Diastereoselectivity in the Alkylation of Enolates having an Adjacent Silyl Group†

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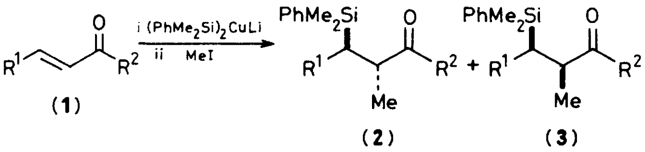
The methylation of open-chain enolates having an adjacent silyl group is highly diastereoselective in favour of the isomer (**2**) having the silyl and methyl groups *trans* on the carbon chain; protonation of the corresponding enolate, already carrying the methyl group, gives the other diastereoisomer (**3**), but with somewhat lower diastereoselectivity.

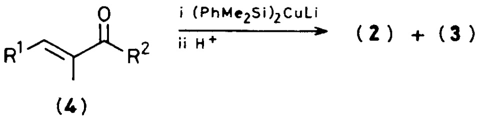
The conjugate addition of a silyl group to an α,β-unsaturated aldehyde, ketone, or ester leads to β-silyl carbonyl compounds.[1,2] We now report that methylation of the intermediate enolate is highly diastereoselective in open-chain systems.

Our silyl-cuprate reagent, $(PhMe_2Si)_2CuLi$,[1,3] reacted with cinnamaldehyde (**1a**), 4-phenylbut-3-en-2-one (**1b**), chalcone (**1c**), methyl cinnamate (**1d**), ethyl crotonate (**1e**), and dec-3-en-2-one (**1f**), as expected.[1] When we added methyl iodide to the intermediate enolate, the β-silyl carbonyl compounds (**2**) and (**3**) were produced with high diastereoselectivity in favour of the isomer (**2**) (Scheme 1). The degree of diastereoselectivity was estimated by ^1H n.m.r. [(**2a**), (**2c**), (**2d**)], by isolation [(**2b**), (**2f**)], or by ^{13}C n.m.r. [(**2e**)]. We got the same ratio (**2d**) : (**3d**) when we carried out the conjugate addition to methyl cinnamate, worked up with ammonium chloride solution, regenerated the enolate (lithium di-isopropylamide), and methylated it with methyl iodide.[4] We also got the same ratio (**2e**) : (**3e**) whether we started from *cis* or *trans* ethyl crotonate. Finally, we got complementary results, although with lower diastereoselectivity, when we added the silyl cuprate reagent to the enones (**4**), and quenched the enolate with aqueous ammonium chloride or trifluoroacetic acid (Scheme 2). Equilibration of the ketones (**2b**) and (**3b**) gave a ratio (**2b**) : (**3b**) of 45 : 55.



	Ratio (**2**) : (**3**)	Yield/%
a; R¹ = Ph, R² = H	92 : 8[a]	74[a]
b; R¹ = Ph, R² = Me	98 : 2	57
c; R¹ = Ph, R² = Ph	—[b]	70
d; R¹ = Ph, R² = OMe	97 : 3	88
e; R¹ = Me, R² = OEt	99 : 1[c]	82[c]
f; R¹ = n-C_6H_{13}, R² = Me	>95 : 5	78

Scheme 1. [a] Determined on the derived and more stable alcohol (**9**). [b] Not determined; only one diastereoisomer detectable. [c] From *trans* crotonate; the values from *cis* crotonate are 98 : 2 and 75%.

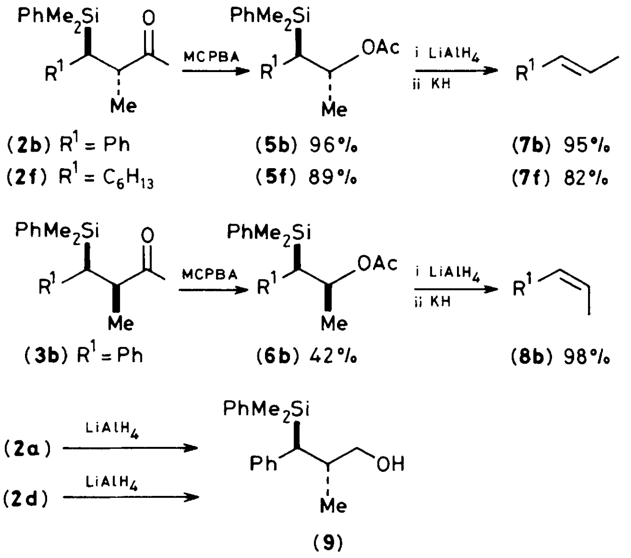


	Ratio (**2**) : (**3**)
b; R¹ = Ph, R² = Me	30 : 70
d; R¹ = Ph, R² = OMe	15 : 85

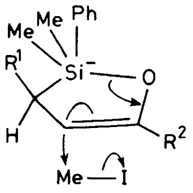
Scheme 2

We proved the sense of the diastereoselectivity with the reactions shown in Scheme 3. Baeyer–Villiger oxidation of the pure, separated ketones (**2b**) and (**3b**) gave the acetates[5] (**5b**) and (**6b**), respectively. Reduction ($LiAlH_4$) of these acetates, and treatment of the alcohols with potassium hydride gave the styrenes (**7b**) and (**8b**). Since the last steps proceed with *syn* stereospecificity,[6] and the Baeyer–Villiger reaction with retention of configuration,[7] the structures of the ketones are those shown. A similar sequence starting from the ketone (**2f**) showed that the diastereoselectivity was in the same sense, and to much the same degree, when R¹ was alkyl or phenyl. We correlated the ester (**2d**) with the ketones (**2b**) by hydrolysis of the ester (KOH) to give the corresponding acid. Regeneration (CH_2N_2) of the ester showed that no epimerisation had taken place in this step. The acid reacted with excess of methyl-lithium to give the ketone (**2b**). Finally, reduction of the aldehyde (**2a**) and the ester (**2d**) gave the same alcohol (**9**). The other structures in Scheme 1 were deduced by analogy, and, in the case of the chalcone series (**2c**), by the reactions described in the following communication.

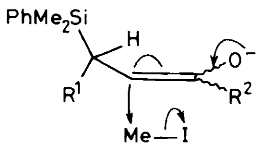
The sense of the diastereoselectivity can be explained in two ways. One possibility is that the enolate is chelated to the silyl group (**10**), and the methyl iodide then attacks the less



Scheme 3. MCPBA = *m*-chloroperbenzoic acid.



(**10**)



(**11**)

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† No reprints available.

hindered side of the five-membered ring. We do not think this important: although silylation of the enolate derived from the ketone (**1b**) gave the *Z*-enol ether (nuclear Overhauser enhancement), silylation of the enolate from the aldehyde (**1a**) gave the *E*-enol ether (*J* 12 Hz). The *E*-enolate cannot form a chelate (**10**), and yet the degree and the sense of diastereoselectivity is very similar for both the aldehyde and the ketone. Furthermore, esters are known[8] generally to form *E*-enolates in the absence of hexamethylphosphoramide, and ours are probably no exception. The alternative explanation follows from the steric and electronic influences in the low-energy conformation (**11**). In this conformation, the hydrogen eclipses the double bond leaving the larger groups staggered. Attack by methyl iodide then takes place *anti* to the silyl group either for electronic or steric reasons or for both combined. It is notable that the face of the double bond of the enolate attacked is the same face as that found to be attacked in allylsilanes;[9] the difference in the two series is that the electrophile settles down on C-3 of the allyl system in allylsilanes but on C-2 of the allyl system of the enolates. The sense of the electrophilic attack on the double bond (**11**) is essentially that predicted by Houk.[10] Protonation (Scheme 2) probably has lower diastereoselectivity both because the proton is smaller and because the product-forming step is the protonation of an enol (rather than an enolate). With a later transition state, such a reaction can be expected to reflect thermodynamic factors to a greater extent than the alkylation reaction does.

One way in which the high diastereoselectivity described in this paper can be put to use is described in the following communication.

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