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Reactions Involving Selenium Metal as an Electrophile: Scope and Limitations of the Enolate-Selenolate Transformation

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ABSTRACT

When lithium enolates are allowed to react with selenium metal, selenolate (selenide) ions are formed. Alkylation of these selenolate ions produces the corresponding α-alkylselenenyl carbonyl derivatives. These derivatives can then be converted to their unsaturated counterparts using the same type of protocols that are employed with arylselenenyl derivatives.

With the exception of selenium dioxide, prior to 1970 selenium reagents were rarely employed in organic synthesis. However, over the past 20 years their use has increased dramatically. Through the use of organoselenium methodology, a variety of important chemical transformations can be accomplished in higher efficiency than alternative methods [1]. This generalization becomes all the more remarkable when one considers that selenium-containing species are almost never synthetic targets in their own right, but instead are intermediates which are prepared en route to some non-selenium-containing substrate. Thus, in order for organoselenium methodology to be superior to other approaches, protocols involving the introduction, manipulation, and ultimate extrusion of selenium must take place with a combined efficiency that is greater than available by other methods.

Without question, the single, most useful application of organoselenium chemistry involves the introduction of double bonds via selenoxide elimination reactions. These reactions are cis-eliminations and typically occur at temperatures between −20 and 30°C. As such, selenoxide eliminations represent the mildest general olefin-forming reactions known.

A particularly useful example of this process was reported by Reich et al. for the conversion of ketones to enones (Scheme 1) [2]. Despite a few minor problems associated with both the selenenation and oxidative elimination steps, the Reich method has enjoyed wide acceptance [2, 3]. Recently, we published a variation of the Reich approach which involves the reaction of a lithium enolate with selenium metal to form a selenolate (selenide) ion. The resulting selenolate can be then directly alkylated to produce the corresponding α-alkylselenenyl derivative (Scheme 2) [4, 5]. These derivatives could then be converted to enones using the same type of oxidation protocols that are employed with arylselenenyl derivatives. Since selenium metal is significantly less expensive than any of the commercially available arylselenenyl halides (or diaryl diselenides), we felt that this enolate-selenolate transformation would prove useful in moderate or large-scale conversions of saturated carbonyl derivatives to their unsaturated counterparts [6]. In this paper we report on the scope and limitations of this process.

In the selenenation of enolates, substitution of selenium metal in place of phenylselenenenyl halides necessitates a more elaborate experimental procedure. For example, reactions of lithium enolates with phenylselenenyl chloride tolerate a range of solvents and reaction temperatures. In the reaction of lithium enolates with selenium metal, four factors are critical to the success of the pro-

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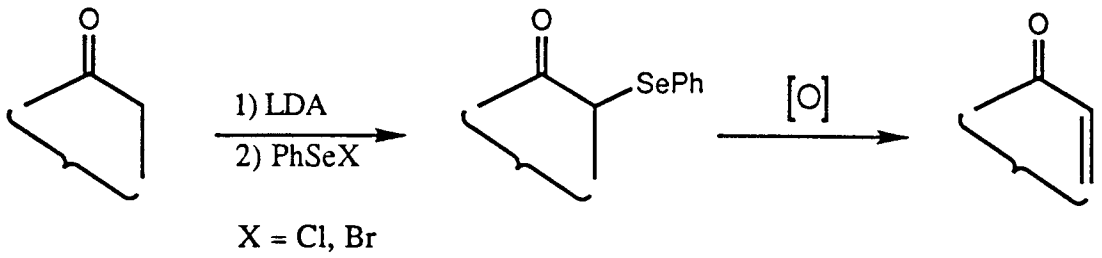
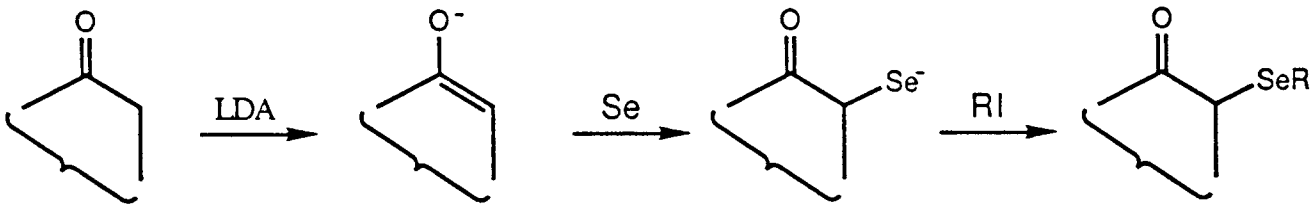


SCHEME 1

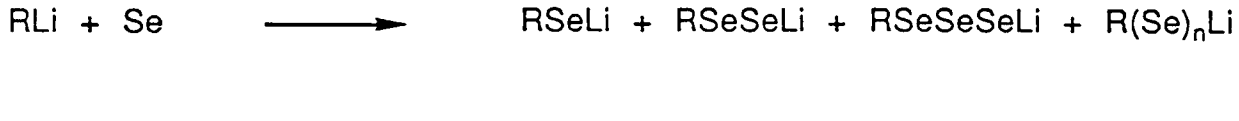


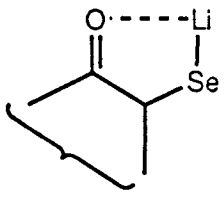
SCHEME 2

cess. These are: (a) the quantities of polar aprotic additives that are used, (b) the particle size and activity of the selenium metal, (c) the reaction temperatures for the selenenation and alkylation reactions and (d) the reaction times allowed for the alkylation reaction.

We have found that addition of three molar equivalents of hexamethylphosphoric triamide (HMPA) or *N,N'*-dimethylpropyleneurea (DMPU) to a lithium enolate/tetrahydrofuran (THF) solution prior to selenium metal addition results in optimal yields. These additives undoubtedly enhance the reactivity of the lithium enolates with selenium metal due to a disproportionate degree of lithium solvation. Too little solvation results in sluggish reactions, while too much yields polyselenides. This latter observation is particularly interesting when lithium enolate/selenium metal reactions are compared with other carbanion/selenium metal reactions. In the former, little, if any, polyselenenation is observed when the reactions are carried out properly. By contrast, reactions of simple alkyl lithium reagents with selenium metal often yield significant quantities of di-, tri- and other polyselenenated products. We speculate that the absence of polyselenenated products from reaction with lithium enolates is at least in part the result of the extra stabilization enjoyed by the favorable lithium-oxygen interaction (Scheme 3) [7].

Grey, finely powdered metallic selenium generally produces the best and most consistent results. We typically grind commercial selenium pellets into powder form using a mortar and pestle [8] and then "activate" the selenium metal by warming it at 100°C *in vacuo* for a few minutes. Selenium metal activation definitely enhances the efficacy of enolate-selenolate transformations. The mode of addition of the metal with the enolate appears to be inconsequential, i.e., comparable results have been obtained by either adding the selenium to the enolate solution or by cannulating the enolate solution into a flask containing selenium.





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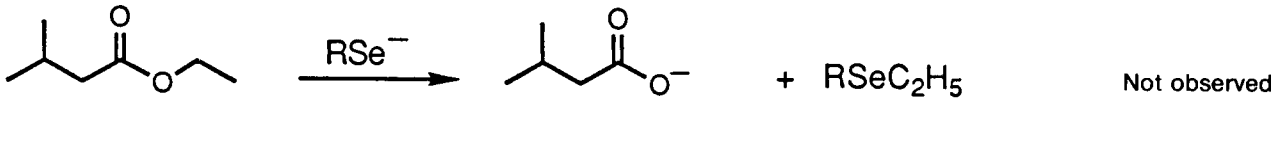


11 24

SCHEME 4

For reactions of selenium metal with simple lithium enolates, temperatures of −20 to −10°C consistently give the best results. Reactions of enolates with selenium metal do not occur below −40°C and proceed quite slowly even at −30°C. Conversely, if reaction temperatures are allowed to rise above 0°C, complex mixtures result. Reactions of stabilized carbanions (e.g., β-dicarbonyl compounds) with selenium metal typically require higher reaction temperatures and longer reaction times (25°C for 12–24 hours) [5].

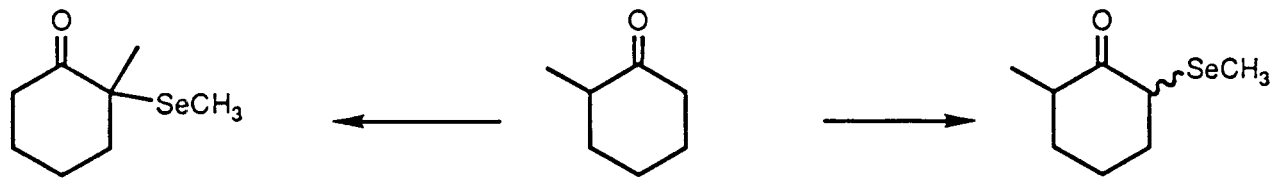
Most of the enolate-selenolate transformations that we have examined have reached completion in less than 1 h at −20°C. As long as the reaction temperatures were kept below 0°C, reaction times for enolate selenenation longer than 1 h did not significantly alter the results. In the selenium alkylation step, the use of short reaction times and a twofold excess of alkylating agent proved to be superior to longer reaction times and stoichiometric amounts of alkylating agent. However, when the former conditions were employed, it was very important to keep the reaction times brief (5–10 min). When longer alkylation reaction times were employed, significantly lower isolated yields were obtained, presumably due to overalkylation of the desired product.

All of the common carbonyl enolates undergo efficient enolate-selenolate transformations. Some examples of these are listed in Table 1 and include esters (conversion of **11** to **12**), lactones (conversion of **5** to **6**), ketones (conversions of **1** to **2**, **3** to **4**, **3** to **23**, **9** to **10**, **13** to **14**, and **17** to **18**), enones (conversions of **7** to **8** and **19** to **20**), lactams (conversion of **21** to **22**), and even nitriles (conversion of **15** to **16**).

Although selenolates have previously been used to cleave esters and lactones by S_N2-type reactions (Scheme 4), we anticipated that these processes, which are slow at −20°C, would not be competitive with the alkylation process [9]. Since both **5** and **11** undergo clean methylselenenation, this assumption appears to be valid.

With ketones, questions regarding the regio- and stereoselectivity of enolate-selenolate transformations become important. For example, generation of the kinetic enolate of **3** and subsequent reaction with selenium metal and methyl iodide led exclusively to a cis/trans mixture of **4** [10]. No trace of **23**, the product derived from reaction of selenium metal with the thermodynamic enolate of **3**, was observed. Thus, the degree of enolate exchange was insignificant under the conditions employed here. Conversely, when **3** was treated in an insufficiency of base, thermodynamic control ensued and **23** was cleanly produced. Based upon our results with many unsymmetrical ketones, we can state that the standard protocols for regioselective generation of ketone enolates can virtually always be utilized to obtain regioselective enolate-selenolate transformations (Scheme 5) [11].

Another potential complication with enolates involves allyl ketones. Upon selenenation, these materials could, in principle, undergo a 2,3-sigmatropic rearrangement [12] and thereby produce allylselenenyl enolates (e.g., the conversion of **25** to **26**). Since no products derived from **26** were observed during the selenenation of **9**, one must either conclude that these processes are not operative or that, through a combination of concentration and reactivity effects, the alkylation of **25** is the over-



23 3 4

Thermodynamic Enolate Formation Kinetic Enolate Formation

SCHEME 5

TABLE 1

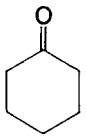
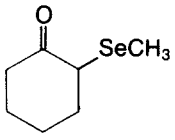
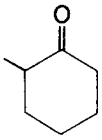
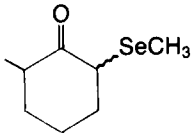
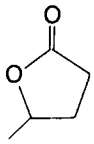
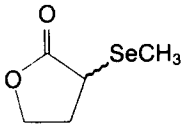
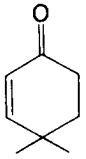
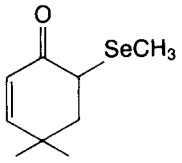
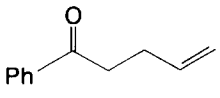
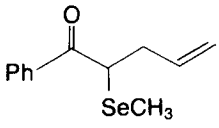
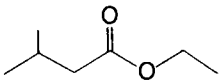
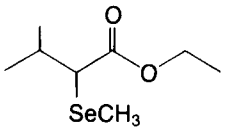
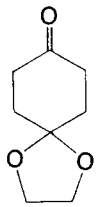
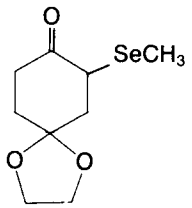
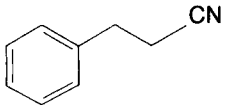
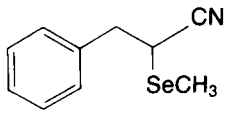
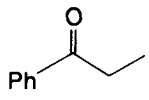
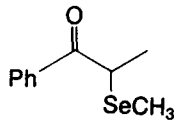
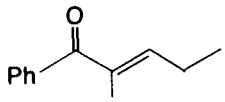
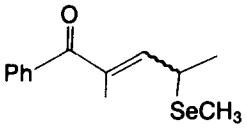
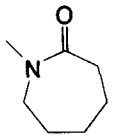
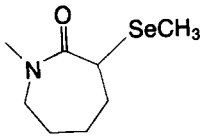
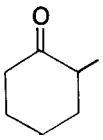
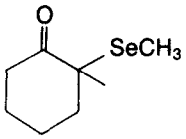
Substrate	*Product*	*Temp.* (°C)	*Yield*[a,b] (T)
 **1**	 **2**	−20	80
 **3**	 **4**	−20	80
 **5**	 **6**	−10	90
 **7**	 **8**	−10	90
 **9**	 **10**	−20	83
 **11**	 **12**	−15	85
 **13**	 **14**	−20	89
 **15**	 **16**	−20	91

TABLE 1 (*continued*)

Substrate	Product	Temp. (°C)	Yield[a,b] (T)
 **17**	 **18**	−20	92
 **19**	 **20**	−20	72
 **21**	 **22**	−10	61
 **3**	 **23**	−20	83[c]

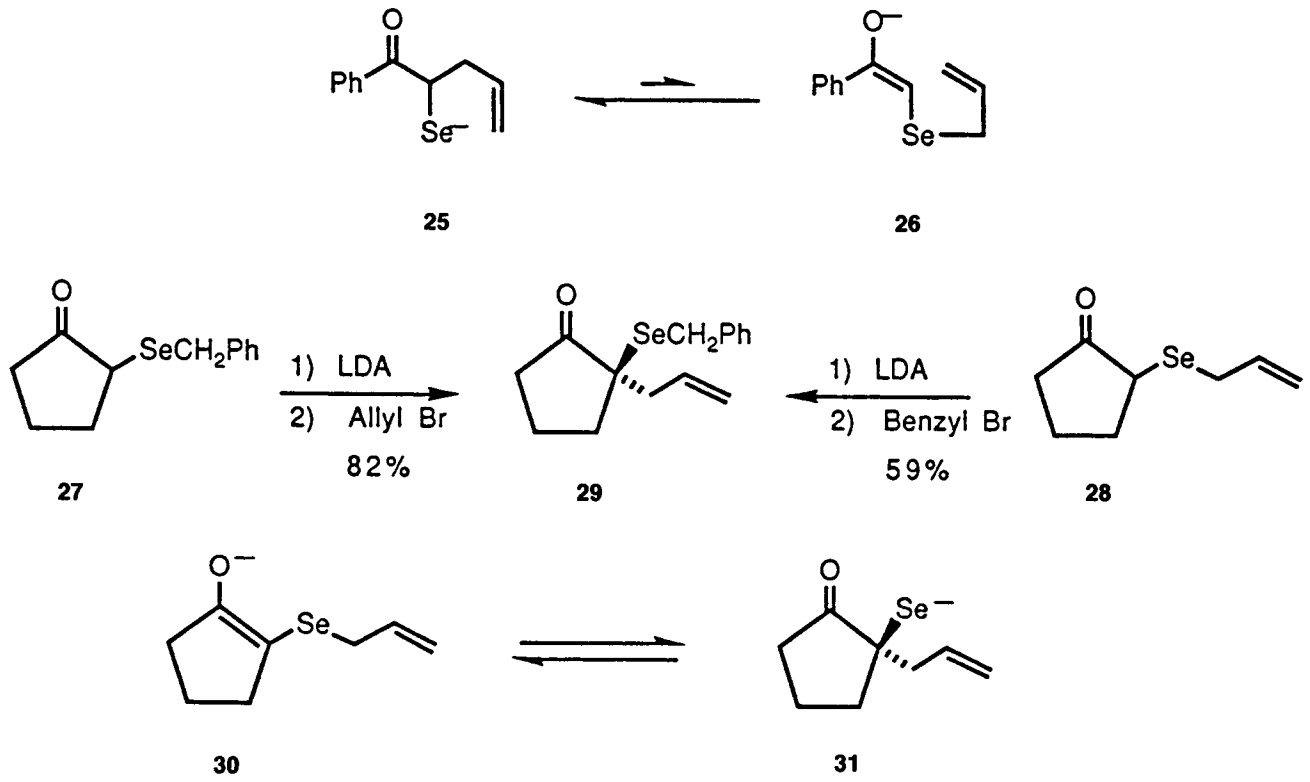
[a] Isolated yields.
[b] Products were identified on the basis of their IR, NMR, and mass spectra.
[c] Performed with 0.95 equivalents of LDA.

whelmingly dominant process. That the latter rationale is correct is apparent from the results of the two reactions shown below. The fact that **27** and **28** both undergo complementary alkylation reactions to yield **29** can best be understood in terms of a selective reaction from an equilibrium mixture of 2,3-sigmatropic rearrangement products **30** and **31** (Scheme 6) [13].

Unlike most other electrophiles, arylselenenyl halides are reported to react with dienolates at the γ rather than the α-position [14]. In this regard we have verified that enolate-selenolate transformations parallel their arylselenenyl counterparts. Specifically, reaction of the enolate of **19** with selenium metal, followed by methyl iodide, gave the γ-selenenation product as a mixture of geometric isomers (E/Z = 8 : 1). Since all of our observations regarding enolate-selenolate transformations suggest that the selenenation step is effectively irreversible, we assume that these processes are kinetically controlled rather than the result of a selenolate equilibration reaction. Of course, when dienolate formation is structurally precluded, enones, such as **7**, undergo α'-selenenation.

Reactions of amide and nitrile enolates with arylselenenyl halides and diaryl diselenides are complicated by the propensity of the initial selenenated product to rapidly equilibrate with the original enolate [15, 16]. An example of this phenomenon is shown below. In this case, enolate formation in the presence of one equivalent of base produced **34** as the major product [15]. Since selenium-stabilized enolates are several orders of magnitude more stable than their nonselenium counterparts, the equilibrium between **34**/**35** and **36**/**33** probably lies far to the right (Scheme 7) [17]. While this concentration effect is partially mitigated by the lower reactivity of **36** as compared with **35**, the net effect is still the predominance of the bisselenenated product, **34**. Synthetically, this problem can be minimized (but not eliminated) by carrying out these reactions in the presence of two equivalents of base. Under these conditions the concentration of the two enolates become comparable, thereby permitting the higher reactivity of **35** to dominate.

Since the proton transfer problem hinges on the ability of selenium to stabilize an adjacent neg-

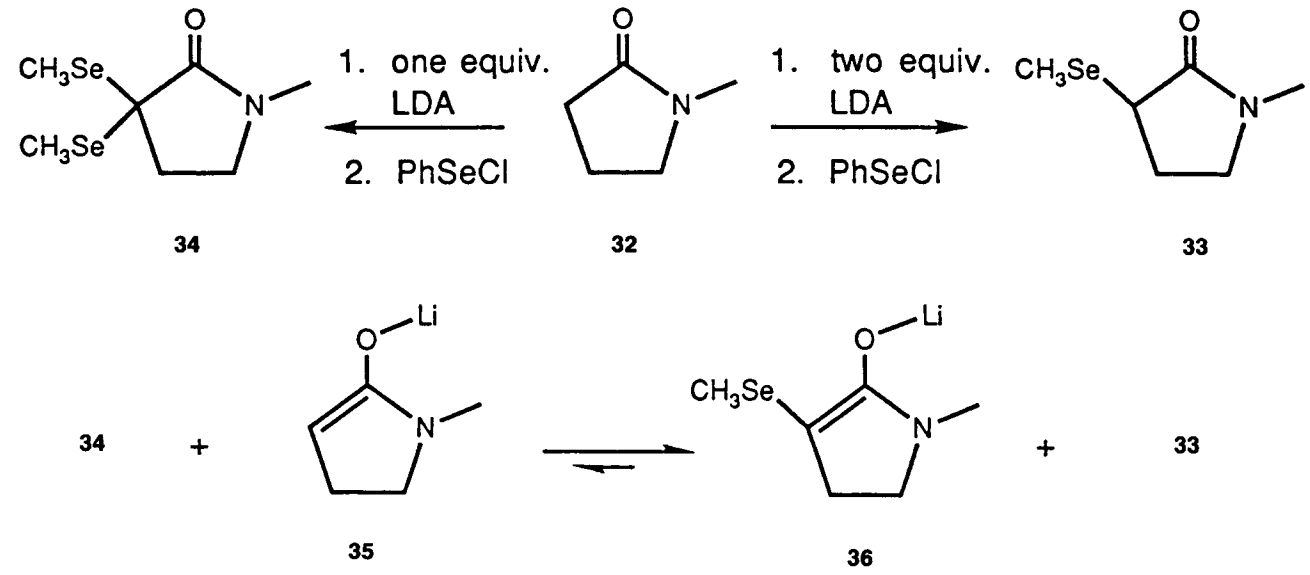


25 26 27 29 28 30 31

2,3-Sigmatropic Rearrangement Heavily Favors Reaction from Selenolate

SCHEME 6

ative charge, one approach for circumventing this problem involves converting the selenium into a substituent that temporarily destabilizes (or, at least, does not stabilize) an adjacent anion. In principle, this can be done most effectively by giving the selenium a formal negative charge, thereby requiring that proton transfers involve the intermediacy of a presumably unstable dianion. In fact, this is exactly what occurs in enolate-selenolate transformations. Under these reaction conditions,



34 32 33 34 + 35 36 + 33

SCHEME 7

21 was efficiently converted to **22** with virtually no competition from bis-selenenation. Similar results are obtained in the conversion of nitrile **15** to its selenium derivative **16** [18]. Thus, one advantage of enolate-selenolate transformations over enolate-arylselenenyl halide (or diselenide) reactions is the suppression of bis-selenenation by-products.

Since these enolate-selenolate transformations involve a selenium alkylation step, one has the option of quenching the intermediate selenolate with a variety of electrophiles. For any given case this ability to vary the substituent on selenium could prove useful in product purification, e.g., by altering the relative polarity of the products formed in a given reaction, as well as in any subsequent manipulations of the selenium-containing intermediate [13]. In general, virtually all of the α-alkylselenenyl carbonyl derivatives that we have prepared have proven to be well-behaved compounds which could be easily converted to a host of different derivatives using the same type of procedures commonly employed for their α-phenylselenenyl counterparts. These procedures include, among others, regiospecific alkylations and selenium migrations, as well as oxidative and reductive deselenenations [1, 13, 19].

Finally, we have demonstrated that these reactions are useful for large-scale preparations. For example, the reactions described here have been carried out on scales as large as 100 mmol with no difficulties and no diminution in isolated yields. Thus, our original hypothesis regarding the synthetic utility of these reactions appears to be confirmed.

EXPERIMENTAL

General Methods

^{1}H nuclear magnetic resonance (HNMR) spectra were recorded on either a Varian T-60 (CW 60 MHz), a Varian EM-390 (CW 90 MHz), or a General Electric QE-300 (FT 300 MHz) and are reported in ppm with $CHCl_3$ (7.26 ppm) as internal standard. ^{13}C NMR (CNMR) spectra were obtained on a General Electric QE-300 instrument (FT 75.48 MHz) and are reported in ppm with $CDCl_3$ (t 77.00 ppm) as internal standard. Infrared (IR) spectra were obtained on a Perkin-Elmer 1430 ratio recording spectrophotometer. Mass spectra (low-resolution EI [LREI] and high-resolution EI [HREI]) were obtained at 70 eV on a VG 70-S Nier Johnson mass spectrometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia. Melting points were taken on a Thomas Hoover uni-melt and are uncorrected. All solvents were distilled and dried with the usual desiccants. The purity of the various synthetic intermediates was assessed by evaluation of their spectral (IR, LREI, HREI, and NMR) and chromatographic thin-layer chromatography (TLC) data. All starting material compounds were purchased from Aldrich Chemical Company with the exception of **9** and **19.** Compound **9** was prepared by the addition of but-3-enyl magnesium chloride to benzaldehyde and then oxidizing the addition product with Collin's reagent. Compound **19** was prepared by simple aldol reaction and dehydration of propiophenone and propionaldehyde.

A Representative Procedure for the Conversion of Ketones to Their Corresponding α-Methylselenenylketones

All work was accomplished in a good working fume hood since small amounts of stenches, methyl senenide, and methyl diselenide are produced. In a 250-mL round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a septum cap with nitrogen inlet, and a Gooch tube connected to a 50-mL Erlenmeyer flask containing activated selenium metal powder (880 mg, 11 mmol)*, is charged with 125 mL dry tetrahydrofuran and a few crystals of 2,2′-bipyridine (as a lithium diisopropylamide [LDA] indicator). Dry diisopropyl amine (1.54 mL, 11 mmol) is added and the solution is cooled to −78°C. After the solution is cooled, *n*-butyllithium (4.7 mL of 2.5 M, 12 mmol) is added. The solution is allowed to warm to ambient temperature for 30 min and cooled again to −78°C. To this solution is added the carbonyl substrate (10 mmol) is 4 mL THF. The mixture is kept at −78°C for 30 min to form the enolate. Then the selenium metal and dimethylpropyleneurea (3.6 mL, 30 mmol) are added to the solution and warmed to −23°C (dry ice/CCl_4). The resulting dark solution is warmed to −15°C for 5 min and cooled again for 1 h. Iodomethane (1.2 mL, 20 mmol) is added and stirred for 5 min. Then 20-mL saturated ammonium chloride solution is added and warmed to ambient temperature. The THF is removed *in vacuo* and the resulting water mixture is extracted with ether (3 × 30 mL). The ether layers are combined and washed with brine and dried over anhydrous magnesium sulfate. The ether is removed *in vacuo* and the oily residue is chromatographed using silica gel (50 g) eluted with (10 : 1) hexane/ethyl acetate.

SPECTRAL DATA AND NOTES

2: HNMR ($CDCl_3$, 60 MHz) δ 3.57–3.39 (m, 1H), 1.99 (s, 3H), 2.47–1.40 (m, 8H); MS (LREI) 192 (M^+).

4: HNMR ($CDCl_3$, 300 MHz) δ 3.46 (m, 1H), 2.30–1.20 (m, 7H), 1.99 (s, 3H), 1.02 (d, J = 7 Hz, 3H); CNMR ($CDCl_3$) δ 209.13, 46.01, 38.17,

*Commercial selenium pellets were ground into powder form using a mortar and pestle and then "activated" by warming the selenium metal at 100°C *in vacuo* for 5 min.

34.91, 32.49, 21.36, 14.05, 4.91; IR (neat) 2985, 2935, 2861, 1699, 1448, 1324, 1128, 1022, 733; MS (LREI) 206 (M^+).

6: HNMR ($CDCl_3$, 90 MHz) δ 5.08–4.21 (m, 1H), 3.62 (t, J = 5 Hz, 1 H), 2.24 (s, 3H), 2.60–1.98 (m, 2H) 1.43 (d, J = 6 Hz, 3H); MS (LREI) 194 (M^+).

8: HNMR ($CDCl_3$, 90 MHz) δ 6.61 (d, J = 10 Hz, 1H), 5.88 (d, J = 10 Hz, 1H), 3.72 (dd, J = 9 Hz, J = 6 Hz, 1H), 2.08 (s, 3H), 2.80–1.80 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H); MS (LREI) 218 (M^+).

10: HNMR ($CDCl_3$, 90 MHz) δ 8.05–7.21 (m, 5H), 6.14–4.85 (m, 3H), 4.30 (t, J = 6 Hz, 1H), 3.10–2.29 (m, 2H), 1.88 (s, 3H); MS (LREI) 254 (M^+).

12: HNMR ($CDCl_3$, 90 MHz) δ 4.19 (q, J = 8 Hz, 2H), 2.95 (d, J = 10 Hz, 1H), 2.06 (s, 3H), 1.50–.96 (m, 10H); IR (neat) 3000–2940, 1730, 1030.

14: HNMR ($CDCl_3$, 300 MHz) δ 3.99 (m, 4H), 3.43 (m, 1H), 3.22 (dt, J = 9 Hz, J = 6 Hz, 1H), 2.46 (dd, J = 14 Hz, J = 6 Hz, 1H), 2.32 (m, 1H), 2.17 (dd, J = 14 Hz, J = 4 Hz, 1H), 2.00 (m, 2H), 1.99 (s, 3H); CNMR ($CDCl_3$) δ 205.06, 106.00, 64.31, 64.02, 43.20, 39.13, 33.48, 33.20, 5.61; IR (neat) 3000–2900, 1710, 1430, 1280, 1115, 1045, 855; MS (LREI) 250 (M^+, 19), 235 (8), 155 (100), 111 (28); (HREI) calcd for $C_9H_{14}O_3{}^{80}Se$: 250.0108154, found: 250.0108150.

16: HNMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5H), 3.66 (t, J = 7 Hz, 1H), 3.14 (dd, J = 8 Hz, J = 7 Hz, 2H), 2.23 (s, 3H); CNMR ($CDCl_3$) δ 135.99, 128.45, 128.26, 127.11, 118.77, 38.44, 22.34, 2.80; IR (neat) 3100, 2900, 2300, 1560, 1425, 799, 725; MS (LREI) 225 (M^+, 90), 120 (11), 91 (100), 77 (24); (HREI) calcd for $C_{10}H_{11}N^{82}Se$: 227.0058584, found: 227.0058584.

18: HNMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 7 Hz, 2H), 7.46 (m, 3H), 4.46 (q, J = 7 Hz, J = 6 Hz, 1H), 1.91 (s, 3H), 1.64 (d, J = 6 Hz, 3H); CNMR ($CDCl_3$) δ 194.44, 134.99, 132.19, 127.89, 127.63, 32.63, 15.39, 1.60; IR (neat) 3070, 2940, 1685, 1344, 1238, 955, 710.

20: The above procedure was used with one modification. The enolate solution was warmed to ambient temperature and stirred for 5 h and then cooled (−78°C) prior to the addition of selenium metal. HNMR ($CDCl_3$, 300 MHz) δ 7.65 (d, J = 9 Hz, 2H), 7.46 (m, 3H), 6.24 (d, J = 11 Hz, 1H), 4.02 (q, J = 11 Hz, 1H), 1.99 (s, 3H), 1.98 (s, 3H), 1.42 (d, J = 11 Hz, 3H); CNMR ($CDCl_3$) δ 197.88, 146.64, 137.68, 133.31, 130.97, 128.69, 127.53, 31.18, 19.72, 12.24, 3.26; IR (neat) 3070, 2980, 2940, 1655, 1450, 1270, 1023, 715.

22: HNMR ($CDCl_3$, 300 MHz) δ 3.85 (dd, J = 8 Hz, J = 3 Hz, 1H), 3.76 (dd, J = 15 Hz, J = 9 Hz, 1H), 3.30 (dd, J = 15 Hz, J = 5 Hz, 1H), 2.99 (s, 3H), 2.05 (s, 3H), 2.03–1.58 (m, 6H); CNMR ($CDCl_3$) δ 173.13, 49.90, 45.17, 36.43, 29.55, 27.10, 26.88, 3.92; IR (melt) 2930, 2870, 1640, 1441, 1402, 1113, 1084; mp 81.2°C (ether, snow-white needles); Anal. calcd for $C_8H_{15}NOSe$: C, 43.64; H, 6.87; N, 6.36; found: C, 43.68; H, 6.88; N, 6.36.

23: HNMR ($CDCl_3$, 300 MHz) δ 3.24 (m, 1H), 2.20–1.50 (m, 7H), 1.84 (s, 3H), 1.47 (s, 3H); CNMR ($CDCl_3$) δ 206.39, 49.25, 39.53, 35.62, 26.05, 23.36, 21.43, 2.39; IR (neat) 2945, 2875, 1700, 1452, 1288, 1131, 1013.

18: MS (LREI) 228 (M^+, 23), 226 (12), 134 (55), 123 (32), 105 (100), 77 (59).

20: MS (LREI) 268 (M^+, 14), 266 (7), 158 (30), 129 (38), 105 (100), 77 (87).

22: MS (LREI) 221 (M^+, 31), 219 (17), 127 (100), 112 (51), 98 (17), 69 (17).

23: MS (LREI) 206 (M^+, 23), 204 (14), 112 (53), 110 (16), 83 (48), 55 (100).

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References and Notes

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