyne functionality on cleavage. In a novel approach to a protecting group linker of Type C (see Figure 1) Gibson and co-workers describe the immobilization of alkyne substrates to polymer-bound triphenylphosphane through π interactions to dicobalt carbonyl complexes (Table 4). The products are liberated by aerial oxidative decomplexation with a PACT Csp≡Csp vestige.[14]

Table 4. Alkyne formation: PACT C≡C or PACT Csp≡Csp linker.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [104] |

## 5. Arene and Heteroarene Formation

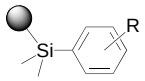
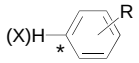
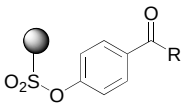
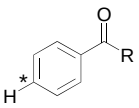
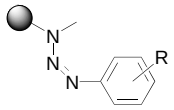
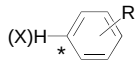
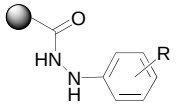
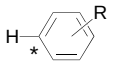
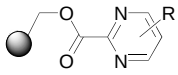
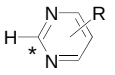
### 5.1. Aromatic C–H Bond Formation

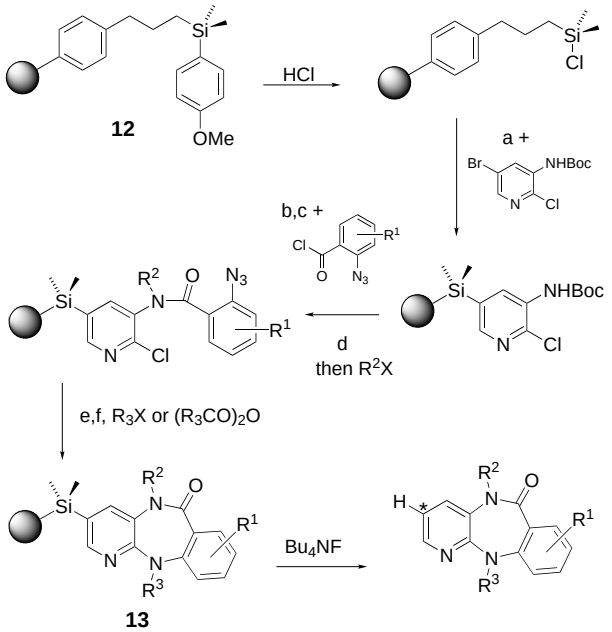
*PACT H–Csp²(arene) Linkers*

Extremely prevalent in organic compounds is the arene or heteroarene system, and the literature details a variety of linkers which release a compound bearing an aromatic C–H bond as the only vestige of the support. Analogous in many ways to those described for alkyl C–H bond formation, these systems expend only one site of molecular diversity and have been applied to phenyl, pyridine, thiophene, and quinazoline substrates.

The seminal report of Plunkett and Ellman of a silicon-based system[15a] (Table 5, entry 1) continues to inspire much research;[15b–q] an example of their work is represented in Scheme 9.[15b] The stable silyl resin **12** is readily prepared in two steps from bromophenyl-substituted polystyrene; activation by brief exposure to $HCl/CH_2Cl_2$ gives an unmasked silyl chloride which will undergo coupling with a metalated arene derivative. Three elements of diversity are incorporated by means of the addition of 2-azidobenzoyl chloride, amide alkylation, and, following reduction with azide and tricycle formation, a second N-alkylation. Cleavage of the tethered product **13** and aromatic C–H bond formation is accomplished with tetrabutylammonium fluoride (TBAF). (The silicon system has also been translated from the solid to the fluorous phase.[15p,q] Curran and co-workers have described the Ugi and Biginelli multicomponent condensations for the preparation of fluorine-tagged benzoylated amino acid amides.[15q] Desilylation was effected with TBAF, followed by separation of the arene product with a simple liquid–liquid extraction.)

Table 5. Aromatic C–H bond formation: PACT H–Csp²(arene) linkers.

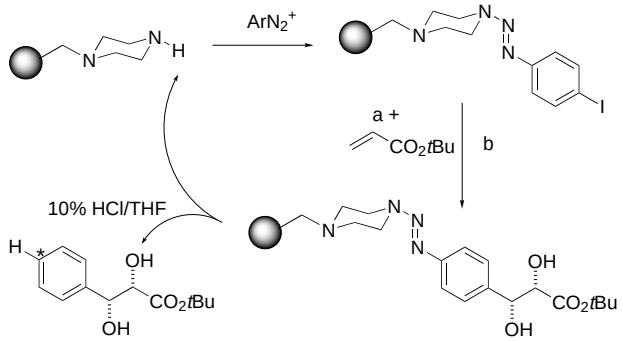
| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [15a–q] |
| 2 |  |  | [16] |
| 3 |  |  | [17a–c] |
| 4 |  |  | [18a,b] |
| 5 |  |  | [19] |




Scheme 9. PACT H–Csp²(arene) linker. Synthesis of pyridine-based tricycles using a silicon linker for aromatic C–H bond formation.[15b] a) KH, BuLi; b) TFA; c) DCM, Py; d) lithiated acetanilide; e) $SnCl_2$, PhSH, $NEt_3$; f) TFA. Boc = *tert*-butoxycarbonyl.

Alternative conditions for the release from the support include treatment with 30–50% trifluoroacetic acid (TFA) in $CH_2Cl_2$[15c–f] or neat TFA.[15g,h] An electron-poor arene, however, requires extremely forcing conditions to effect *ipso* electrophilic substitution of silicon: anhydrous HF gas was applied by Plunkett and Ellman[15i] to the release of a benzodiazepine substrate. Replacement of silicon with the less acid-stable germanium derivative,[15i,j] though rather expensive, is one solution to this problem. Another solution, however, is offered by Wustrow and co-workers (Table 5 entry 2):[16] The aryl sulfonate system undergoes efficient Pd(0)-catalyzed reductive cleavage with electron-poor arenes.

An attractive linker is depicted in Table 5, entry 3.[17a–c] Not only robust and somewhat more accessible than the silicon linkers so-far reported, it liberates the regenerated resin upon product release. The piperazine resin depicted in Scheme 10

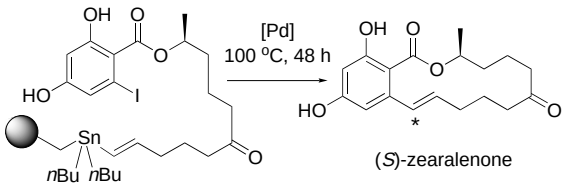



Scheme 10. PACT H–Csp²(arene) linker. A system boasting a recyclable resin for aromatic C–H bond formation.[17a] a) $Pd(OAc)_2$, $PPh_3$, $NEt_3$, DMF; b) AD-mix $\beta$.

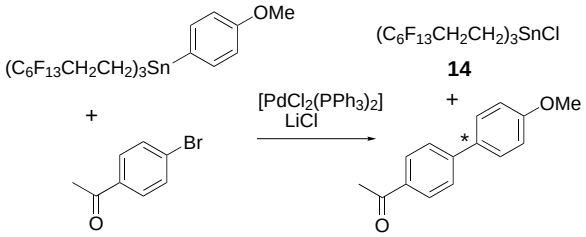
undergoes coupling with the arene diazonium salts derived from primary aromatic amines. A variety of Heck reactions and subsequent chemistry on the unsaturated substrate (including asymmetric dihydroxylation, Diels–Alder reactions, and palladium-catalyzed allylic substitution) have been carried out. Cleavage of the triazene with aromatic C–H bond formation was effected with acid. A similar linking system (Table 5, entry 4) from which release occurs by alcoholysis or aminolysis is an aryldiazene which is formed prior to cleavage by the oxidation of the arylhydrazide.[18a,b]

The decarboxylative C–H bond formation detailed in Section 2 has also been applied to an aromatic substrate (Table 5, entry 5).[19]

Interestingly, an additional facet of the arylsilane, arylgermane, and triazene linkers described above (Table 5, entries 1 and 3) is cleavage by electrophilic *ipso*-halogenation using ICl, $Br_2$, or NCS to obtain iodides, bromides, or chlorides, respectively (PACT X–$Csp^2$(arene)).




Scheme 11. PACT $Csp^2$(arene)–$Csp^2$(alkene) linker. A Stille coupling methodology resulting in diene or styrene derivatives on release.[20a]




Scheme 12. PACT $Csp^2$(arene)–$Csp^2$(arene) linker. Fluorous-phase synthesis of biarenes using the Stille coupling reaction.[20c]

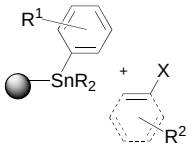
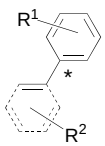
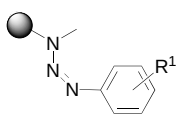
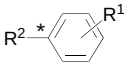
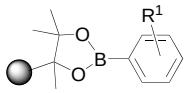
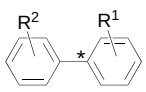
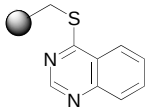
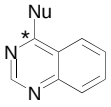
## 5.2. Aromatic C–$Csp^2$ Bond Formation

*PACT C–$Csp^2$(arene) Linkers*

The formation of a C–C bond on cleavage of a product from the resin does, perhaps, have advantages over simple C–H bond formation, in that a further degree of diversity is incorporated.

The Stille coupling reaction (Table 6, entry 1) has been applied to just this transformation.[20a–c] The system will not only deliver the styryl functionality as demonstrated by the synthesis of (*S*)-zearalenone by Nicolaou et al. (Scheme 11),[20a] but is equally well suited to diene, enyne, or biaryl formation.[20b] The fluorous phase approach also accommodates this chemistry very elegantly: Curran and Hoshino have prepared a variety of biaryls according to Scheme 12, wherein the tin chloride **14** is recovered in high yield and re-used following a simple extraction.[20c]

Table 6. Aromatic C–$Csp^2$ bond formation: PACT C–$Csp^2$(arene) linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [20a–c] |
| 2 |  |  | [21a,b] |
| 3 |  |  | [22] |
| 4 |  |  | [23] |

A Heck cross-coupling strategy using the triazene linker seen previously for aromatic C–H bond formation (see Table 5, entry 3) has been equally successful (Table 6, entry 2).[21a,b] Suzuki coupling has been applied to the macrocyclization/cleavage of $\beta$-turn mimetics containing a biaryl component (Table 6, entry 3).[22]

Nucleophilic displacement of a thioether tether from a quinazoline nucleus also results in aromatic $Csp^2$–C bond formation (Table 6, entry 4). Using such a linker Hennequin and Piva-Le Blanc have prepared oxindole quinazolines, which constitute a novel series of tyrosine kinase inhibitors.[23]

## 5.3. Aromatization

*PACT $Csp^2$–$Xsp^2$ and $Xsp^2$–$Csp^2$(arene/heteroarene) Linkers*

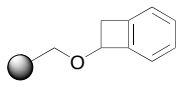
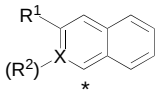
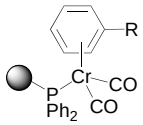
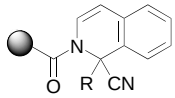
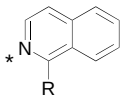
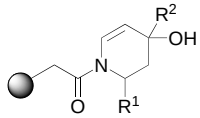
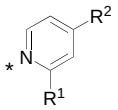
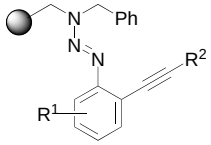
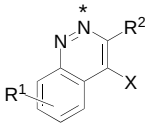
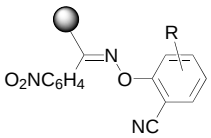
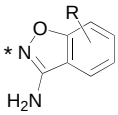
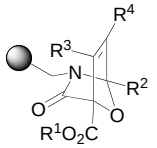
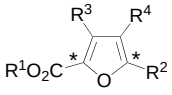
Numerous linking technologies have been elaborated for which product release is driven by an aromatization process (Table 7).

Employing a resin-bound *o*-quinodimethane (Table 7, entry 1) Craig et al. have demonstrated the principle in the synthesis of naphthalene and isoquinoline derivatives by means of both homo- and hetero-Diels–Alder reactions with dimethylacetylene dicarboxylate, benzoquinone, and trichloroacetonitrile as dienophiles.[24]

Analogous to the PACT Csp≡Csp linker described in Section 4, arenes have been immobilized onto a resin-bound phosphane through π interactions to a chromium dicarbonyl complex (Table 7, entry 2).[25] The ($\eta^6$-arene)-tricarbonyl chromium complexes are polymer-loaded under photolytic conditions and, following substrate manipulation, are released on decomplexation by aerial oxidation or refluxing pyridine.

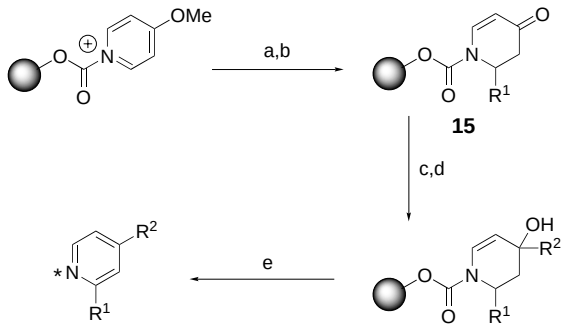
The preparation of isoquinoline-based compounds is represented by entry 3 of Table 7. The precursor to release is formed when resin-bound benzoyl chloride is treated with isoquinoline and trimethylsilyl cyanide (TMSCN); subsequent alkylation at C1 is a facile process and the product is released with a KOH-promoted Reissert hydrolysis. The

Table 7. Arenes released on aromatization: PACT $Csp^2$–$Xsp^2$ and PACT $Xsp^2$–$Csp^2$(arene/heteroarene) linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [24] |
| 2 |  |  | [25] |
| 3 |  |  | [26a,b] |
| 4 |  |  | [27] |
| 5 |  |  | [28] |
| 6 |  |  | [29] |
| 7 |  |  | [30a,b] |

linker is stabile to isoxazoline formation[26a] and Suzuki coupling.[26b]

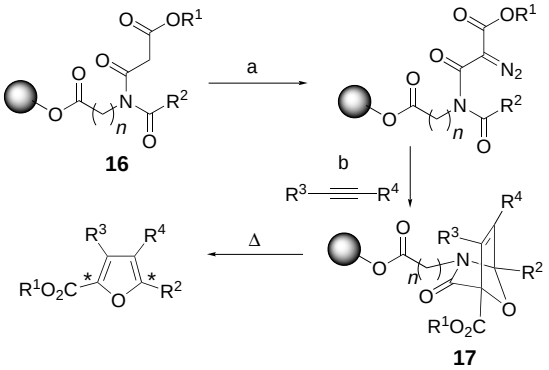
A technology proposed by Chen and Munoz (Table 7, entry 4) allows for the functionalization of pyridine analogues.[27] Successive alkylations, first to form the dihydropyridone **15** (Scheme 13) and then a 1,2-addition using an organocerium reagent afford an enamide alcohol, which, when treated with acid under oxidative conditions, aromatizes to release the product (PACT $Csp^2$–$Nsp^2$(pyridine)).




Scheme 13. PACT $Csp^2$–$Nsp^2$(pyridine) linker. Regioselective alkylations and an oxidative cleavage release of a pyridine derivative bearing no additional vestige of the polymer.[27] a) $R^1MgX$; b) $H_3O^+$; c) $CeCl_3$, $R^2MgX$; d) $H_3O^+$; e) TFA, $O_2$.

In a further demonstration of its versatility, the triazine linker seen twice previously favors cyclization in the presence of a suitable nucleophilic *ortho* substituent. Bräse et al. applied such thinking to the cyclization and release of cinnolines (Table 7, entry 5), wherein triazene-bound *ortho*-alkynylarenes were cyclized with aqueous HCl or HBr.[28] Not dissimilar is the acid-mediated cyclorelease of 3-aminobenzisoxazoles which has been shown to take place from the aryloxime polymeric precursor shown in Table 7, entry 6.[29]

The system depicted in Table 7, entry 7 allows for the liberation of tetrasubstituted furans by means of a cycloreversion/aromatization process.[30] The synthesis is illustrated in Scheme 14:[30b] diazotransfer of substrate **16**, synthesized on Wang resin in two steps, results in the diazoester onto which the rhodium(II)-mediated 1,3-dipolar cycloaddition with activated acetylenes is carried out. The cycloadduct **17** is isolable at ambient temperature such that cleavage may be effected by heating.




Scheme 14. PACT $Csp^2$–$Csp^2$(furan) linker. Rhodium(II) perfluorobutyramide (pfbm) mediated 1,3-dipolar cycloaddition and cycloreversion/aromatization to release furans.[30b] a) $MsN_3$, $NEt_3$; b) $Rh_2(pfbm)_4$.

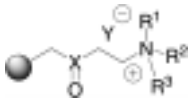
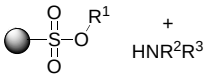
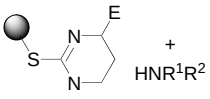
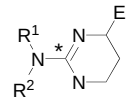
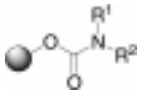
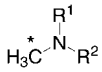
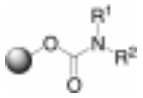
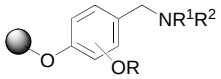
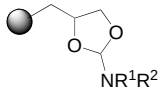
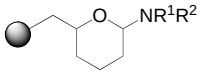
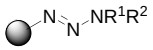
## 6. Amine Formation

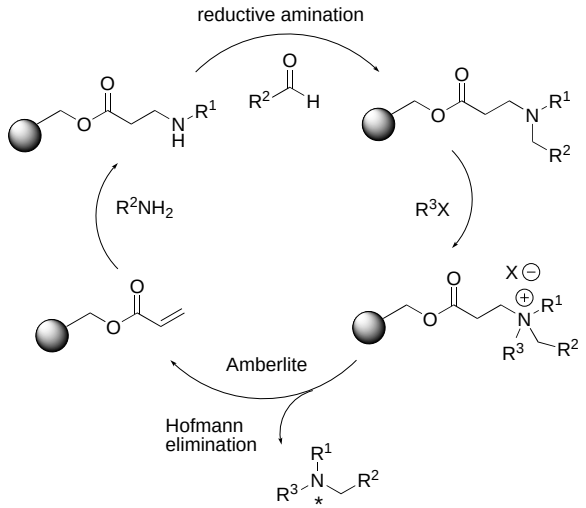
*PACT $NR_3$, PACT $R^1$–$NR^2R^3$, and PACT $(H–)_3CNR_2$ Linkers*

The incorporation of an amine on release from the resin may be effected in a variety of ways. Tertiary amines are a particularly widespread functionality in terms of drug discovery, and in particular are commonly found in drugs active within the central nervous system.

Entry 1 of Table 8 portrays an eliminative release first developed by Rees and co-workers:[31a–g] the absence of a dash from the descriptor for linkers of this kind (PACT $NR_3$) is indicative of a reduction in the nitrogen valence on cleavage (linker type B, Figure 1). The quaternary amine salt is constructed stepwise: first by an aza-Michael addition of a secondary amine to an acrylate-tethered resin and then quaternization with an alkyl halide allows for a Hofmann elimination in the presence of base, with the acrylate resin being regenerated in high purity. Murphy has elaborated the process by means of a reductive amination after the initial Michael addition (Scheme 15).[31c] Elimination is promoted by the ion-exchange resin Amberlite and a simple filtration from this novel two-resin system affords the products without need of further purification. Vinyl sulfone systems which operate

Table 8. Amine formation: PACT $NR_3$, $R^1$–$NR^2R^3$, and $(H-)_3CHR_2$ linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [31a–g] |
| 2 |  |  | [32a–c] |
| 3 |  |  | [33a–c] |
| 4 |  |  | [34a,b] |
| 5 |  |  | [35a–c] |
| 6 |  |  | [36a–d] |
| 7 |  |  | [37] |
| 8 |  |  | [38] |
| 9 |  |  | [39] |



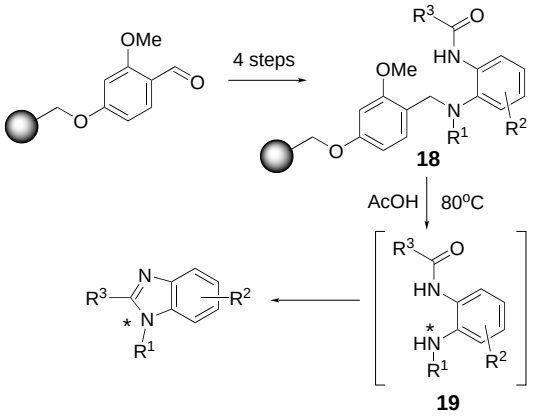

Scheme 15. PACT $NR_3$ or $Nsp^3$ linker. Hofmann elimination of the product follows a three-step construction of the amine through aza-Michael addition, reductive amination, and quaternization.[31c]

similarly, exhibit high stability to such nucleophiles as Grignard reagents[31f] and the conditions for Mitsunobu esterification.[31g]

A sulfonate resin has also been employed in the formation of a tertiary amine (Table 8, entry 2).[32a–c] The tether, formed from an arylsulfonyl chloride resin and an alcohol, has demonstrated a tolerance to wide-ranging chemistries including Grignard additions, Wittig reactions, sodium borohydride reduction, reductive amination, and Suzuki coupling.[32b] Nucleophilic displacement by the amine-forming heteroatom incorporates a further element of diversity (PACT R–$NR_2$). Alternative nucleophiles such as azide, iodide, or acetate (PACT X–$Csp^3$) enable additional cleavage conditions to be used.[32d]

In a similar vein, pyridazines have been released from a thiophenyl tether by an $S_nAr$ displacement using primary and secondary amines,[33a] and pyrimidines have been constructed on a sulfide linker. Oxidation to the sulfone permits nucleophilic displacement (Table 8, entry 3).[33b,c] A novel application of the carbamate tether is shown in entry 4 of Table 8: reduction with lithium aluminum hydride reveals a latent *N*-methylamine.[34a,b] In this case, the valences of the carbon atom involved in the linkage (indicated by the asterisk as before) are replaced by hydrogen atoms during reduction (PACT $(H-)_3CNR_2$). Cleavage of the linkers which follow proceeds by substitution of the nitrogen valence. More conventionally, therefore, the same carbamate can be cleaved by hydrolysis to liberate primary or secondary amines (Table 8, entry 5; PACT H–$NR_2$).[35a–c]

Amines attached to a benzylic carbon atom with the ability to stabilize a cation can be released under acidic conditions. Several such linkers possessing *ortho*- and *para*-alkoxy substituents, the Rink amide linker being one example, have been developed (Table 8, entry 6).[36a–d] A synthesis of benzimidazoles using a linker of this kind is summarized in Scheme 16. Resin-bound substrate **18**, formed in four steps from the aldehyde resin, undergoes cyclization to give the product heteroarenes (anilines **19**; PACT H–NHAr) via a solution-phase intermediate.




Scheme 16. PACT H–NHAr or H–$Nsp^3$ linker. Release of **19** and solution-phase cyclization/aromatization to afford benzimidazoles.[36a]

The acetal-derived linker in entry 7 of Table 8 has been applied to the release of indoles;[37] cleavage is effected in excellent yield and purity by hydrolysis and subsequent treatment with 2 N NaOH. A resin based on a tetrahydropyranyl (THP) protecting group for the linkage of substrates through an aminal (Table 8, entry 8)[38] is base stable and cleaved with weak acid. This is true also of the multifaceted

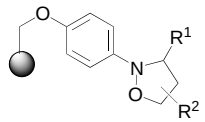
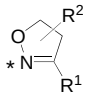
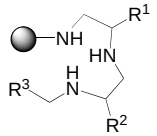
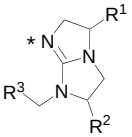
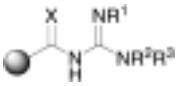
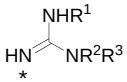
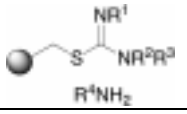
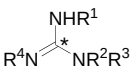
triazene linkage reported by Bräse et al. (Table 8, entry 9)[39] which enables the release of arenes (see Tables 5 and 6) and heteroarenes (see Table 7).

## 7. Formation of an Unsaturated Nitrogen Group

*PACT $R_2C{=}NR$ or $Csp^2{=}Nsp^2$(isoxazoline/guanidine) and PACT $R^1N{=}CR^2R^3$(guanidine) Linkers*

Kobayashi and Akiyama have demonstrated the 1,3-dipolar cycloaddition reaction of tethered nitrones with alkenes to form the precursor depicted in entry 1 of Table 9. Oxidative cleavage delivers the 2-isoxazoline derivatives.[40] Another example representative of this linker type is described by Houghton and co-workers.[41] The exhaustive reduction of resin-bound *N*-acylated dipeptides forms the cleavage precursor in entry 2 of Table 9. Treatment with thiocarbonyldiimidazole results in the *N*-tethered bicyclic guanidine which is liberated using hydrogen fluoride. Guanidines have also been liberated by more conventional means: an amide-derived linkage, drawn schematically in entry 3 of Table 9 can be cleaved under acidic conditions[42a–c] and an isothiourea has been cleaved by aminolysis (Table 9, entry 4).[43]

Table 9. Formation of an unsaturated nitrogen group: PACT $R_2C{=}N$ and $R_2Csp^2{=}Nsp^2$(isoxazoline/guanidine) linkers as well as the $N{=}CR_2$(guanidine) linker (entry 4).

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [40] |
| 2 |  |  | [41] |
| 3 |  |  | [42a–c] |
| 4 |  |  | [43] |

## 8. Formation of Carboxylic Acid Derivatives

Carboxylic acid derivatives, which form the basis of solid-phase peptide synthesis and have led to the development of novel linking technologies, are the antithesis of "tracelessness". A comprehensive survey of this expansive area is inappropriate here; important details, however, such as resin type, linkers, and cleavage conditions are fully documented in several excellent reviews.[1] The following section uses selected developments to illustrate the PACT approach.

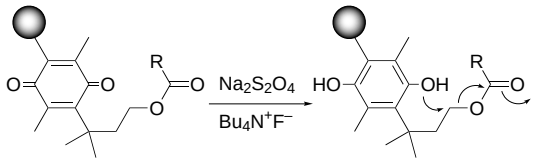
### 8.1. Formation of Carboxylic Acids

*PACT $H{-}O_2CR$ and PACT $HO{-}C(O)R$ Linkers*

Classically, immobilization of a growing peptide chain by means of an ester link to the C-terminus of an amino acid led to the liberation of a carboxylic acid on acid hydrolysis: PACT $H{-}O_2C$ vestige. Merrifield's benzylic esters required the very strong acid HF and early improvements such as the Wang (50 % TFA) or Sasrin linkers (1 % TFA) were achieved by modulating the electron density of the linker's phenyl ring.

Recent examples which make use of the Wang linker include the construction of polyheterocyclic compounds through Diels–Alder reactions by Sun and Murray[44a] and the synthesis of bicyclo[2.2.2]octane derivatives through tandem Michael addition reactions by Ley et al.[44b] Gallop and co-workers have successfully involved the Sasrin linker in a combinatorial synthesis of highly functionalized monocyclic $\beta$-lactams.[44c]

An alternative cleavage strategy to access carboxylic acids employs the so-called "safety-catch" linkers: Hulme et al. have described a Boc activation of a benzamide linker[45a] immediately prior to cleavage with LiOH (PACT $HO{-}C(O)$), and Backes and Ellman have employed Kenner's acylsulfonamide linker[45b] which is stable under basic conditions but activated to nucleophilic displacement with LiOH by N-methylation with diazomethane. Along similar lines, an unusual linking device possessing the redox-sensitive *p*-benzoquinone core (Scheme 17) cyclizes on reduction to the hydroquinone to expel the acid.[45c] The mild reduction and base-catalyzed formation of the cyclic ether (using $Na_2S_2O_4$ and $Bu_4N^+F^-$, respectively) provide an alternative procedure where acid conditions are undesirable.



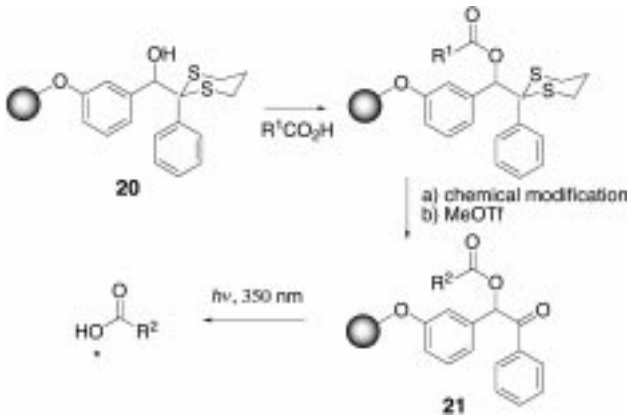

Scheme 17. PACT $H{-}O_2C$ linker. Reduction to the hydroquinone and base-catalyzed formation of a cyclic ether effect expulsion of the product.[45c]

A wide variety of photolabile supports, which are commonly based on the *o*-nitrobenzyl moiety,[46a] also release carboxylic acids. Lee and Balasubramanian report a novel example (Scheme 18) in which a diisopropylcarbodiimide coupling of a carboxylic acid to dithiane derivative **20** allows for subsequent chemical manipulation of the substrate on the solid phase.[46b] The dithiane unit, which acts as a "safety catch" against premature photorelease, is removed by alkylation with methyl triflate to afford photolabile linker **21** from which the product is released in excellent yield.

### 8.2. General Amide Formation

*PACT $N{-}C(O)$ and PACT $H{-}NC(O)$ Linkers*

Amide bond formation has been thoroughly optimized throughout the years and is consequently used extensively in




Scheme 18. PACT H–$O_2$C linker. Photorelease from a benzoin system employing a dithiane "safety-catch".[46b]

solid-phase methodologies and combinatorial synthesis. It is integral to the pharmacophore of a multitude of therapeutic drugs, and is found not only in its simple form but also in numerous guises (Table 10).

### 8.2.1. Formation of Acyclic Amides

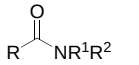
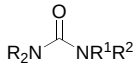
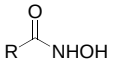
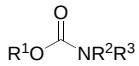
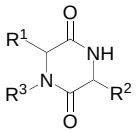
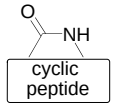
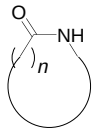
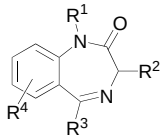
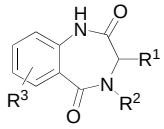
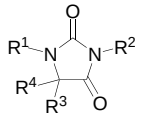
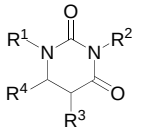
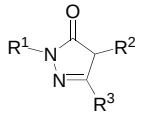
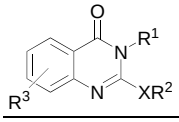
The release of simple linear amides, such as **22** (Table 10), is thoroughly documented: well-established protocols such as the acidic cleavage of an amide from the Rink amide resin[47a–d] and photorelease from an *o*-nitrobenzyl linker[44c] can be defined as PACT H–NC(O). Aminolysis of an ester[44b, 47e–n] or of linkers based on *N*,*N*-methylacylsulfonamide (Kenner's "safety-catch")[45b, 47o,p] give secondary or tertiary amides (PACT N–C(O)). Ureas **23** (Table 10) are accessible by aminolysis of resin-bound carbamates[48a–d] and hydroxamic acids **24** (Table 10) by aminolysis of esters with hydroxylamine.[49a,b] Proteolytic release from an immobilized trityl[49c–e] or *p*-alkoxybenzyl[49f–h] hydroxamate also gives hydroxamic acids (PACT H–ON(H)C(O) or PACT RON(–H)C(O)[49h]).

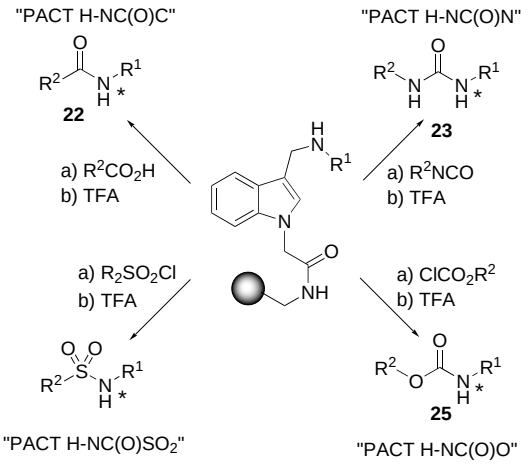
An interesting variant is the acylative dealkylation of resin-bound tertiary benzylamines with acid chlorides[47q] or chloroformates.[47r] The latter are examples of linker type B (see Figure 1), wherein release occurs from an electron-rich benzyl tether after quaternization of the linking amide nitrogen atom (PACT RRNC(O)). Along similar lines, a particularly versatile linking system which releases a variety of functionalities of this kind is reported by Estep et al. (Scheme 19).[47s] Primary amines are linked to the resin by means of an indole and immobilized by the reductive amination of a resin-bound aldehyde. Subsequent reaction with various electrophiles (carboxylic acids, isocyanates, chloroformates, or sulfonyl chlorides) forms tethered secondary amide derivatives which are liberated as primary derivatives (amides **22**, ureas **23**, carbamates **25**, or sulfonamides, respectively) on treatment with 2–5% TFA in $CH_2Cl_2$.

### 8.2.2. Formation of Cyclic Amides

With few exceptions, cyclic amidic structures are liberated from a solid support by lactamization; this comes as a direct result of the most deeply rooted solid-phase peptide synthesis protocol whereby an amino acid or derivative is immobilized through the C-terminus. A pendant NH functionality of the linear product precursor consequently effects an intramolecular cleavage of the ester linkage to create the amide vestige (PACT N–C(O)). Numerous systems of this kind are to be

Table 10. General formation of amides: Acyclic and cyclic products accessible with PACT H–NC(O) and N–C(O) linkers.

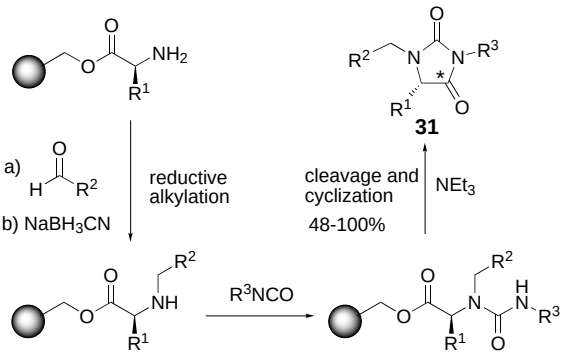
| Amidic structure | Formula number and ref. |
|---|---|
|  | **22**[44b,45b,47a-s] |
|  | **23**[47s,48a–d] |
|  | **24**[49a–h] |
|  | **25**[47r,s] |
|  | **26**[50a–i] |
|  | **27**[51a–g] |
|  | **28**[52a–c] |
|  | **29**[53] |
|  | **30**[54a–c] |
|  | **31**[55a–m] |
|  | **32**[56a–d] |
|  | **33**[57a–d] |
|  | **34**[58] |




Scheme 19. A versatile support for the release of amide functionalities.[47s] Amides, ureas, carbamates, and sulfonamides are accessible.

found for every heterocycle listed in Table 10: diketopiperazines **26**,[50a–i] cyclic peptides **27**,[51a–g] lactams **28**,[52a–c] benzodiazepines **29**,[53] 1,4-benzodiazepine-2,5-diones **30**,[54a–c] hydantoins **31**,[55a–m] quinazoline-2,4-diones and pyrimidine-2,4-diones **32**,[56a–d] pyrazolones **33**,[57a–d] and 3*H*-quinazoline-4-ones **34**.[58]

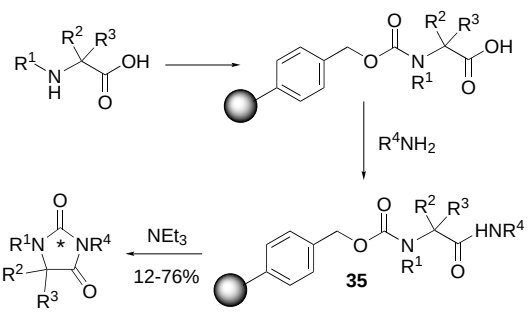
An example representative of the general methodology is detailed in Scheme 20.[55c] Matthews and Rivero describe a




Scheme 20. PACT N–C(O)(hydantoin) linker. The amino acid is attached at the C-terminus through an ester tether. The amide functionality is incorporated through cleavage and cyclization.[55c]

synthesis of 1,3,5-trisubstituted hydantoins which takes advantage of the host of commercially available amino acids, primary amines, and aldehydes. Scheme 20 depicts the reductive alkylation of a C-terminus-bound $\alpha$-amino acid with aldehydes, acylation of the secondary amine with an isocyanate to generate an acyclic urea precursor, and base-promoted cleavage and cyclization to give the product **31** in moderate to quantitative yield.

However, other strategies for the liberation of a cyclic amide have been employed. Immobilization of an amino acid or derivative at the N-terminus through a carbamate linker presents a scaffold that is also set for lactamization on cleavage: cyclic peptides **27**,[51e] quinazoline-2,4-diones **32**,[56c,d] and hydantoins **31**[55j] have been isolated in this way. The system illustrated in Scheme 21 can be compared to that in




Scheme 21. PACT N–C(O)(hydantoin) linker. The amino acid is connected at the N-terminus through a carbamate tether. The amide functionality is then incorporated through cleavage and cyclization.[55j]

Scheme 20. The coupling of the N-terminus of an amino acid to an activated carbonate resin followed by standard elaboration to give the linear substrate **35** sets the stage for a base-induced cleavage and cyclization of the carbamate tether.[55j]

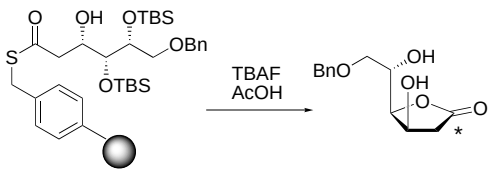
### 8.3. Formation of Esters and Lactones

*PACT O–C(O) or PACT O=C(OR) Linkers*

Esters[45a, 59a–f] and lactones[60a–h] are analogous in many ways in terms of their release from a solid support to the amides already discussed. Alcoholysis of simple esters[59a] and silyl esters[59b] (transesterification) or of amides[45a, 59c] has been used to liberate acyclic esters (PACT RO–C(O)R).

Another widely used protocol is the formation of acetates from substrates bound through a benzyl ether linker by a Lewis acid ($ZnBr_2$) catalyzed reaction with acetyl bromide.[59d] Similarly, 1-*O*-acetyl glycosides are released from a glycosyl ether tether with $Ac_2O/BF_3 \cdot OEt_2$.[59e,f]

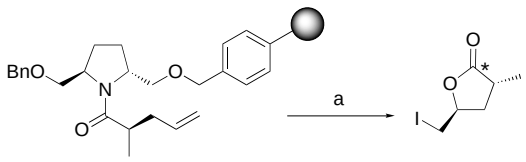
Kobayashi et al. have developed an intramolecular solid-phase synthesis of monosaccharide derivatives (Scheme 22)[60a] whereby a thioester tether is cleaved by a pendant



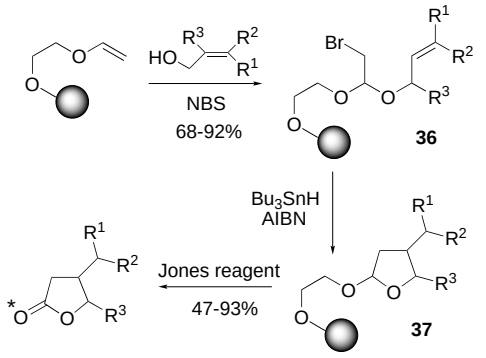

Scheme 22. PACT O–C(O)(lactone) linker. Monosaccharide synthesis with a lactonization/cleavage step.[60a]

hydroxy group. Homoserine lactones[60b] and phthalides[60c] have been prepared using the same concept, whereby lactonization cleaves an amide linker. Cyclorelease of oxazolidinones[60d] and $\gamma$- and $\delta$-lactones[60e] has also been induced by nucleophilic ring opening of epoxides prepared on the solid phase. A variation on this theme is given by Kurth and coworkers (Scheme 23). High diastereoselectivity is induced by a "$C_2$-symmetric" pyrrolidine-based tether during the course of an iodolactonization.[60f,g]

Using a different release strategy, the oxidation of resin-bound cyclic acetals using the Jones reagent also serves to liberate $\gamma$-lactones (Scheme 24).[60h] A series of $\beta$-bromoace-




Scheme 23. PACT O–C(O)(lactone) linker. Iodolactonization with a pyrrolidine-induced diastereoselectivity.[60g] a) $I_2$, THF, $H_2O$, *tert*-butyldimethylsilyl.




Scheme 24. PACT O=C(OR)(lactone) linker. Radical cyclization and an oxidative release.[60h]

tals **36** was prepared by treatment of the immobilized vinyl ether with allyl alcohols in the presence of *N*-bromosuccinimide (NBS). Radical cyclization, a process rarely exploited on the solid phase, proceeded efficiently with $Bu_3SnH$/AIBN to give only the 5-membered lactone precursor **37**. The products were isolated in high yield following oxidative release (PACT O=C(R)OR).

## 9. Aldehyde Formation

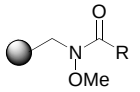
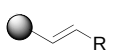
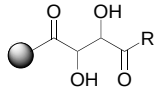
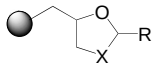
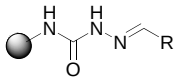
*PACT H–C(O)R and PACT O=CHR Linkers*

The release of the aldehyde functionality is relatively undeveloped on the solid phase, and has been primarily directed towards the synthesis of C-terminal peptide aldehydes, which are of interest as inhibitors of several classes of enzymes. Five distinct approaches are summarized in Table 11.

Aldehydes have been formed by reduction of a tether based on the Weinreb amide with lithium aluminum hydride (Table 11, entry 1; PACT H–C(O)R).[61a,b] The preparation of small, non-peptidic molecules using the same methodology is also described,[61c,d] but yields are generally low and problems associated with purification and racemization are important considerations, especially in peptide synthesis.

The resin-bound product precursor in entry 2 of Table 11 is attached by an alkenyl tether, ozonolysis of which liberates the aldehyde product PACT O=C(H)R.[62a–d] Ozonolytic release is a very clean methodology which proceeds without detectable racemization of a peptidic substrate, and hence has clear advantages over the system detailed in entry 1 of Table 11. Not dissimilar is the oxidative cleavage of the tether based on tartaric acid (Table 11, entry 3).[63] The 1,2-diol moiety, protected as an acetonide during chemical manipulation of the substrate, is cleaved using sodium periodate to release $\alpha$-ketoaldehyde derivatives.

Table 11. Aldehyde formation: PACT H–C(O)R or O=CHR linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [61a–d] |
| 2 |  |  | [62a–d] |
| 3 |  |  | [63] |
| 4 |  |  | [64a–e] |
| 5 |  |  | [65] |

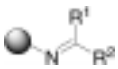
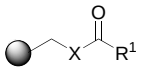
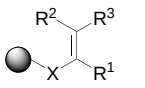
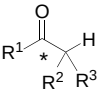
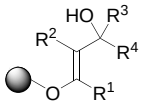
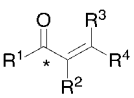
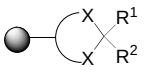
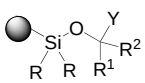
General protecting group chemistry has also been applied to the immobilization of aldehydes in the form of their acetals[64a–d] or oxazolidine derivatives[64e] (Table 11, entry 4); cleavage is effected by acid hydrolysis. A tether based on a semicarbazone derivative has also been described (Table 11, entry 5),[65] but the system suffers from two drawbacks: the linker is preformed in solution prior to loading onto the resin and the products are liberated with formaldehyde.

## 10. Ketone Formation

*PACT $R^1$–C(O)$R^2$ and PACT O=C$R^1R^2$ Linkers*

The ketone is a widespread functionality in organic compounds, be it found in its simple form, in conjugation with an unsaturated carbon backbone, or as the enol tautomer. The various methods by which it can be achieved are summarized in Table 12.

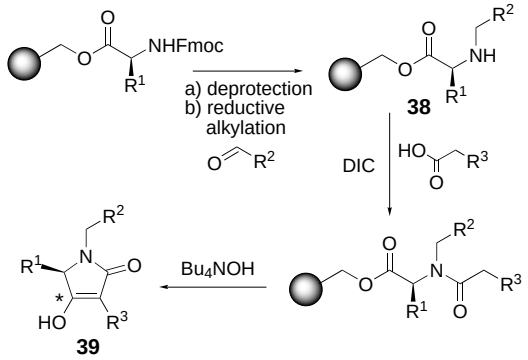
Table 12. Ketone formation: PACT $R^1$–C(O)$R^2$ or O=C$R^1R^2$ linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [66a–c] |
| 2 |  |  | [61c,d;67a–e] |
| 3 |  |  | [68a–e] |
| 4 |  |  | [69] |
| 5 |  |  | [70a–c] |
| 6 |  |  | [71] |

The use of a semicarbazone linkage as an anchor and reversible protecting group is depicted in entry 1 of Table 12.[66a] The product ketone is resistant to both mildly basic and anhydrous acidic conditions, and can be released with aqueous HCl (PACT O=CRR). Ketones immobilized through an imine[66b] or hydrazine[66c] can be similarly released.

Substrates bound to the resin by means of an ester or amide tether have been liberated as ketones by the addition of a carbon nucleophile (Table 12, entry 2; PACT $R^1$–C(O)$R^2$). The Weinreb amide linker, described earlier for the synthesis of aldehydes, undergoes cleavage in this way with Grignard reagents.[61c,d]

The base-induced carbon nucleophile inherent to the Dieckmann condensation has also been exploited.[67a–e] The ketone products revealed on cleavage and cyclization from the resin contain a $\beta$-keto or ester group and hence exist as their enol tautomers. Scheme 25 illustrates one of several

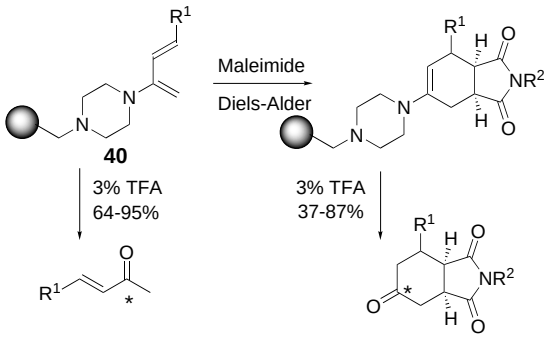



Scheme 25. PACT R(OC)C=CROH linker. Synthesis of tetramic acids where Dieckmann cyclization effects cleavage and cyclization and subsequent enol formation.[67b]

solid-phase syntheses of tetramic acids.[67b] Wang resin bound amino acids underwent acylation with an acetic acid derivative after deprotection of the 9-fluorenylmethoxycarbonyl (Fmoc) group and reductive alkylation with an aldehyde to give **38**. Cleavage and cyclization proceeded using tetrabutylammonium hydroxide as the base, which is effectively scavenged after the reaction with acid Amberlyst A-15 resin to deliver the products **39** in excellent yield (PACT R(OC)C=CROH).

An enamine linkage, represented schematically in entry 3, of Table 12 has also been shown to release ketones on treatment with weak acid (Scheme 26). In the preparation of resin-bound 2-aminobutadienes as substrates for [4+2] cycloadditions, a piperazine tether is used to immobilize propargylphosphonium bromide, which is converted into **40** after a Wittig reaction. Direct cleavage with TFA gives enones,[68a] and the enamine resulting from a Diels–Alder reaction affords saturated cyclic ketones with a PACT O=C(R)$CR_2$H vestige.[68b]

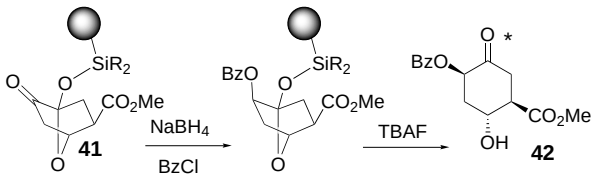
Processes employing a resin-bound enol ether[68c] and a silyloxydiene tether[68d] have been shown to react in the same way. The acid labile ketone linker shown in entry 4 of Table 12 has been used for the synthesis of a variety of 2-cyclohexenones.[69]




Scheme 26. PACT O=C($R^1$)$CR_2$H linker. 2-Aminobutadiene as Diels–Alder substrates, cleaved under mild acidic conditions.[68a,b]

As for aldehydes, ketones can be immobilized by means of an acetal[70a] or thioacetal tether[70b,c] (Table 12, entry 5). The former, as before, is cleaved using acid while the sulfur analogues liberate the ketone products on oxidative desulfurization with [bis(trifluoroacetoxy)iodo]benzene or anhydrous periodic acid.

Scheme 27 shows an example reported by Schlessinger and Bergstrom of the general, structurally more involved, linker summarized in entry 6 of Table 12. Immobilized substrate **41**,




Scheme 27. PACT O=C(R)$CR_2CR_2$C(R)OH linker. 4-Hydroxycyclohexanones released from a silyloxy tether by fluoride.[71]

constructed by means of the Diels–Alder reaction of a resin-bound furan, undergoes stereoselective reduction prior to fluoride cleavage.[71] For this specific example, the 4-hydroxy substituent of cyclohexanone **42** is also created during this cleavage and the linker can be named accordingly as PACT O=C(R)$CR_2CR_2$C(R)OH. This is an example of how the length of the "PACT" term may often prove to be proportional to the generality of the linker.

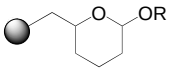
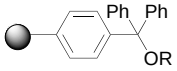
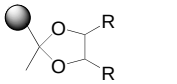
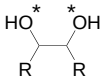
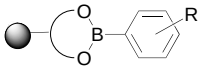
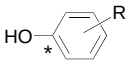
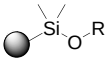
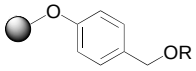
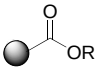
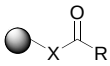
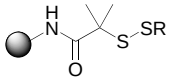
## 11. Formation of Alcohols and Thiols

*PACT H–OR, PACT H–SR, and PACT HO–R Linkers*

Some of the first new linking technologies to depart from the formation of carboxylic acid derivatives were those designed for the immobilization and release of alcohols. An expansive array of linkers with this capacity have now been developed (Table 13).

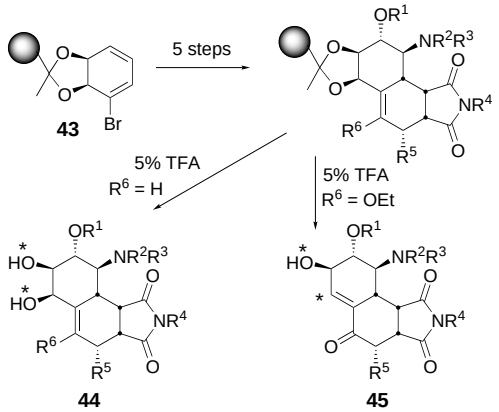
Ellman and co-workers' linker based on the tetrahydopyranyl (THP) protecting group is analogous to a simple resin-bound vinyl ether proposed by Wang and is cleaved under the usual acidic conditions, (Table 13, entry 1; PACT H–OR).[72a–e] Leznoff and co-workers have made use of the acid-labile trityl protecting group in the synthesis of

Table 13. Alcohol and thiol formation: PACT H–OR, H–SR, and HO–R linkers.

| Entry | Polymeric precursor | Released functionality | Ref. |
|---|---|---|---|
| 1 |  |  | [72a – e] |
| 2 |  |  | [73a – g] |
| 3 |  |  | [74a – c] |
| 4 |  |  | [75a,b] |
| 5 |  |  | [77a – f] |
| 6 |  |  | [79a – g] |
| 7 |  |  | [80a – d] |
| 8 |  |  | [44b,82a – h] |
| 9 |  |  | [83a,b] |

various insect pheromones on the solid phase (Table 13, entry 2).[73a,b,d,e]

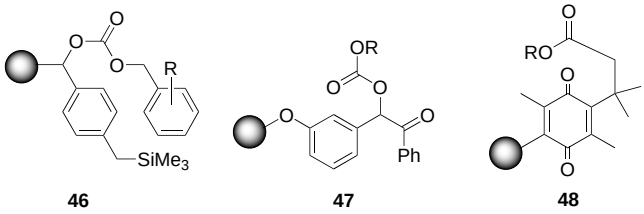
Table 13, entry 3, outlines the use of the acetal tether for the immobilization and release of 1,2-diols or catechols.[74a–c] Employing such a system, Wendeborn et al. has elaborated a resin-bound cyclohexadienediol substrate **43** (Scheme 28)[74a] by means of epoxidation, nucleophilic ring-opening, $Pd^0$ cross-coupling, and Diels – Alder reactions. The highly functionalized products were cleaved from the resin under acidic conditions: depending on the substitution pattern, diols **44** (PACT H–$OCR_2CR_2O$–H vestige) or $\gamma$-hydroxy-$\alpha,\beta$-enones **45** (PACT H–$OCR_2CH$=CRC(O)R vestige) were released.



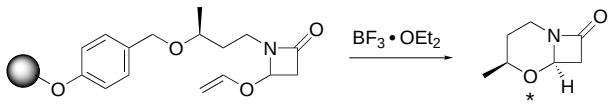

Scheme 28. PACT H–$OCR_2CR_2O$–H and PACT H–$OCR_2CH$=CRC(O)R linker. Immobilization of cyclohexadiene diols onto a ketal tether and their release as 1,2-diols or $\gamma$-hydroxyenones.[74a]

Oxidative cleavage of resin-bound aryl boronic acids with hydrogen peroxide in the presence of sodium hydroxide has been shown to liberate phenols in high yield (Table 13, entry 4).[75a,b] Transesterification or acid hydrolysis will release a boronic ester[75a] or acid.[75b] This linker involves a resin-bound diol: reversal of the tether such that the boronic ester is resin-bound allows for the release of diols;[76a–c] this system has been applied to the selective blocking of *cis*-hydroxyl groups of carbohydrates.

The trialkylsilyl,[73g, 77a–e] dialkylarylsilyl[77e] or dialkyloxysilyl[77f] linkers depicted in entry 5 of Table 13 have been used with success for the release of alcohols by fluoridolysis. These release conditions have also been employed in the formation of benzylic alcohols from the more complex silyl-activated linker **46**.[78]



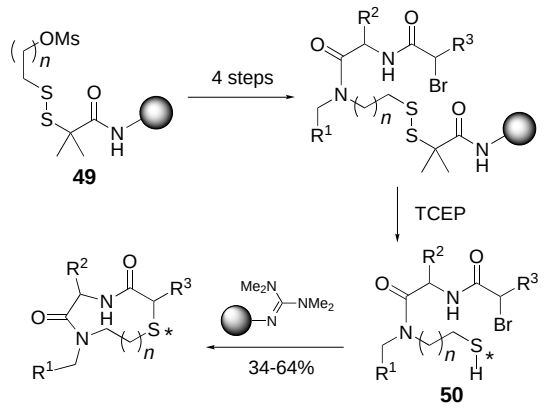

Both phenolic and alcoholic products are accessible using the *p*-alkoxybenzyl tether in entry 6 of Table 13. The benzylic ether bond is typically cleaved with TFA,[79a–d] but 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has the same effect.[79e] An interesting application of such a linker, the synthesis of 1-oxacephams, has been reported by Chmielewski and co-workers (Scheme 29).[79f,g] The Lewis acid induced loss of the vinyloxy substituent followed by trapping of the resulting carbocation by the benzylic oxygen atom results in cleavage and cyclization.




Scheme 29. PACT H–OR linker. 1-Oxacepham synthesis by nucleophilic displacement at the C4 position of the azetidine-2-one ring.[79f,g]

Alcohols or phenols bound to the solid phase by means of a simple ester linkage (Table 13, entry 7) are cleavable by basic hydrolysis.[80a,b] Many interesting variants have been synthesized: **47** is photolabile[80c] and an alternative to the *o*-nitrobenzyl linker,[46a, 81a,b] whereas **48**, with the redox-sensitive *p*-benzoquinone core, cyclizes to expel the product on reduction with sodium hydrosulfite to the hydroquinone.[80d] The formation of primary alcohols by reductive cleavage of esters,[44b, 82a,b,h] thioesters,[82c–f] or amides[82g] with diisobutylaluminum hydride (DIBAL-H), $LiAlH_4$, or $LiBH_4$ has also been exploited (Table 13, entry 8).

An interesting linker with the capacity to release thiols has been reported by Ellman and co-workers (Table 13; entry 9).[83] In a synthesis of $\beta$-turn mimetics (Scheme 30), the resin-bound mesylate **49** undergoes amine substitution, amino




Scheme 30. PACT H–SR linker. Synthesis of putative $\beta$-turn mimetics. Disulfide cleavage with TCEP precedes an intramolecular $S_N2$ reaction that is catalyzed by a resin-bound guanidine base.[83a,b]

acid coupling, and acylation to incorporate three degrees of diversity. The acyclic mimetic **50** is liberated by disulfide cleavage with tris-(2-carboxyethyl)phosphane (TCEP) and cyclization is induced by a resin-bound guanidine base which serves also to scavenge excess reagent and by-products. Significantly, potent ligands to somatostatin receptors have been identified following the screening of a mimetic library prepared with this technology.[83b]

## 12. Summary and Outlook

In the past decades, few areas of chemistry have enjoyed such an explosion of interest as solid-phase chemistry. Although conceived for peptide synthesis, gone are the days when the technology was applied solely to this end; the repertoire of organic reactions developed on the solid phase is considerable and approaching that used in conventional solution-phase chemistry.

Concurrent with and complementary to the diverging of this field, we have witnessed the rapid growth of novel linking technologies and there now exist means for the incorporation of most fundamental functional groups at the former linkage site of a product liberated from its support.

While some of these are very general and could, in theory, be applied to the release of a myriad of product classes, such as the PACT alkyl or PACT aryl linkers, others are arguably less so and are cleaved to release rather more specific functionalities. All have their value, however, in view of the requirement for cleavage conditions that are both compatible with a product's integrity and applicable to robotic techniques.

Concerned, as it is, only with the functionalities released on cleavage, the classification suggested in this article allows for a universal linker nomenclature which avoids the necessity for ambiguous terms such as "traceless". It is anticipated that such a classification will also facilitate the choice of a linker in regard to a given target for solid-phase synthesis.

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