

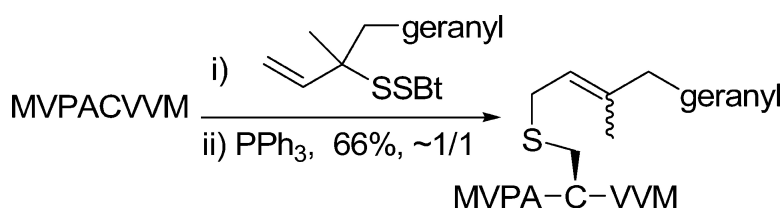
Article

Dechalcogenative Allylic Selenosulfide and Disulfide Rearrangements: Complementary Methods for the Formation of Allylic Sulfides in the Absence of Electrophiles. Scope, Limitations, and Application to the Functionalization of Unprotected Peptides in Aqueous Media

David Crich, Venkataramanan Krishnamurthy, Franck Brebion, Maheswaran Karatholuvhu, Venkataraman Subramanian, and Thomas K. Hutton

J. Am. Chem. Soc., **2007**, 129 (33), 10282-10294 • DOI: 10.1021/ja072969u • Publication Date (Web): 27 July 2007

Downloaded from <http://pubs.acs.org> on February 15, 2009



A = Ala, C = Cys, M = Met, P = Pro, V = Val, Bt = 2-benzothiazolyl

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 9 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



ACS Publications
 High quality. High impact.

Dechalcogenative Allylic Selenosulfide and Disulfide Rearrangements: Complementary Methods for the Formation of Allylic Sulfides in the Absence of Electrophiles. Scope, Limitations, and Application to the Functionalization of Unprotected Peptides in Aqueous Media

David Crich,^{*,†} Venkataramanan Krishnamurthy, Franck Brebion, Maheswaran Karatholuvhu,[†] Venkataraman Subramanian,[†] and Thomas K. Hutton

Contribution from the Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

Received April 27, 2007; E-mail: dcrich@chem.wayne.edu

Abstract: Primary allylic selenosulfates (seleno Bunte salts) and selenocyanates transfer the allylic selenide moiety to thiols giving primary allylic selenosulfides, which undergo rearrangement in the presence of PPh₃ with the loss of selenium to give allylically rearranged allyl alkyl sulfides. This rearrangement may be conducted with prenyl-type selenosulfides to give isoprenyl alkyl sulfides. Alkyl secondary and tertiary allylic disulfides, formed by sulfide transfer from allylic heteroaryl disulfides to thiols, undergo desulfurative allylic rearrangement on treatment with PPh₃ in methanolic acetonitrile at room temperature. With nerolidyl alkyl disulfides this rearrangement provides an electrophile-free method for the introduction of the farnesyl chain onto thiols. Both rearrangements are compatible with the full range of functionality found in the proteinogenic amino acids, and it is demonstrated that the desulfurative rearrangement functions in aqueous media, enabling the derivatization of unprotected peptides. It is also demonstrated that the allylic disulfide rearrangement can be induced in the absence of phosphine at room temperature by treatment with piperidine, or simply by refluxing in methanol. Under these latter conditions the reaction is also applicable to allyl aryl disulfides, providing allylically rearranged allyl aryl sulfides in good yields.

The development of methods for the functionalization of biopolymers, especially peptides and proteins, under the mildest possible conditions, dubbed ligation, is a current frontier in organic chemistry.^{1–16} High chemoselectivity, stability, and compatibility with protic solvents, and even aqueous media, are requirements for such ligations.

Thiols, and in particular cysteine residues, have proven popular targets for chemoselective ligation.^{1,2,17} Native chemical

ligation (NCL) for the synthesis of peptides and proteins, and its enzyme-promoted biochemical equivalent, expressed protein ligation,^{18–21} is one such reaction that takes advantage of the sulfhydryl group and which uses it to great advantage in the highly chemoselective formation of amide bonds in aqueous solution.^{10,21–31} Another thiol-based method, the selective formation of mixed disulfides, is both one of the oldest and most enduring of ligation methods.^{1,2,32–38} The mildness of the

[†] Current address: Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202.

- (1) Hermanson, G. T. *Bioconjugate Techniques*; Academic Press: San Diego, 1996.
- (2) Lundblad, R. L. *Chemical Reagents for Protein Modification*, 3 ed.; CRC Press: Boca Raton, 2005.
- (3) van Swieten, P. F.; Leeuwenburgh, M. F.; Kessler, B. M.; Overkleeft, H. S. *Org. Biomol. Chem.* **2005**, *3*, 20–27.
- (4) Peri, F.; Nicotra, F. *Chem. Commun.* **2004**, 623–627.
- (5) Pratt, M. R.; Bertozzi, C. R. *Chem. Soc. Rev.* **2005**, *34*, 58–68.
- (6) Prescher, J. A.; Dube, D. H.; Bertozzi, C. R. *Nature* **2004**, *430*, 873–877.
- (7) Hang, H. C.; Bertozzi, C. R. *Acc. Chem. Res.* **2001**, *34*, 727–736.
- (8) Nilsson, B. L.; Hondal, R. J.; Soellner, M. B.; Raines, R. T. *J. Am. Chem. Soc.* **2003**, *125*, 5268–5269.
- (9) Bode, J. W. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765–775.
- (10) Nilsson, B. L.; Soellner, M. B.; Raines, R. T. *Ann. Rev. Biophys. Biomol. Struct.* **2005**, *34*, 91–118.
- (11) Kalia, J.; Raines, R. T. *Chem. Biol. Chem.* **2006**, *7*, 1376–1383.
- (12) Lin, H.; Walsh, C. T. *J. Am. Chem. Soc.* **2004**, *126*, 13998–14003.
- (13) Langenhan, J. M.; Thorson, J. S. *Curr. Org. Synth.* **2005**, *2*, 59–81.
- (14) Agard, N. J.; Baskin, J. M.; Prescher, J. A.; Lo, A.; Bertozzi, C. R. *ACS Chem. Biol.* **2006**, *1*, 644–648.
- (15) Köhn, M.; Breinbauer, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3106–3116.
- (16) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
- (17) Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160–187.

- (18) Muir, T. W.; Sondhi, D.; Cole, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 6705.
- (19) Noren, C. J.; Wang, J. M.; Perler, F. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 450.
- (20) Muralidharan, V.; Muir, T. W. *Nat. Methods* **2006**, *3*, 429.
- (21) Coltart, D. M. *Tetrahedron* **2000**, *56*, 3449–3491.
- (22) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. H. *Science* **1994**, *266*, 776–779.
- (23) Dawson, P. E.; Kent, S. B. H. *Ann. Rev. Biochem.* **2000**, *69*, 923–960.
- (24) Yeo, D. S. Y.; Srinivasan, R.; Chen, G. Y. J.; Yao, S. Q. *Chem. Eur. J.* **2004**, *10*, 4664–4672.
- (25) Johnson, E. C. B.; Kent, S. B. H. *J. Am. Chem. Soc.* **2006**, *128*, 6640–6646.
- (26) Brik, A.; Ficht, S.; Yang, Y.-Y.; Bennett, C. S.; Wong, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 15026–15033.
- (27) Liu, L.; Hong, Z.-Y.; Wong, C.-H. *Chem. Biol. Chem.* **2006**, *7*, 429–432.
- (28) Hondal, R. J.; Nilsson, B. L.; Raines, R. T. *J. Am. Chem. Soc.* **2001**, *123*, 5140–5141.
- (29) Clive, D. L. J.; Hisaindee, S.; Coltart, D. M. *J. Org. Chem.* **2003**, *68*, 9247–9254.
- (30) Tchertchian, S.; Hartley, O.; Botti, P. *J. Org. Chem.* **2004**, *69*, 9208–9214.
- (31) Wu, B.; Chen, J.; Warren, J. D.; Chen, G.; Hua, Z.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4116–4125.
- (32) Kenyon, G. L.; Bruce, T. W. *Methods Enzymol.* **1977**, *47*, 407–430.
- (33) Wynn, R.; Richards, F. M. *Methods Enzymol.* **1995**, *251*, 351–356.
- (34) Faulstich, H.; Heintz, D. *Methods Enzymol.* **1995**, *251*, 357–366.

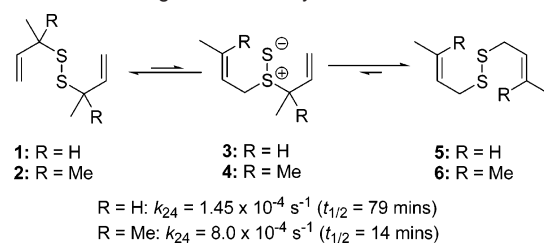
disulfide ligation and its established chemoselectivity for the cysteine thiol in the presence of all the proteinogenic amino acids stands in stark contrast to the various other methods for cysteine functionalization, most of which involve the capture of the cysteine thiol by electrophilic species, and which consequently have obvious potential chemoselectivity issues.^{1,2,39} The practicality of the disulfide ligation, with its direct applicability to cysteine-containing peptides, also contrasts with the various ingenious indirect methods that have been developed for the preparation of S-functionalized cysteine derivatives,¹⁷ including, for example, the Michael addition of thiols to dehydroalanine units,⁴⁰ the alkylation of thiolates with peptide-based β -halo-alanine units,^{41–43} and other electrophiles,^{44,45} the opening of peptide-based aziridines by thiolates,^{46,47} and the synthesis of peptides with previously functionalized cysteine building blocks,^{48–50} each of which requires the synthesis of modified peptides. The many advantages of the disulfide ligation are offset, however, by its impermanence, which results from the lability of the disulfide bond in the presence of thiols and other reducing agents.

Consideration of the practical advantages of the disulfide ligation, and the disadvantages of its impermanence, led us to investigate methods for rendering it permanent. The result of our search was the dechalcogenative allylic selenosulfide and disulfide ligations, whose scope we describe in full in this article.^{51,52}

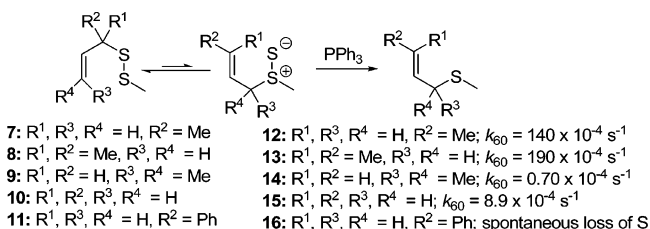
Results and Discussion

Background. The phosphine-promoted desulfurative allylic rearrangement of diallyl disulfides to give allyl sulfides^{53–57} proceeds by way of a [2,3]-sigmatropic rearrangement via a diallyl thiosulfoxide intermediate^{58,59} and, thus, is closely related

Scheme 1. Rearrangement of Diallyl Disulfides⁵⁸



Scheme 2. Pseudo-First-Order Rate Constants for Phosphine-Mediated Rearrangement in Benzene⁵⁸



to the well-known Evans–Mislow rearrangement of allylic sulfoxides.⁶⁰ This dechalcogenative rearrangement, which may also be induced to operate in the reverse direction on treatment of allyl sulfides with elemental sulfur,⁶¹ and which is potentially important in the chemistry of essential oils derived from garlic,⁶² appeared to us to hold promise as a means of rendering disulfides permanent if it could be caused to function at ambient temperatures in protic solvents. The seminal work of Höfle and Baldwin revealed that the reaction is rapid in benzene at room-temperature provided that the thiosulfoxide is removed from the equilibrium. Thus, the diallyl disulfides **1** and **2** rearrange via the thiosulfoxides **3** and **4** to the thermodynamically more stable disulfides **5** and **6** via two sequential sigmatropic rearrangements with half-lives of 79 and 14 min, respectively, at 24 °C (Scheme 1).⁵⁸

In the absence of a thiophile, simple alkyl allyl sulfides **7** and **8** were found by Höfle and Baldwin to be stable at room temperature and could be purified by vacuum distillation, whereas **10** and **11** were reported to lose sulfur spontaneously at room temperature, albeit without mention of a time scale for this process.⁵⁸ A comparable dependence of rearrangement rate on substituent pattern was observed by Moore and Trego in their early work on the reaction.⁵³ Pseudo first-order rate constants were measured by Höfle and Baldwin for the reaction of the alkyl allyl disulfides **7–11** with PPh₃ in benzene at 60 °C, leading to the conclusion that increased bulk around the thiosulfoxide reduces its concentration in the equilibrium and so retards reduction.⁵⁸ While this remains possible, we consider it more likely that the equilibrium is shifted more toward the thiosulfoxide when a more highly substituted alkene is formed at the expense of a less substituted one, and when a more highly substituted C–S bond is replaced by a less substituted one (Scheme 2).⁵⁸

A single example of the corresponding deselenative rearrangement of a diallyl diselenide, that of di(geranyl) diselenide to geranyl linalyl selenide, was reported to proceed with a half-life of approximately 2.5 h at 25 °C on exposure to excess PPh₃

- (35) Macindoe, W. M.; van Oijen, A. H.; Boons, G.-J. *Chem. Commun.* **1998**, 847–848.
(36) Grayson, E. J.; Ward, S. J.; Hall, A. J.; Rendle, P. M.; Gamblin, D. P.; Batsanov, A. S.; Davis, B. G. *J. Org. Chem.* **2005**, *70*, 9740–9754.
(37) Gamblin, D. P.; Garnier, P.; van Kasteren, S.; Oldham, N. J.; Fairbanks, A. J.; Davis, B. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 828–833.
(38) Gamblin, D. P.; Garnier, S. J.; Ward, N. J.; Oldham, A. J.; Fairbanks, A. J.; Davis, B. G. *Org. Biomol. Chem.* **2003**, *1*, 3642–3644.
(39) Ludolph, B.; Eisele, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 5954–5955.
(40) Zhu, Y.; van der Donk, W. A. *Org. Lett.* **2001**, *3*, 1189–1192.
(41) Thayer, D. A.; Yu, H. N.; Galan, M. C.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4596–4599.
(42) Jobron, L.; Hummel, G. *Org. Lett.* **2000**, *2*, 2265–2267.
(43) Pachamuthu, K.; Zhu, X.; Schmidt, R. R. *J. Org. Chem.* **2005**, *70*, 3720–3723.
(44) Cohen, S. B.; Halcomb, R. L. *Org. Lett.* **2001**, *3*, 405–407.
(45) Cohen, S. B.; Halcomb, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 2534–2543.
(46) Galonic, D. P.; van der Donk, W.; Gin, D. Y. *J. Am. Chem. Soc.* **2004**, *126*, 12712–12713.
(47) Galonic, D. P.; Ide, N. D.; van der Donk, W. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2005**, *127*, 7359–7369.
(48) Palomo, J. M.; Lumbierres, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 477–481.
(49) Durek, T.; Alexandrov, K.; Goody, R. S.; Hildebrand, A.; Heinemann, I.; Waldmann, H. *J. Am. Chem. Soc.* **2004**, *126*, 16368–16378.
(50) Kragol, G.; Lumbierres, M.; Palomo, J. M.; Waldmann, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5839–5842.
(51) Crich, D.; Krishnamurthy, V.; Hutton, T. K. *J. Am. Chem. Soc.* **2006**, *128*, 2544–2545.
(52) Crich, D.; Brebion, F.; Krishnamurthy, V. *Org. Lett.* **2006**, *8*, 3593–3596.
(53) Moore, C. G.; Trego, G. R. *Tetrahedron* **1962**, *18*, 205–218.
(54) Evans, M. B.; Higgins, G. M. C.; Moore, C. G.; Porter, M.; Saville, B.; Smith, J. F.; Trego, B. R.; Watson, A. A. *Chem., Ind.* **1960**, 897.
(55) Blackburn, G. M.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1968**, 1261–1262.
(56) Barnard, D.; Houseman, T. H.; Porter, M.; Tidd, B. K. *J. Chem. Soc., Chem. Commun.* **1969**, 371–372.
(57) Pilgram, K.; Phillips, D. D.; Korte, F. *J. Org. Chem.* **1964**, *29*, 1844–1847.
(58) Höfle, G.; Baldwin, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 6307–6308.
(59) Kutney, G. W.; Turnbull, K. *Chem. Rev.* **1982**, *82*, 333–357.

- (60) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155.
(61) Baechler, R. D.; Hummel, J. P.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 4442–4444.
(62) Block, E.; Iyer, R.; Grisoni, S.; Saha, C.; Belman, S.; Lossing, F. P. *J. Am. Chem. Soc.* **1988**, *110*, 7813–7827.

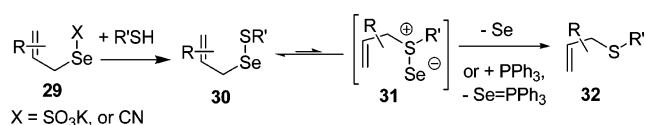
Table 1. Preliminary Survey of Disulfides and Phosphines
$$\text{R-SH} + \text{R}'\text{-CH}_2\text{-CH(S-X)-CH}_2 \longrightarrow \text{R}'\text{-CH}_2\text{-CH(S-S-R)-CH}_2 \xrightarrow{\text{PR}_3} \text{R-S-CH}_2\text{-CH(R)CH}_2$$

X = S-Py, SO₂Ph, SO₃⁻Na⁺ R = Ph or (NEt₂)₃

Entry	Thiol	Donor	Disulfide (% yield)	Solvent	Temp (°C)	PR ₃	Product (% yield)
1	Me(CH ₂) ₇ SH	geranyl-S-S-Py 17	geranyl-S-S-(CH ₂) ₇ Me 18 (72)	PhMe	110	PPh ₃	linalyl-S-(CH ₂) ₇ Me 19 (71)
2	PhSH	geranyl-S-S-Py 17	geranyl-S-S-Ph 20 (95)	PhMe	110	PPh ₃	geranyl-S-Ph 21 (69)
3	PhSH	 22	 23 (73)	C ₆ D ₆	rt	P(NEt ₂) ₃	 24 (80)
4	 25	 26	 27 (77)	CD ₃ OD	rt	P(NEt ₂) ₃	 28 (73)

in chloroform, thereby indicating the selenium version of this reaction to be considerably faster than the original sulfur protocol.⁶³ Guillemain and co-workers subsequently were able to obtain crude preparations (~80% pure) of diallyl diselenide, dicrotyl diselenide, and diphenyl diselenide, characterize them spectroscopically, and study their reactions with tributylstannane, indicating such diselenides to have at least moderate stability at room temperature.⁶⁴

Preliminary Studies. We initiated our investigations with a brief survey of methods of mixed disulfide formation, of solvents, and of phosphines for the allylic disulfide rearrangement. As shown in Table 1, allylic pyridyl sulfides,^{1,2,65} allylic thiosulfonates,³⁸ and allylic Bunte salts (*S*-allylic thiosulfates)^{66,67} all proved adept at the transfer of allylic sulfides to a range of simple thiols. The phosphine-promoted rearrangement, however, was not so simple. Thus, it was necessary to heat the alkyl geranyl disulfide **18** with PPh₃ in toluene at reflux in order to achieve efficient conversion to the rearranged linalyl sulfide **19** (Table 1, entry 1). It is important to note that, consistent with our aim of developing a practical process suitable for application to biologically relevant systems, our reactions were carried out with a minimal excess of phosphine, unlike the work of Höfle and Baldwin.⁵⁸ The difference in the amount of phosphine

Scheme 3. Formation and Rearrangement of Se-Allylic Selenosulfides

presumably accounts for the differences in reaction times and temperatures observed. Under the same conditions, the phenyl geranyl disulfide **20**, however, gave the unrearranged phenyl geranyl sulfide **21** (Table 1, entry 2), thereby drawing attention to the relatively fine dividing line between the desired dechalcogenative allylic rearrangement and the better known nucleophilic removal of a sulfur atom from a disulfide.⁶⁸ As is evident from the comparison of entries 1 and 2 in Table 1, the replacement of an alkylthiyl moiety by an arylthiyl group is sufficient to tip the balance in favor of nucleophilic attack by the phosphine on the native disulfide. Entry 3 of Table 1 illustrates how the replacement of PPh₃ by the more nucleophilic hexaethylphosphoramine enabled the reaction temperature to be reduced to the ambient but, unfortunately, with continued formation of the simple desulfurization product. Finally, Table 1, entry 4, ruled out any future use of hexaethylphosphoramine, at least in the context of amino acid and peptide-based systems, owing to both transesterification and racemization evidenced by incorporation of deuterium from the solvent at the α-center.

Allylic Selenosulfide Rearrangement. The somewhat inauspicious results reported in Table 1 led us to consider the possibility of the deselenative rearrangement of Se-allylic

(63) Sharpless, K. B.; Lauer, K. B. *J. Org. Chem.* **1972**, *37*, 3973–3974.(64) Riague, E. H.; Guillemain, J.-C. *Organometallics* **2002**, *21*, 68–73.(65) Stoner, E. J.; Negrón, G.; Gaviño, R. In *Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide, and Peptide Synthesis*; Crich, D., Ed.; Wiley: Chichester, 2005; pp 330–338.(66) Klayman, D. L.; White, J. D.; Sweeney, T. R. *J. Org. Chem.* **1964**, *29*, 3737–3738.(67) Milligan, B.; Swan, J. M. *J. Chem. Soc.* **1963**, 6008–6012.(68) Harpp, D. N.; Gleason, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 2437–2445.

Table 2. Formation and Rearrangement of Selenosulfides

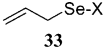
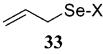
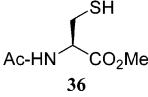
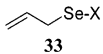
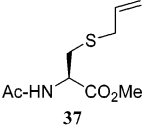
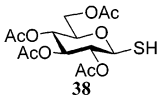
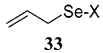
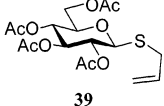
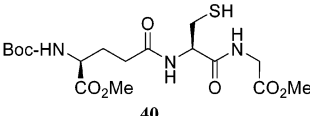
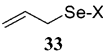
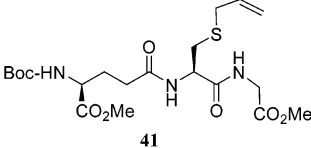
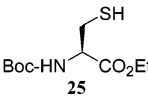
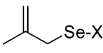
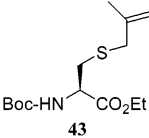
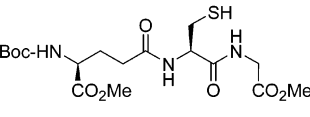
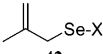
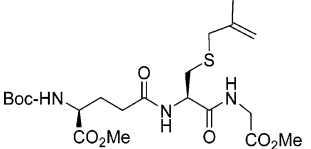
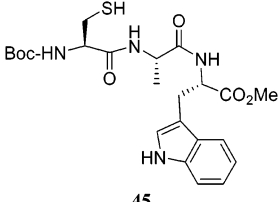
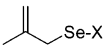
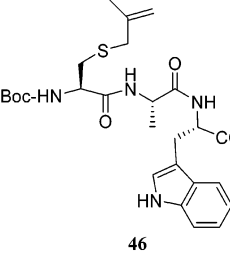
Entry	Thiol	Donor	Donor (% yield)		Product ^{a,b}	Rearrangement yield (equiv of PPh ₃)	
			X = SO ₃ ⁻ K ⁺	X = CN		from X = SO ₃ ⁻ K ⁺	from X = CN
1	Me(CH ₂) ₁₅ SH	 33	56	84	Me(CH ₂) ₁₅ S-allyl 34	74% (0)	70% (0)
2	Ph-CH ₂ -CH ₂ -SH	 33	56	84	Ph-CH ₂ -CH ₂ -S-allyl 35	70% (0)	70% (0)
3	 36	 33	56	84	 37	61% (2.5)	80% (0)
4	 38	 33	56	84	 39	50% (2.5) ^c	55% (2.5) ^d
5	 40	 33	56	84	 41	58% (2.5)	75% (0)
6	 25	 42	58	73	 43	62% (2.5)	68% (0)
7	 40	 42	58	73	 44	60% (2.5)	71% (0)
8	 45	 42	58	73	 46	60% (2.5)	65% (2.5)
9	Me(CH ₂) ₇ SH	geranyl-Se-X 47	40	80	linalyl-S-(CH ₂) ₇ Me 19	62% (2.5)	70% (2.5)

Table 2 (Continued)

10		geranyl-Se-X 47	40	80		46% (2.5)	66% (2.5)
11		geranyl-Se-X 47	40	80		43% (2.5)	55% (2.5)
12		geranyl-Se-X 47	40	80		51% (2.5)	50% (2.5)
13		farnesyl-Se-X 51	35	85		47% (2.5)	40% (2.5)
14			28	75		31% (2.5)	65% (2.5)

^a Unless otherwise stated all reactions were conducted in MeOH. ^b At room temperature. ^c $T = 65\text{ }^{\circ}\text{C}$. ^d CDCl_3 was used as a solvent at $T = 65\text{ }^{\circ}\text{C}$.

selenosulfides, which should be more facile than the desulfurative rearrangement of the allylic disulfides.⁶⁹ The clean formation of simple mixed alkyl selenosulfides can be realized at room temperature by the reaction of Se-alkyl seleno-Bunte salts with thiols.^{70,71} Accordingly, a number of Se-allyl seleno Bunte salts were prepared by the reaction of potassium seleno sulfate, prepared in situ from potassium sulfite and selenium powder, with allyl halides. These compounds were typically orange crystalline solids that, while not indefinitely stable, could be handled in air at room temperature. Reaction with a range of aliphatic thiols then resulted in the formation of a series of selenosulfides, that could be readily detected by thin layer chromatography and/or NMR spectroscopy, but which were allowed to undergo the subsequent deselenative rearrangement,

either with or without the addition of phosphine as required (Scheme 3, Table 2).

We have also prepared the Se-allyl selenosulfides by the reaction of allyl selenocyanates⁶⁴ with thiols, a process that also takes place readily at room temperature (Scheme 3), and which had been reported for the formation of simple diaryl selenosulfides.⁷² The formation of allyl selenosulfides from the reaction of allylselenols with disulfides was not investigated because of anticipated difficulties in the preparation and handling of the allylic selenols.⁶⁴ Overall, it is clear from Table 2 that allyl selenocyanates may generally be prepared in higher yields than the corresponding Se-allyl seleno Bunte salts, but that in most cases both selenenylation systems perform the transfer of the Se-allyl group to the thiol comparably well, as evidenced by the yield of the subsequent rearrangement products.

It is of some interest to note that the primary allylic selenocyanates prepared and employed in this study were readily

(69) The use of the deselenative allylic diselenide rearrangement was excluded from consideration on the grounds that selenocysteine is too uncommon in Nature to form the basis for a broad general methodology.

(70) Patarasakulchai, N.; Southwell-Keely, P. T. *Phosphorus Sulfur* **1985**, *22*, 277–282.

(71) Klayman, D. L.; Günther, W. H. H., Eds. *Organic selenium compounds: their chemistry and biology*; Wiley-Interscience: New York, 1973.

(72) Clark, E. R.; Al-Turaihi, M. A. S. *J. Organomet. Chem.* **1977**, *134*, 181–187.

handled at room temperature and showed no tendency to undergo rapid rearrangement. This observation parallels that of Riague and Guillemain, who had earlier prepared several of the same allylic selenocyanates and reported their purification by vacuum distillation,⁷³ but it stands in contrast to the reported chemistry of simple allylic thiocyanates which are reported to undergo [2,3]-sigmatropic rearrangement to the corresponding allylic isothiocyanates in a matter of hours at room temperature.^{74,75} On the basis of the work of Sharpless with 2-methyl-3-selenocyanato-1-heptene, secondary and presumably tertiary selenocyanates can be expected to undergo a [1,3]-sigmatropic rearrangement to their primary regioisomers.⁶³

The transfer of a simple allyl or methallyl group did not necessitate the addition of phosphine and proceeded spontaneously over a 2 h period at room temperature. In the case of geranyl and farnesyl Se-Bunte salts and selenocyanates, proceeding with allylic rearrangement to the linalyl and nerolidyl sulfides, respectively, it was necessary to add PPh₃ to provoke the loss of selenium. The more difficult rearrangement of the geranyl and farnesyl systems corresponds to the pattern observed originally with the allylic disulfides (Scheme 2), with the prenyl system **9** undergoing the phosphine-promoted rearrangement least rapidly. This is clearly the consequence of the formation of the less stable isoprenyl substitution pattern. The anomeric thiol **38** rearranged slowly over a period of several days at room temperature in the presence of PPh₃, and much more rapidly at 65 °C. The fluorine-substituted methallyl system **53**, unlike the simple methallyl transfer reactions, necessitated the addition of PPh₃ in order to proceed at room temperature. These latter two observations are understood in terms of the mechanism of Scheme 3, with the formation of the intermediate selenosulfoxide disfavored by either an electron-withdrawing substituent on the allyl group or by the involvement of the sulfur atom in an exo-anomeric type interaction that serves to remove electron density from sulfur. When the reaction takes place with the formation of a new stereogenic center, this was typically obtained as an almost equimolar mixture of two diastereomers and, accordingly, no attempt was made to distinguish the isomers.

The range of examples presented in Table 2, which were all conducted at room temperature with the exception of the carbohydrate-based example, displays the broad functional group compatibility of the method. A series of further experiments in which the reaction of cysteine derivative **25** with the Se-methallyl seleno Bunte salt **42** and PPh₃ was conducted in methanol at room temperature in the presence of equimolar amounts of *N*-benzyloxycarbonyl tyrosine benzyl ester, *N*-benzyloxycarbonyl methionine, *N*α-benzyloxycarbonyl lysine methyl ester, *N*-benzyloxycarbonyl arginine methyl ester, and *N*-benzyloxycarbonyl aspartic acid α-methyl ester, with no loss of yield and with recovery of the spectator amino acid, further confirmed the applicability of the reaction in the presence of most standard functional groups.

Unfortunately, all attempts at the preparation of tertiary allylic seleno Bunte salts or the equivalent selenocyanates, such as would be necessary for the introduction of a simple geranyl or

farnesyl group to a sulfide, failed. This result, which is not surprising in view of the instability of secondary allylic selenocyanates and even phenylselenides noted by Sharpless,⁶³ forced us to return to the allylic disulfides.

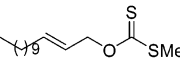
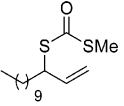


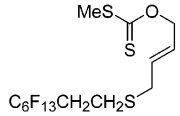
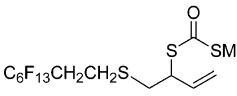
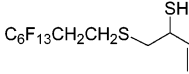
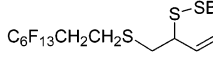
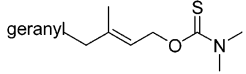
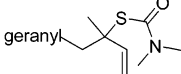
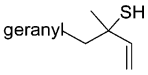
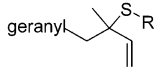
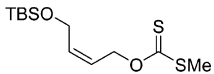
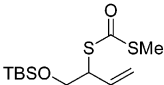
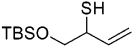
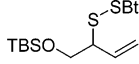
Allylic Disulfide Rearrangement. The early work on the allylic disulfide rearrangement (Scheme 2)^{53,58} indicated the considerable effect of substituents in the allylic moiety on reaction rate with the secondary and tertiary allylic disulfides undergoing rearrangement several orders of magnitude more rapidly than their primary counterparts in hot benzene, thereby providing grounds for hope that the rearrangement could be induced to function as required at room temperature with the correct substituent pattern. In addition, consideration of the mechanism of the allylic disulfide rearrangement leads to the hypothesis that the reaction should be facilitated in polar solvents capable of stabilizing the dipolar thiosulfoxide intermediate.^{76,77} Indeed, the early workers in the field noted a 6–10 fold increase in the rate of desulfurative rearrangement of 1,3-dimethylbut-2-enyl *tert*-butyl disulfide with PPh₃ on going from benzene to ethanol/benzene (9/2) at 80 °C,⁵³ and Höfle and Baldwin commented on the instability of methanolic solutions of **10** and **11** with respect to rearrangement, as compared to the neat samples.⁵⁸

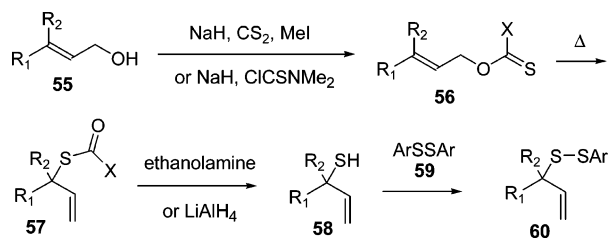
A series of secondary and tertiary allylic thiols were prepared by the [3,3]-sigmatropic rearrangement of a variety of primary allylic thiocarbonyl derivatives (Scheme 4, Table 3).^{78–83} While this chemistry was straightforward, caution was necessary in the conversion of the rearrangement products to the thiols, as these were found to undergo a known⁸⁰ 1,3-shift to the isomeric primary allylic thiols under basic conditions. The optimum conditions for this cleavage involved the reduction of the thiol carbamates with lithium aluminum hydride,⁸⁰ and the cleavage of the dithiocarbonates with ethanolamine. The thiols were then allowed to react with either 2,2'-dipyridyl disulfide, 2,2'-di(5-nitropyridyl) disulfide, or 2,2'-di(1,3-benzothiazolyl) disulfide^{1,2,32–34,65,84–87} for conversion to the corresponding allyl heteroaryl disulfides and ultimate transfer to the target thiols (Scheme 4, Table 3). It is noteworthy that sulfonylating agents derived from hindered allylic thiols have drawn little attention so far, with only a limited number of allylic benzothiazolyl disulfides being described in the literature.^{88,89} In addition to these allylic heteroaryl disulfides, we also prepared a single example **75** of an *S*-allyl Se-phenyl selenosulfide, by reaction

(73) Guillemain, J. C.; Bouayad, A.; Vijaykumar, D. *Chem. Commun. (Cambridge, U. K.)* **2000**, 13, 1163–1164.
 (74) Emerson, D. W.; Booth, J. K. *J. Org. Chem.* **1965**, 30, 2480–2481.
 (75) Carbohydrate-based allylic thiocyanates, however, require higher temperatures for rearrangement. Ferrier, R. J.; Vethaviaser, N. *J. Chem. Soc. (C)* **1971**, 1907–1913.

(76) We assign the dipolar structure to the thiosulfoxides, a class of compounds, which have not been isolated or characterized spectroscopically, by reasonable analogy with the sulfoxides. Thiosulfonates (ROS(S)OR) have been isolated and studied crystallographically, spectroscopically, and computationally, with the evidence pointing to the polar structure.⁷⁷
 (77) Zysman-Colman, E.; Nevins, N.; Eghbali, N.; Snyder, J. P.; Harpp, D. N. *J. Am. Chem. Soc.* **2005**, 128, 291–304.
 (78) Garmaise, D. I.; Uchiyama, A.; McKay, A. F. *J. Org. Chem.* **1962**, 27, 4509–4512.
 (79) Ferrier, R. J.; Vethaviaser, N. *J. Chem. Soc., Chem. Commun.* **1970**, 1385–1387.
 (80) Hackler, R. E.; Balko, T. W. *J. Org. Chem.* **1973**, 38, 2106–2110.
 (81) Ueno, Y.; Sano, H.; Okawara, M. *Tetrahedron Lett.* **1980**, 21, 1767–1770.
 (82) Eto, M.; Tajiri, O.; Nakagawa, H.; Harano, K. *Tetrahedron* **1998**, 54, 8009–8014.
 (83) Nakai, T.; Ari-Izumi, A. *Tetrahedron Lett.* **1976**, 17, 2335–2338.
 (84) Talgooy, M. M.; Bell, A. W.; Duckworth, H. W. *Can. J. Biochem.* **1979**, 57, 822–833.
 (85) Kimura, T.; Matsueda, R.; Nakagawa, Y.; Kaiser, E. T. *Anal. Biochem.* **1982**, 122, 274–282.
 (86) Brzezinska, E.; Ternay, A. L. *J. Org. Chem.* **1994**, 59, 8239–8244.
 (87) Rabanal, F.; DeGrado, W. F.; Dutton, P. L. *Tetrahedron Lett.* **1996**, 37, 1347–1350.
 (88) Watson, A. A. *J. Chem. Soc. (C)* **1964**, 2100–2107.
 (89) Morrison, N. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 101–106.

Table 3. Preparation of Allylic Thiols and the Corresponding Allyl Heteroaryl Disulfides

Allylic Xanthates (% yield)	Rearranged Thiocarbamate (% yield)	Thiol (% yield)	Disulfide (% yield)
 61 (80)	 62 (99)	 63 (93)	 R = 2-Py 64 (96) R = 4-NO ₂ -2-Py 65 (86) R = Bt 66 (81)
 67 (92)	 68 (99)	 69 (-)	 70 (15)
 71 (80)	 72 (83)	 73 (87)	 R = SBt 74 (83) R = SePh 75 (56)
 76 (87)	 77 (94)	 78 (-)	 79 (45 from 77)

Scheme 4. Preparation of Secondary and Tertiary Allylic Thiols and Heteroaryl Disulfides

of the thiol with *N*-phenylselenophthalimide, as it had been reported that the selenosulfides were more effective at sulfonyl transfer than the corresponding disulfides.³⁷

As anticipated these allylic heteroaryl disulfides enabled smooth sulfonyl transfer to a selection of primary thiols in either benzene or methanol/acetonitrile mixtures at room temperature (Table 4). Addition of either PPh₃ or (4-dimethylaminophenyl)-diphenylphosphine then provoked the desired desulfurative allylic rearrangement. For those reactions that were carried out in benzene, the sulfonyl transfer was affected at room temperature, after which the phosphine was added and the reaction mixture heated to reflux to bring about the rearrangement. On the other hand, as expected from mechanistic considerations, when reactions were conducted in methanol and acetonitrile, no heating was required for the entire sequence. With the more highly substituted allyl heteroaryl disulfides, sulfonyl transfer was relatively slow but was accelerated very significantly by

the addition of triethylamine. Interestingly, sulfonyl transfer from the selenosulfide **75** was also slow but was accelerated in the presence of triethylamine, and we conclude that there is no practical advantage to the use of the selenosulfide transfer protocol.⁹⁰ No obvious consequence in terms of reactivity was observed when the sulfonyl transfer group was changed from 5-nitro-2-pyridyl, to 2-pyridyl, to 2-benzothiazolyl, but the differing polarities of the corresponding heteroaryl sulfides formed as byproducts can be used to advantage in the case of otherwise difficult purifications. Similarly, no significant difference in the rate of the desulfurative rearrangement was observed on changing from PPh₃ to (4-dimethylaminophenyl)-diphenylphosphine **84**, but the latter did afford a practical advantage in terms of purification of the final products.

The desulfurative rearrangement of the secondary allylic disulfides takes place with high *E*-selectivity as anticipated on the basis of related [2,3]-sigmatropic rearrangements such as the Evans–Mislow rearrangement⁶⁰ or the [2,3]-Wittig rearrangement.⁹¹ With the tertiary allylic disulfides, *E/Z* mixtures of the rearranged products are formed that slightly favor the *E*-isomer. Interestingly, in the case of the merolidyl selenosulfide **75**, the product **86** was obtained as a more complex mixture of isomers, presumably because of isomerization of the central alkene in the resulting farnesyl chain by the selenide byproducts

(90) The accelerated reactions reported in the literature³⁷ for sulfonyl transfer from selenosulfides, as compared to disulfides, also appear to be the result of the inclusion of triethylamine.

(91) Nakai, T.; Mikami, K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 46, pp 105–209.

Table 4. Formation and Rearrangement of Secondary and Tertiary Allylic Disulfide

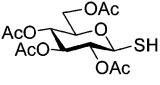
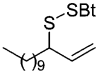
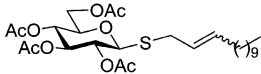
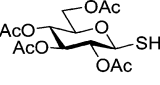
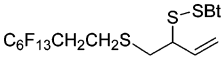
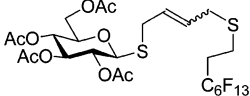
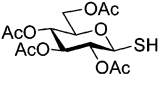
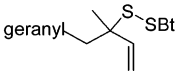
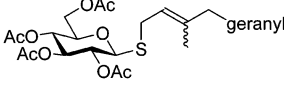
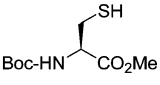
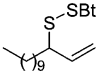
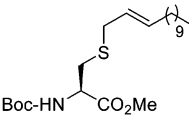
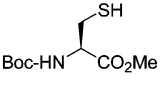
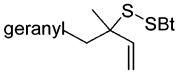
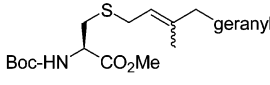
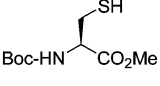
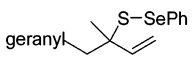
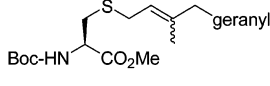
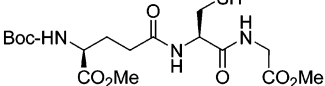
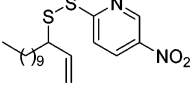
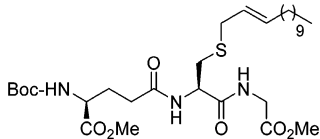
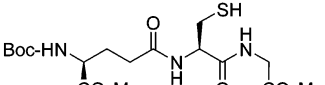
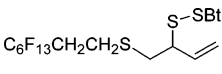
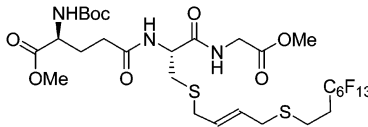
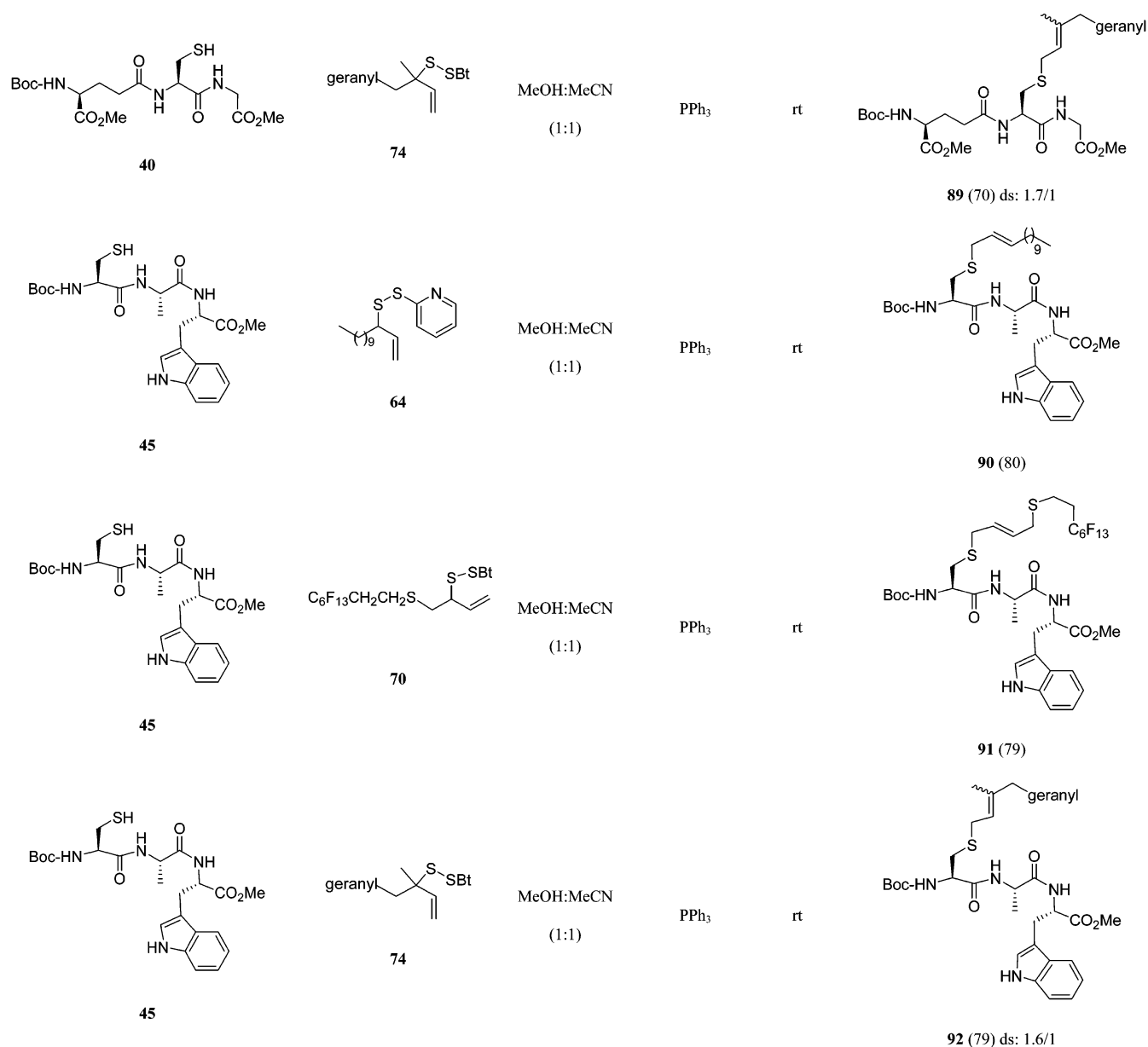
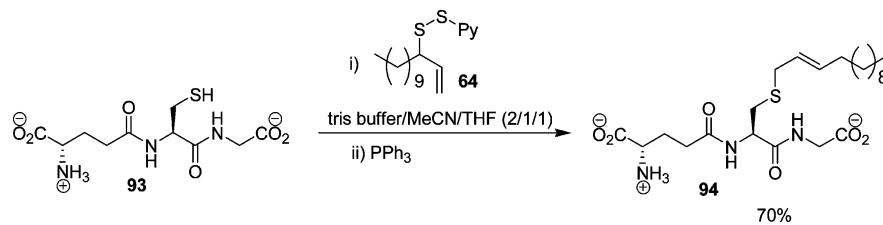
Thiol	Sulfenating agent	Solvent	PR ₃	T (°C)	Product (% yield)
		C ₆ H ₆	PPh ₃	80	 80 (73) ds: 12/1
		C ₆ H ₆	PPh ₃	80	 81 (75) ds: 7.9/1
		C ₆ H ₆	PPh ₃	80	 82 (66) ds: 1.8/1
		MeOH:MeCN (1:1)	Ph ₂ P- (4-C ₆ H ₄ NMe ₂) 84	rt	 85 (85)
		MeOH:MeCN (1:1)	PPh ₃	rt	 86 (84) ds: 1.87/1
		MeOH:MeCN (1:1)	PPh ₃	rt	 86 (80) mixture of isomers
		MeOH:MeCN (1:1)	Ph ₂ P- (4-C ₆ H ₄ NMe ₂) 84	rt	 87 (70)
		MeOH:MeCN (1:1)	PPh ₃	rt	 88 (75)

Table 4 (Continued)



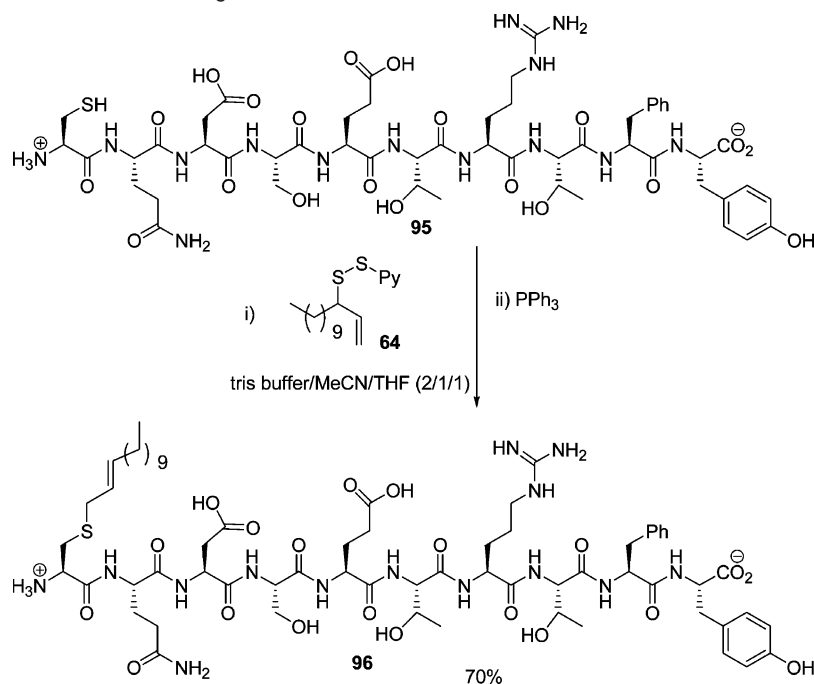
Scheme 5. Functionalization of Glutathione



in combination with light.⁹² When the reaction of the cysteine derivative **83** with the sulfenyl transfer agent **66** and PPh₃ was carried out in a mixture of deuteriomethanol and deuterioacetonitrile, no incorporation of deuterium at the amino acid α -center was observed, indicating that the reaction conditions do not provoke racemization.

(92) Barrett, A. G. M.; Barton, D. H. R.; Johnson, G.; Nagubandi, S. *Synthesis* **1978**, 741.

The examples presented in Table 4 attest to the broad functional group compatibility of the formation and desulfurative rearrangement of secondary and tertiary allylic disulfides and draw attention to the complementary nature of the process with the deselenative allylic selenosulfide protocol, with all classes of primary, secondary, and tertiary allylic sulfides accessible by one of the two reaction sequences at room temperature and without the need for electrophilic reagents.

Scheme 6. Functionalization of a Fibronectin Fragment

Peptide Functionalization in Aqueous Media. The applicability of the desulfurative allylic rearrangement to unprotected peptides in aqueous media was first probed with glutathione **93** and sulfenylating agent **64**. In the event, reaction of disulfide **64** with glutathione **93** in a 2/1/1 mixture of tris buffer/MeCN/THF, with a substrate concentration of 0.02 M at room temperature, followed by addition of PPh₃ smoothly yielded the lipidated glutathione **94** in 70% yield (Scheme 5).

The chemoselectivity of the rearrangement was further explored with the commercial decapeptide fibronectin fragment **95**.^{93,94} This decapeptide was selected as a proving ground because of the dense array of the more challenging amino acid side chains that it presents. As with glutathione **93**, sulfenylation of the cysteine moiety of the decapeptide **95**, followed by phosphine-promoted rearrangement, was accomplished at room temperature in aqueous buffer, with the aid of organic cosolvents, and resulted in the isolation of the lipidated decapeptide **96** in 70% yield (Scheme 6). The location of the tridecene chain on the cysteine group in **96** was established by MS/MS experiments.

As a second demonstration of the protocol in aqueous media, we prepared an octapeptide **101** in which the cysteine residue was located four residues from a C-terminal methionine unit, so as to mimic the Cys-AA¹-AA²-Met sequence targeted by the farnesyl transferase enzymes.^{95–97} The other amino acids in this synthetic peptide were selected so as to provide a measure of steric hindrance to the cysteine moiety. Two tetrapeptides were assembled routinely,^{98,99} and **97**, which was destined to become the N-terminal fragment of the target, was saponified, converted to the ethylthio ester **98** with HATU and ethanethiol,^{100,101} and

finally released from the carbamate protecting group (Scheme 7). This sequence resulted in an inseparable mixture of two diastereomers **99** at the C-terminal alanine, a problem known to plague thioester synthesis for NCL.¹⁰² Coupling of thioester **99** with tetrapeptide **100** under conditions of NCL afforded the target octapeptide **101** in 51% yield as a 1.3/1 mixture of two diastereomers, which was separated by preparative RP-HPLC. The major diastereoisomer, presumed to be the all L-octapeptide, was then allowed to react with the nerolidyl benzothiazolyl disulfide **74** under buffered aqueous conditions at room temperature, followed by addition of PPh₃, leading overall to the farnesylated octapeptide **102** in 66% isolated yield (Scheme 7). This farnesylation reaction occurred with the formation of *E/Z*-isomers mixtures in approximately equal ratio in line with the model experiments in organic solution (Table 4).

The examples of Schemes 5–7 are distinct from other recent functionalizations of sulfur in cysteine-containing peptides,¹⁷ as they require neither the use of electrophilic reagents,^{1,2,39} nor the incorporation of modified amino acid residues into the peptide backbone prior to functionalization,^{40–47} nor the synthesis of peptides with previously functionalized amino acid building blocks.^{48–50} These factors combine to render this chemistry both highly chemoselective, and highly efficient in terms of steps required on the actual peptide target. In contrast to other methods involving the addition of nucleophilic thiols to dehydroalanine groups inserted into peptides,⁴⁰ the products are obtained as single diastereomers with the sole exception being the formation of *E/Z*-mixtures when the allylic sulfide

(93) Boucaut, J.-C.; Darribère, T.; Poole, T. J.; Aoyama, H.; Yamada, K. M.; Thierry, J. P. *J. Cell. Biol.* **1984**, *99*, 1822–1830.

(94) Yamada, K. M.; Kennedy, D. W. *J. Cell. Biol.* **1984**, *99*, 29–36.

(95) Casey, P. J. *Science* **1995**, *266*, 221–.

(96) Kale, T. A.; Hsieh, S.-a. J.; W., R. M.; Distefano, M. D. *Curr. Top. Med. Chem.* **2003**, *3*, 1043–1074.

(97) Brunsveld, L.; Kuhlmann, J.; Alexandrov, K.; Wittinghofer, A.; Goody, R. S.; Waldmann, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6622–6646.

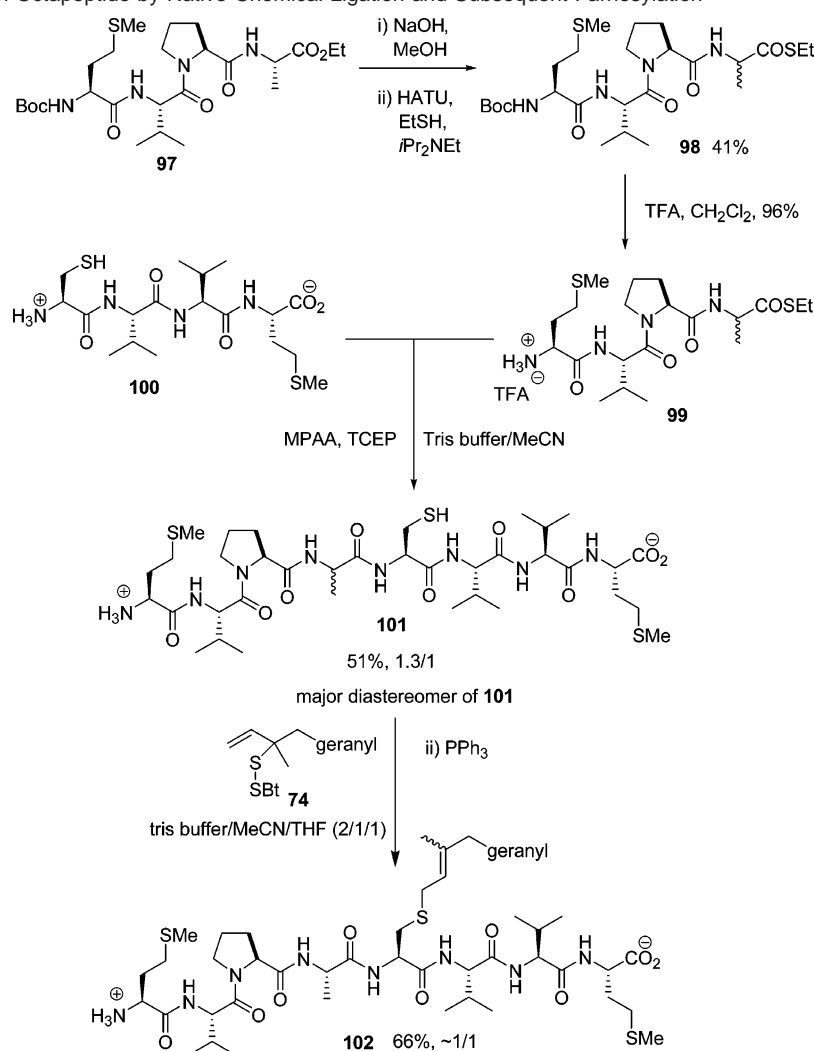
(98) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; 2nd ed.; Springer-Verlag: Heidelberg, 1994.

(99) Goodman, M.; Mahwah, A. F.; Moroder, L.; Toniolo, C., Eds. *Houben-Weyl. Methods in Organic Chemistry. Synthesis of Peptides and Peptidomimetics*; Thieme: Stuttgart, 2002–2003; Vol. E22a–e.

(100) Schnolzer, M.; Alewood, P.; Jones, A.; Alewood, D.; Kent, S. B. H. *Int. J. Pept. Protein Res.* **1992**, *40*, 180–193.

(101) Clippingdale, A. B.; Barrow, C. J.; Wade, J. D. *J. Pept. Sci.* **2000**, *6*, 225.

(102) Kajihara, Y.; Yoshihara, A.; Hirano, K.; Yamamoto, N. *Carbohydr. Res.* **2006**, *341*, 1333–1340.

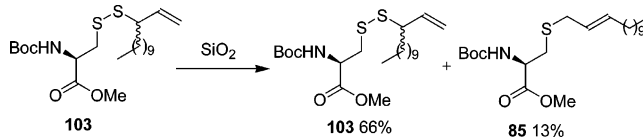
Scheme 7. Synthesis of an Octapeptide by Native Chemical Ligation and Subsequent Farnesylation

contains a trisubstituted alkene. We anticipate that the use of a water-soluble phosphine should be possible in the above experiments, with the proviso that it not be sufficiently nucleophile and/or basic to lead to the type of problems outlined for hexaethylphosphoramine encountered in our preliminary survey of conditions.

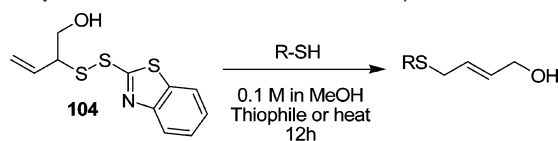
Rearrangement in the Absence of Phosphines. Finally, we turn to the question of the requirement for a phosphine to promote the desulfurative rearrangement of the allylic disulfides. Several factors indicated that conditions may be found under which the reaction would function in the absence of the phosphine. For example, the attempted purification of disulfide **103** by chromatography over silica gel resulted in the isolation of 13% of the allylically rearranged thioether **85** along with the disulfide itself (Scheme 8).⁵² Second, on standing in deuteriochloroform that had not been treated to remove acidic impurities, the same disulfide **103** underwent partial rearrangement to **85** with loss of sulfur.⁵² More tangentially related are the reported use of morpholine or piperidine to drive the related allylic sulfoxide/sulfenate rearrangement,⁶⁰ and the uptake of molecular sulfur by allylic sulfides leading to rearranged allylic disulfides.⁵⁶

The apparent acid-catalyzed rearrangement of **103** to **85** with loss of sulfur could not be developed into a satisfactory general method. However, after some investigation, we have found that

the rearrangement can be achieved by stirring with 2 equiv of piperidine at room temperature in methanol, or simply by heating to reflux in methanol with no added thiophile for a period of several hours. Examples of rearrangements so-conducted are presented in Table 5 using a sulfenyl transfer reagent **104** derived by removal of the silyl group from sulfenyl donor **79**. Appropriate control experiments conducted with PPh₃ at room temperature are also reported in Table 5.

Scheme 8. Rearrangement in the Absence of Phosphines

It is of some interest that both the piperidine and the refluxing methanol conditions enable the desulfurative rearrangement of allyl aryl disulfides for the first time, thereby opening up new avenues for the synthesis of allyl aryl sulfides and extending the overall scope of the reaction. The rearrangements of the allyl aryl disulfides presented in Table 5, and conducted in the absence of phosphine but with the aid of either piperidine or hot methanol, are to be contrasted with the attempted promotion

Table 5. Desulfurative Rearrangement of Allylic Disulfides in the Absence of Phosphine

Entry	Thiol	Product	Method		
			PPh ₃ % yield, <i>E/Z</i>	Piperidine % yield, <i>E/Z</i>	Heat % yield <i>E/Z</i>
1		 105	45 <i>E</i> only	62 2.6:1	78 <i>E</i> only
2		 106	-	-	67 <i>E</i> only
3		 107	-	-	68 <i>E</i> only
4	Me(CH ₂) ₇ SH	 108	-	-	75 <i>E</i> only
5	4-Me-C ₆ H ₄ -SH	 109	18 <i>E</i> only	66 2.5:1	66 <i>E</i> only
6	PhSH	 110	-	-	63 <i>E</i> only
7	4-Cl-C ₆ H ₄ -SH	 111	-	-	62 <i>E</i> only
8	4-NO ₂ -C ₆ H ₄ SH	 112	-	-	20 <i>E</i> only
9	2-PySH	 113	-	-	45 <i>E</i> only
10	2-HO-C ₆ H ₄ SH	 114	-	-	57 <i>E</i> only

of such a rearrangement set out in Table 1, when the excision of sulfur was observed without the allylic rearrangement. We also note the application of the overall process to a tertiary thiol

and draw attention to the absence of racemization in the case of the cysteine derivative as determined in the usual manner by the use of deuteriomethanol as solvent.

Conclusions

The deselenative allylic rearrangement of primary allyl selenosulfides and the desulfurative rearrangement of secondary and tertiary allylic are powerful and complementary techniques for the synthesis of primary, secondary, and tertiary allylic sulfides at room temperature. The preparation of the selenosulfides and disulfides requires no electrophilic reagent, leading to highly chemoselective methods for the permanent modification of thiols. The chemoselectivity of the two reactions enables their application to unprotected peptides in aqueous media in the presence of all types of standard amino acid side chains, thereby providing a powerful means for the direct and permanent modification of cysteine-containing peptides.

Acknowledgment. We thank the NIH (AI 56575 and GM 62160) for partial support of this work, and the Ministère des Affaires Étrangères, France, for the award of a Lavoisier Fellowship to F.B. D.C. thanks Professor Yasuhiro Kajihara, Yokoyama City University, for a helpful discussion regarding native chemical ligation.

Supporting Information Available: Full experimental protocols and copies of spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA072969U