Traceless Solid-Phase Organic Synthesis

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I. Introduction

A. Background

The concept of solid-phase synthesis was first realized when Merrifield,[1] in his seminal 1963 paper, published his synthesis of L-leucyl-L-alanylglycyl-L-valine via attachment of the intermediates to a polymer backbone (Scheme 1). The solid support he chose was polystyrene, which was 2% cross-linked with divinylbenzene for optimum rigidity, swelling properties, and strength.

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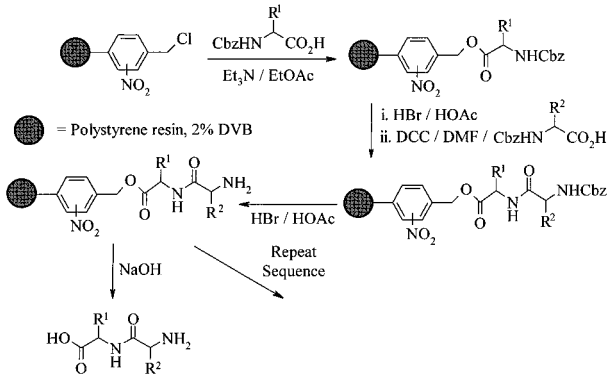
Scheme 1



This was soon to revolutionize the synthesis of peptides due to the speed and simplicity of the technique. The major benefits over standard solution-phase techniques included the following: the ease of product isolation via filtration; use of excess reagents to force reactions to completion; reduced overall time scale for synthesis; and finally the method was open to automation. The principles and benefits of combinatorial and solid-phase synthesis are now well documented.[2]

Solid-phase synthesis remained the mainstay of the peptide chemist for almost three decades, until Ellman and co-worker[3] published their convenient and high-yielding synthesis of 10 1,4-benzodiazepines (Scheme 2) in 85−100% yield.

This proved to be a pivotal publication in the area of solid-phase synthesis, and Ellman later went on to produce a library of 192 analogues.[4]

B. Traceless Linkers

The new wave of interest in solid-phase chemistry focusing on the synthesis of drug-like molecules found limitations in the use of conventional linkers, which were designed for the synthesis of peptides. Invariably, the linkage to polymer was done at the carboxylic acid, or "C-Terminus", of the peptide. This meant that the traditional linkers such as Merrifield, Wang, and Rink resins[5] required acidic functionality in the starting material for loading and also regenerated such functionalities after conventional cleavage methods. In Ellman's synthesis of 1,4-benzodiazepines (Scheme 2), linkage was achieved via a phenolic or carboxylic acid residue and after cleavage these functionalities were unmasked.

Functional groups have a dramatic outcome on the potential medicinal efficacy of the final drug-like target molecules. With this in mind, the solid-phase chemists set about designing new linkers that were

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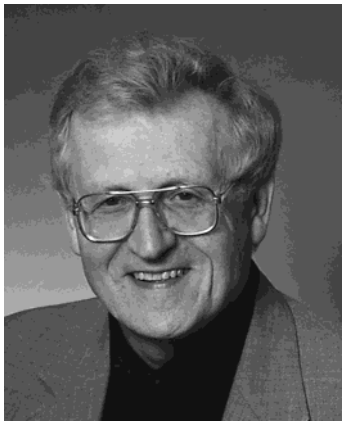
Paul Blaney studied for his first degree at Sheffield Hallam University. This incorporated an industrial placement for one year at Sterling Winthrop Pharmaceutical Research Division, Alnwick, U.K., working in chemical development. After graduating in 1995, he worked at Oxford Diversity, Oxfordshire, U.K., where he first became involved with solid-phase synthesis. He returned to academia in 1997 and received his Ph.D. degree in Organic Chemistry under the supervision of Professor Ron Grigg at the University of Leeds. At the beginning of 2001, he joined UFC Ltd., Manchester, U.K., where he is a Senior Chemist and is involved in custom synthesis.



Ron Grigg's Ph.D. work at Nottingham University was on porphyrins, corrins, and their metal complexes with Professor A. W. Johnson. He did postdoctoral work at Cambridge with Professor Lord Todd on vitamin B_{12}. He was appointed Professor of Organic Chemistry at Queens University in 1974, and in 1989 he moved to Leeds University, where he is now Professor of Medicinal Chemistry and Director of the Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre. He is a fellow of the Royal Society and has received the Tilden lectureship, the Pedler lectureship, the Heterocyclic Chemistry medal, and, most recently (2000), the Organic Synthesis medal of the Royal Society of Chemistry. His research interests include the design of catalytic cascade reactions and their application to medicinal and biochemical problems.

termed "traceless linkers", where the point of attachment is not apparent in the final molecule.

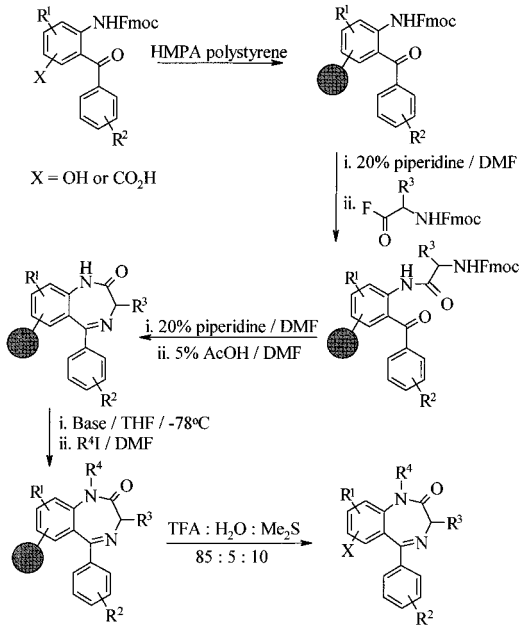
1. Silicon Linkers

The design of this type of linker is based on the well-known protodisilylation of the Si−Ar bond. Ellman was again one of the pioneers in this field. He developed a silicon-based traceless linker[6] and used it in the synthesis of 1,4-benzodiazepine derivatives **4** (Scheme 3).

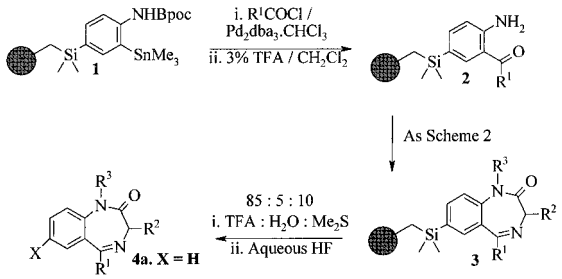
The resin-bound arylstannane **1** was coupled with acid chlorides via the Stille reaction followed by deprotection of the Bpoc group to give resin-bound aniline **2**. Following the same procedure outlined in

V. Sridharan obtained his Ph.D. degree from Queen's University, Belfast, under the supervision of Professor Ron Grigg. Currently he is working as a Senior Research Officer in the Chemistry Department at Leeds University. His research interests are palladium-catalyzed reactions, 1,3-dipolar cycloaddition reactions, asymmetric synthesis, and combinatorial chemistry.

Scheme 2



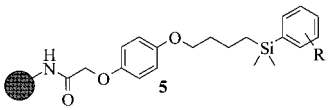
Scheme 3



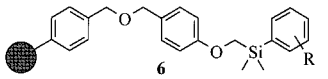
Scheme 2, the functionalized 1,4-benzodiazepines **3** were obtained. Any protecting groups that remained in the side chains R^1−R^3 of **3** were removed using TFA. Stronger acid was required for cleavage from the resin, which occurred upon treatment with aqueous HF to give 1,4-benzodiazepines **4** in 50−68% yield.

The linker **5** was quite laborious (5 steps) to synthesize.[6] The resin used was aminomethyl poly-

styrene which forms the amide bond in **5**. The functionality on the aryl ring can be adapted for the desired target molecule.



Another version on the silyl linker **6** was used in palladium-catalyzed Suzuki coupling reactions before derivatization and cleavage with TFA, cesium fluoride, or liquid HF.[7]



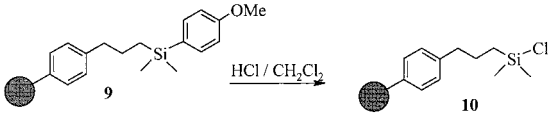
The linker was synthesized in solution (3 or 4 steps) and loaded onto Merrifield polystyrene resin. Cesium fluoride in DMF at 110 °C proved the most effective cleavage protocol, and yields of 66−78% of functionalized biaryls were obtained.

Two other versions of silicon-based traceless linkers **7**[8] and **8**[9] were reported, of which Showalter's linker **8** has become the most synthetically important.

The main drawback with the silyl traceless linkers **5**−**8** was the need to build functionality onto the silyl linker before loading onto resin, hence increasing the work of the combinatorial chemist. A more user-friendly silyl linker **10** was developed where direct loading of aromatic compounds onto the solid phase was possible.[10]

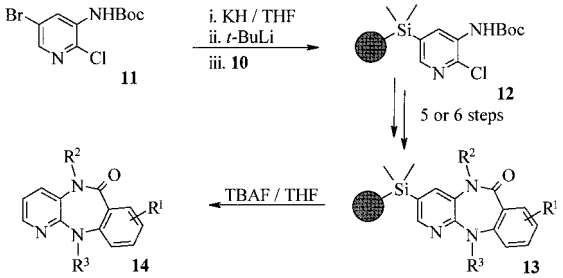
The synthesis of polystyrene-based **10** is much simpler than for the earlier silicon-based linkers. Precursor **9** is synthesized in 2 steps and stored in this form. The silyl chloride resin **10** is then generated (Scheme 4) and loaded with the desired arene.

Scheme 4



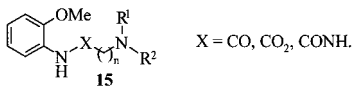
This linker was used to synthesize the therapeutically useful pyridine-based tricyclic compounds **14**[11] (Scheme 5) in 48−65% yield.

Scheme 5



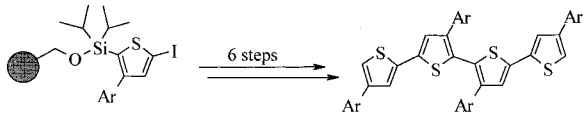
The linker also benefits from cleavage using TBAF as opposed to aqueous HF.

This revised version of Ellman's traceless silyl linker was utilized by Langlois[12] for the synthesis of 2-methoxyaniline derivatives **15** in 53−90% yield as potential ligands for the 5-HT_4 seratonin receptor subtype.



Showalter's silyl linker was utilized[13] in the synthesis of oligo-3-arylthiophosphines (Scheme 6), which

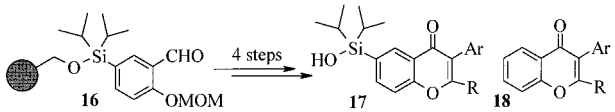
Scheme 6



were constructed using a series of Suzuki couplings and cleaved by TBAF.

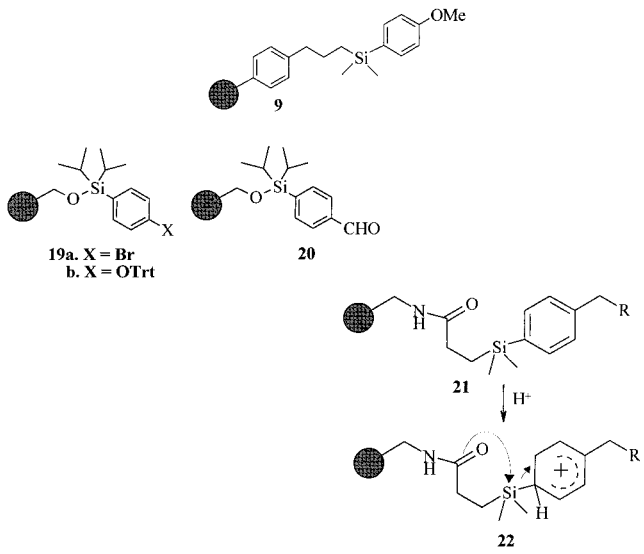
2,3-Disubstituted benzopyran-4-ones **18** were synthesized in 20−74% yields, with varying degrees of purity (51−100%)[14] using his linker (Scheme 7).

Scheme 7



When TBAF was used as the cleavage reagent, the diisopropyl silanol derivative **17** was obtained. Cleavage with cesium fluoride provided the desired benzopyran-2-ones **18**.

The linkers of Ellman[10] and Showalter[9] are commercially available.[15] The Ellman linker is provided as the protected 4-methoxyphenyl resin **9** and the Showalter linker as three functionalized versions **19**−**21**.



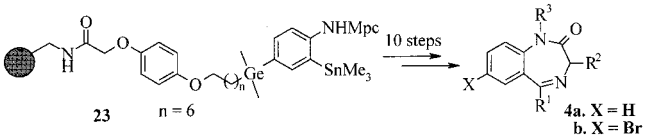
A number of similar aryl-based silane linkers[16−19] have been developed for traceless solid-phase synthesis of aryl, biaryl, and heteroaryl compounds and

tamoxifen[20] derivatives. The use of a strategically placed amide within the linker, i.e., **21**, accelerates the protodesilylation[16,19] in appropriate cases (**22**, arrows).

2. Germanium Linkers

Germanium, an element with similar properties to silicon, has also been used in traceless linkers chiefly by Ellman.[15] The linker **23** was also used in the synthesis of 1,4-benzodiazepine derivatives **4a** and **4b** (Scheme 8).

Scheme 8

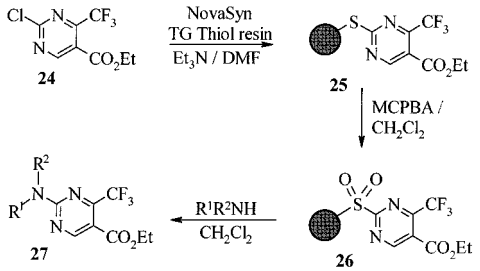


The germanium linker **23** is very similar to the silicon linker **5**, and the chemistry performed to synthesize 1,4-benzodiazepines **4** was identical. The bromo derivatives **4b** were obtained via cleavage of the germanium−carbon bond using bromine in 47−59% yield. Conventional cleavage using TFA gave derivatives **4a** in 58−68% yield. The linker is again laborious to synthesize (6 steps). Recently Spivey developed a related germanium-based linker to synthesize pyrazoles.[21]

3. Sulfur Linkers

The first example of a sulfur-based traceless linker was introduced by Suto.[22] Oxidative activation of a sulfide to a sulfone allowed nucleophilic displacement of the sulfone, incorporating further diversity into the final compound. Suto used this technique to synthesize functionalized pyrimidines **27** (Scheme 9).

Scheme 9



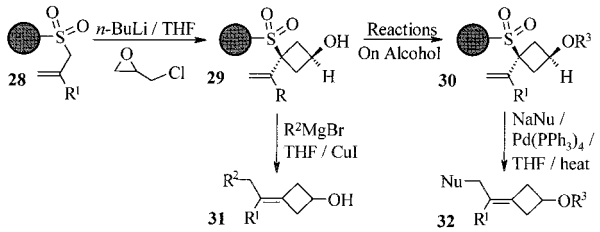
The 2-chloropyrimidine **24** was loaded onto Tentagel thiol resin, a PEG resin. The sulfide resin **25** is oxidized using MCBPA to the sulfone **26**, which was cleaved from the resin using primary and secondary amines to give pyrimidines **27** in 50−93% yield. The purity of the cleaved compounds were generally excellent (mainly >90%). The ester was also manipulated to synthesize amides and ethers. Others have reported similar nucleophilic cleavage on highly reactive sulfonamide linkers (safety catch) for solid-phase synthesis of amides, carboxylic acids, or amines.[23−25]

A further example of oxidation activation of sulfur was reported,[26] where the oxidation was followed by reduction of the C−S bond of an aliphatic sulfone using Na−Hg. Again, the resin used was PEG based (Scheme 10).

A feature of this process was the use of OXONE as a selective oxidant[27] as opposed to MCPBA. The overall yield for the above process was >90%.

The chemistry of allylic sulfone derivatives[28] has been exploited for the solid-phase synthesis of cyclobutylidenes (Scheme 11).

Scheme 11

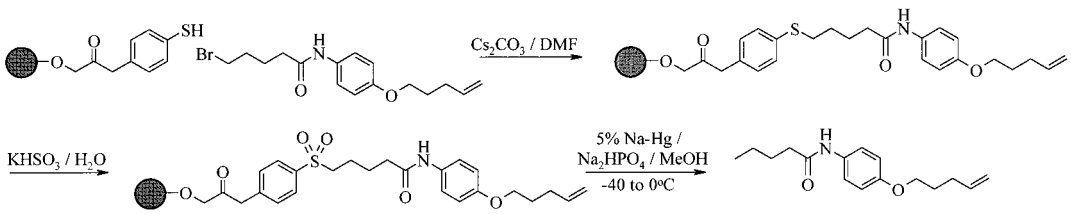


The allyl sulfone resin **28** was synthesized in 2 steps from polystyrene resin, the sulfone being linked to the phenyl ring of the polymer. This was converted to the cyclobutanol **29** by reaction of the lithiated sulfone and epichlorohydrin. Cleavage with Grignard reagents gave cyclobutylidene derivatives **31**, proceeding via allylic attack of the Grignard with displacement of the phenyl sulfinate resin. Alternatively the alcohol was derivatized to cyclobutylidene derivatives **30**. This was then cleaved using palladium-catalyzed allylic alkylation with sodium enolates to give cyclobutylidene derivatives **32**. The copper-assisted Grignard displacement occurred in poor yield in the solid-phase process (11%), and the palladium-catalyzed allylic alkylations were only a little better (30−38%).

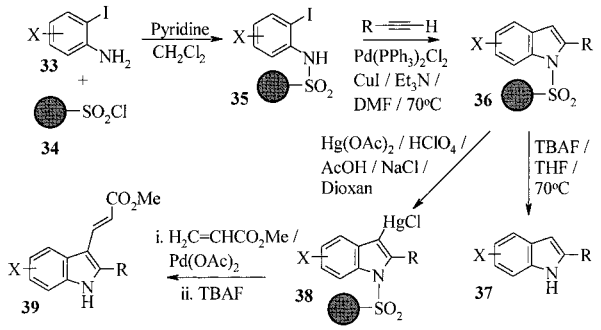
Recent work utilizing a traceless sulfonyl linker[29] involved the synthesis of substituted indoles via a palladium-catalyzed cyclization (Scheme 12).

2-Iodoanilines **33** were loaded onto commercially available sulfonyl chloride polystyrene resin **34**. Palladium-mediated heteroannulation of the resin-bound iodoaniline **35** with terminal alkynes gave the indole **36**. This was cleaved directly using TBAF, releasing the substituted indoles **37** in 85−100% yield with 85−100% purities. Alternatively, direct mercuration of the indole at the 3-position gave **38**, which

Scheme 10



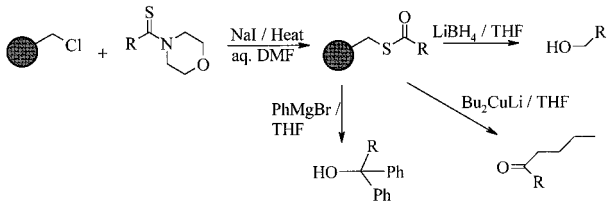
Scheme 12



was coupled with methyl acrylate using a palladium catalyst. Cleavage with TBAF released the 2,3-disubstituted indole derivatives **39** in a 60% yield. The opportunity is available to further exploit the 3-indolylmercury species via solid-phase radical reactions.

Recently the chemistry of thioesters was utilized[30] as a means of "traceless" synthesis of alcohols, ketones, and lactones (Scheme 13). The main focus

Scheme 13

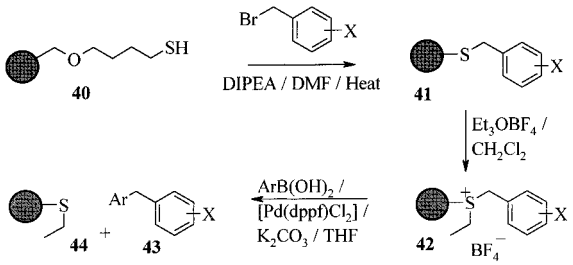


was on the preparation of the resin-bound thioesters.

It may be argued that the linker is not traceless, as memory of the carbonyl is contained in the product alcohols and ketones.

Wagner and co-workers[31] recently reported a truly traceless sulfur-based linker, exploiting the chemistry of benzylsulfonium salts (Scheme 14).

Scheme 14



The alkyl sulfide polystyrene resin **40** was synthesized in 4 steps from Merrifield resin. It was loaded with a range of benzyl bromides to give sulfide resin **41**. Reaction of this with triethyloxonium tetrafluoroborate gave the resin-bound sulfonium salt **42**. The key step was the cleavage where a palladium cross-coupling reaction occurs with boronic acids to give biphenylmethyl derivatives **43** in 24−99% yield and the sulfide resin **44**. The biphenylmethyl derivatives **43** were contaminated with biaryl products from homocoupling of the boronic acid (~20%), which were removed by chromatography.

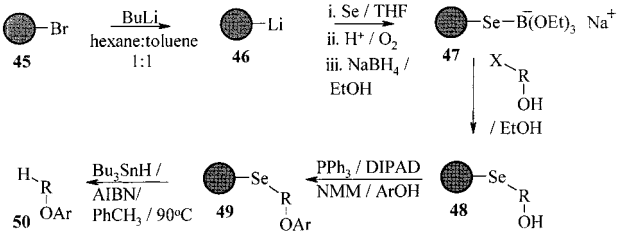
Resin-bound aryl sulfonates can be cleaved under reductive conditions to yield arenes,[32] while Takahashi reported the synthesis of a trisaccharide library by using a phenylsulfonate traceless linker on synphase crowns.[33]

Holms[34,35] developed a novel traceless perfluoroalkyl sulfonyl linker for deoxygenation of phenols and for biaryl synthesis via a Suzuki cleavage.

4. Selenium Linkers

Selenium has proved to be a useful element for traceless solid-phase synthesis, attracting much recent interest. The first example of a selenium-based traceless synthesis[36] (Scheme 15) used bromopoly-

Scheme 15

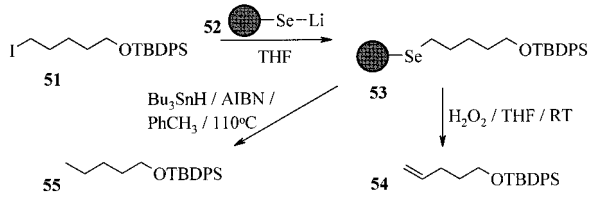


styrene **45**, which was lithiated, and the lithiated resin **46** was treated with selenium powder.

Air oxidation gave diselenides, which were reduced using sodium borohydride to give the resin-bound sodium seleno(triethyl)borate complex **47**. This was reacted with halo alcohols to give **48**, which underwent the Mitsunobu reaction with phenols to give **49**. The phenolic ethers **50** were cleaved from the resin via a radical mechanism in 57−83% yield and 78−88% purity.

Nicolaou[37] developed a complementary technique for the production of seleno−polystyrene resins, and within this publication he outlined the use of resin-bound selenium as a solid-phase reagent, with an additional cleavage protocol (Scheme 16).

Scheme 16

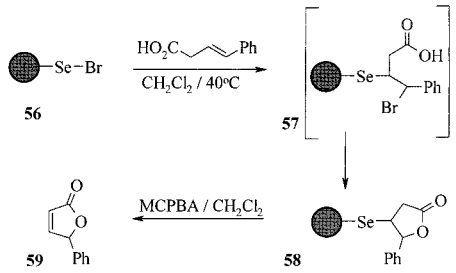


The protected iodo alcohol **51** was loaded onto the lithium selenide resin **52**[37] to give **53**. Oxidation followed by spontaneous cleavage released alkene **54**, with generation of a resin-bound selenol. Radical cleavage was also achieved releasing the alkane **55**. A number of examples were reported with 48-94% yield achieved on a diverse range of substrates. The benefits of using resin-bound selenium reagents include their odorless nature and negligible toxicity, the solution-phase equivalents being toxic and foul smelling.

Included within Nicolaou's initial publication was a cyclative loading technique, which was used sub-

sequently by a different group[38] in their synthesis of γ-lactones (Scheme 17).

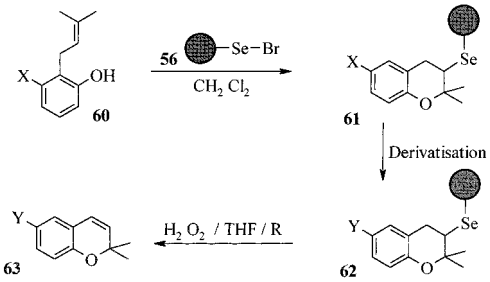
Scheme 17



The selenium bromide polystyrene resin **56**[37,38] was loaded with a β,γ-unsaturated carboxylic acid to give **57**, which underwent spontaneous lactonization to **58**. Oxidative cleavage with MCPBA released the γ-lactone **59** from the resin in 20−56% yield.

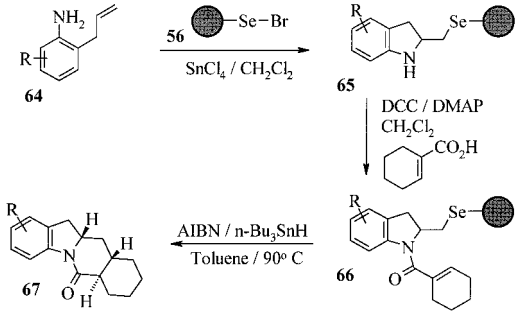
The cyclative loading technique has been applied to the synthesis of natural products from the Guttiferae classification,[39] 2,2-dimethylbenzopyran containing natural products,[40] and the synthesis of medicinally relevant benzopyrans[41] (Scheme 18).

Scheme 18



The functionalized phenol **60** was loaded onto the selenium resin **56** with concomitant 6-*exo*-trig cyclization to give benzopyran **61**. The function X was derivatized in a number of ways, including cyclocondensation reactions, Stille couplings, and novel resin-bound lithiation−substitution reactions to produce **62**. Oxidative cleavage facilitated the release of an array of diverse benzopyrans **63** in generally >80% yield.

Scheme 19



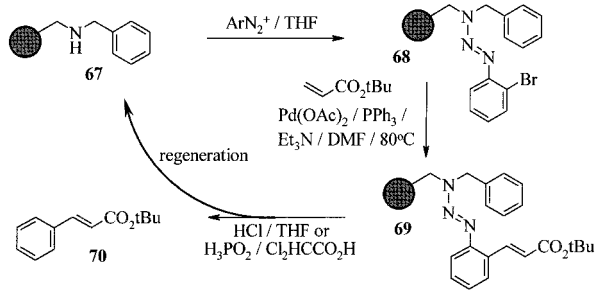
Substituted indolines[42] (Scheme 19) have been synthesized from anilines **64** loaded onto the selenyl bromide resin **56**. 5-*Exo*-trig cyclization gives resin-bound indoline **65**, and the indoline nitrogen was derivatized by coupling to a cyclic α,β-unsaturated carboxylic acid giving **66**. Upon radical cleavage, the carbon-radical generated cyclizes onto the olefin, which produced the tetracylic indoline **67** in a 36% overall yield.

This versatility of selenium as a traceless linkage should attract much future attention.

5. Nitrogen Linkers

The use of nitrogen as the element of linkage in traceless linkers has been centered around the chemistry of diazonium compounds. Brase and Enders[43] introduced a triazene linker, later to be named the T1-triazene traceless linker (Scheme 20).

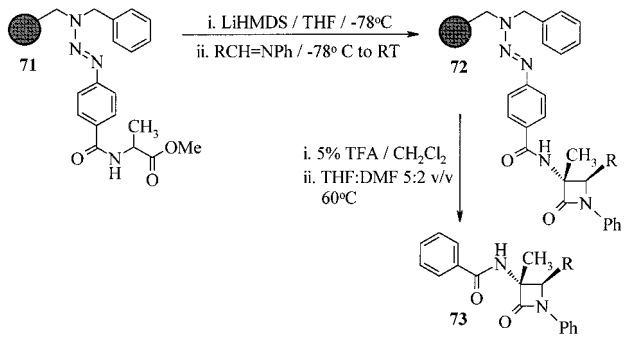
Scheme 20



The benzylamine resin **67** was synthesized in 1 step from Merrifield resin. Diazonium salts were coupled to the resin to give the triazene **68**, which was used in a Heck coupling reaction to give **69**. The cleavage was facilitated with either HCl in THF or reductive deamination using H_3PO_2 in dichloroacetic acid to give the Heck coupling product **70** in 81% yield. Other reactions were performed after the Heck reaction on different substrates, including Sharpless dihydroxylation and Diels−Alder, in good yields (29−78%). The linker can then be reused with only slight loss of activity (<10%).

Enders[44] recently used the T1-triazene linker to synthesize β-lactams (Scheme 21). The α-amidoester

Scheme 21

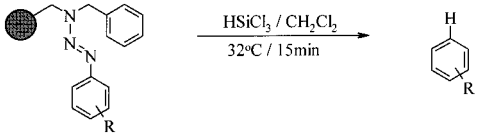


resin **71** was synthesized in 2 steps from the benzylamine resin **67**.

Ester enolate−imine condensation gave the resin-bound β-lactams **72**, which were cleaved using TFA in dichloromethane. The residual diazonium functionality was removed by heating in a THF/DMF mixture to give β-lactams **73** in 53−71% yield. The purity and diastereomeric excess of the final compound were generally >90%.

Bräse[45] recently reported a more efficient cleavage protocol for the T1-triazene linker where trichlorosilane was used as the reductant (Scheme 22). The

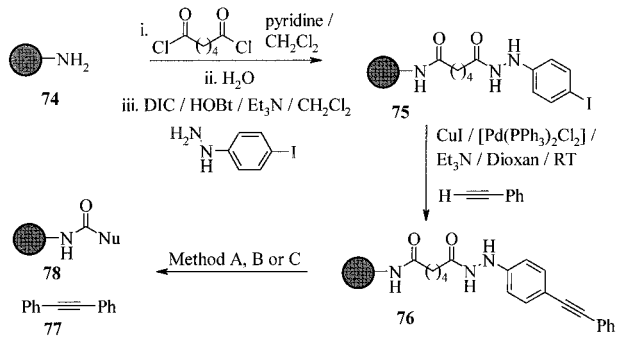
Scheme 22



cleavage proceeded in >92% yield, and product purities were >91%.

An aryl hydrazine oxidation labile traceless linker has been reported[46] (Scheme 23). Different amino-

Scheme 23



functionalized polymers **74** (polystyrene-NH_2, Tentagel-NH_2, Argopore-NH_2) were loaded with 4-iodophenylhydrazine to give **75**.

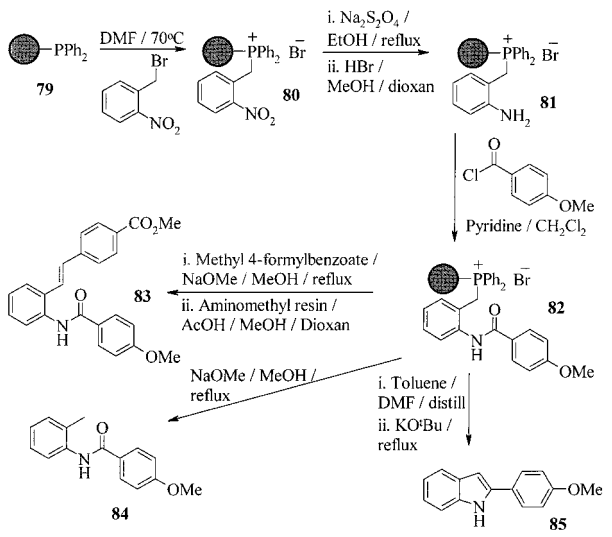
This was subjected to Heck, Suzuki, Sonagashira, or Stille couplings, the example shown being the Sonagashira coupling with phenylacetylene, to give **76**. Three different cleavage methods were used (Method A, $Cu(OAc)_2$/MeOH/pyridine/RT/2 h; Method B, $Cu(OAc)_2$/*n*-propylamine/RT/2 h, Method C, NBS/pyridine/CH_2Cl_2/RT/45 min then MeOH) with 50−93% yield of **77** depending on the resin and cleavage method. Yields for the other coupled products were 50−96%. The cleavage proceeds via oxidation to the acyl diazenes, with subsequent attack of a nucleophile present (MeOH, *n*-propylamine). This produces a resin-bound amide or ester **78**, nitrogen gas, and the coupled product. Moore has reported the synthesis of phenyl acetylene oligomers utilizing a novel 3-propyl-3-(benzyl supported) triazine linkage.[47]

6. Phosphorus Linkers

There has been little interest in the use of phosphorus as a traceless linkage, with the only example being that employed by Hughes[48] (Scheme 24).

Commercially available polystyrene-bound phosphine **79** was loaded with 2-nitrobenzylbromide to give the resin-bound phosphonium salt **80**, which was converted to the aniline **81** then acylated giving the phosphonium resin **82**. Cleavage could then be facilitated by intermolecular Wittig reaction giving a 3:1 *E*/*Z* mixture of **83** in 82% overall yield. The aminomethyl resin was used as a solid-phase scavenger reagent for the excess aldehyde used. Hydrolysis of the carbon−phosphonium bond generated the 2-methylanilide **84** in 81% overall yield. Intramo-

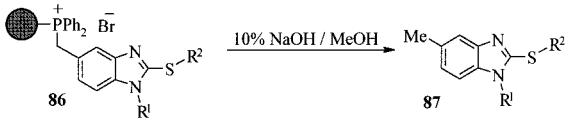
Scheme 24



lecular Wittig reaction occurred upon distillation prior to adding base, giving indole **85** in 78% yield. It was found that DMF was a necessary cosolvent in the intramolecular Wittig reaction.

This method was later used in the synthesis of a 2-alkylthiobenzimidazole library[49] (Scheme 25).

Scheme 25

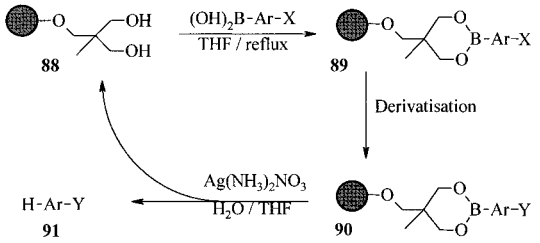


The thiobenzimidazole phosphonium resin **86** was constructed in 5 steps. Cleavage leaves a residual methyl group, giving 2-alkylthiobenzimidazoles **87** in varying yields and purities (<10−98%).

7. Boron Linkers

A novel boronate linker[50] (Scheme 26) was developed from **88**, which allows boronic acids to be attached to give **89**.

Scheme 26



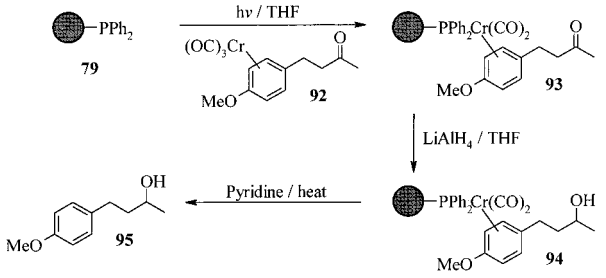
A function X was then derivatized in a number of ways including ester and amide formation, reductive amination, and a Ugi four-component condensation, giving derivatized boronate **90**. A mild protodeboronation cleavage protocol was developed using silver diamine nitrate in water and THF to release the functionalized aromatic compound **91**, regenerating the initial linker **88**. The processes that were performed using this linker gave >45% overall yield and

>80% product purity, although the chemistry was somewhat limited.

8. Chromium Linkers

A traceless synthesis protocol has been developed[51] using chromium carbonyl complexes of aromatic compounds (Scheme 27).

Scheme 27



Chromium carbonyl complex **92** was photochemically loaded onto polystyrene phosphine resin **79** to give resin-bound complex **93**. Reduction of the ketone gave **94**, with cleavage facilitated by heating in pyridine to release alcohol **95**. The yields for the individual steps were calculated using ^{31}P NMR. The reduction proceeded in 62% yield and the cleavage in 90% yield. Rigby also reported a similar traceless π-arene chromium linker for the synthesis of tertiary alcohols and esters.[52]

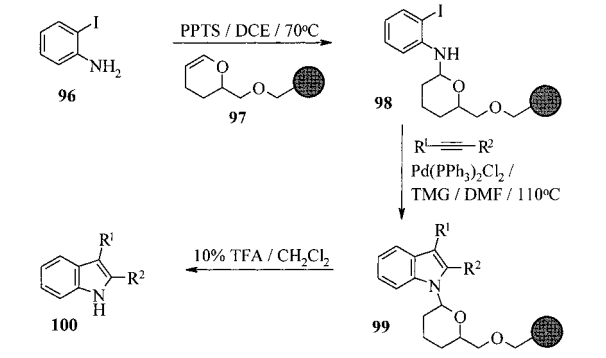
C. Miscellaneous Traceless Linkers

The linkers described in the previous section were based on the chemistry of a particular element and its use in solid-phase traceless synthesis. This section will concentrate on linkers based around protecting groups, auxiliaries, or chemically specific traceless linkers. Photolabile linkers are not included in this section since Bochet recently reviewed this topic.[53]

1. Protecting-Group-Based Traceless Linkers

A THP traceless linker,[54] which acts as a protecting group for the indole nitrogen (Scheme 28), has been used to synthesize 2,3-disubstituted indoles.

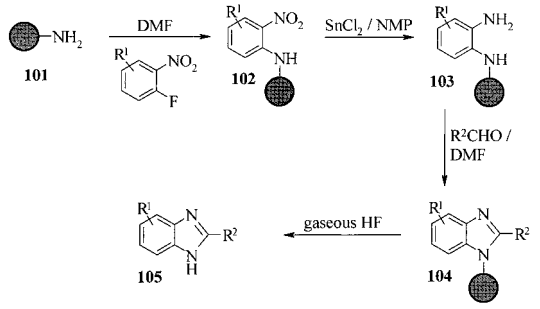
Scheme 28



2-Iodoaniline **96** was loaded onto THP−polystyrene resin **97** to give **98**. A modified palladium-catalyzed cyclization based on a procedure described by Larock gave resin-bound indoles **99**, which were released from the resin under acidic conditions giving indoles **100** in 53−97% yield.

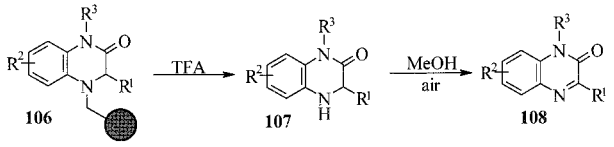
MBHA polystyrene has been used in the synthesis of benzimidazoles[55] (Scheme 29).

Scheme 29



MBHA polystyrene **101** was loaded with 2-fluoronitrobenzene derivatives to give **102**. Reduction of the nitro group gave resin-bound aniline **103**, which was condensed with aldehydes to produce the resin-bound benzimidazoles **104**. Cleavage was achieved using gaseous HF to give benzimidazoles **105**. A traceless synthesis of 2-aminobenzimidazole was also developed by Krchnak using MBHA resin.[56] Krchnak[57] later applied this to the synthesis of quinoxalinones (Scheme 30) and tetrahydroquinoxalines.[58]

Scheme 30

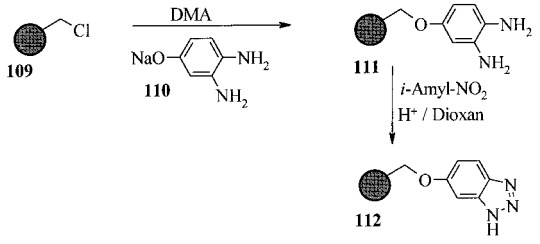


The resin-bound dihydroquinoxalinones **106** were constructed in 4 steps from 4-(4-formyl-3-methoxyphenoxy)butyryl aminomethyl polystyrene. Cleavage was facilitated with TFA or gaseous HCl or HF to give dihydroquinoxalinones **107**, which air oxidized on stirring in methanol overnight to give quinoxalinones **108** in 50−99% yield.

2. Auxiliary-Based Traceless Linkers

The use of benzotriazole as an auxiliary has been well documented by Katritzky,[59] and he recently described a polymer-bound version of the auxiliary,[60] which was constructed from Merrifield resin (Scheme 31).

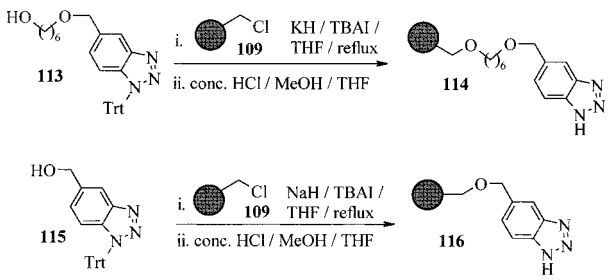
Scheme 31



Merrifield resin **109** was loaded with the sodium phenolate **110** to give the resin-bound 1,2-phenylenediamine **111**. Treatment of this with *i*-amyl nitrite in acidic conditions gave the resin-bound benzotriazole **112**.

Another group published a synthesis[61] of resin-bound benzotriazoles using Merrifield polystyrene (Scheme 32).

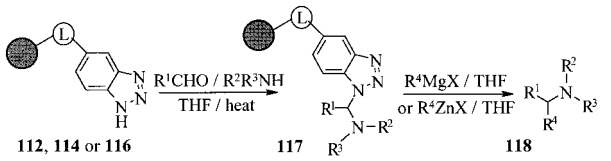
Scheme 32



The functionalized benzotriazoles **113** and **115** were synthesized and loaded onto Merrifield resin **109** using phase-transfer catalysis, and the protecting trityl group was removed to give the benzotriazole resins **114** and **116**.

The three different versions of the benzotriazole linker (**112**, **114,** and **116**) were used in the traceless synthesis of secondary and tertiary amines, independently by the two groups, using the same reaction sequence (Scheme 33).

Scheme 33



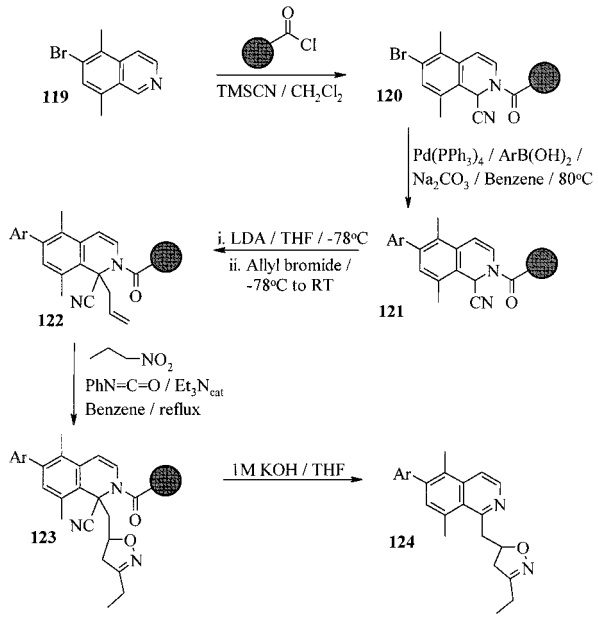
An aldehyde and a primary or secondary amine were condensed with the benzotriazole linkers **112**, **114**, and **116** to give the resin-bound benzotriazole derivatives **117**. The benzotriazole is displaced upon the introduction of Grignard or organozinc reagents, releasing α-substituted secondary or tertiary amines **118** in >60% yield with all three linkers. The Katritzky linker **112** is probably the best of the three as it is easier to synthesize. The other two linkers **114** and **116** require several steps in solution[61] to derivatize the benzotriazole. Paio also reported the synthesis of tertiary amines and unsymmetrical ureas using benzotriazole linkers.[62,63]

3. Chemically Specific Traceless Linkers

A novel solid-phase application of the Reissert reaction, where the Reissert complexes are bound to an acyl polystyrene resin (Scheme 34), provides isoxazolidinoquinolines.[64]

The functionalized isoquinoline **119** is loaded onto acid chloride polystyrene in the presence of TMSCN to give the Reissert intermediate **120**. A Suzuki coupling then gives **121**, which are alkylated to give the allyl Reissert intermediates **122**. A 1,3-dipolar cycloaddition reaction of **122** with a nitrile oxide generated in situ gives the resin-bound isoxazali-

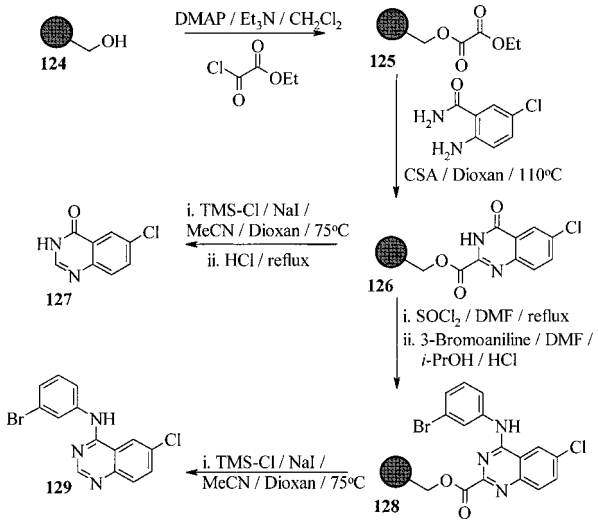
Scheme 34



noisoquinolines **123**. Base-induced cleavage gives isoxazalinoisoquinolines **124** in 17−19% yield.

Abell[65] developed a decarboxylative traceless linker for the synthesis of quinazolines (Scheme 35).

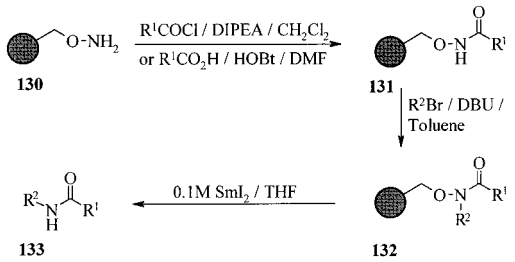
Scheme 35



Hydroxymethyl polystyrene resin **124** was reacted with ethyl oxalyl chloride to give the ethyl oxalate linker **125**. Cyclocondensation with 2-amino-5-chlorobenzamide gave the resin-bound 2-carboxyquinazolinone **126**, which was cleaved directly with TMS−I formed in situ followed by acid-induced decarboxylation to give **127** in a 67% overall yield and 97% purity. Alternatively, **126** was activated with thionyl chloride to give the 4-chloro intermediate, which reacted with 3-bromoaniline to give **128**. Cleavage and decarboxylation was facilitated with TMS−I to give **129** in 69% yield and 95% purity. This linker and cleavage strategy could be applied to the synthesis of other classes of heterocycles.[65]

Abell[66] developed another traceless linker based on the cleavage of the N−O bond of a hydroxylamine linker using samarium(II) iodide (Scheme 36).

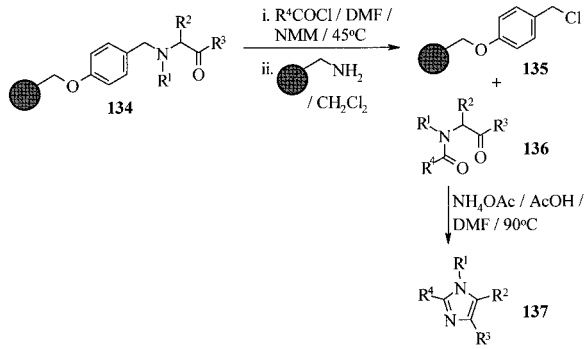
Scheme 36



The hydroxylamine linker **130** is synthesized in 2 steps from Wang polystyrene resin and loaded with acid chlorides or carboxylic acids to give the hydroxamates **131**. Alkylation of the nitrogen with a range of alkyl halides gave derivatives **132**, which were released from the resin via samarium(II) iodide reductive cleavage of the N−O bond, to give amides and ureas **133** in 30−54% yield and 84−99% purities. This novel cleavage technique for the hydroxylamine linker was shown to tolerate functionality such as halogen, olefin, alkyne, and phenolic ethers.

A novel cleavage strategy was recently reported[67] for the synthesis of 1,2,4,5-tetrasubstituted imidazoles. Traceless cleavage was followed by solution-phase cyclocondensation to form the imidazoles (Scheme 37). The polystyrene-bound tertiary amine

Scheme 37



134 was constructed in 3 steps from Merrifield resin using standard solid-phase chemistries. Treatment of **134** with acid chlorides gave quaternary acylammonium intermediates that underwent spontaneous cleavage via attack of the chloride anion to give the chloro resin **135** and solution-phase β-keto amides **136**.

Aminomethyl polystyrene resin was employed as a scavenger for excess acid chloride to provide amides **136** in 10−87% yield and 71−100% purity. Cyclization of **136** with ammonium acetate gave the tetrasubstituted imidazoles **137** in 23−84% overall yield and 49−100% purity. This methodology has the added bonus of producing two distinct compound libraries **136** and **137**.

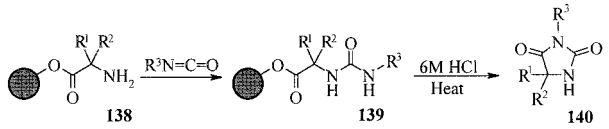
D. Cyclization–Cleavage Strategies in Traceless Synthesis

Cyclization−cleavage, or cyclative cleavage, is a much-used strategy, and the technique has been developed into a powerful tool for traceless solid-phase synthesis in which the final compounds are generally obtained with a high degree of purity.

1. Synthesis of Hydantoins

Following Ellman's[3] initial lead, DeWitt and coworkers[68] synthesized hydantoin derivatives on solid-phase (Scheme 38).

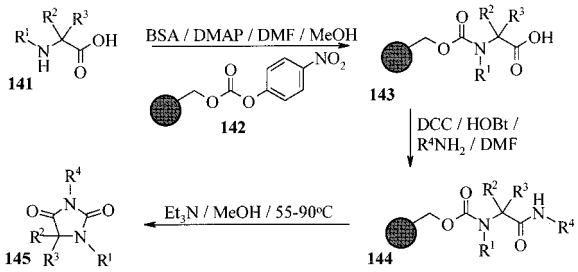
Scheme 38



The resin-bound amino acid **138** was reacted with isocyanates to give ureas **139**. Upon heating these in 6 M HCl, spontaneous cyclization and cleavage occurred, releasing the hydantoins **140** in high yield and purity. DeWitt synthesized 39 derivatives using this method.

An alternative strategy for hydantoin synthesis[69] employs a carbamate linker with base-induced cyclative cleavage (Scheme 39).

Scheme 39

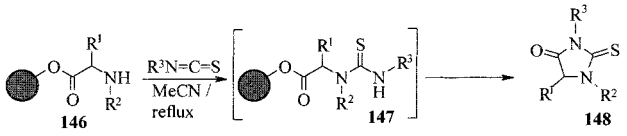


Amino acids **141** were loaded onto the polystyrene carbonate linker **142** to give the carbamate-linked amino acid **143**. This was coupled with primary amines to give **144**, which underwent base-induced cyclative cleavage releasing hydantoins **145** in 12−73% yield and 74−99% purity. This synthesis benefits from the mild cleavage conditions and also the use of primary amines (>3000 available) as a source of diversity as opposed to isocyanates (<300) and was used for the synthesis of an 800 compound library.

A different cleavage protocol utilized neat diisopropylamine[70] as opposed to 6 M HCl with heating and gave hydantoins **140** in 82−93% yield and >95% purity.

Hamuro[71] reported the use of Phoxime resin (phosgenated *p*-nitrophenyl(polystyrene)ketoxime) to synthesize 3-amino hydantoins via oxime carbonates in good yield. Thiohydantoins were synthesized in a related procedure[72] employing isothiocyanates (Scheme 40).

Scheme 40

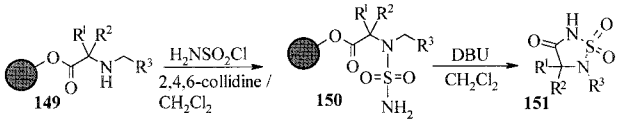


Polystyrene-bound amino acids **146** were reacted with isothiocyanates in boiling acetonitrile to give

thioureas **147**, which spontaneously cyclized and cleaved giving thiohydantoins **148** in 92−98% yield and >90% purity. Excess isothiocyanate was removed using aminomethyl polystyrene as a scavenger resin.

A recent modification[73] to DeWitt's procedure led to the synthesis of sulfahydantoins (Scheme 41).

Scheme 41

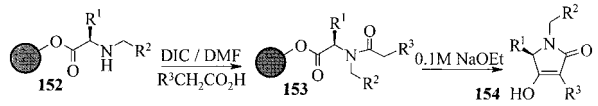


Polystyrene-bound amino acids **149** were reacted with sulfamoyl chloride to give sulfamides **150**, which cyclized and cleaved from the resin with base to give sulfahydantoins **151** in 7−31% yield and 60−100% purity.

2. Synthesis of Tetramic Acids

The use of cyclocondensation reactions as the cleavage step is a convenient method for traceless synthesis. This was applied to the synthesis of tetramic acids,[74] which occur in many biologically important compounds.[74] The key cyclative cleavage step was a Dieckman condensation (Scheme 42).

Scheme 42



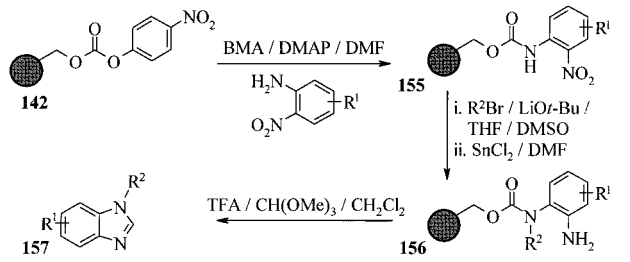
Amino acids were coupled to the Wang polystyrene-bound secondary amines **152** to give **153**. Treatment with sodium ethoxide gave tetramic acids **154** in quantitative yield and purity.

A later publication[75] on the synthesis of tetramic acids, employing Meldrum's acid derivatives, followed by Dieckman condensation, is less efficient (43−92%).

3. Synthesis of Benzimidazoles

Cyclocondensation has been employed for the synthesis of benzimidazoles[76] (Scheme 43).

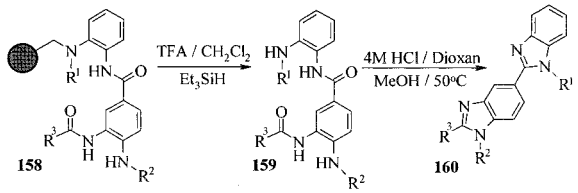
Scheme 43



The polystyrene-bound carbonate linker **142** is loaded with 2-nitroanilines to give the carbamates **155**. The carbamate nitrogen was alkylated and the nitro group reduced to the aniline **156**. Treatment with TFA in the presence of a water scavenger led to cyclocondensation and cleavage of the benzimidazoles **157** in 80−95% yield and >95% purity. The cyclization may take place after cleavage from the resin, according to solution-phase observations, but the overall process is a satisfactory traceless cyclative cleavage.

A recent traceless synthesis of dibenzimidazoles (Scheme 44)[77] utilizes the derivatized resin **158**,

Scheme 44

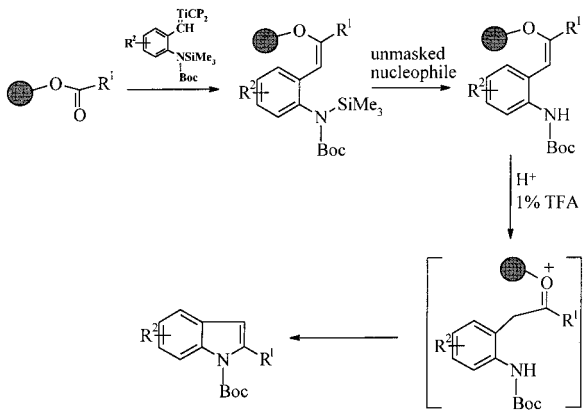


which was constructed from 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene resin in 6 steps.

The acidic resin cleavage conditions were insufficient to promote cyclization, and the diaminediamides **159** were isolated. Cyclization was achieved using 4 M HCl and heating, affording dibenzimidazoles **160** in 88−95% overall yield and 90−95% purity.

Synthesis of Indoles. Titanium(IV) benzylidines bearing a masked nitrogen nucleophile in the ortho position converted Merrifield resin-bound esters into enol ethers. Hartley utilized this initial strategy to synthesize substituted N−Boc indoles (Scheme 45).

Scheme 45



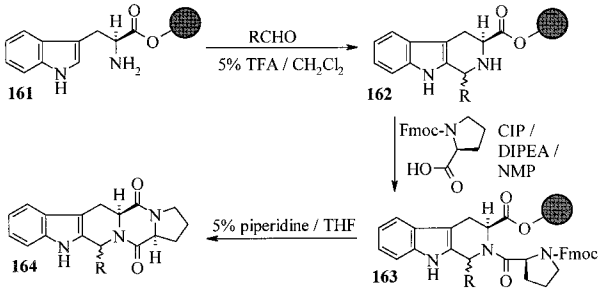
An unusual protecting group, N-silylated *tert*-butyl carbamate, was employed. One percent TFA released N−Boc indoles in high yield and purity (Scheme 45).[78] N−Boc-substituted indoles were synthesized in a one-pot sequence.

4. Synthesis of Indolyl Diketopiperazine Alkaloids

This family of alkaloids, which includes fumitremorgins, verruculogens, and tryprostatins, has attracted much recent interest.[79] They are tremorgenic mycotoxins that interfere with cell growth and the release of neurotransmitters in the CNS.[80] Convenient access to analogues of these alkaloids was achieved[81] via sequential Pictet−Spengler reaction, peptide coupling, and cyclative cleavage (Scheme 46).

L-Tryptophan-derivatized hydroxymethyl polystyrene **161** underwent a Pictet−Spengler reaction with aldehydes to give the β-carbolines **162**. Fmoc-protected amino acids were coupled via in situ conversion to the acid chlorides using CIP to give **163**. The

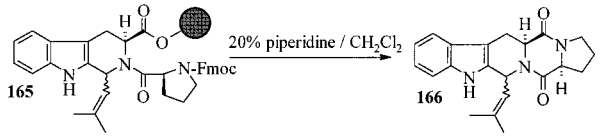
Scheme 46



Fmoc group was removed with concomitant cyclative cleavage to give the alkaloid analogues **164** in 50−99% yield and 58−90% purity. The proline analogue is very closely related to the alkaloids, all of which contain the proline moiety. A library of 42 analogues was synthesized, each of which consisted of four diastereomers, apart from the proline analogues where two diastereomers were obtained.

A slightly modified synthesis was used for the synthesis of demethoxyfumitremorgin C **166** (Scheme 47), which was obtained in 49% yield as a 53:47 cis/

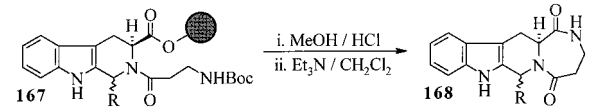
Scheme 47



trans mixture, the desired isomer being trans. Several other nonproline analogues were made as approximately 1:1 cis/trans mixtures in 36−88% yield. Although cis/trans selectivity was poor, only two diastereomers were found.

A similar approach was used to synthesize tetrahydro-β-carboline-2,3-bis-lactams,[83] with the seven-membered version shown in Scheme 48. The product

Scheme 48



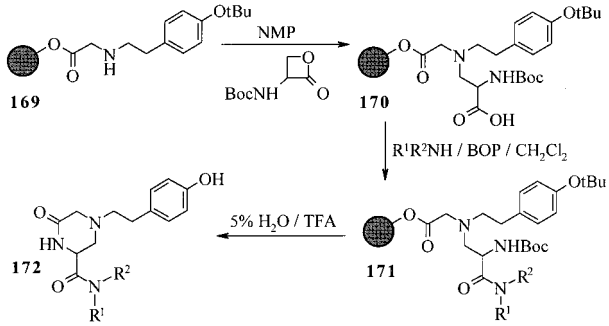
after the Pictet−Spengler reaction was coupled with Boc-protected β-alanine to give **167**. Removal of the Boc group and lactamization produced the tetrahydro-β-carboline-2,3-bis-lactam **168** in a 68% yield and >95% purity.

Diketopiperazine formation by intramolecular nucleophilic cleavage proceeds smoothly if a linker prone to facile nucleophilic cleavage is chosen. In most of these examples hydroxymethyl polystyrene or polystyrene with the PAM linker were used.[84−91] The Wang linker, although being slightly more resistant toward nucleophilic cleavage than Merrifield or PAM resin, can also be used for the preparation of diketopiperazines.

5. Synthesis of Ketopiperazines

The ketopiperazine moiety occurs in many natural products and is a desirable pharmacophore; cyclative

Scheme 49

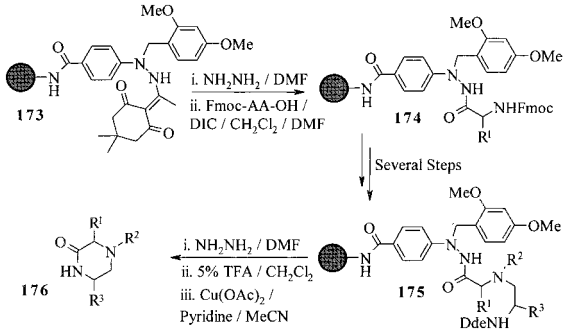


cleavage has been used for their synthesis, e.g., the enkephalin mimetics **172** (Scheme 49).[92]

The precursor **169** was synthesized in 2 steps from Wang polystyrene resin and was reacted with Boc-(D or L)-Ser-β-lactone to give the resin-bound carboxylic acid **170**. This was coupled with secondary amines to give amides **171**. Boc and *tert*-butyl group removal effected cyclative cleavage to give monoketopiperazines **172** in 29−72% yield as single enantiomers. One of the eight mimetics synthesized was shown to have an affinity at 400 nM for the μ-opioid receptor, a very promising result.

Monoketopiperazines have been prepared using a novel latent aryl hydrazine "safety catch" linker[93] (Scheme 50).

Scheme 50

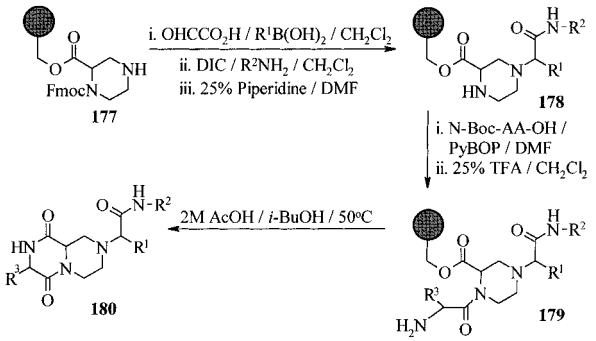


The hydrazine safety catch linker **173** was constructed in 5 steps and loaded onto Argogel amine resin. Removal of the Dde protecting group followed by peptide coupling gave **174**, which could be derivatized in a number of ways to give **175**. Sequential removal of the Dde group and the 2,4-dimethoxybenzyl safety catch group allowed cyclative cleavage to be induced with $Cu(OAc)_2$ producing monoketopiperazine derivatives **176** in 34−76% yield and 75−95% purity.

Recently diketopiperazines were constructed[94] for use as β-turn mimetics via a Petasis reaction with subsequent cyclative cleavage releasing the diketopiperazine (Scheme 51).

The resin-bound piperazinic acid derivative **177** was constructed in 2 steps on hydroxymethyl polystyrene resin. This underwent the Petasis reaction with a range of boronic acids, followed by amine coupling and subsequent Fmoc removal to give functionalized piperazines **178**. Peptide coupling followed by Boc removal gave **179**, which underwent cyclative cleavage on heating in acetic acid/*i*-butanol at 50 °C

Scheme 51

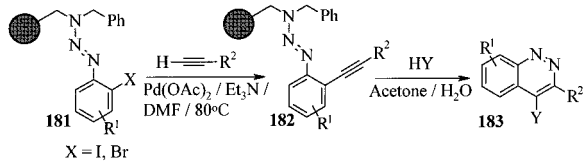


releasing the diketopiperazines **180** in 56−96% yield and 70−88% purity. A 1:1 mixture of epimers was obtained in the Petasis reaction step, and all cleaved compounds retained this epimeric ratio.

6. Synthesis of Miscellaneous Ring Systems via Cyclative Cleavage

A Richter-type cleavage protocol was applied to the synthesis of cinnolines[95] using the T1-traceless linker, where part of the triazene is incorporated into the cinnoline ring system (Scheme 52).

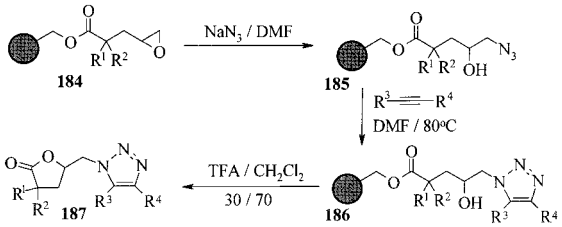
Scheme 52



The triazene resin **181** was synthesized in the normal way (Scheme 20), followed by palladium-catalyzed cross-coupling with a terminal alkyne to give **182**. The Richter cleavage reaction with HCl or HBr gave the cinnolines **183**, where Y = Cl or Br. Cleavage with dilute acid and extended reaction time gave the phenol (Y = OH) as the major product The cinnolines were obtained in 47−95% yield and 60−95% purity. The halo derivatives are useful intermediates as nucleophilic substitution at this position is a facile process.

A recent synthesis[96] of γ-methyl-substituted-γ-butyrolactones applied a cyclative cleavage protocol, where derivatization was achieved in a number of ways (Scheme 53).

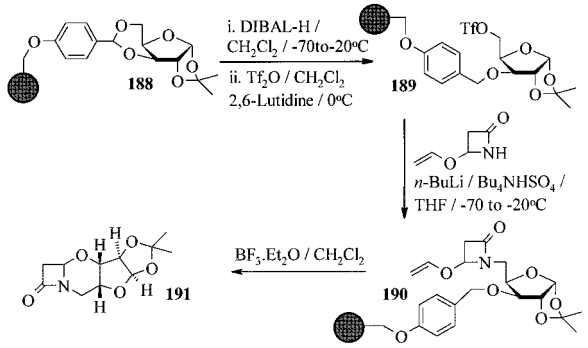
Scheme 53



The epoxide **184** was synthesized on Merrifield resin. Addition of azide to the epoxide gave **185**, which underwent a 1,3-dipolar cycloaddition reaction with substituted alkynes to give triazoles **186**. TFA cleavage with concomitant lactonization generated the γ-butyrolactones **187** in 20−35% yield after purification. Other examples included the transformation of the azide into amides (13−70% yield) and an alternative synthesis of amines from iodo-substituted epoxides (25−71% yield).

A novel synthesis of 1-oxacephems employs a cyclative cleavage process[97] (Scheme 54).

Scheme 54



The acetal **188** was synthesized in 3 steps on Merrifield polystyrene resin. Ring opening of the acetal with DIBAL-H occurred regioselectively. The resulting alcohol was converted to the triflate **189**, which was displaced by the substituted β-lactam to give **190**. Treatment of **190** with boron trifluoride etherate effected cyclative cleavage generating the 1-oxacephem **191** in 20% yield and >97% de.[98]

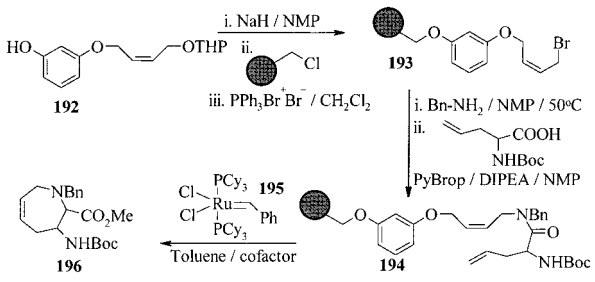
Other types of ring systems that have been synthesized by cyclative cleavage techniques include the following: oxazolidinones,[99] 4-hydroxyquinolinones,[100] phenols,[101] cyclic imides,[102] 1,2,3-thiadiazoles,[103] pyrrolo[3,4-*b*]pyridines and related pyridine-fused heterocycles,[104] 2,4-quinazolinediones,[105] and a novel triaza tricyclic ring system.[106] Unfortunately, due to space constraints, these cannot be discussed in detail.

7. Use of Particular Reactions in Cyclative Cleavage

This section will focus on core reactions that have been utilized as the cyclative cleavage step.

(1) Ring-Closing Metathesis. Ring-closing metathesis (RCM) has been applied to traceless cleavage. In the first literature example, van Maarseveen[107] used RCM cyclative cleavage for the synthesis of lactams (Scheme 55).

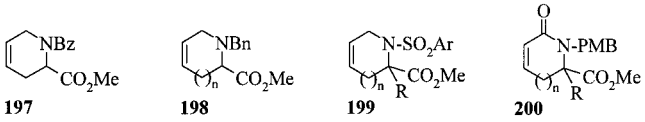
Scheme 55



The linker **192** was synthesized in 2 steps (55% yield) and loaded onto Merrifield resin and then converted to the allylic bromide resin **193**. This was reacted with benzylamine followed by a peptide coupling with N−Boc−allylglycine to give **194**. The RCM reaction on **194** was achieved with Grubbs

ruthenium benzylidene catalyst **195**, which released the seven-membered protected lactam **196**. The yield depended on the alkene cofactor, conditions, and catalyst loading. The cofactor is used to regenerate the ruthenium methylidene, which is the active catalyst. Using ethylene as the cofactor gave 5% yield of **196** after 7 days, while doubling the catalyst loading (14% to 30%) produced a 44% yield of **196** after 2 days. Alternatively, 1-octene as cofactor gave a 32% yield of **196** in 7 days and with heating at 50 °C a 37% yield after 2 h, both with 12% catalyst loading. The best yield of 57% was achieved with a 100% catalyst loading with 1-octene at 50 °C, but this is unattractive due to the cost of the catalyst **195**.

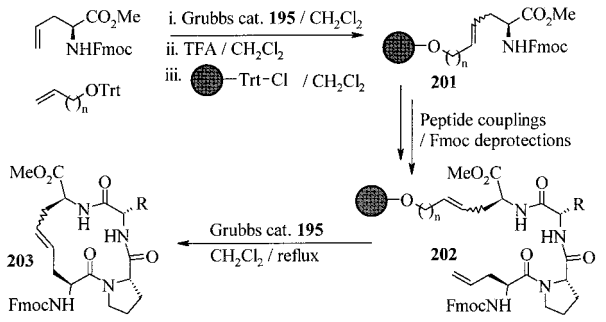
The same approach was later developed by van Maarseveen[108] for the synthesis of **197**−**200**



The six-membered cyclic compounds **197**−**200** (n = 1) were obtained in 48−97% yield, and the seven-membered analogues **198**−**199** (n = 2) were synthesized in 26−59% yield. The only unfavored[109] eight-membered analogue successfully synthesized **199** (n = 3, R = H) was obtained in 12% yield.

Macrocyclic β-turn mimetics have been synthesized by RCM of tetrapeptides[110] on chlorotrityl polystyrene (Scheme 56).

Scheme 56

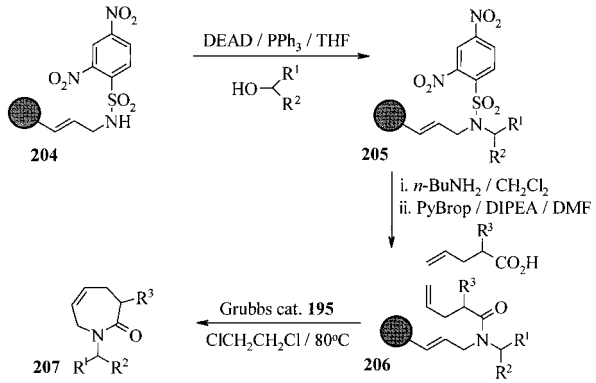


The two olefinic components were cross-coupled via a selective metathesis reaction, followed by trityl deprotection and chlorotrityl polystyrene reprotection to give **201**. A series of peptide couplings and Fmoc deprotections were carried out to obtain **202**, which underwent the RCM to **203** in 30−70% yield and 65−85% purity. Better yields were achieved with a longer spacer (for R = Bn, n = 1; 30% yield, n = 8; 70% yield).

Another class of β-turn mimetics are Freidinger lactams, which were first synthesized by RCM cyclative cleavage by Piscopio and co-workers.[111] This first example was later improved by Piscopio[112] by combining the Fukuyama−Mitsunobu reaction with RCM (Scheme 57).

The sulfonamide resin **204** was made in 3 steps from aldehyde polystyrene resin, and primary and secondary alcohols were loaded using the Fukuyama−Mitsunobu reaction to give **205**. The 2,4-

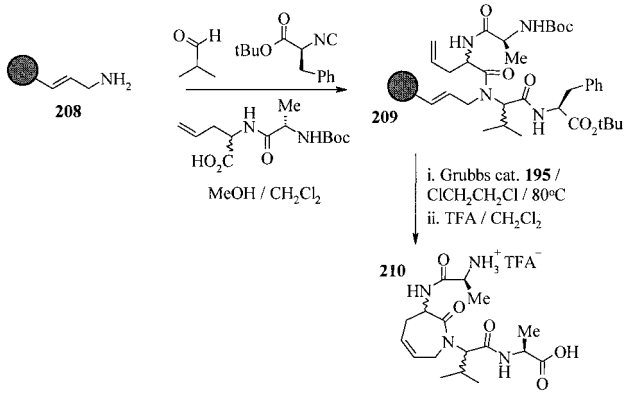
Scheme 57



dinitrobenzenesulfonyl group was removed followed by peptide coupling to give **206**. RCM cyclative cleavage gave the Freidinger lactams **207** in 13−36% overall yield and 90−95% purity.

A further improvement[113] was made where the Ugi four-component reaction was combined with RCM cyclative cleavage (Scheme 58). The cinnamylamine

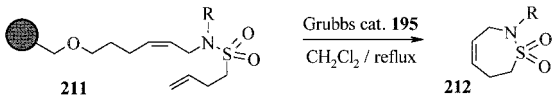
Scheme 58



resin **208** was synthesized in 5 steps from aldehyde polystyrene resin. An Ugi four-component reaction was carried out to give **209**, which underwent RCM cyclative cleavage followed by deprotection to give Freidinger lactam **210**, as a mixture of diastereomers, in 61% overall yield and >95% purity. The Ugi−RCM combination results in the rapid assembly of complex molecules.

A recent variation[114] provides cyclic sulfonamides (Scheme 59). The diene **211** was made in 3 steps on

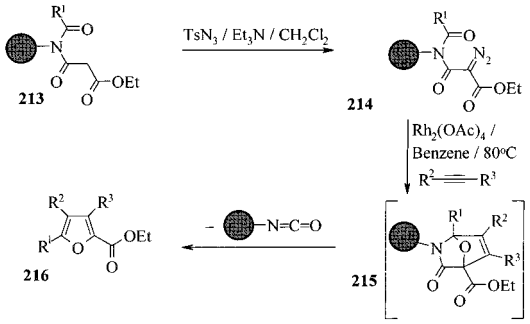
Scheme 59



Merrifield polystyrene resin, and RCM gave sulfonamides **212** in 38−66% yield after purification.

(2) Cycloaddition Reactions. There are few examples of cycloaddition reactions being used as the cleavage step, but the few that have been used are innovative examples of cyclative cleavage. Thus, 1,3-diploar cycloaddition reactions of isomunchnones gives substituted furans[115] (Scheme 60).

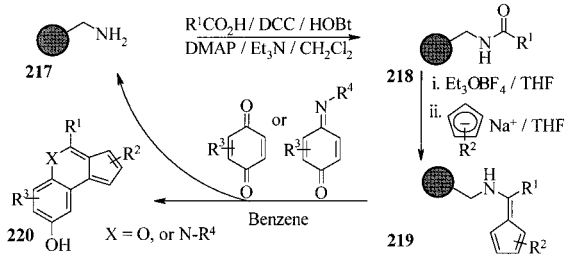
Scheme 60



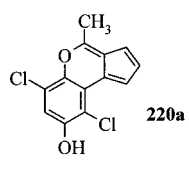
Functionalized resin **213** was synthesized in 2 steps from PEG Tentagel-amine resin. This was converted to the diazo resin **214**, which when exposed to rhodium acetate forms an isomunchnone that undergoes a 1,3-diploar cycloaddition with acetylenes to give intermediates **215**. Cycloreversion−cleavage with expulsion of resin-bound isocyanate produces the furans as single regioisomers in 51−70% yield after purification.

A fulvene [6+3] heterocycloaddition was employed[116] as the cleavage step in a concise synthesis of a heterosteroid framework (Scheme 61).

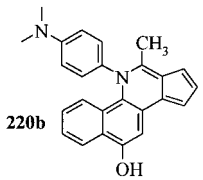
Scheme 61



Aminomethyl polystyrene resin **217** was loaded with a carboxylic acid to give resin-bound amide **218**. Treatment of this with triethyloxonium tetrafluoroborate and addition of a sodium cyclopentadienide gave the fulvene resin **219**. Exposure of this to a benzene solution of benzoquinone derivatives gave the heterosteroid **220** via a [6+3] cycloaddition with regeneration of the aminomethyl resin **217**. The products **220** were obtained with 32−42% overall yield and >95% purity. A 110-member library was synthesized and screened against a number of cancer cell lines with two compounds **220a** showing moderate inhibitory activity and **220b** showing high inhibitory activity against two breast cancer cell lines.



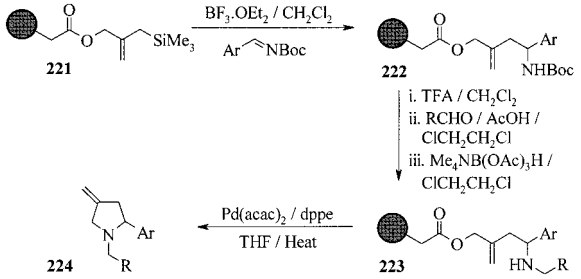
220a



220b

(3) Palladium-Catalyzed Cyclative Cleavage. A palladium-catalyzed cyclative cleavage of an allylic system containing an internal amine nucleophile to give pyrrolidines has been reported[117] (Scheme 62).

Scheme 62

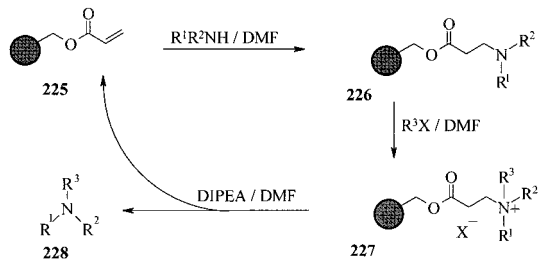


The silane resin **221** was synthesized in 1 step from a carboxylic-acid-functionalized polystyrene resin. An imino−Sakurai reaction gave resin **222**, which on deprotection, imine formation, and subsequent reduction provided the secondary amine resin **223**. Exposure to a palladium catalyst resulted in expulsion of the carboxylate resin with formation of a π-allyl palladium intermediate, which cyclized to pyrrolidines **224** in 16−95% yield after purification.

E. Traceless Linkers for Tertiary Amine Synthesis

Tertiary amines are attractive drug targets due to their good CNS penetration, intestinal absorption, and the potential involvement of the nitrogen in ligand binding.[118] There are several methods for the solid-phase synthesis of tertiary amines, although most of these are not traceless.[119] The REM linker (REgeneratable Michael linker)[120] was specifically developed for the traceless synthesis of tertiary amines (Scheme 63):

Scheme 63

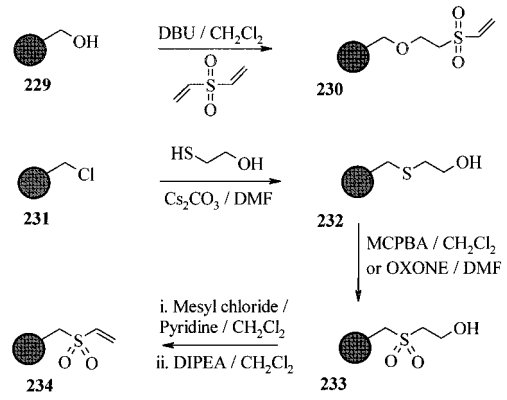


The resin-bound α,β-unsaturated ester **225** was loaded with secondary amines via Michael reactions to provide resin-bound tertiary amines **226**. These were quaternized with alkyl and benzyl halides to give the resin-bound quaternary salts **227**, which underwent the Hofmann elimination reaction to regenerate the Michael linker **225** and release tertiary amines **228**. The tertiary amines were synthesized in 25−88% yield and >96% purity.[121] Only quaternized material can undergo the Hofmann elimination, hence the high final product purity.

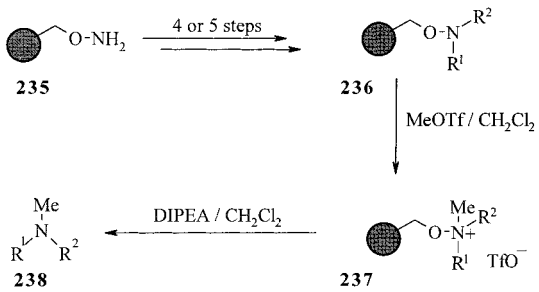
Subsequently a vinyl sulfone linker was introduced, which relied on the same quaternization−Hofmann elimination principle. Two groups[122,123] simultaneously published the same type of linker (Scheme 64).

The first example[122] simply loaded hydroxymethyl polystyrene **229** with divinyl sulfone to give the vinyl sulfone linker **230**. The loading was low (200−270 μmol g^{-1}), although no measure of initial hydroxy-

Scheme 64



Scheme 65

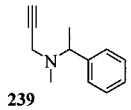


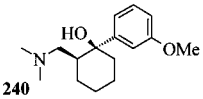
methyl loading was given. The second example[123] used a more laborious construction where Merrifield resin **231** was loaded with mercaptoethanol to give sulfide **232**. This was oxidized to the sulfone using MCPBA or OXONE to give **233**, which was converted to the vinyl sulfone linker **234** by activating the alcohol to a mesylate followed by elimination.

These linkers **230** and **234** were used in the same way as REM (Scheme 63) to produce tertiary amines and regenerate the vinyl sulfone linkers. Yields of tertiary amines from linker **230** were reported as 25−100%. The yields of tertiary amines from linker **234** were reported as 5−86% with >95% purity. The linker **234** was also shown to be stable to Grignard reagents. The REM and vinyl sulfone linker benefit from the purity of the final tertiary amine. The benzotriazole auxiliary linkers **112**, **114**, and **116** suffer from contamination of the cleaved amine with organometallic reagents.

A recent application of a hydroxylamine linker toward the synthesis of tertiary methylamines has been reported[124,125] using the same quaternization and cleavage principal as REM and the vinyl sulfone linkers (Scheme 65).

Tertiary methylamines were synthesized via a hydroxylamine linker **235** using a Boc-protection/N-alkylation/Boc-deprotection/reductive alkylation protocol (4 steps)[124] or a Boc-protection/N-alkylation/Boc-deprotection/benzotriazole Mannich base/Grignard reaction protocol (5 steps)[125] to give resin-bound tertiary hydroxylamines **236**. Cleavage was achieved via quaternization with methyl triflate to give **237**, followed by a base-induced fragmentation to release tertiary amines in 18−80% overall yields with >99% purity. The linker was shown to be stable to strong acids (TFA),[124] organometallic nucleophiles (Grignard reagents),[125] and organometallic reducing agents ($LiAlH_4$).[124] The linker was employed in the synthesis of the MAO inhibitor α-methylpargyline **239** (75%) and the analgesic Tramadol **240** (57%) to demonstrate its application toward medicinal active compounds.





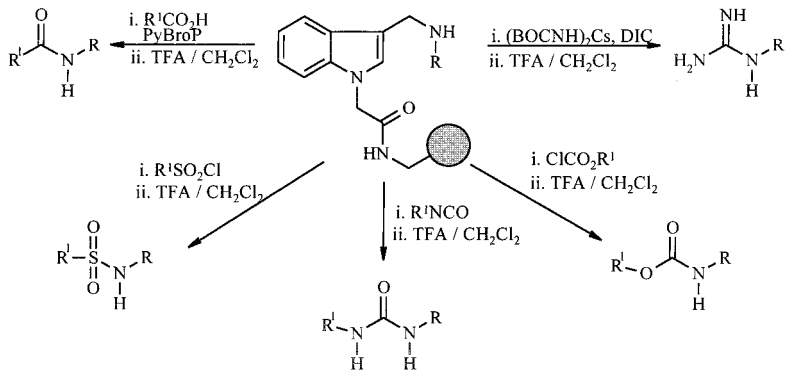
F. Traceless Linkers for Ureas, Secondary Amides, Sulfonamides, Carbamates, and Guanidines

Access to this large group of useful molecules is provided by a new versatile indole-based traceless linker developed by Estep which generates ureas, secondary amides, sulfonamides, guanidines, and carbamates in good yield (Scheme 66).[126, 127]

Complementary chemistry to Scheme 66, which utilizes a resin-bound benzotriazole, has been reported by Paio and co-workers.[62] They employed the commercially available benzotriazole-5-carboxylic acid linked to aminomethylpolystyrene or to Argogel amino resin. Treatment of the polymer-bound benzotriazole with phosgene generates the supported carbonyl chloride **241** (Scheme 67).

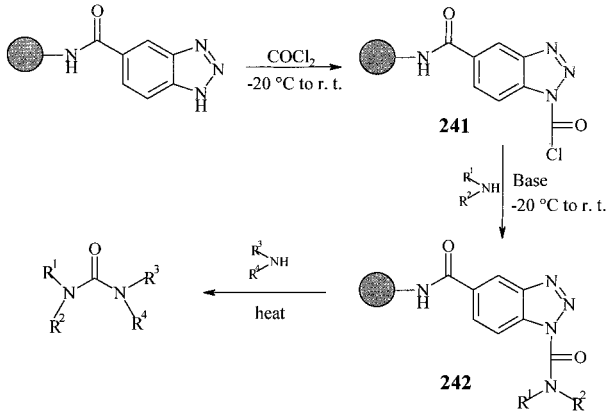
Carbonyl chloride **241** reacts with primary or secondary anilines generating **242**. Nucleophilic displacement of the benzotraizole leaving group by a second primary or secondary aryl or aliphatic amine takes place at 75−100 °C in dioxane or chloroben-

Scheme 66



PyBrOP = bromotrispyrrolidinophosphoniumhexaflurophosphate.

Scheme 67



zene. The intermediate **242** can be stored at room temperature for several weeks. Product purities are generally >80%.

II. Acknowledgments

We thank the EPSRC, the EU, Leeds University, and Organon Laboratories for support.

III. References

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