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Efficient One-Pot Conversion of Carbonyl Compounds to Their α,β-Unsaturated Derivatives Using a Recoverable, Minimally Fluorous Organoselenium Reagent

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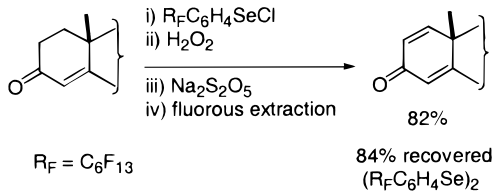
ABSTRACT



A protocol for the preparation of a fluorous arylselenenyl chloride is described. This selenenyl chloride may be used for the direct α-selenation of ketones and, following oxidation and *syn*-elimination, formation of α,β-unsaturated carbonyl compounds. Treatment of the crude reaction mixtures with sodium metabisulfite reduces the various selenium species to the diaryl diselenide, which is then recovered in high yield by continuous fluorous extraction.

The formal dehydrogenation of carbonyl compounds to their α,β-unsaturated derivatives by introduction of an α-arylselenyl group, followed by oxidation to a selenoxide and eventual *syn*-elimination,[1,2] has become a mainstay of organic synthesis since its introduction in 1973 by the Clive,[3] Reich,[4] and Sharpless[5] laboratories. Application of this reaction on an industrial scale is, however, not nearly as widespread as in academic laboratories. The reasons for this are obvious and stem from environmental and economic factors as well as issues relating to purification and recyclability. The immediate byproduct of the reaction is an areneselenenic acid (ArSeOH) which is not stable and, as demonstrated by Reich[6] and Kice,[7] undergoes disproportionation to the diaryl diselenide and the areneseleninic acid ($ArSeO_2H$). Purification can therefore sometimes be difficult owing to the need to remove at least two organoselenium byproducts of widely differing polarity. Barton and his co-workers addressed this problem through the introduction of benzeneseleninic acid/anhydride, a reagent that could be used in catalytic quantities to achieve dehydrogenation of ketones.[8] Unfortunately, this method has not been adopted widely, perhaps because of the hypervalent iodine species used as the in situ stoichiometric oxidant. Much more recently the Nicolaou group has introduced polystyrene-bound organoselenium reagents to

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(2) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979.
(3) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1973**, 695.
(4) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.
(5) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.
(6) Reich, H. J.; Willis, W. W.; Wollowitz, S. *Tetrahedron Lett.* **1982**, *23*, 3319.
(7) Kice, J. L.; McAfee, F.; Slebocka-Tilk, H. *Tetrahedron Lett.* **1982**, *23*, 3323.
(8) Barton, D. H. R.; Godfrey, C. R. A.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1947.

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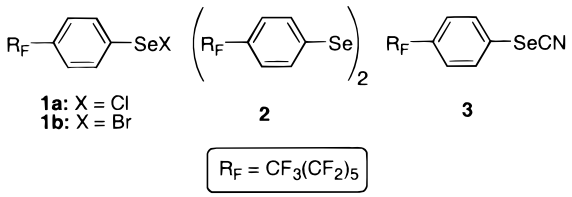
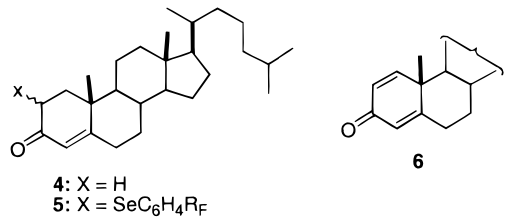
circumvent the purification problem,[9] but no mention was made of the recyclability of these species. Here we describe our own solution to this problem in the form of a minimally fluorous arylselenium reagent, which, following treatment of the crude reaction mixtures with sodium metabisulfite, is recovered almost quantitatively as the diselenide by extraction with a water-cooled continuous extractor. We anticipate that the ease of operation of the protocol and the high recoverability of the reagent by a simple continuous extraction technique will facilitate the use of this type of chemistry beyond the academic laboratory.

The areneselenyl halides **1a** and **1b** were prepared from the diselenide **2**,[10,11] by treatment with sulfuryl chloride, and from the selenocyanate **3**,[10,11] by exposure to bromine, respectively, followed by evaporation to dryness. The chloride (**1a**) was a red crystalline solid while the bromide (**1b**) was obtained in the form of dark red crystals. Both substances were somewhat hygroscopic, and the bromide was slowly converted to the diselenide (**2**) on storage under vacuum in the ambient laboratory light.

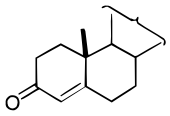
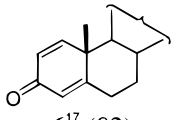
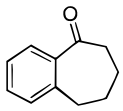
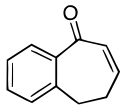
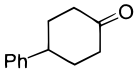
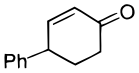
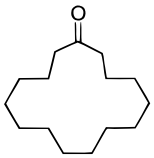
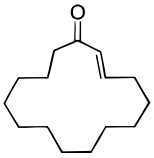
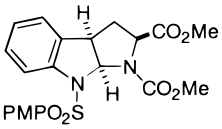
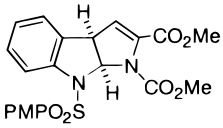


Treatment of the steroidal enone **4** with LDA in THF followed by the bromide **1b** provided the α-arylselenoketone **5**, which was not isolated but exposed at room temperature to hydrogen peroxide. Chromatography of the crude reaction mixture enabled isolation of the cross-conjugated dienone **6** in 70% yield. The ability of the fluorous arylselenyl groups to take part in a typical selenation, oxidation, *syn*-elimination sequence was therefore established. We next investigated a protocol, following an early lead by Sharpless,[5] in which the ketone was simply stirred in THF with the chloride **1a** leading directly to the α-arylseleno ketone, presumably by an acid-catalyzed enolization, followed by oxidation with hydrogen peroxide and *syn*-elimination. This second protocol was found to be operationally simpler, not requiring generation of the lithium enolate, and gave comparable, even better, overall yields. It was, therefore, adopted as the standard protocol.



We next turned to recovery of the fluorous selenium moiety. The minimally fluorous (52% F) diselenide **2** is nicely soluble in halogenated solvents and in perfluorinated solvents, as noted previously,[10,11] such that it may be conveniently recovered by brief continuous extraction.[10−12] The higher oxidation state species (ArSeOH, $ArSeO_2H$)[6,7] and their anhydrides[6,7] generated in the course of the oxidation/elimination were found to be much less soluble in either phase and accumulated at the phase boundary in any extraction, continuous or classical. Therefore, we turned to in situ reduction protocols with the aim of recovering the reagent in the form of the more soluble diselenide. With isolated samples of the oxidized selenium byproducts we favored brief treatment with hydrazine hydrate,[13] which wrought clean and complete conversion to the diselenide (**2**) in a matter of minutes. However, fears of reaction between the enone and hydrazine as well as of possible reduction of the enones by diimide led us to select sodium metabisulfite[14] as the in situ reductant. Thus, a protocol was developed in which the crude reaction mixtures were treated for 1 h at room temperature with this reagent before being subjected to an aqueous wash. The organic layer was then partitioned between FC-72[15] and dichloromethane in the continuous

Table 1. Dehydrogenation of Carbonyl Compounds and Recovery of the Fluorous Diselenide **2**

Substrate	Product (% Yield)	% 2 Rcvd.
 **4**	 **6**[17] (82)	84
 **7**	 **8**[18] (81)	92
 **9**	 **10**[19] (86)	97
 **11**	 **12**[20] (90)	99
 **13**	 **16**[21] (86)	95

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(12) Curran has termed such "minimally" fluorous reagents "light" fluorous reagents and has presented an alternative protocol for their recovery involving chromatography over fluorous silica gel: Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069.

extractor for several hours. Distillation of the recyclable FC-72 then yielded the diselenide **2** whereas the organic phase yielded the enone after chromatography on silica gel.

Table 1 presents four examples of the overall procedure involving stirring the ketone with chloride **1a** and then with hydrogen peroxide before treatment with sodium metabisulfite and continuous fluorous extraction.[16] It will be noted that the yields of enone are generally good, as is that of the recovered diselenide. The final example of Table 1 was conducted with the LDA/ArSeBr protocol, but isolation involved standard treatment with sodium metabisulfite and continuous extraction.

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(15) FC-72 is a relatively inexpensive perfluorinated hydrocarbon solvent available from 3M Speciality Chemicals Division.

(16) **General Experimental Protocols: (a) Preparation of Chloride 1a.** To a solution of **2** (0.25 mmol) in CCl_4 (2 mL) was added SO_2Cl_2 (0.04 mL, 0.5 mmol), and the resulting solution stirred at room temperature for 30 min. Evaporation to dryness then gave a red crystalline solid that was used as such for the dehydrogenations. **(b) Dehydrogenation with 1a.** The ketone (0.5 mmol) and freshly prepared **1a** (0.5 mmol) were stirred in THF (2 mL) at room temperature for 24 h before 30% aqueous H_2O_2 (0.15 mL) was added dropwise, and the mixture stirred for an additional hour. Sodium metabisulfite (5 mmol) was then added and the mixture stirred for 1 h. The reaction mixture was then diluted with ethyl acetate (4 mL), and the organic phase was washed with water and brine and concentrated in vacuo to give a residue which was partitioned between CH_2Cl_2 (6 mL) and FC-72 (25 mL) in the water-cooled continuous extractor[11] for 2 h. Evaporation of the FC-72 phase provided the recovered diselenide **2**, whereas the organic phase afforded the enone after filtration on silica gel.

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