Linkers for solid-phase synthesis of small molecules: coupling and cleavage techniques

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Combinatorial chemistry has an impact on lead discovery as well as on lead optimization. The efficient synthesis of individual compounds, which has replaced the initial goal of synthesizing highly complex mixtures, can be carried out in solution or on a suitable support material. The role of a linker in solid-phase chemistry is to connect the starting material reversibly with the solid support. The main challenges in choosing an appropriate linker molecule are that the starting compounds can be easily attached to it, that it is chemically stable in the envisaged synthesis conditions and that it should be possible to cleave the final products with high efficiency.

Both solid-phase and liquid-phase synthetic strategies are used in combinatorial chemistry. To date, the majority of small-molecule combinatorial libraries have been assembled by solid-phase organic synthesis (SPOS). One advantage of SPOS is the simplification of purification procedures, thereby making it particularly useful in multistep automated synthesis.

In SPOS, every synthesis starts with the immobilization of a scaffold or building block on a polymeric protecting group, a so-called linker. After the synthesis of a compound library, the final step usually comprises a detachment reaction from the resin, which either restores a previously protected functionality or introduces an additional element of diversity.

The basic requirements for the first step in a solid-phase synthesis are the availability of suitable linker resins and efficient loading with as little excess as possible of rare and expensive reagents. Many recent articles have dealt with optimization of the loading process of well-known linkers that were initially developed for oligomer synthesis, thus broadening the scope of their application. In this review, these new methods are taken into account as well as newly designed linkers. Linkers functionalized with the first building block in solution and coupled after several synthetic transformations to polymeric supports are usually not suitable for rapid library generation. Nevertheless, some examples of such strategies are given in the traceless linker section of this review.

Recently, the requirements for the detachment of the final products have changed, with the subsequent automation of purification methods such as solid-phase extraction. Cleavage with easily removable reagents such as volatile acids is no longer a crucial feature of linker methodology. Thus, cleaving procedures with reagents that introduce additional diversity at the former point of attachment to the resin are gaining importance, making post-cleavage work-up procedures necessary. These new purification methods also bring transition metal catalysed cleavage reactions back into focus.

Categorization of linkers has been made according to cleavage conditions, except in the case of traceless linkers and cyclization-cleavage strategies, which are considered separately:

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- Acid-labile linkers
- Nucleophile-labile linkers
- Photolabile linkers
- Traceless linkers
- Cyclization-cleavage reactions

Acid-labile linkers

Most acid-labile linkers that have been developed for solid-phase synthesis (SPS) of peptides are derived from mono-alkoxy- or multi-alkoxybenzylic protecting groups and from trityl systems. They were designed to enable mild acidic conditions for carboxylic acid cleavage. The strength of the acid required to induce cleavage is related to the electron donor substituents on the aromatic system that stabilizes the transient resin-bound cation. The greater the resonance stabilization conveyed by additional alkoxy groups or aryl rings, the milder the acidic conditions required for cleavage.

Wang support

The Wang support[1] **1** (X = OH), a polymer functionalized with an alkoxybenzyl anchoring group[2], is without doubt the most widely used resin in SPOS. Cleavage of esters involves concentrated trifluoroacetic acid (TFA) or TFA–dichloromethane (DCM) to provide the corresponding carboxylic acids. A general method to couple and cleave primary, secondary and tertiary alcohols was presented by Hannesian and coworkers[3]. In this method, the polymeric benzylic alcohol is converted into the reactive Wang trichloroacetimidate **1** [X = $OC(NH)CCl_3$], which couples with the chosen alcohol in the presence of catalytic amounts of mild Lewis acid. Alcohols are cleaved from the Wang resin by treatment with 10% TFA–DCM for 30 min at ambient temperature.

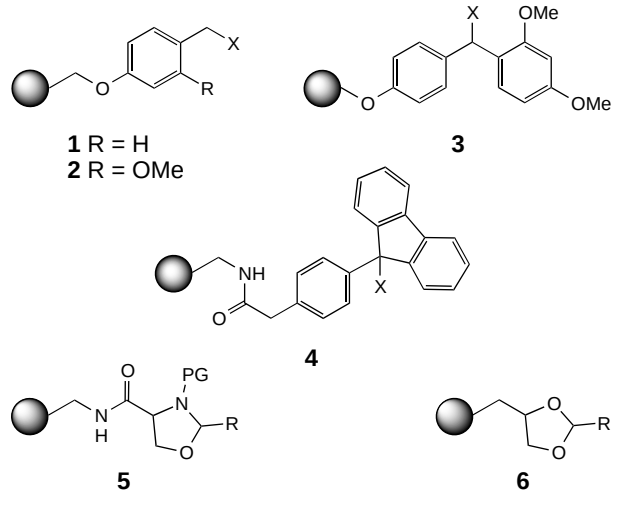

Figure 1. *Acid-labile linkers: Wang (**1**), Sheppard (**2**), Rink (**3**), phenylfluorenyl (**4**), oxazolidine (**5**) and acetal (**6**) linkers for aldehydes.*

Conditions under which such Wang ethers are stable include Grignard reactions, ester saponification with lithium hydroxide, Weinreb amide formation, Mitsunobu reactions and enolate alkylations, as well as Heck reactions[4,5]. A similar approach was used for solid-phase synthesis of oligosaccharides via anomeric attachment to Wang polymer[6].

The use of the Wang linker for amines was demonstrated earlier. *p*-Nitrophenyl chloroformate is coupled onto Wang resin to yield the corresponding carbonate, which is reacted with amines to give the polymer-bound carbamates[7]. An alternative approach for the coupling of amines is the reductive amination of Wang aldehyde[8]. After conversion of the immobilized amines into ureas, sulphonamides and amides, the products can be cleaved with TFA containing 2.5% Et_3SiH as a scavenger. A similar approach using the more acid-labile Sheppard linker **2** (X = OH), which carries an additional methoxy group in the ortho-position to the cleavage site, has been described by Fivush and coworkers[9]. In this case, release can be achieved by treatment with 5% TFA–DCM.

The immobilization of phosphate esters to Wang resin **1** was accomplished by reaction with phosphoramidites through sonication in tetrazole–tetrahydrofuran (THF) solution[10]. Oxidation using *N*-methylmorpholine *N*-oxide provides the protected phosphate resin. The chemical stability of these immobilized phenyl phosphates under peptide coupling conditions, reductive amination with $Na(OAc)_3BH$ and palladium(0)-catalysed allyl ester cleavage has been demonstrated.

Rink linker

Another linker originally developed for SPS of peptides and peptide amides is the Rink linker[11] **3** (X = NHFmoc). As in the case of the Wang linker, the scope of its application was extended from carboxylic acids and amides to the immobilization of amines, substituted amides, thiols and alcohols.

Libraries of primary amines have been synthesized by the treatment of Rink amine **3** (X = NH_2) resin with aldehydes to form aldimines, which are subsequently reacted

with Grignard reagents or lithium reagents to yield amines with two sites of diversity[12]. These amines are released from resin by treatment with TFA–water–DCM (5:5:90) for 5 h at room temperature. This strategy allows the production of libraries of amines that are not commercially available and which can themselves be used as building blocks.

N-Substituted amides are obtained by reducing the above-mentioned aldimines with $Na(CN)BH_3$ to the corresponding amines, followed by acylation with acid chlorides or symmetrical anhydrides[13]. The products are cleaved with TFA–water–DCM (5:1:94) for 20 min at room temperature. The immobilization of alcohols and thiols was recently described in two independent articles. One describes the conversion of Rink acid resin **3** (X = OH) to the corresponding Rink chloride **3** (X = Cl). The chloride can then easily be substituted by various nucleophiles, such as primary and secondary amines, anilines and phenols as well as thiols and alcohols[14]. Direct functionalization with nucleophiles was carried out starting from Rink amine linker **3** (X = NH_2) on pins[15]. The authors treated **3** (X = NH_2) with 70% TFA–DCM for 5 h at room temperature. After removal from the cleavage solution the crowns were dried *in vacuo* for 30 min, then treated with 0.5 M solutions of different nucleophiles (for example, 4-methoxyaniline in DCM for 1 h). Cleavage with 70% TFA–DCM for 30 min at room temperature provided the desired products.

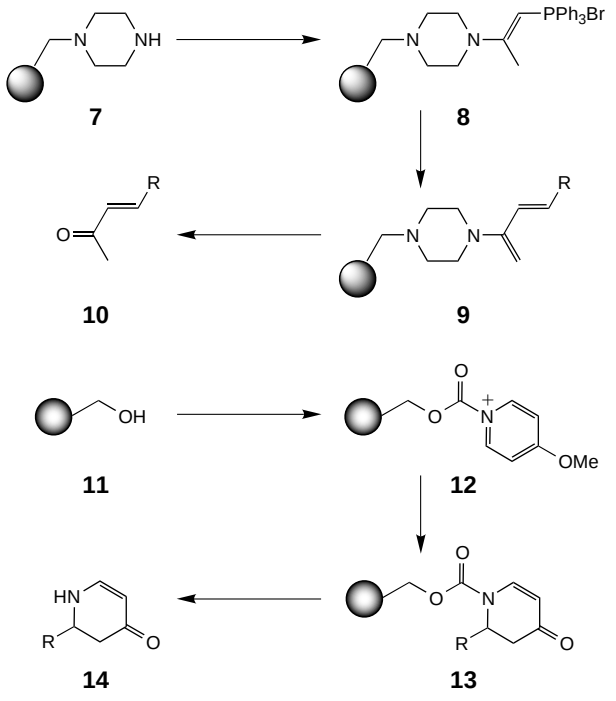

Figure 2. *Synthesis of α,β-unsaturated ketones* ***10*** *(Ref. 24) and synthesis of dihydropyridone scaffold* ***14*** *(Ref. 26) on polymers derived from Merrifield resins.*

Other linkers

Trityl linkers are very useful for the immobilization of carboxylic acids, primary amines and alcohols[16] (PepChem, Tübingen, Germany). To obtain a higher acid stability while preserving the broad applicability of this linker type, the phenylfluorenyl (PhFl) linker **4** (X = Cl) was designed[17,18]. This linker differs from the trityl linker in that two phenyl rings are bridged to form a fluorenyl system. Fluorenyl cations formed under cleavage conditions are destabilized by their antiaromatic character, leading to markedly increased acid stability compared with trityl linkers. Several applications for aniline and amines are presented. Cleavage from this resin is performed with TFA–DCM–methanol (MeOH) (2:7:1) for 2 h at ambient temperature.

An acid-labile linker for the binding and release of aldehydes was developed by chemists at Chiron[19–21]. Aldehyde substrates were condensed with pin-bound serine or threonine to give imine intermediates, which spontaneously cyclize to give stable oxazolidines **5**. Optimum coupling conditions consist of the treatment of the threonine polymer with 0.1 M aldehyde in 1% diisopropylethylamine (DIEA)–MeOH for 2 h at 60°C. After peptide synthesis under standard Fmoc conditions, C-terminal peptide aldehydes were obtained upon treatment with 5% aqueous acetic acid at 60°C for 30 min. An interesting aspect of the oxazolidine linker is that, when the oxazolidine nitrogen is acylated, it shows almost complete stability towards acidic reaction conditions. This property can be exploited by introducing an orthogonal protecting group onto the ring nitrogen, thereby obtaining a linkage that is stable in many SPOS reaction conditions, including acid and base treatment. After a preactivation step (i.e. deprotection of the linker nitrogen), aldehydes can be cleaved under the above conditions. An alternative to this procedure is the linkage of aldehydes to solid phase via an acetal functionality **6** (Refs 22,23).

A new linker strategy for the synthesis of libraries of α,β-unsaturated methyl ketones and trisubstituted cyclohexanones was reported by Hird and coworkers[24]. The acid-labile linker is generated on the resin by reacting

piperazine-derivatized Merrifield resin **7** with propargyltriphenylphosphine. Resin **8** was then treated with potassium *t*-butoxide in DCM to form the corresponding ylide within 5 min. Wittig reaction with various aldehydes leads to amino butadienes **9**, which are readily cleaved by mild acidic treatment to yield ketones **10**. Furthermore, such amino butadienes are activated towards [4 + 2] cycloaddition chemistry, which has been exploited for library synthesis of 3,4,5-trisubstituted cyclohexanones[25].

Nucleophile-labile linkers

The most simple linkers from which carboxylic acids or alcohols can be cleaved are hydroxyalkyl and carboxylic acid resins, respectively. Looking at the usually applied basic cleavage conditions, it is obvious that postcleavage work-up procedures are necessary to obtain pure products. However, the advantage of this kind of anchorage is the high stability under many reaction conditions.

Oxycarbonyl resin

The Merrifield resin also belongs to this group. A recent application of hydroxymethylated polystyrene resin included the synthesis of a dihydropyridone scaffold **14** (Ref. 26). Hydroxymethylated polystyrene beads **11** are converted into the chloroformate solid support to which a premixed solution of 4-methoxypyridine and the chosen Grignard reagent in anhydrous THF is added to yield polymer-bound dihydropyridone **13**. The reaction is quenched after a few minutes with 3 M aqueous HCl–THF (1:1), thus removing unreacted pyridinium **12**. Cleavage of the final products is carried out with NaOH in MeOH–THF (Ref. 27).

The resin-bound dihydropyridone **13** was used for the synthesis of polymer-bound enamide alcohols by subjecting it to a 1,2 addition reaction, using organocerium reagents. These products were released from the resin with 70% TFA–DCM. By choosing between oxidative (oxygen) and reductive (Et_3SiH) conditions, the authors obtained 2,4-disubstituted pyridines as the major product in the first case, and 2,4-disubstituted 1,2,5,6-tetrahydropyridines in the latter case.

Other linkers

A new linker **15** for carboxylic acids, amines, alcohols and thiols has been derived from methacrylic acid[28]. It is stable to a range of acidic conditions and tertiary amines, yet is susceptible to basic or nucleophilic cleavage using secondary amines or fluoride ions. The stability against nucleophiles increases in the order where R = H <Me <i-Pr <Ph.

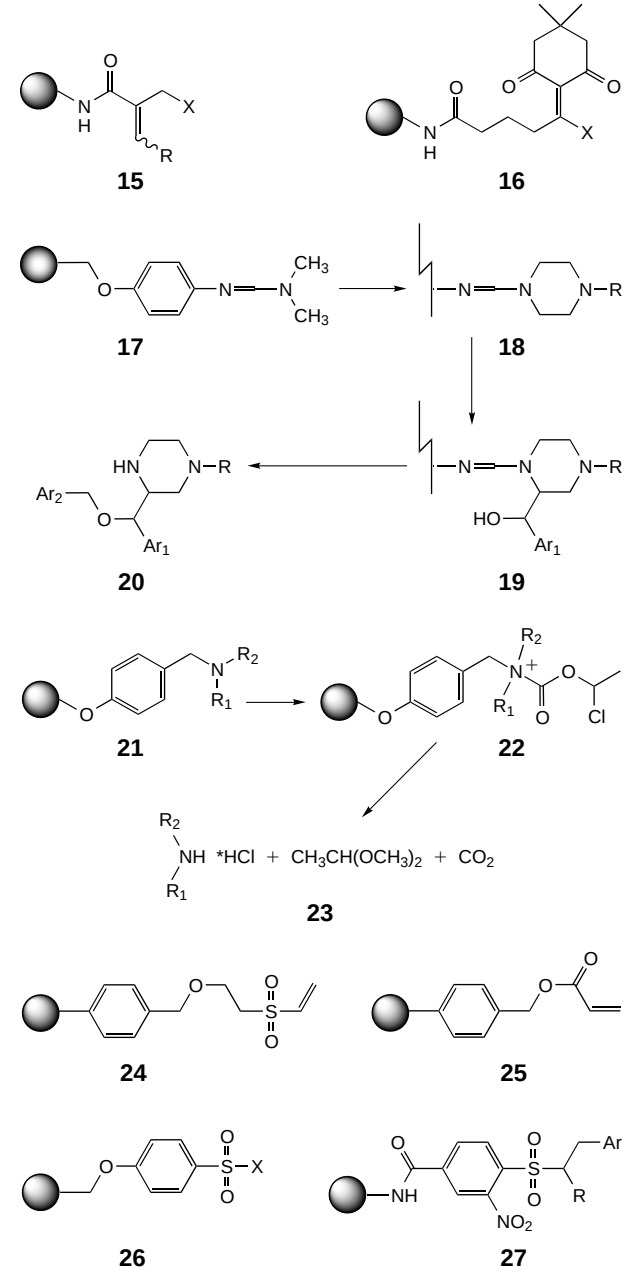

Figure 3. *Nucleophile-labile linkers: methacrylic linker (**15**); DDE linker (**16**); synthesis of amino ethers **20** starting from solid-supported dimethylformamidine (**17**); cleavage of secondary amines **23** (as hydrochlorides) from polymeric* p*-alkoxy benzyl group **21**; polymeric vinyl sulphone (**24**); REM linker (**25**); sulphonyl chloride resin (**26**); and sulphone linker (**27**).*

A 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl-derived linker **16** was developed for the attachment of primary amines to solid support[29]. The linker is stable to acidic and

basic conditions, such as piperidine or 1,8-diazabicyclo[5.4.0]undec-7-en (DBU), but is easily cleaved by 2% hydrazine in dimethylformamide (DMF). Another linker that is selectively cleaved by hydrazine was introduced by Furth and coworkers[30]. Solid-supported dimethylformamidine **17** can be treated with several secondary amines, to yield immobilized amidines through an amine exchange reaction. In a model reaction, *N*-alkylated piperazines were coupled to yield **18**, which in a second step were alkylated with aromatic aldehydes, resulting in **19**. The resulting secondary alcohol was alkylated in a Williamson reaction with a benzylic halide to generate the corresponding ether. Cleavage of the amino ethers (**20**) could be accomplished using either aqueous hydrazine–acetic acid or lithium aluminum hydride[31]. Since the building blocks employed are commercially available in great variety, libraries synthesized according to this scheme can incorporate a high degree of diversity.

Applications for amine release

An increasing number of publications deal with the binding of amines to polymeric carriers and their release upon nucleophilic treatment. A method for the immobilization of secondary amines to Wang resin which circumvents the attachment of amines via carbamate linkage was described by Organon chemists[32]. Secondary amines were coupled onto chloro-Wang resin **1** (X = Cl) by stirring it with 10 equiv. of amine in *N*-methylpyrrolidone at 50°C for 17 h. After synthetic transformations, the polymer-bound amine **21** was quaternized with α-chloroethyl chloroformate to yield **22**, followed by nucleophilic attack on the chloride anion at the benzylic carbon atom, which releases the secondary amines in refluxing MeOH as their HCl salts **23**. The same method works with Merrifield resin as well as with Sheppard resin. When other chloroformates are used for the cleavage step, the corresponding carbamates are obtained in excellent yield and purity. This protocol is remarkably selective because primary amines are not cleaved and *N*-dibenzyl groups elsewhere in the molecule remain unaffected.

By action of acetyl chloride or benzoyl chloride no cleavage is observed from Merrifield resin, while treatment of the corresponding Wang resins under these conditions yields tertiary amides in an acylative *N*-dealkylation step. In this manner, the cleavage step can be utilized as an element of diversity by using various acid chlorides[33]. However, these products have to be freed in a postcleavage work-up procedure of excess acid chloride via acidic ion-exchange resins.

Another example that follows a similar strategy uses the immobilization of secondary amines by a Michael-type addition to polymeric vinyl sulphones **24** (Ref. 34). Tertiary amines are obtained from such resins upon quaternization with alkyl iodide or benzyl bromide and subsequent elimination with the help of DIEA. Independently, the same linker was used by Organon chemists[35], who had earlier introduced the REM linker **25** (Ref. 36) for such applications. (The REM linker was so named because it is regenerated after cleavage of the product and is functionalized via a Michael reaction.)

Sulphonyl and sulphon linkers

A very interesting approach involves the use of a new sulphonyl chloride resin **26** (X = Cl). This resin can be functionalized with alkoxy groups by reaction with 5 equiv. each of alcohol and NEt_3 in DCM for 24–48 h at room temperature[37]. After synthetic transformations, cleavage can be carried out by treatment with various nucleophiles, such as amines, thiolate and imidazole, again leading to diversification in the cleavage step. The preferred cleavage conditions are 18 h at 60°C in acetonitrile. Among typical reaction conditions towards which the linkage is chemically stable are the reduction of aromatic nitro groups with $SnCl_2.H_2O$ in DMF, Grignard reactions, reductive aminations, Wittig reactions and Suzuki couplings[38].

A further example for a robust amine-releasing linker is given by Kay and coworkers[39]. They employ 2-nitrobenzosulphonamide, introduced by Fukuyama and coworkers[40], as a linker for SPOS of secondary amines. The preloaded linker is synthesized in solution, then coupled via a carboxylic functionality onto amino resin to yield **27**. The amino group is alkylated with various primary alcohols under Mitsunobu conditions (the same conditions fail with secondary alcohols). Treatment of the resin-bound sulphonamides **27** with 2 equiv. of potassium thiophenolate achieves the desired secondary amines. The excess reagent has to be removed by basic extraction during work-up.

Photolabile linkers

Photolysis is a mild cleavage method that is orthogonal to acidic and basic reaction conditions and is attractive for combinatorial drug discovery because the product can be released directly into neutral aqueous solution suitable for immediate screening[41,42].

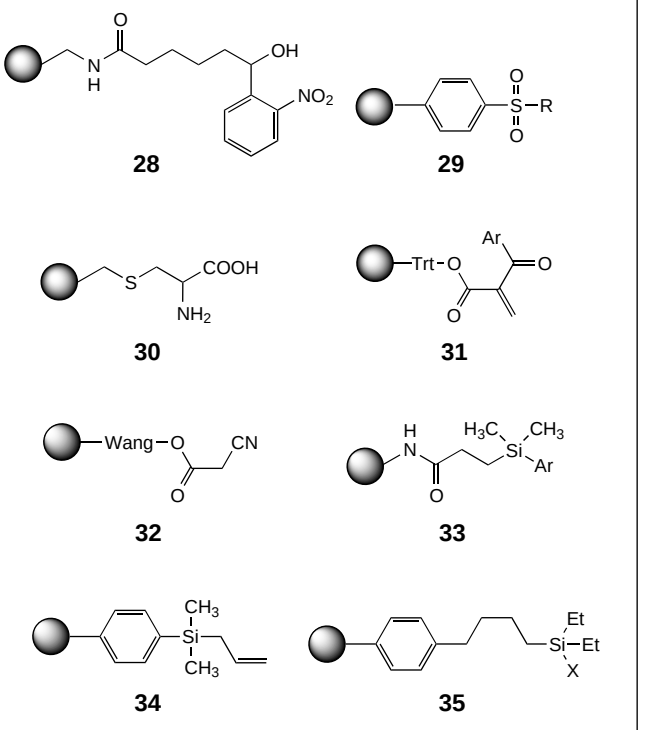

Figure 4. *Photolabile linker (**28**); traceless cleavage: arylsulphonate linkers (**29**), cysteine linker (**30**), decarboxylative cleavage reactions from trityl (**31**) and Wang bound (**32**) β-carboxylic acid esters; silicon-containing traceless linkers **29**–**35**.*

An improved photolabile linker **28** for carboxylic acids, amides and reducing carbohydrates was presented by the group of Fraser-Reid[43]. Cleavage from this linker occurs by irradiation of the resin in THF for 16 h at 365 nm.

Traceless linkers

Many efforts have been made to develop linkers that allow the traceless cleavage of products from the resin. One recent example uses polymeric allylic sulphone **29** (R = allyl) for the synthesis of trisubstituted olefins[44]. Dianion formation of the polymeric allylsulphone with *n*-BuLi in THF, followed by addition of excess alkylating agent, delivers α,α′-dialkylated allylsulphones. The cleavage process is initiated through substitution of the polymeric sulphonyl group with Mg-organyls under Cu catalysis. The overall yields of the olefins obtained do not exceed 20–30%. However, the ready availability of all reactants could compensate for the drawback of low yields.

Jin and coworkers[45] demonstrated how resin-bound arylsulphonates **29** (R = OAr) can lead to the corresponding aryl products upon reductive cleavage using a mixture of NEt_3–formic acid–$Pd(OAc)_2$–$PPh_2(CH_2)_3PPh_2$ in DMF at 110–140°C for 12 h. The yields range from 5% to 85%, depending on the nature of the substrate. The drawback of low yields and difficult work-up again could be compensated for by the fact that it is one of the rare examples for a traceless linker that can be functionalized on the resin by readily available phenols.

A library of dehydroalanines was synthesized from side-chain attached, unprotected cysteine **30** (Ref. 46). After derivatization at the C- and N-termini, the thioether bound to the resin is oxidized to the sulphone with 3 equiv. of *m*-chloroperbenzoic acid in DCM for 1 h at room temperature. After washing, β-elimination is induced by adding 1 equiv. of DBU to a suspension of the resin in DCM for 5 min.

Traceless decarboxylation

Two examples of traceless syntheses that use decarboxylation reactions have been reported. Novo Nordisk chemists showed the application of trityl resins as supports for the traceless synthesis of α-aminoketones[47]. They exploit in their strategy the fact that β-keto carboxylic acids readily decarboxylate. Commercially available 2-aroylacrylic acids are esterified with trityl chloride resin (**31**). After Michael-type addition of secondary amines, the products are cleaved from the resin with glacial acetic acid. But decarboxylation leading to α-amino ketones was only achieved by allowing the cleavage solution to stand for 8 h before evaporation. Interestingly, no decarboxylation was observed under standard cleavage conditions from trityl resin, which leads to another set of products.

The other example of decarboxylative cleavage strategy involves cyanoacetic acid linked to Wang resin **32** (Ref. 48). This resin is mixed with 5 equiv. each of benzoic acid and diethyl phosphorocyanidate (DEPC) in the presence of 1 equiv. of NEt_3 to afford the corresponding β-keto esters. Resin cleavage accompanied with concomitant decarboxylation produces benzoylacetonitriles with yields in the range of 30–80%.

Homoserine lactones

A series of various homoserine lactones[49] was synthesized on aminomethylpolystyrene. N^{α}-Fmoc-L-methionine is coupled under standard hydroxybenzotriazole (HOBt)–diisopropylcarbodiimide (DIC) conditions onto the resin. After Fmoc deprotection and acylative manipulations at the amino group, treatment with 15 equiv. of cyanogen

bromide and two drops of 99% TFA in $CHCl_3$–H_2O (5:2) for 24 h at room temperature generates the corresponding homoserine lactones with retention of stereochemistry in a cleavage-cyclization reaction. After aqueous extraction the products are obtained in 32–53% yield.

Silicon-containing linkers

Arylsilane linkers are designed to release unsubstituted aryl moieties. They are labile towards acidic treatment and/or fluoride ions. Most of them cannot be functionalized on resin, which is an obstacle for the fast generation of compound libraries.

An acid-labile traceless arylsilyl linker that proved to be stable under Mitsunobu conditions, acylating reactions with HOBt–DIC and basic saponification of methyl esters was published by a group from SmithKline Beecham (**33**)[50]. The aryl moiety is released upon treatment with neat TFA, either in liquid or vapor phase. The same linker, immobilized on aminomethylpolystyrene proved to be stable towards Suzuki and Stille coupling conditions and reductive aminations[51]. As reported by a group from Oxford Diversity, products are cleaved using 50% TFA–DCM for 2 h at room temperature.

The application of silyl linkers for TFA–DCM release of alkenes has also been described[52]. Cross-coupling between functionalized terminal alkynes and allylsilylpolystyrene **34** (Ref. 53) via selective Ru-catalysed yne–ene metathesis yields 1,3-dienes. Cleavage is carried out with 1.5% TFA–DCM.

A silyl linker resin that can be used for direct attachment of both oxygen- and carbon-based functional groups is the trialkylsilane resin **35** (Ref. 54). The linker is converted into the active trialkylsilyl chloride, which reacts readily with alkyl lithium or Grignard reagents. Electron-rich aromatic silane derivatives are cleaved by 50% TFA–DCM for 3 h at room temperature, while for electron-deficient aromatic compounds, 1 M tetrabutylammonium fluoride (TBAF)–THF for 12 h has to be used.

Cyclization-cleavage reactions

Many new strategies for SPOS of heterocyclic compounds that incorporate simultaneous cyclization-cleavage reactions of final products have been published recently. The major advantage of this approach, with the solid support acting as a leaving group during final cyclization of the resin-bound precursor, lies in the intrinsic product purification. When the cleavage is induced by a cyclization reaction and the functionality required for this is introduced with the last building block, cleavage is essentially restricted to the desired product, whereas side-products from incomplete reactions remain attached to the solid support. The first example following such a strategy was the synthesis of hydantoins[55].

Linkers based on allylic protecting groups, which are cleaved by palladium(0)-catalysed allyl transfer to nucleophiles, have been used for the immobilization of carboxylic acids, amines and alcohols[56,57]. The advantages of these linkers are the mild cleavage conditions and the orthogonality to many other protecting groups. However, the drawback of this type of linker is the necessity to purify the products by subsequent chromatographic work-up to remove the catalyst and traces of triphenylphosphine oxide, the oxidized ligand of the metal complex. A strategy that combines Ru-catalysed ring-closing metathesis with concomitant cleavage was used for the synthesis of six- and seven-membered ring systems, such as dihydropyrans, pipecolinic acid derivatives or Freidinger lactams **38** (Ref. 58). The latter are obtained after Mitsunobu reaction between *N*-Boc-2,4-dinitrobenzosulphonamide and cinnamic alcohol resin, synthesized according to the procedure developed by Fréchet's group in 1971. The resin-bound *N*-Boc-*N*-sulphonamide is deprotected from the Boc group and alkylated with secondary alcohols under Fukuyama–Mitsunobu conditions. After removal of the sulphonyl group by treatment with benzylamine, the amine is acylated with racemic N^{α}-Boc-allylglycine, which provides the penultimate resin-bound diene **37**, R_3 = NHBoc. Cyclization-cleavage with Grubbs' ruthenium catalyst yields the corresponding cycloalkene, in this case a Freidinger lactam **38** (Ref. 59). As with the Pd-catalysed cleavage of allylic linkages, the products contain, besides the catalyst itself, impurities of tricyclohexane phosphine oxide and have to be purified by chromatographic work-up.

Cycloreversion

The synthesis of a furan library by cycloreversion has been described by a group from Affymax[60]. They acylated amino-TentaGel S with various carboxylic acids using DIC in the presence of catalytic amounts of 4-dimethylaminopyridine. Conversion of amide **39** to imide is accomplished by treating the resin twice with a 1:1 mixture of malonyl chloride in benzene at 60°C for 1.5 h. Quantitative diazo transfer to the imide is effected at room temperature using tosyl azide in DCM–NEt_3. These diazoimides **40** are

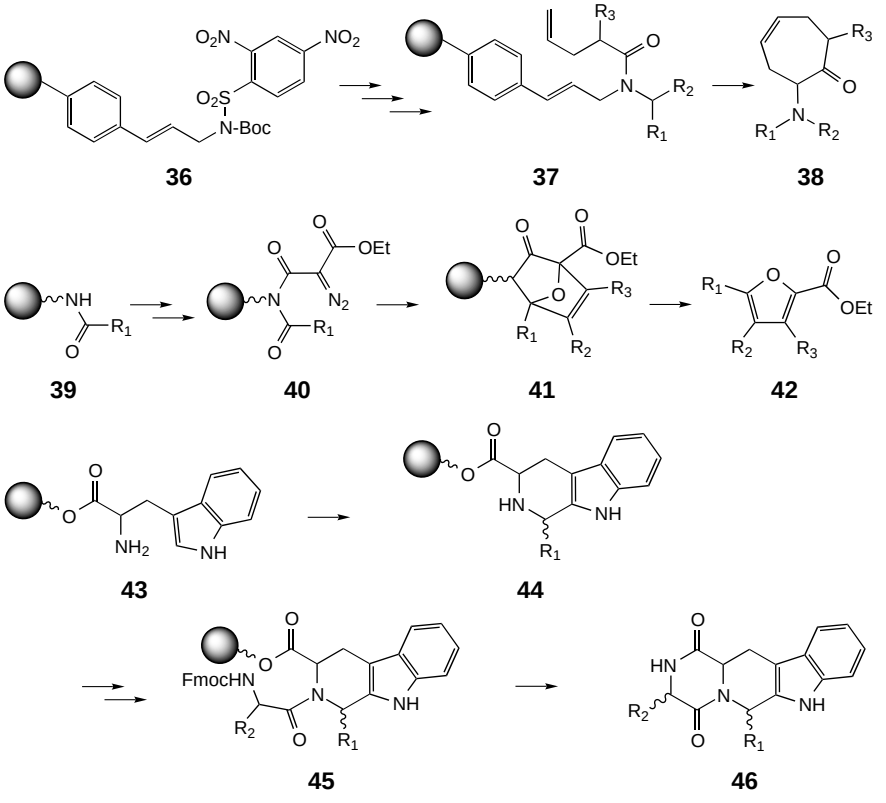

Figure 5. *Cyclization-cleavage reactions: synthesis of Freidinger lactams* ***38*** *(Ref. 58), furans* ***42*** *(Ref. 60) and indolyl diketopiperazine alkaloids* ***46*** *(Ref. 61).*

reacted with 10 equiv. of different acetylenes in benzene at 25°C for 2 h in the presence of $Rh_2(OAc)_4$ as the catalyst to yield isomünchones **41** through cycloaddition. Excess acetylene is removed by washing, after which the resin is taken into fresh solvent and heated at 80°C to promote cycloreversion. After filtration, the organic solvents are washed with water to remove any traces of the rhodium catalyst. The crude products contain only the desired furans **42**. While this protocol works for acetylenes with two electron-withdrawing groups, acetylenes with a single electron-withdrawing moiety are less reactive and do not form the intermediate isomünchones at room temperature. These products are synthesized at 80°C with concomitant release of the corresponding furans **42**. In this case, excess acetylenes are fortunately sufficiently volatile and can be removed *in vacuo* to provide furans of high purity.

Indolyldiketopiperazine alkaloids

Indolyldiketopiperazine alkaloids **46** are synthesized on hydroxyethylated polystyrene resin[61]. The resin is esterified with L-tryptophan and **43** is subjected to Pictet–Spengler condensation with excess aldehydes. Optimum conditions comprise reaction in DCM in the presence of 5% TFA at room temperature for 16 h. Subsequent acylation of the resulting secondary amines **44** with Fmoc-amino acid chlorides, conveniently prepared by treatment with $SOCl_2$ followed by isolation, or generated *in situ* with tetramethylchloroformamidinium hexafluorophosphate[62] or commercially available 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate[63] leads to indolyldiketopiperazine alkaloids **46**.

Further examples for cyclization-cleavage reactions include the synthesis of hydantoins[64], oxazolidinones[65] and pyrazolones[66].

Conclusion

Through the modification of peptide linkers for SPOS, a huge number of acid-labile linkers are available, covering the whole spectrum between mild and harsh acidic-cleavage conditions. At most, progress in this area can be expected for the optimization of coupling and cleavage procedures for the different functionalities. In the field of nucleophile-labile linkages many new linkers and methodologies are presented. But the main focus of these developments is on the immobilization and release of amino functionalities. A promising strategy is nucleophilic cleavage with simultaneous introduction of additional diversity such as with different amines. It is hoped that more examples for such strategies will emerge in the future, especially with the consequent use of scavenger resins to remove excess reagents. Many approaches for traceless synthesis have also been published. Some of them make use of the intrinsic lability of the cleaved product – for example, in the decarboxylation reaction of β-carboxylic acids. A more general approach is the use of silicon-containing linkers. But in this case more convenient loading procedures of the immobilized silicium linkers with scaffold need to be developed. Cyclization-cleavage

reactions have the advantage of leading to products of high purity. However, this method is restricted to certain core structures.

It will be interesting to follow future developments in the important field of linking strategies.

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