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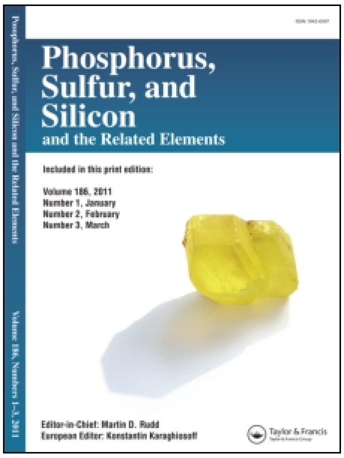

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A New Stereoselective Aldol Reaction using α-(Phenylseleno)Cycloalkanones

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A NEW STEREOSELECTIVE ALDOL REACTION USING α-(PHENYLSELENO)CYCLOALKANONES

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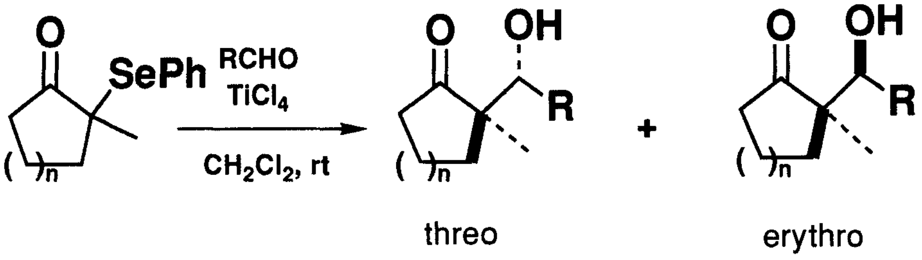
Abstract The $TiCl_4$-catalyzed reaction of α-(phenylseleno)-cycloalkanones with aldehydes gives aldol products with high threo selectivity. High stereoselectivity is also achieved in the formation of spiro aldol products starting with α-(phenylseleno)cycloalkanones bearing an aldehyde chain.

INTRODUCTION

The use of titanium enolates to effect stereoselective aldol reactions has been the subject of recent attention.[1] Titanium enolates are usually prepared from silyl enol ethers[2] or alkali-metal enolates.[3] The difficulty of the regioselective formation of these enol ethers or enolates is often encountered when unsymmetrical ketones bearing α-hydrogens on both alkyl chains are used.[4] We here describe the regiospecific, stereoselective aldol reaction of α-(phenylseleno)cycloalkanones with aldehydes to construct quaternary centers.

RESULTS AND DISCUSSION

To a CH_2Cl_2 solution of 2-methyl-2-(phenylseleno)cyclopentanone[5] **1** (n=1) was added $TiCl_4$ at room temperature. Immediately following, 3 equiv of benzaldehyde was added and the mixture was stirred for 15 h. The reaction gave the aldol product in 83% yield with high threo selectivity. This reaction proved to be general with other selenocycloalkanones and aldehydes.



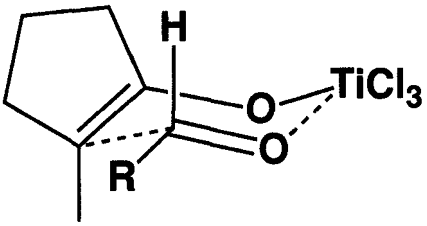
1 2 3

TABLE I Stereochemistry of the $TiCl_4$-Mediated Aldol Reaction of Selenoketones **1**

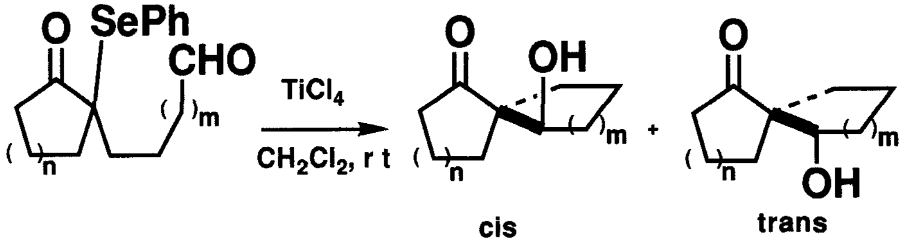
entry	selenoketone	RCHO	reaction time, h	yield %	threo:erythro **2**:**3**
1	n = 1	PhCHO	15	83	93:7[a]
2	n = 1	i-PrCHO	2.5	87	89:11[b]
3	n = 2	PhCHO	4	74	94:6[c]
4	n = 2	i-PrCHO	2	60	93:7[d]

[a,c,d] Determined by ^{1}H NMR ($CDCl_3$). a: CHOH d 4.84 (threo), d 4.88 (erythro);α-Me 1.06 (threo), 0.89 (erythro). b: CHOH 3.41 (threo), 3.76 (erythro);α-Me 1.12 (threo), 1.01 (erythro). c: CHOH 4.94 (threo), 5.09 (erythro);α-Me 1.18 (threo), 1.07 (erythro). d: CHOH 3.69 (threo), 3.66 (erythro),α-Me 1.24 (threo), 1.20 (erythro). [b] Isolated ratio.

The results are summarized in Table I. Reactions examined showed high threo selectivity. These results are in sharp contrast with those in the Lewis acid-mediated aldol reactions of persubstituted enol silyl ethers, which often show low levels of stereoselection,[6] whereas the major product diastereoisomer is the same as that observed in the metal enolate-mediated aldol process;[6] however, it is noteworthy that high stereoselectivity could be achieved in our reaction even if the reaction was carried out at ambient temperature. High threo selectivity in the present reaction suggests the chair-like transition state as illustrated.



This reaction also was found to proceed with α-(phenylseleno)cycloalkanones **4** bearing an aldehyde chain at the α-position. The addition of $TiCl_4$ to a solution of **4** in CH_2Cl_2 at room temperature gave spiro aldol products[7] **5** and **6** in high yields. The stereochemical outcome was uniformly excellent, with each case favoring the cis spiro aldol as shown in Table II.



4 **5** **6**

TABLE II Stereochemistry of the Aldol Reaction to the Spiro-ketones **5** and **6**

entry	selenoketone 4	reaction time	yield %	cis:trans 5:6[a]
1	n=1 m=1	30 min	95	70:30
2	n=1 m=2	1.5 h	93	only **5**[b]
3	n=2 m=1	15 min	77	94:6
4	n=2 m=2	15 min	95	98:2

[a] Ratios were determined by GLC. [b] Homogeneity was confirmed by ^1H and ^{13}C NMR and GLC.

In summary, the present reaction offers a new use of α-selenoketones for the regiospecific and stereoselective construction of quaternary centers.

TYPICAL PROCEDURE

To a solution of 2-methyl-2-(phenylseleno)cyclohexanone **1** (n=2) (55 mg, 0.205 mmol) in CH_2Cl_2 (0.8 ml) was added $TiCl_4$ (25 μl, 0.226 mmol) followed by benzaldehyde (63 μl, 0.615 mmol). The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched by the addition of H_2O (5 ml) and ether (5 ml) under vigorous stirring. The separated organic solution was washed with H_2O and the aqueous layers were extracted several times with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The 94:6 ratio for aldol adducts **2**:**3** (n=2) was determined by integration of the ^{1}H NMR spectrum of the crude product. Flash chromatography (9:1 hexane-ethyl acetate) gave the aldol product (33 mg, 74% yield).

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