Synthesis and Cycloaddition Reactivity of Selenoaldehydes

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Abstract: A variety of substituted selenoaldehydes has been prepared via fluoride desilylation of α-silyl selenocyanates or base-induced elimination of HCN from simple selenocyanates containing electron-accepting or conjugating substituents. Cycloaddition reactions of electron-deficient or conjugated selenoaldehydes with electrically biased dienes proceed efficiently giving substituted selenapyrans. Selenal cycloadditions exhibit typical "ortho–para" regiochemistry for electron-deficient selenals and "meta" regiochemistry for selenobenzaldehyde and selenoformaldehyde. Alkyl-substituted selenals react preferentially with α-selenocyanate precursors or themselves, except when generated in the presence of highly reactive dienes such as cyclopentadiene or 1,3-diphenylisobenzofuran. Selenobenzaldehyde and selenoformaldehyde also react with 2,4,6-trimethylbenzonitrile *N*-oxide to generate 1,2,4-selenoxazoles.

Until recently, selenoaldehydes (selenals **1a**) and selenoketones (selones **1b**) have been elusive molecules. Only a few papers discussing the synthesis of these selenocarbonyl compounds had

1a **1b**

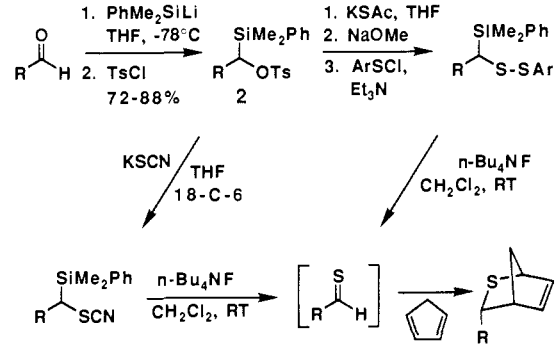
appeared prior to 1986.[1] Noteworthy among these were reports describing the initial synthesis of sterically hindered selenoketones (Back et al.)[2] and subsequent chemical and spectroscopic studies of these selenoketones (Guziec et al.).[3] Reid et al.[4] prepared and isolated several stable selenoaldehydes with vinylogous selenoformamide structures, their stability being derived from resonance delocalization of nitrogen lone pair electrons onto selenium. A number of papers have described selenocarbonyl compounds as ligands in organometallic complexes.[5-9] Fischer has reported the synthesis and reactivity of several selenoaldehydes and selenoketones stabilized by coordination to tungsten and chromium complexes,[5] and other papers describe selenoformaldehyde as a bridging ligand in binuclear osmium[6] and manganese[7] complexes and as a simple ligand in mononuclear rhodium complexes.[8]

Even fewer reports dealing with the preparation of unstabilized selenals and selenoketones have been published. Early papers[10] had discussed attempts to prepare selenals by treatment of aldehydes with H_2Se under acidic conditions, but these approaches resulted in the formation of oligomeric or polymeric selenides via selenal self-condensation reactions. Dittmer et al. also has speculated on the likely intermediacy of an electron-deficient selenoketone in the formation of an oxaselenole from reaction of desyl selenocyanate with NaH/THF.[11] No simple unstabilized selenal has been isolated, though a number of reports describe pyrolytic formation and spectroscopic studies of selenoformaldehyde and selenoacetaldehyde in the gas phase.[12] Furthermore, prior to our initial report,[13] no study had described preparatively useful routes to selenals or well-defined chemical reactions of selenals.

In 1986 we described a mild and efficient method that permitted controlled generation of aryl- and alkyl-substituted selenoaldehydes by addition of *n*-Bu_4NF to α-silyl selenocyanates.[13] When these selenals were formed in the presence of cyclopentadiene, good to excellent yields of [4 + 2] cycloadducts were obtained. More recently, we described the preparation of acceptor-substituted selenals and the cycloaddition reactivity of these and previously described selenals with a variety of unsymmetrically substituted dienes.[14] In this paper we provide a comprehensive description of the chemistry involved in the preparation and cycloaddition reactions of selenoaldehydes containing diverse functionality.

The investigation of selenoaldehydes in our laboratory grew out of synthetic and mechanistic studies of thioaldehydes. We were exploring the mechanism of 2-(2′-mercaptoalkyl)furan formation in the photochemical reaction of phenacyl sulfides with

Scheme I



furan.[15] Photolysis of phenacyl sulfides had been shown by Vedejs et al. to be an excellent route to thioaldehydes,[16] but our studies

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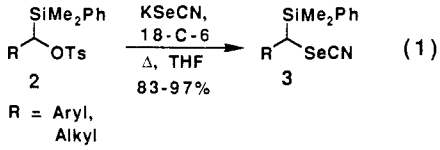
required the development of an alternative, nonphotochemical thioaldehyde synthesis. Consequently, we developed a method to prepare thioaldehydes via the fluoride-mediated desilylation/elimination of α-silyl disulfides, as illustrated in Scheme I.[17] We had also prepared several α-silyl thiocyanates as potential thioaldehyde precursors and found that these reactants formed thioaldehydes when treated with fluoride in the same manner as described for the α-silyl disulfides.[18] In general, however, these thiocyanates proved to be less useful than the α-silyl disulfides, due to competing formation of isothiocyanates during their synthesis and to less efficient generation and trapping of the thioaldehydes. Nevertheless, these experiments involving α-silyl thiocyanates suggested the obvious extension to reactions involving α-silyl selenocyanates, permitting access to the more elusive selenoaldehydes.

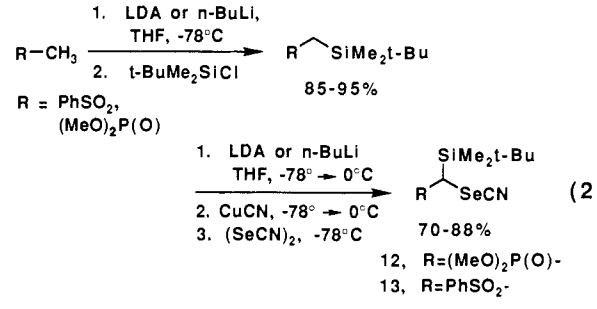
Synthesis of α-Silyl Selenocyanates. Preparation of aryl- and alkyl-substituted selenocyanates was accomplished effectively by the pathway outlined in eq 1. α-Phenyldimethylsilyl *p*-



(1)

toluenesulfonates **2**, prepared in good yields (72–88%) by inverse addition of aldehydes to $PhMe_2SiLi$[19] in THF at −78 °C and subsequent O-sulfonylation with *p*-toluenesulfonyl chloride (Scheme I), represented useful and versatile synthons for α-silyl carbocations and, for our immediate purposes, facilitated the synthesis of α-silyl selenocyanates **3** by simple displacement with potassium selenocyanate. Most of the α-silyl tosylates were stable molecules and were purified by silica gel flash chromatography.[20] Benzylic α-silyl tosylates were quite sensitive to hydrolysis and were purified by repeated trituration with pentane to remove diphenyltetramethyldisilane, the major contaminant that accompanies formation of the $PhMe_2SiLi$ reagent.[19] The aryl- and alkyl-substituted α-silyl selenocyanates were formed in excellent yields (83–97%) by reaction of the α-silyl tosylates with KSeCN[21] in refluxing THF/catalytic 18-crown-6 and were isolated as stable materials after purification by silica gel flash chromatography. (Trimethylsilyl)methyl selenocyanate, the precursor to selenoformaldehyde, was obtained from the commercially available (chloromethyl)trimethylsilane by displacement of chloride with KSeCN under similar conditions.

Access to α-silyl selenocyanates bearing electron-accepting substituents via the tosylate displacement route was difficult, since the α-silyl tosylates were not readily available in many instances. Furthermore, attempted KSeCN displacements on several tosylates that had been prepared successfully led to complex reaction mixtures. Therefore, an alternative approach that would exploit the normal nucleophilic reactivity of carbon atoms adjacent to electron-accepting groups was sought, though such an approach required incorporation of selenocyanate via an electrophilic reagent, rather than the convenient nucleophilic source, KSeCN. Ultimately, several α-silyl selenocyanates were prepared by treatment of cyanocuprate reagents with selenocyanogen [$(SeCN)_2$],[22] as illustrated in eq 2, permitting access to acceptor-sub-



(2)

stituted selenals via the fluoride desilylation pathway.[23] This methodology, however, was not successful for the preparation of several desired α-silyl selenocyanates (e.g., R=CO_2Et, CN), leading us to search further for a more general strategy.

Synthesis of Simple Selenocyanates. During the course of our studies involving selenoaldehydes, we succeeded in generating and trapping a selenoketone (selenofluorenone), simply by treating fluorenyl selenocyanate with Et_3N in the presence of dipolar or diene reactants.[24] The ease and efficiency with which these reactions proceeded led us to prepare a variety of simple selenocyanates containing adjacent electron-accepting substituents. These simple selenocyanates were prepared readily by nucleophilic displacement of halides with KSeCN in refluxing THF/catalytic 18-crown-6. Purification was accomplished by silica gel flash chromatography, and most compounds were reasonably stable, with the exception of the cyanomethyl, 4-nitrobenzyl, and 2,4-

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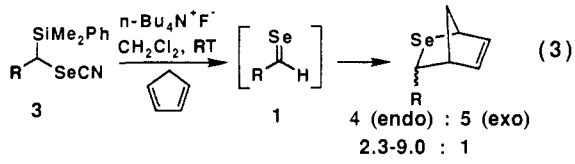
dinitrobenzyl selenocyanates, which decomposed over a period of several hours at room temperature. The (phenylsulfonyl)methyl selenocyanate could not be prepared by displacement of the corresponding halides, which proved to be completely unreactive, even when heated to 150 °C in HMPA for 24 h.[25] Therefore, this simple selenocyanate was prepared by the cyanocuprate cyanoselenation route discussed above.[23]

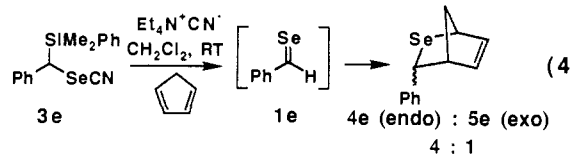
Generation of Selenoaldehydes. Aryl- and alkyl-substituted selenoaldehydes were generated by treatment of the α-silyl selenocyanates with *n*-Bu_4NF in THF at room temperature in the presence of 1.5–10 equiv of a suitable cycloaddition trapping reagent (e.g., cyclopentadiene) as illustrated in eq 3. The fluoride



(3)

was added via syringe pump over a period of 1–2 h, and in the initial stages of the reactions, selenal formation appeared to be controlled by the rate of fluoride addition. During later stages of these reactions, we observed that the α-silyl selenocyanates were completely consumed after addition of only 0.5–0.7 equiv of fluoride. This observation could be explained if cyanide ion that was eliminated from the α-silyl selenocyanates in early stages of the reaction induced desilylation and selenal formation in a manner similar to fluoride.

To test this supposition, the α-silyl selenocyanate precursor (**3e**) to selenobenzaldehyde was stirred with 1.0 equiv of $Et_4N^+CN^-$ in the presence of cyclopentadiene at room temperature (eq 4).

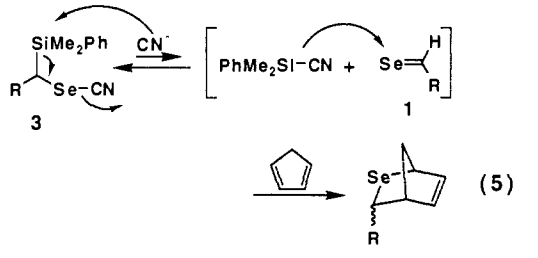


(4)

Under these conditions, selenobenzaldehyde was generated and cycloadduct formation occurred in 66% yield. It is noteworthy that syringe pump addition of the $Et_4N^+CN^-$ was not necessary to avoid selenal self-condensation reactions, indicating (as would be expected) that cyanide-induced desilylation and selenal generation proceeded at a rate significantly slower than had been observed for fluoride-induced reactions.

The ability of cyanide to induce selenal formation was somewhat surprising, since our original strategy was based on the supposition that generation of the highly reactive selenium–carbon double bond would require formation of the highly stable fluoride–silicon bond. Apparently, formation of the much weaker cyanide–silicon bond (60–70 kcal/mol vs 136 kcal/mol for Si–F)[26] was sufficient to induce cyanide elimination and selenal generation.

An alternative explanation for the successful cyanide-induced selenal formation involves reversible formation of the selenoaldehyde and 1,2-addition of $PhMe_2SiCN$ to the selenium–carbon double bond to regenerate α-silyl selenocyanate, as outlined in eq 5. In this reaction, thermodynamic parameters could well favor



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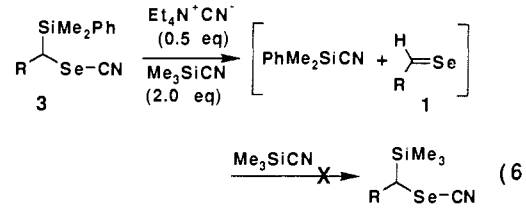
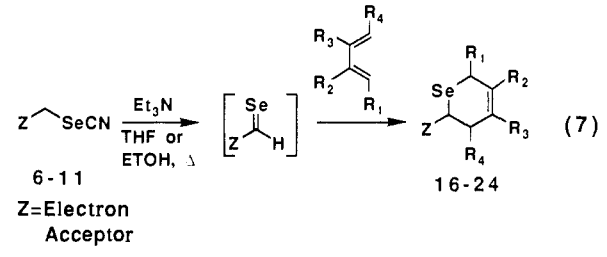
the α-silyl selenocyanate, but trapping of the transient, reactive selenal in the subsequent cycloaddition reaction would lead eventually to complete conversion of α-silyl selenocyanate to selenal cycloadduct. In an attempt to probe the likelihood of this scenario, a crossover experiment was conducted in which α-dimethylphenylsilyl selenocyanate was stirred with 2.0 equiv of trimethylsilyl cyanide and 0.5 equiv of $Et_4N^+CN^-$ (eq 6). This



(6)

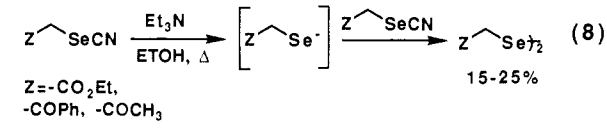
reaction was allowed to proceed until half of the starting material was consumed (ca. 1 h), at which time the reaction was filtered through a small column of neutral alumina to remove salts and excess trimethylsilyl cyanide. Analysis of the reaction mixture by TLC indicated the presence of starting α-dimethylphenylsilyl selenocyanate and two components that were significantly less polar. NMR confirmed the presence of the α-(dimethylphenylsilyl selenocyanate and showed resonances that could be attributed to selenide and diselenides resulting from selenal self-condensation reactions. However, no signals attributable to the corresponding α-trimethylsilyl selenocyanate could be detected, indicating that trimethylsilyl cyanide did not react with selenal generated from α-dimethylphenylsilyl selenocyanate. Failure to detect crossover product suggests that reversible selenal–α-silyl selenocyanate interconversion is not an important process in these reactions.

Selenoaldehydes containing electron-acceptor substituents were generated by the fluoride disilylation route or by base-induced HCN elimination (eq 7). In the latter instance, Et_3N was added



(7)

via syringe pump to a solution of the selenocyanate and cycloaddition reactant. Et_3N was sufficiently basic to generate selenals from all of the selenocyanate precursors that were examined, though in many instances, elimination to form selenal required elevated temperatures. THF was the preferred solvent for these reactions, though EtOH containing dissolved $CaCl_2$ was used for selenocyanates with adjacent carbonyl groups. These latter conditions had been employed successfully by Kirby et al.[27] in the generation of ethyl selenoxoacetate, and they presumably suppress attack by the enolate oxygen on the selenocyanate nitrile. The major drawback associated with the use of EtOH as solvent for these reactions was the formation of 15–25% yields of symmetrical diselenide byproduct, as outlined in eq 8.[28]



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Selenoaldehyde Cycloaddition Reactions

Generation of selenoaldehydes in the presence of dienes led to the formation of cycloadducts in good to excellent yields for all cases (Tables I–III), except for alkyl-substituted selenals. In these

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(27) Kirby, G. W.; Trethewey, A. N. *J. Chem. Soc., Chem. Commun.* **1986**, 1152–1154.

(28) Alkaline hydrolysis of selenocyanates is an important procedure for the preparation of diselenides: Bulka, E. In *The Chemistry of Cyanates and Their Derivatives*; Patai, S., Ed.; Wiley-Interscience: Chichester, 1977; Vol. 2, pp 901–902, and references therein.

Table I. Selenoaldehyde/Cyclopentadiene Adducts

Selenocyanate	R	endo : exo[a] 4 : 5	Yield %[b]
3a	Me	2.3 : 1	83
3b	Et	4.3 : 1	78
3c	Pr	3.4 : 1	76
3d	t-Bu	9.0 : 1	39
3e	Ph	2.6 : 1	81
3f	$PhCH_2$	3.5 : 1	89
3g	H	-----	66

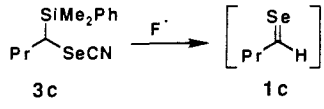
[a] Ratios of stereoisomers determined by integration of ^1H NMR signals. [b] Yields are for purified mixtures of stereoisomers.

Table II. Cycloadditions of Aryl Selenoaldehydes and Selenoformaldehyde

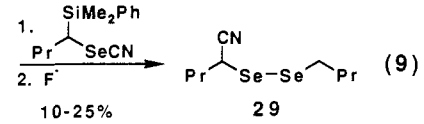
Selenocyanate	Diene	Adduct	Regioisomer(s) a : b	Yield (%)
3g	R = H	14[a]	1 : >25	70
3e	R = Ph	15[a]	1 : >25	83
10	Ar = 4-NO_2-Ph	18[b]	1 : 17	74
11	Ar = 2,4-di-NO_2-Ph	19[b]	6.5 : 1	55

[a] Prepared by method A. [b] Prepared by method B.

instances, cycloadducts only formed with highly reactive dienes such as cyclopentadiene (Table I) or 1,3-diphenylisobenzofuran. For less reactive dienes such as cyclohexadiene, isoprene, 1,3-pentadiene, 2-methyl-1,3-pentadiene, 1- or 2-alkoxybutadiene, or cyclohexadiene, the predominant products resulted from polymerization or self-condensation reactions. The major characterizable product was identified as the α-cyano diselenide **29**, formed by condensation of selenal with α-silyl selenocyanate starting material, followed by desilylation (eq 9). Inverse addition of the α-silyl



3c 1c



10-25% 29 (9)

selenocyanate to fluoride in the presence of diene, use of large excesses of diene, elevated reaction temperatures, or a combination of these conditions failed to generate any detectable quantity of [4 + 2] cycloadduct. This indicated that the alkyl-substituted selenals were relatively unreactive toward cycloaddition but highly reactive with respect to polymerization or condensation reactions. Several reactions with electron-poor dienes such as methyl coumalate, tetraphenylcyclopentadienone, or ethyl sorbate were attempted to investigate the possibility of inverse electron demand cycloaddition reactivity,[29] but no cycloadducts were obtained in these reactions.

Selenoformaldehyde and selenoacetaldehyde gave cycloadducts when generated in the presence of 1,3-diphenylisobenzofuran. The

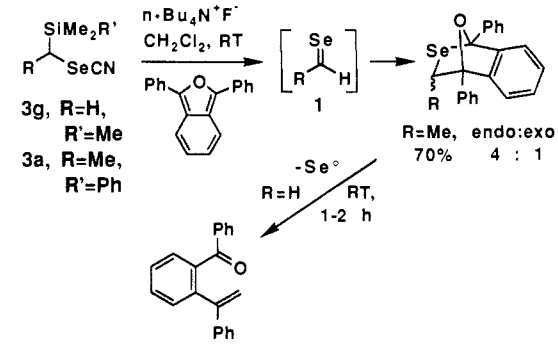
(29) For examples and discussion of inverse electron demand cycloadditions, see: Boger, D. L. *Chem. Rev.* **1986**, *86*, 781–793, and references therein.

Table III. Cycloadditions of Acceptor-Substituted Selenoaldehydes

Selenocyanate	Diene	Adduct	Regioisomer(s) a : b	Yield (%)
6	R = CN	16[b]	19 : 1	75
12	R = $PO(OMe)_2$	17[d]	>25 : 1	55
6	R = CN; R' = CH_3; R" = CH_3	20[b,e]	5.4 : 1	80
8	R = CO_2Et; R' = H; R" = CH_3	21[c,e]	2.9 : 1	40
8	R = CO_2Et; R' = CH_3; R" = CH_3	22[c,e]	4.2 : 1	43
9	R = COPh; R' = CH_3; R" = CH_3	23[c,e]	8.3 : 1	68
7	R = $COCH_3$; R' = H; R" = CH_3	24[c,e]	6.0 : 1	58
13	R = SO_2Ph; R' = CH_3; R" = CH_3	25[d,f]	>25 : 1	54
13	R = SO_2Ph; R' = H; R" = CH_3	26[d,f]	3.0 : 1	72
12	R = $PO(OMe)_2$; R' = CH_3; R" = H	27[d]	4.5 : 1	25
12	R = $PO(OMe)_2$; R' = CH_3; R" = CH_3	28[d]	Major[40]	65

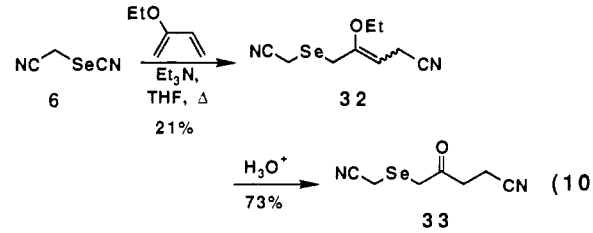
[b] Prepared by method B. [c] Prepared by method C. [d] Prepared by method D. [e] ca. 1:1, endo:exo. [f] >25:1, endo:exo.

Scheme II



selenoformaldehyde adduct was unstable and extruded elemental selenium on standing in chloroform solution at room temperature over a period of 1–2 h to give the known 3-(1-styryl)benzophenone[30] (Scheme II). An analogous extrusion of SO_2 had been reported by Block and Aslam for the corresponding sulfone adduct.[30] The selenoacetaldehyde adduct, formed in a 4:1 mixture of endo:exo isomers, did not exhibit similar instability.

Under certain reaction conditions, several acceptor-substituted selenocyanates (**6**, R = CN; **3h**, R = $PhSO_2$) participated in electrophilic 1,4-addition reactions to electron-rich dienes such as 2-ethoxybutadiene, 2-siloxycyclohexadiene, or isoprene, as exemplified by eq 10.[31] Additional confirmation of the structures



6 32 33 (10)

of the 1,4-addition products to the 2-alkoxy or 2-siloxy dienes was obtained by acid hydrolysis to the corresponding ketones, as in the conversion of **32** to **33**. This side reaction accounted for only 10–25% of the total products obtained and could be suppressed by lowering the temperature from reflux to 40 °C. The elec-

(30) Block, E.; Aslam, M. *Tetrahedron Lett.* **1982**, *23*, 4203–4206.
(31) Electrophilic addition of phenyl selenocyanate to electron-rich olefins has been observed: Tomoda, S.; Takeuchi, Y.; Nomura, Y. *Tetrahedron Lett.* **1982**, *23*, 1361–1364.

trophilic addition reaction was observed only for selenocyanates containing more potent electron-withdrawing substituents that were capable of enhancing the selenium electrophilicity.

The reactivity of selenoaldehydes in cycloaddition reactions and other undesired reactions appeared to be higher than the reactivities of the corresponding thioaldehydes[16,17] and was significantly higher than the corresponding olefin analogues. In all experiments involving selenoaldehyde generation, no blue or violet color, characteristic of sterically stabilized selenoketones,[3d,l] was ever observed, even when generation occurred under dilute conditions in the absence of cycloaddition reactant. This indicated that cycloaddition reactions or self-condensation reactions occurred too rapidly to permit buildup of significant selenal concentrations. On the other hand, thiobenzaldehyde generated by the thiosulfinate pyrolysis persisted long enough at concentrations sufficiently high to give off a characteristic purple color,[32] and thiopivaldehyde generated by pyrolysis of its trimer persisted as a violet compound in dilute solution for 16 h.[16b] Substitution of selenals with alkyl groups lowered the cycloaddition reactivity relative to self-condensation reactivity. Selenals with electron-acceptor substituents reacted faster than alkyl-substituted selenals. No significant quantities of undesired byproducts were isolated from reactions of acceptor-substituted selenals, indicating that these selenals reacted preferentially in cycloaddition reactions than in self-condensation processes.

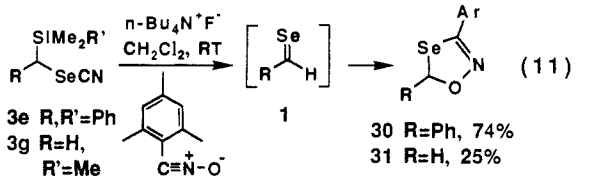
Regiochemical Preferences in Selenal Cycloaddition Reactions. The predominant regioisomers in cycloaddition reactions of acceptor-substituted selenoaldehydes (Table II) were the typical "ortho–para" isomers formed in Diels–Alder cycloaddition reactions of the all-carbon dienophile counterparts with donor-substituted dienes.[33,34] The major adducts formed with selenium bonding to the diene terminus bearing the larger HOMO coefficient.[35,36] The extent of regioselectivity exhibited in cycloaddition reactions of these acceptor-substituted selenals was dependent on the type of diene employed and on the selenal substituent. In general, higher regioselectivity was exhibited for 1- and 1,3-substituted dienes than for 2-substituted dienes.[33,34] More potent electron-acceptor substituents also resulted in somewhat higher regioselectivities. This regioselectivity also was similar to that observed for analogous thioaldehyde reactions[16] and for reactions of selenoketones substituted with one or two electron-accepting substituents.[37]

In all instances, the regioisomers were inseparable by flash chromatography and HPLC. In some cases, capillary GC indicated that more than one isomer was present in an eluting peak, but quantitation was not possible in these instances. Therefore, the ratios of regioisomers were determined by integration of suitable resonances in the ^1H NMR spectrum. In several instances, only one regioisomer could be detected, and these cases are indicated as >25:1 selectivity to indicate a conservative detection limit. The structures of cycloadducts were determined by ^1H and ^{13}C NMR, including decoupling experiments and, in several instances, by acid hydrolysis of enol ether adducts to the corresponding ketones [e.g., **16** to 2-cyano-3,6-dihydro-5-oxoselenopyran (**16c**)].

Cycloaddition reactions of selenals containing conjugating substituents (Ph, 4-NO_2-Ph) gave uncharacteristic "meta" type Diels–Alder adducts as the predominant regioisomer (Table III), with selenium bonded to the diene terminus bearing the smaller HOMO coefficient. This regiochemistry is similar to that observed in analogous reactions of thiobenzaldehyde.[16a,c,f] Not surprisingly, the strongly electron-withdrawing 2,4-dinitrophenyl substituent reversed the regiochemistry to give a predominant product similar to those observed for acceptor-substituted selenoaldehydes. The adducts of selenobenzaldehyde and selenoformaldehyde (vide infra) with 2-ethoxybutadiene were relatively unstable, even after chromatography on neutral alumina, and formed mixtures of unidentified rearrangement and selenium extrusion products. Such instability was characteristic only of adducts with this regiochemistry, since the 2-ethoxybutadiene adducts of acceptor-substituted selenals were quite stable.

Selenoformaldehyde was the only selenal containing a so-called "donor" substituent (H), which reacted with electronically biased dienes. Its cycloaddition reactions gave adducts with regiochemistry similar to that observed for selenobenzaldehyde. This regiochemical preference also was identical with that displayed by thioformaldehyde.[16f] The ability to obtain cycloadducts from selenoformaldehyde, but not from other donor-substituted selenals, probably was due to diminished steric hindrance in the cycloaddition transition state and to the relatively lower LUMO energy of a proton-substituted dienophile vs an alkyl-substituted dienophile.

Selenobenzaldehyde and selenoformaldehyde also reacted with the dipolar reagent 2,4,6-trimethylbenzonitrile *N*-oxide to give 1,4,2-oxaselenazoles in 74 and 25% yields, respectively (eq 11).



(11)

The efficiency of adduct formation in the selenoformaldehyde reaction was probably significantly higher than 25%; however, purification was difficult, and the adduct (**31**) was quite unstable. The regiochemistry of the oxaselenazole cycloadducts was consistent with expectations based on the regioselectivities displayed in diene cycloadditions and corresponding thioaldehyde cycloadditions of these molecules.[16e,f] Only one regioisomer was observed in these reactions, though for this particular dipolar cycloaddition reaction this result should not be interpreted as exclusive regioselectivity, since the other regioisomer would be a selenenic ester of dubious stability and probably would not survive to be detected. We did not attempt this dipolar cycloaddition reaction with acceptor-substituted selenals, since the predominant isomer was expected to be this unstable selenenic ester adduct.

Although we were unable to isolate [4 + 2] cycloadducts of alkyl-substituted selenoaldehydes with electronically biased dienes, we did observe a reaction of selenobutyraldehyde with the reactive dipolar reagent, 2,4,6-trimethylbenzonitrile *N*-oxide. None of the selenide or diselenide condensation products observed in the failed [4 + 2] cycloaddition reactions were detected in this reaction, and an inseparable mixture containing at least two components was obtained after flash chromatography. An appropriate mass peak for the parent ion of the expected adduct was present in the mass spectrum of this mixture. However, because we were unable to further purify this material, we could not make a definitive structural identification of this adduct, based on the ^1H NMR spectrum.

The overall picture of selenal cycloaddition regiochemistry, summarized within the context of frontier molecular orbital theory,[35,36] is provided in Figure 1. This qualitative FMO characterization, which places the large LUMO coefficient on selenium for acceptor substituents and on carbon for donor (H) or conjugating substituents, is consistent with all of the results described above and with experimental and calculated results obtained by Houk, Vedejs, and co-workers for analogous thioaldehydes.[16c] However, this model is not consistent with regiochemical results obtained in cycloadditions of two conjugated selenoketones, selenobenzophenone and selenofluorenone.[24,37] For these cases it is important to recognize that the carbon–selenium π bond is sufficiently polarizable and quite weak (12–17 kcal/

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(33) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381–7396, and references therein.

(34) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923–3941.

(35) Fukui, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 801–809, and references therein.

(36) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361–369, and references therein.

(37) Meinke, P. T.; Krafft, G. A. *J. Am. Chem. Soc.*, following article in this issue.

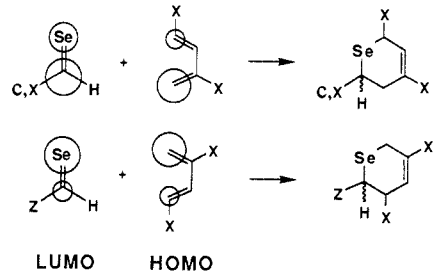

Figure 1. Qualitative frontier molecular orbital summary of selenoaldehyde regiochemistry, based on the normal mode of [4 + 2] cycloaddition ($HOMO_{diene} - LUMO_{dienophile}$). X, electron releasing; C, conjugating; Z, electron accepting.

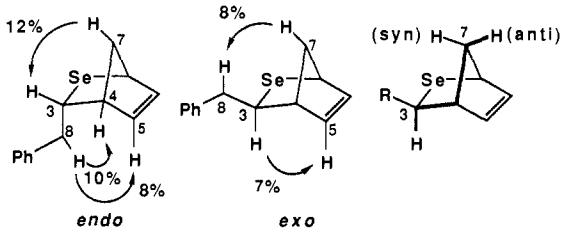

Figure 2. Nuclear Overhauser enhancements for endo and exo isomers **4f** and **5f**. "*W*" coupling of 0.5–0.7 Hz between the C-3 methine proton and the anti C-proton is evident for all of the exo cyclopentadiene adducts.

mol)[38] so that particular substituents and conditions could reverse the regiochemistry expected on the basis of FMO theory for conjugating substituents. The 2,4-dinitroselenobenzaldehyde cycloaddition is a reaction in which the regiochemistry of the major adduct is that expected for an electron-accepting substituent rather than a conjugating substituent. This result is consistent with the reactivity model for normal mode Diels–Alder reactions proposed recently by Kahn and Hehre,[33,39] a model that also could be used to rationalize the anamolous results obtained in the selenobenzophenone and selenofluorenone cycloaddition reactions.[24,37]

Stereochemistry of Selenoaldehyde Cycloadditions. Significant levels of diastereoselectivity were observed in many selenal cycloadditions, with the major diastereomer arising from an endo orientation of the selenal and the diene. Alkyl-substituted selenoaldehydes afforded cyclopentadiene adducts (eq 3) in which the endo isomers predominated in ratios ranging from 2.3:1 to 9.0:1, with the sterically demanding selenopivaldehyde giving the highest diastereoselectivity and selenoacetaldehyde giving the lowest. The stereoisomers were not separated by chromatography, except for the selenobenzaldehyde adducts (**4e** and **5e**) which could be separated by HPLC. Quantitation of isomer ratios was accomplished by integration of suitable resonances in the ^1H NMR spectrum.

Delineation of the particular stereoisomers of these cyclopentadiene adducts was accomplished by NOE experiments and by comparison with analogous thioaldehyde adducts.[16f,17] Figure 2 illustrates significant enhancements obtained for the 2-phenylselenoacetaldehyde adducts. This series of cycloadducts exhibited qualitatively similar characteristics in the ^1H NMR spectra for all exo isomers and for all endo isomers. In every instance, the two vinylic proton resonances of the endo isomer bracketed the two vinylic resonances of the exo isomer. The epimeric proton of the exo isomer resonated at slightly lower field than the epimeric proton of the endo isomer for all adducts examined. A third feature, characteristic of all exo isomers was fine "*W*" coupling of the anti proton of C-7 with the epimeric C-3 methine, as shown below.

The aromatic-substituted selenals also displayed significant endo selectivity in cycloaddition reactions. In the reactions of 4-nitro- and 2,4-dinitroselenobenzaldehyde with 2-(*tert*-butyldimethylsiloxy)cyclohexadiene, only the endo isomers (**18** and **19**) were detected. These structures also were identified by NOE experiments.

The stereoselectivity observed in the reactions of acceptor-substituted selenoaldehydes was affected by the reaction conditions. For reactions involving Et_3N in refluxing EtOH, mixtures of diastereomers ranging from 1:1 to 1.2:1 were obtained, and in reactions with acyclic dienes where one isomer did predominate slightly, it was impossible to establish the identity of that diastereomer, since the isomers were inseparable. It is conceivable that these isomer mixtures represented kinetic mixtures, though it is more likely that the mixtures resulted from isomerization of the epimeric center under the basic reaction conditions. When Et_3N in CH_2Cl_2 at 25 °C was used to generate the 4-nitrophenyl-, the 2,4-dinitrophenyl-, and the phenylsulfonyl-substituted selenals in reactions with cyclohexadiene or 2-(*tert*-butyldimethylsiloxy)cyclohexadiene, endo selectivities ranging from 8:1 for the 4-nitroselenobenzaldehyde/cyclohexadiene adduct to exclusively endo for the other reactions were observed. Under the same conditions, however, the cyano-substituted selenal gave a 1:1.2 endo:exo ratio with cyclohexadiene. This latter ratio may be a thermodynamic ratio, again the result of epimerization. Generation of the phenylsulfonyl-substituted selenal with fluoride in the presence of cyclohexadiene or 2-methyl-1,3-pentadiene generated endo adducts exclusively. The 2-methyl-1,3-pentadiene adduct exhibited a 1.5 Hz coupling constant between the $PhSO_2$ methine proton and the adjacent allylic methine, indicative of a cis relationship. Attempts were made to epimerize this adduct to a mixture of stereoisomers using a variety of bases and reaction conditions, but all attempts failed to generate the trans isomer.

As a general matter, it can be concluded from the stereochemically informative experiments that the endo rule associated with Diels–Alder cycloadditions of all-carbon dienophiles also applies to cycloadditions of selenoaldehydes. However, in instances involving higher temperatures or conditions sufficiently basic to deprotonate at the epimeric center, the endo selectivity is compromised.

Conclusions. The experimental results described in this paper indicate that selenoaldehydes containing a variety of functionalities can be prepared easily and participate with good to excellent efficiency in cycloaddition reactions. These cycloaddition reactions are useful in the synthesis of a wide spectrum of functionalized selenopyrans, molecules that would be difficult to prepare by other routes. The cycloaddition regiochemistry parallels that observed in reactions of the analogous thioaldehyde derivatives and is consistent with the FMO characterization of thioaldehydes. The regiochemical results also can be interpreted by the reactivity modeling approach of Kahn and Hehre. Good diastereofacial selectivity is exhibited in many selenal cycloadditions and should facilitate the use of selenals in stereospecific syntheses. Efforts are continuing in our laboratory to exploit the chemistry of these new, highly reactive heterodienophiles.

Experimental Section

General Procedure for Synthesis of α-Silyl *p*-Toluenesulfonates. 1-(Dimethylphenylsilyl)ethyl *p*-Toluenesulfonate (2a). To a solution containing 34.2 mL (26.0 mmol) of 0.76 M $PhMe_2SiLi$ in THF at −78 °C was added slowly 1.40 mL (25 mmol) of freshly distilled acetaldehyde as a solution in 15 mL of THF. The deep brown color of the anion persisted throughout the addition. The solution was stirred for 15 min at −78 °C and then transferred via cannula to a solution containing 5.52 g (29 mmol) of *p*-toluenesulfonyl chloride in 20 mL of THF at −78 °C, whereupon the brown color promptly disappeared. After 1 h at −78 °C and 1 h at room temperature, the cloudy yellow solution was poured into saturated $NaHCO_3$ (25 mL), and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. Flash chromatography on silica gel (25:1:1 hexane/Et_2O/CH_2Cl_2 as eluent) yielded pure **2a** (5.98 g, 72%) as a viscous, colorless oil.

1-(Dimethylphenylsilyl)propyl *p*-toluenesulfonate (2b): isolated as a viscous, colorless oil in 77% yield.

1-(Dimethylphenylsilyl)butyl *p*-toluenesulfonate (2c): isolated as a viscous, colorless oil in 81% yield.

(38) Calculations on selenoformaldehyde have been carried out. See: References 12i, 12n, and Burton, P. G.; Peyerimhoff, S. D.; Buenker, R. J. *J. Chem. Phys.* **1982**, *73*, 83–98.

(39) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663–666.

1-(Dimethylphenylsilyl)-2,2-dimethylpropyl *p*-toluenesulfonate (2d): isolated as a white, waxy solid in 87% yield.

α-(Dimethylphenylsilyl)benzyl *p*-Toluenesulfonate (2e). To a solution containing 33.7 mL (30 mmol) of 0.89 M $PhMe_2SiLi$ in THF at −78 °C under an argon atmosphere was added 3.18 g (30 mmol) of freshly distilled benzaldehyde as a solution in 15 mol of THF over 15 min. The solution remained a deep brown and was permitted to stir at −78 °C for 20 min. The alkoxide solution was transferred via cannula to 6.65 g (35 mmol) of *p*-toluenesulfonyl chloride in 20 mL of THF at −78 °C over 10 min. After being stirred for 1 h at −78 °C, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. The reaction mixture was diluted with 200 mL of pentane, cooled to 0 °C, and washed once (quickly) with 75 mL of ice-cold saturated NaCl. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The organic layers were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The resultant viscous oil was dissolved in pentane (50 mL), and cooling to −32 °c caused separation of a dense oil. This oil was subjected to trituration two additional times with pentane, at which point the product was sufficiently pure as to crystallize. The waxy yellow crystals thus obtained were recrystallized from pentane yielding 10.47 g (88%) of **2e** as white crystals.

1-(Dimethylphenylsilyl)-2-phenylethyl *p*-toluenesulfonate (2f): isolated as a viscous, colorless oil in 77% yield.

General Procedure for the Preparation of α-Silyl Selenocyanates. 1-(Dimethylphenylsilyl)ethyl Selenocyanate (3a). To a solution containing 625 mg (1.87 mmol) of 1-(dimethylphenylsilyl)ethyl *p*-toluenesulfonate and 10 mg (0.03 mmol) of 18-crown-6 in 20 mL of THF at room temperature was added 323 mg (2.24 mmol) of KSeCN. The reaction mixture was heated to reflux for 1–5 h and then cooled to room temperature. The solution was poured into saturated $NaHCO_3$ (10 mL), and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The reaction crude was purified by flash chromatography on silica gel (25:1:1 hexanes/Et_2O/CH_2Cl_2) yielding 481 mg (96%) of **3a** as a pale yellow oil.

1-(Dimethylphenylsilyl)propyl selenocyanate (3b): isolated as colorless oil in 89% yield.

1-(Dimethylphenylsilyl)butyl selenocyanate (3c): isolated as a pale, yellow oil in 91% yield.

1-(Dimethylphenylsilyl)-2,2-dimethylpropyl selenocyanate (3d): isolated as a viscous, colorless oil in 83% yield.

α-(Dimethylphenylsilyl)benzyl selenocyanate (3e): isolated as a vile smelling, pale yellow oil in 97% yield.

1-(Dimethylphenylsilyl)-2-phenylethyl selenocyanate (3f): isolated as a foul smelling, colorless, viscous oil in 90% yield.

(Trimethylsilyl)methyl Selenocyanate (3g). To a solution containing 5.67 g (39.4 mmol) of KSeCN and 100 mg (0.35 mmol) of 18-crown-6 in THF (25 mL) at room temperature was added 5 mL (35.8 mmol) of (chloromethyl)trimethylsilane. The solution was heated to reflux for 3 h. The reaction mixture was then cooled to 0 °C, poured into Et_2O (20 mL), and washed with saturated $NaHCO_3$ (20 mL). After separation of layers, the aqueous layer was extracted with Et_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure to give a brown, oily residue. Pure **3g** (6.40 g, 93%) was obtained as vile smelling, colorless oil by flash chromatography on silica gel (25:1:1 hexane/Et_2O/CH_2Cl_2 as eluant).

General Procedure for Selenal Cycloadditions with Cyclopentadiene. 2-Selena[2.2.1]bicyclohept-5-ene (4g). To a solution containing 1.87 g (11.4 mmol) of (trimethylsilyl)methyl selenocyanate and 3.76 g (57 mmol) of freshly distilled cyclopentadiene in 20 mL of CH_2Cl_2 at 0 °C was added 11.4 mL (11.4 mmol) of 1 M *n*-Bu_4NF in THF over 5 h at 0 °C via syringe pump. The reaction was poured into H_2O (10 mL), and after separation of layers, the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. Pure **4g** (1.20 g, 66.2%) was obtained as a pale yellow liquid by flash chromatography on activated neutral alumina (25:1:1 pentane/Et_2O/CH_2Cl_2 as eluant).

***endo*- and *exo*-3-Methyl-2-selena[2.2.1]bicyclohept-5-ene (4a and 5a).** This pale yellow oil was isolated as an inseparable mixture of endo/exo isomers in 83% yield. The isomer ratio was determined to be 2.3:1 by proton NMR integration of the vinyl resonances, with the endo isomer predominating.

***endo*- and *exo*-3-Ethyl-2-selena[2.2.1]bicyclohept-5-ene (4b and 5b).** This colorless oil was isolated as an inseparable mixture of endo/exo isomers in 78% yield. The isomer ratio was determined to be 4.3:1 by proton NMR integration of the vinyl resonances, with the endo isomer predominating.

***endo*- and *exo*-3-Propyl-2-selena[2.2.1]bicyclohept-5-ene (4c and 5c).** This colorless oil was isolated as an inseparable mixture of endo/exo isomers in 76% yield (174 mg). The isomer ratio was determined to be 3.4:1 by proton NMR integration of the vinyl resonances, with the endo isomer predominating.

***endo*- and *exo*-3-*tert*-Butyl-2-selena[2.2.1]bicyclohept-5-ene (4d and 5d).** This colorless oil was isolated as an inseparable mixture and endo/exo isomers in 39% yield. The isomer ratio was determined to be 9.0:1 by proton NMR integration of the vinyl resonances, with the endo isomer predominating.

***endo*- and *exo*-3-Phenyl-2-selena[2.2.1]bicyclohept-5-ene (4e and 5e).** This colorless oil was isolated as an inseparable mixture of endo/exo isomers in 81% yield. The isomer ratio was determined to be 2.6:1 by proton NMR integration of the vinyl resonances, with the endo isomer predominating. Small quantities of pure endo and pure exo isomers were obtained by repeated HPLC purification using 99:0.5:0.5 hexanes/CH_2Cl_2/Et_2O as eluant on an Alltech/Applied Science 10-μm RSil silica gel (25 cm × 10 mm) column.

***endo*- and *exo*-3-Benzyl-2-selena[2.2.1]bicyclohept-5-ene (4f and 5f).** This colorless oil was isolated as an inseparable mixture of endo/exo isomers in 89% yield (80.1 mg). The isomer ratio was determined to be 3.5:1 by proton NMR integration of the vinyl resonances, with the endo isomer predominating.

(Selenocyanato)acetonitrile (6): prepared from 2-chloroacetonitrile and potassium selenocyanate, and isolated as a dense, pale yellow oil in 58% yield.

1-(Selenocyanato)propan-2-one (7): prepared from chloroacetone and isolated as a viscous pale yellow oil in 78% yield.

Ethyl (selenocyanato)acetate (8): prepared from ethyl bromoacetate and isolated as a pale yellow oil in 82% yield.

1-Phenyl-2-(selenocyanato)acetaldehyde (9): prepared from α-chloroacetophenone and isolated as pure white crystals (mp 77–79 °C) in 83% yield.

4-Nitrobenzyl selenocyanate (10): prepared from α-chloro-4-nitrotoluene and isolated as a grey-white powder in 86% yield.

2,4-Dinitrobenzyl selenocyanate (11): prepared from α-bromo-2,4-dinitrotoluene and isolated as pale yellow needles (mp 70–72 °C) in 79% yield.

Selenoaldehyde Cycloadditions with Unsymmetrical Dienes and Dipoles. Four general procedures were employed to generate and trap selenoaldehydes.

Method A. To a solution containing 0.50 mmol of an α-silyl selenocyanate and 1–3 mmol of freshly distilled diene in CH_2Cl_2 (20 mL) at 25 °C was added a solution containing 0.50 mL (0.50 mmol) of 1 M *n*-Bu_4NF diluted to 10 mL with THF over 2–3 h via syringe pump. The reaction mixture was diluted with pentane (30 mL) and filtered through a 4-cm activated neutral alumina plug (using 25:1:1 pentane/Et_2O/CH_2Cl_2 as eluant). The filtrate subsequently was concentrated at reduced pressure. Pure cycloadduct was obtained by flash chromatography on activated neutral alumina (25:1:1 pentane/Et_2O/CH_2Cl as eluant).

Method B. A solution containing 0.50 mmol of selenocyanate and 1–5 mmol of diene in 20 mL of CH_2Cl_2 was prepared. To this was added, at room temperature, 77 μL (0.55 mmol) of Et_3N as a solution in 10 mL of CH_2Cl_2 over 1 h via syringe pump. The reaction mixture was diluted with pentane (30 mL) and filtered through a 4-cm activated neutral alumina pig (using 8:1:1 pentane/Et_2O/CH_2Cl_2 as eluant). The filtrate subsequently was concentrated at reduced pressure. Pure cycloadduct was obtained by flash chromatography on silica gel (8:1:1 pentane/Et_2O/CH_2Cl_2 as eluant).

Method C. A solution containing 0.50 mmol of selenocyanate, 5–10 mmol of diene, and 94 mg (0.50 mmol) of $CaCl_2 \cdot 2H_2O$ in absolute ethanol (10 mL) was prepared. This solution was heated to reflux, and 77 μL (0.55 mmol) of Et_3N was added over 1 h as a solution in absolute ethanol (10 mL) via syringe pump. The reaction was cooled to 0 °C, poured into cold water (50 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The resultant crude product was purified by flash chromatography on silica gel with 8:1:1 hexane/Et_2O/CH_2Cl_2 as eluant.

Method D. A solution containing 0.50 mmol of an α-silyl selenocyanate and 5–10 mmol of freshly distilled diene in THF (20 mL) was prepared. This solution was heated to reflux, and 0.50 mL (0.50 mmol) of 1 M *n*-Bu_4NF diluted to 10 mL with THF was added over 1 h via syringe pump. The reaction mixture was cooled to 0 °C, diluted with pentane (30 mL), filtered through a 4-cm activated neutral alumina plug (using 8:1:1 pentane/Et_2O/CH_2Cl_2 as eluant) and subsequently concentrated under reduced pressure. Pure cycloadduct was obtained by flash chromatography on silica gel (8:1:1 pentane/Et_2O/CH_2Cl_2 as eluant).

3,6-Dihydro-4-ethoxy-2*H*-selenopyran (14). This selenopyran was prepared by reaction of **3g** with 2-ethoxybutadiene via method A and was

isolated as a colorless oil in 70% (62.0 mg) after purification on neutral, activated alumina.

3,6-Dihydro-4-ethoxy-2-phenyl-2*H*-selenopyran (15). This selenopyran was prepared by reaction of **3e** and -ethoxybutadiene via method A and was isolated as a pale yellow oil in 83% yield (21.9 mg) after purification on neutral, activated alumina.

2-Cyano-3,6-dihydro-4-ethoxy-2*H*-selenopyran (16a). This selenacycle was prepared by reaction of **6** with 2-ethoxybutadiene via method B and was isolated as a pale yellow oil in 75.1% (950 mg) after purification on neutral, activated alumina.

2-Cyano-3,6-dihydro-5-oxoselenopyran (16c). To a solution containing 10 mg (4.6 μmol) of **16a** and 2 drops of H_2O in THF (2 mL) at room temperature was added 1 drop of 0.1 N HCl. After 30 min, the reaction mixture was diluted with pentane (5 mL) and cooled to 0 °c, and the solution was neutralized and dried with 25 mg of anhydrous K_2CO_3. The solution was filtered and concentrated under reduced pressure, and pure selenopyrone **16c** was isolated as a pale yellow liquid in 84% (7.3 mg) upon purification on silica gel using 4:1:1 hexane/Et_2O/CH_2Cl_2 as eluant.

3,6-Dihydro-2-(dimethylphosphono)-5-ethoxy-2*H*-selenopyran (17). This selenopyran was prepared by reaction of dimethyl[(selenocyanato)(trimethylsilyl)methyl]phosphonate[23] with 2-ethoxybutadiene via method D and was isolated as a colorless oil in 55% yield (50.8 mg) after purification on silica gel using 1:1 THF/hexanes.

***endo*-(4-Nitrophenyl)-6-[(dimethyl-*tert*-butylsilyl)oxy]-2-selenabicyclo[2.2.2]oct-5-ene (18a) and *endo*-(4-Nitrophenyl)-5-[(dimethyl-*tert*-butylsilyl)oxy]-2-selenabicyclo[2.2.2]oct-5-ene (18b).** These bicyclic selenacycles were prepared by reaction of **10** with 2-(*tert*-butyldimethylsiloxy)cyclohexadiene via method B and were obtained as an inseparable mixture of endo isomers in a ratio of 1:1.7, respectively. The isomer ratio was determined by ^1H NMR integration. These compounds were isolated as a bright yellow, viscous oil in 74% (164 mg).

***endo*-(2,4-Dinitrophenyl)-6-[(dimethyl-*tert*-butylsilyl)oxy]-2-selenabicyclo[2.2.2]oct-5-ene (19a) and *endo*-(2,4-Dinitrophenyl)-5-[(dimethyl-*tert*-butylsilyl)oxy]-2-selenabicyclo[2.2.2]oct-5-ene (19b).** These bicyclic selenacycles were prepared by reaction of **11** with 2-(*tert*-butyldimethylsiloxy)cyclohexadiene via method B and were obtained as an inseparable mixture of endo isomers in a ratio of 6.5:1, respectively. The isomer ratio was determined by ^1H NMR integration. These compounds were isolated as a deep yellow, viscous oil in 55% (162 mg).

2-Cyano-3,6-dihydro-3,5-dimethyl-2*H*-selenopyran (20a) and 2-Cyano-3,6-dihydro-4,6-dimethyl-2*H*-selenopyran (20b). The cycloadducts were prepared by reaction of **6** with 2-methyl-1,3-pentadiene via method B and isolated as a pale yellow oil in 80% yield (165 mg). These selenopyrans were obtained as an inseparable mixture of isomers, the ratio of which was determined by ^1H NMR integration. The adducts were obtained in a 1:1 mixture of epimers for each regioisomer and a ratio of 5.4:1 mixture of regioisomers.

Ethyl 3,6-Dihydro-3-methyl-2*H*-selenopyran-2-carboxylate (21a) and Ethyl 3,6-Dihydro-6-methyl-2*H*-selenopyran-2-carboxylate (21b). The cycloadducts were prepared by reaction of **8** with (*E*)-1,3-pentadiene via method C and isolated as a pale yellow oil in 40% yield (128 mg). These selenopyrans were obtained as an inseparable mixture of isomers, the ratio of which was determined by ^1H NMR integration. The adducts were obtained in a 1:1 mixture of epimers for each regioisomer and a 2.9:1 mixture of regioisomers.

Ethyl 3,6-Dihydro-3,5-dimethyl-2*H*-selenopyran-2-carboxylate (22a) and Ethyl 3,6-Dihydro-4,6-dimethyl-2*H*-selenopyran-2-carboxylate (22b). The cycloadducts were prepared by reaction of **8** with (*E*)-2-methyl-1,3-pentadiene via method C and isolated as a pale yellow oil in 43% yield (197 mg). These selenopyrans were obtained as an inseparable mixture of isomers, the ratio of which was determined by ^1H NMR integration. The adducts were obtained in a 1:1 mixture of epimers for each regioisomer and a 4.2:1 mixture of regioisomers.

2-Benzoyl-3,6-dihydro-3,5-dimethyl-2*H*-selenopyran (23a) and 2-Benzoyl-3,6-dihydro-4,6-dimethyl-2*H*-selenopyran (23b). The cycloadducts were prepared by reaction of **9** with (*E*)-2-methyl-1,3-pentadiene via method C and isolated as a pale yellow oil in 68% yield (363 mg). These selenopyrans were obtained as an inseparable mixture of isomers, the ratio of which was determined by ^1H NMR integration. The adducts were obtained as a 1:1 mixture of epimers for each regioisomer and a 8.3:1 mixture of regioisomers.

2-Acetyl-3,6-dihydro-3-methyl-2*H*-selenopyran (24a) and 2-Acetyl-3,6-dihydro-6-methyl-2*H*-selenopyran (24b). The cycloadducts were prepared by reaction of **7** with (*E*)-1,3-pentadiene via method C and isolated as a pale yellow oil in 58% yield (86.6 mg). These selenopyrans were obtained as an inseparable mixture of isomers, the ratio of which was determined by ^1H NMR integration. The adducts were obtained as a 1:1 mixture of epimers for each regioisomer and a 6.0:1 mixture of regioisomers.

***endo*-3,6-Dihydro-3,5-dimethyl-2-(phenylsulfonyl)-2*H*-selenopyran (25).** This cycloadduct was prepared by reaction of (*tert*-butyldimethylsilyl)(selenocyanato)methyl phenyl sulfone (**13**)[23] with (*E*)-2-methyl-1,3-pentadiene via method D and isolated as a pale yellow oil in 55% yield (54.4 mg).

***endo*-3,6-Dihydro-3-methyl-2-(phenylsulfonyl)-2*H*-selenopyran (26a) and *endo*-3,6-Dihydro-6-methyl-2-(phenylsulfonyl)-2*H*-selenopyran (26b).** The cycloadducts were prepared by reaction of (*tert*-butyldimethylsilyl)(selenocyanato)methyl phenyl sulfone (**13**)[23] with (*E*)-1,3-pentadiene via method D and isolated as a pale yellow oil in 72% yield (91.7 mg). These selenopyrans were obtained as an inseparable mixture of isomers, the ratio of which was determined by ^1H NMR integration. The adducts were obtained as a 3.0:1 mixture of regioisomers and only the endo isomers were detected.

3,6-Dihydro-2-(dimethylphosphono)-5-methyl-2*H*-selenopyran (27a) and 3,6-Dihydro-2-(dimethylphosphono)-4-methyl-2*H*-selenopyran (27b). The cycloadducts were prepared by reaction of dimethyl[(selenocyanato)(*tert*-butyldimethylsilyl)methyl]phosphonate (**12**) with isoprene via method D and isolated as a pale yellow oil in 25% yield (12.7 mg). These selenopyrans were obtained as an inseparable mixture of isomers, the ratio of which was determined by ^1H NMR integration. The adducts were obtained in a 4.5:1 mixture of regioisomers.

3,6-Dihydro-3,5-dimethyl-2-(dimethylphosphono)-2*H*-selenopyran (28). The cycloadducts were prepared by reaction of dimethyl[(selenocyanato)(*tert*-butyldimethylsilyl)methyl]phosphonate (**12**)[23] with (*E*,-*E*)-2-methyl-1,3-pentadiene via method D and isolated as a viscous, colorless oil in 65% yield (73.3 mg).[40]

1-Cyanobutyl butyl diselenide (29): isolated in 10–25% yields from attempted cycloadditions of selenobutyraldehyde with a variety of dienes and purified by silica gel flash chromatography.

5-Phenyl-3-(2,4,6-trimethylphenyl)-1,4,2-oxaselenazole (30): prepared by reaction of **3e** with 2,4,6-trimethylbenzonitrile *N*-oxide via method D and isolated as colorless crystals in 74% yield (53.5 mg).

3-(2,4,6-Trimethylphenyl)-1,4,2-oxaselenazole (31): prepared by reaction of **3g** with 2,4,6-trimethylbenzonitrile *N*-oxide via method D and isolated as a pale yellow oil in 25% yield (37.5 mg) after purification by flash chromatography on neutral alumina.

Cyanomethyl 4-cyano-2-ethoxybuten-2-yl selenide (32): isolated as a pale yellow oil in 21% yield (319 mg) as a byproduct from the reaction that generated compound **16**.

Cyclomethyl 4-Cyano-2-oxobutyl Selenide (33). To a solution containing 10 mg (4.1 μmol) of **32** and 2 drops of H_2O in THF (2 mL) at room temperature was added 1 drop of 0.1 N HCl. After 30 min, the reaction mixture was diluted with pentane (5 mL) and cooled to 0 °C, and the solution was neutralized and dried with 25 mg of anhydrous K_2CO_3. The solution was filtered and concentrated at reduced pressure, and pure selenide was isolated as a pale yellow liquid in 73% (6.3 mg) upon purification on silica gel using 4:1:1 hexane/Et_2O/CH_2Cl_2 as eluant.

Acknowledgment. We thank the National Science Foundation for financial support of this work and the American Cancer Society for a faculty fellowship to G.A.K., 1983–1986.

Registry No. 1 (R = Pr), 100604-96-4; **2a**, 100604-82-8; **2b**, 100604-83-9; **2c**, 100604-84-0; **2d**, 100604-87-3; **2e**, 100604-85-1; **2f**, 100604-86-2; **3a**, 100604-89-5; **3b**, 100604-90-8; **3c**, 100604-91-9; **3d**, 100604-94-2; **3e**, 100604-92-0; **3f**, 100604-93-1; **3g**, 114083-13-5; **4a**, 100605-00-3; **4b**, 100605-02-5; **4c**, 100605-04-7; **4d**, 100605-10-5; **4e**, 100605-06-9; **4f**, 100605-08-1; **4g**, 100605-12-7; **5a**, 100605-01-4; **5b**, 100605-03-6; **5c**, 100605-05-8; **5d**, 100605-11-6; **5e**, 100605-07-0; **5f**, 100605-09-2; **6**, 89831-32-3; **7**, 69310-35-6; **8**, 68278-25-1; **9**, 67131-27-5; **10**, 83293-39-4; **11**, 116808-95-8; **12**, 114083-23-7; **12** ($SiMe_3$ analogue), 116809-06-4; **13**, 114083-22-6; **14b**, 114082-84-7; **15b**, 114082-85-8; **16a**, 114082-86-9; **16c**, 116809-05-3; **17a**, 114082-87-0; **18a**, 114082-88-1; **18b**, 114082-89-2; **19a**, 114105-44-1; **19b**, 114082-90-5; *cis*-**20a**, 116808-96-9; *trans*-**20a**, 116809-07-5; *cis*-**20b**, 114083-01-1; *trans*-**20b**, 114083-00-0; *cis*-**21a**, 116808-97-0; *trans*-**21a**, 116809-08-6; *cis*-**21b**, 114083-03-3; *trans*-**21b**, 114083-02-2; *cis*-**22a**, 116808-98-1; *trans*-**22a**, 116809-09-7; *cis*-**22b**, 114083-05-5; *trans*-**22b**, 114083-04-4; *cis*-**23a**, 116808-99-2; *trans*-**23a**, 116809-10-0; *cis*-**23b**, 114083-07-7; *trans*-**23b**, 114083-06-6; *cis*-**24a**, 116809-00-8; *trans*-**24a**, 116809-11-1; *cis*-**24b**, 114083-09-9; *trans*-**24b**, 114083-08-8; *cis*-**25a**, 116809-01-9; *cis*-**26a**, 116809-02-0; *cis*-**26b**, 116809-04-2; **27a**, 114082-98-3; **27b**, 114083-12-4;

(40) Two isomers were obtained in a 6:1 ratio. The major isomer is the regioisomer shown, and probably the endo (cis) stereoisomer. The minor isomer is probably the other regioisomer, also with endo (cis) stereochemistry. The exact structures could not be verified because the epimeric methine protons were obscured by the phosphonate methyl resonances.

cis-**28a**, 116809-03-1; *cis*-**28b**, 116808-94-7; **29**, 114105-45-2; **30**, 114083-16-8; **31**, 114083-15-7; **32**, 114083-17-9; **33**, 114083-18-0; $PhMe_2SiLi$, 3839-31-4; MeCHO, 75-07-0; EtCHO, 123-38-6; PrCHO, 123-72-8; *t*-BuCHO, 630-19-3; PhCHO, 100-52-7; $PhCH_2CHO$, 122-78-1; KSeCN, 3425-46-5; Me_3SiCH_2Cl, 2344-80-1; $ClCH_2CN$, 107-14-2; $ClCH_2COCH_3$, 78-95-5; $BrCH_2CO_2Et$, 105-36-2; $ClCH_2COPh$, 532-27-4; $ClCH_2C_6H_4$-4-NO_2, 100-14-1; $BrCH_2C_6H_3$-2,4-$(NO_2)_2$, 3013-38-5; CH_2=C(OEt)CH=CH_2, 4747-05-1; (*E*)-CH_2=C(CH_3)CH=$CHCH_3$, 926-54-5; (*E*)-CH_2=CHCH=$CHCH_3$, 2004-70-8; CH_2=C(CH_3)C-H=CH_2, 78-79-5; cyclopentadiene, 542-92-7; 2-[(*tert*-butyldimethylsilyl)oxy]-1,3-cyclohexadiene, 71106-34-8; 2,4,6-trimethylbenzonitrile *N*-oxide, 2904-57-6.

Supplementary Material Available: General experimental procedures and ^1H and ^{13}C NMR, IR, and MS data (26 pages). Ordering information is given on any current masthead page.

Preparation and Cycloaddition Reactions of Selenoketones

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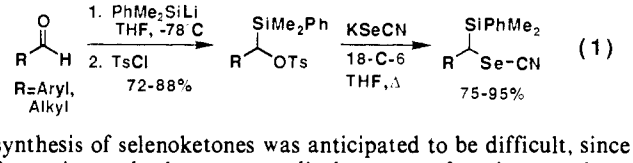
Abstract: Dienophilic selenoketones have been prepared by base-induced elimination of cyanide from selenocyanates containing electron-withdrawing or conjugating substituents. Cycloaddition reactions of selenoketones with dienes or dipolar reagents proceed efficiently to generate highly functionalized selenopyran and oxaselenazole derivatives. The cycloaddition regiochemistry is discussed in the context of frontier molecular orbital theory and the reactivity modeling approach of Kahn and Hehre.

During the past decade, significant interest in the chemistry of highly reactive carbon–heteroatom double bonds has developed. Notable accomplishments include the synthesis of carbon–silicon double bonds by West et al.[1] and by T. Barton[2] and the synthesis of reactive carbon–sulfur bonds in thioaldehydes by Vedejs,[3] Baldwin,[4] and others.[5] The synthesis of selenium–carbon double bonds also has attracted attention, with the first synthesis of sterically hindered selenoketones by D. H. R. Barton and co-workers[6a,b] and by Guziec et al.,[6b-n] and more recently, with the first synthesis of unstabilized aryl and alkyl selenoaldehydes in our laboratories.[7] Since our description of selenoaldehyde cycloaddition reactions, Kirby has reported the synthesis of ethyl selenoxoacetate,[8] and Fischer has reported elegant chemistry involving selenoaldehydes and selenoketones stabilized by tungsten and chromium complexes.[9]

Recently, we communicated the simple and efficient generation of selenofluorenone and its cycloaddition reactions with dienes and dipoles.[10] In this paper we present further details of that study and describe methodology that expands the scope and generality of selenoketone synthesis. We also describe a variety of selenoketone cyloaddition reactions with electronically biased diene and dipole components.

The present study was motivated by our initial work involving selenoaldehyde generation via fluoride-mediated desilylative elimination of cyanide from α-silyl selenocyanates and their cycloaddition reactions with various diene and dipole reactants.[7,11] The α-silyl selenocyanates were readily accessible from aldehydes via silyl anion addition, tosylation, and displacement by KSeCN, as illustrated in eq 1. Extension of this methodology to the



(1)

synthesis of selenoketones was anticipated to be difficult, since formation and selenocyanate displacement of tertiary tosylates would be required. Further difficulty was expected from competing deprotonation of enolizable ketones in the silyl anion addition reaction, diminishing the overall efficiency of this strategy. A reasonable alternative for selenoketone generation was the base-induced elimination of cyanide from simple selenocyanates, since the analogous sulfur-based reactions involving conversion of thiocyanates to thioketones had been demonstrated by Miotti

Table I[a]

Selenocyanate			Method	Diene		Product(s)		Yield (%)[†]
1	R_1 =	R_2 =		R_3 =	R_4 =	3 : 4		
a	CO_2Et	O P(OEt)$_2$	A	Me	H	2.0 : 1		63
b	CO_2Et	Ph	A	Me	H	2.0 : 1		54
c	CO_2Et	Me	A	Me	H	2.0 : 1		62
d	PhC(O)	Me	A	Me	H	2.1 : 1		45
e	Ph	CN	B	Me	H	3.3 : 1		95
l	$PhSO_2$	Me	B	Me	H	2.8 : 1		85
g	CO_2Et	CO_2Et	A	H	Me	>25 : 1	††	65
h	Ph	Ph	C	Me	Me	>25 : 1	††	70
d	PhC(O)	Me	D	Me	Me	>25 : 1 endo exo 4.2 1	††	68

[a] Method: (A) Et_3N, EtOH, heat, 1–2 h; (B) Et_3N, THF, heat, 1–2 h; (C) *t*-BuOK, THF, heat, 1–2 h; (D) KH, THF, heat, 1–2 h. [†] Yields correspond to isolated purified material. Regioisomers were not separable by HPLC or GC. [††] A single regioisomer was detected by ^1H NMR. >25:1 is a conservative estimate of detection limit.

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