Solid Phase Heterocyclic Chemistry

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1. Introduction

To synthesize a dipeptide from two amino acids, the carboxy group of the C-terminal amino acid and the amino group of the N-terminal amino acid are usually protected. When Merrifield first performed his ingenious concept of solid phase synthesis,[1] the carboxy-terminal amino acid was attached to the solid support via an ester linkage. The ester served two simultaneous functions: (i) it allowed tethering of the amino acid to the solid support, and (ii) it protected the carboxylate function from participating in subsequent reactions. Thus, the carboxylate, an inherent part of the target peptide, was a very useful functionality for the application of the solid phase synthetic method. The benzyl ester type of linkage became very popular, and its properties, particularly acid lability and sensitivity toward nucleophiles, have been optimized for various synthetic tasks (for excellent reviews, see refs 2 and 3). A similar concept was developed for the preparation of peptide amides, whereby the most commonly used linker is a derivatized benzhydrylamine function.

Not surprisingly, solid phase synthesis did not remain limited to peptides, and early contributions were made to its use for general organic synthesis, particularly by Leznoff,[4,5] Fréchet,[6] and Rapoport.[7] Solid phase organic synthesis is attractive from at least three perspectives: (i) it allows very simple separation of synthetic intermediates from soluble components of a reaction mixture by simple filtration and washing of the resin-bound reaction product. A straightforward consequence is the ability to use a high-boiling reaction solvent such as DMF, DMSO, NMP, without the need to evaporate the solvent. (ii)

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Viktor Krchňák was born in Brno, Moravia, in 1947. He studied chemistry at the Faculty of Natural Sciences of Masaryk University in Brno. After receiving his Ph.D. in organic chemistry under the supervision of Prof. Zdenek Arnold at the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague, his research interest focused on solid phase synthesis. In the Peptide Department of Leciva Pharmaceuticals, Prague, he developed solid phase commercial production of peptides and initiated a research program of synthetic peptide antigens for antibody detection. In 1992, he joined Selectide Corp., Tucson, AZ, and since then his research interests have included combinatorial chemistry and solid phase synthesis methodology. After a short sabbatical at Houghten Pharmaceuticals, San Diego, CA, he returned to Tucson to build a high-throughput combinatorial chemistry unit at Systems Integration Drug Discovery Co. (SIDDCO). He also started his own company, Torviq, developing novel tools for solid phase chemistry. This paper reviews solid phase traceless synthesis of heterocyclic compounds, one of the research activities of his former New Concepts Development group at SIDDCO. He is a Chief Scientific Officer of Encore International. In addition to chemistry and instrumentation, he enjoys listening to baroque music, driving historical sport cars, and photographing landscapes.

Mark W. Holladay started his career in chemistry as an undergraduate researcher while pursuing a bachelor's degree at Vanderbilt University. After receiving a Ph.D. in organic chemistry under the direction of Prof. Richard B. Silverman at Northwestern University, he conducted postdoctoral studies at the University of Wisconsin—Madison with Prof. Daniel H. Rich. He spent 15 years in the Medicinal Chemistry department at Abbott Laboratories, where his research focused on discovery of novel agents for treatment of neurological diseases. Among his accomplishments at Abbott, he led the team of chemists who discovered novel nicotinic acetylcholine receptor ligands that have entered clinical trials for the treatment of pain. In 1998, he moved to Systems Integration Drug Discovery Company (SIDDCO) in Tucson, AZ, which is now part of ChemRx Advanced Technologies, a Discovery Partners International Co. He is currently Senior Director of Chemistry at ChemRx.

A high concentration of reactants in solution facilitates driving reactions to completion. Note that the high concentration of reagents (obviously in excess) plays the key role rather than the excess of reagent per se. Peptide synthesis on beaded cellulose with substitution of 0.005 mmol/mL using a 5-fold excess of activated amino acid did not drive the reaction to completion (the concentration of active species was 0.025 M).[8] (iii) A simple repetitive process (adding reagent, mixing, washing) allows for integration and/or automation of solid phase synthesis.

When Merrifield was looking for a suitable insoluble support for his solid phase peptide synthesis, his choice ended up as a beaded form of copolymer of styrene and divinylbenzene.[9] Since then a variety of solid phase supports was introduced, a number of them claiming superior properties when compared to the original Merrifield resin. However, after almost 40 years, the copoly(styrene−1% divinylbenzene) is still the most commonly used resin (Figure 1). The

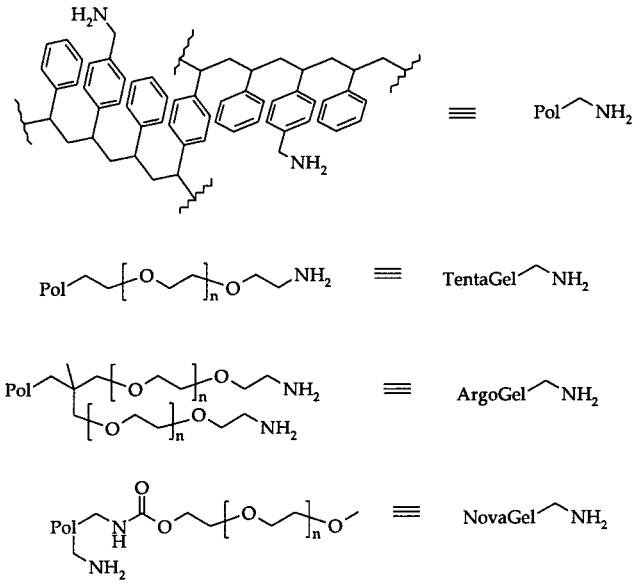


Figure 1. Amino group functionalized solid phase resins. Note: Copoly(styrene−divinylbenzene) is abbreviated Pol and the substituent is always located at position 4 on the benzene ring. Three different PEG grafted copoly(styrene−divinylbenzene) resins are shown: TentaGel (Rapp Polymere), ArgoGel (Argonaut), and NovaGel (NovaBiochem).

polymeric matrix surrounds the synthesized compound and it behaves as a solvent. Thus, synthesis on copoly(styrene−divinylbenzene) resembles performing the reactions in toluene.[10,11] The highly hydrophobic nature of the polymer prompted Rapp to graft the polystyrene copolymer with linear poly(ethylene glycol) chains.[12,13] A new resin termed TentaGel (Argonaut and NovaBiochem introduced later similar resins, ArgoGel and NovaGel, respectively) gained popularity, and better kinetics for reactions requiring polar media was reported.[11] However, there is no single polymer support that favors all reactions, and the need to use polar or nonpolar media should influence the choice of support.[11]

Until the early 1990s, solid phase organic synthesis was not widely used, and its domains remained principally peptides, nucleic acids, and, later, carbohydrates. The renaissance of solid phase organic synthesis was triggered by the advent of combinatorial chemistry techniques.[14−16] Synthesis of combinatorial libraries of organic compounds on a solid phase, pioneered by Ellman[17] and DeWitt,[18] initially

utilized linkers such as carboxylic ester or amide, in analogy to those commonly used in peptide synthesis. Subsequently, linkers that released the products as alcohols, amines, or the like were developed. Thus, the majority of synthetic procedures for organic compounds resulted in products tagged by a specific functional group. Consequently, one challenge for contemporary solid-phase organic synthesis has been to design methods to synthesize organic molecules lacking functional groups that are obvious traces of the linkage to the solid support.

In this review, we describe methods for the traceless solid-phase synthesis of various heterocyclic compounds, whereby the presence of obvious traces of linkage to the solid support are eliminated. (The term "traceless synthesis" describes a synthetic route yielding compounds composed only from atoms inherent to the particular target compound and should not be confused with the term "traceless linker", used to refer to a C−H linker.) Although there is some overlap between the various methods, we have attempted to organize these approaches into several distinct categories as follows:

(1) Use of C−H linkers results in formation of a C−H bond in the seceding molecule during the cleavage step. The products are viewed as traceless, since they lack the functional groups commonly associated with linkage to the solid support. Nevertheless, there may remain functionality (e.g., an aromatic ring) that was present in order to activate the tethered molecule to cleavage under the prescribed conditions. Traceless linkers were reviewed by Bräse.[19,20]

(2) Use of N−H linkers results in formation of an N−H bond in the seceding molecule. In this review, such products are viewed as traceless when the nitrogen atom in question is an integral part of the target heterocyclic nucleus.

(3) Application of a cyclative cleavage strategy yields a newly formed C−N bond that is integral to the heterocyclic system and therefore formally traceless.

(4) Inducement of modifications to the target molecule during or after the cleavage step obscures or obliterates the previous point of attachment to the solid support. Particular examples of this approach include the following:

(a) cyclization,

(b) decarboxylation,

(c) oxidation,

(d) linker replacement, and

(e) miscellaneous.

Three reviews on linkers were published in the recent past. Excellent comprehensive reviews by James[2] and Guillier, Orain, and Bradley[3] summarized the literature on linkers and are indispensable tools for application of individual linkers and designing solid phase routes. In their review article, Comely and Gibson[21] described rigorous analytical classification of linkers with respect to functionality remaining on the target compound.

2. C–H Linkers

The C−H bond is an inherent feature of organic compounds, and accordingly, C−H linkers provide a general approach to many classes of target molecules. In this review, the discussion is restricted to aromatic C−H linkers, because a benzo moiety is an integral part of numerous heterocyclic target molecules (e.g., benzimidazoles, benzodiazepines, quinoxalines, quinazolines).

2.1. Arylsilanes

Silicon-based traceless linkers were introduced independently by Plunkett and Ellman[22] and by Veber's group.[23] The silicon−aryl bond can be cleaved using acidic conditions or by a fluoride ion, leaving hydrogen on the aromatic ring in the place of silicon. The evolution of aryl silane linkers is shown in Figure 2. Linkers **1**−**4**, where the R-substituted arene is the

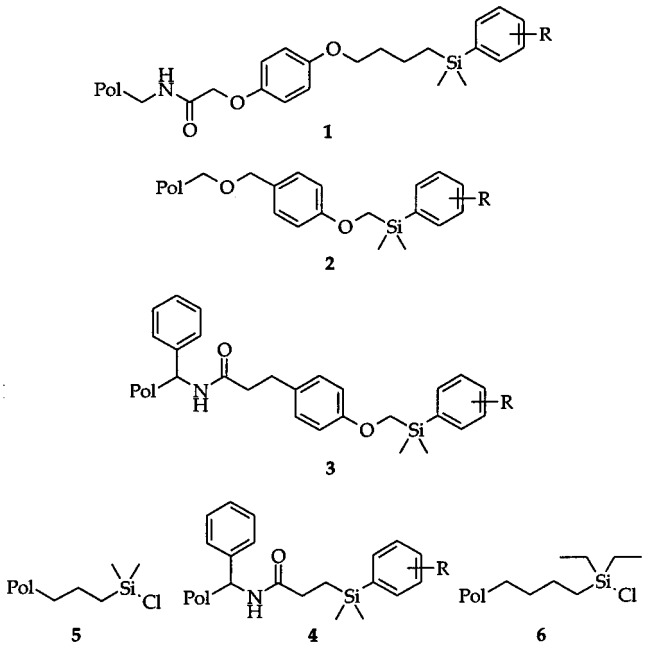
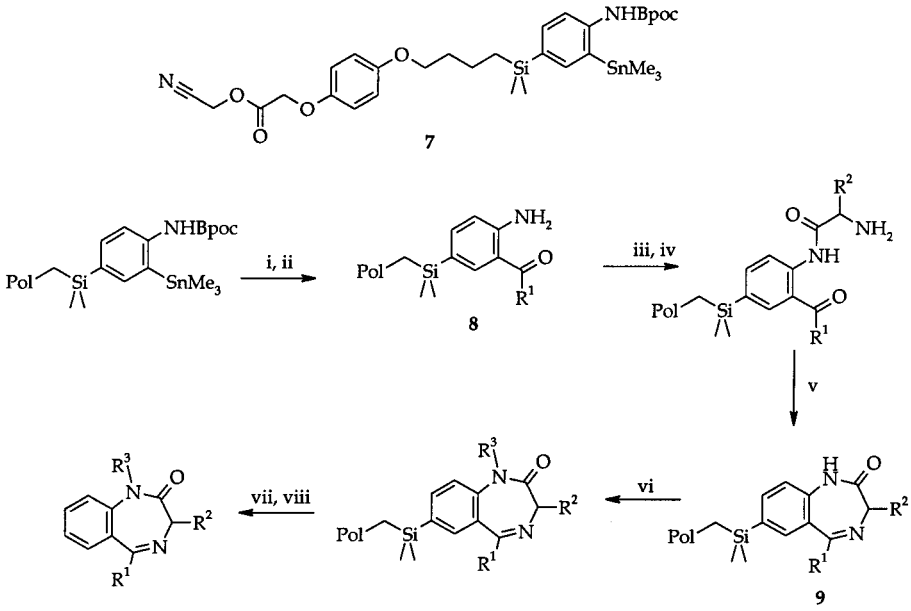


Figure 2. Silicon-based traceless linkers.

starting material for organic solid phase synthesis, required solution synthesis of intermediates prior to attachment to the solid support, whereas linkers **5** and **6** allowed direct loading of the starting material onto the solid support.

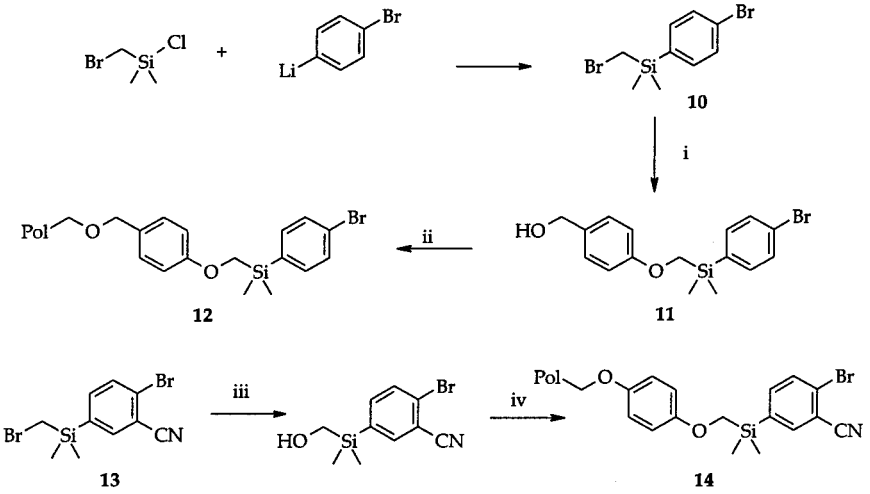
Plunkett and Ellman[22] described the solution synthesis of the linker−first building block unit **7** for combinatorial synthesis of benzodiazepines (Scheme 1). The activated ester **7** was coupled onto (aminomethyl)polystyrene resin. Stille coupling of the resin-bound stannane with acid chlorides provided ketone **8**. The amino group was deprotected and acylated with an Fmoc-protected amino acid, and the Fmoc group was removed. The linear precursor was then cyclized to benzodiazepine **9**. Alkylation of amide nitrogen introduced the third diversity point. Any amino acid side chain protecting groups were removed by TFA, and the target compounds cleaved from the resin in liquid HF.

Scheme 1[a]



[a] Reaction conditions: (i) acid chloride, $Pd_2(dba)_3 \cdot CHCl_3$; (ii) 3% TFA; (iii) Fmoc-amino acid fluoride; (iv) 20% piperidine in DMF; (v) 5% AcOH, 65 °C; (vi) lithiated oxazolidinone, then alkyl halide, DMF; (vi) TFA/DMS/H_2O (85:10:5); (vii) HF.

Scheme 2[a]



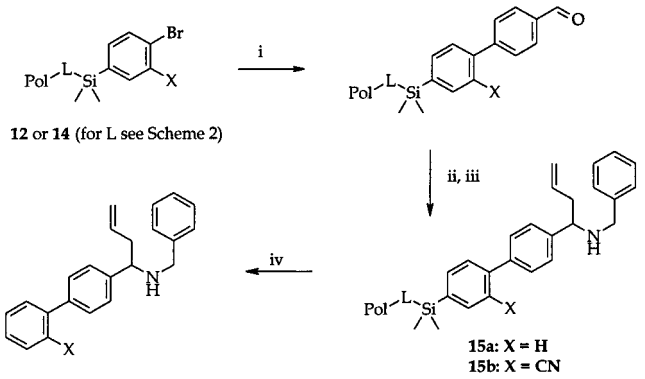
[a] Reaction conditions: (i) K_2CO_3, DMF; (ii) chloromethylated Merrifield resin, NaH, THF, 70 °C; (iii) NaOAc, DMF followed by 3 N HCl; (iv) phenol resin, PPh_3, DIAD, NMM.

Veber's group[23] independently described silicon linker **2** (Scheme 2). The synthesis started with the preparation of the linker−first building block intermediate **10** in solution. Lithiated *p*-bromobenzene was reacted with (bromomethyl)chlorodimethylsilane to afford aryl silane **10**, which alkylated *p*-hydroxybenzyl alcohol to yield intermediate **11** (Scheme 2). The benzyl alcohol **11** was then attached to the Merrifield resin using sodium hydride in DMF to afford resin **12**. An alternative route was devised for chemically unstable cyano derivative **13**, which was converted to an alcohol and coupled under Mitsunobu conditions to the phenol resin (prepared from Merrifield chloromethylated resin and monoacylated *p*-catechol), yielding resin **14**.

Both resins **12** and **14** were used in palladium-catalyzed Suzuki coupling with (*p*-formylphenyl)-boronic acid and subsequent derivatization of the resin-bound aldehyde to prepare biphenyl derivatives **15** (Scheme 3). The product was cleaved by TFA in the case of **15a**; when an electron-withdrawing cyano group was present on the aromatic ring (**15b**), no cleavage was observed in TFA. However, the product was cleaved in the latter case with CsF at elevated temperature.

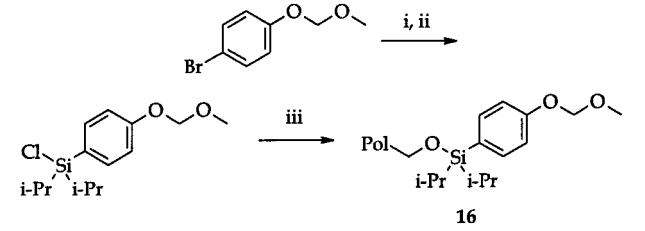
A practical limitation of both linkers is the requirement for a multistep synthesis of linker−first building block intermediate and the fact that the acid sensitivity of the aryl−silicon bond depends largely on the electronic properties of other substituents on the aromatic ring, necessitating long exposure to TFA or the use of HF for cleavage. Instead of using an alkylsilane bond for attaching the silicon to the aromatic nucleus, Boehm and Showalter[24] designed linker **16**, in which the arylsilane is linked to a solid support via a silyl ether bond (Scheme 4). The cleavage of the silicon−aryl bond was achieved by fluoride ion. The synthesis of the linker in solution

Scheme 3[a]



[a] Reaction conditions: (i) (*p*-formylphenyl)boronic acid; (ii) benzylamine; (iii) allylmagnesium bromide; (iv) TFA for **15a**, CsF, DMF/H_2O, 100 °C for **15b**.

Scheme 4[a]



[a] Reaction conditions: (i) *n*-BuLi, THF, −78 °C; (ii) $Cl_2Si(i\text{-}Pr)_2$, −78 °C; (iii) hydroxymethyl PS resin, imidazole, DMF, rt.

preceded its attachment to the hydroxymethyl resin (Scheme 4).

The practical usefulness of this linker was documented by the synthesis of benzofurans (Scheme 5). The resin-bound silyl ether **16** was subjected to ortho-lithiation, followed by quenching with DMF. The resin-bound aldehyde **17** was reacted with *p*-lithioanisole, and the resulting benzhydrol was oxidized by IBX to yield **18**. The alcohol protection group was removed with 5% TFA and reacted with α-bromo ketones. The cyclization of linear precursor **19** to benzofurans was achieved by DBU in NMP. Target benzofurans **20** were cleaved from the linker with TBAF.

Briehn et al.[25] used similar strategy for tethering a thiophene nucleus in order to synthesize oligo(3-arylthiophene)s.

Linker **3**, designed by Moore's group,[26] is similar to **2** but permits attachment of the linker to MBHA resin via straightforward amide bond formation. An unexpected mode of cleavage of this linker was reported. When model compound **21** was exposed to TFA, compound **22** and a product tentatively formulated as **23** were detected, instead of the expected product **24** (Scheme 6).

This undesirable pathway of cleavage prompted design of an alternative linker that maintained the advantages of **3** but could not undergo the undesired cleavage mode.[26] The new linker **4** (Scheme 7), synthesized via malonate adduct **25**, excluded any heteroatom in the chain. Model experiments have shown that cleavage with TFA provides the expected product devoid of side products.

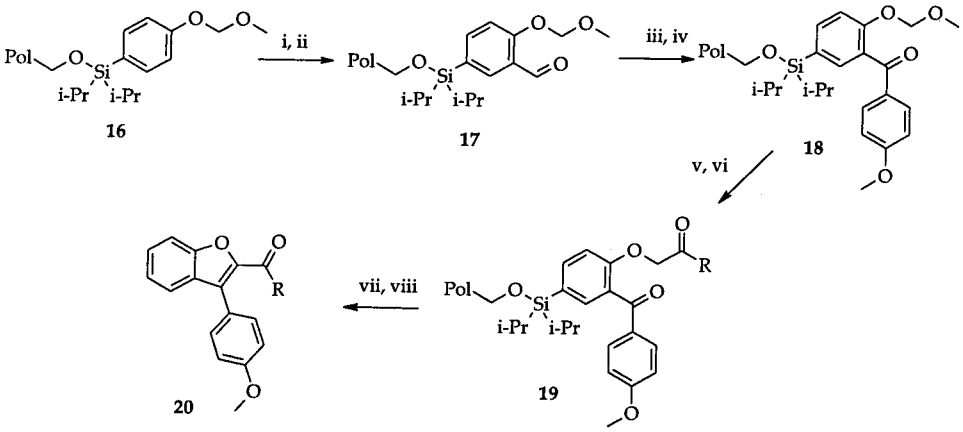
Two other groups independently reported the use of the same linker. Brown and Armstrong[27] coupled the linker to ArgoGel amine resin and used it in the synthesis of tamixofen derivatives. Hone et al.[28] demonstrated the utility of this linker by the synthesis of biaryl compounds.

The principal drawback to use of the above linkers has been the requirement for a multistep solution phase synthesis preceding attachment to the solid support. To overcome this disadvantage, Woolard et al.[29] designed the silyl-derivatized solid support **27** from bromo-substituted polystyrene resin and **26** (Scheme 8). Resin **27** is stable and can be converted to reactive silyl chloride resin **5** by treatment with HCl in DCM and used for the direct loading of aromatic compounds. To document the usefulness of the silyl resin **5**, pyridine-based tricyclics have been prepared.[29] Obviously, resin **27** also can be used directly for solid phase modification, as described by Curtet and Langlois[30] for preparation of 2-methoxyaniline derivatives.

A similar approach was described by Hu et al.,[31] who synthesized the shelf-stable silicon linker **29** from the resin-bound butene **28** (Scheme 9). The linker **29** was converted to reactive chloride **6** prior to loading of starting material to the linker via various functional groups.

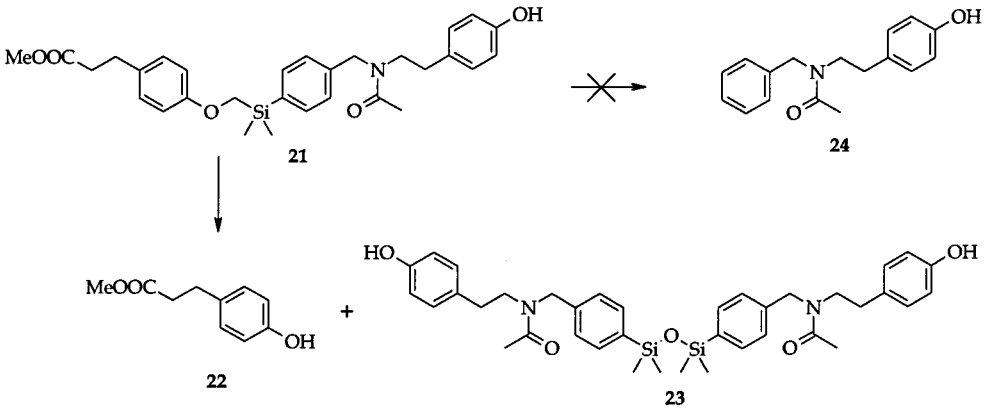
To increase lability to acidic cleavage, Plunkett and Ellman[32] replaced the silicon in linker **1** by germanium and applied the resulting linker to the synthe-

Scheme 5[a]

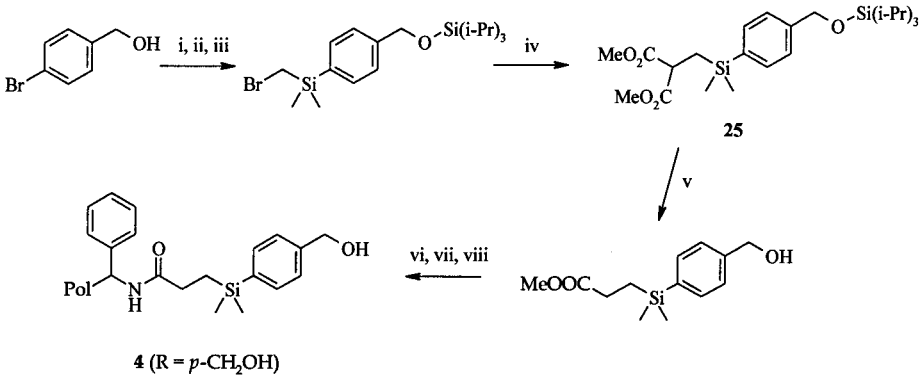


[a] Reaction conditions: (i) *n*-BuLi, TMEDA, Et_2O, 0 °C; (ii) anhydrous DMF, 0 °C; (iii) 4-bromoanisole, *n*-BuLi, THF, −78 °C; (iv) IBX, DMSO/THF, rt; (v) 5% TFA in DCM, 0 °C; (vi) α-bromo ketone, DIEA, NMP, 80 °C; (vii) DBU, NMP, 80 °C, (viii) TBAF, DMF, 65 °C.

Scheme 6

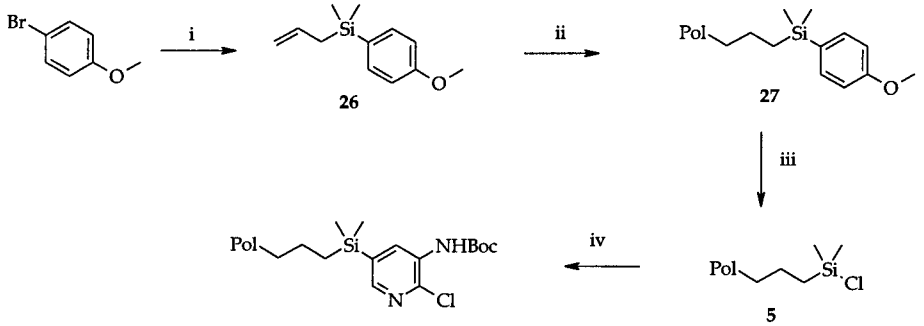


Scheme 7[a]



[a] Reaction conditions: (i) TIPS−Cl, imidazole, DMF; (ii) Mg, THF; (iii) (bromomethyl)chlorodimethylsilane; (iv) dimethyl malonate, NaOMe, MeOH; (v) HOAc, H_2O, THF; (vi) LiCl, H_2O, DMSO, 140 °C, 24 h; (vi) NaOH, H_2O, dioxane; (vii) HCl; (viii) BHA resin, DCC, HOBt, DMF.

Scheme 8[a]



[a] Reaction conditions: (i) *n*-BuLi, THF, followed by allyldimethylsilyl chloride; (ii) 9-BBN, THF, followed by bromo-substituted PS resin, $Pd(PPh_3)_4$, Na_2CO_3; (iii) HCl, DCM; (iv) 5-bromo-2-chloro-3-Boc-aminopyridine, KH, THF, then *t*-BuLi, then silyl resin **27**.

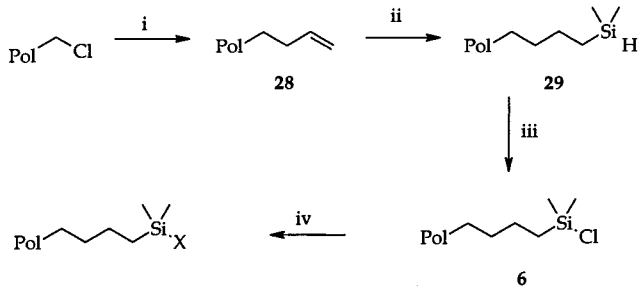
sis of benzodiazepines using a route analogous to the previous one using silicon. Neat TFA at 60 °C was used to cleave the product benzodiazepines from the germanium linker, thus demonstrating a significant increase in acid lability over the original linker. Similar to Han's observation[33] (cf. section 6.1), the germanium linker can also be cleaved by electrophiles such as Br_2 and ICl.

Spivey et al.[34] were inspired with a similar idea and designed the germanium-based linker **30** (Scheme 10). The usefulness of the linker was demonstrated by the synthesis of pyrazoles.

2.2. Arylsulfonates

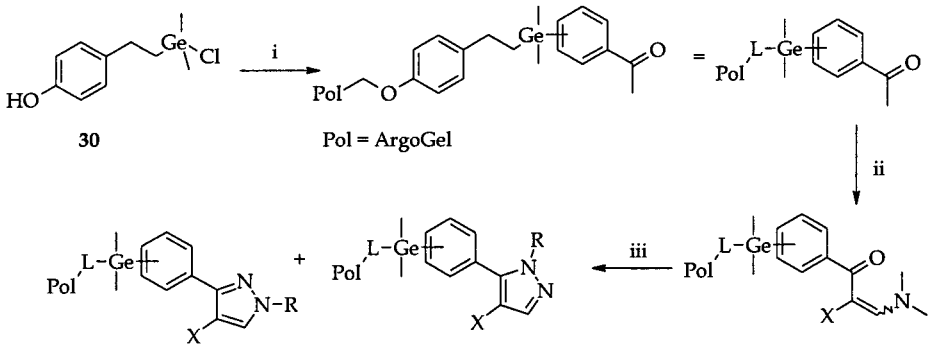
Resin-bound arylsulfonates can be cleaved under reductive conditions to yield arenes[35] (Scheme 11).

Scheme 9[a]



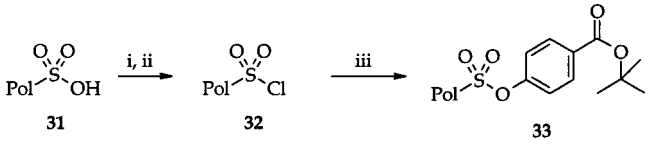
[a] Note (i): allylmagnesium chloride, toluene, 60 °C; (ii) R_2SiH_2, toluene, $RhCl(PPh_3)_3$; (iii) 1,3-dichloro-5,5-dimethylhydantoin, DCM, 1.5 h; (iv) X = O−R: alcohol, imidazole, DCM, 4 h; X = Ar: ArLi, THF, −78 to 0 °C; X = allyl: allylmagnesium chloride, THF, −78 to 0 °C.

Scheme 10[a]



[a] Reaction conditions: (i) ArgoGel, *N*,*N*,*N*′,*N*′-tetramethylazocarboxamide, PBu_3, benzene, 16 h; (ii) *t*-butoxybis(dimethylamino)methane, THF, 70 °C, 3 h; (iii) arylhydrazine hydrochloride, *n*-BuOH/AcOH (50:1), 100 °C, 1 h.

Scheme 11[a]

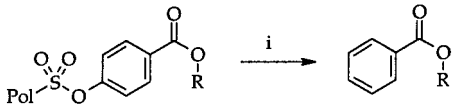


[a] Reaction conditions: (i) pyridine, reflux, 4 h; (ii) $SOCl_2$, reflux, 4 h; (iii) *tert*-butyl 4-hydroxybenzoate, TEA, DCM.

The resin-bound linker was prepared from benzenesulfonic acid resin (Dowex ion-exchange resin). The acid **31** was converted to the corresponding chloride **32** and reacted with *tert*-butyl 4-hydroxybenzoate to form the aryl sulfonate **33**.

The arylsulfonate can be modified at this stage, for example, by elaboration of the ester function, to obtain the polymer-supported target structure. Release of the arene from the resin was achieved by a Pd(0)-catalyzed reductive cleavage (Scheme 12). The

Scheme 12[a]



[a] Reaction conditions: (i) TEA, formic acid, $Pd(OAc)_2$, DPPP, DMF, 110−140 °C, 12 h.

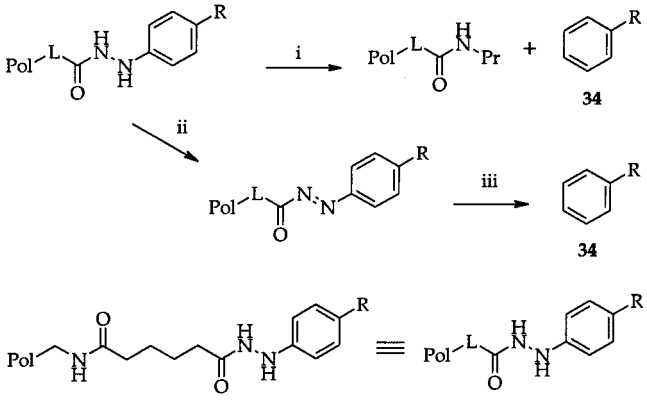
presence of an electron-withdrawing group in the para position to the sulfonate oxygen is critical for efficient cleavage. The yield varied from 36 to 74% for benzoate esters and 13 to 45% for benzamides.

2.3. Arylhydrazides

Acid and base stable aryl hydrazides have originally been used to prepare fully or partially protected peptides.[36] However, the linker attached to the solid support via the acyl group was cleaved by mild oxidation in the presence of base and a nucleophile to release the arene **34** (Scheme 13). The hydrazide was converted to acyl diazene, which was attacked by a nucleophile (amine) to yield resin-bound amide with release of arene.

Stieber et al.[37] prepared carboxylic acid functionalized resin from commercially available amino-resin and adipic acid dichloride. Reaction of this resin with 4-iodophenylhydrazine and the resin-bound iodo-derivatized hydrazide was used in Pd-catalyzed coupling reactions. The target products were released

Scheme 13[a]



[a] Reaction conditions: (i) $Cu(OAc)_2$, NH_2Pr, rt, 2 h; (ii) NBS, pyridine, DCM, rt, 2 h; (iii) MeOH, rt, 2 h.

by oxidation with copper(II) acetate in methanol in the presence of pyridine or *n*-propylamine. A practical advantage is offered by a two-step procedure, where the hydrazide is oxidized to acyl diazene in the absence of a nucleophile and washed and then the acyl diazene is cleaved by methanol (Scheme 13).

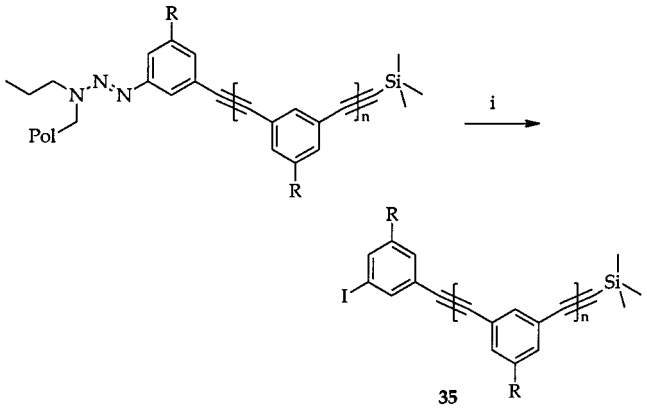
The same principle, i.e., oxidation followed by nucleophilic cleavage of hydrazides, with build in "safety-catch" features, was described by Berst et al.[38] and applied for the synthesis of piperazinones.

2.4. Aryltriazenes

The triazene linkage was introduced to solid-phase chemistry by Nelson et al.[39] for the synthesis of phenylacetylene oligomers **35** (Scheme 14). Cleavage from the resin was accomplished using iodomethane and produced an aryl iodide. The triazene linker was also used by Jones et al.[40] for the preparation of oligo-(1,4-phenyleneethylene)s with thioester termini as molecular scale wires with alligators clips. The thiols served as the clips for adhesion to gold probes. The 128 Å long 16-mer was synthesized on a triazene-derivatized Merrifield resin using iterative divergent/convergent approaches.

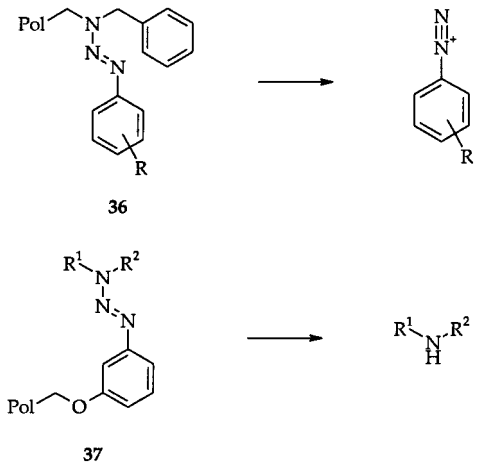
The use of triazenes for traceless synthesis of arenes[41,42] and amines[43] and for a multidirectional cleavage strategy[19,44] has been developed by the Bräse group. The triazene moiety can serve as a linker in two different synthetic scenarios, depending

Scheme 14[a]



[a] Reaction conditions: (i) MeI, 110 °C, 6−48 h.

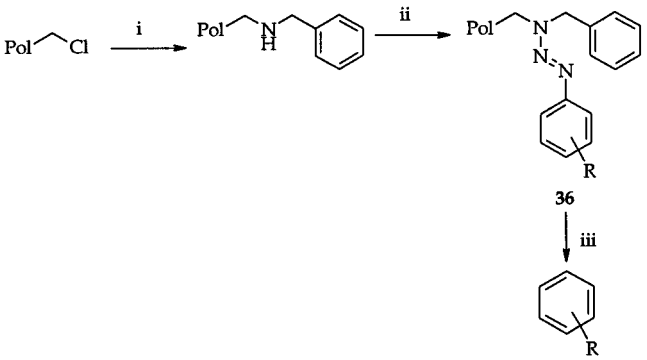
Scheme 15



on the site of attachment to the resin (Scheme 15). The T1 linker **36** releases arenes, whereas the T2 linker **37** is used to prepare amines (and derivatives including amides, ureas, and hydrazines).

Reduction of diazonium compounds is known to yield arenes. Aryl diazonium salts, formed from readily available anilines, can be treated with amines to produce triazenes, which revert to diazonium compounds under acidic conditions (Scheme 16). For

Scheme 16[a]



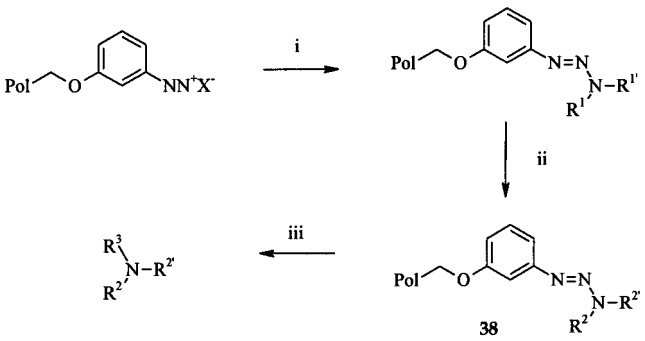
[a] Reaction conditions: (i) benzylamine, DMF, 48 h, 60 °C; (ii) aryldiazonium salt, THF, 15 min, 25 °C, repeat three times; (iii) $HSiCl_3$, DCM, 32 °C, 15 min.

the traceless synthesis of arenes, the triazene linker **36** was constructed on the solid support from reaction of a polymer-supported secondary amine with a diazotized aniline.[41,44] Various chemical modifications have been performed on the aromatic ring of **36**, including Heck reactions, Diels−Alder reactions, and metal−halogen exchange followed by reaction with diethyl phthalate. After chemical modifications, the arene derivative underwent reductive deamination in H_3PO_2.[41] In a subsequent paper,[42] the cleavage procedure was improved by using trichlorosilane.

An additional beneficial feature of the T1 triazene linker is the possibility of recycling the secondary amine resin after cleavage of the target compounds.

Incidentally, the triazene moiety from reaction of resin-bound diazonium salts with amines was reported to be a useful linker for the traceless synthesis of functionalized amines[43] (Scheme 17). Cleavage

Scheme 17[a]



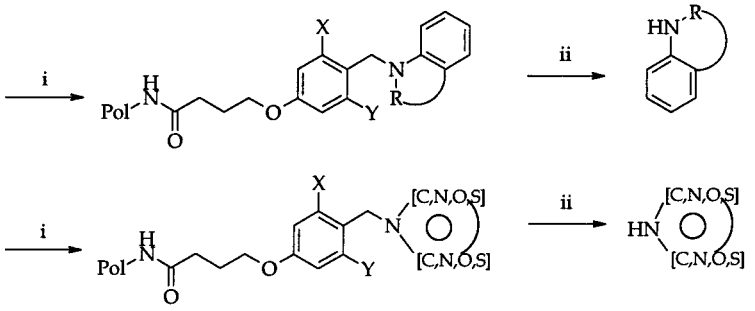
[a] Reaction conditions: (i) $R^1R^{1'}NH$, NEt_3; (ii) Chemical transformations (iii) for $R^3 = H$: 10% TFA in DCM, rt, 5 min, or $HSiCl_3$, DCM, 32 °C, 15 min; for $R^3 = Ac$: AcCl, THF, rt, 12 h.

of the N−N bond of triazene **38** could be effected with acid or alternative electrophiles, e.g. acylating agents.

3. N–H Linkers

N−H linkers link a nitrogen atom of the synthetic molecule to the solid support and leave a proton (or, in some cases, an alternative electrophilic residue) on this nitrogen after cleavage. When the linking nitrogen atom is an integral part of a heterocyclic system in the target molecule, such products may be viewed as traceless. Both C−H and N−H linkers suffer from the limitation that the linking atom is, except in special cases, excluded from substitution. A principal strategy for N−H linkers requires connection of the nitrogen atom to an electron-rich carbon atom (often benzylic with the presence of additional electron-donating groups). Other substituents on the nitrogen atom influence the facility of cleavage in such systems. For example, simple primary or secondary amines can be released from a triarylmethyl (e.g., trityl) linker by acid treatment. By contrast, the seceding nitrogen atom generally must be in an electron-deficient environment to enable cleavage from less electron rich linkers under reasonably mild conditions. Thus, acylation (sulfonylation, carbamoylation) of the nitrogen atom is a common method for activating the labile C−N bond to cleavage from such linkers. With regard to the synthesis of heterocyclic compounds, the observation that N-arylation or incorporation of the nitrogen atom as part of a heteroaromatic system activates

Scheme 18[a]



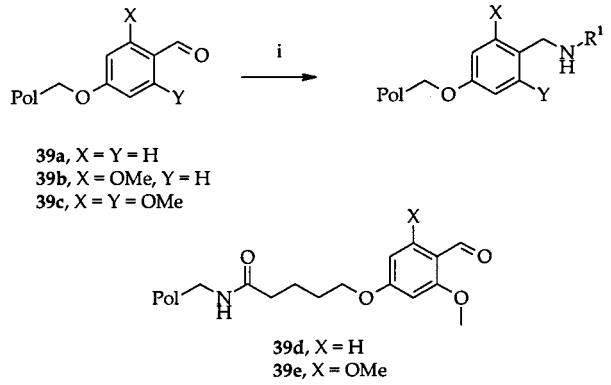
[a] Reaction conditions: X, Y = H or OMe. (i) Sequence of chemical modifications; (ii) TFA, HCl, or HF.

the labile C−N bond to cleavage is particularly noteworthy (Scheme 18). In this section we focus on examples demonstrating the construction of heterocyclic systems around resin-linked nitrogen atoms, followed by cleavage to provide traceless products.

The polymer-supported equivalent of the commonly used Boc group introduced by Hernández and Hodges[45] may well serve the purpose of traceless synthesis of nitrogen-containing heterocyclic compounds; however, it has not been applied so far.

Aldehyde resins **39** afford secondary amines when subjected to reductive amination with primary amines and thereby provide a convenient entry to this chemistry (Scheme 19). Aldehyde resin **39a**, with no

Scheme 19[a]



[a] Reaction conditions: (i) R^1NH_2, reductive amination conditions.

additional methoxy group, yields the most acid stable C−N bonds.[46] The AMEBA (*a*cid-sensitive *me*thoxy *b*enz*a*ldehyde) resin **39b** has been applied to the synthesis of sulfonamides, amides, ureas, and carbamates.[46,47] Resin **39c** (BAL, backbone amide linker) was originally developed for attachment of peptides to the solid support via the peptide backbone[48−51] and represents the most acid labile linkage. Linkers were attached either directly to Merrifield resin[47,52] and ArgoGel[46] (**39a** to **39c**) or via a pentanoic acid spacer (**39d** and **39e**).[48−51] Commercially available aldehyde resins contain a butanoic acid spacer.

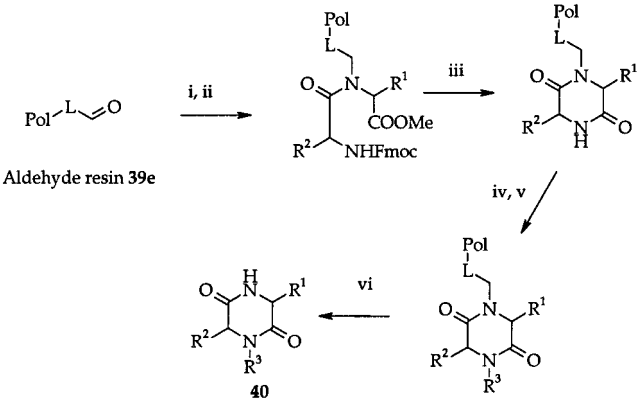
The resin **39d** became very popular in our laboratory for the synthesis of nitrogen-containing heteroaromatic compounds. Examples from our and other laboratories in the use of this and analogous resins are presented in sections 3.1−3.3.

3.1. Traceless Synthesis via Cleavage of Benzylic Amides

3.1.1. Piperazine-2,5-diones

The BAL linker **39c** can serve as a traceless linker for heterocyclic compounds containing an amide bond (Scheme 20). Del Fresno et al.[53] described the synthesis of piperazine-2,5-diones **40**. The dipeptide ester attached to the BAL linker **39c** was cyclized on resin, the nitrogen of the newly formed amide bond was alkylated, and the target compound **40** cleaved from the resin with TFA.

Scheme 20[a]



[a] Reaction conditions: (i) α-amino acid methyl ester·HCl, $NaBH_3CN$, DMF, 25 °C, 1 h; (ii) Fmoc-protected amino acid, HATU, DIEA, DCM:DMF (9:1), 25 °C, 2 h, repeated; (iii) piperidine, DMF, 3 × 1 min, 3 × 5 min; (iv) lithiated oxazolidinone, THF, −78 °C, 90 min; (v) alkyl halide, THF, DMF (7:3); (vi) TFA/H_2O (9:1), rt, 2 h.

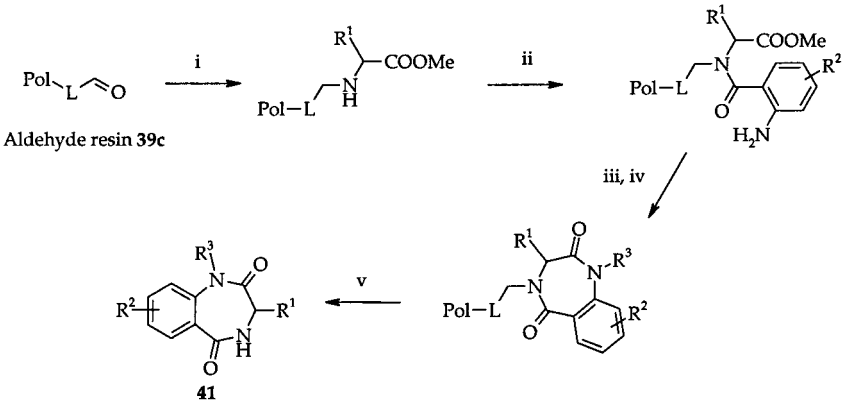
3.1.2. 1,4-Benzodiazepine-2,5-diones

Boojamra et al.[52,54] first reported the use of the dimethoxy aldehyde linker **39c** for the synthesis of 1,4-benzodiazepine-2,5-diones (Scheme 21). The aldehyde linker was reductively aminated with amino acid esters, the secondary resin-bound amino group was acylated by anthranilic acids, and the seven-membered ring was closed. Alkylation of the amide nitrogen resulted in the synthesis of benzodiazepines **41** with three points of diversity.

3.1.3. Dibenzo[b,f]oxazocines

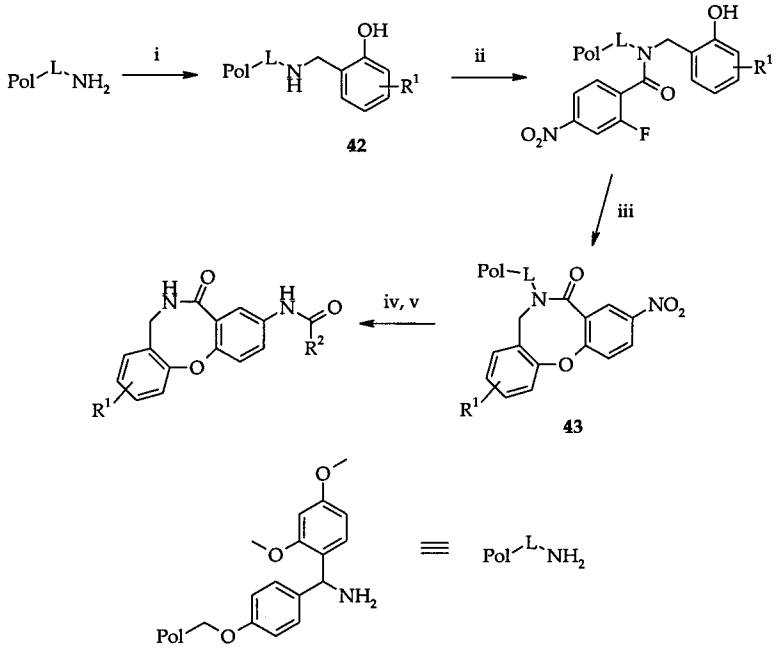
Ouyang and Kiselyov[55] reported the synthesis of oxazocines, whereby the secondary amine intermediate **42** was obtained from Rink amino resin (Scheme

Scheme 21[a]



[a] Reaction conditions: (i) α-amino acid ester·HCl, AcOH, DMF, then $NaB(OAc)_3H$; (ii) anthranilic acid, EDC, NMP; (iii) lithiated acetanilide, THF, DMF, rt, 30 h; (iv) alkyl halide; (v) TFA, DMS, H_2O.

Scheme 22[a]



[a] Reaction conditions: (i) salicylaldehyde, TMOF, $NaB(OAc)_3H$, DMF, 12 h; (ii) 2-fluoro-5-nitrobenzoic acid, HOAt, DIC, DMF, 24 h; (iii) DBU, DMF, 24 h, rt; (iv) $SnCl_2·2H_2O$, DMF, 12 h; (v)acyl chloride, DIEA, DMF, rt, 8 h; (vi) 20% TFA, DCM, 40 min.

22). The eight-member ring of the oxazocine targets **43** was closed by nucleophilic displacement of fluorine by a phenolate anion.

3.2. Traceless Synthesis via Cleavage of N-Benzylic Anilines and Heteroanilines

3.2.1. 2-Aminobenzimidazoles

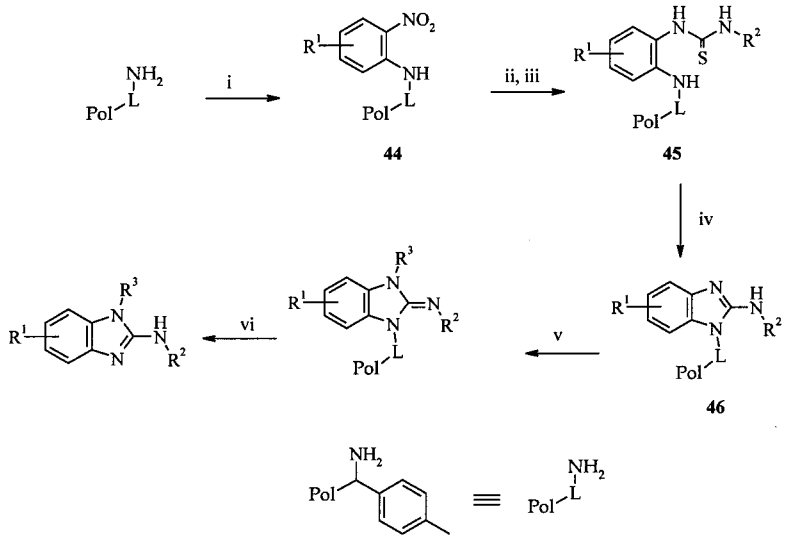
A traceless synthesis of 2-aminobenzimidazoles was developed using MBHA resin according to Scheme 23.[56] Aromatic nucleophilic substitution of fluorine in *o*-fluoronitrobenzenes by the resin-bound amino group of MBHA resin provided *o*-nitroaniline **44**. The nitro group was reduced by tin(II) chloride dihydrate in NMP and then reacted with isothiocyanates to form polymer-supported thioureas **45**. Cyclization to 2-arylaminobenzimidazoles was promoted by DIC. To introduce a third combinatorial step, the resin-bound 2-arylaminobenzimidazoles **46** were alkylated with an electrophile.

The alkylation could in principle have occurred on either the ring nitrogen or on the exocyclic nitrogen at position 2. To distinguish these possibilities, we prepared the sample products from 2,4-difluoronitrobenzene and 2,5-difluoronitrobenzene. Following alkylation with R^3 and cleavage, products **47** and **48** (Scheme 24) showed a slight difference in HPLC retention times (two peaks on coinjection), leading to the conclusion that the alkylation had occurred on the ring nitrogen. In the event of alkylation on the exocyclic nitrogen, the two products would have been identical.

3.2.2. Tetrahydroquinoxalines

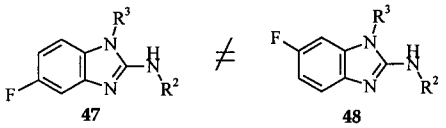
Tetrahydroquinoxalines were prepared on linker **39d**, in a route initiated by reductive amination with β-amino alcohols[57] (Scheme 25). The key step in the synthesis involved the formation of the heterocyclic six-member ring via nucleophilic displacement of mesylate by aniline nitrogen. The nitro group of the

Scheme 23[a]

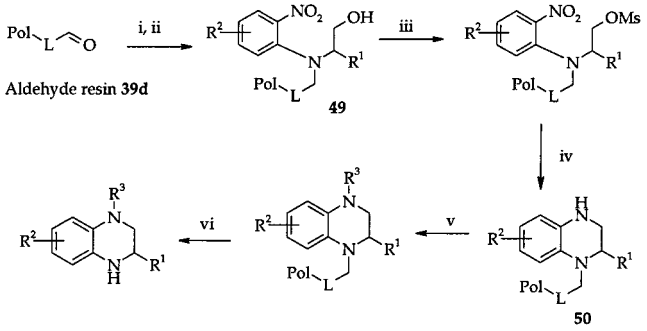


[a] Reaction conditions: (i) 1 M *o*-fluoronitrobenzene in NMP, 75 °C, overnight; (ii) 2 M $SnCl_2 \cdot 2H_2O$ in NMP, rt, 2 h; (iii) 1 M isothiocyanate in NMP, rt, overnight; (iv) 1 M DIC in NMP, rt, overnight; (v) 1 M alkyl halide, K_2CO_3, in DMF, 75 °C, overnight, (vi) gaseous HF, rt, 2 h or TFA overnight.

Scheme 24



Scheme 25[a]



[a] Reaction conditions: (i) amino alcohol, $NaB(AcO)_3H$, DMF/AcOH, rt, overnight; (ii) *o*-fluoronitrobenzene, DMSO, 70 °C, 16 h; (iii) Ms−Cl, pyridine or proton sponge, DCM, 0 °C to rt; (iv) $SnCl_2 \cdot 2H_2O$, NMP, rt, 2 h; (v) acyl chlorides/DIEA or isocyanates in NMP, overnight; (vi) TFA, rt, 2 h.

o-fluoronitrobenzene served two functions. It activated the aromatic ring for the nucleophilic substitution by resin-bound amines and served as a protecting group while the hydroxy group was being converted to a mesylate.

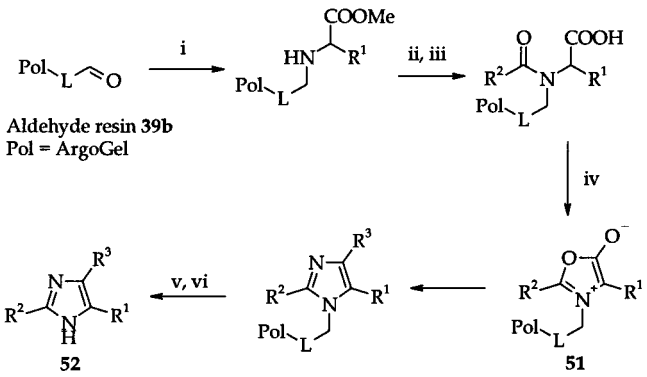
To close the six-member ring, the hydroxy group of **49** was reacted with mesyl chloride, and the nitro group of the resulting resin-bound *o*-nitroaniline was reduced by 2 M tin(II) chloride dihydrate solution in NMP. The reduced intermediate spontaneously cyclized to tetrahydroquinoxaline **50**, with the exception of the case where R^1 = H, in which heating the intermediate was required to complete the cyclization. The third combinatorial step involved decorating the tetrahydroquinoxaline scaffold at the aniline nitrogen. Various methods were applied, including acylation, alkylation, and carbamoylation.

3.3. Traceless Synthesis via Cleavage of N-Benzylic Heteroaromatics

3.3.1. Imidazoles

A traceless synthesis of imidazoles[58] took advantage of the acid lability of an resin-bound electron rich benzylic substituent on a core nitrogen of an imidazole ring (Scheme 26). Aldehyde ArgoGel resin

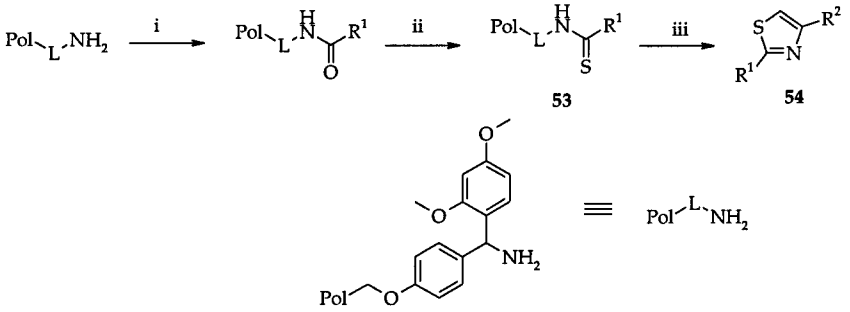
Scheme 26[a]



[a] Reaction conditions: (i) amino acid ester·HCl, $NaB(OAc)_3H$, AcOH, DMF; (ii) acid chloride, DIEA, DCM; (iii) KOH, dioxane/H_2O (3:1); (iv) EDC, tosylimine, DCM; (v) TFA/H_2O; (vi) AcOH, 100 °C.

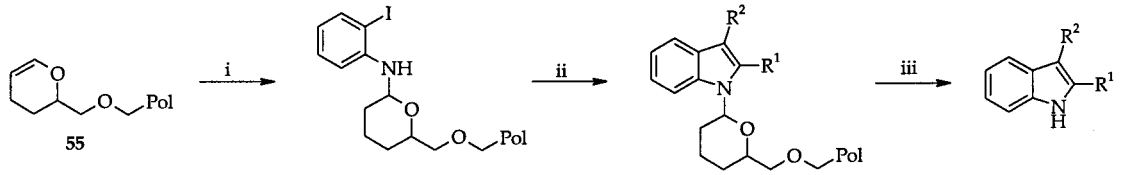
39b was reductively alkylated with amino acid esters, then the polymer-supported secondary amino group was acylated by aromatic acid chlorides, and the ester function was hydrolyzed. Dehydration to the 1,3-oxazolium-5-olate ('münchnone') dipole **51** was followed by the key 3 + 2 cycloaddition with the dipolarophilic aryltosylimines to afford the 2,4,5-trisubstituted imidazoles, which were cleaved by treatment with AcOH at elevated temperature. Prior to cleavage, brief treatment with TFA induced the cleavage mainly of undesired side products. This route provided 2,4,5-trisubstituted imidazoles **52** with excellent purity and high yield; however, it is limited to aromatic substituents on the imidazole ring.

Scheme 27[a]



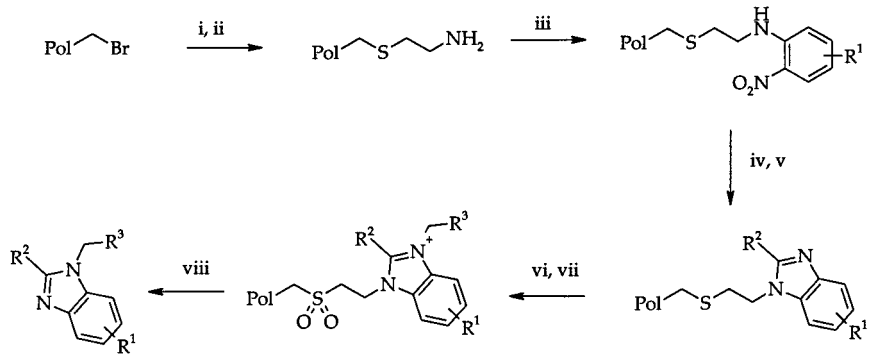
[a] Reaction conditions: (i) acid, DIC, DMAP; (ii) Lawesson's reagent, THF, reflux, 4 h; (iii) bromo ketone, reflux 16 h.

Scheme 28[a]



[a] Reaction conditions: (i) 2-iodoaniline, PPTS, DCE, 70 °C, 2h; (ii) acetylene, $Pd(PPh_3)_2Cl_2$, TMG, 110 °C, 1 × 5 h, 1 × 16 h; (iii) 10% TFA/DCM.

Scheme 29[a]



[a] Reaction conditions: (i) *tert*-butyl N-(2-mercaptoethyl)carbamate, K_2CO_3, NMP, 60 °C under N_2, 12 h; (ii) TFA, DMS, DCM, 2 × 0.5 h, then DIEA, DCM, 2 × 0.5 h; (iii) *o*-nitrofluoro/chloroarene, DIEA, NMP, 60 °C, 12 h; (iv) $SnCl_2 \cdot 2H_2O$, 12 h, rt; (v) aldehyde, NMP, 12 h, 50 °C; (vi) aqueous oxone, 12 h, rt; (vii) benzyl bromide, NaI, 18 h, 70 °C; (viii) triethylamine, DCM, 18 h, rt.

3.3.2. Thiazoles

Rink linker, developed for the synthesis of carboxamides, was used to provide a traceless route to thiazoles[59] (Scheme 27). Acids were coupled to the Rink linker resin, and the amide was converted to thioamide **53** using Lawesson's reagent. Cleavage using α-haloketones provided thiazoles **54**.

3.3.3. Indoles

Synthesis of 2,3-disubstituted indoles using the THP linker **55** provides an example of traceless heterocycle synthesis in which the nitrogen atom of the product is linked to a electron rich carbon atom that is nonbenzylic[60] (Scheme 28). 2-Iodoaniline was loaded onto THP linker resin **55**, followed by Pd(0)-mediated reaction with acetylenes in the presence of a base to form the indole nucleus. Complete regioselectivity was observed for three out of four acetylenes. The products were cleaved by TFA/DCM.

3.4. Traceless Synthesis via Hofmann Elimination

Linkers allowing cleavage of amines via Hofmann elimination have been used for the solid phase synthesis of tertiary amines on numerous occasions.[61−63] Tumelty et al.[64] applied this principle to the traceless synthesis of benzimidazoles (Scheme 29). The linker was synthesized using bromo TentaGel resin, and the benzimidazole core was built by nucleophilic substitution of halogen in *o*-fluoro/chloronitrobenzene by the resin-bound amino group, reduction of the nitro group, and cyclization by an aldehyde. To cleave the product, the sulfide was oxidized to sulfone, the resin-bound benzimidazole alkylated by benzylbromide, and the product released by treatment with a base.

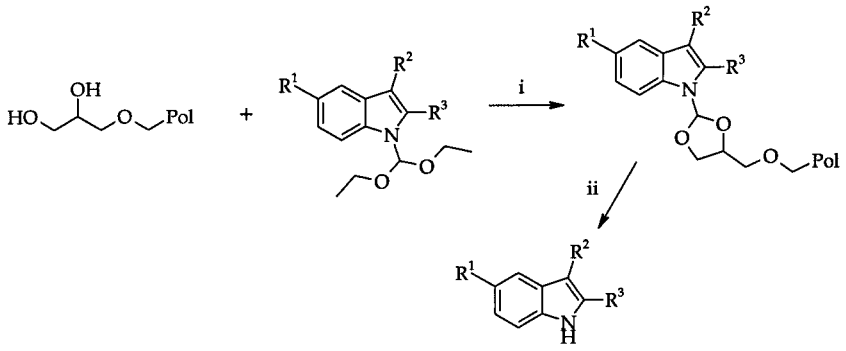
3.5. Dialkoxymethyl Linker

Diethoxymethyl linker, introduced by Leznoff and Wong,[65] was used as a nitrogen-protecting group for amides and indoles.[66] Kraxner et al.[67] tethered indole via the alkoxymethyl linker to a solid support for subsequent chemical transformations (Scheme 30). Derivatized indole was cleaved from the linker under acidic conditions. This chemical route represents an example of attaching the preformed scaffold to a polymer support for subsequent chemical transformation.

4. Cyclative Cleavage

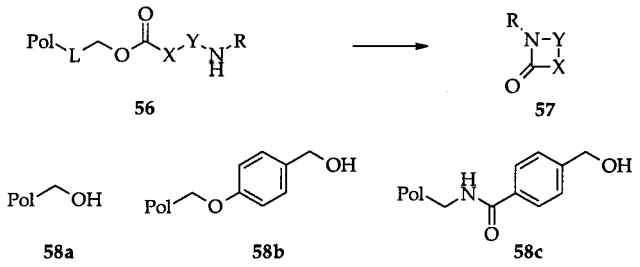
Cyclative cleavage by nucleophilic displacement is a frequently used methodology whereby a nucleo-

Scheme 30[a]



[a] Reaction conditions: (i) Tos-OH, dioxane, rt, 3 h; (ii) 2 N HCl, dioxane, 40 °C, 3 h.

Scheme 31



philic atom (e.g. nitrogen) of an acyclic precursor **56** attacks an electrophilic group (e.g. carbonyl) attached to the solid support, displacing a resin-bound leaving group and forming a ring **57** (generally five-, six-, or seven-membered) (Scheme 31). Esters of the Merrifield resin **58a** are the most often used precursors for cyclative cleavage, Wang resin **58b** esters are less reactive, and 4-hydroxymethylbenzoic acid attached to aminomethylated Merrifiled resin **58c** provides esters more susceptible to a nucleophilc attack.

A valuable advantage of this approach is that only cyclic compounds are released from the resin, and therefore the purity of target compounds is typically high. On the other hand, the rate of cleavage is often very dependent on the electronic and steric factors of substituents, complicating optimization of reaction conditions for sizable diverse libraries. (A sizable library contains tens of thousands individual compounds.)

Ring-closing metathesis represents an alternative methodology for cyclative cleavage and is covered in section 4.2.

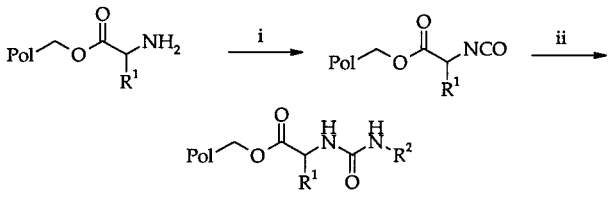
4.1. Nucleophilic Displacement

4.1.1. Five-Membered Rings

Hydantoins and Related Heterocycles. The traditional route to hydantoins entails alkylation of the amino group of an amino acid, followed by reaction with an isocyanate and cyclization of the urea derivative to the hydantoin (Scheme 32). The first combinatorial solid phase synthesis of hydantoins was described on Wang resin by DeWitt et al.,[18] who performed the cyclative cleavage under strong acid conditions. Syntheses communicated by Kim et al.[68] (Scheme 32) and Mathews and Rivero[69] used basic conditions (diisopropylamine[68] or TEA[69]) for the cyclative cleavage step rather than aqueous HCl.

To increase the limited diversity of commercially available isocyanates, Mathews and Rivero[69] prepared the urea intermediate derivatives also from amines and resin-bound isocyanates (Scheme 33). In

Scheme 33[a]

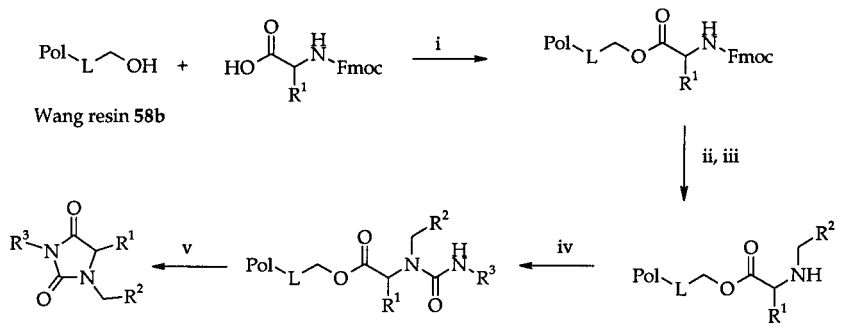


[a] Reaction conditions: (i) phosgene, DCM, pyridine; (ii) amine, DCM.

the same paper, they also reported synthesis of thiohydantoins, following the same route with isothiocyanates.

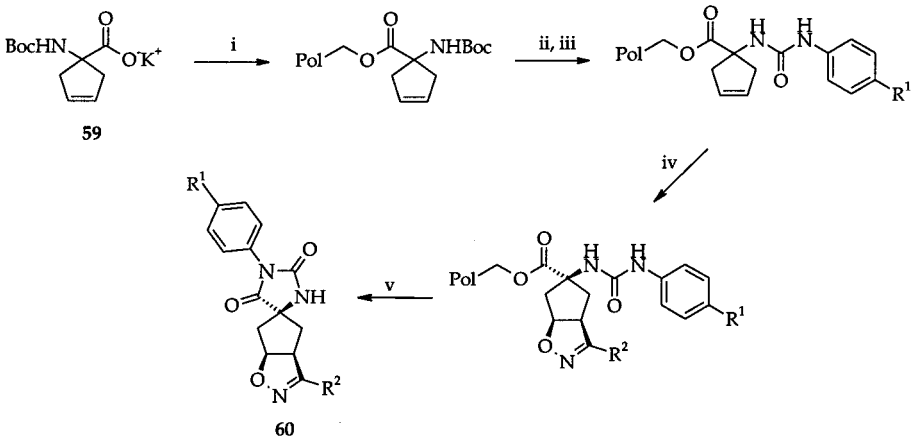
The reaction routes discussed thus far have used aldehydes for the reductive alkylation of the resin-

Scheme 32[a]



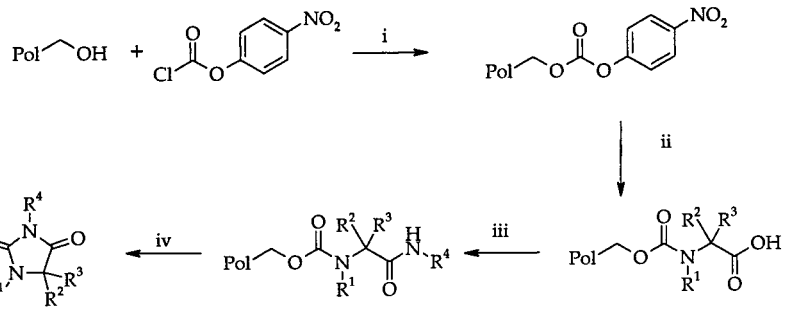
[a] Reaction conditions: (i) DIC, DMAP in DMF, rt, 12 h; (ii) 20% piperidine in DMF, 1 h; (iii) aldehyde in 1% AcOH in DMF followed by $NaBH_3CN$; (iv) isocyanate, DMF/toluene (1:1); (v) DIEA, rt, 1 h.

Scheme 34[a]



[a] Reaction conditions: (i) chloromethylated Merrifield resin, 18-crown-6, DMF; (ii) 50% TFA in DCM; (iii) isocyanate, DCM; (iv) $R_2CH_2NO_2$, isocyanate, TEA, THF; (v) TEA, THF.

Scheme 35[a]



[a] Reaction conditions: (i) NMM, DCM, 0 °C; (ii) *N*-alkylamino acid, DMAP, BSA, DMF, 48 h, rt; (iii) amine, DCC, HOBt, DMF, rt, 24 h; (iv) TEA, 55−90 °C, 48 h.

bound amino group. Lee et al.[70] prepared resin-bound ketimines from N-H ketimines and resin bound amines. The reduction to secondary amines was carried out by $NaBH_3CN$.

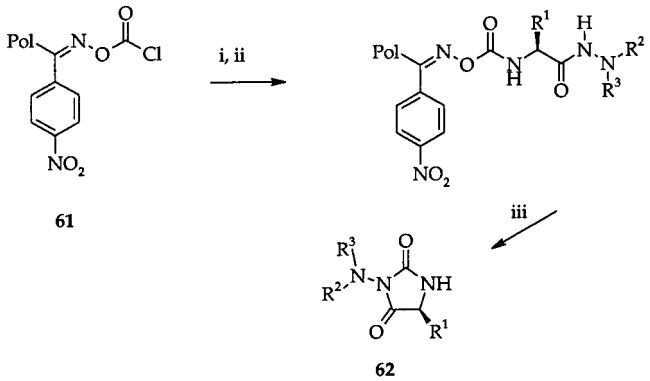
Kurth's group reported diastereoselective synthesis of fused heterocyclic rings, isoxazoloimidazolidinediones, containing both hydantoin and isoxazoline moieties[71] (Scheme 34). Merrifield resin was esterified with amino acid **59**, the Boc group was removed, and the amino group was reacted with isocyanates to afford resin-bound urea derivatives. The isoxazoline ring was built in the next step by 1,3-dipolar cycloaddition of the alkene with Mukaiyama-generated nitrile oxide. This transformation proceeded with complete diastereoselectivity. Base-catalyzed cyclative cleavage released the target structure **60**.

The effect of (i) the structural and electronic features of the linear urea precursor and (ii) the character of the ester linkage on the rate of cyclization was studied by Karnbrock et al.[72] and Park and Kurth.[73] The rate of hydantoin formation was slower for urea linked directly to TentaGel resin when compared to urea attached via 4-hydroxymethylbenzoic acid.[72] As expected, the cyclative release was faster on the Merrifield resin **58a** when compared to Wang resin **58b** and also for N^1-substituted ureas when compared to N^1-unsubstituted ureas.[73] Consequently, the combination of Merrifield resin and N^1-substituted precursor caused premature cleavage of target compounds.

Dressman et al.[74] reported hydantoin synthesis from N-alkylated amino acids attached to the carbamate linker[75] (Scheme 35). The carboxylic acid was activated on resin and reacted with amines. The linear intermediate was cleaved by cyclization in TEA.

Oxime carbamates derived from phoxime resin **61** serve as a solid phase, heat labile isocyanate equivalent[76] (Scheme 36). Hamuro et al.[77] reported the use

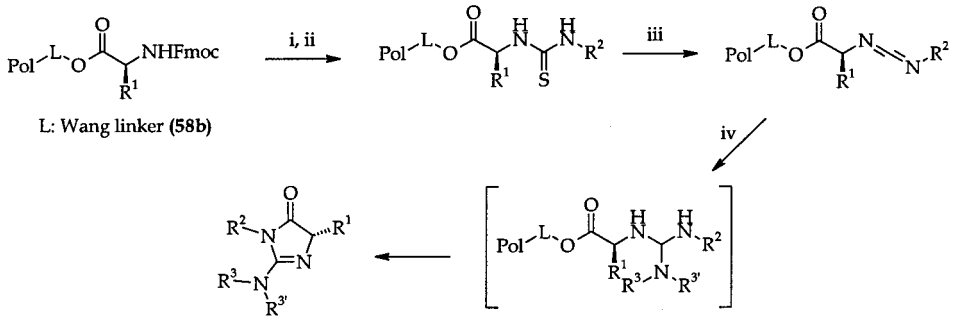
Scheme 36[a]



[a] Reaction conditions: (i) α-amino acid, TMS-Cl, pyridine; (ii) *N*,*N*-disubstituted hydrazine, DIC, HOBt, DMF; (iii) DIEA, DMF, 80 °C.

of phoxime resin to yield 3-aminohydantoins. The phoxime resin, prepared from *p*-nitrophenyl(polystyrene)ketoxime, was reacted with α-amino acid in

Scheme 37[a]



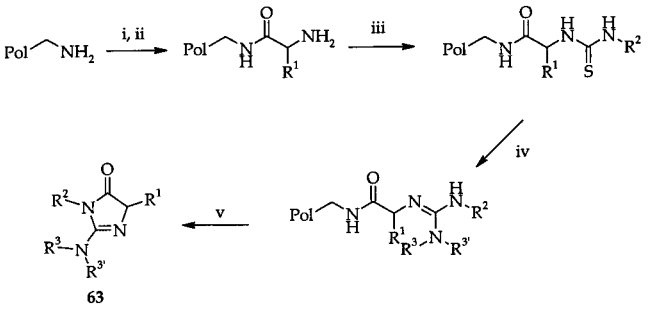
[a] Reaction conditions: (i) 30% piperidine, DMF, 1 h; (ii) isothiocyanate, THF, 15 h; (iii) 2-chloro-1-methylpyridinium iodide, TEA, DCM, 45 °C, 3.5 h; (iv) amine, THF, rt, 24 h, then isocyanate scavenger resin.

TMS-Cl containing pyridine. The carboxy group was activated and coupled with substituted hydrazines. Intramolecular cyclization produced the five-membered ring **62**.

2-Aminoimidazolones. Two groups reported synthesis of 2-aminoimidazolones. Drewry and Ghiron[78] reacted resin-bound amino acids with isothiocyanate and then converted the resulting thioureas into carbodiimides by Mukaiyama's reagent (Scheme 37). The carbodiimides were converted to guanidines that spontaneously cyclized to 2-aminoimidazolones.

Solid phase synthesis of trisubstituted 2-aminoimidazolones using the cyclative cleavage protocol was also reported by Li and Wilson[79] (Scheme 38). Aminomethyl resin acylated with an amino acid was reacted with isothiocyanate, and the resulting thiourea was converted to guanidine by an amine upon DIC activation. The linear precursor cyclized in acidic conditions to yield target 2-aminoimidazolones **63**. Unlike the previous example, the cyclization occurred on an amide carbonyl, resulting in a slower cyclization rate. The resin-bound intermediate was washed before the release occurred, thus eliminating the use of a scavenger resin.

Scheme 38[a]



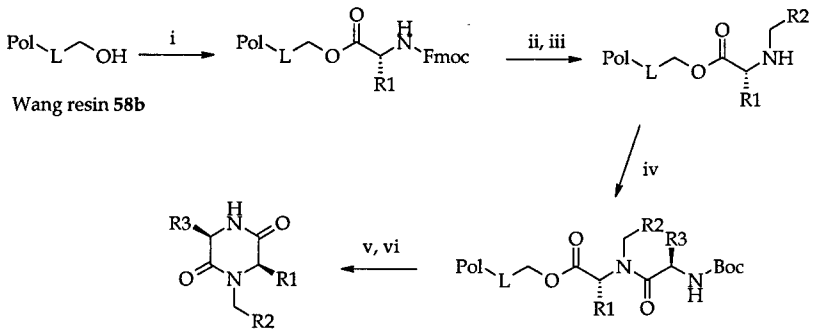
[a] Reaction conditions: (i) Boc-amino acid, DIC, HOBt, DMAP, rt, 15 h; (ii) 30% TFA in DCM, followed by 10% TEA in DCM; (iii) isothiocyanate, DCM, rt, 15 h; (iv) amine, DIC, DIEA, $CHCl_3$; (v) 10% AcOH in DCM, rt, 15 h.

4.1.2. Six-Membered Rings

Piperazine-2,5-diones. Cyclization of dipeptide esters to piperazine-2,5-diones has been used on numerous occasions to make combinatorial libraries on a solid phase. Gordon and Steele[80] described the synthesis of diketopiperazines on Wang resin esterified with Fmoc-amino acids (Scheme 39). After Fmoc cleavage with piperidine, the liberated amino groups were reductively alkylated and the resin-bound secondary amino groups were acylated by Boc-protected amino acids. It is worthwhile to mention that the acylation of the weakly nucleophilic and sterically hindered amino group can be problematic. We have found[8] that acylation by symmetrical anhydrides prepared in situ with no added tertiary base according to Bourne et al.[81] provided the best results.

The same route was followed by Szardenings et al.[82,83] in the synthesis of piperazine-2,5-diones on PEG-PS resin (hydroxy TentaGel and ArgoGel), using HATU-activated amino acids for the acylation of the secondary amino group. Because of the acid stability of the ester linkage, amino acids with TFA cleavable side chain protecting groups were used, and the side chain protecting groups were removed prior to cyclization. The cyclative cleavage was done in toluene.

Scheme 39[a]

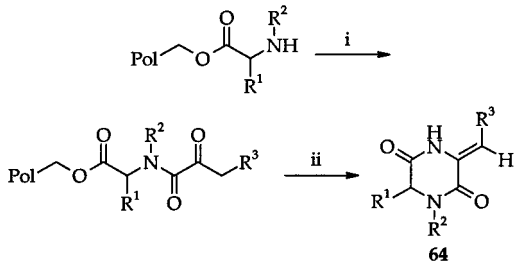


[a] Reaction conditions: (i) Fmoc-amino acid, HOBt, DIC, DMAP; (ii) 40% piperidine, DMF; (iii) aldehyde, $NaB(OAc)_3H$, DCM, sonicate; (iv) Boc-amino acid, PyBroP, DIEA, DCM; (v) neat TFA; (vi) toluene, reflux.

Kowalski and Lipton[84] used acetic acid in toluene for cyclative cleavage.

Smith et al.[85] developed a solid phase synthesis of piperazine-2,5-diones on Kaiser oxime resin. Diazepinediones were prepared the same way. For the preparation of histidine-containing piperazine-2,5-diones, Sabatino et al.[86] linked the histidine via the side chain to the trityl resin. When a polymer supported N-alkylated amino acid was acylated by an α-keto acid, cyclative cleavage in the presence of ammonium acetate yielded 3-alkylidene-piperazine-2,5-dione **64**,[87] predominantly as the *Z* isomer (Scheme 40).

Scheme 40[a]

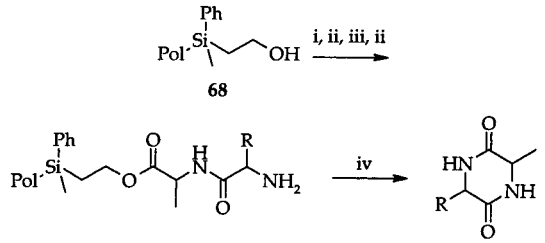


[a] Reaction conditions: (i) α-ketoacid, DIC, DCM; (ii) NH_4OAc, AcOH, toluene.

Scott et al.[88] built Wang resin-bound secondary amino acid esters from α-bromocarboxylic acids to prepare a library of 22 000 tetrasubstituted piperazine-2,5-diones (Scheme 41). The resin-bound *N*-(α-bromoacyl)amino acid ester **65** was also used for cyclization to diketomorpholines **66**, whereby cleavage from the resin and subsequent cyclization were mediated by TFA. While preparing the piperazine-2,5-diones **67**, cyclization to release the piperazine-2,5-dione did not always occur, particularly when the amino acid α-substituents were sterically demanding. In such cases, cleavage and cyclization in the presence of TFA led to the piperazine-2,5-dione.

Polymer-supported 2-(trialkylsilyl)ethanol resin **68** was prepared by Wang et al.[89] from 4-bromopolystyrene resin and subsequently used for synthesis of a dipeptide ester (Scheme 42). The cyclative cleavage

Scheme 42[a]



[a] Reaction conditions: (i) Fmoc-Ala, HATU, DIEA, HOBt, DMF; (ii) 20% piperidine, NMP; (iii) Fmoc-amino acid, HATU, DIEA, HOBt, DMF; (iv) 30% AcOH in MeOH, rt.

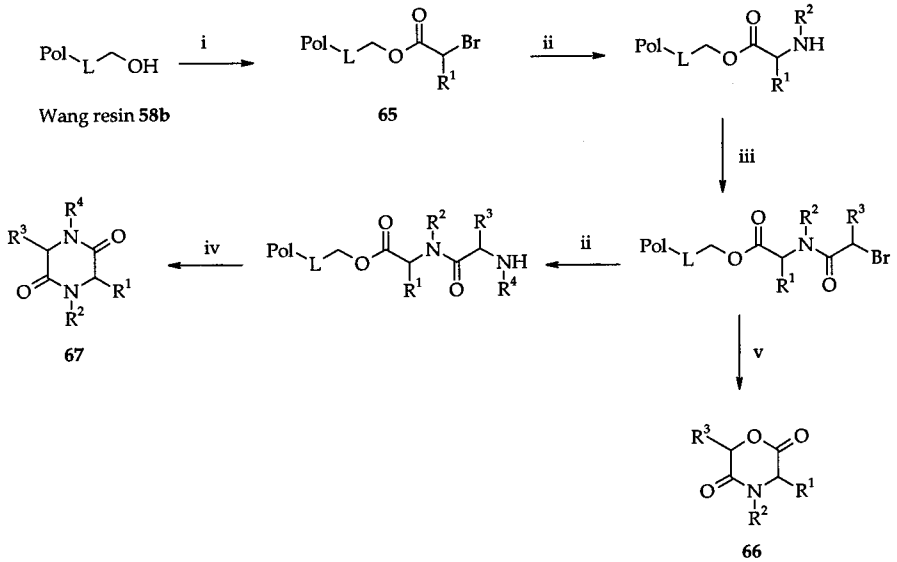
in 30% acetic acid in MeOH at ambient temperature yielded piperazine-2,5-diones.

Cyclative cleavage on a tetrahydro-β-carboline skeleton to yield fused piperazine-2,5-dione analogues was reported by Fantauzzi and Yager[90] (Scheme 43). Starting with resin-bound tryptophan **69**, Pictet–Spengler cyclization with a variety of aldehydes provided the tetrahydro-β-carboline **70**. Acylation of the secondary amino group with amino acid prepared the substrate for formation of the piperazine-2,5-dione ring by cyclative cleavage. Structural analogues of indolopiperazine-2,5-dione alkaloids (fumitremorgin, verruculogen, and tryprostatin) have been synthesized analogously by van Loevezijn et al.[91] on hydroxyethyl polystyrene resin.

Synthesis of β-turn mimetics containing the piperazinedione ring was reported by Golebiowski et al.[92] The precursor was built using the boronic acid Mannich (Petasis) reaction, and the product was released by cyclative cleavage.

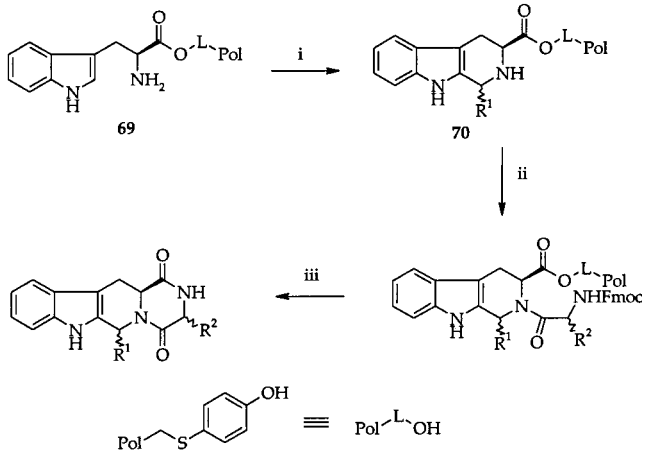
1,2,4-Triazine-3,6-diones. In close analogy to a hydantoin synthesis discussed previously, acyclic hydrazides with the appropriate nitrogen substitu-

Scheme 41[a]



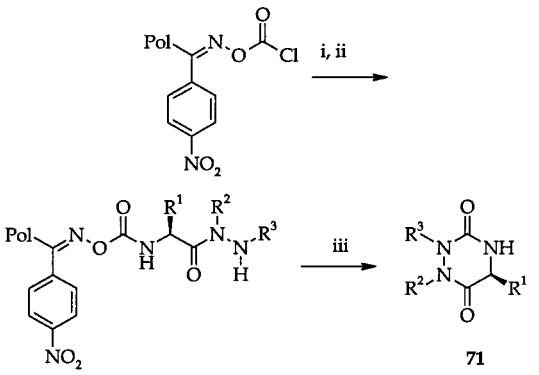
[a] Reaction conditions: (i) α-bromo acid, DIC, DMF; (ii) amine, DMSO, 50 °C; (iii) PyBroP, DIEA, THF, 50 °C; (iv) spontaneous cyclative cleavage or TFA; (v) TFA.

Scheme 43[a]



[a] Reaction conditions: (i) aldehyde, TFA, DCM, rt, 18 h; (ii) Fmoc-amino acid, CIP, DIEA, NMP, rt, 16 h; (iii) 5% piperidine, THF, rt, 16 h.

Scheme 44



tion pattern can be cyclized to six-membered rings **71**, as demonstrated by Hamuro et al.[77] (Scheme 44).

5,6-Dihydropyrimidine-2,4-diones. When β-amino acids are used instead of α-amino acids in the synthetic route for the preparation of hydantoins, 5,6-dihydropyrimidine-2,4-diones **72** are formed (Scheme 45). Kolodziej and Hamper[93] prepared the polymer-supported β-amino esters by Michael addition of amines to an acrylate ester of Wang resin. The β-ureido ester, prepared by reaction with isocyanates, was cleaved and cyclized in HCl/toluene at elevated temperature. The products were contaminated by β-amino acid, and the contaminant was removed by filtration through silica, providing yields of 13−76%.

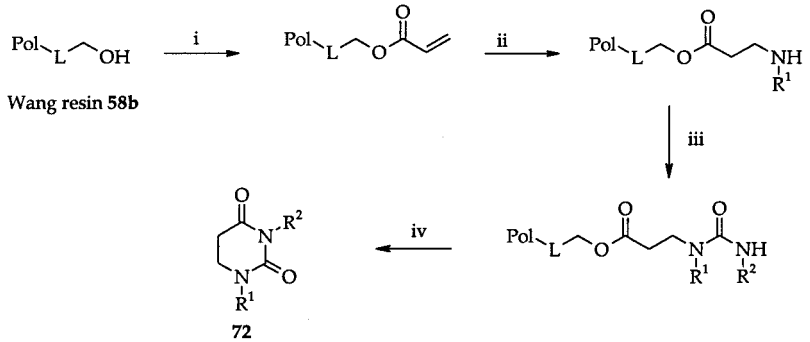
Quinolin-2-ones. Cyanoacetic acid attached to Wang resin was C-acylated using diverse isatoic anhydrides to produce resin-bound cyano esters **73** (Scheme 46). Upon heating, the 4-hydroxyquinolin-2-ones were released from the resin.[94] Isatoic anhydrides were prepared from anthranilic acids. To increase diversity, they were N-alkylated.

2-Quinolone and coumarine was prepared by Kondo et al.[95] by photoinduced cyclative release (Scheme 47). The REM resin **74** was used in a Heck coupling reaction with *o*-iodoaniline and *o*-iodophenol. The resulting linear precursor **75** was subjected to irradiation with a 400 W high-pressure mercury lamp. The 2-quinolone and coumarin were isolated in 66% and 53% yield, respectively.

Quinazolin-4-one. A new approach to quinazolin-4-ones by aza Wittig mediated annulation was reported by Villalgordo et al.[96,97] (Scheme 48). The Merrifield resin was esterified with *o*-azidobenzoic acids, and the azide was converted by PPh_3 to the iminophosporane **76**. The aza Wittig reaction with isocyanates yielded carbodiimides. Nucleophilic reaction with amines or thiols generated guanidines or isothioureas, which spontaneously cyclized to quinazolin-4-ones.

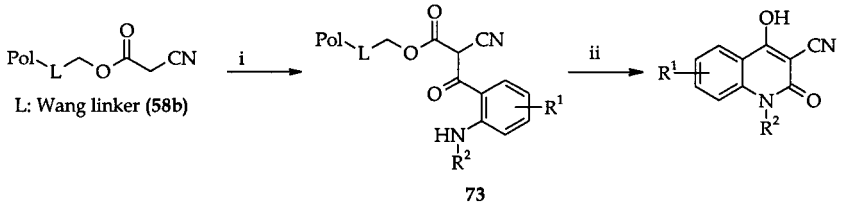
Yang and Kaplan[98] reported a different release strategy for the synthesis of quinazolinones (Scheme 49). Thiourea was loaded to a chloromethylated resin, and the resin-bound isothiourea was exposed to

Scheme 45[a]



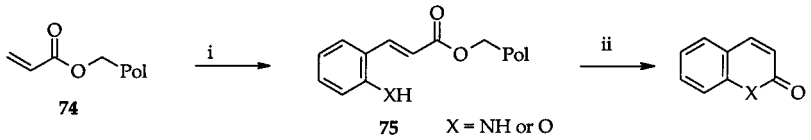
[a] Reaction conditions: (i) acryloyl chloride, TEA, DCM or acrylic acid, DCC; (ii) amine, DMSO; (iii) isocyanate, DCM; (iv) HCl/toluene, 95 °C.

Scheme 46[a]



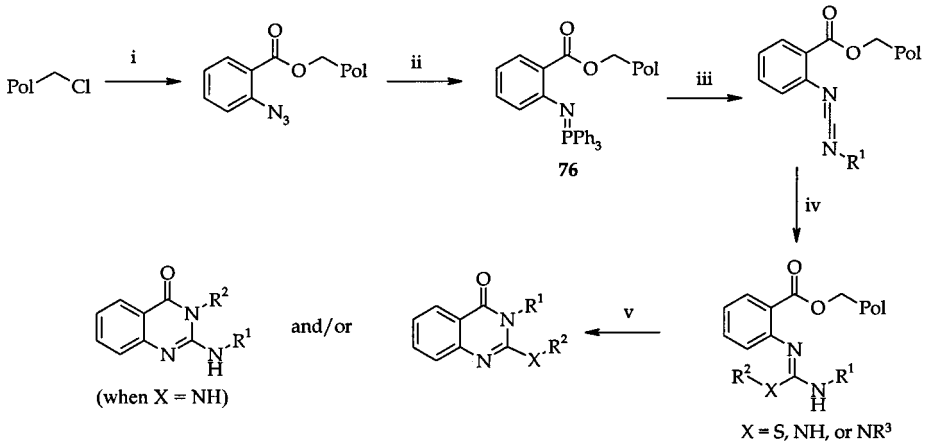
[a] Reaction conditions: (i) isatoic anhydride, TEA, DMF, rt, 24 h; (ii) toluene, 80 °C, 24 h.

Scheme 47[a]



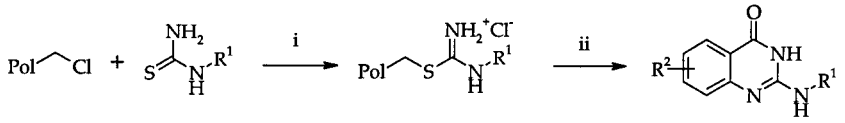
[a] Reaction conditions: (i) *o*-iodoaniline or *o*-iodophenol, Pd_2dba_3, $P(2\text{-Tol})_3$, TEA, DMF, 80 °C, 24 h; (ii) *hν*, toluene, 5 h.

Scheme 48[a]



[a] Reaction conditions: (i) o-azidobenzoic acid, Cs_2CO_3, DMF, KI, 80 °C, 8 h; (ii) PPh_3, THF, rt, 6 h; (iii) isocyanate, DCM, rt; (iv) R^2XH (amine or thiol), THF, 50 °C, 4 h.

Scheme 49[a]

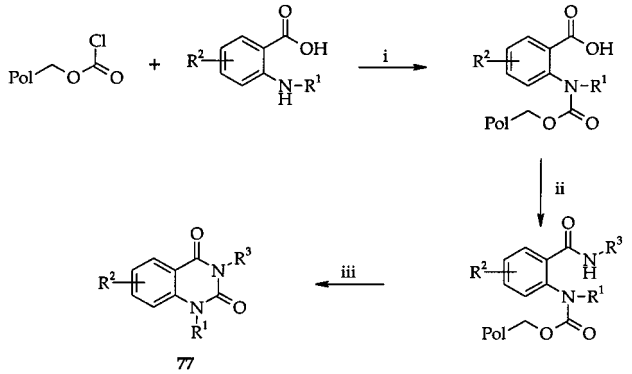


[a] Reaction conditions: (i) DMF, 80 °C; (ii) isatoic anhydride, DIEA, 80 °C.

isatoic anhydride at elevated temperature. The 2-alkylaminoquinazolinone was released into solution. The authors reported that the reaction requires only a stoichiometric amount of isatoic anhydride.

Quinazoline-2,4-dione. A very simple and robust route was devised by Smith et al.[99] for the synthesis of 1,3-disubstituted quinazoline-2,4-diones (Scheme 50). Anthranilic acids were linked to chloroformate

Scheme 50[a]



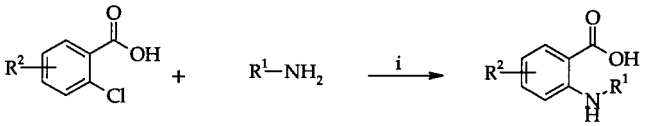
[a] Reaction conditions: (i) DIEA in DCM, rt, 1 h; (ii) PyBOP, DIEA, amine in NMP, rt, 1 h, repeated; (iii) DMF, 125 °C, 16 h.

resin through the nitrogen, the carboxylic acid was activated and reacted with amines to form a linear precursor of target compounds. Exposure to elevated temperature released quinazolinediones **77** from the resin.

The same pathway to quinazoline-2,4-diones was independently described by Gouilleaux et al.[100] The differences were mainly in reaction conditions; thus, the hydroxymethyl polystyrene resin was activated by *p*-nitrophenyl chloroformate for reaction with anthranilic acid, and the final cleavage was achieved by heating for 24 h in TEA/methanol solution.

Because of limited availability of various anthranilic acids, much greater diversity was achieved when the anthranilic acids were prepared from *o*-chlorobenzoic acids and amines[99] (Scheme 51).

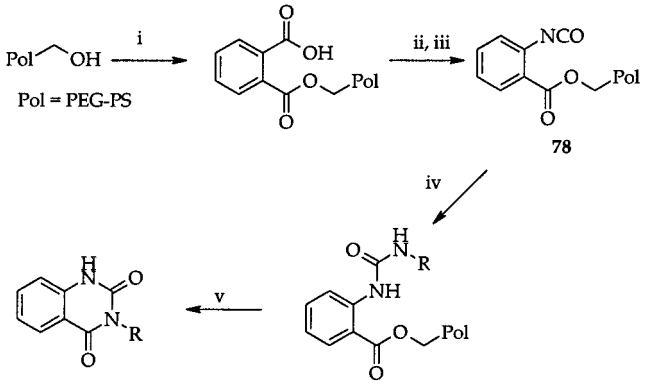
Scheme 51[a]



[a] Reaction conditions: (i) K_2CO_3, CuBr (cat.), DMF, 150 °C, 1 h.

An alternative approach was described by Shao et al.[101] (Scheme 52). Phthalic anhydride was immobilized on PEG-derivatized PS, and the carboxylic acid was converted to azide, which was transformed by Curtius rearrangement into the polymer-supported isocyanate **78**. By reaction with amines, the corresponding ureas were prepared. The cyclative cleavage was performed in acetonitrile in the presence of K_2CO_3. Although providing excellent purity (>90%), the diversity of products was limited.

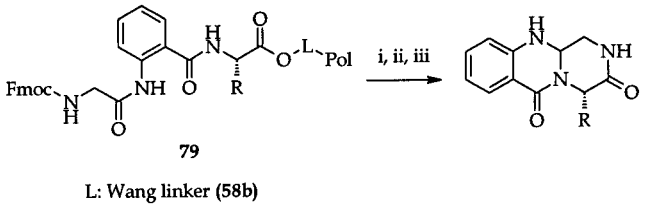
Scheme 52[a]



[a] Reaction conditions: (i) phthalic anhydride, TEA, DMA; (ii) DPPA, TEA, toluene, rt, 2 h; (iii) toluene, 90 °C, 4 h; (iv) amine, DCM, 4 h; (v) K_2CO_3, acetonitrile, 60 °C.

Pyrazino[2,1-*b*]quinazoline-3,6-diones. Wang and Ganesan extended their chemistry for the preparation of fumiquinazoline alkaloids to combinatorial synthesis on the solid phase.[102] The linear tripeptides **79** assembled on Wang resin were subjected to dehydratation and cyclative release to yield pyrazino-[2,1-*b*]quinazoline-3,6-diones (Scheme 53). The synthetic sequence represents an excellent example of combinatorial synthesis of a library of natural products, fumiquinazoline alkaloids.

Scheme 53[a]

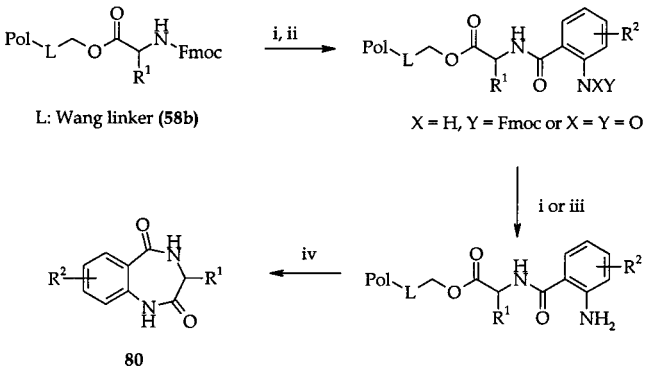


[a] Reaction conditions: (i) Ph_3P, I_2, DIEA (11/11/22 equiv); (ii) piperidine; (iii) acetonitrile, DCM (1:1), reflux overnight.

4.1.3. Seven-Membered Rings

1,4-Benzodiazepine-2,5-diones. The synthesis of 1,4-benzodiazepine-2,5-diones **73** by Mayer et al.[103] illustrates cyclative cleavage yielding a seven-membered ring (Scheme 54). Wang resin esterified with Fmoc-protected amino acids was treated with piperidine, and the liberated amino group was acylated either by Fmoc-protected anthranilic acids or *o*-nitrobenzoic acids. After either Fmoc removal or nitro group reduction, the cyclization was promoted by NaO*t*Bu in THF. The synthesis provided target compounds **80** with high purity (81−99%).

Scheme 54[a]



[a] Reaction conditions: (i) 20% piperidine, DMF, 2 × 20 min; (ii) N-Fmoc-anthranilic acid or *o*-nitrobenzoic acid, DCC, HOBt, 4 h; (iii) $SnCl_2 \cdot 2H_2O$, DMF; (iv) NaOtBu, THF, 60 °C, 24 h.

This pathway was later modified to include reductive alkylation of the amino group of the first amino acid, yielding 1,4-benzodiazepine-2,5-diones with three points of diversity. Dimethylethylamine was used for cyclative cleavage, making the protocol more amenable to synthesis of sizable libraries (tens of thousands of compounds).[8]

Cyclic Peptidosulfonamides. While preparing peptidosulfonamides, a class of peptidomimetics having a peptide bond replaced by a sulfonamide moiety, de Bont et al.[104] described the synthesis of 1,1-dioxo-[1,2,5]thiadiazepan-4-one **81** (Scheme 55). Hydroxy TentaGel was esterified with an Fmoc-amino acid, the Fmoc group was removed, and liberated amine was reacted with substituted Boc-amino ethanesulfinyl chloride. The formed sulfinamide was oxidized to sulfonamide, the Boc group was cleaved, and the product was released from the resin by cyclative cleavage.

4.1.4. Other Ring Sizes

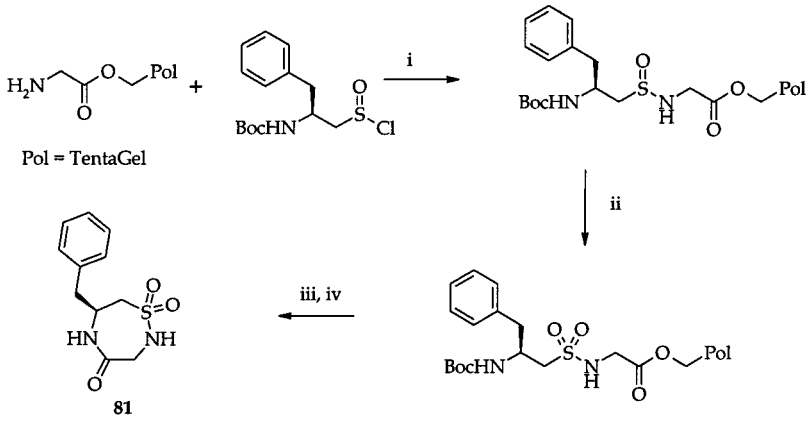
Cyclative cleavage is also applicable to the synthesis of medium-ring lactams **82** from corresponding amino acids (Scheme 56), as shown by Huang and Kalivretenos.[105] The active ester formed from a Boc-protected ω-amino acid and polymer-supported HOBt (see also[106]) was prepared, the Boc group was cleaved, the TFA salt was neutralized, and the product cyclized off the resin (room temperature, 24 h). The yields were 23% (n = 1), 13% (n = 2), 5% (n = 3), and 34% (n = 4). Polymer-supported HOBt has also been used by Scheimann and Showalter[106] as a traceless linker.

4.2. Ring-Closing Metathesis

Ring-closing metathesis is a powerful method for approaching a variety of ring sizes of carbocyclic and heterocyclic cycloalkenes. The solution methodology using a ruthenium carbene catalyst **83**, discovered by Grubbs and co-workers,[107] has recently been successfully applied to solid-phase synthesis (Scheme 57). Schuster at al.[108] demonstrated the concept of solid phase ring-closing metathesis on several nitrogen-containing heterocycles attached to the solid supported linker by the heteroatom.

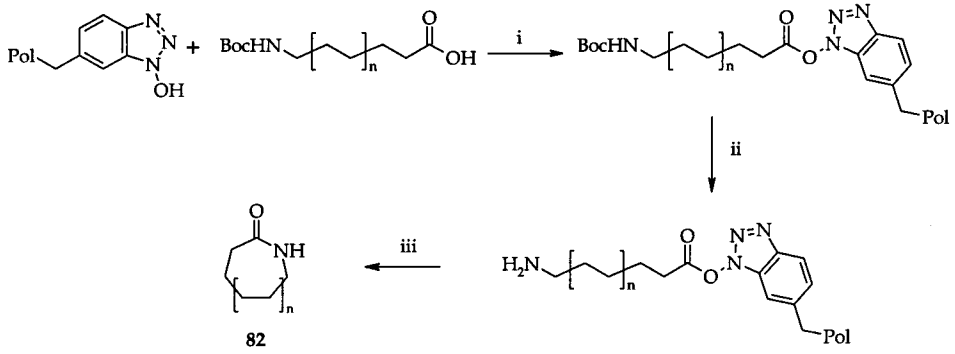
The application of ring-closing metathesis for traceless solid phase synthesis of unsaturated *N*-heterocycles on a solid phase was described by van Maarseveen et al.[109,110] As a proof of the cyclative cleavage concept, 3-amino-1,3,4,7-tetrahydro-azepin-2-one **84** was prepared (Scheme 58). In a subsequent fullpaper,[110] the authors optimized conditions for the cyclative cleavage and isolated the product in 89% yield. The beneficial effect of olefin addition and cyclization of different ring sizes were also studied.

Scheme 55[a]



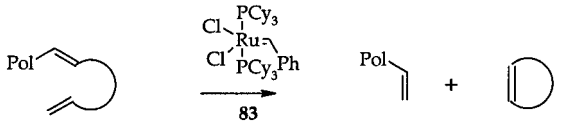
[a] Reaction conditions: (i) NMM; (ii) OsO_4, NMO or tetrabutylammonium oxone; (iii) TFA, DCM; (iv) TEA (cat.), THF, reflux.

Scheme 56[a]



[a] Reaction conditions: (i) DCC, DCM; (ii) TFA, DCM; (iii) TEA, DCM.

Scheme 57



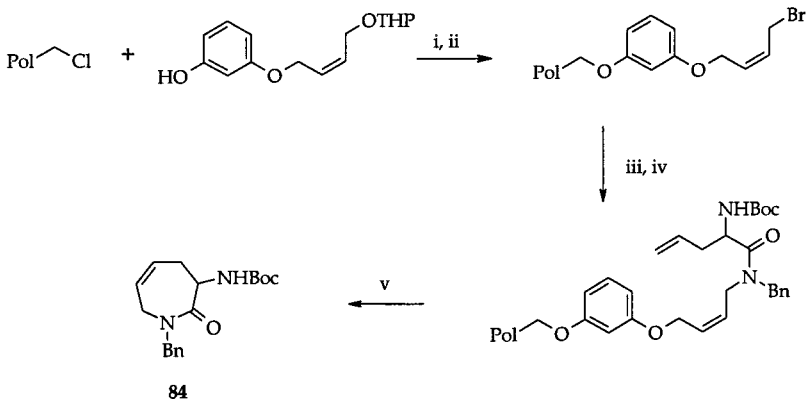
Ring-closing metathesis has also been used as cyclative cleavage pathway by Piscopio et al.[111] for the preparation of dihydropyrans, pipecolinic acid derivatives **85** (Scheme 59), and Freidinger lactams.

The synthesis of Freidinger lactams was later modified[112] (Scheme 60). The resin-bound sulfonamide **86** was prepared and the nitrogen was alkylated under Mitsunobu conditions. The secondary resin-bound amine was liberated and acylated by the substituted pent-4-enoic acid. Metathesis catalyzed with ruthenium effected cyclative cleavage of the target lactam **87**.

Ring-closing olefin methatesis has also been reported for the cyclative release of resin-bound sulfonamides.[113] A flexible linker was required in order to obtain an efficient release using 2.5−5 mol % of the Grubbs catalyst.

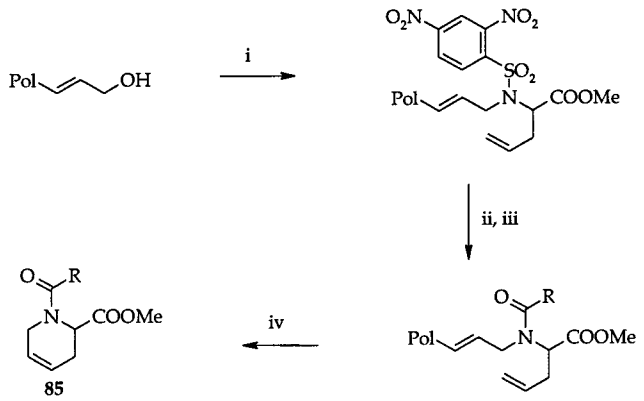
Ring-closing metathesis has also been successfully applied to the solid-phase synthesis of cycloalkenes.[114−116]

Scheme 58[a]



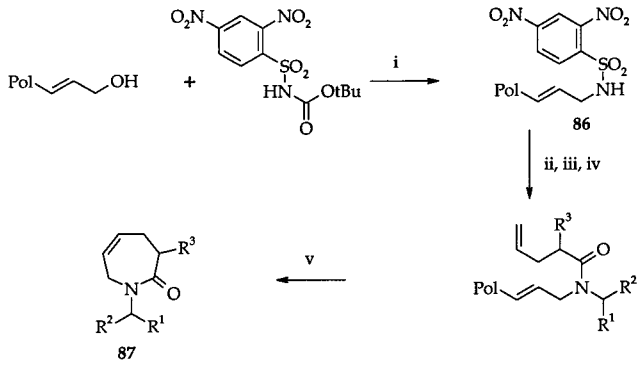
[a] Reaction conditions: (i) NaH, NMP, then Merrifield resin; (ii) $PPh_3Br^+Br^-$, DCM; (iii) benzylamine, NMP, 50 °C; (iv) N-Boc-allylglycine, PyBroP, DIEA, NMP; (v) ruthenium carbene catalyst, toluene.

Scheme 59[a]



[a] Reaction conditions: (i) allyl glycine methyl ester-2,4-dinitrobenzenesulfonamide, DEAD, PPh_3, THF, rt, 16 h; (ii) *n*-butylamine, DCM, rt, 2 h; (iii) *p*-methoxyphenylacetic acid, 1-methyl-2-chloropyridinium iodide, DIEA, DCM, reflux, 2 h; (iv) ruthenium catalyst **83**, DCM, 16 h.

Scheme 60[a]



[a] Reaction conditions: (i) DEAD, PPh_3, rt, 16 h; (ii) TFA, DCM, rt, 16 h; (iii) alcohol, DEAD, PPh_3, THF, rt, 16 h; (ii) *n*-butylamine, DCM, rt, 1 h; (iii) *ω*-unsaturated pentenoic acid, PyBroP, DIEA, DMF, 48 h; (iv) ruthenium catalyst, DCE, 80 °C, 16 h.

5. Postcleavage Modification

Postcleavage modification, particularly if it proceeds spontaneously, is a very compelling approach for traceless solid phase synthesis. On the other hand, in analogy to Houghten's library from the library concept,[117] cases in which a separate postcleavage step is required may offer the opportunity to evaluate the properties of both the primary cleavage products as well as the compounds obtained by subsequent modification, for example in drug discovery lead generation screens.

Cyclization of a linear precursor has been the most frequently used method for postcleavage modification to provide traceless products. Thermodynamically favorable formation of a five- or six-membered ring has provided clean products in high yields. Decarboxylation has the advantage that the carboxylate group constitutes a convenient linker that can subsequently be removed, but it is limited to situations in which decarboxylation can occur under relatively mild conditions, for example, carboxylate groups on an electron deficient ring. Last, but not least, oxidation of partially oxidized heterocyclic compounds to heteroaromatic compounds represents an attractive postcleavage modification, especially since the resulting compounds do not bear any trace of the linker, not even a hydrogen atom.

5.1. Cyclization

5.1.1. Piperazinones

Shreder et al.[118] studied cyclative release yielding piperazinones (Scheme 61) in connection with synthesis of piperazinones analogues of Leu-enkephalin. Wang resin esterified with N-alkylated glycine was reacted with *β*-lactone derived from Boc-serine. The resulting carboxylic acid was activated and reacted with amines. Exposure to TFA resulted in cleavage, deprotection, and cyclization to piperazinones.

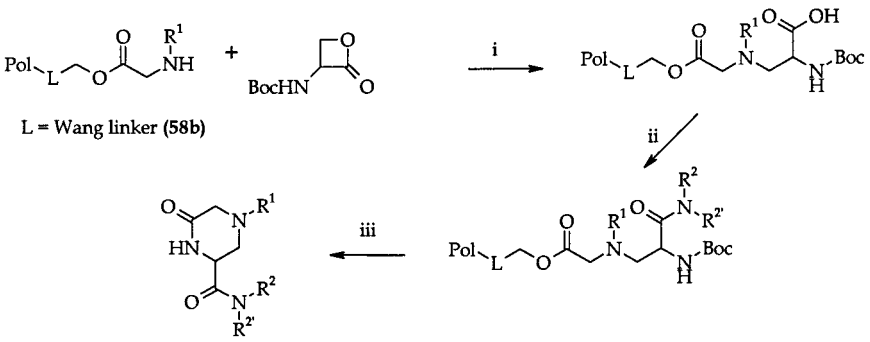
5.1.2. 1-Acyl-3-oxopiperazines

An elegant method of spontaneous postcleavage cyclization was reported by Pátek's group[119] (Scheme 62). Tandem *N*-acylium ion cyclization−nucleophilic addition was used to provide direct access to new bi-, tri-, and tetracyclic derivatives of 1-acyl-3-oxopiperazines. Bromoacetaldehyde diethyl acetal was attached to hydroxy TentaGel resin, bromide was displaced by amines, and the resin-bound amino group was acylated with amino acids. After removing the Fmoc protecting group, the amino group was acylated by carboxylic acids containing different nucleophilic centers. Upon cleavage from the resin, the product cyclized to give traceless bicycle products **88**.

5.1.3. Benzofurans

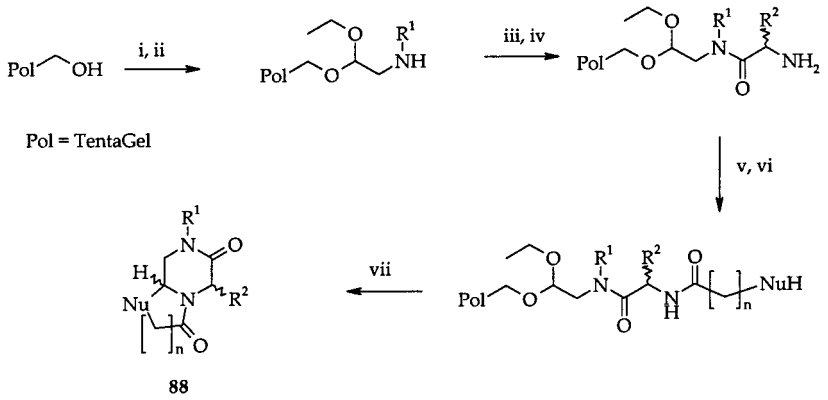
The key step of a traceless synthesis of benzofurans described by Guthrie et al.[120] was conversion of polymer-supported esters into enol ethers using a

Scheme 61[a]



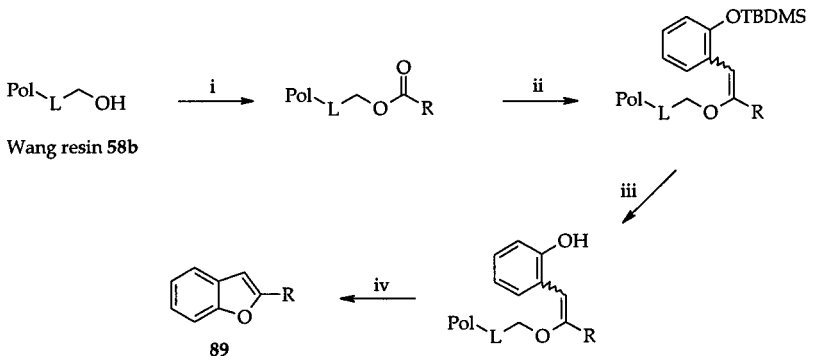
[a] Reaction conditions: (i) NMP, 40 °C, 52 h; (ii) $NHR^2R^{2'}$, BOP, DCM; (iii) 5% H_2O in TFA.

Scheme 62[a]



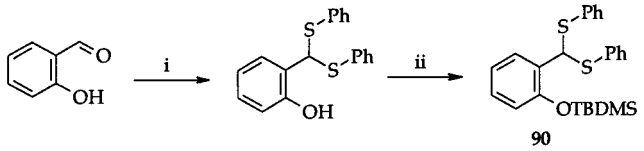
[a] Reaction conditions: (i) Bromoacetaldehyde diethyl acetal, quinoline *p*-toluenesulfonate, DCE, reflux, 4 h; (ii) 1° amine, DMSO, 60 °C, 15 h; (iii) Fmoc-amino acid, TFFH, DIEA, DCE, 48 h; (iv) 20% piperidine, DMF; (v) Prot-Nu-$(CH_2)_n$COOH (e.g., Fmoc-Cys(S-*t*Bu)-OH), TFFH, DIEA, DCE, 48 h; (vi) deprotection; (vii) formic acid, rt to 60 °C.

Scheme 63[a]



[a] Reaction conditions: (i) carboxylic acid, DIC, DMAP, THF; (ii) thioacetal, $Cp_2Ti[P(OEt)_3]_2$, THF, rt, 18 h; (iii) TBAF, THF, rt, 3 h; (iv) TFA/H_2O (1:1), DCM, rt, 30 min.

Scheme 64[a]



[a] Reaction conditions: (i) PhSH, BF_3·OEt_2, AcOH, toluene; (ii) TBDMSCl, imidazole, DMF.

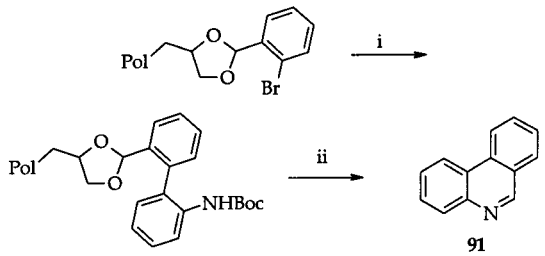
titanocene alkylidene, prepared from thioacetals and a low-valent titanium complex, $Cp_2Ti[P(OEt)_3]_2$ (Scheme 63). The critical thioacetal intermediate **90** was prepared in solution from salicylaldehyde according to Scheme 64.

An ester from Wang resin was reacted with the thioacetal **90** and the titanium complex in THF to afford enol ethers (Scheme 64). After cleaving the hydroxy protecting group, the intermediate was cleaved from the resin by TFA, which was followed by spontaneous cyclization to target benzofurans **89**.

5.1.4. Phenanthridines

Chamoin et al.[121] used the Leznoff acetal linker[65] to tether *o*-bromobenzaldehydes for Suzuki−Miyaura cross coupling with aryl and heteroaryl boronic acids (Scheme 65). Use of phenylboronic acid substituted in the ortho position with a protected amino group afforded, after TFA cleavage and spontaneous cyclization, the phenanthridine product **91**.

Scheme 65[a]



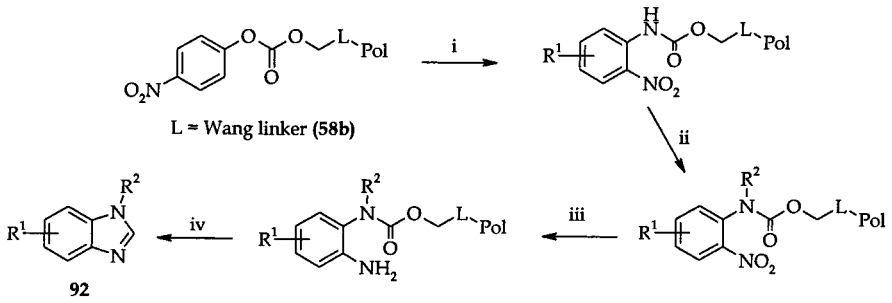
[a] Reaction conditions: (i) boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME; (ii) TFA.

5.1.5. Benzimidazoles

Huang and Scarborough[122] described the traceless synthesis of benzimidazoles **92** with two combinatorial steps, followed by postcleavage cyclization (Scheme 66). Substituted *o*-nitroanilines were attached to the *p*-nitrophenyl carbonate Wang resin in DMF with BSA and DMAP. The carbamate nitrogen was alkylated with benzyl bromides, and the nitro group was reduced by tin(II) chloride. The linear resin-bound precursor was then treated with a TMOF/TFA/DCM mixture, resulting in cleavage and cyclization to the target structure.

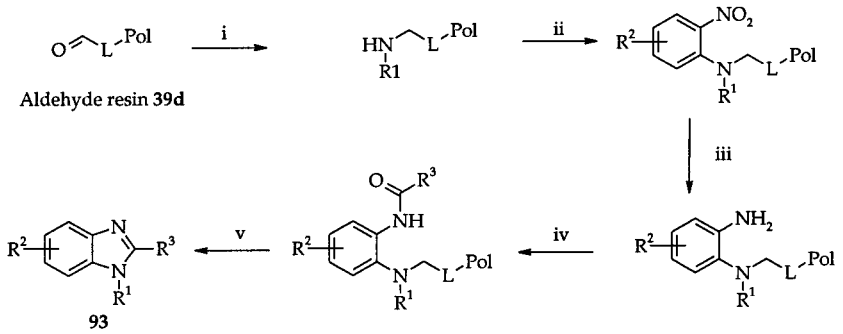
The proposed mechanism of cleavage and cyclization involves initial formation of dimethylformamidine with TMOF, followed by cleavage from the resin mediated by TFA and cyclization to benzimidazole in solution.

Scheme 66[a]



[a] Reaction conditions: (i) *o*-nitroaniline, BSA, DMAP in DMF, rt, 20 h; (ii) benzyl bromide, lithium *t*-butoxide in THF/DMSO, rt, 5 h; (iii) $SnCl_2 \cdot 2H_2O$ in DMF, rt, 3 h; (iv) TMOF/TFA/DCM (1:1:2), rt, 3 h.

Scheme 67[a]



[a] Reaction conditions: (i) amine/$NaB(OAc)_3H$ in DMF/AcOH; (ii) o-fluoronitrobenzene, DMSO, rt, overnight; (iii) $SnCl_2 \cdot 2H_2O$ in NMP, rt, overnight; (iv) acid chloride/DIEA in DCM, rt, overnight; (v) AcOH, 80 °C, overnight.

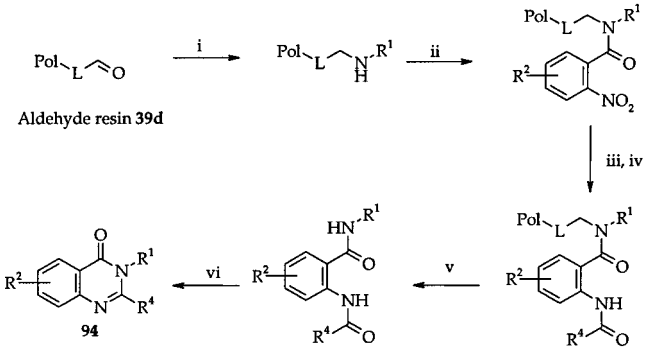
A variant of the above process is shown in Scheme 67. This route to benzimidazoles serves as an example of a synthesis of 1-alkylamino-2-acylaminobenzene, a linear precursor of benzimidazoles.[123−125] Cleavage from the resin was performed under conditions whereby the *N*-acyl-*o*-phenylenediamine cyclized to benzimidazole **93**.

Aldehyde resin was reductively aminated with primary amines to afford resin-bound secondary amines. Various *o*-fluoronitrobenzenes were reacted with the secondary amine resin in DMSO, yielding tethered *o*-nitroanilines. The nitro group was reduced by tin chloride in NMP and the aniline was acylated by acid chlorides in DCM. When the acylated intermediate was exposed to TFA, a mixture was isolated containing mostly the benzimidazole contaminated by some uncyclized precursor. Completion of the cyclization process could be effected in acetic acid at 80 °C overnight. To shorten the two-step procedure, the resin-bound intermediates were exposed to AcOH at elevated temperature. The target benzimidazoles **93** do not carry any memory of the linker, since the nitrogen valence used to attach the intermediate to the resin is utilized in the subsequent cyclization step.

5.1.6. Quinazolinones

Precursor construction on solid phases followed by cleavage from the resin and cyclization to the target structure in solution is further exemplified by the synthesis of quinazolinones **94** (Scheme 68).[126] A resin-bound secondary amine, prepared from aldehyde resin and amine, was acylated by *o*-nitrobenzoic acids, the nitro group was reduced under standard conditions with tin(II) chloride dihydrate, and the

Scheme 68[a]



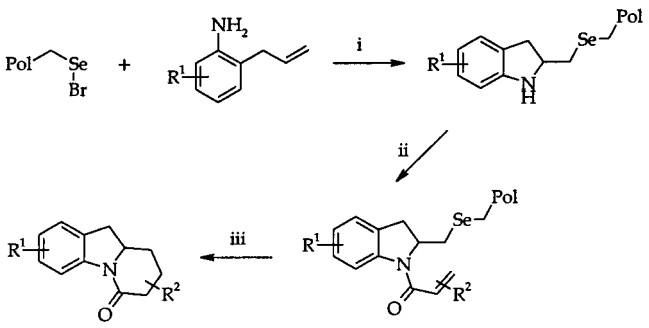
[a] Reaction conditions: (i) amine, $NaB(OAc)_3H$, DMF/AcOH; (ii) *o*-nitrobenzoic acid, DIC, HOBt, DMF, rt, 16 h; (iii) $SnCl_2 \cdot 2H_2O$, NMP, rt, 2 h; (iv) carboxylic acid, DIC, pyridine/THF, rt, overnight; (v) TFA or gaseous HCl or gaseous HF, rt, 2 h; (vi) DMEA, TMS-Cl, MeCN, rt, overnight.

product was acidolytically cleaved from the resin. The cyclization of *N*-acylanthranilic acid amides was accomplished with TMS-Cl to yield volatile byproducts, thus permitting massive parallel synthesis of quinazolones in three combinatorial steps using amines and *o*-nitrobenzoic acids (or protected anthranilic acids).

5.1.7. Polycyclic Indolines

Indolines were prepared from polymer-based selenyl bromide resin and *o*-allyl anilines.[127] The resin-bound indolines were further acylated on the nitrogen by α,β unsaturated acids. Upon a novel reductive cleavage (nBu$_3$SnH), the allyl group reacted with the selenium tether generated carbon radical to form an additional cycle (Scheme 69).

Scheme 69[a]



[a] Regents: (i) $SnCl_4$, DCM, −20 °C, 0.5−1 h; (ii) α,β unsaturated acid, DCC; (iii) nBu$_3$SnH, 2,2′-azobisisobutyronitrile (AIBN), 90 °C.

5.2. Decarboxylation

5.2.1. Dihydropyrimidinone

Acidolytic cleavage of an ester linker leaves the carboxyl group on the cleaved molecule. Besides being useful in cyclative cleavage strategies, as discussed previously, the ester linker has been used for traceless synthesis in cases that are conducive to postcleavage decarboxylation. Hamper et al.[128] synthesized dihydropyrimidinones **95** from polymer-supported malonic acid (Scheme 70). Macroporous Wang resin was reacted with Meldrum's acid, and the product was converted to the malonate ester with TFE and DIC. Knoevenagel condensation with aromatic aldehydes gave methylene malonates. The cyclization with amidines yielded resin-bound dihydropyrimidinones, which underwent decarboxylation upon TFA cleavage.

5.2.2. Quinazolines

A decarboxylative traceless linker strategy has been developed for the synthesis of quinazolines **96**[129] (Scheme 71). The hydroxymethyl resin was converted to resin-bound ethyl oxalate that was reacted with an *o*-aminobenzamide to yield resin-bound quinazolinone. To introduce the next combinatorial step, the quinazolinone was converted to the 4-chloro derivative with thionyl chloride. Nucleophilic substitution of chlorine with aniline resulted in the resin-bound target structures. Cleavage was accomplished by trimethylsilyl iodide, followed by decarboxylation in refluxing HCl. The solid phase reactions were monitored by FTIR.

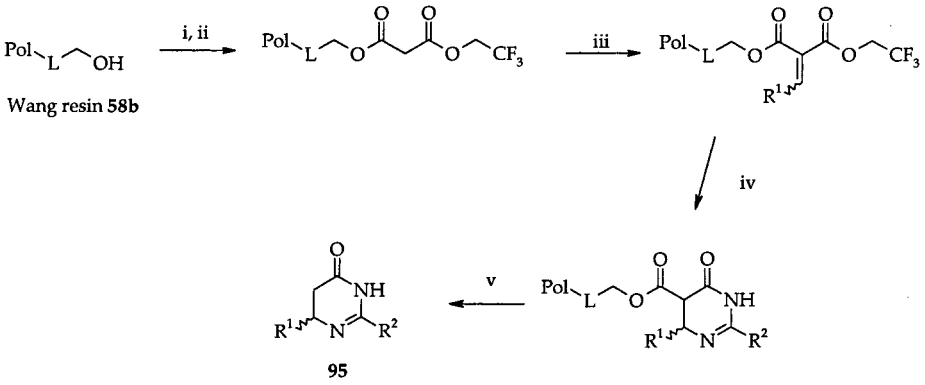
Postcleavage decarboxylations on acyclic systems have been described in several reports.[130−132]

5.3. Oxidation

5.3.1. Pyridines

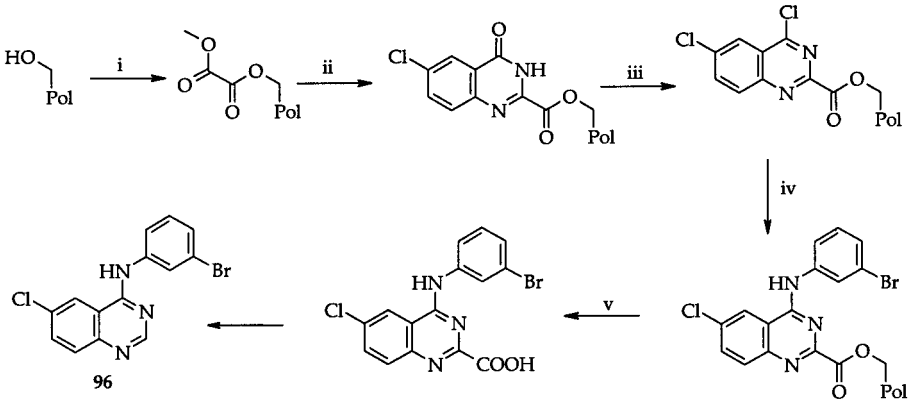
Chen and Munoz[133−136] have shown that the purpose of the linker need not be restricted to im-

Scheme 70[a]



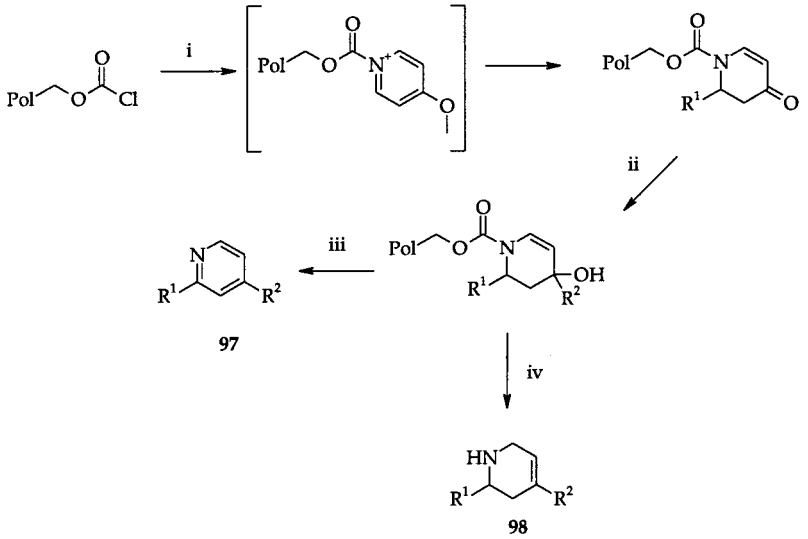
[a] Reaction conditions: (i) Meldrum's acid; (ii) TFE, DIC, DMA; (iii) aldehyde, piperidine acetate, toluene, reflux with water trap, 1−3 h; (iv) amidine hydrochloride, K_2CO_3, DMA, 70 °C, 4−8 h; (v) TFA.

Scheme 71[a]



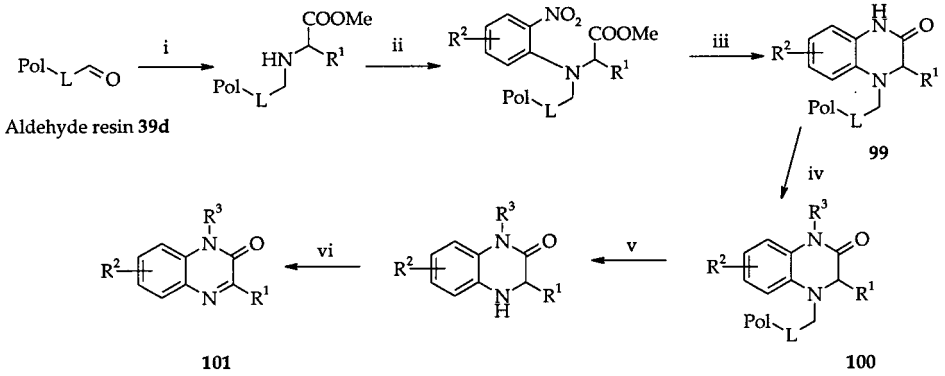
[a] Reaction conditions: (i) ethyl oxalyl chloride, DMAP, TEA, DCM, 0−25 °C, 2 h; (ii) 2-amino-5-chlorobenzamide, CSA·H_2O, dioxane, 110 °C, 48 h; (iii) $SOCl_2$ in DMF, reflux, 3h; (iv) 3-bromoaniline, *i*-propanol/DMF/HCl, rt, 18 h; (v) TMS-Cl, NaI, MeCN/dioxane, 75 °C, 72 h.

Scheme 72[a]



[a] Reaction conditions: (i) 4-methoxypyridine, Grignard reagent, THF, a few minutes, then aqueous 3 N HCl:THF (1:1); (ii) Grignard reagent, $CeCl_3$; (iii) TFA:DCM (2:1), bubbling air; (iv) Et_3SiH, TFA:DCM (2:1).

Scheme 73[a]



[a] Reaction conditions: (i) amino acid ester, $NaB(OAc)_3H$, DMF/AcOH; (ii) *o*-fluoronitrobenzene, DMSO, 75 °C, 1−3 days; (iii) $SnCl_2 \cdot 2H_2O$, NMP, rt, 2 h; (iv) BEMP, alkyl halide, DMF, rt, 2 h; (v) TFA or gaseous HCl or gaseous HF, rt, 2 h; (vi) air oxidation, MeOH, rt, overnight.

mobilization of the scaffold for solid phase synthesis, but it can also be used for generation of reactive resin-bound intermediates. The new strategy, referred to as REACAP technology (*re*sin *ac*tivation/*c*apture *ap*proach), was documented by activation of 4-methoxypyridine, followed by alkylation by a Grignard reagent (Scheme 72). The vinylogous imide was subjected to a 1,2-addition reaction using organocerium reagents. Acidolytic cleavage was effected under oxidizing conditions (bubbling oxygen/air) and yielded the pyridine **97**, whereas cleavage under reducing conditions (presence of triethylsilane) yielded a tetrahydropyridine **98**.

5.3.2. Quinoxalinones

The traceless synthesis of quinoxalinones followed the route shown in Scheme 73.[137] Aldehyde resin was reductively aminated with amino acid esters. The second combinatorial step involved nucleophilic fluorine displacement using *o*-fluoronitrobenzene with the polymer-supported secondary amine. The nitro group of the resin-bound *o*-nitroaniline was reduced by 2 M tin(II) chloride dihydrate solution in NMP. The reduced intermediate spontaneously cyclized to the dihydroquinoxalinone **99**. The amide nitrogen was alkylated with electrophiles to provide dihydroquinoxalinones **100**. Products were cleaved from the resin by TFA or gaseous HCl or HF. The dihydroquinoxalinones are prone to air oxidation to the corresponding quinoxalinone **101**. To isolate the dihydroquinoxalinone, the product was stored under a nitrogen atmosphere.

5.4. Elimination

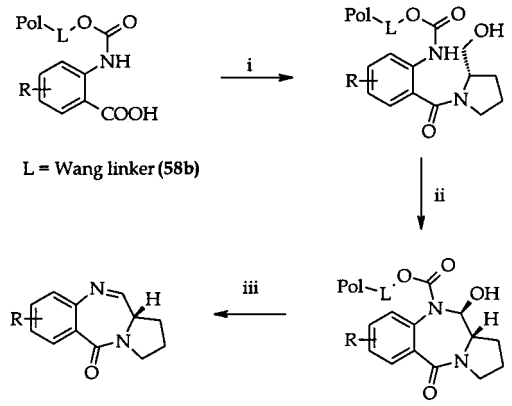
5.4.1. Benzodiazepines

Traceless synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines, prepared on *p*-nitrophenyl carbonate Wang resin, took advantage of dehydratation following the cleavage from the resin.[138] The ring closure was affected by oxidation of alcohol with variety of oxidizing agents, the favorite one being Dess−Martin periodinane (Scheme 74).

6. Linker Displacement

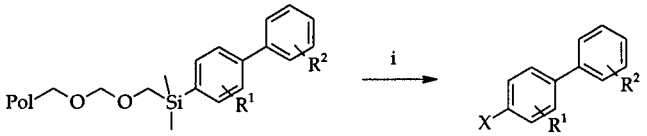
Cleavage with functionalization of the atom that was used as a point of attachment to the linker

Scheme 74[a]



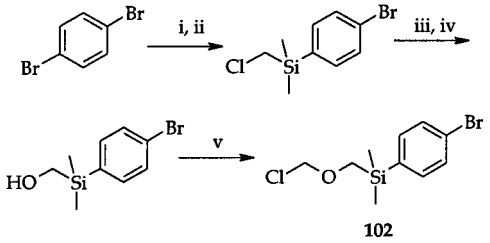
[a] Reaction conditions: (i) pyrrolidinemethanol, TBTU, DIEA, DMF, rt, 6 h, repeated; (ii) 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (Dess−Martin periodinane), DCM, rt, 20 min; (iii) 50% TFA, DCM.

Scheme 75[a]



[a] Reaction conditions: (i) for X = I: ICl, DCM; for X = Br: Br_2 (6 equiv), pyridine (3 equiv) in DCM, 24 h.

Scheme 76[a]



[a] Reaction conditions: (i) n-BuLi in THF, −78 °C, 5 min; (ii) (chloromethyl)dimethylsilyl chloride, −78 °C, 5 min; (iii) NaOAc, n-Bu_4NI in DMF, 80 °C, 24 h; (iv) Dibal-H, toluene, −78 to 0 °C, 2 h; (v) trioxane, HCl(g).

represents another approach to traceless solid phase synthesis.

6.1. Silicon Linker

Silicon linkers were originally designed for the traceless synthesis of aromatic compounds by acidolytic cleavage. However, Han et al.[33] have cleaved the aryl−silicon bond with a variety of electrophiles (Scheme 75).

The linker−first building block unit **102** was synthesized from bromoarenes according to Scheme 76. The linker−scaffold unit was attached to the Wang resin (DIEA in DMF, 40−50 °C, overnight) and subjected to Suzuki cross-coupling reaction conditions with a variety of boronic acids. The products were cleaved by different electrophiles (H^+, I^+, Br^+) to afford ipso-substituted biphenyl derivatives.

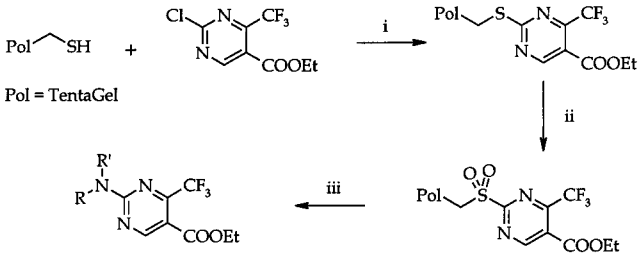
6.2. Sulfur Linker

Chucholowski et al.[97] introduced an elegant strategy whereby the linker attached to the target molecule is replaced by a reagent that cleaves the compound from the resin and introduces an additional combinatorial step at the point of original attachment to the solid support.

As a proof of concept, 2,4,6-trisubstituted pyrimidines **103** were synthesized (Scheme 77). Resin-bound thiouronium salt, prepared from the Merrifield resin and thiourea, was reacted with an acetylenic ketone to yielded a pyrimidine. The ester was cleaved and the carboxylic acid activated and reacted with amines. Oxidation to the sulfone activated the position for nucleophilic displacement with amines.

Gayo and Suto[139] applied the same strategy on almost identical target compounds (Scheme 78).

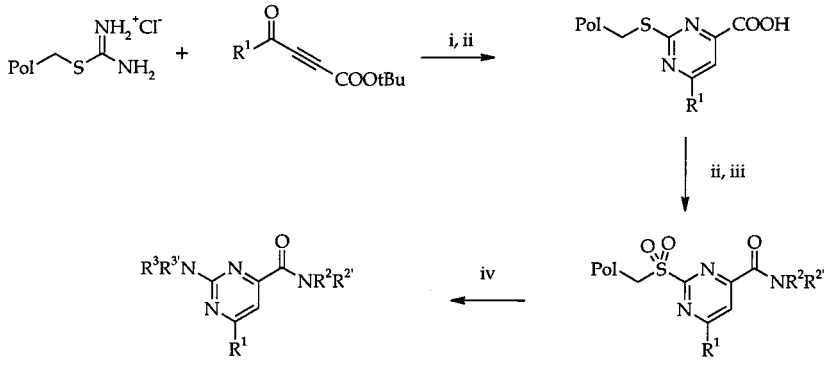
Scheme 78[a]



[a] Reaction conditions: (i) TEA in DMF, rt, 1 h; (ii) mCPBA in DCM, rt, overnight; (iii) RR′NH in DCM, rt, 24 h.

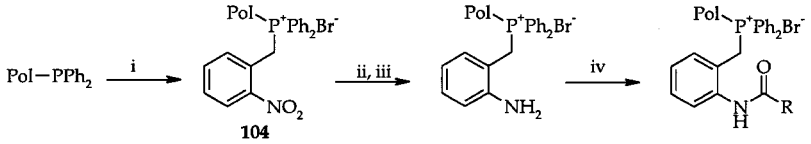
Nucleophilic substitution of the chlorine in 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate by thiol resin produced the sulfide. The stoichiometry of

Scheme 77[a]



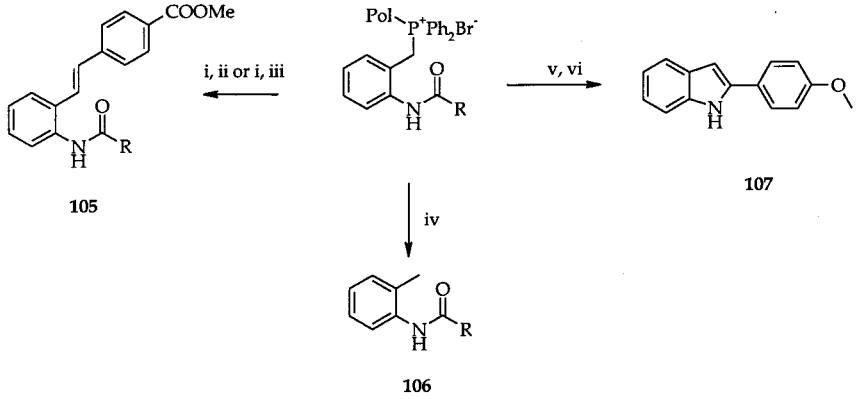
[a] Reaction conditions: (i) DIEA, DMF, rt; (i) 50% TFA in DCM, rt; (iii) amine, EDC, HOSu, DCM; (ii) mCPBA in DCM, rt, overnight; (iii) secondary amine in dioxane, rt to 50 °C, 24 h.

Scheme 79[a]



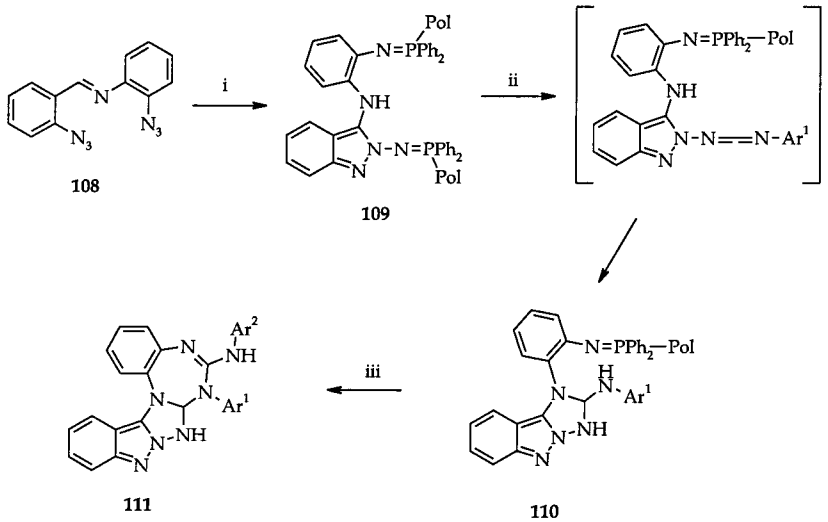
[a] Reaction conditions: (i) 2-nitrobenzyl bromide, DMF, 70 °C, 48 h; (ii) $Na_2S_2O_4$, EtOH, reflux, 90 min; (iii) HBr, MeOH/dioxane; (iv) 4-methoxybenzoyl chloride, pyridine, DCM, rt, 5 h.

Scheme 80[a]



[a] Reaction conditions: (i) methyl 4-formylbenzoate, NaOMe, MeOH, reflux, 2 h; (ii) Girard's reagent T, AcOH, 18 h; (iii) aminomethyl resin, AcOH, MeOH/dioxane, 18 h; (iv) NaOMe, MeOH, reflux, 4 h; (v) toluene, DMF, distill; (vi) KO*t*Bu, reflux, 45 min.

Scheme 81[a]



[a] Reaction conditions: (i) Resin-bound triphenyl phosphine, DCM, rt; (ii) isothiocyanate, DCM, rt; (iii) isothiocyanate, toluene, reflux.

amine was limiting in the cleavage process in order to circumvent the need for a final purification step.

6.3. Phosphonium Linker

Hughes[140] exploited the polymer-bound phosphonium salt **104** as a traceless linker for the synthesis of alkyl, alkenyl, and heteroaryl products. Polymer-bound phosphonium salts were prepared from commercially available polymer-bound triphenyl phosphine and a nitrobenzyl bromide, then the nitro group was reduced and acylated (Scheme 79).

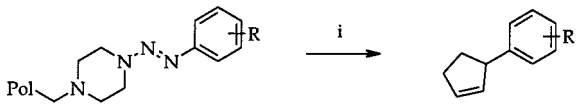
The product was cleaved from the resin by three pathways, as shown in Scheme 80. Wittig cleavage with aldehyde produced stilbene **105**, hydrolysis of the carbon−phosphonium bond resulted in toluene derivative **106**, and intramolecular Wittig reaction afforded indole derivative **107**.

Resin-bound triphenylphosphine was also used by Slade et al.[141] to tether 4-fluoro-3-nitrobenzyl bromide for the synthesis of 2-alkylthiobenzimidazoles. Cleavage with sodium hydroxide led to the formation of a methyl group at the attachment point.

6.4. Iminophosphorane Linker

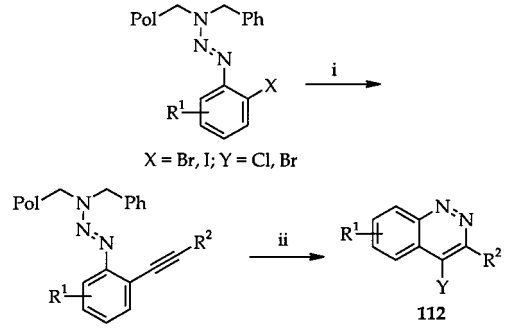
An attractive route for immobilization of azides via resin-bound iminophosphorane was reported by López-Cremades et al.[142] (Scheme 81). The cleavage of iminophosphorane by arylisothiocyanate released a carbodiimide derivative. In a trial example, bis-azide **108** was immobilized via both azido groups to form the resin-bound iminophosphorane **109**, showing different reactivities of the azido groups. When exposed to isothiocyanates, the more reactive iminophosphorane formed the carbodiimide, which spon-

Scheme 82[a]



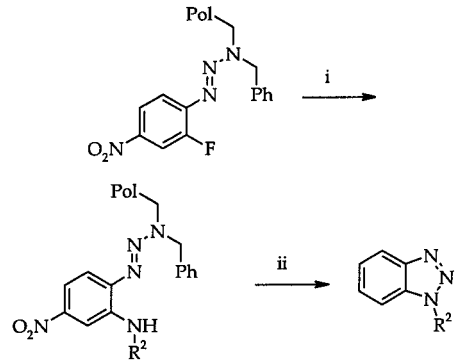
[a] Reaction conditions: (i), TFA, MeOH, 0 °C, then cyclopentene $Pd(OAc)_2$, MeOH, 40 °C, 2−12 h.

Scheme 83[a]



[a] Reaction conditions: X = halide. (i) alkyne, $Pd(OAc)_2$, TEA, DMF, 80 °C, 12 h; (ii) HCl or HBr, acetone/H_2O.

Scheme 84[a]



[a] Reaction conditions: (i) amine, CsF, Cs_2CO_3, DMF, 80 °C, 36 h; (ii) TFA, MeOH.

taneously cyclized to monoiminophosphorane **110**. Subsequent treatment with a different isothiocyanate in refluxing toluene released the target pentacyclic compound **111**.

6.5. Triazene Linker

The T1 triazene linker was developed by the Bräse group and shown to be a very useful linker for the traceless synthesis of arenes (section 2.4.). However, the arene diazonium salts generated from the triazene linkers offer diverse opportunities for multidirectional cleavage.[19] An example of cleavage with cross-coupling functionalization is shown in Scheme 82. In an elegant manner, the Heck reaction of arene diazonium salts with olefins was applied to the arenes attached to the solid support via the triazene linker.[44] TFA was used to liberate the diazonium salt, which was reacted with olefins in the presence of Pd-(II) acetate catalyst.

In addition to numerous routes for arene derivatization,[19] the arene diazonium salts substituted at the ortho-position afforded cinnoline derivatives **112**[143] (Scheme 83).

Cyclization to form benzotriazole derivatives is illustrated in Scheme 84.[144] In another variation, the diazonium salt was reduced to the corresponding hydrazine, a useful intermediate for building heterocyclic compounds.[144]

7. Miscellaneous

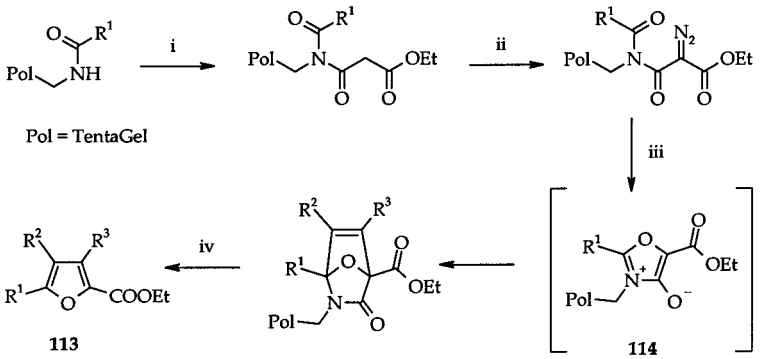
7.1. Furans

Cowravaram and Gallop[145] reported the preparation of functionalized furans **113** by 1,3-dipolar cycloaddition of acetylenes with isomünchnones (Scheme 85). Amino TentaGel resin was acylated with carboxylic acids, the resin-bound amide was reacted with malonyl chloride, and the resulting imide was converted to the diazoimide using tosyl azide. Rhodium-catalyzed formation of isomünchnones **114** was followed by 1,3-dipolar cycloaddition with acetylenes, to release furans **113** that were then purified by column chromatography.

7.2. Pyrazoles

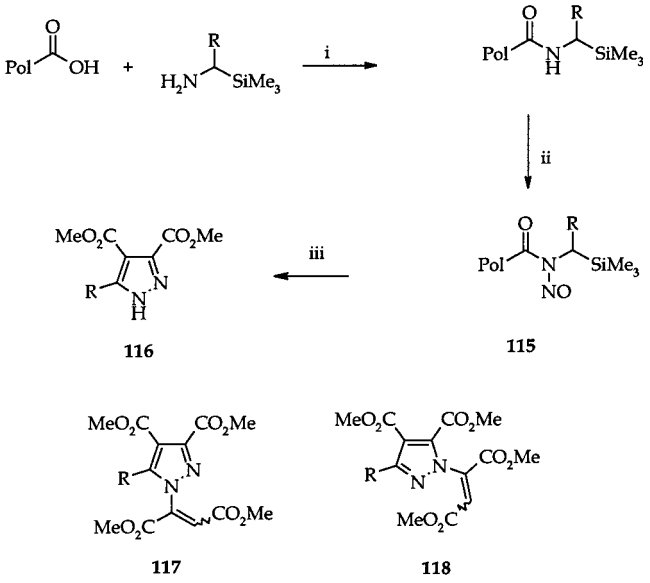
Washizuka et al.[146] reported the traceless synthesis of pyrazole derivatives from resin-bound α-silylnitrosoamide **115** (Scheme 86). The carboxy polystyrene resin was activated by DIC and reacted with an α-trimethylsilylamine. Nitrosation with dinitrogen tetroxide gave the α-silylnitrosoamide, which underwent intramolecular 1,4-silatropic shift to give resin-bound azomethine imine. 1,3-Dipolar cycloaddition with dipolarophile dimethyl acetylenedicarboxylate (DMAD) yielded the pyrazole derivative **116** in low yield. Attempts to improve the yield by insertion of

Scheme 85[a]



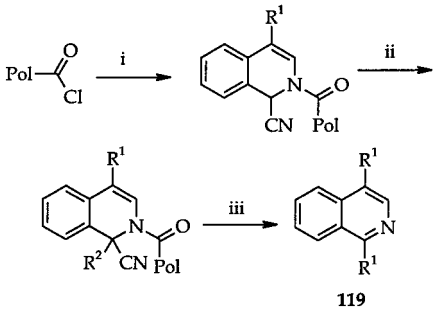
[a] Reaction conditions: (i) methyl malonyl chloride, benzene (1:1), 60 °C, 1.5 h; (ii) tosyl azide, TEA, DCM, 24 h; (iii) acetylenes, $Rh_2(OAc)_4$, benzene, rt, 4 h; (iv) benzene, 80 °C, 2 h.

Scheme 86[a]



[a] Reaction conditions: (i) DIC, DCM; (ii) N_2O_4, NaOAc, CCl_4; (iii) DMAD, toluene, 80 °C.

Scheme 87[a]



[a] Reaction conditions: (i) isoquinoline, TMS-CN, DCM, rt, 48 h; (ii) LDA, THF, −78 °C, 30 min then ethyl iodide, −78 °C to room temperature, 48 h; (iii) KOH, THF:H_2O (2:1).

a spacer yielded pyrazoles **117** and **118**, which overreacted in Michael fashion with DMAD.

7.3. Isoquinoline

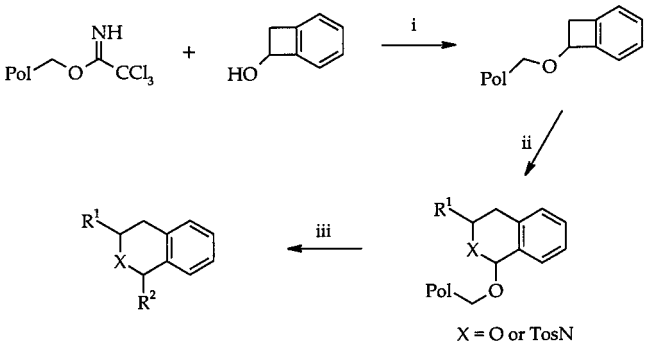
Derivatization of isoquinolines by alkylation at the C-1 position of resin-bound 2-acyl-1,2-dihydroisoquinaldonitriles, followed by a traceless release of product **119** (Scheme 87), was described by Kurth's group.[147,148]

Hetero-Diels−Alder reaction of *o*-quinodimethanes was exploited by Craig et al.[149] for a traceless solid phase synthesis of the tetrahydroisoquinolines and dihydrobenzopyrans (Scheme 88). Benzocyclobutenol was attached via the 2,2,2-trichloroacetimidate-derivatized polymer support, and a hetero-Diels−Alder reaction with tosylbenzaldimines and aldehydes yielded the resin-bound target structures. Cleavage with a Lewis acid−nucleophile combination allowed the introduction of additional substitution on the point of attachment to the resin.

8. Conclusion

To select the best linking strategy for a traceless solid phase synthesis of an individual heterocycle,

Scheme 88[a]



[a] Reaction conditions: (i) triflic acid, DCM:hexane (1:1), 0 °C to room temperature, 16 h; (ii) R^1-CH=X, solvent, 105−110 °C, 14 h; (iii) acid, R^2M, DCM, rt, 16 h (e.g., TFA, Et_3SiH, or Me_3Al).

several factors have to be taken into account. The basic requirements for a linker, such as the stability of linkage to reaction conditions during the synthesis, and stability of target compounds toward cleaving conditions are obvious. However, practical aspects are important as well, particularly if large compound arrays are to be prepared. The practical usefulness of a linker is limited when a multistep solution phase synthesis of the linker, starting building blocks containing particular functional groups, or a linker-scaffold unit is needed. Some cleavage conditions are not easily adapted to massive parallel synthesis, since they include nonvolatile components that need to be removed in an additional purification step.Fortunately, an ever expanding list of linkers is commercially available; however, their price may sometimes also play a critical role.

As in many other research activities, there is no single linker strategy that meets all synthetic demands. Therefore, the chemist's ingenuity in approaching any particular project is the most influential factor contributing to the successful culmination of a project. It is hoped that this review will provide a basis for spurring the imagination of those whose ingenuity will be so challenged.

9. Abbreviations

Ac	acetyl
AcOH	acetic acid
AMEBA	*a*cid-sensitive *me*thoxy *benza*ldehyde linker
Ar	aryl
BAL	backbone amide linker
9-BBN	9-borabicyclo(3.3.1)nonane
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorane
BHA	benzhydrylamine
Boc	*tert*-butyloxycarbonyl
Bpoc	1,3-biphenyprop-2-yloxycarbonyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
CDI	carbonyldiimidazole
CIP	2-chloro-1,3-dimethylimidazolium hexafluorophosphate
m-CPBA	*m*-chloroperbenzoic acid
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
Dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	dichloroethane

DCM	dichloromethane
DEAD	diethylazadicarboxylate
Dibal-H	diisobutylaluminum hydride
DIAD	diisopropylazadicarboxylate
DIC	*N*,*N*′-diisopropylcarbodiimide
DIEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DME	1,2-dimethoxyethane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
DPPP	1,3-bis(diphenylphosphino)propane
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
Fmoc	fluorenylmethyloxycarbonyl
HATU	*o*-(7-azabenzotriazol-1-yl)-1,1,4,4,-tetramethyluronium hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	N-hydroxybenzotriazole
IBX	1-hydroxy-1,2-benziodoxol-3(1*H*)-one
L	linker (specified for each scheme)
LDA	lithium diisopropylamide
MBHA	*p*-methylbenzhydrylamine
Ms	mesyl
mCPBA	3-chloroperoxybenzoic acid
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methylpyrrolidinone
Nu	nucleophile
PEG	poly(ethylene glycol)
Pol	insoluble polymer solid phase support; copoly(styrene−1% divinylbenzene), unless specified otherwise
PPTS	pyridinium *p*-toluenesulfonate
PS	polystyrene
PyBroP	bromotris(pyrrolidino)phosphonium hexafluorophosphate
PyBOP	benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
TBAF	tetrabutylammonium fluoride
TBDMSCI	1-(*tert*-butyldimethylsilyl)imidazoles
TBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
TFFH	fluoro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMG	tetramethylguanidine
TMS-Cl	trimethylsilyl chloride
TMS-CN	trimethylsilyl cyanide
TMOF	trimethylorthoformate
Tol	*p*-toluoyl
Tos	*p*-toluenesulfonyl
Wang resin	*p*-benzyloxybenzyl alcohol functionalized polystyrene beads

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