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Jovi Tze Wai Kan[a]; Patrick H. Toy
[a] Department of Chemistry, The University of Hong Kong, Hong Kong, People's Republic of China

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REVIEW ARTICLE

Sulfur- and selenium-based linkers in polymer-supported organic synthesis

JOVI TZE WAI KAN and PATRICK H. TOY*

Department of Chemistry, The University of Hong Kong, Pokfulam Road,
Hong Kong, People's Republic of China

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The use of sulfur- and selenium-based linkers in polymer-supported organic synthesis (PSOS) is reviewed. The literature describing the application of sulfur-based linkers in the PSOS of small molecules and combinatorial library preparation from 2000 to the present is summarized. The development and use of selenium-based linkers in PSOS, highlighting the work of the Nicolaou and Huang groups, is also presented.

Keywords: Sulfur; Selenium; Linker; Traceless linker; Solid-phase synthesis

1. Introduction

Since Merrifield first introduced the concept of solid-phase peptide synthesis approximately 40 years ago [1], this methodology has become standard practice for the synthesis of amino acid oligomers. Due to the numerous inherent advantages of this methodology over traditional solution-phase methods, the use of polymeric synthesis supports spread form the fields of peptide [2–6] and oligonucleotide [7–9] library synthesis, to the synthesis of small organic molecules [10–24] in what is known as polymer-supported organic synthesis (PSOS). This has been particularly true in the field of drug discovery, where large numbers of compounds of high purity are desired for screening in biological assays. It should be noted that the term PSOS is used in this review rather than solid-phase organic synthesis (SPOS) since PSOS is more general and encompasses the use of soluble (non-solid) polymers as synthesis supports.

One general requirement for successful PSOS is the use of a linker moiety by which to attach the synthesis substrate to the polymer support. The main criteria in selecting a suitable linker group are: (1) the starting substrates can be easily attached to it, (2) it is inert to the reaction conditions used in the synthesis, and (3) it is able to release the final synthesis products under mild conditions. Due to the wide range of synthetic targets and reaction conditions being used with PSOS, no single universal linker exists and new linkers and linking strategies are

*Corresponding author. Email: phtoy@hku.hk

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continuously being developed [25–37]. This review will summarize the sulfur- and selenium-based linkers that have been reported. Since sulfur-based linkers are well established and have been covered in the previous general reviews of linker groups [32, 37], only their use since 2000 will be covered here.

The first portion of this review covers the applications of sulfur-based linkers in PSOS, with the examples organized according to the method of synthesis product cleavage. The use of selenium-based linkers in solid-phase synthesis will be covered in the second section, where the examples are primarily organized according to the research group responsible for reporting them and the class of compounds prepared.

2. Sulfur-based linkers

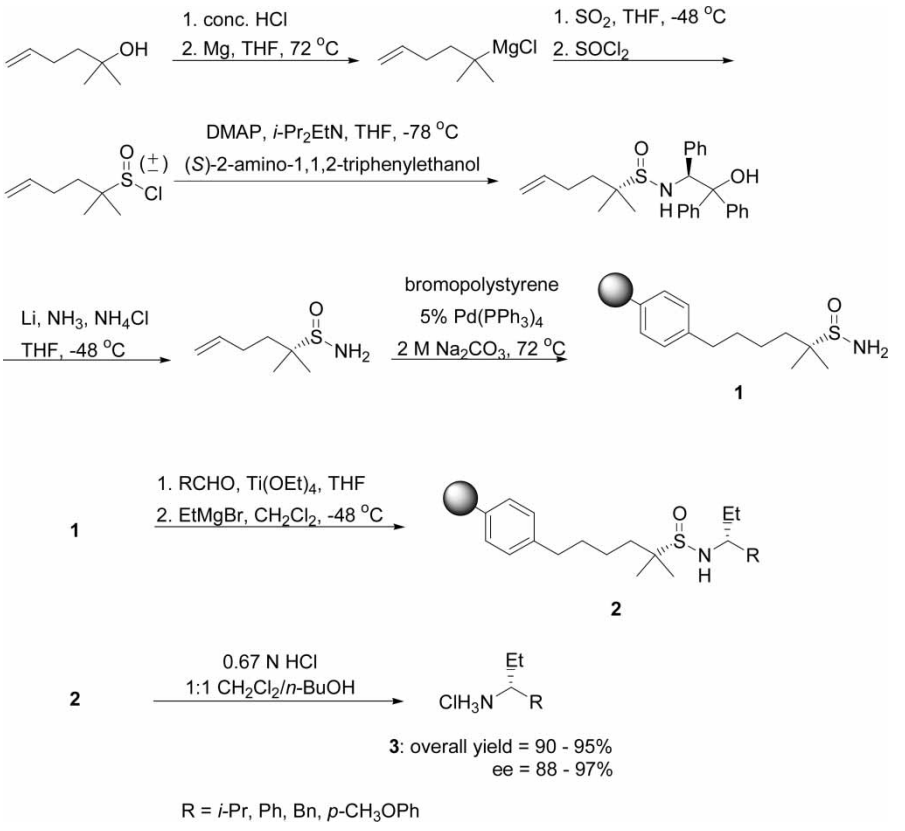
Sulfur-based linker groups used in PSOS utilize three different oxidation states of sulfur (sulfide, sulfoxide and sulfone groups) to modulate their reactivity and affect the stereoselectivity and chemoselectivity of the reactions performed using them. The categories into which they are divided in this review are based on the method for compound cleavage. These divisions are meant to be descriptive and some overlap among these classifications exists, especially with the traceless, safety-catch, and cyclization and rearrangement release linkers. In all of these cleavage reactions, the reactivity of the linker groups closely mirrors that of their solution-phase, small molecule counterparts.

2.1 *Acid labile linkers*

Ellman *et al.* have reported an efficient synthesis of polystyrene-supported chiral *t*-butylsulfinamide derivative **1** (the SBS linker) and demonstrated its utility in the asymmetric synthesis of enantioenriched amines [38]. In this work, they chose to link *t*-butylsulfinamide to the solid support using an all-carbon tether. The utility of polymer-supported **1** was first explored in the synthesis of chiral α-branched amines (scheme 1). Condensation of aldehydes with **1** was efficiently achieved using $Ti(OEt)_4$ as both a Lewis acid and water scavenger. Subsequent addition of ethylmagnesium bromide provided the desired α-branched amine products **2**. The thus formed products were treated with HCl in a CH_2Cl_2/n-BuOH solvent mixture, chosen for maximum swelling of the polystyrene support, to obtain amine hydrochlorides **3** in nearly quantitative overall yields in three steps based on the loading of the starting brominated polystyrene resin. This report is significant in that the enantiomeric excesses of the products were high, and only slightly lower than that reported for the corresponding solution-phase synthesis.

In an example of a new analytical construct that allows for easy analytical analysis of synthetic PSOS intermediates, Ladlow and co-workers have reported the preparation of construct resin **4** [39]. By incorporating an acid-labile linker, **4** was conveniently used to develop optimized conditions for the preparation of a library of compounds employing reductive amination, acylation and Suzuki coupling reactions (scheme 2). Resins **5** were treated with TFA:triethylsilane:H_2O (90:5:5; 2×1 h) to afford carboxamides **6**. The yields and purities of the cleaved compounds were found to be good.

Albericio *et al.* recently reported a linker based on a chromane system for anchoring arginine and guanidine groups [40]. The success of this linker system relies on the handle (3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)acetic acid (**7**), which was used after attachment to an aminomethyl resin and subsequent chlorosulfonation, for anchoring arginine



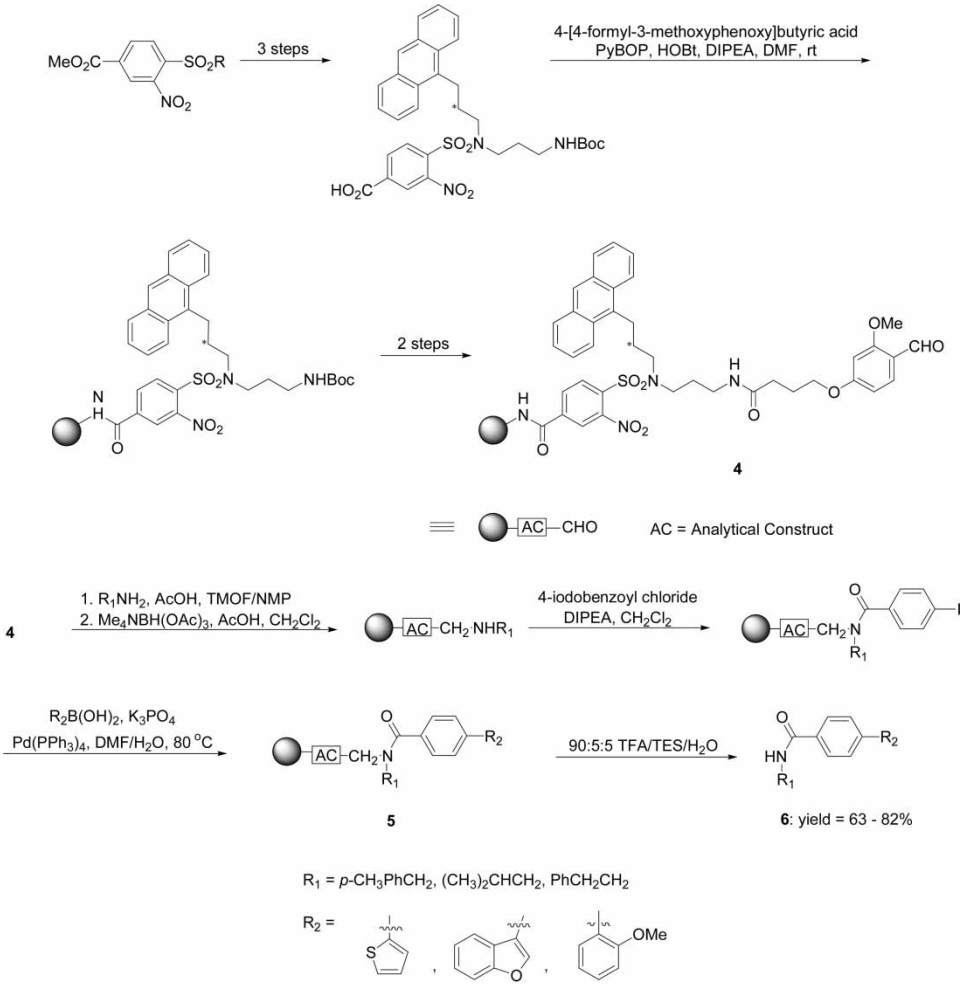
SCHEME 1

and guanidine-containing molecules through their side-chains. Incorporation of Fmoc-Arg-OAllyl was carried out in $CHCl_3$ in the presence of DIEA for 8 h at 25 °C to afford resin **8** (scheme 3). Compounds were released from the solid support by treatment with TFA in the presence of scavengers. This linker system is compatible with the Fmoc/*t*-Bu strategy for peptide synthesis and is being used in their laboratory for the solid-phase preparation of C-terminal arginine *p*-nitroanilide and cyclic peptides through side-chain anchoring of arginine.

2.2 *Traceless linkers*

Mioskowski *et al.* reported an efficient anchoring/activation/cleavage sequence for the traceless solid-phase synthesis of biarylmethane derivatives [41]. Initially, an arene scaffold was linked to the resin through a benzylic carbon−sulfur bond (scheme 4). Activation of the sulfide group was carried out by alkylation of the sulfur atom, leading to a sulfonium salt, which was followed by treatment with a palladium catalyst in the presence of an aryl boronic acid. This reaction sequence afforded biarylmethane derivatives **9** in moderate to high yields and is noteworthy in that release of the substrate is accompanied with formation of a new carbon-carbon bond.

In 2001, Tumelty *et al.* reported the development of the solid-phase synthesis of diverse benzimidazole compounds in a traceless route using a modified base-labile linker strategy to release the final target compounds in moderate yields with high purities (scheme 5) [42].

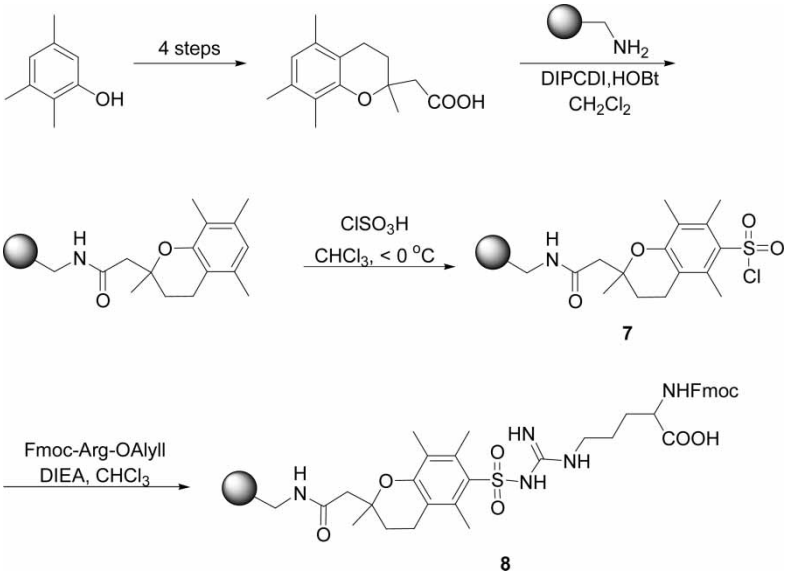


SCHEME 2

Tentagel-Br resin was treated with *t*-butyl *N*-(2-mercaptoethyl)carbamate, in the presence of base to yield the Boc-protected resin/linker **10**. After the series of reactions (1) protecting group removal, (2) nucleophilic aromatic substitution, (3) nitro group reduction, (4) intramolecular cyclization, (5) sulfide oxidation, and (6) alkylation, resins **11** were obtained in acceptable yields. The final products **12** were released from the resin by an overnight treatment with 5% triethylamine/CH_2Cl_2 in order to maximize the product yield, even though a time-course cleavage study carried out showed that 70% of the product was released from the resin within the first 5 h of the cleavage reaction.

In another report, Pan and Holmes demonstrated another traceless linker, polymer-supported perfluoroalkylsulfonyl (PFS) linker **13**, which was used in deoxygenation reactions of phenols (scheme 6) [43]. Attachment of the PFS fluoride group to the resin and subsequent coupling of a phenol afforded stable arylsulfonates **14**, that behave as supported aryl triflates. Palladium-mediated reductive cleavage of a wide variety of these phenol sulfonates afforded the parent arene compounds **15** in good yields.

In the preparation of functionalized 4,5,6,7-tetrahydroisoindoles reported by Kurth *et al.*, a traceless solid-phase sulfone linker strategy was described [44]. Thermolytic extrusion



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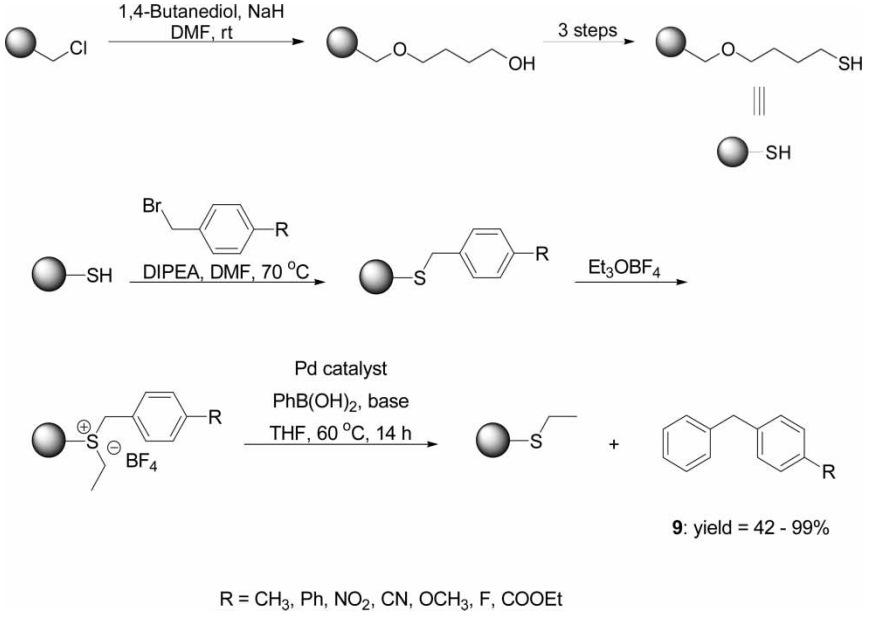
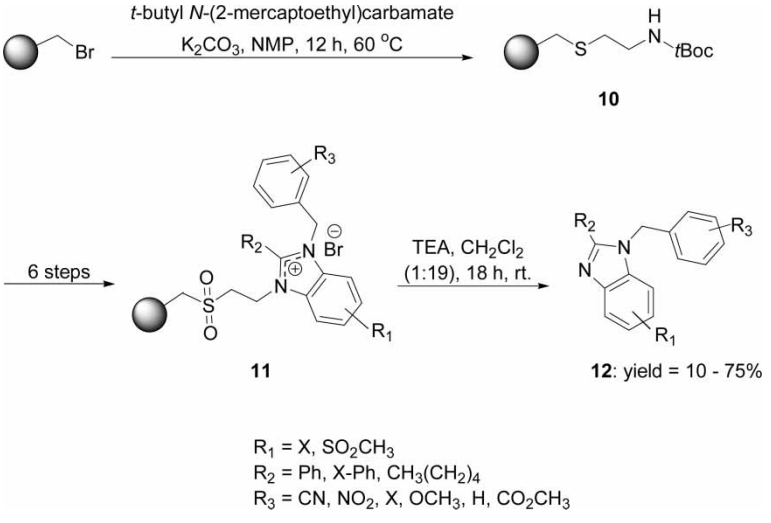


SCHEME 4

of SO_2 from polymer-bound 3-(phenylsulfonyl)-3-sulfolene **16** generated supported 2-(phenylsulfonyl)-1,3-butadiene **17** in situ, which underwent Diels-Alder cycloaddition with various dienophiles to furnish vinyl sulfone resins **18** (scheme 7). To complete the traceless linker cleavage strategy, (*p*-tolysulfonyl)methyl isocyanide was reacted with the vinyl sulfone moiety of **18** to liberate functionalized 4,5,6,7-tetrahydroisoindole products **19**. Alternatively, 3-sulfolene **20** could be formed by reacting **16** with ethyl isocyanoacetate.



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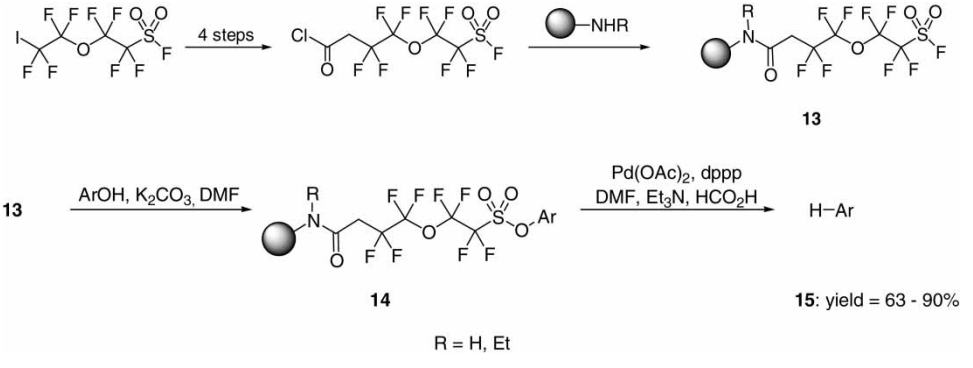
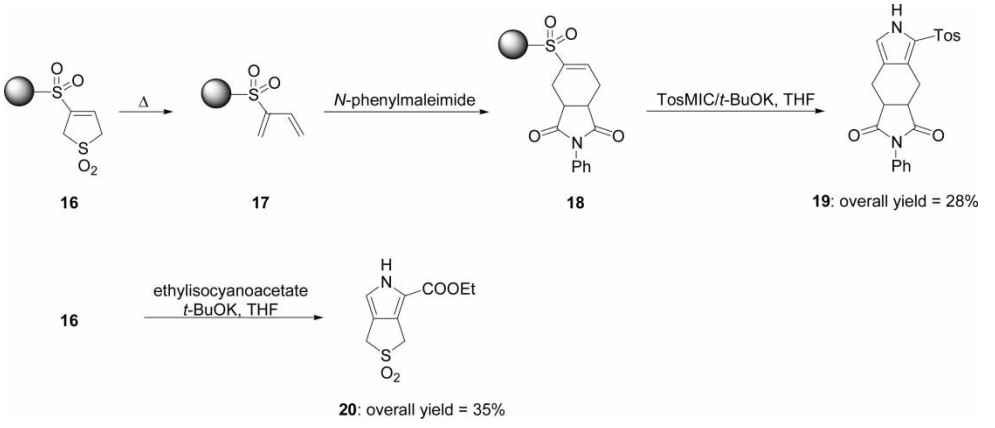


SCHEME 6

Bertini and co-workers reported the synthesis and use of 1,3-propanedithiol resin **21** in selective reductions of ketones **22a–d** in the presence of an ester or a second ketone group [45]. Attachment of ketones to this resin followed by reductive cleavage of the thus formed 1,3-dithiane groups resulted in the formation of the corresponding methylene group containing compounds **23a–d** (scheme 8). The system is noteworthy in that the process of reducing the ketones to alkanes, including the preparation of **21**, is completely odorless and can be done to selectively reduce one ketone functional group in the presence of an ester moiety or even a second ketone group in good yield.

The first Pummerer cyclization reactions in PSOS were reported by Procter *et al.* in 2003 [46]. They found that α-sulfanyl *N*-aryl acetamides, attached to resin via the sulfur atom, undergo efficient Pummerer cyclization upon activation of the sulfur group to give oxindole **24** (scheme 9). As the sulfur linkage to resin remains intact after cyclization, further synthetic steps allow access to elaborated oxindole scaffolds. Resin **24** was oxidised to the sulfone **25** and then efficient alkylation was carried out to give allylated sulfone **26**. Heterocyclic product **27** was cleaved from the resin in a traceless manner using samarium(II) iodide.



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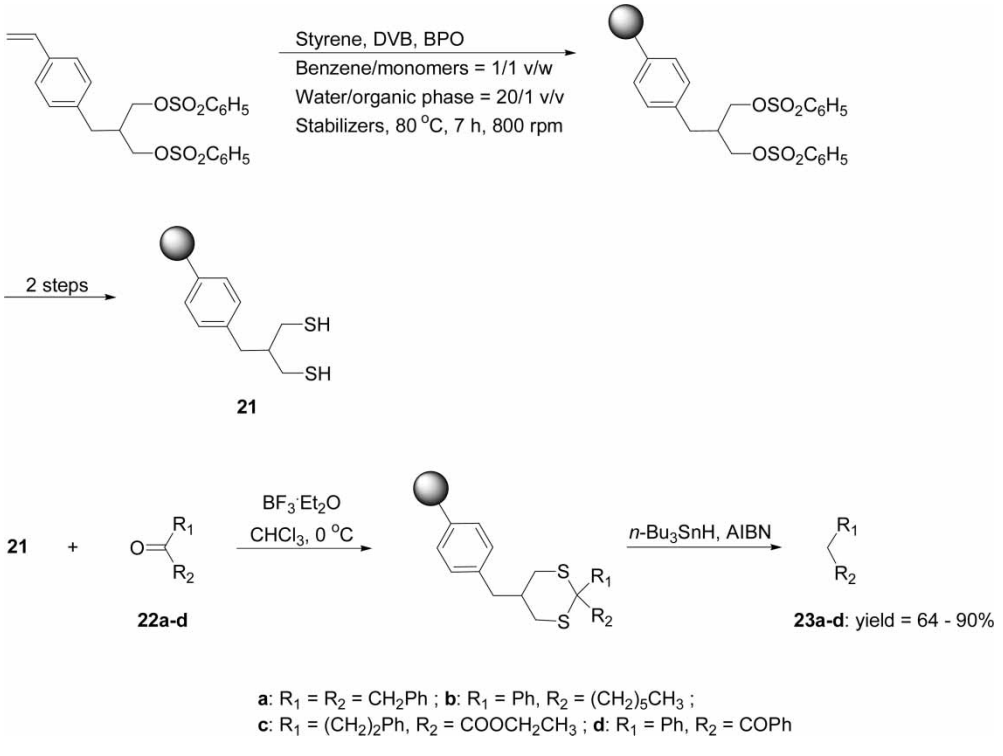
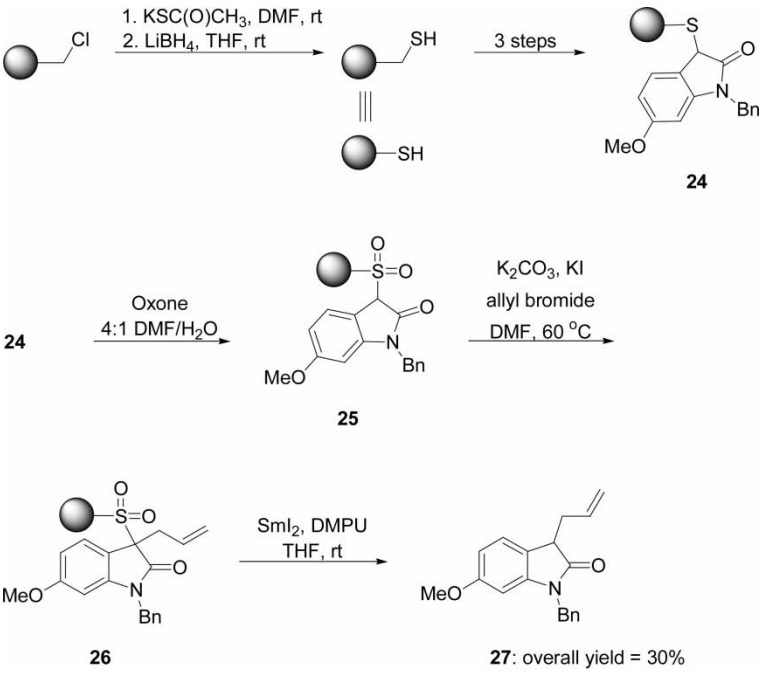


SCHEME 8

2.3 *Safety-catch linkers*

Bertini *et al.* have reported the use of one of their polymer-supported 1,3-propanedithiol reagents **21** in the conversion of benzaldehyde to various ketones via chemistry analogous to that of solution-phase 1,3-dithianes [47]. Thus, formation of polymeric 1,3-dithianes **28** was accomplished by reaction with benzaldehyde and a Lewis acid (scheme 10). This was followed by a lithiation/alkylation sequence at C2. Finally, oxidative cleavage of the dithiane group afforded the cleaved ketones **29**.



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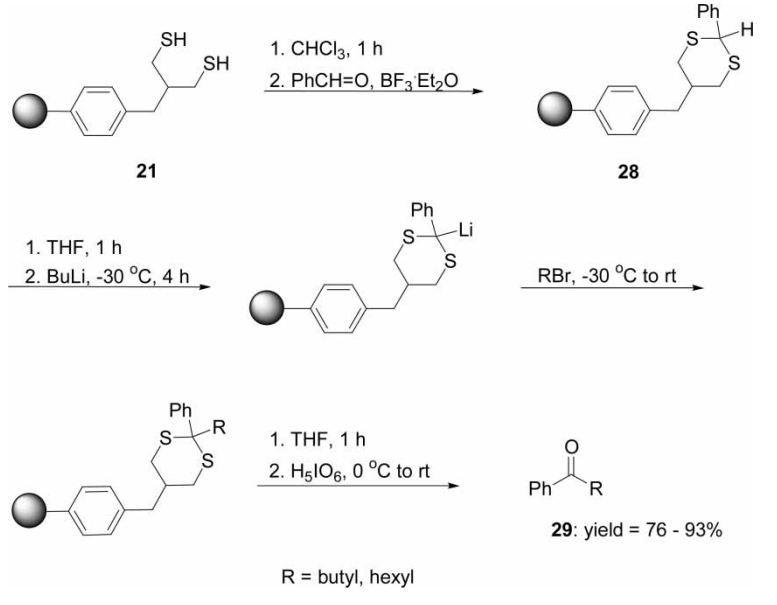
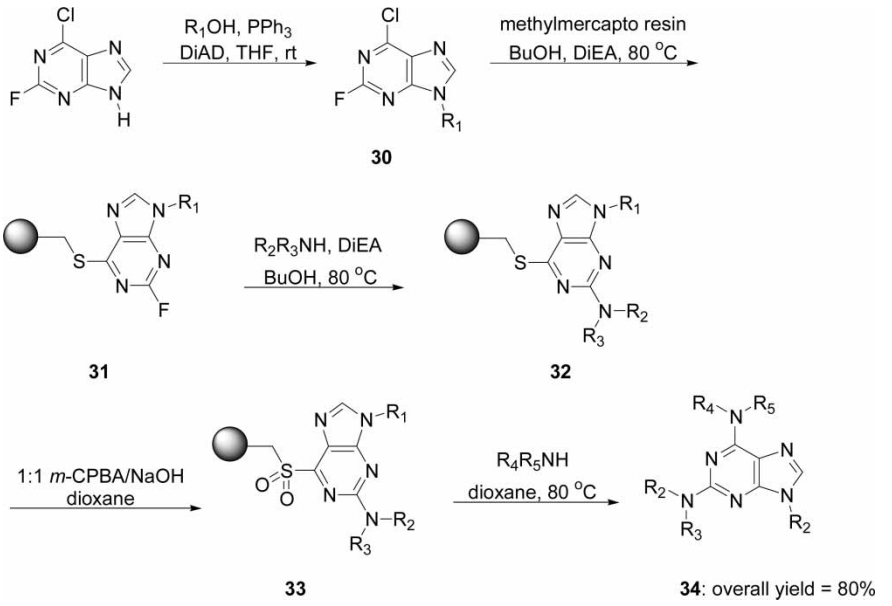


SCHEME 10

A resin-capture and release strategy for the solid-phase synthesis of combinatorial 2,6,9-trisubstituted purine libraries was reported by Schultz *et al.* [48]. This was accomplished by capturing an N9-substituted 2-fluoro-6-chloropurine **30** at the C6 position using an alkyl thiol resin via a thioether linkage to form resins **31** (scheme 11). The C2 fluoro groups were subsequently substituted by primary and secondary amines to form **32**. This was followed by



SCHEME 11

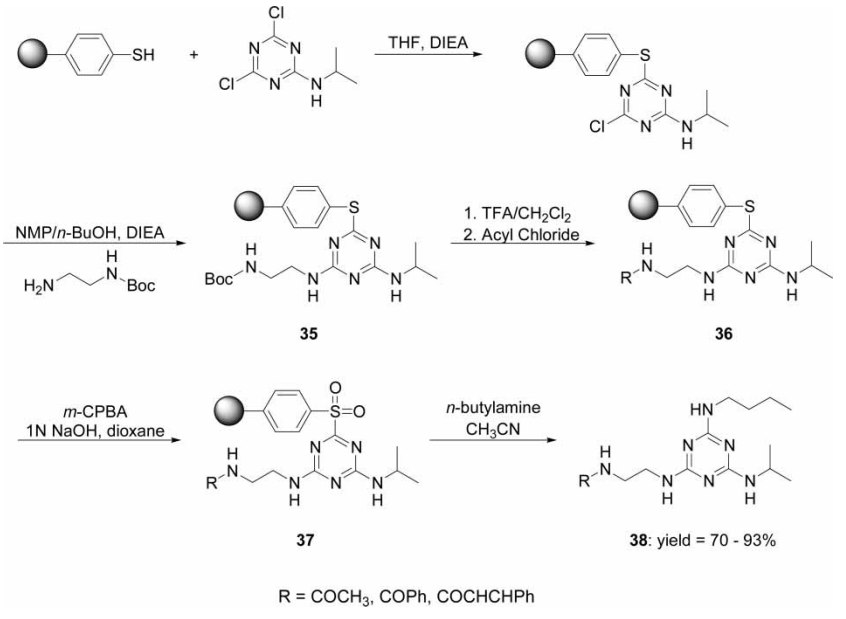
sulfide oxidation to **33** and release by C6 substitution with amines and anilines to afford the 2,6,9-trisubstituted purine derivatives **34**.

Chang and co-workers have developed a safety-catch method for the orthogonal synthesis of highly pure trisubstituted triazines [49]. Resin **35** was subjected to trifluoroacetic acid mediated Boc removal, followed by treatment with a variety of acyl chlorides to result in compounds **36** (scheme 12). These subsequently underwent oxidation to activated sulfones **37**, which were displaced by nucleophiles to release acylated derivatives **38** with high yield.

2.4 *Cyclization release linkers*

A general and high-yielding solid-phase method for the synthesis of 2,4-diaminothiazoles **44** starting from a polymer-bound thiouronium salt **39** was reported by Masquelin *et al.* [50]. This synthetic strategy involves the formation of polymer-bound thioureido-thiourea intermediates **41** from the combination of polymer-bound thiouronium salt **39** and isothiocyanates **40** (scheme 13). Treatment of these with α-bromo-ketones **42** afforded S-alkylated intermediates **43**, which underwent subsequent base-catalyzed intramolecular ring-closure/cleavage to give 2,4-diaminothiazoles **44** in high yield and purity. A notable feature of this methodology is the use of a polymer-supported auto-scavenging strategy (PSAS) that provides a clean, high-yielding, and traceless synthesis of 2,4-diaminothiazoles.

In 2001, Lam and co-workers reported the use of polystyrene-supported sodium benzenesulfinate **45** as a solid support for PSOS and showed the resulting sulfone linker **46** derived from **45** to be a versatile and robust tether [51]. Since then, they explored many new applications for **45** in PSOS. In 2002, they reported the preparation of the first library of imidazo[1,2-a]pyridine derivatives on a solid support employing a sulfone linker strategy in the synthesis [52] (scheme 14). The target molecules were released from the solid support by sulfinate elimination with 10% NaOH. The versatility of this chemistry was illustrated by the preparation of a library of imidazo[1,2-a]pyridine derivatives **47** in acceptable yields with excellent purities.



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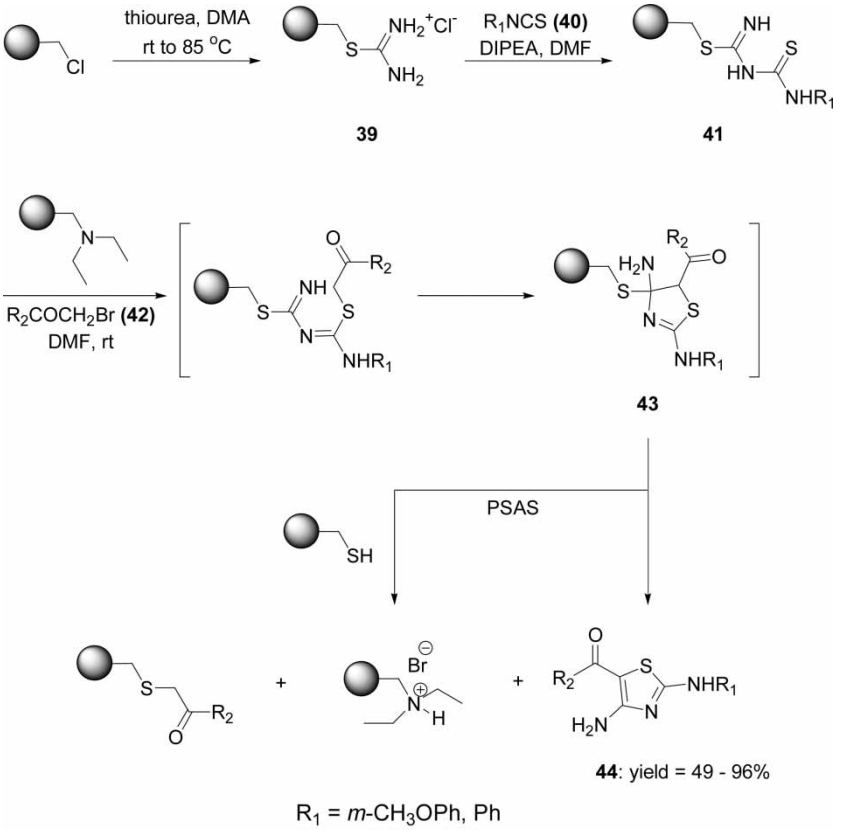
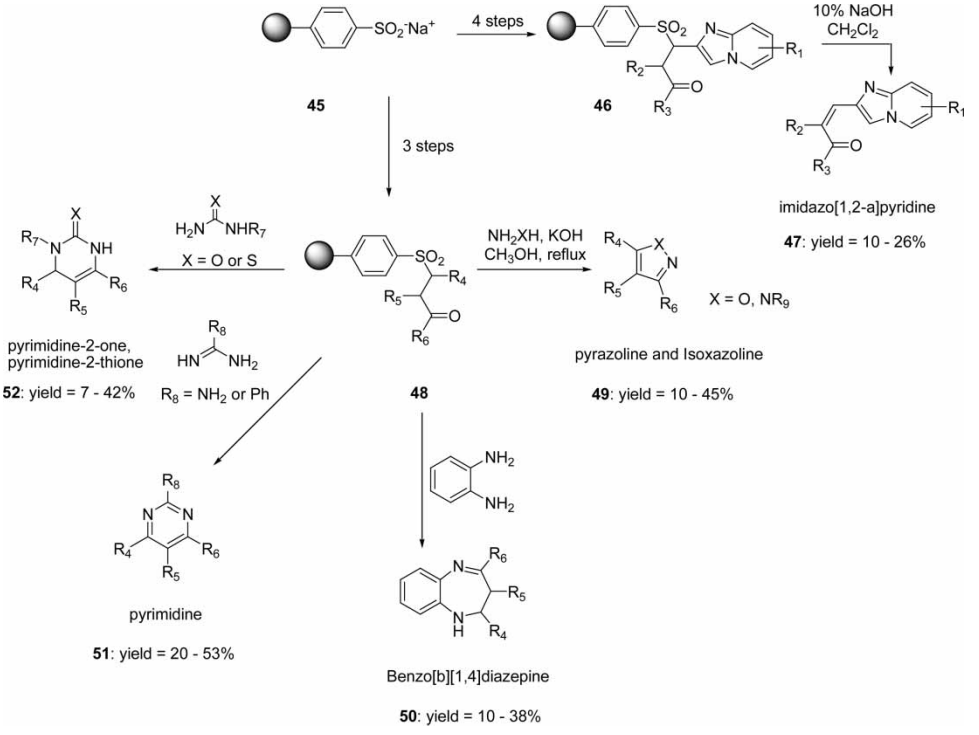


SCHEME 13



SCHEME 14

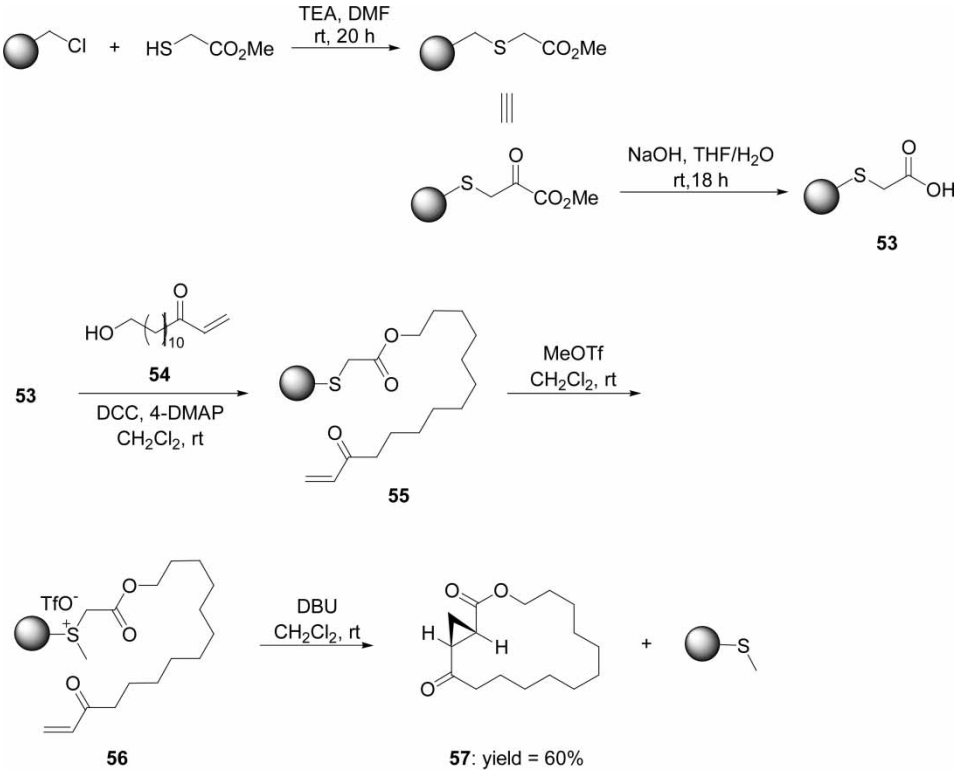
In 2003, they demonstrated the utility of **45** in the preparation of pyrazoline and isoxazoline derivatives employing the same traceless sulfone linker strategy as before [53]. Treatment of resin γ-ketosulfone **48** with substituted hydrazine or hydroxylamine in KOH/CH_3OH under nitrogen afforded **49**. In this way, a library of pyrazoline and isoxazoline derivatives **49** was prepared in reasonable yield and excellent purity.

More recently, they have reported the further use of **45** in the synthesis of a number of other nitrogen-containing heterocyclic compounds [54]. The preparation of benzo[b][1,4]diazepine **50**, pyrimidine **51** and pyrimidine-2-thione or pyrimidine-2-one derivatives **52** using their traceless sulfone linker strategy was described. All of these compounds were obtained in moderate overall yields.

Gennari *et al.* reported a novel synthesis of macrolactones bearing a cyclopropyl ring via a cyclization-release strategy that makes use of a polymer-supported stabilized sulfur ylide [55]. Functionalized resin **53** was reacted with hydroxy vinylketone **54** to give supported vinylketone **55** (scheme 15). The sulfide group of **55** was alkylated with MeOTf in CH_2Cl_2 to afford the corresponding resin bound sulfonium salt **56**, which was purified by filtration and washing. Treatment of **56** with DBU generated the stabilized sulfur ylide which underwent cyclative cleavage to give the macrocyclic lactone (+/−)-**57**, bearing a cyclopropyl ring condensed to the macrocycle, in good yield and purity as a single diastereoisomer (*trans*).

2.5 *Rearrangement release linkers*

Solladié *et al.* have introduced an alkoxyphenyl-sulfinyl linker that is suitable for the PSOS of 1,2-diols. *p*-Hydroxyphenyl-β-ketosulfides were attached to Wang resin and oxidized to



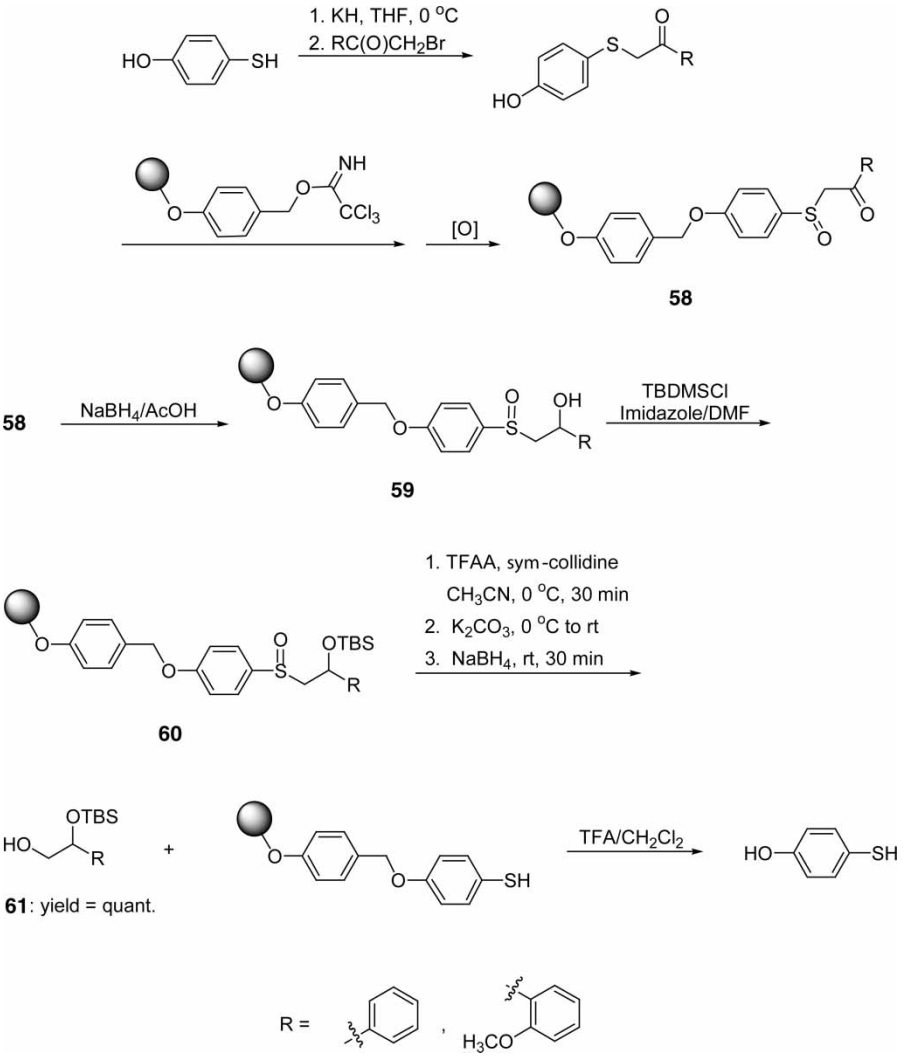
SCHEME 15

the corresponding sulfoxides **58** (scheme 16) [56]. Reduction of **58** with sodium borohydride afforded the corresponding β-hydroxysulfoxides **59**. Finally, protected diols **61** were efficiently released nearly quantitatively from **60** through Pummerer reactions in a traceless manner.

Li and co-workers reported the use of a sulfide linkage as a safety-catch linker that significantly is stable to acidic as well as basic conditions [57]. The synthetic utility of this linker system was demonstrated by the preparation of amides (scheme 17). In the synthesis of amide **67**, alcohol **63** was coupled to resin **62** by a Mitsunobu reaction followed by the removal of trityl protecting group using TFA. The thus formed resin **64** was alkylated with bromide **65** in the presence of K_2CO_3 to give resin amide **66**, which was then oxidized by *t*-BuOOH followed by cleavage from the resin using trichloroacetic anhydride (TCAA) and Et_3N to afford amide **67** in 65% overall yield.

3. Selenium-based linkers

The use of organoselenium reagents in organic syntheses is common practice for functional group manipulation since they generally require mild reaction conditions and afford good yields [58–64]. Recently, the adaptation of selenium chemistry for use in selenium-based linker strategies for PSOS, especially with regards to the synthesis of alkene containing target molecules, has been reported by a number of research groups, most notably by those of Nicolaou and Huang. As with the sulfur-based linker groups, the reactivity of these selenium-based ones are similar to analogous small molecules. However, it is important to note that

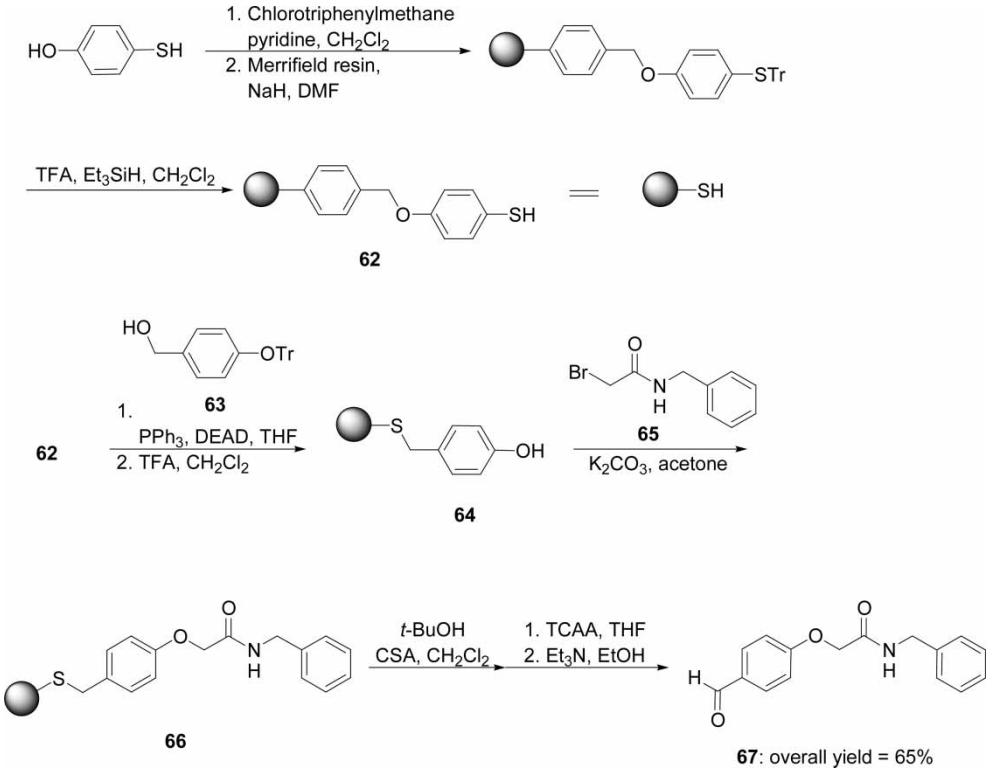


SCHEME 16

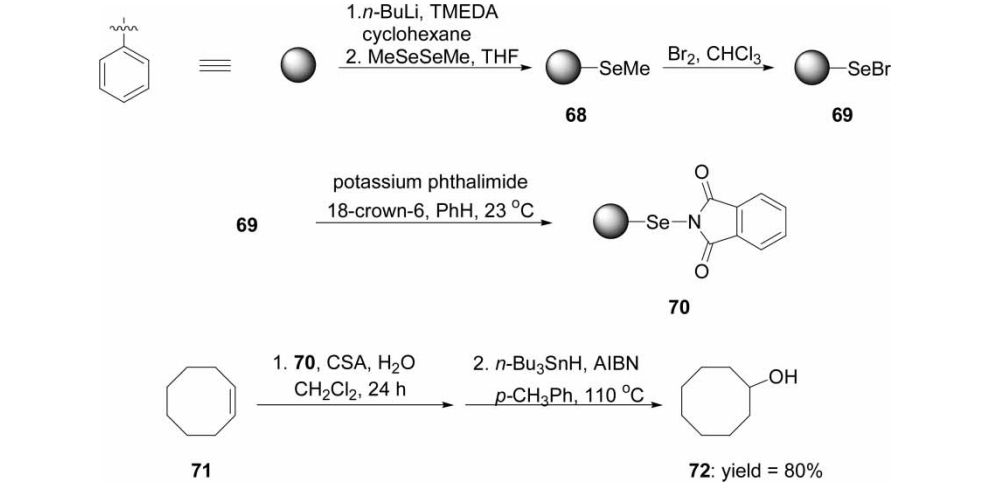
the use of a supported selenium reagent as a linker group minimizes some of the intrinsic problems associated with handling such reagents, such high toxicity and foul odor, since they are rendered non-volatile. The following section summarizes the literature describing the use of selenium-based linkers in PSOS for small molecule synthesis and combinatorial library development.

3.1 *Nicolaou group reports*

In 1998, Nicolaou *et al.* reported the first synthesis of polymer-bound phenylselenium bromide [65]. Selenium bromide **69** was prepared from commercially available divinylbenzene cross-linked polystyrene resin by lithiation followed by treatment with dimethyl diselenide to give polymer-bound methyl selenide **68** (scheme 18). Exposure of **68** to bromine afforded selenenyl bromide **69** with quantitative conversion.



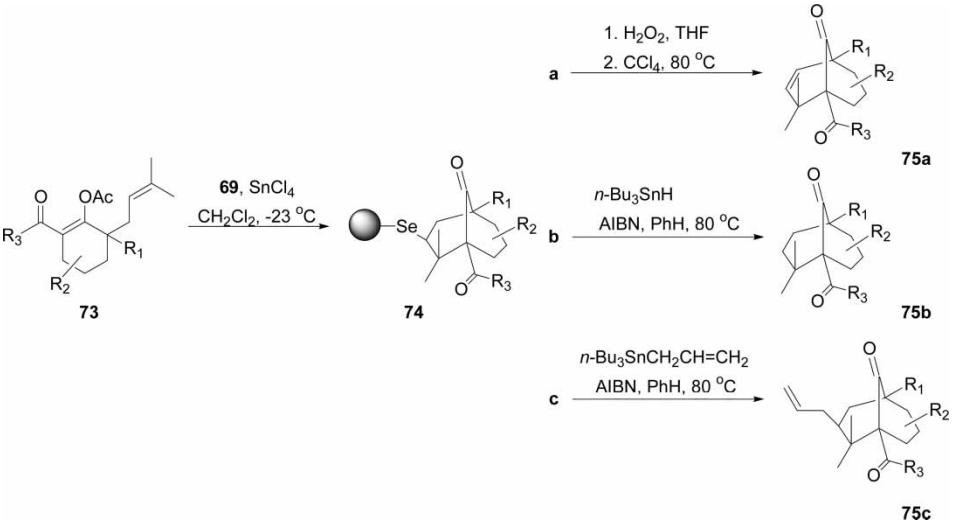
SCHEME 17



SCHEME 18

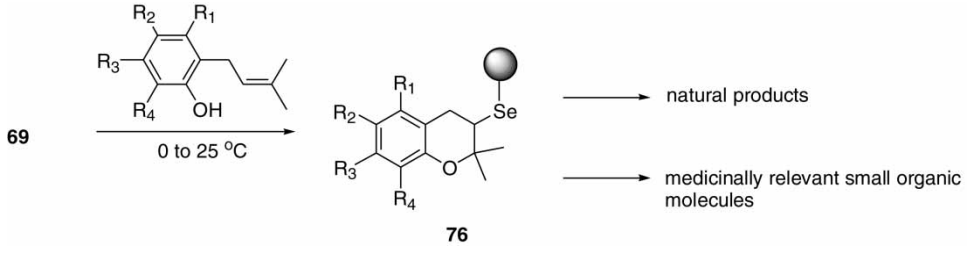
The utility of resin **69** was demonstrated through converting it to selenium phthalimide resin **70** by reaction with potassium phthalimide in the presence of 18-crown-6. Cyclic alkene **71** was converted to alcohol **72** in high yield by reaction with **70** and CSA in the presence of H_2O, followed by reductive cleavage of the resulting polymer-bound alcohol from the solid support using *n*-Bu_3SnH and AIBN.

In 2000, Nicolaou *et al.* reported use of polymer-bound selenium bromide **69** in the synthesis of a variety of bicycle[3.3.1]nonan-9-ones [66]. They demonstrated the development of an improved method for the selenium-mediated cyclization of alkenyl-substituted β-dicarbonyl compounds **73** to bicycle[3.3.1]nonan-9-ones **75a–c** (scheme 19). Compound **73** was reacted with **69** in CH_2Cl_2 to afford **74**, which was subsequently subjected to different cleavage protocols. Both traceless and functionalizing cleavage resulted in access to novel classes of rigid, carbocyclic scaffolds in high yields.



SCHEME 19

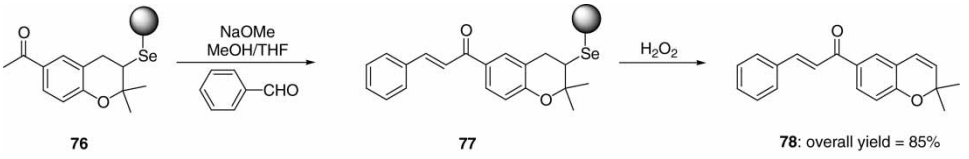
With selenium bromide **69** in hand, Nicolaou *et al.* also explored its application in combinatorial synthesis of natural products and other medicinally relevant small organic molecules [67, 68]. The key of step to these syntheses is based on the employment of a novel selenium-based cyclo-loading strategy for the formation of the 2,2-dimethylbenzopyran scaffolds **76** (scheme 20).



SCHEME 20

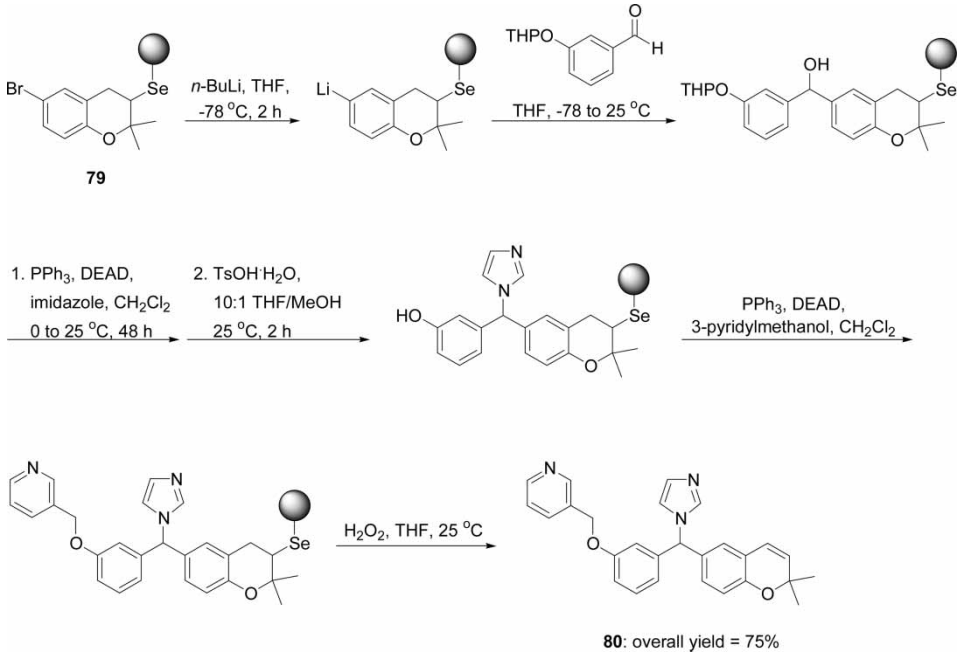
With this collection of functionalized, resin-bound benzopyran platforms, they demonstrated their utility for elaboration toward natural products and combinatorial libraries. As illustrated in the construction of several chalcone natural products (scheme 21), resin-bound benzopyran methyl ketones **76** were condensed with substituted aldehydes in the presence of NaOMe. After condensation and in situ elimination to form the chalcone framework in *i.e.* **77**,

the substrates were subjected to oxidative cleavage with H_2O_2 to afford products such as **78** in high yield.



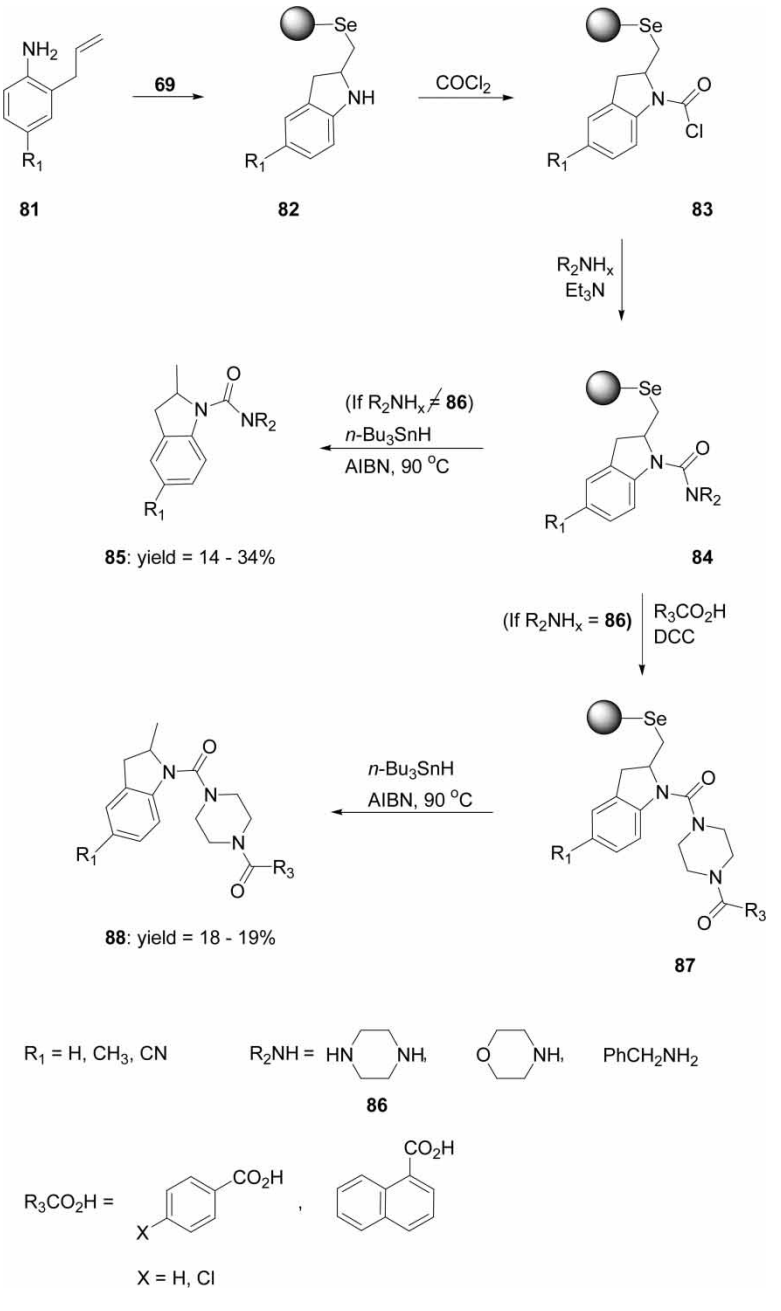
SCHEME 21

Further demonstration of the versatility and applicability of the dimethylbenzopyran scaffolds **79** was illustrated by the synthesis of some medicinally relevant small organic molecules. They performed a solid-phase synthesis of aldosterone biosynthesis inhibitor **80** in high overall yield (scheme 22).



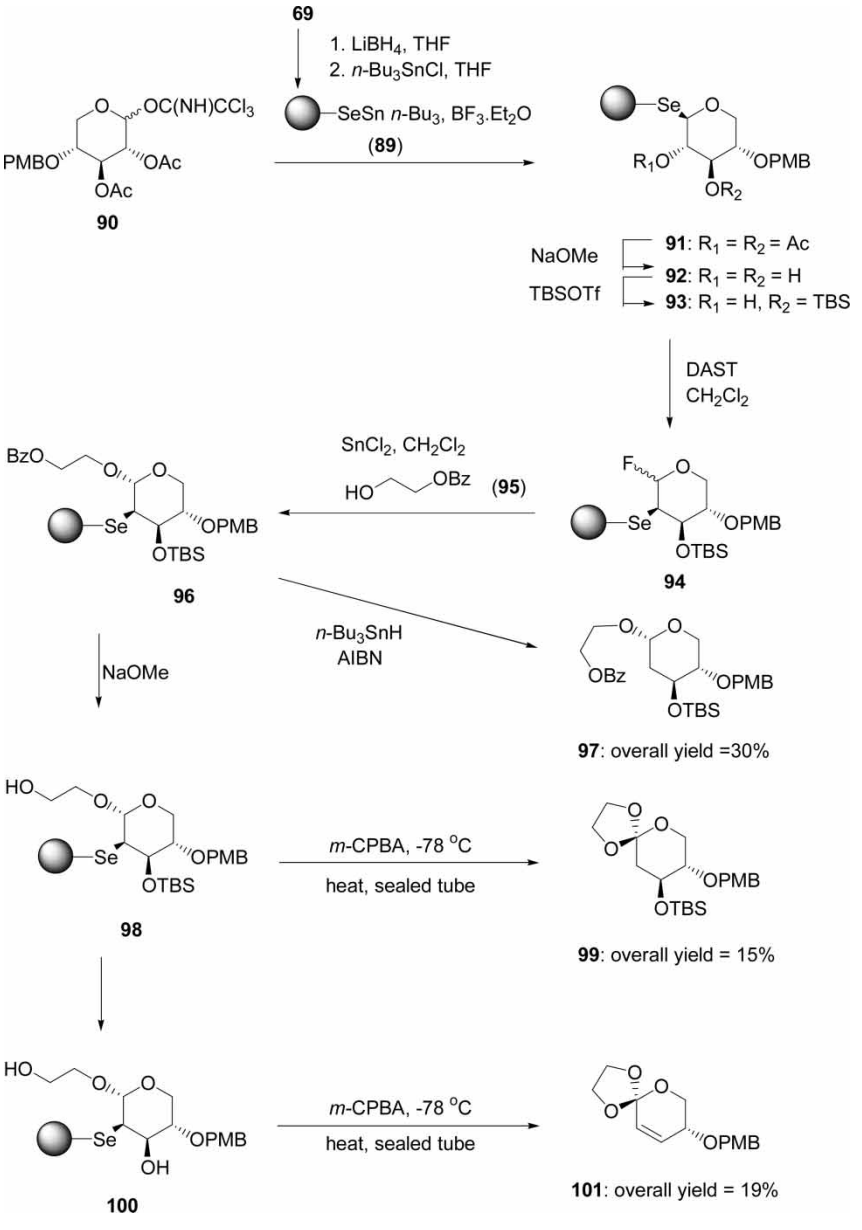
SCHEME 22

Most recently, Nicolaou and co-workers described a highly efficient method for the solid-phase synthesis of substituted indoline scaffolds [69]. Given the versatility of the cyclo-loading strategy for the solid-phase combinatorial synthesis of benzopyran-containing natural products in their previous studies, they extended this strategy to the cyclo-loading of *o*-allyl anilines **81** to afford resin-bound indoline scaffolds **82** (scheme 23). The indoline scaffolds can be elaborated and tracelessly cleaved to provide access to members of the medicinally important 1-methyl indoline class of compounds. Resin-bound indolines **82** were converted to the corresponding acyl chlorides **83** by treatment with phosgene, and these acyl chlorides were then reacted with various amines to afford ureas **84**. When the amine used was piperazine **86**, the remaining secondary amine was then coupled with a carboxylic acid. All of the resulting indolines **84** and **87** were tracelessly cleaved to produce compounds of type **85** or **88**, respectively.



SCHEME 23

Nicolaou *et al.* also reported the solid-phase synthesis of 2-deoxy glycosides, orthoesters and allyl orthoester with good stereoselectivities and in high yields, employing a selenium-based linking strategy and facilitated by a 1,2-selenium migration (scheme 24) [70]. They demonstrated the utility of the 1,2-seleno-migration chemistry in PSOS by attachment of a carbohydrate donor to resin **89**. Resin **89** was readily prepared from polymer-supported selenium bromide **69** by lithiation followed by quenching with excess *n*-Bu_3SnCl. Treatment

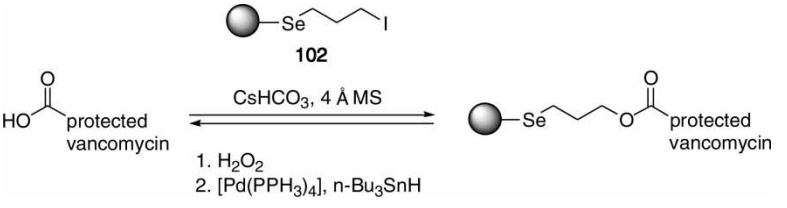


SCHEME 24

of resin **89** with trichloroacetimidate donors **90** in the presence of $BF_3{\cdot}Et_2O$ led to excellent loading of the sugar. The carbohydrate group of **91** was further manipulated to remove the ester groups to afford **92** followed by selective silylation to afford **93**. Treatment of the 2-hydroxy compound with DAST initiated the 1,2-selenophenyl migration, affording the 2-seleno-1-fluoro donor **94**. The glycosyl fluoride donor was coupled with alcohol **95** in the presence of $SnCl_2$ to selectively form the α-glycoside **96**. Formation of the 2-deoxyglycoside **97** was achieved by exposure of this to *n*-Bu_3SnH/AIBN via radical cleavage of the Se-C bond. Deprotection of the ester group of **96**, to afford **98**, was followed by oxidation of the selenide group to the selenoxide oxidation state. Heating of this in a sealed tube led to the formation of

2-deoxy orthoester **99**. On the other hand, removal of the silyl group from **98**, to afford diol **100**, followed by oxidation to the selenoxide and heating in a sealed tube, led to elimination of the C-2 hydroxyl group with simultaneous migration of the double bond and formation of the orthoester to afford the 2,3-allylorthoester **101**.

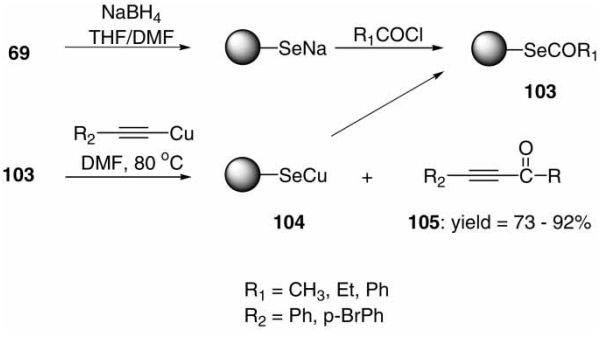
In 2000, Nicolaou *et al.* and co-workers reported the synthesis of a set of selenium-based safety-catch linkers for carboxylic acids, alcohols and amines [71, 72]. One of these linkers, **102**, was demonstrated in a solid-phase semisynthesis of vancomycin. The developed technology and sequence has potential for the construction of vancomycin libraries for biological screening purposes starting from the readily available vancomycin scaffold (scheme 25).



SCHEME 25

3.2 *Huang group reports*

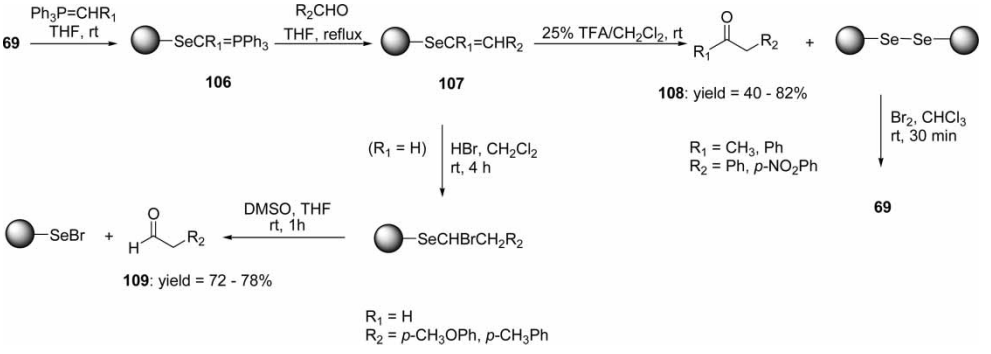
In 2001, Huang and co-workers reported the preparation of polystyrene supported selenol esters and their use in acetylenic ketones synthesis [73]. The polystyrene supported selenol esters **103** were easily prepared from the polymer-bound selenium bromide **69** by reaction with sodium borohydride and subsequent acylation with acyl chlorides (scheme 26). Resins **103** reacted with a variety of alkynylcoppers reagents to give, upon simple filtration, resins **104** and the acetylenic ketones **105** in high yields. It is notable that resin **104** can be reacylated to regenerate **103.**



SCHEME 26

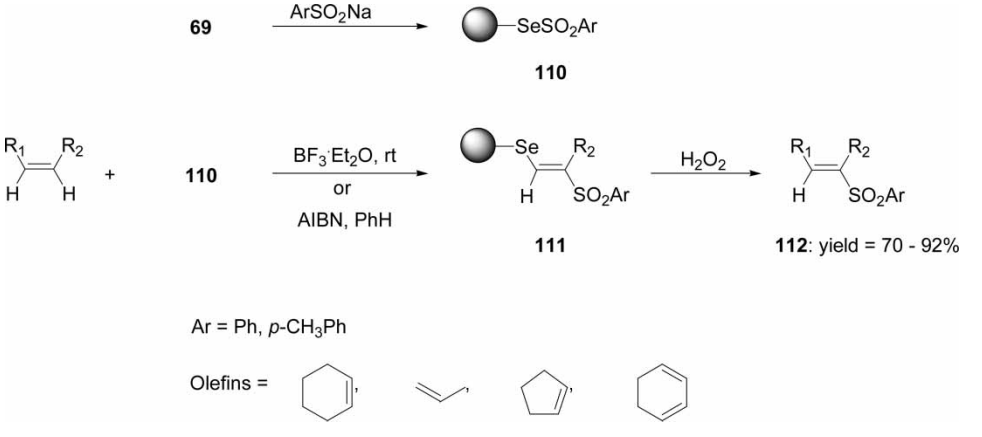
In a separate report, this group demonstrated another use of the polymer-bound selenium bromide **69** in PSOS [74]. They developed a solid-phase route to ketones and aldehydes in good yields and purities (scheme 27). The transylidation reactions of **69** with akylidenetriphenylphosphoranes afforded resins **106**, which were sufficiently reactive to undergo Wittig-type reactions to afford the vinylic selenide resins **107**. Cleavage of the bound substrates gave

ketones **108** and aldehydes **109** under the appropriate conditions in good yields and high purities.



SCHEME 27

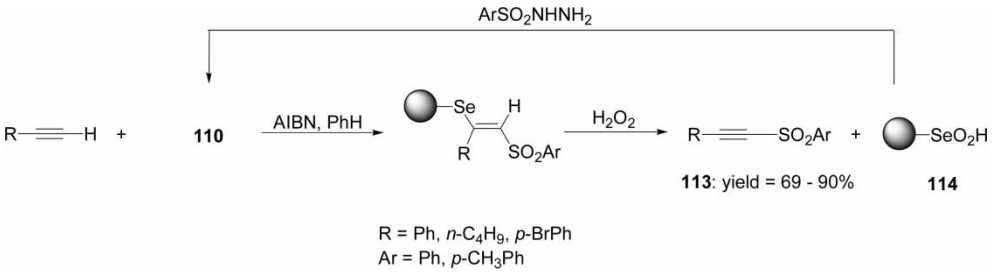
Meanwhile, Huang and Qian developed two novel polystyrene-supported selenosulfonates reagents **110** that were prepared in nearly quantitative yield by reaction of polymer-bound selenium bromide **69** with sodium benzenesulfinate or sodium toluenesulfinate in DMF at room temperature (scheme 28) [75]. They examined the selenosulfonation of olefins by resins **110** under boron trifluoride or AIBN catalysis. Resins **111** were converted to vinyl sulfones **112** regio- and stereoselectively in good yields and high purities using H_2O_2.



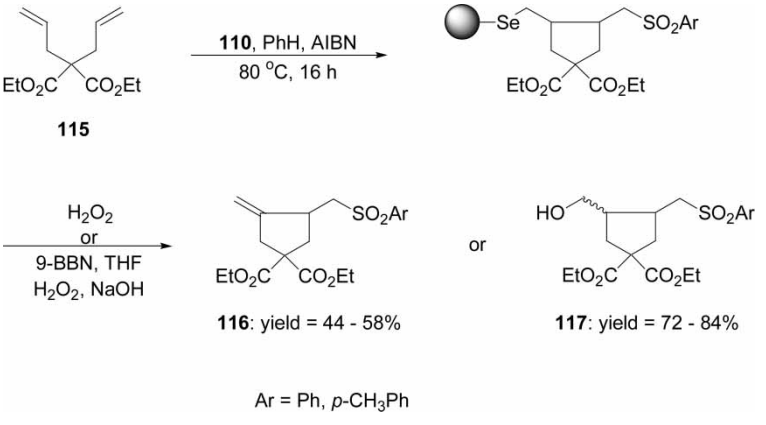
SCHEME 28

Later they demonstrated another use of the polystyrene-supported selenosulfonates reagents **110** (scheme 29) [76]. AIBN catalyzed selenosulfonation of acetylenes with reagents **110**, followed by oxidation and stereospecific selenoxide syn-elimination, proved to be a convenient method for the synthesis of acetylenic sulfones **113**. Resins **110** were regenerated by reacting resin **114** with sulfonylhydrazides.

Recently, Huang and Qian developed another use for reagent **110** [77]. These were applied in the free radical cyclization reactions of 1,6-dienes **115** followed by subsequent release via an oxidation-elimination reaction to afford methylenecyclopentanes **116** as the only products. Alternatively, cyclopentanylmethyl alcohols **117** were obtained as the only product by employing a hydroboration-oxidation reaction sequence (scheme 30).

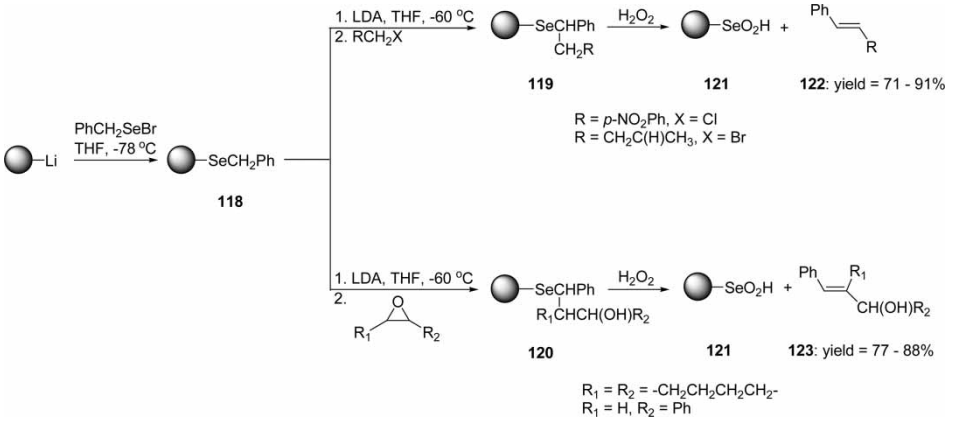


SCHEME 29



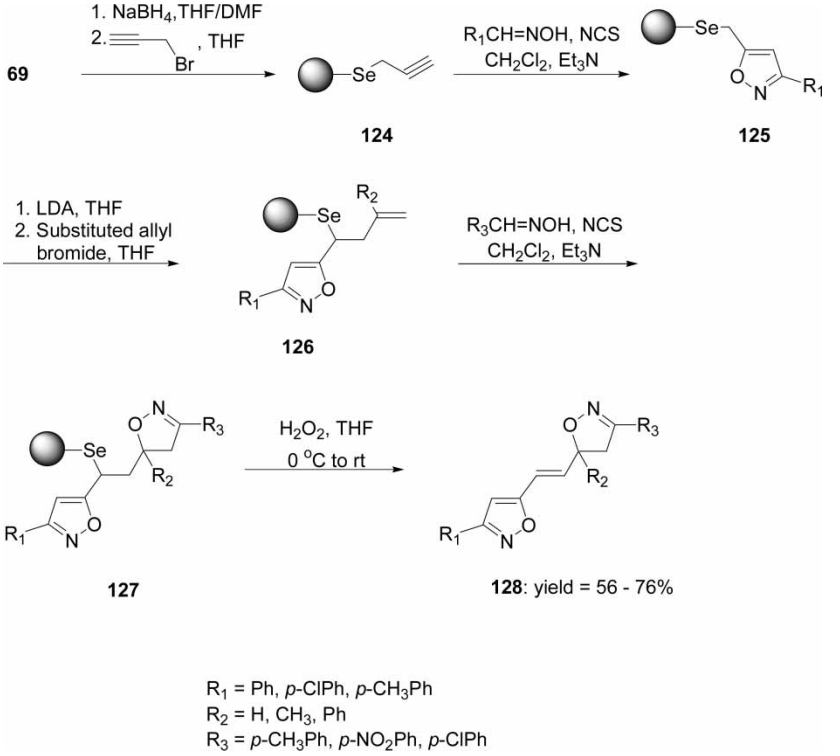
SCHEME 30

Huang and Xu reported the preparation of polystyrene-supported benzyl selenide and its use for the synthesis of olefins and allylic alcohols [78]. The benzyl selenide reagent **118** was treated with LDA to produce a selenium-stabilized carbanion, followed by substitution with alkyl halides and epoxides to give resins **119** and **120**, respectively (scheme 31). Resins **119** and **120** were converted to olefins **122** and allylic alcohols **123**, respectively and resin **121** through selenoxide syn-elimination using hydrogen peroxide. Further enhancing the utility of this process is the fact that **121** could be converted back to **118**.



SCHEME 31

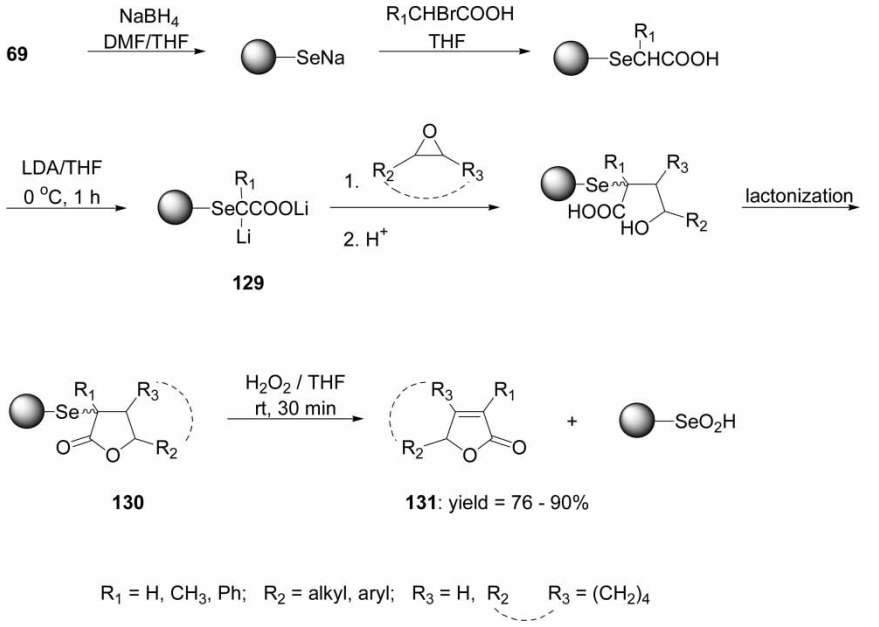
In another report, Huang and Xu described the convenient syntheses of *E*-isoxazolyl and isoxazolinyl-substituted alkenes using polymer-bound selenium bromide **69** with the advantages of easy operations, odorlessness, stability, and good purity of the products [79]. Their syntheses were based on the reaction sequence of propargylation of **69** to form **124**, heterocycle formation by 1,3-dipolar cycloaddition to yield **125**, α-alkylation to produce **126**, further 1,3-dipolar cycloaddition to **127** and cleavage through stereospecific selenoxide syn-elimination to afford products **128** in good yields (scheme 32).



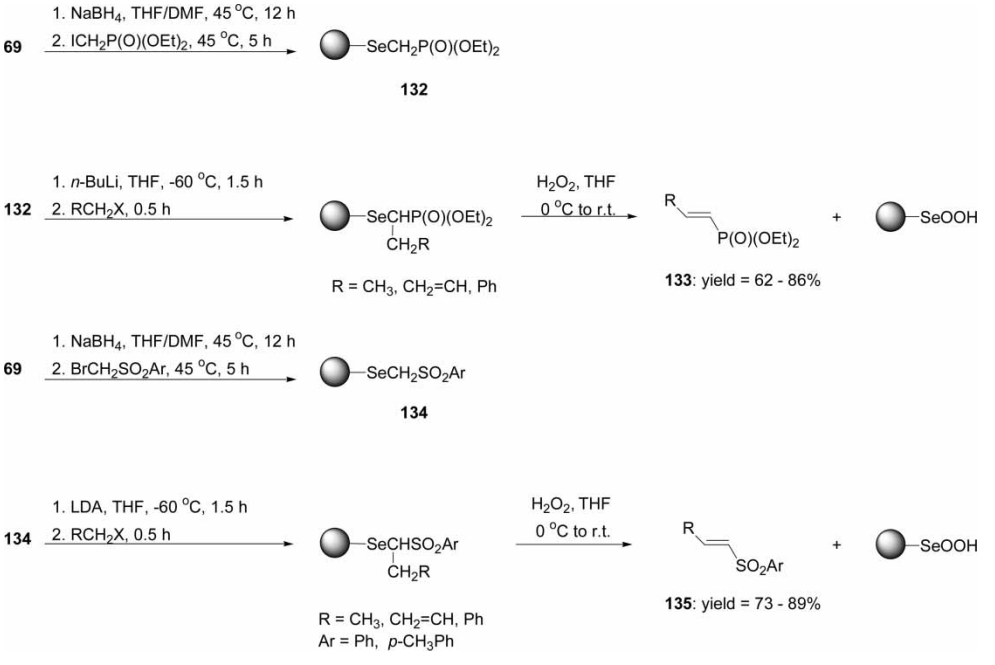
SCHEME 32

Huang and Sheng have developed an efficient method for the solid-phase synthesis of substituted 2(5H)-furanones from polymer-supported α-selenocarboxylic acids employing a selenium-based traceless linker strategy [80]. The synthesis of polystyrene-supported α-selenoacetic acid, α-selenopropionic acid, and α-selenophenylacetic acid was described (scheme 33). Reaction of the dilithio derivatives of polymer-supported α-selenocarboxylic acids **129** with racemic epoxides or optically active styrene oxide afforded polystyrene-supported γ-substituted α-selenobutyrolactones **130**. Subsequent oxidation-elimination with an excess of 30% H_2O_2 at room temperature afforded 3- and 5-mono; 3,4- and 3,5-di-substituted 2(5)-furanones **131** in high yields and good purities.

Recently, Huang and co-workers prepared polystyrene-supported selenomethyl-phosphonate **132** and polystyrene-supported selenomethyl-sulfonates **134** [81, 82]. These reagents were treated with LDA (or *n*-BuLi) to produce polystyrene-supported α-seleno carbanions (scheme 34), which were reacted with alkyl halides. This was followed by stereo-specific selenoxide syn-elimination to give *E*-vinylphosphonates **133** and *E*-vinylsulfones **135** respectively in high yields and purities.

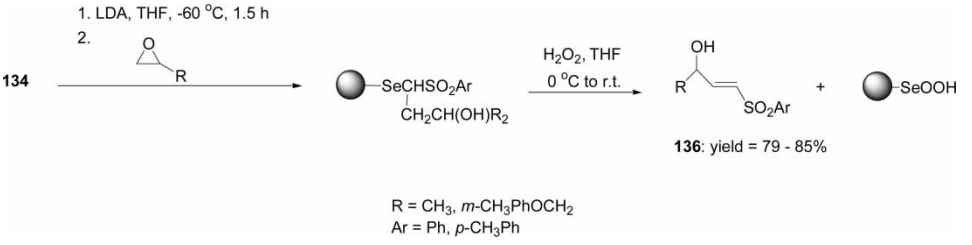


SCHEME 33



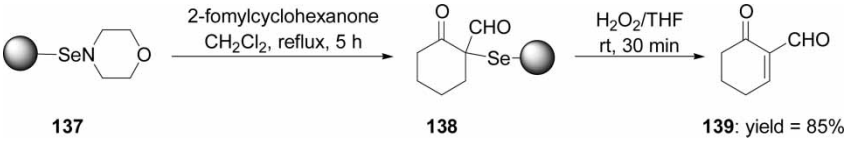
SCHEME 34

In another report, Huang and co-workers demonstrated the utility of the polystyrene-supported selenomethyl-sulfonates **134** with epoxides [83]. Polymer **134** was reacted with LDA and then epoxides followed by oxidation and stereospecific selenoxide syn-elimination, to provide γ-hydroxy-substituted *E*-vinyl sulfones **136** (scheme 35). The polystyrene-supported selenomethyl-sulfonates **136** can be regenerated and reused.



SCHEME 35

Most recently, Huang and co-workers reported a traceless cleavage strategy to prepare unsaturated β-dicarbonyl compounds using polymer-supported 4-(phenylseleno)morpholine [84]. Treatment of resin **137** with α-formylcycloalkanones gave the corresponding β-dicarbonyl selenide resins **138**. Subsequent oxidation-elimination with 30% H_2O_2 at room temperature efficiently afford the corresponding products **139** in good yields and with high purities of crude materials in all cases (scheme 36).

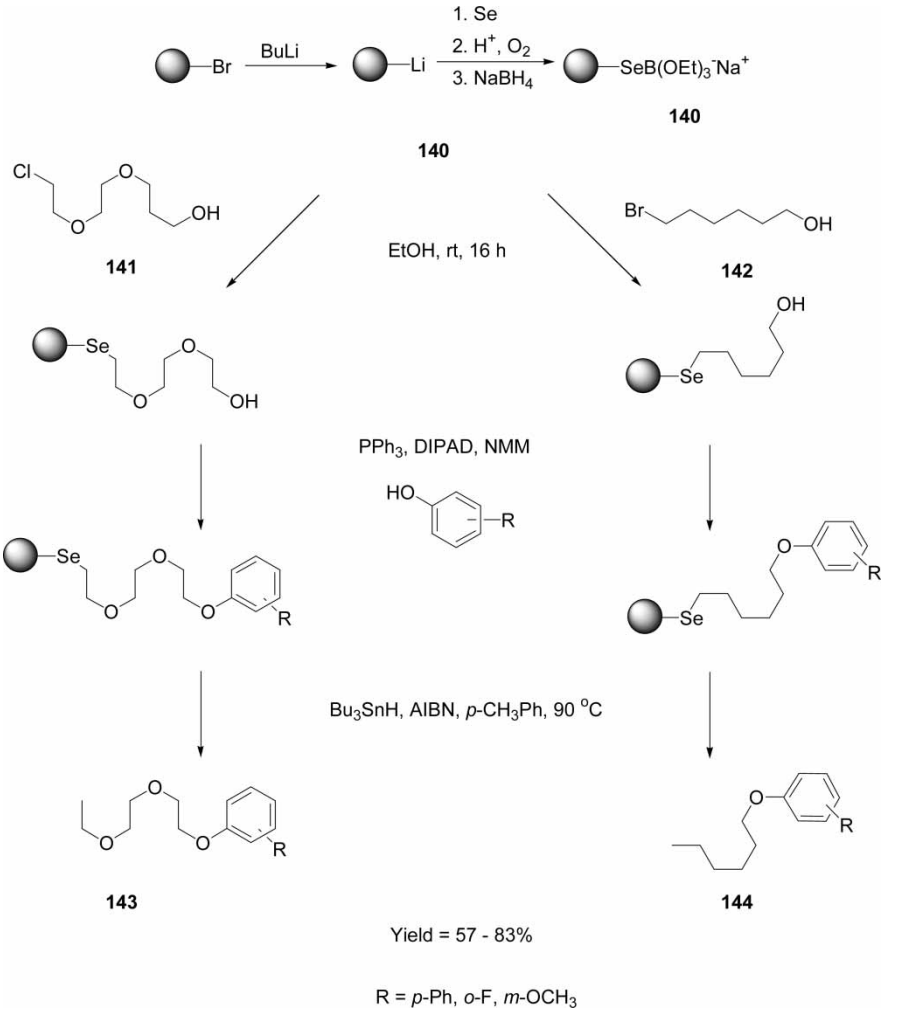


SCHEME 36

3.3 *Reports by other groups*

In an early report, Ruhland *et al.* described the use of polystyrene-bound selenium in a C−H bond forming traceless linking strategy in the solid-phase synthesis of an aryl alkyl ether library [85]. Without the requirement of an auxiliary spacer, the first building blocks **141** and **142** were attached to the polymer **140**, and the final compounds **143** and **144** were cleaved selectively under mild conditions (scheme 37). No contamination of the isolated products with toxic substances such as selenium and organostannyl compounds was reported. The selenium atom remained immobilized during the entire synthesis, and in the cleavage step, tributylstannyl phenyl selenide remained attached to the resin. The alkyl aryl ethers were obtained as single, discrete compounds in good yield and high purity after purification by solid-phase extraction.

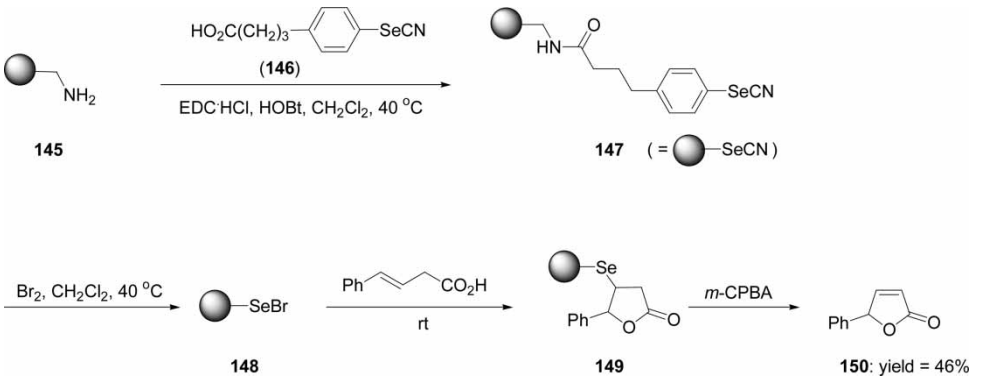
In a report by Fujita *et al.*, the use of polymer-supported selenocyanates in oxyselenenylation-deselenenylation reactions in PSOS was described [86]. Polymer-supported selenocyanates were readily prepared from substituted polystyrene resins such as Merrifield resin or aminomethyl-polystyrene (scheme 38). Aminomethyl polystyrene resin



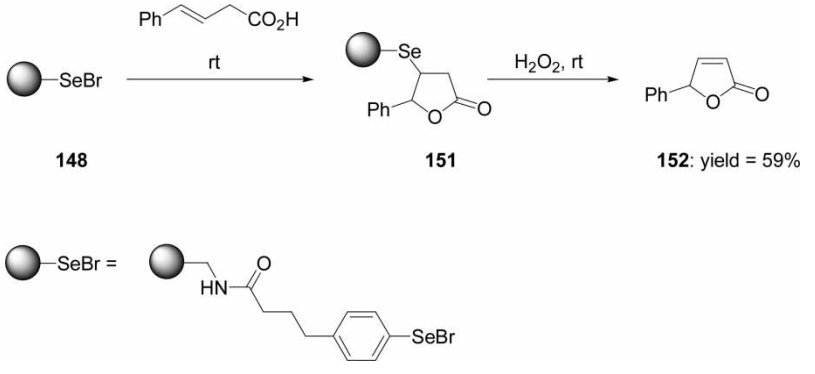
SCHEME 37

145 and arylselenocyanate **146** and were combined in the presence of EDC·HCl and HOBt in CH_2Cl_2, to afford arylselenocyanate **147** in nearly quantitative yield. The corresponding selenium bromide **148** was easily prepared by the addition of bromine. Subsequent solid-phase selenolatonization of (*E*)-4-phenyl-3-butenoic acid proceeded in CH_2Cl_2 to give polymer **149**. Oxidation of **149** with *m*-CPBA afforded the deselenenation product **150** in moderate yield.

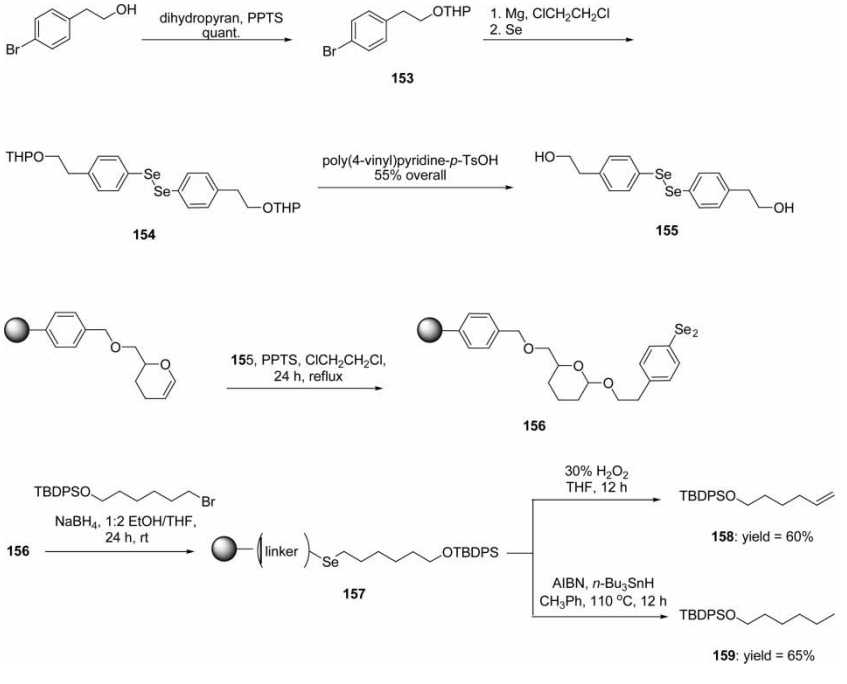
In another more recent report, Fujita and co-workers demonstrated the same chemistry in water [87]. Polymer-bound arylselenium bromide **148**, prepared as before from aminomethyl polystyrene resin, was reacted with (*E*)-styrylacetic acid in water at room temperature for 15 h to afford selenolactone **151** (scheme 39). Subsequent oxidation of **152** with 30% H_2O_2 in water at room temperature for 15 h followed by the usual workup and purification afforded deselenenylation product **152** in moderate yield, which was higher than observed previously when CH_2Cl_2 was the solvent.



SCHEME 38



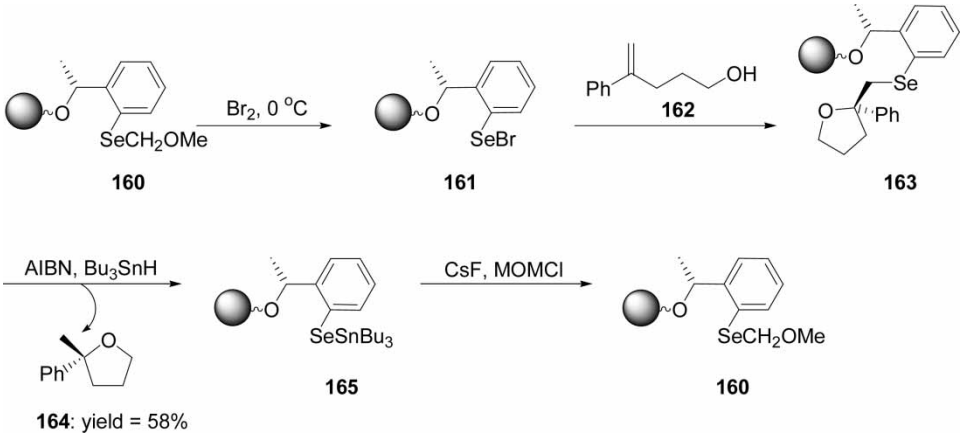
SCHEME 39



SCHEME 40

Kulkarni and co-workers reported another selenide linker in 2001 [88]. Their linker was prepared from 4-bromophenethyl alcohol in three steps (scheme 40). The alcohol was protected with a tetrahydropyranyl (THP) group to form **153**, which was subjected to Grignard reaction with selenium to afford diselenide **154**. This was then deprotected using polymer-supported pyridinium *p*-toluenesulfonate to afford diselenide diol **155** in good overall yield, which was subsequently immobilized on THP resin to provide polymer-bound diselenide **156**. The selenide anion generated by reductive Se−Se bond cleavage of **156** was trapped by suitable electrophiles. For example, addition of resin **156** to 1-bromo-6-[(*tert*-butyldiphenylsilyl)oxy]hexane afforded immobilized selenide **157**. Alkanes **158** and alkenes **159** were obtained under reductive and oxidative conditions, respectively.

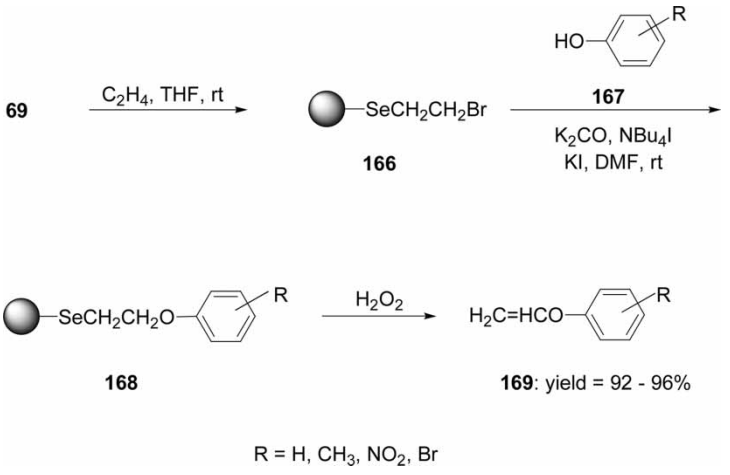
In 2001, Wirth and Uehlin reported the use of polymer-bound chiral electrophilic selenium reagents in stereoselective selenenylation reactions of various alkenes [89, 90]. For example, they illustrated that polymer-bound chiral electrophilic selenium reagent **161** could be successfully used for the reaction with alkenes such as **162** (scheme 41). After radical cleavage of the C−S bond of product **163**, the stereoselectively formed tetrahydrofuran derivative **164** and selenenylstannane **165** were obtained. Furthermore, they established that regeneration of regent **160** could be achieved by treatment of **165** with CsF and MOMCl.



SCHEME 41

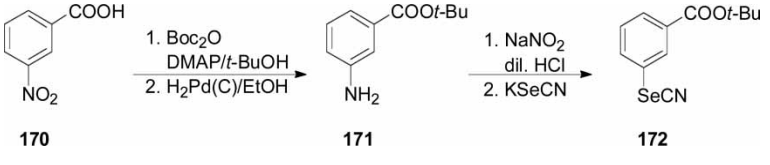
Sheng and co-workers reported a simple and efficient procedure for the solid-phase synthesis of aryl vinyl ethers using polymer-supported β-bromoethyl selenide **166** in a traceless linker strategy [91]. Resin **166** was prepared in nearly quantitative yield from reaction of polymer-bound selenium bromide **69** in THF at room temperature with an excess of anhydrous ethene (scheme 42). This was then alkylated with a variety of phenols **167** in the presence of a base, to form **168**. Oxidation-elimination of **168** was very rapid and efficient with an excess of 30% H_2O_2 at room temperature to afford the corresponding aryl vinyl ethers **169** in good yields and high purities in all cases.

In 2003, Nakamura *et al.* developed a linker possessing and a masked carboxylic acid for the solid-phase synthesis of dehydroalanine-containing peptides [92]. Synthesis of **172** started with *ortho*-nitrobenzoic acid, which was converted into the corresponding *t*-butyl ester **171** (scheme 43). The nitro group of **171** was reduced to the corresponding aniline, followed



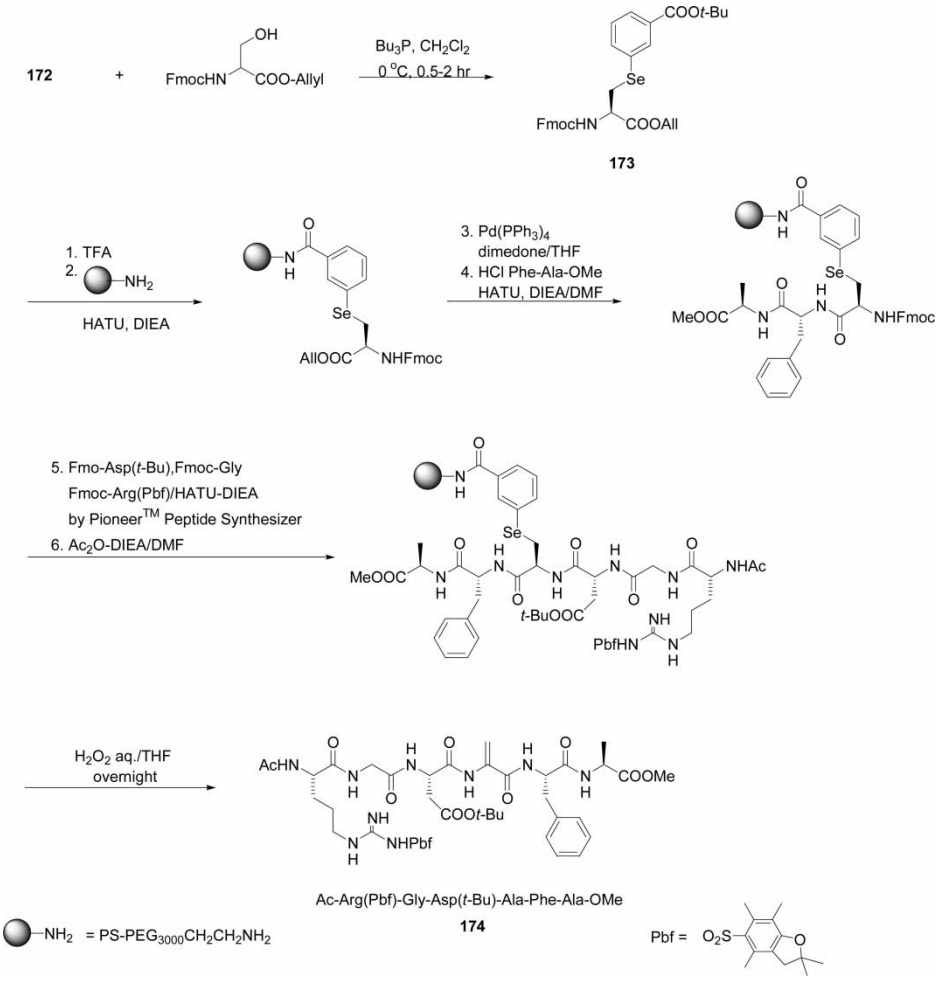
SCHEME 42

by subsequent Sandmeyer reaction with potassium selenocyanate in aqueous media to afford **172**. Solid-phase synthesis using **172** was demonstrated by the synthesis of a RGD-conjugated dehydroalanine-containing peptide (scheme 44). After deprotection of selenide **173** with 95% TFA, the resultant benzoic acid was immobilized to a commercially available aminomethyl resin. After a series of manual (C-terminal) and automatic (N-terminal) procedures, the desired RGD-conjugated dehydroalanine-containing peptide **174** was obtained by oxidative cleavage with H_2O_2 in THF from the resin via a selenoxide intermediate.



SCHEME 43

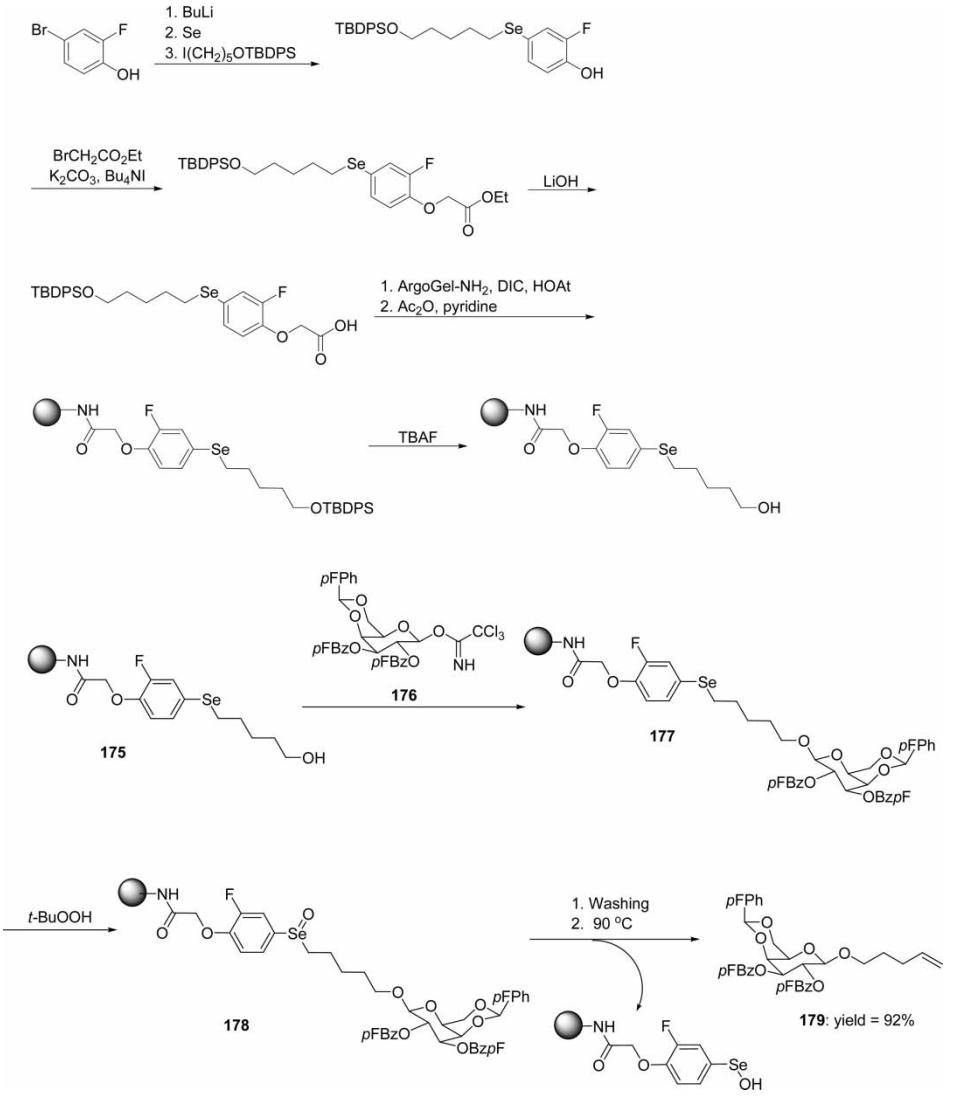
Recently, Elofsson *et al.* established an efficient route for the preparation of a fluorine-labeled selenide linker [93]. Incorporation of the fluorine group in the linker allowed for reactions to be monitored by gel-phase ^{19}F NMR and the versatility of the linker for installing terminal isolated olefins was demonstrated by solid-phase synthesis of a pentenyl glycoside (scheme 45). The primary hydroxyl group of the linker could be glycosylated with glycosyl trichloroacetimidate **176** or the corresponding glycosyl fluoride to afford **177**. After oxidation with *t*-BuOOH, the selenoxide resin **178** was stable at room temperature, but decomposed when it was subjected to heat. *N*-Pentenyl glycoside **179** was released and isolated in excellent yield and purity without purification via this mild, reagentless cleavage reaction.



SCHEME 44

4. Conclusion

In summary, as PSOS becomes a more widely adopted technology in the area of medicinal chemistry and other applications requiring large numbers of relatively pure compounds, the need for new linker groups becomes more evident. The unique chemistry of sulfur and selenium functional groups allows linker groups based on them to be used in the preparation of a diverse range of compounds. Such strategies benefit from following the known chemistry of these functional groups while reducing any associated odor or toxicity issues. Thus is expected that more of these sulfur- and selenium-based linkers will be developed that take advantage of the full range of chemistry that sulfur and selenium functional groups undergo in small molecules, and in the future they will become more widely used for generating collections of complex molecules [94–98].



SCHEME 45

Acknowledgements

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