

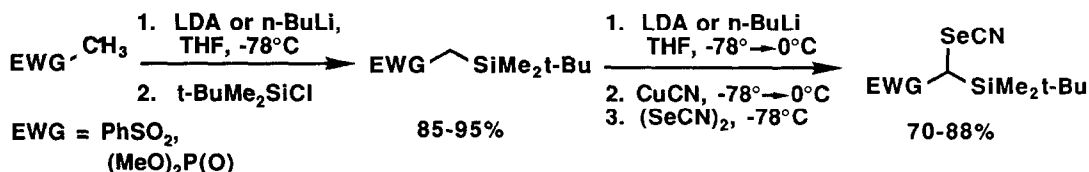
REGIOCHEMICAL PREFERENCES IN SELENOALDEHYDE CYCLOADDITIONS

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Summary: The regiochemical preferences of substituted selenoaldehydes in cycloaddition reactions with electronically biased dienes have been examined. Selenoaldehydes substituted with electron withdrawing groups exhibit "ortho-para" orientation, while selenoaldehydes substituted with donating or conjugating groups exhibit "meta" orientation. Nitrile oxide dipolar cycloadditions of selenoformaldehyde and selenobenzaldehyde are also described.

Recently, we described the first general synthesis of selenoaldehydes via fluoride induced elimination of α -silylselenocyanates.¹ Aryl and alkyl selenoaldehydes reacted efficiently with cyclopentadiene via Diels-Alder cycloaddition reactions. In this Letter, we describe the first reactions of selenoaldehydes that provide information on the electronic nature of the selenium-carbon double bond. We also describe a new method for the preparation of a wider spectrum of α -silylselenocyanate and selenocyanate precursors to substituted selenoaldehydes.



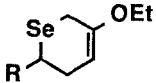
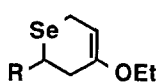

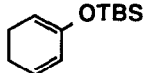
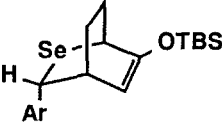
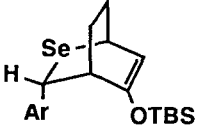

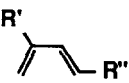
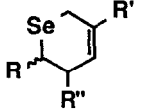
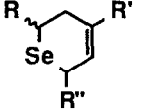
The synthesis of α -silylselenocyanates that potentially would be precursors to selenoaldehydes with electron withdrawing substituents could not be accomplished via the silyl anion route published previously.¹ However, sequential silylation and cyanoselenation of organocuprates provided an effective alternative route, as outlined below. It was necessary to incorporate the bulkier *tert*-butyldimethylsilyl group into α -silylselenocyanates containing electron withdrawing groups, due to instability of the corresponding α -trimethylsilylselenocyanates. The α -silylselenocyanate precursors to alkyl and aryl selenoaldehydes were prepared as described earlier.¹



Access to electron deficient selenals also was possible directly from simple selenocyanates by Et_3N induced elimination.^{2,3} These selenocyanates were prepared in good yield by nucleophilic displacement of halides with KSeCN , or by cyanoselenation of cyanocuprates with selenocyanogen ($(\text{SeCN})_2$), as illustrated above.

The results of Diels-Alder cycloaddition reactions of substituted selenoaldehydes to electronically biased dienes are presented in Table I.⁴ Electron deficient selenals gave ortho-para type adducts as the predominant products, while those with conjugating (-Ph) and donating (-H) substituents formed meta type adducts. The regiochemistry exhibited by the 4-nitrophenyl substituted selenoaldehyde paralleled that of the simple phenyl, though selectivity was reduced markedly. The influence of the 2,4-dinitrophenyl group on adduct regiochemistry was similar to that of electron deficient substituents.

Table I. Diels-Alder Cycloaddition Reactions of Substituted Selenoaldehydes.⁵

Selenal	Conditions	Diene	Product(s)	Yield (%)		
						
R = H	Method A		1	> 25	70	
Ph	Method A		1	> 25	83	
CN	Method B		19	1	75	
PO(OMe) ₂	Method D		> 25	1	55	
	Method B					
Ar = 4-NO ₂ -Ph			1	1.7	74	
2,4-di-NO ₂ -Ph			6.5	1	55	
			Endo isomer only (>20:1)			
						
R =		R' =	R'' =			
CN	Method B	CH ₃	CH ₃	5.4	1	80
CO ₂ Et	Method C	H	CH ₃	2.9	1	40
CO ₂ Et	Method C	CH ₃	CH ₃	4.2	1	43
COPh	Method C	CH ₃	CH ₃	8.3	1	68
COCH ₃	Method C	H	CH ₃	6.0	1	58
SO ₂ Ph	Method D	CH ₃	CH ₃	>20	1	54
SO ₂ Ph	Method D	H	CH ₃	3.0	1	72
PO(OMe) ₂	Method D	CH ₃	H	4.5	1	25
PO(OMe) ₂	Method D	CH ₃	CH ₃	Major ⁶		65

Method A - α -Silylselenocyanate treated with Bu₄NF/THF/CH₂Cl₂ at 25°C for 2-6 h.¹

Method B - Selenocyanate treated with Et₃N/CH₂Cl₂ at 25°C for 1-24 h.²

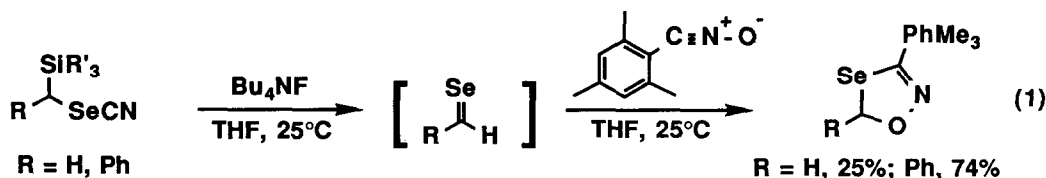
Method C - Selenocyanate treated with Et₃N in refluxing EtOH over CaCl₂ for 1 h.³

Method D - α -Silylselenocyanate treated with Bu₄NF in refluxing THF for 1h.

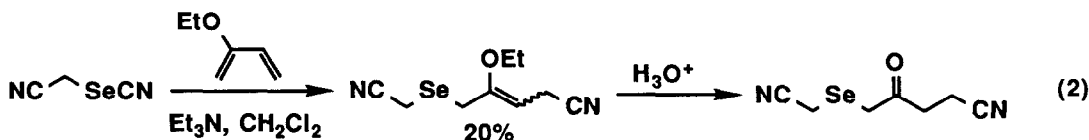
The internal diastereoselection favored products arising from endo transition states; however, in reactions conducted with Et₃N in refluxing EtOH (Method C), equilibration to mixtures of diastereomers occurred.

The regiochemistry of Diels-Alder adducts was determined by $^1\text{H-NMR}$ and decoupling experiments. Adduct stereochemistry was determined by NOE experiments, analysis of coupling constants, and by correlation with other adducts of known stereochemistry.⁶

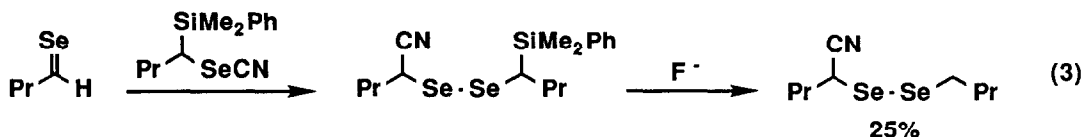
Selenoformaldehyde and selenobenzaldehyde also reacted with the dipolar reagent 2,4,6-trimethylbenzonitrile-*N*-oxide (Equation 1), and gave adducts with regiochemistry that paralleled Diels-Alder regiochemistry.⁷



In reactions of electron deficient selenoaldehydes with electron rich dienes such as 2-ethoxybutadiene, 2-*tert*-butyldimethylsiloxycyclohexadiene, isoprene or 2-methyl-1,3-pentadiene, small quantities (10-20%) of 1,4 electrophilic addition products also were isolated (Equation 2). These products were observed in reactions involving fluoride or base-mediated selenal formation. In these instances, the electrophilicity of the selenocyanate selenium is enhanced significantly by the electron withdrawing substituents.⁸



Notable by their absence in Table I are reactions of alkyl substituted selenoaldehydes with electronically biased dienes. The only successful Diels-Alder trapping of these selenals occurred with cyclopentadiene or 1,3-diphenylisobenzofuran, which are highly reactive. For less reactive dienes such as 2-ethoxybutadiene, 1,3-pentadiene, 2-methyl-1,3-pentadiene, 1- or 2-methoxycyclohexadiene, or 1-acetoxybutadiene, no cycloadducts were formed. Several electron deficient dienes also failed to react, and no cycloadducts were isolated from reactions with 2,4,6-trimethylbenzonitrile-*N*-oxide. The predominant reactions of alkyl selenals were self-condensations or polymerizations. Selenals also reacted with unreacted α -silylselenocyanate to give diselenides (Equation 3). Elevated temperatures or addition of α -silylselenocyanate to Bu_4NF and excess diene also failed to provide cycloadducts.



The observed regiochemistry for substituted selenoaldehydes is consistent with the frontier molecular orbital interpretation⁹ outlined in Figure 1, in which the predominant transition state interaction is assumed to involve the selenoaldehyde LUMO and the diene HOMO.¹⁰ Although no molecular orbital calculations have been conducted for selenoaldehydes, these results and this interpretation agree completely with observed regiochemical trends and FMO calculations for substituted thioaldehydes.¹¹

These results provide insight into the effects of substituents on selenoaldehyde cycloaddition regiochemistry and reactivity, and begin to define the scope and limitations of selenoaldehyde chemistry. Efforts to expand and exploit the chemistry of selenoaldehydes are continuing in our laboratory.

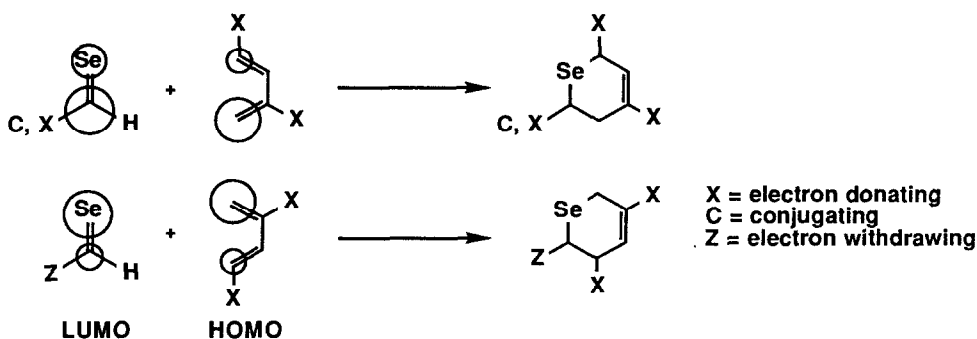


Figure 1. Frontier molecular orbital interpretation of selenoaldehyde regiochemistry.

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REFERENCES AND NOTES

- Krafft, G. A., Meinke, P. T. *J. Am. Chem. Soc.* **1986**, 108, 1314-1315.
- Selenofluorenone has been prepared by this method and trapped with a variety of dienes. Meinke, P. T., Krafft, G. A. *Tetrahedron Letters*, Manuscript submitted.
- Ethyl selenoglyoxalate has been prepared and trapped with cyclopentadiene in modest yield from ethyl selenocyanatoacetate and other 2-selena-acetate precursors by treatment with Et_3N in refluxing EtOH. Kirby, G. W., Trethewey, A. N. *J. Chem. Soc., Chem Commun.* **1986**, 1152-1154.
- All products were fully characterized and exhibited satisfactory spectral data.
- Yields correspond to chromatographed material. Ratios of inseparable regioisomers were determined by NMR.
- The stereochemistry of bicyclic adducts (e.g. 2-siloxycyclohexadiene) was determined by NOE experiments.¹ The PhSO_2 -substituted selenoaldehyde adduct of 1,3-pentadiene exhibited a 1.5 Hz coupling constant between the PhSO_2 -methine and the adjacent allylic methine, indicative of a cis relationship. Two adducts, in a 6:1 ratio, formed in the reaction of the dimethyl phosphonate substituted selenal with (E)-2-methyl-1,3-butadiene. In all likelihood, the minor component is the regioisomer, with both isomers having cis stereochemistry. However, this could not be verified by NMR, since the $(\text{MeO})_2\text{P}(\text{O})$ -methine protons were completely obscured by the phosphonate methyl resonances.
- Selenofluorenone exhibited the same regiochemistry with 2,4,6-trimethylbenzointrile-N-oxide (reference 2).
- Electrophilic addition of phenyl selenocyanate to electron rich olefins is known. See for instance, Tomoda, S., Takeuchi, Y., Nomura, Y. *Tetrahedron Letters* **1982**, 21, 1361-1364.
- Fukui, K. *Angew. Chem., Int. Ed. Engl.* **1982**, 21, 801-809, and references therein.
- This assumption is bolstered by the observation that the electron rich alkyl selenals are much less reactive in cycloadditions than electron deficient or conjugated selenals.
- Vedejs, E., Perry, D. A., Houk, K. N., Rondan, N. G. *J. Am. Chem. Soc.* **1983**, 105, 6999-7001; Vedejs, E., Eberlein, T. H., Mazur, D. J., McClure, C. K., Perry, D. A., Ruggeri, R., Schwartz, E., Stults, J. S., Varie, D. L., Wilde, R. G. and Wittenberger, S. *J. Org. Chem.* **1986**, 51, 1556-1562.

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