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ALKALOID CATALYSED ASYMMETRIC SYNTHESIS[1]. THE ADDITION OF SELENOPHENOLS TO 2-CYCLOHEXEN-1-ONES AND CONVERSION TO OPTICALLY ACTIVE ALLYLIC ALCOHOLS

by Henk Pluim and Hans Wynberg*

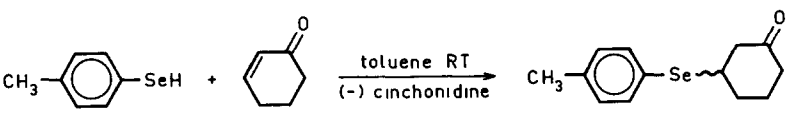
Department of Chemistry, The University,

Nijenborgh 16, 9747 AG Groningen,

The Netherlands

Summary The cinchona alkaloid catalyzed 1,4-addition reaction of selenophenols to cyclohexenols has been shown to proceed with asymmetric induction. Optically active selenium adducts are formed in quantitative chemical and up to 43% enantiomeric yields. The transformation to an optically active chiral allyl alcohol is described.

Selenium methodology plays an increasingly important role in synthetic strategies[2,3,4,5]. The use of selenophenols (and other selenides) as nucleophiles in 1,4 addition reactions to α,β-unsaturated ketones is known[4,6,7], but has not yet been extended to the synthesis of optically active compounds in the presence of chiral catalysts. We wish to report that selenophenols (I a,b,c) add readily to 2-cyclohexen-1-ones (II a,b) in the presence of cinchona alkaloids (e.g. cinchonidine, quinine) to form optically active adducts (III e-f) in excellent chemical and acceptable optical yields. In view of the versatility of selenium compounds in synthesis, the potential of optical activation leading to chiral, selenium free compounds (e.g. optically active allylic alcohols) is evident.



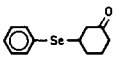
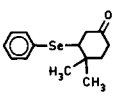
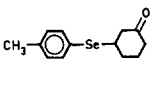
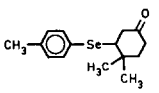
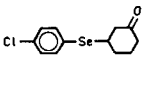
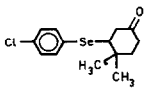
I II III

R $[\alpha]_{578}^{RT}$ + 37 8

e e 43 %

The following experiment is typical: Selenophenol[8] (1.57 g, 10 mmol) and 2-cyclohexen-1-one (0.96 g, 10 mmol) were added to 25 ml of toluene containing (-) cinchonidine (30 mg, 0.1 mmol).

The reaction mixture was magnetically stirred in a nitrogen atmosphere in the dark for 2 hours at room temperature. The product could be isolated readily by removal of the catalyst by extraction with dilute hydrochloric acid and subsequent extraction with a dilute potassium hydroxide solution to remove any unreacted selenophenol, followed by evaporation of the solvent. Thus 2.40 g (95%) of 3-phenylselenocyclohexanone was obtained as a pale yellow oil; enantiomeric excess 36%, $|\alpha|^{RT}_{578}$ + 29.3 (c=6.60, $CHCl_3$). Table I lists the results of the addition reactions for some selenophenols and two 2-cyclohexen-1-ones using similar reaction conditions.

Selenophenol	Adduct [a c]	bp(mmHg) (°C)	mp (°C)	rotation ($CHCl_3$) $[\alpha]^{RT}_{578}$	rotation ($CHCl_3$) conc $\left(\frac{g}{100ml}\right)$	enant [b] excess(%)
		128-130(0.1)		+29.3	6.60	36
			35 - 37	+23.1	2.12	20
			23 - 25.5	+37.8	8.20	43
			72 - 74	+28.8	1.00	26
			68.5-72	+17.8	1.18	20
			81.5-84	+11.6	1.58	11

a) Chemical yiels for all compounds >95%

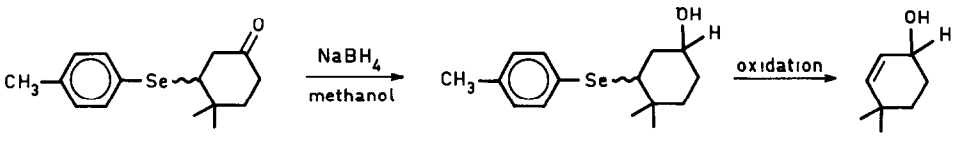
b) Determined by the method developed in our laboratory[1c,9] The diastereomeric acetals were prepared using a slight excess of R(-)-butane-2,3-diol. Distinct ^{13}C NMR spectra capable of reliable integration were obtained.

c) 3-Phenylselenohexanone has been reported earlier by Sharpless[4], but no analytical and spectroscopic data were furnished. The other adducts were new compounds. All compounds gave analytical and spectroscopic data in agreement with the structures assigned.

Of practical importance is our experience that the enantiomeric excess of the solid adducts can be substantially enhanced (e.g. to 85%) in most cases by a few crystallisations from pentane or pentane-ethanol (10 : 1). Analysis of the CD spectra of the chiral selenoketones indicates that the absolute configurations of the compounds in Table I are identical to the corresponding sulfides[1c] in agreement with similar correlation made by Craig[10,11].

Mechanistically the reaction seems to show great similarity to the 1,4 addition of thiols to α,β-unsaturated systems[1c, 12 a,b,c].

Conversion of the chiral ketoselenides to a variety of chiral alcohols, hydrocarbons and derived products by published procedures[13,14,15] can readily be conceived.
A typical example is the conversion of 4,4-dimethyl-2-cyclohexen-1-one[16] to optically active 4,4-dimethyl-2-cyclohexen-1-ol (V) via the chiral selenides III and IV



III IV V

Reduction of III ($NaBH_4$) proceeds readily yielding IV (one diastereoisomer*, $|\alpha|^{RT}_{578}$ + 6.7 (C=1.07, $CHCl_3$), quantitative yield), which can be converted to the allylic alcohol V, $|\alpha|^{RT}_{578}$ -10.8 (C=1.90, $CHCl_3$) using an oxidative protocol [13,14,15] The alcohol V was identical in all respects (except rotation) with the known racemic product[17]. Based on the knowledge of the enantiomeric excess and absolute configuration of the starting ketone (e e. 25%, R) the absolute rotation of V is estimated to be -44 ± 4 and the absolute configuration to be S.

The paucity of data on chiral selenides[10,18,19] adds additional value to this easy method of obtaining a variety of optically active selenium compounds.

*H.O. House, "Modern Synthetic Reactions", W.A. Benjamin, Inc., 1972, pp. 54-62. Z-isomer was assumed to be present.

References and notes:

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