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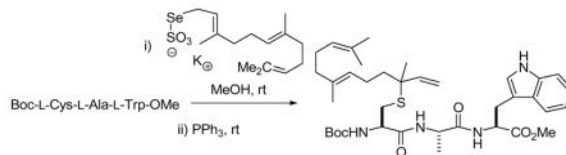
Allylic Selenosulfide Rearrangement: A Method for Chemical Ligation to Cysteine and Other Thiols

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Abstract

Alkylation of potassium selenosulfate with allylic halides gives *Se*-allyl seleno Bunte salts. On reaction with thiols at room temperature these afford mixed dialkyl selenosulfides, which undergo 2,3-sigmatropic rearrangement with loss of selenium, either spontaneously or with assistance by triphenylphosphine, thereby providing mixed dialkyl sulfides and a new permanent chemical ligation method. The process is illustrated through the ligation of cysteine containing tripeptides and by the allylation of 1-thioglucose tetraacetate.



The development of methods for the chemical ligation of small molecules to peptides and proteins, for conjoining two proteins, and for the attachment of oligosaccharides to peptides and proteins is a current frontier in chemical biology.¹ One established ligation method involves the formation of mixed disulfide linkages,² various modifications of which have recently been applied to the synthesis of glycopeptides and proteins.³ The disulfide ligation is especially attractive in conjunction with native peptide ligation, however, the ease of disulfide exchange renders the method impermanent.⁴ We report preliminary results on the development of a new method of chemical ligation based on the facile formation of mixed selenosulfides, which are then rendered permanent by a sigmatropic rearrangement with loss of selenium.

Allylic disulfides are in equilibrium with allylic thiosulfoxides, by virtue of a 2,3-sigmatropic rearrangement.⁵ The equilibrium very strongly favors the allylic disulfide and is only revealed when the reaction is driven in the forward direction, either by a further rearrangement, or by the addition of a thiophilic reagent, typically a phosphine. At 60 °C in benzene rate constants for the rearrangement with transfer of sulfur to triphenyl phosphine were found to range from 0.7 – 190 × 10⁻⁴ s⁻¹ depending on the substituent pattern.^{5a}

Allylic diselenides on the other hand undergo the analogous rearrangement at room temperature in a matter of hours.^{6,7}

We hypothesized that *Se*-allyl selenosulfides **2** would undergo a similar 2,3-sigmatropic rearrangement at room temperature and that the weakness of the Se-S bond in the selenosulfoxide product **3** would result in the facile loss of selenium, thereby driving the reaction even in the absence of a phosphine. We further hypothesized that the requisite *Se*-allylic selenosulfides could be readily accessed at room temperature from simple *Se*-allyl seleno Bunte salts **1**, as was known for *Se*-alkyl seleno Bunte salts,⁸ and that the combination of these two processes would provide a convenient new chemical ligation process (Scheme 1).

Reaction of K₂SO₃ with Se powder and, then, allyl bromide gave potassium *Se*-allyl selenosulfate **5** as an orange solid.^{8b,9} Reaction of this *Se*-Bunte salt with primary aliphatic thiols in methanol at room temperature resulted in transfer of the allyl group to sulfur, with loss of selenium (Scheme 1), establishing the validity of the initial hypothesis.

We next examined the attachment of allyl and substituted allyl groups to cysteine derivatives (Table 1). These reactions were conducted in two stages, with formation of the selenosulfide in methanol, and, following filtration on silica gel, triphenylphosphine-promoted deselenylative rearrangement in CDCl₃, all at room temperature. The 2,3-sigmatropic nature of the rearrangement step is unmasked with the formation of the *S*-linalyl cysteine **14** starting from the *Se*-geranyl *Se*-Bunte salt **13**.¹⁰

Functionalization of small cysteine-containing peptides was explored with Boc-(α -OMe)- γ -L-Glu-L-Cys-Gly-OMe, **15**, and with Boc-L-Cys-L-Ala-L-Trp-OMe **16** using a selection of allylic *Se*-Bunte salts (Table 2). These reactions were conducted in methanol at room temperature with filtration of the excess Bunte salt before addition of the phosphine. It is noteworthy that this new cysteine functionalization method is compatible with the indole in tryptophan, and enables the incorporation of the geranyl and farnesyl chains as the transposed linalyl and nerolidyl groups. We have also demonstrated application to a carbohydrate-based thiol **24** (Scheme 3). This rearrangement, which proceeded spontaneously over a period of several days at room temperature, or in a matter of hours on addition of triphenyl phosphine, took place with complete retention of the anomeric stereochemistry.

In summary, we describe a new, permanent chemical ligation method. The method has potential for the attachment of lipids to protein-based thiols, an area of considerable current interest.¹¹ Applications in combinatorial chemistry and for the attachment of a wide variety of groups, including polyethylene glycol¹² and fluoros chains,¹³ and oligosaccharide units to thiols^{3,14} of biological interest, are currently under development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

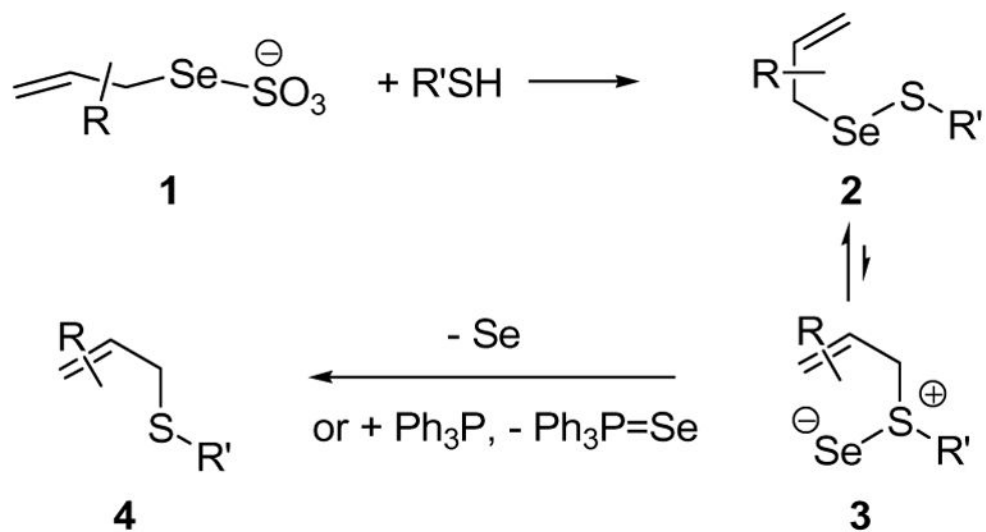
Acknowledgments

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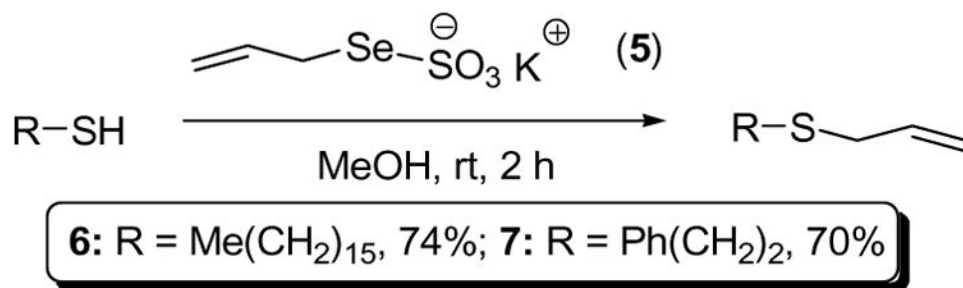
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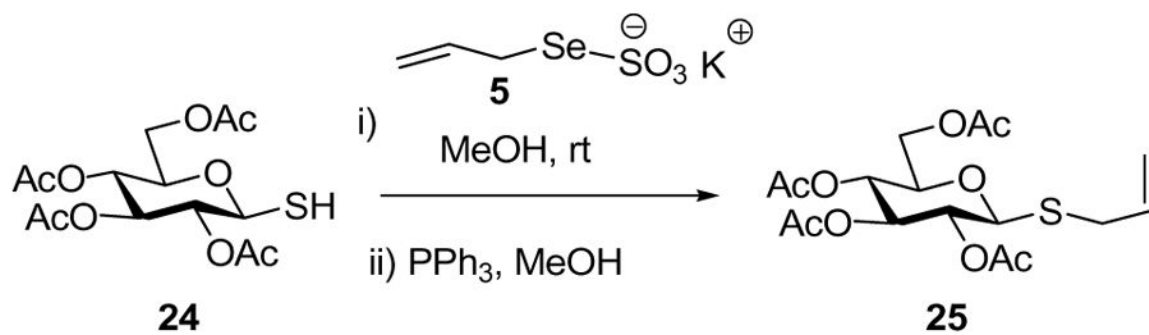
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Scheme 1.
Chemical Ligation via *Se*-Allyl Selenosulfides



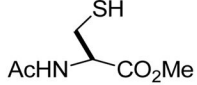
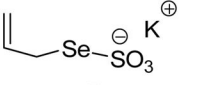
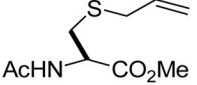
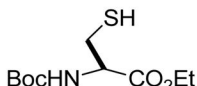
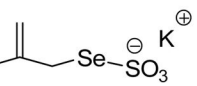
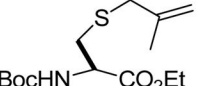
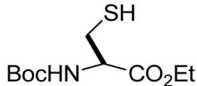
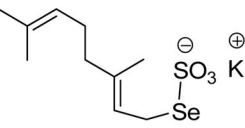
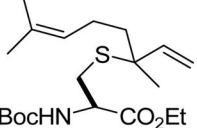
Scheme 2.
Allylation of Simple Thiols



Scheme 3.
Alkylation of an Anomeric Thiol

Table 1

Application to Cysteine Derivatives^{a,b}

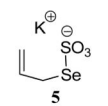
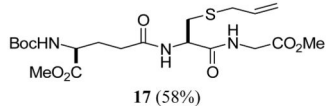
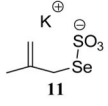
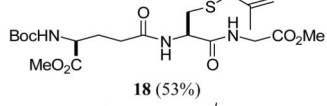
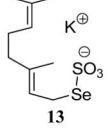
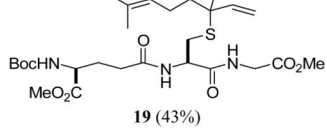
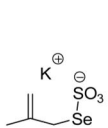
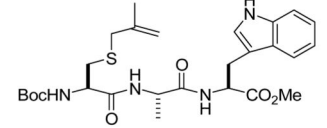
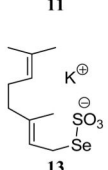
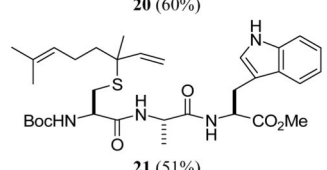
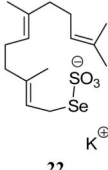
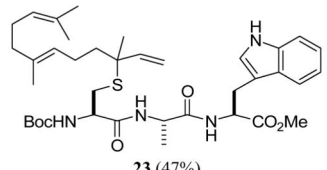
Thiol	Se-Bunte Salt	Product (Yield)
 8	 5	 9 (61%)
 10	 11	 12 (62%)
 10	 13	 14 (46%)

^a: With Se Bunte salt **13**, the first step was conducted in a methanol/CH₂Cl₂ mixture.

^b: Compound **14** was formed as an approximately 1:1 unassigned mixture of diastereomers.

Table 2

Application to Cysteine Containing Tripeptides^a

Peptide	Se-Bunte Salt	Product (Yield)
15		
15		
15		
16		
16		
16		

^a: Compounds **19**, **21**, and **23** were formed as an approximately 1:1 unassigned mixture of diastereomers.