

SULFUR AND SELENIUM SAFETY CATCH LINKERS

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INTRODUCTION

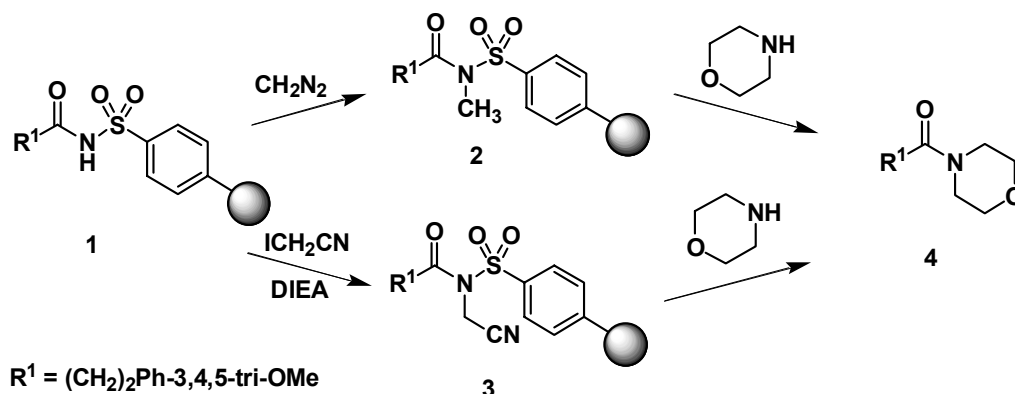
As the demand for libraries of small organic molecules increases, improved methods for the solid phase construction of those libraries are required. Choosing a linker is a key consideration in a solid phase synthesis plan because the properties of the linker dictate the chemistry available. Therefore, a linker that is inert to the reaction conditions used to prepare the target compounds but that allows release of the synthesized products under mild conditions is desirable. The term “safety catch principle” was introduced by Kenner in 1971 to describe a strategy that allows a linker to remain stable until it is activated for cleavage by a chemical modification.¹ Currently, the term safety catch is applied to a linker that is cleaved by performing two different reactions rather than the usual single step. Sulfur and selenium linkers are particularly promising because the relatively weak carbon-sulfur and carbon-selenium bonds can be cleaved under a number of reaction conditions.^{2,3} Additionally, sulfur and selenium can be oxidized to sulfoxides and selenoxides making them good candidates for safety catch linkers. Reported herein is recent progress in the development of sulfur and selenium safety catch linkers.

SULFUR SAFETY CATCH LINKERS

Kenner Safety Catch Linker

Kenner reported the first safety catch linker that utilized a *N*-acylsulfonamide linkage for synthesis of primary amides, hydrazones and carboxylic acids (Scheme 1).¹ This linker was stable to both basic and strongly nucleophilic conditions.⁴ Activation of the acylsulfonamide **1** by diazomethane alkylation allowed for cleavage through nucleophilic displacement. The Kenner linker suffered from poor loading efficiencies, racemization in the loading step, and poor reactivity of the activated group requiring excess reagent to be used.⁵ Backes and Ellman increased the reactivity of the linker to nucleophilic displacement by activating with a haloacetonitrile rather than diazomethane.⁴ The cyanomethyl derivative **3** is > 150-fold more reactive to nucleophilic displacement and is rapidly cleaved using limiting amounts of amines including sterically hindered amines. For example, cleavage of acylsulfonamide **3** with *tert*-butylamine and aniline provided the amide products in 92% and 96% yield, respectively.

Scheme 1. Kenner Safety Catch Linker



Attempting to increase the loading efficiencies of amino acids onto the linker, Backes and Ellman produced an alkylsulfonamide linker (Figure 1). By employing a alkylsulfonamide linker which was not only slightly more nucleophilic than the acylsulfonamide linker but also situated the resin environment farther from the reactive site, they were able to load all twenty amino acids with minimal racemization and high loading efficiencies.⁶ For example, treatment of the resin with sterically hindered Fmoc-Ile-OH provided a loading efficiency of 80% with < 1% racemization. In another approach, Ingenito and coworkers employed the alkanesulfonamide safety catch linker to synthesize C-terminal thioesters.⁷ Previous linkers required Boc (*t*-butoxycarbonyl) as the *N*-protecting group because the thioester linkage attached to solid support was unstable to the piperidine used in removal of Fmoc (9-fluorenylmethoxycarbonyl) groups. Since the alkanesulfonamide linker was compatible with both Fmoc and Boc methods, the thioesters could efficiently be prepared using a combination of the two strategies.

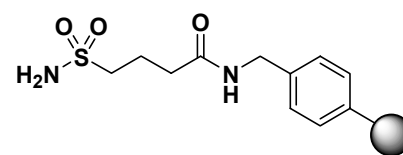
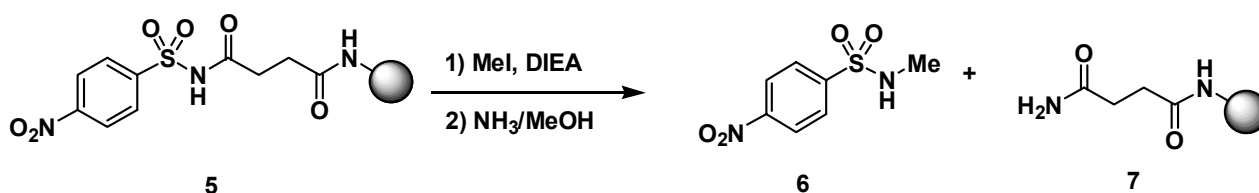


Figure 1. Alkanesulfonamide Linker.

Traditional Kenner safety catch strategies released the products as acids, amides, thioesters, or peptides and left the sulfonamide linker bound to the resin. Attempting to find a solid-phase method to prepare sulfonamides, Maclean and coworkers produced a “reverse Kenner” linker where, upon cleavage, the acyl component remained attached to the solid support while the sulfonamide was released (Scheme 2).⁸ As shown in Scheme 2, *N*-methylation of the alkanesulfonamide resin **5** with methyl

Scheme 2. Reverse Kenner Safety Catch Linker.



iodide followed by cleavage with methanolic ammonia produced the sulfonamide **6** and the resin bound amide **7**.

Thiopyrimidine Safety Catch Linkers

Further product diversification can be created by employing a linker that is capable of being cleaved by a variety of nucleophiles. Using a multidirectional cleavage procedure, Obrecht and coworkers reported the synthesis of substituted pyrimidines **10** through the cyclocondensation reaction of resin-bound salt **8** with acetylenic ketones (Scheme 3).⁹ Activation of the thiopyrimidine carboxylic acids **9** by oxidation produced a sulfone that was displaced by various heterocyclic amines and an azide to produce the desired thiopyrimidine-carboxylic acids **10** in 85-90% yields with purities greater than 90%. Additional diversity was created by subjecting the resin-bound pyrimidine-carboxylic acids **9** to a Ugi four-component reaction.¹⁰ Condensation of **9** with amines R^2NH_2 , aldehydes R^3CHO , and isonitriles R^4NCO followed by activation and cleavage provided the Ugi reaction products **12** in good yield and purity (Table 1).

Scheme 3. Thiopyrimidine Linker.

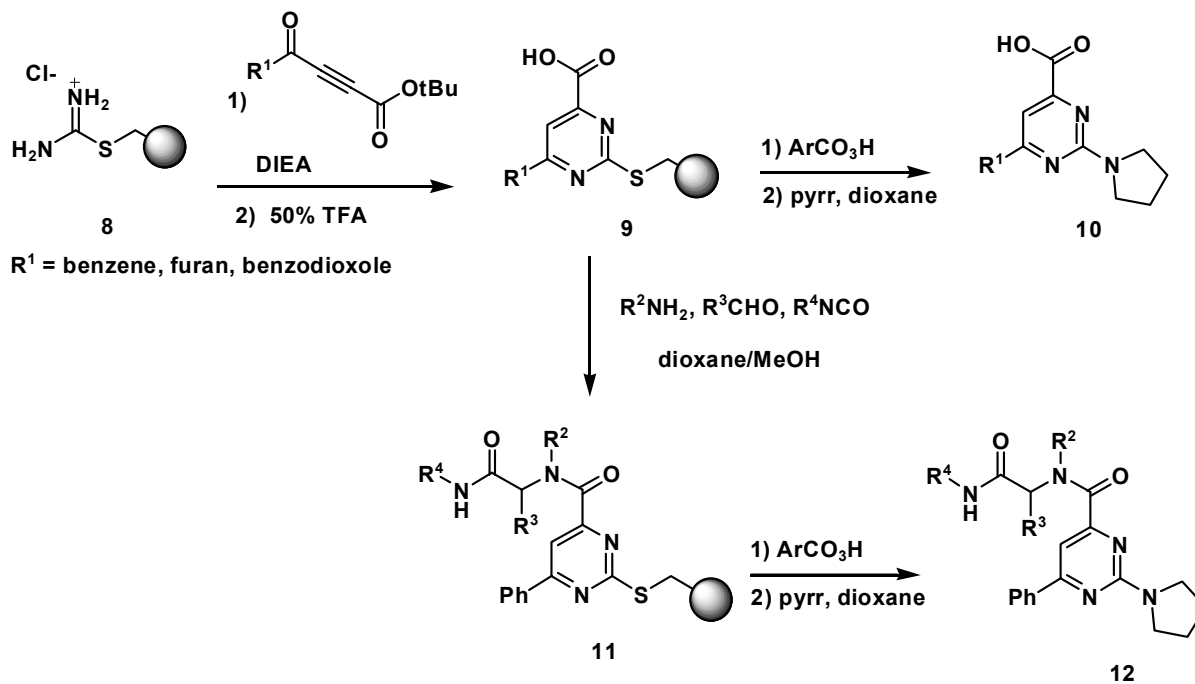


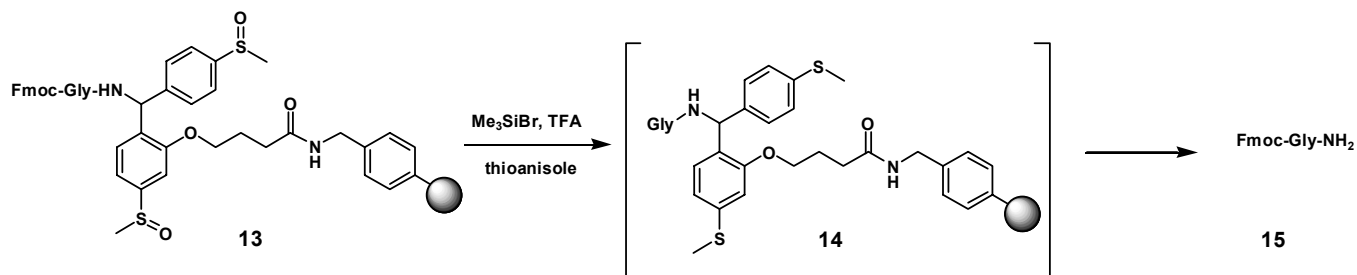
Table 1. Pyrimidine derivatives from Ugi reaction (see Scheme 3).

Entry	R^2	R^3	R^4	Yield (%)	Purity (%)
1	4-(MeO) C_6H_4	Pr	Cy	86	95
2	Cy	i-Pr	Cy	72	98
3	Pr	i-Pr	Cy	65	90
4	Bn	i-Pr	Bu	77	91
5	4-(MeO) C_6H_4	i-Pr	Cy	87	94

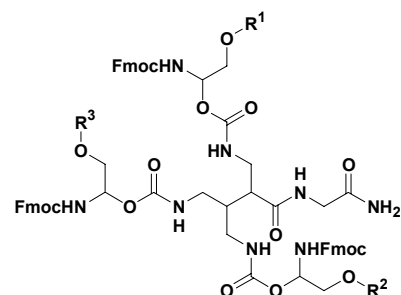
Safety Catch Acid-labile (SCAL) Linker

Desiring to extend the orthogonality in solid phase synthesis of C-terminal peptide amides, Lebl reported the preparation of a safety catch acid-labile (SCAL) linker that was activated by reduction of the sulfoxide (Scheme 4).¹¹ Sulfoxide **13** was stable to conditions used for removal of Fmoc and Boc groups. Upon treatment of **13** with Me₃SiBr/TFA/thioanisole, reductive acidolysis proceeded through the intermediate sulfide **14** to afford the peptide amide **15**.¹²

Scheme 4. Safety Catch Acid-labile Linker.

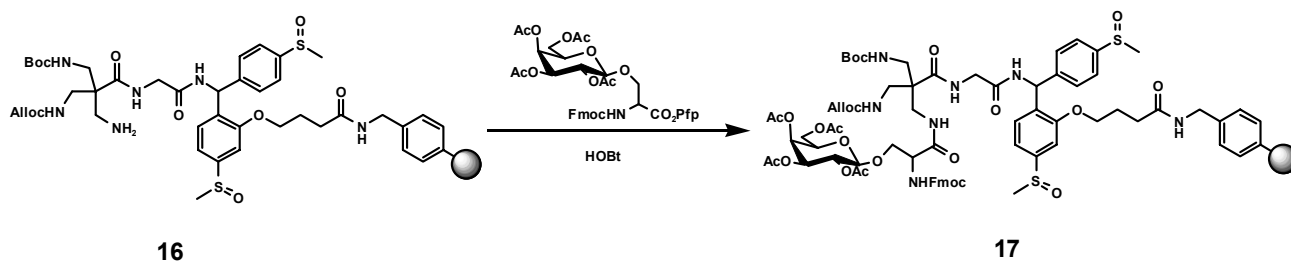


Katajisto and coworkers employed the SCAL linker to construct glycoclusters (Scheme 5).¹³ Attachment of the SCAL linker to a branching unit containing Boc, Fmoc, and Alloc (allyloxycarbonyl) protection groups followed by removal of the Fmoc protecting group afforded the resin-bound linker **16**. The free amino group was coupled to an activated *O*-glycosylserine building block to produce the protected solid support scaffold **17**. Subsequently, the Boc group on the branching unit was removed and the second galactosylated serine building block was coupled. Finally, the Alloc group was removed and the third glycosylated serine building block was coupled to afford the resin-bound glycocluster. Activation with HBr in AcOH followed by cleavage using 50% TFA afforded the protected glycocluster in 10% overall yield after HPLC purification (Figure 2). Extension of this procedure was demonstrated



R¹, R², R³ = β -Gal, β -Glc, α -Man, or β -Rib
Figure 2. Protected Glycoclusters.

Scheme 5. Construction of Glycoclusters.

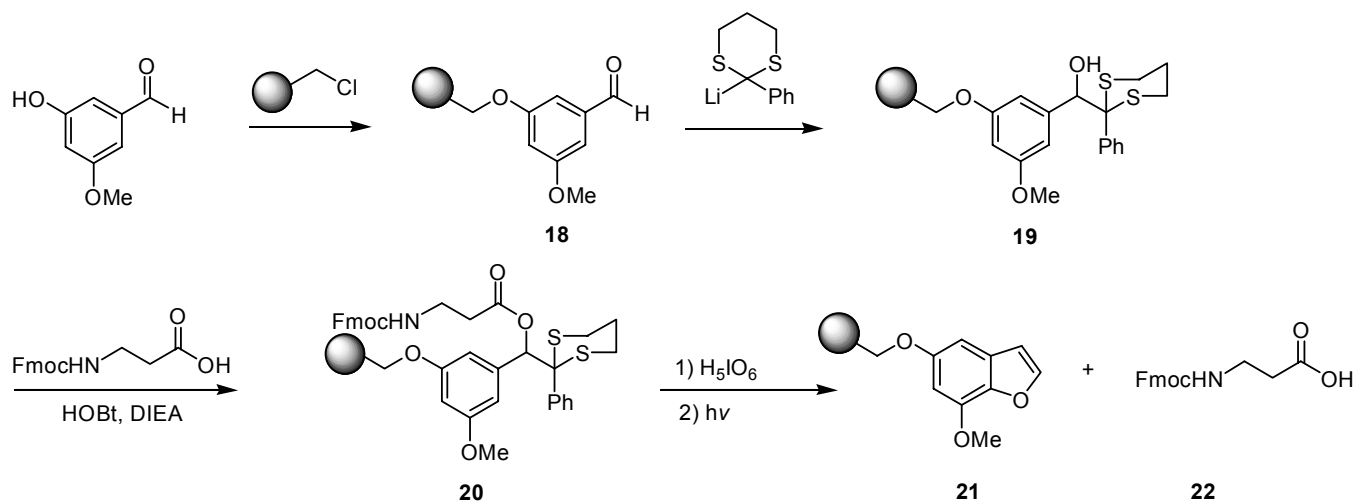


by preparing three other glycoclusters by coupling each with three of four different *trans*-1,2-glycopyranosyl peracetates (β -Gal, β -Glc, α -Man, β -Rib).

Dithiane-protected Benzoin Photolabile Safety Catch (BPSC) Linker

Photocleavable linkers offer a mild and broadly orthogonal method of cleavage that occurs under neutral conditions. Using a dithiane-protected 3'-methoxy-benzoin linker in solution, Chan and coworkers showed that the photoinitiated cyclization of dimethoxybenzoin is very rapid, with a rate constant on the order of 10^{10} s^{-1} .¹⁴ This method released peptide and easily detectable, nonreactive benzofuran products with high quantum yields. Encouraged by these results, Balasubramanian and coworkers employed the dithiane-protected benzoin as a safety-catch linker for solid phase synthesis of Fmoc-protected amino acids (Scheme 6).¹⁵ Reaction of the resin-bound aldehyde **18** with lithiated 2-phenyl-1,3-dithiane produced the dithiane derivative **19**. After loading the Fmoc-protected amino acid, the resin-bound substrate **20** was capable of undergoing further reactions.¹⁶ Activation of **20** with H_5IO_6 followed by photolytic cleavage released the Fmoc-protected amino acid **21** and the resin-bound benzofuran **22**.

Scheme 6. Photocleavable safety catch linker.

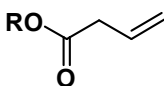
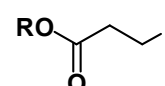
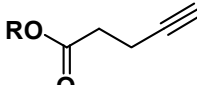
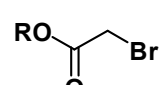
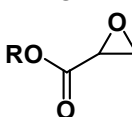
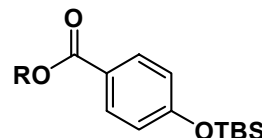
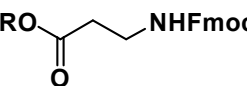


Attempting to improve the loading of sterically hindered substrates, Balasubramanian and coworkers developed a method of preloading the linker to the substrate in solution prior to resin attachment.¹⁷ As an example, efforts to load Fmoc-valine onto the solid supported linker resulted in a yield of only 65% in contrast to a 90% yield obtained by preloading the Fmoc-valine in solution prior to resin attachment. Therefore, the problem of loading hindered substrates was probably attributable to the resin environment rather than the BPSC linker. Since the preloading strategy required nine steps and

afforded lower overall yields, it is questionable whether the strategy offers an improvement over the direct loading protocol.

Using a dual-linker analytical construct, Balasubramanian and coworkers tested the stability of the linker.¹⁸ Results revealed that the benzoin linker is stable under a wide range of reaction conditions including NaBH₄ reduction, H₂O₂ oxidation, alkylation, basic and moderately acidic conditions, amide and ester coupling, and Suzuki and Wittig reagents. The stability of functionalities toward the periodic acid treatment necessary for removal of the dithiane safety catch was also tested. Though periodic acid reacts with a wide range of organic compounds, the conditions used for removal of the safety catch are mild using only 2 equivalents of H₅IO₆ in dry THF for less than 30 minutes. Olefin, amine and epoxide functionalities loaded onto the dual-linker construct were shown to be stable to the oxidation conditions used for removal of the safety catch linker (Table 2). The *tert*-butyldimethylsilyl (TBS) protective group was the only group to be cleaved.

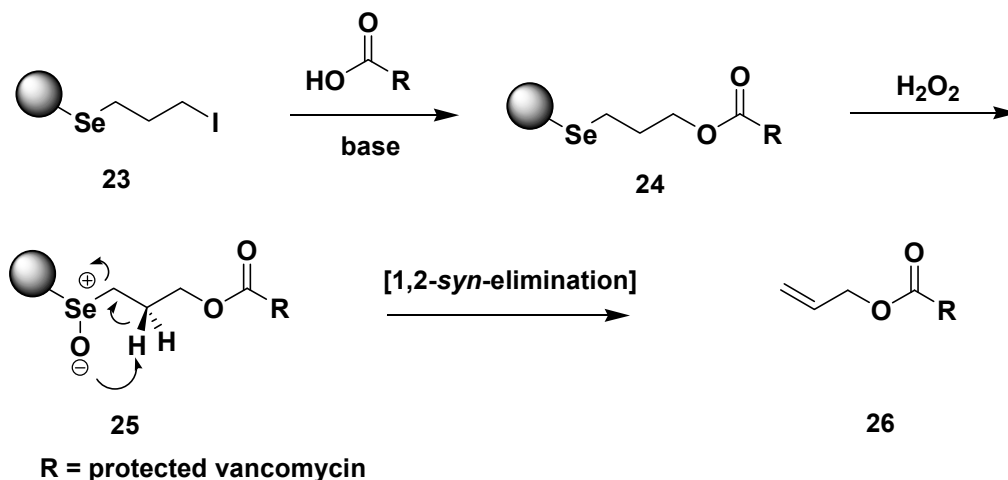
Table 2. Functional group integrity under H₅IO₆ reduction.

Acid	Functional Group Integrity	Acid	Functional Group Integrity
	yes		yes
	yes		yes
	yes		no
	yes		

SELENIUM SAFETY CATCH LINKER

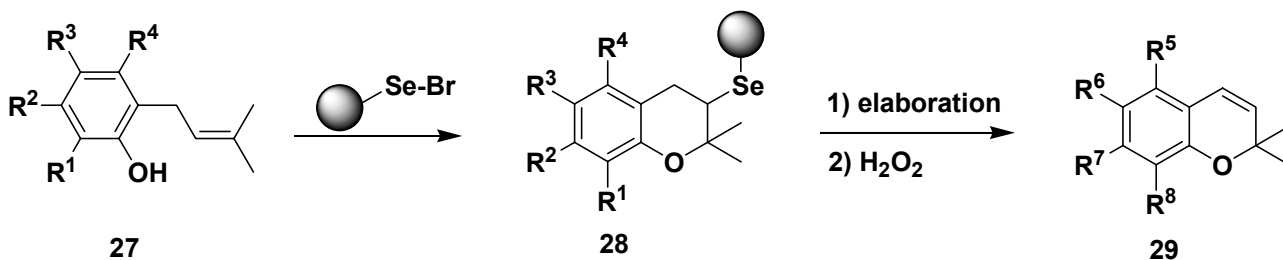
Selenium and sulfur share similar properties; however, the use of selenium reagents is often preferable to sulfur because not only does the oxidation of selenides proceed more quickly than that of sulfides but also the C-Se bond is weaker than the C-S bond.² During their studies on the semisynthesis of vancomycin, Nicolaou and coworkers found that a selenoether resin could be used to mask an allylic ester (Scheme 7).¹⁹ Reaction of the free carboxylic acid with resin **23** afforded the resin-bound selenopropyl ester **24**.²⁰ Oxidation to the selenoxide **25** followed by *syn*-elimination released the *O*-Alloc derivative **26** from the resin.

Scheme 7. Selenium safety catch linker



Capitalizing on the ability to load the selenoether resin through a cyclization reaction, Nicolaou and coworkers utilized this linking strategy to synthesize a 10,000 membered library based on the 2,2-dimethylbenzopyran scaffold (Scheme 8).²¹ The cyclized derivative **28** was further elaborated through reactions including annulations, Knoevenagel condensations, Pd-catalyzed cross couplings, reductive aminations, Mitsunobu inversions, glycosidations, and organometallic additions to produce the modified resin-bound benzopyran **28**. Benzopyran **28** was oxidized and cleaved to provide several benzopyran-containing products **29** including chalcones, pyranocoumarins, chromene glycosides, stilbenoids, *N*-heterocycles, and pyranoflavones.²²

Scheme 8. Solid-Phase Loading, Elaboration and Cleavage of 2,2-Dimethylbenzopyran.



R¹ to R⁴ = H, OH, OMe, Br, CH₃, I, CN, NO₂, CH₃CO, HCO, COOH

CONCLUSION

Sulfur and selenium safety catch linkers are viable alternatives to other linker strategies for attachment of small organic molecules onto solid phase supports. The efficient linker attachment and small molecule loading protocols coupled with cleavage via two different reactions are key factors in the development of safety catch linkers for solid phase synthesis. The sulfur and selenium linkers tolerate a

wide range of reaction conditions and can be activated using various methods demonstrating their potential for applicability in a variety of synthetic protocols. One advantage of these linkers is that compounds can be synthesized with additional functionality introduced through the cleavage step. The applicability of the selenium and sulfur linkers has been demonstrated by the construction of small libraries and a large benzopyran library. These linkers should find broad utility in solid phase and combinatorial synthesis due to their versatility and ease of use.

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