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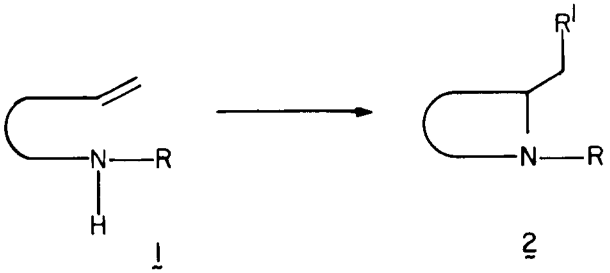
UREIDOALLYLATION OF DOUBLE BONDS

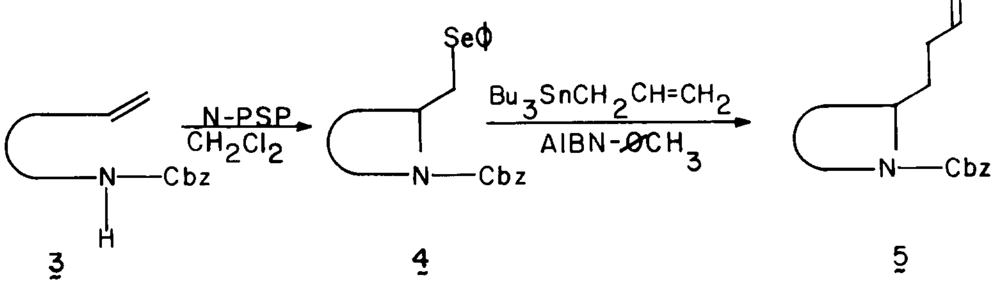
Robert R. Webb II† and Samuel Danishefsky*
Department of Chemistry, Yale University, New Haven, CT 06511

Summary: Intramolecular ureidoselenenylation of double bonds followed by allylative de-selenenylation accomplishes a net ureidoallylation.

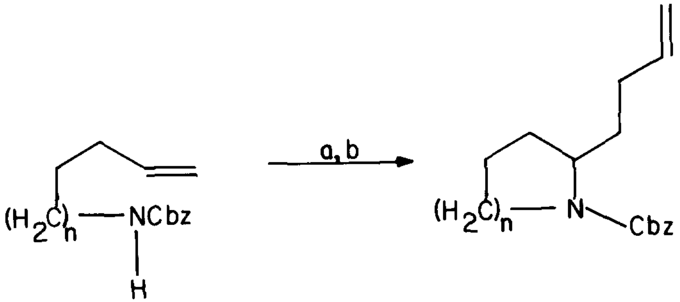
In furtherance of some new departures in the synthesis of alkaloids, methodology directed toward the formalism 1 → 2 was investigated. The sequence of intramolecular addition of a nitrogen-based group to an unactivated double bond followed by attachment of a functionalized carbon array would find broad application.[1,2] The attainment of this scheme for the case of R' = allyl is described below.

Intramolecular ureidoselenenylation of the general system 3, using the Nicolaou reagent N-phenylselenophthalimide (N-PSP),[3] establishes the carbon-nitrogen bond. An allyl group is introduced by the action of 4 with tri-n-butylallylstannane with initiation by azobisisobutyronitrile (AIBN). Such a protocol was developed by Keck and co-workers[4] for the replacement of carbon bound halogens by allyl functions and used in the Utah synthesis of perhydrohistrionicotoxin.[5]





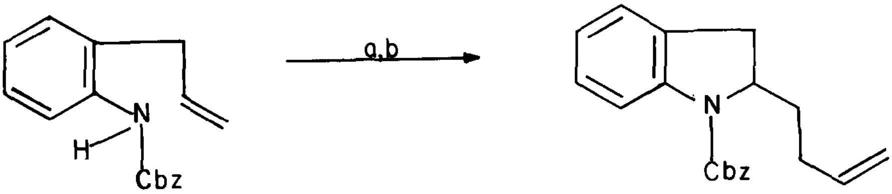
The feasibility of this approach was demonstrated with the unsaturated urethanes 6a and 6b. After the two-step sequence[6] compounds 7a[7] and 7b[7] were obtained in the indicated yields. Products arising from the alternate mode of ureidoselenenylation were not observed. In a similar way, N-Cbz o-allylaniline 8 was transformed to the indoline, 9.[7]



6a,b

7a,b

a n=1(70%); b n=2 (73%)

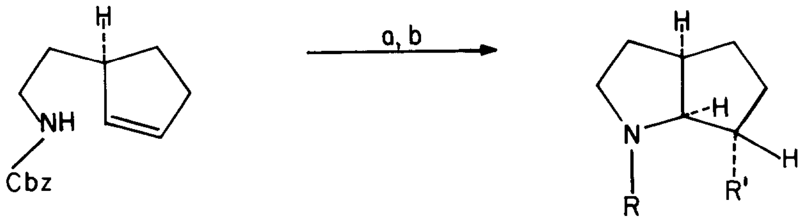


8

9 (76%)

a. N-PSP/CH_2Cl_2, rt. b. $^nBu_3SnCH_2\text{-}CH{=}CH_2$; AIBN, ϕCH_3

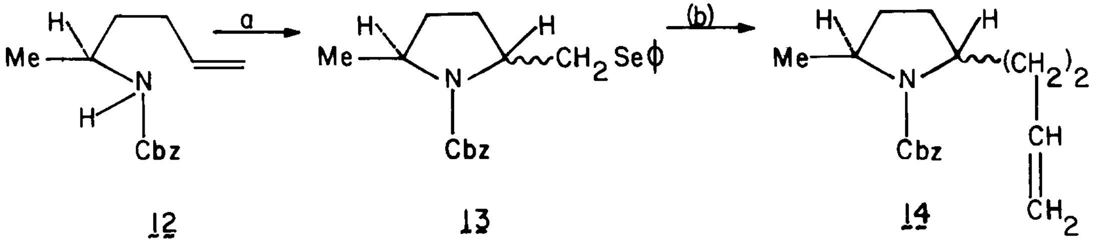
The extension of this method to embrace the case of a cyclic unactivated olefin was clearly of interest. Indeed, the transformation of 10 → 11a[7,8] was carried out in 82% yield. Both at the stage of the intermediate selenide and after coupling with the allyl tin reagent,[4,5] only single diastereomers were noted. It seems likely that the stereochemistry is as shown, though, in fact, our spectral measurements on both 11a and its derived (H_2/Pd-C/EtOH) amine 11b[7,9] do not allow for an unambiguous assignment of relative configurations.



10

11a (R=Cbz; R'=$CH_2CH=CH_2$; 82%)
11b (R=H; R'=^nPr)

Less satisfying from a stereochemical standpoint was the outcome with substrate 12. It will be recalled that with mercuric acetate as the electrophile, Harding[10] observed high stereoselectivity in favor of formation of the trans isomer. We encountered a similar result in the mercury series in the context of reductive coupling of the mercurial with methyl acrylate.[1] However, with N-PSP as the electrophile, an essentially 1:1 mixture of selenides 13 is generated.[11] Upon allylative de-selenenylation[4,5] this is converted into an ca. 1:1 mixture of pyrrolidines 14.[11]



12 13 14

Studies directed toward applying this new capability to problems in total synthesis are in progress.

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References

† National Institutes of Health Postdoctoral Fellow, 1983-84.

1. S. Danishefsky, E. Taniyama and R. R. Webb, *Tetrahedron Letters*, 11, (1983).
2. For the reductive alkylation of selenolactones by acrylates see: S. D. Burke, W. F. Fobare and D. M. Armistead, J. Org. Chem., **47**, 3348 (1982).
3. K. C. Nicolaou, D. A. Claremon, W. E. Barrette and S. P. Seitz, *J. Am. Chem. Soc.*, **101**, 3704 (1979).
4. G. E. Keck and J. B. Yates, *J. Am. Chem. Soc.*, **104**, 5829 (1982).
5. G. E. Keck and J. B. Yates, *J. Org. Chem.*, **47**, 3590 (1982).
6. *Typical Procedure*: Addition of 1eq of the unsaturated urethane to a stirred solution of 1eq of N-PSP in dry CH_2Cl_2 (2.5ml/mmol) was followed by addition of 0.001eq of *d*-10-camphorsulfonic acid. Reactions are conveniently monitored by nmr analysis to indicate consumption of starting material (4-6 hr.). The solid phthalimide is removed by filtration, and the volatiles are removed *in vacuo*, giving essentially pure selenide. The selenides may be further purified by chromatography to provide analytical samples.

   Subsequent addition of a toluene solution of 1eq of the selenide (2ml/mmol) to 2eq allyltributylstannane[4,5] in toluene (2ml/mmol) containing AIBN (0.010mmol/mmol selenide), thorough degassing with argon and heating for ca. 6-10 hr is followed by cooling, removal of the toluene *in vacuo* and partitioning of the crude reaction mixture between acetonitrile and pentane. Evaporation of the acetonitrile followed by chromatography and/or Kugelrohr distillation, affords the pure allyl compounds in the indicated yields.
7. All compounds were characterized by infrared and nmr measurements. The proton spectra of the products were complicated by multiple signals arising from apparent rotamers of the N-Cbz group. In these cases clear and richly detailed proton NMR spectra were obtained at 70°C in DMSO-d_6 (at 500 MHz), using the procedure of Clive.[8] In addition conversion of **11a** to the free amine **11b** helped to clarify its proton nmr spectrum. Satisfactory combustion analyses were obtained for compounds **6a**, **7a**, **7b**, **9**, **11a** and **14**, as well as for all selenide precursors.
8. Similar selenides corresponding to **10** as well as to **6a**, **6b** and **8**, where nitrogen carries a carboethoxy group, have been reported. See: D. L. J. Clive, V. Farina, A. Singh, C. K. Wong, W. A. Kiel and S. M. Menchen, *J. Org. Chem.*, **45**, 2120 (1980). These workers used selenenyl chloride to effect cyclization.
9. *Amine 11b*: ^{1}H NMR(500 MHz,$CDCl_3$TMS) 4.90(br s, 1H, disappears w/D_2O), 3.12(dd,J=5,7Hz, 1H), 3.00(m,2H), 2.60(m, 1H), 1.90(m, complex, 3H), 1.85(m,1H), 1.55(m, complex, 2H), 1.40 (m,2H), 1.29(m,2H), 1.10(m,1H), 0.91(t,J=6Hz,3H); IR($CHCl_3$) 3450(w), 2950, 1420; ^{13}C NMR ($CDCl_3$,TMS) 69.87, 46.50, 46.13, 42.59, 36.63, 33.18, 32.08, 31.86, 21.43, 14.29; Picrate: mp 79.5-80.5° C.
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11. The diastereomers obtained were readily separated by HPLC.

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