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Cross-Aldol Reaction Between Benzaldehyde And β-Phenylselanyl Enoxysilanes Derived From Phenylselanylmethylketones.

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Abstract : *The BF_3-mediated aldol reaction between benzaldehyde and β-phenylselanyl enoxysilanes* ***1*** *derived from α-phenylselanylmethylketones has led to syn aldols* ***2*** *and α,α-bis(phenylselanyl) ketones* ***3*** *as by-products. Using tetrabutylammonium fluoride, the syn and anti aldols* ***2a*** *were formed from* ***1a****. Syn, syn-2-phenylselanyl 1,3-diols* ***5a*** *and* ***5d*** *were obtained by borane reduction of aldols* ***2a*** *and* ***2d*** *respectively.*

α-Phenylselanyl aldehydes and ketones[1] are useful intermediates in organic synthesis[2] and we have recently described some novel reactions of these compounds[3-6]. We present, in this letter, our first results concerning the cross-aldol reactions between benzaldehyde and silyl enol ethers **1** derived from phenylselanylmethylketones.

The formation of aldols **2** was carried out under Lewis acid activation[7] (Scheme 1, Table) or on reaction in the presence of tetrabutylammonium fluoride[7] (Scheme 2). The enoxysilanes[1,5] **1**, excepted **1d**, were formed as mixtures of E and Z isomers[8] and have been used as such.

Scheme 1

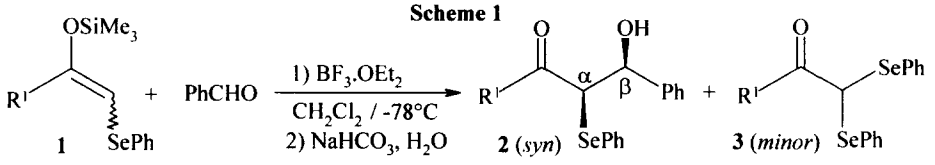
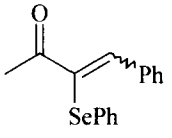


Table. BF_3-catalyzed aldolisation of enoxysilanes **1**

Entry	R^1	Substrate N°	*E/Z*	**2** Yield (%)
1	Me	**1a**	50/50	75
2	Me	**1a**	66/34	71
3	Me	**1a**	80/20	73
4	Et	**1b**	34/66	77
5	*n*-Pr	**1c**	30/70	79
6	Ph	**1d**	-	56



4d

The reaction takes place with complete *threo* diastereoselectivity[9] in the case of aldol **2a** (Entries 1-3). The stereochemistry was assigned according to the value of the coupling constant $J_{H\alpha H\beta}$ = 5.2 Hz , analogous to those given for α-alkylated aldols[10]. A small amount of α,α-bis(phenylselanyl)ketone **3**[4] (5-10 %) was also

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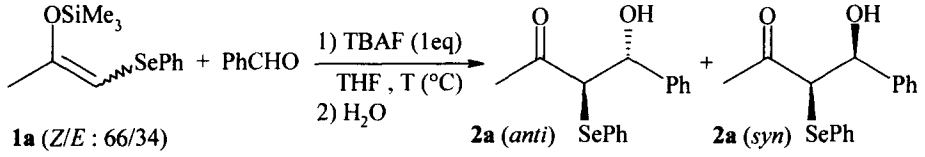
recovered, in each case, besides the β-hydroxy α-phenylselanyl ketone **2**[11] and the modest yield observed for **2d** (Table, entry 6) results from its partial dehydration into α-phenylselanyl enone **4d**[12] during the work-up (**2d/4d** : 65/35).

A similar diastereoselection has been already reported in other aldol reactions[9b] involving zirconium[13a], titanium[13b], dialkoxyboron[13c] and tin[13d] enolates as well, irrespective to the stereochemistry of the enolate.

The reaction takes another course when carried out on benzaldehyde and the enolates generated by tetrabutylammonium fluoride treatment[14] since it delivers a anti/syn mixture of compounds in which the anti-stereoisomers prevail at -78°C (Scheme 2). These diastereoisomers are easily distinguished from their ^{1}H and ^{77}Se NMR spectra. ($J_{H\alpha H\beta}$ (*anti*) = 8.5 Hz, $J_{H\alpha H\beta}$ (*syn*) = 5.2 Hz), ($\delta^{77}Se$ (*anti*) = 351 ppm, δ ^{77}Se (*syn*) = 394 ppm). As already observed, the temperature is an important factor[7]. Interestingly, the *syn* stereoisomer became the major one if the reaction is performed at higher temperature. With the same *Z/E* ratio of enoxysilane **1a**, the ***anti-2a/syn-2a*** ratio was 80/20 at -80°C and 38/62 at -10°C. We suspect that the increasing amount of the *syn* isomer results from the equilibrium between the two aldolates, leading to the thermodynamic *syn* aldol, after hydrolysis.

Scheme 2

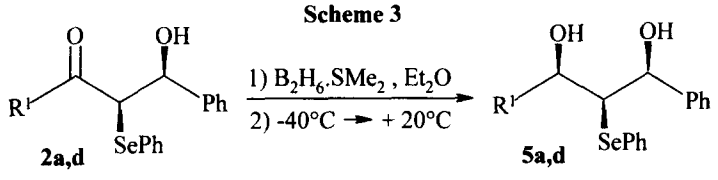


1a (*Z/E* : 66/34) **2a** (*anti*) **2a** (*syn*)

T (°C)	Yield (%)	Ratio *anti* / *syn*
-80	81	80 / 20
-10	75	38 / 62

The borane reduction of the *syn* aldols **2a** and **2d** was also achieved (Scheme 3). The 2-phenylselanyl 1,3-diols **5a** and **5d** were isolated in fair yields (68 and 61 % respectively). Some 2-phenylselanyl 1,3-diols have been obtained by electrophilic addition of benzeneselenenic acid to allylic alcohols[15].

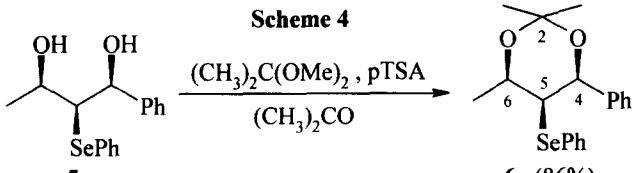
Scheme 3



2a,d **5a,d**

The *syn, syn* stereochemistry of the 2-phenylselanyl 1,3-diols **5** was assigned from the NMR spectra of the acetonide **6a** prepared from **5a**, according to the usual procedure[16] (Scheme 4).

Scheme 4

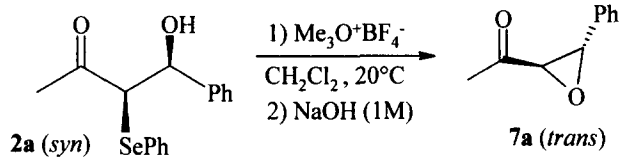


5a **6a** (86%)

Noe experiments (H_4-H_6 : 4%, H_4-H_5 : 4%, H_4-CH_3 : 1%) and coupling constants ($J_{H_4H_5}$=1.6 Hz, $J_{H_6H_5}$=1.5 Hz) agree with the proposed stereochemistry of the acetonide **6a**. Furthermore, the difference between the chemical shifts of the axial and equatorial methyl groups, in the ^{13}C spectra can be compared with those observed for *syn* acetonides[17] ($\delta_{CH_3\,ax}$ = 19.7 ppm, $\delta_{CH_3\,eq}$ = 29.7 ppm).

In order to confirm the stereochemistry of the *syn* aldol **2a**, we decided to prepare the corresponding epoxide using a known method[18] involving the intermediate formation of a selenonium salt. We were rather surprised to observe the exclusive formation (62 % yield) of the *trans* epoxide isomer of **7a**[19], ($J_{H_2H_3}$ = 1.8 Hz), instead of the expected *cis*-epoxide (Scheme 5). The same result was observed when the reaction was performed on a 1/1 *syn/anti* mixture of aldol **2a**. This result can be compared with the high *trans* selectivity observed for the epoxide formation involving an aromatic aldehyde and sulfonium ylides[20].

Scheme 5



2a (*syn*) **7a** (*trans*)

In conclusion, we have observed that the BF_3-catalyzed cross aldol reaction involving β-phenylselanyl enoxysilanes **1** produces the *syn* isomer whatever the stereochemistry of the silyl enol ethers. The borane reduction of the *syn* aldols **2** generates the *syn, syn* 2-phenylselanyl 1,3-diols **5**. The stereochemistry of these 1, 3-diols has been confirmed by a NMR study of the acetonide **6a**. Surprisingly aldol **2a** (*syn*) or a 1/1 *syn/anti* mixture, led to the exclusive formation of the *trans* epoxide **7a**. Other experiments are needed to explain the *syn* selectivity observed in the aldol reaction achieved under Lewis acid conditions and the stereoselective formation of the *trans* epoxide **7**. In addition, a general study using others β-phenylselanyl enoxysilanes is undertaken to determine the factors favouring the formation of α,α-bis(phenylselanyl) ketone **3** beside the aldol **2**. A selenophilic attack of the enoxysilane **1** on the aldol **2** could explain the presence of this by-product.

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8. The ^1H, ^{13}C and ^{77}Se NMR study of the enoxysilanes **1** will be described elsewhere. The *E/Z* isomer mixtures result from various fractions of chromatography.
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11. *General procedure for BF_3-catalyzed aldolisation of enoxysilanes* **1**. To a stirred solution of benzaldehyde (0.117 g, 1.1 mmol) in CH_2Cl_2 (5 ml) cooled at -80°C, $BF_3.OEt_2$ (0.156 g, 1.1 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After 10 min., the enoxysilane **1** (1 mmol) in CH_2Cl_2 (3 ml) was slowly introduced. The reaction was stirred for 8 h. at -80°C and the mixture quenched with a $NaHCO_3$ saturated solution (3 ml). After separation and extraction of the aqueous phase with dichloromethane (3 x 10 ml), the organic fractions were dried and concentrated. The oily residue was dissolved in hexane (5 ml) and cooled at -20°C. The crude solid obtained was crystallized in hexane providing the *syn* β-hydroxy α-phenylselanyl ketones **2**. The α,α-bis(phenylselanyl) ketone **3** was then obtained from the hexane solution.

***syn*-4-Hydroxy-4-phenyl-3-phenylselanyl butan-2-one 2a.** m.p : 107-108°C. ^1H NMR ($CDCl_3$), δ : 7.42-7.19 (10H, m, 2 Ph), 5.15 (1H, dd, J = 5.2 Hz, J = 2.0 Hz, H-4), 3.82 (1H, d, J = 5.2 Hz, H-3), 3.59 (1H, d, J = 2.0 Hz, O*H*), 2.18 (3H, s, H-1). ^{13}C NMR ($CDCl_3$), δ : 205.0, 140.3, 135.2, 129.2, 128.7, 128.1, 127.7, 126.5, 71.0, 62.3, 28.9. ^{77}Se NMR ($CDCl_3$), δ : 393.6.

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14. *Aldolisation of enoxysilane* **1a** *using TBAF*. To a stirred solution of benzaldehyde (0.117 g, 1.1 mmol) and enoxysilane **1a** (0.286 g, 1 mmol), in THF (5 ml) cooled at -80°C, a tetrabutylammonium fluoride solution (1.1 ml, 1M. THF) was slowly added. The reaction was stirred for 2h. at -80°C and treated with water (3 ml). After an usual work-up, the crude solid formed was crystallized in hexane providing a *syn/anti* mixture of aldol **2a**.

***anti*-4-Hydroxy 4-phenyl 3-phenylselanyl butan-2-one 2a.** ^1H NMR ($CDCl_3$), δ : 5.06 (1H, d, J = 8.5 Hz, H-4), 3.94 (1H, d, J = 8.5 Hz, H-3), 3.31 (1H, d, J = 2.0 Hz, O*H*), 2.30 (3H, s, H-1). ^{13}C NMR ($CDCl_3$), δ : 205.5, 74.0, 58.1, 28.9. ^{77}Se NMR ($CDCl_3$), δ : 350.9.

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