Aldol Condensation *via* Germanium Enolates. Stereoselection Dictated by the Co-presence of Lithium Halides

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Trimethylgermanium enolates, prepared *in situ* from lithium enolates and trimethylgermanium halides, underwent a rapid aldol condensation with benzaldehyde to give the *erythro*-aldol predominantly, while the same enolates produced the *threo*-aldol preferentially if the coexisting lithium halides were removed before condensation.

We previously reported that the aldol condensation reaction of aldehydes with tin enolates generated *in situ* from lithium enolates and R_3SnCl gave moderate *erythro* selectivity.[1] Later, Stille observed predominately *threo* selectivity in reactions of aldehydes with tin enolates which had been synthesized and then isolated prior to condensation.[2] Mukaiyama demonstrated *erythro* selectivity in the aldol condensation *via* tin(II) enolates prepared *in situ* from ketones and tin trifluoromethanesulphonate in the presence of an amine.[3] To help clarify the origin of this apparent stereochemical difference, we investigated the aldol reaction of germanium

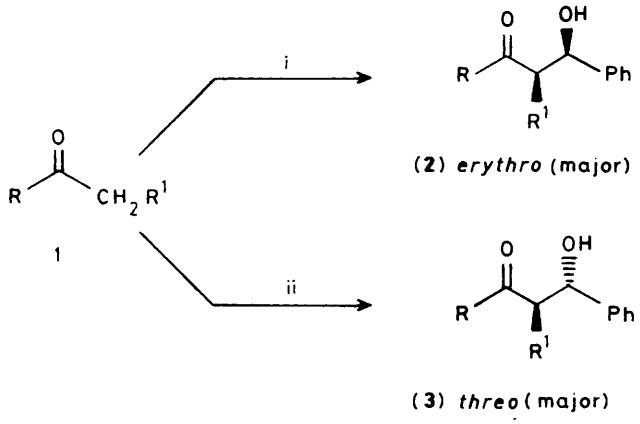
Table 1. Germylation of lithium enolates of ketones.

	(1)		R^2_3GeCl		
Entry	R	R^1	R^2	Solvent	(4) : (5)
1	Ph	H	Me	Et_2O	9 : 91
2	Ph	H	Me	Tetrahydrofuran	9 : 91
3	Ph	H	Me	n-Hexane	0 : 100
4	Ph	Me	Me	Et_2O	89 : 11
5	Ph	Me	Me	n-Hexane	70 : 30
6	Ph	Me	Ph	Et_2O	6 : 94

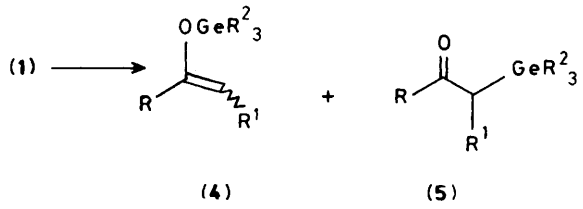
Table 2. Aldol-type reaction of germanium enolates with benzaldehyde.[a]

Entry	Ketone (1) R	R¹	R^2_3GeCl, R^2	Additive	Temp./°C	Ratio[c] (2):(3)	Total isolated yield (%)
1	Ph	Me	Me	None	−78 to −40	30:70	27
2	Ph	Me	Me	BF_3·OEt_2	−78	45:55	88
3	Ph	Me	Me	LiBr	−78 to −40	76:24	82
4[d]	Ph	Me	Me	LiBr	−78 to −40	75:25	60
5	$-(CH_2)_4-$		Me	None	−78 to −40	45:55	55
6	$-(CH_2)_4-$		Me	BF_3·OEt_2	−78	30:70	91
7[d]	$-(CH_2)_4-$		Me	LiBr	−78 to −40	62:38	58
8[d]	$-(CH_2)_4-$		Me	LiCl	−78 to −40	60:40	35
9	Ph	Me	Ph	None	−78 to −40	79:21	90
10	Ph	Me	Ph	LiBr	−78 to −40	75:25	88

[a] To an ether solution of (4) and (5), prepared as described in Table 1 (1 mmol scale) and free from LiCl, was added benzaldehyde (0.5 mmol) and the additive. When BF_3·OEt_2 was used as the additive, CH_2Cl_2 was the solvent. [b] The reaction was quenched either at −78 or at −40 °C. [c] By ^1H n.m.r. spectroscopy. [d] The reaction was carried out without isolating the intermediate germanium enolates; treatment of (1) LDA, then addition of Me_3GeX, then addition of PhCHO.



Scheme 1. *Reagents and conditions*: i, $LiNPr^i_2$ (LDA), Me_3GeX, then PhCHO; ii, LDA, Me_3GeCl, *removal of LiCl*, then PhCHO.



Scheme 2. *Reagents and conditions*: LDA, R^2_3GeCl.

enolates. It was expected that germanium enolates would be more stable than the corresponding tin enolates and thus be handled easily,[4] but would be more reactive than silyl enol ethers.

We now report that the co-presence of lithium halides dictates the stereoselection; Me_3Ge-enolates generated *in situ* from Li-enolates and Me_3GeX produce the *erythro* aldol predominantly, while the same enolates in the absence of LiX afford the *threo* aldol preferentially (Scheme 1).

First, we examined whether trapping of lithium enolates with germanium chlorides would give the *O*-germylated product (**4**) or the *C*-germylated product (**5**) (Scheme 2). The results are summarized in Table 1. Treatment of (**1**) with LDA in ether followed by addition of germanium chlorides, and then by removal of LiCl using a centrifuge under nitrogen,† gave the germylated products. The structures of (**4**) and (**5**) could be easily distinguished by their ^1H n.m.r. spectra (270 MHz, $CDCl_3$):‡ $PhC(OGeMe_3)=CH_2$ δ 4.59 and 4.03 (s), $PhC(O)CH_2GeMe_3$ δ 2.66 (s); $PhC(OGeMe_3)=CHMe$ δ 5.31 (q), $PhC(O)CHMeGeMe_3$ δ 3.51 (q); $PhC(OGePh_3)=CHMe$ δ 5.11 (q), $PhC(O)CHMeGeMe_3$ δ 3.47 (q). Judging from their n.m.r. spectra, the enolates consisted of a single isomer and were tentatively assigned the *E*-configuration; the tin analogue was also assumed to be the *E*-isomer.[2] Similar reactions of cyclohexanone gave the *O*-trimethylgermylated product; the vinyl proton appeared at δ 4.42 (CCl_4). However, the exact proportion of the *C*-germylated product was not clear, since the $-C(O)CH(GeMe_3)-$ signal appeared in a similar region to the methylene signals.

Acetophenone gave (**5**) either exclusively or predominantly, as expected from the previous results[4a,5] (Table 1, entries 1—3). Use of hexane as a solvent tended to increase the extent of *C*-germylation. Trimethylgermylation of propiophenone afforded (**4**) predominantly in both ether and hexane solvents (entries 4 and 5). Sato and Inoue reported that (**5**) was produced preferentially in hexane.[4a] The reason for these different observations is not clear at present. Interestingly, triphenylgermylation of propiophenone gave (**5**) predominantly (entry 6).

Next, we examined the aldol reaction between benzaldehyde and the germylated products (**4**) and (**5**) (Scheme 1). The results are summarized in Table 2. The *erythro* aldol (**2**) was obtained predominantly in the presence of LiX (entries 3, 4, 7, and 8). This tendency had been observed previously in the aldol reactions of tin enolates prepared *in situ*.[1] Interestingly, however, the *threo* aldol (**3**) was produced preferentially without LiX (entries 1 and 5). It was confirmed that equilibration between (**2**) and (**3**) essentially did not take place under the reaction conditions and thus (**2**) and (**3**) were produced under kinetic control. The ratio of (**2**) to (**3**) in the presence of BF_3·OEt_2 (entry 6) was similar to that obtained under Mukaiyama conditions [(**2**):(**3**) = 25:78 in the case of the corresponding silyl ether–$TiCl_4$].[6]

On the other hand, the *C*-triphenylgermylated product gave (**2**) predominantly regardless of the presence or absence of LiX (entries 9 and 10). α-Mercurioketones afford the *erythro* aldol *via* an S_E2 type transition state,[5] and thus the result in

† The germylated products (**4**) and (**5**) gradually decomposed to (**1**) in the presence of moisture, and thus were treated under dry N_2.

‡ The acetophenone derivatives were studied by 90 MHz n.m.r. spectroscopy in CCl_4 solvent.

entry 9 is in good agreement with the previous observation. The result of entry 10 also agrees with the *erythro* selectivity of triphenyltin enolates.[1]

In conclusion, it is clear that the presence of LiX plays an important role in controlling the stereoselectivity. Although the aldol reaction *via* the metal enolate, prepared by the enolization of ketones with LDA followed by addition of RMX, is frequently used in organic synthesis, the effect of LiX upon the stereoselectivity has tended to be neglected. The discrepancy between our results[1] and Stille's observations may be due to this effect of the co-presence of LiX.

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