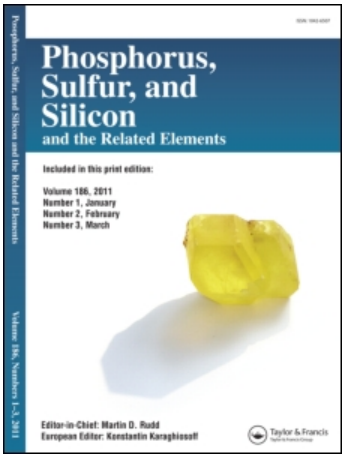

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STEREOSELECTIVE ALDOL REACTION OF α-PHENYLSELENO ESTERS

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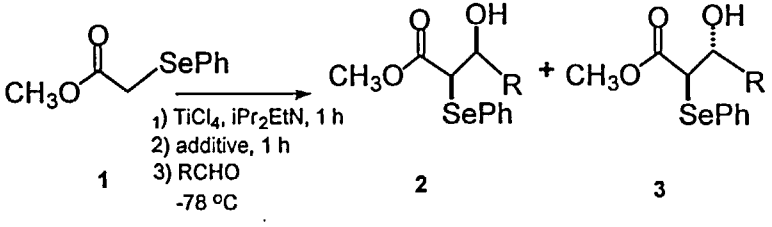
Abstract The $TiCl_4$-catalyzed reaction of a-phenylseleno esters with aldehydes in the presence of Ph_3P or $Ph_3P{=}O$ gives aldol products with high syn selectivity.

INTRODUCTION

The stereoselective aldol reaction is one of the most important carbon-carbon bond forming reactions.[1] Highly stereoselective aldol reaction has been developed through titanium enolates from ketones or amides,[2] but it is not easy to prepare titanium enolates directly from esters.[3] It is important to introduce an arylseleno group at the position α to the carbonyl in order to increase the acidity of the α-proton.[4] Furthermore, the arylseleno group is a useful functional group which can be efficiently transformed to a variety of functional groups under mild conditions.[4] Aldol reactions of lithium enolates derived from α-seleno carbonyl compounds have been reported to give the products with low stereoselectivity.[5] We now report an efficient stereoselective aldol reaction starting with α-phenylseleno esters.

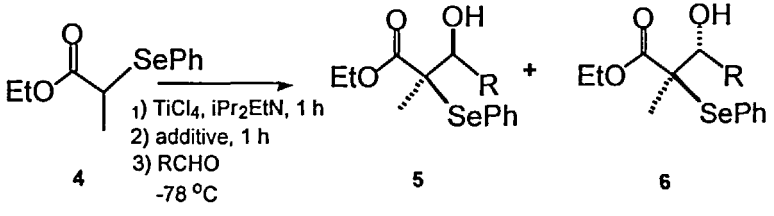
RESULTS AND DISCUSSION

A CH_2Cl_2 solution of methyl 2-(phenylseleno)acetate **1** was treated with 1.1 equiv. of $TiCl_4$ and 1.1 equiv. of N-ethyldiisopropylamine at –78 °C for 1 h and subsequently with benzaldehyde at the same temperature to give the aldol product in 96 % yield in a syn/anti ratio of 80:20. A similar reaction with 2-methylpropanal gave the product in a syn/anti ratio of 72:28.



The reaction of tert-butyl 2-(phenylseleno)acetate showed lower stereoselectivity. The stereoselectivity slightly increased when the ether was added as solvent: The syn/anti ratios were 81:19 and 82:18 in diethyl ether- and diisopropyl ether-methylene chloride, respectively. These results suggested some interaction of the ether with the titanium enolate to increase the stereoselectivity. When 1.1 equiv. of triphenylphosphine was added before the addition of the aldehyde, the stereoselectivity was strikingly improved to a ratio of 95:5. Other triphenylphosphines such as tributylphosphine, 1,2-bis(diphenylphosphino)ethane also showed an increase of the selectivity in comparison with the reaction without the phosphine. It has been

reported that the aldol reaction by treatment of ketenesilylacetal with $TiCl_4$ improves the stereoselectivity by the addition of triphenyl-phosphine.[6] We found that the addition of triphenylphosphine oxide was even more effective on the stereoselectivity to give the product with a stereoselectivity of 97:3. Reactions of methyl 2-(phenylseleno)acetate **1** with various aldehydes showed excellent stereoselectivities in the presence of triphenyl-phosphine oxide. The results are summarized in Table I.



4 **5** **6**

TABLE I The $TiCl_4$-Mediated Aldol Reaction of Methyl 2-(Phenylseleno)acetate **1** with Aldehydes under Vaious Conditions

RCHO	additive	reaction time, h	yield %	syn : anti **2** : **3**
PhCHO	-	3	97	80 : 20
i-PrCHO	-	1	89	72 : 28
PhCHO[a]	-	3	74	71 : 29
i-PrCHO[a]	-	4	64	63 : 37
i-PrCHO[b]	-	1	94	81 : 29
i-PrCHO[c]	-	1	87	82 : 18
PhCHO	Ph_3P	2	85	95 : 5
iPrCHO	Ph_3P	2.5	86	90 : 10
PhCHO	Bu_3P	4	89	90 : 10
PhCHO	$(Ph_2PCH_2)_2$	1	62	91 : 9
PhCHO	Ph_3PO	2	92	97 : 3
p-ClC_6H_4CHO	Ph_3PO	1	95	95 : 5
p-$MeOC_6H_4CHO$	Ph_3PO	2.5	93	95 : 5
$Ph(CH_2)_2CHO$	Ph_2PO	2	92	88 : 12
(*E*)-PhCH=CHCHO	Ph_3PO	5	81	>98 : 2
n-$C_5H_{11}CHO$	Ph_3PO	1	83	95 : 5

[a] tert-Butyl 2-(phenylseleno)acetate was used. [b] The reaction was carried out in a 2/1 mixture of Et_2O and CH_2Cl_2. [c] The reaction was carried out in a 2/1 mixture of iPr_2O and CH_2Cl_2.

TABLE II The $TiCl_4$-Mediated Aldol Reaction of Ethyl 2-(Phenylseleno)propionate **4** with Aldehydes

RCHO	additive	reaction time, h	yield %	**5** : **6**
PhCHO	-	0.5	95	93 : 7
i-PrCHO	-	1	76	92 : 8
PhCHO[a]	Ph_3P	2.5	93	>98 : 2
i-PrCHO[a]	Ph_3P	4	78	>98 : 2

We also studied the reaction of ethyl 2-phenylselenopropionate **4**. The reactions with benzaldehyde and 2-methylpropanal gave the products **5** and **6** in ratios of 93:7 and 92:8, respectively. When both reactions were carried out in the presence of triphenylphosphine, the syn products **5** were formed exclusively. Stereospecific conversion of thus obtained syn aldol products to (Z)-α,β-unsaturated esters will be reported elsewhere.

TYPICAL PROCEDURE

To a solution of methyl 2-(phenylseleno)acetate **1** (97 mg, 0.43 mmol) in CH_2Cl_2 (2.1 ml) was added $TiCl_4$ (51 ml, 0.49 mmol) and N-ethyldiisopropylamine (82 ml, 0.47 mmol) at -78 °C. After stirring for 1 h, a solution of triphenylphosphine oxide (130 mg, 0.47 mmol) in CH_2Cl_2 (0.2 ml) was added. The mixture was stirred for an additional 1 h and then a solution of *p*-chlorobenzaldehyde (66 mg, 0.47 mmol) in CH_2Cl_2 (0.2 ml) was added. The mixture was stirred for 1 h and quenched with aqueous NH_4Cl (3 ml). The resulting solution was extracted with CH_2Cl_2 (4x5 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The syn/anti ratio of 95:5 was determined by the HPLC analysis of the crude product. Column chromatography (8:2 hexane-ethyl acetate) gave the aldol product (139 mg, 95 %).

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