Diastereoselectivity in the Alkylation and Protonation of Some β-Silyl Enolates†

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A wide variety of β-silyl enolates are alkylated or protonated with high diastereoselectivity, which appears to be substantially electronic in origin.

We reported earlier[1] the diastereoselective methylation of the β-silyl enolate produced by conjugate addition of our silyl cuprate reagent to methyl cinnamate (**1a**). We also reported that protonation of the corresponding enolate derived from methyl α-methylcinnamate (**4a**) took place in the same sense to give largely the opposite diastereoisomer (**5a**). In a separate paper[2] we reported that the β-silyl esters (**2a**) and (**5a**) can be converted in two steps, with retention of configuration, into the β-hydroxy esters (**3**) and (**6**), respectively. We explained the diastereoselectivity of alkylation by suggesting that the lowest-energy conformation[3] (**7**) of the enolate was attacked *anti* to the silyl group for steric or for electronic reasons, or for both combined. In this paper, we report further studies, in

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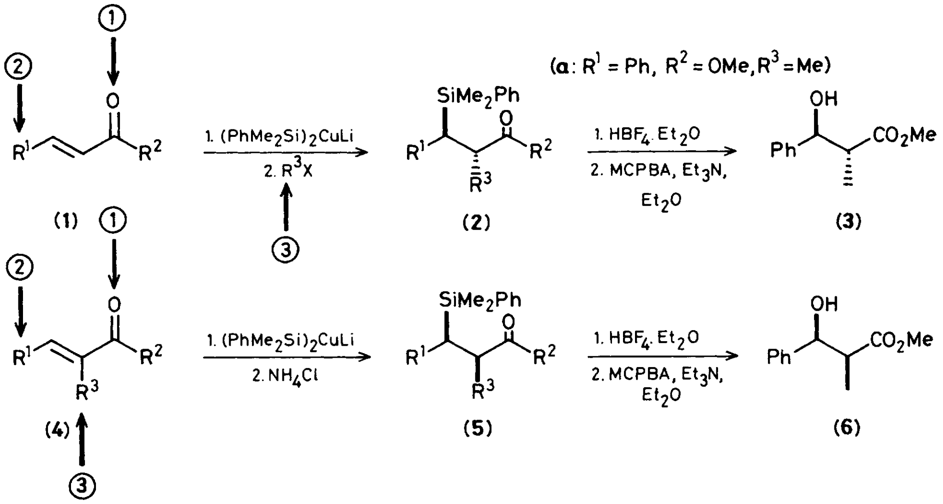


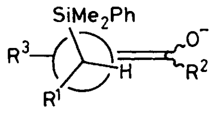
Scheme 1. MCPBA = *m*-chloroperbenzoic acid.

Table 1. Diastereoselectivity in the alkylation of enolates derived from (**1**) and in the protonation of enolates derived from (**4**) (Scheme 1).

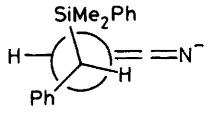
				Alkylation (from **1**)		Protonation (from **4**)	
Entry	R^{1}	R^{2}	R^{3}(X)	Ratio (**2**) : (**5**)	Yield %	Ratio (**2**) : (**5**)	Yield %
a	Ph	OMe	Me(I)	97 : 3[a]	88[a]	15 : 85[a]	84[a]
b	Ph	Me	Me(I)	98 : 2[a]	57[a]	30 : 70[a]	
c	Ph	H	Me(I)	92 : 8[a]	74[a]	11 : 89	86
d	Ph	Ph	Me(I)	high[a,b]	70[a]	—[b]	0
e	Ph	NMe$_2$	Me(I)	97 : 3	86	18 : 82	83
f	Ph	CN for COR^{2}	Me(I)	54 : 46	65	14 : 86	77
g	Me	OMe	Me(I)	91 : 9	78	13 : 87	82
h	Pr^{i}	OMe	Me(I)	85 : 15	95	4 : 96	56
i	Bu^{t}	OMe	Me(I)	66 : 34	83	4 : 96	38
j	Ph	OMe	Et(I)	95 : 5	83	20 : 80	77
k	Ph	OMe	Bu^{n}(I)	94 : 6	86	27 : 73	77
l	Ph	OMe	Pr^{i}(I)	95 : 5	26	60 : 40	78
m	Ph	OMe	PhCH$_2$(Br)	97 : 3	74	71 : 29	66
n	Ph	OMe	CH$_2$=CHCH$_2$(Br)	95 : 5	76	31 : 69	83
o	Ph	OMe	MeO$_2$CCH$_2$(Br)	98 : 2	50	10 : 90	82

[a] Ref. 1. [b] See text.

which we have varied the structures and the reagents at the points marked by the arrows 1—3 in Scheme 1.

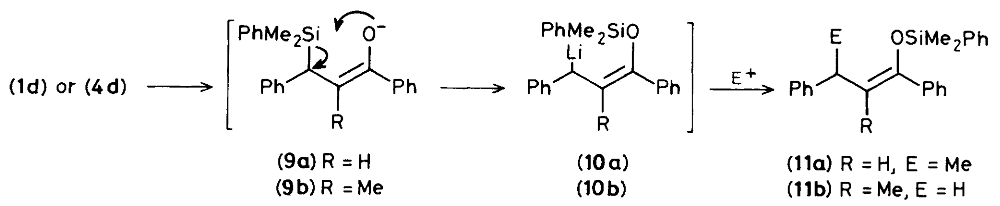


(**7**)

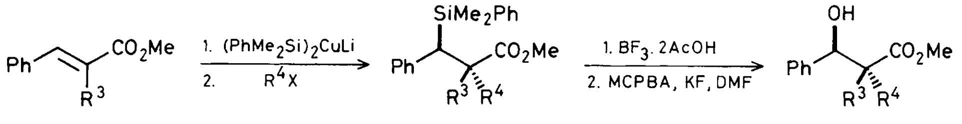


(**8**)

Arrow 1. We varied the carbonyl group (COR^{2}) and record all our results (entries **a**—**f**) in Table 1. The diastereoselectivity is uniformly high, except for methylation of the nitrile (**1f**). For the nitrile, the conformation (**8**), corresponding to (**7**) in the ester series, is no longer necessarily the lowest in energy (there is now no substituent *cis* to the chiral centre), and the smallest group (H) on the chiral centre is not the only one which can comfortably eclipse the double bond. In consequence, it is no longer easy to predict which conformation has the lowest energy, and it is therefore reasonable, although not inevitable, that the diastereoselectivity is lower. The same argument accounts for why the aldehyde (**1c**) is somewhat less selective than the other carbonyl derivatives: in this case, the enolate corresponding to (**7**) has only a hydrogen *cis* to the chiral centre, whereas the other carbonyl derivatives inevitably have oxygen or carbon atoms there. The phenyl ketone is a special case. We studied this one because Zimmerman,[4] in an early attempt to produce a rule for the diastereoselectivity of electrophilic attack on trigonal carbon adjacent to a chiral centre, had suggested that the enol of a phenyl ketone would have diastereoselectivity in the opposite sense to that of a methyl ketone. However, we were only able to test this in the alkylation sense, starting from (**1d**). When we started with (**4d**) and protonated the intermediate, we isolated only the silyl enol ether (**11b**) (58%), which must have arisen by 1,4-silyl transfer (**9**, arrows). We were unable to stop this reaction, and even in the alkylation case (**1d**→**2d**) there was a by-product (**11a**) (20%), which arose from the same sequence (Scheme 2), but with methylation quenching the allyl-lithium intermediate (**10a**). The 1,4-silyl transfer (**9**) is only possible with a *Z*-enolate. We have found with several ketones and esters [but not with the aldehyde (**1c**)[1]] that the enolate produced by conjugate addition of our silyl cuprate reagent has this geometry. Thus we find that conjugate addition to methyl cinnamate, and trapping the enolate as a trimethylsilyl enol ether, gave only (^{1}H n.m.r.)



Scheme 2



Scheme 3. DMF = dimethylformamide.

Table 2. Diastereoselectivity in the alkylation of enolates derived from (**12**) (Scheme 3).

Entry	R^3	R^{4}X	Ratio (**13**) : diastereoisomer	Yield %	(**14**) Yield %
a	Me	EtI	83 : 17	94	79
b	Et	MeI	89 : 11	95	74
c	Me	$CH_2{=}CHCH_2Br$	83 : 17	90	52
d	$CH_2{=}CHCH_2$	MeI	80 : 20	90	67
e	Me	MeO_2CCH_2Br	92 : 8	45	
f	MeO_2CCH_2	MeI	90 : 10	83	
g	Me	Pr^{i}I	90 : 10	63	
h	Pr^i	MeI	60 : 40	77	

the *Z*-isomer, whereas trapping with a proton and regeneration (lithium di-isopropylamide) and silylation gave, as expected,[5] only the *E*-isomer. Since the lithium enolates prepared by both routes showed the same diastereoselectivity in methylation,[1] we have now confirmed that a cyclic pentaco-ordinated silicon intermediate is almost certainly not involved.

Arrow 2. We have also completed the series of results in which we have systematically varied R^1 (entries **a** and **g**—**i** in Table 1). The degree of diastereoselectivity in methylation falls off in the series Ph>Me>Pr^i>Bu^t, *but stays in the same sense*. Since the standard measures[6,7] of the effective size of the various groups rank a t-butyl group as 'larger' than a trimethylsilyl group, we suggest that *a substantial proportion of the diastereoselectivity is electronic in origin*. This is supported by our results with a trialkyltin group in place of the silyl,[8] where we again got high diastereoselectivity, even though a trimethylstannyl group, in its A-value at least,[9] is ranked as significantly 'smaller' (1.1) even than a methyl group (1.8). We cannot, of course, be certain of this conclusion, since no agreed scale of effective size is reliable when taken from one situation to another. A remarkable and not yet explicable result is that, in protonation, the diastereoselectivity rises uniformly as R^1 gets larger. We note also, in the nitrile series (**4f**), that protonation retains its diastereoselectivity. We earlier suggested[1] that the diastereoselectivity observed for protonation (entries **a** and **b**) was lower than that for methylation, because the transition state for protonation of an enol is likely to be later, and more product-like, than that for alkylation of an enolate. The diastereoselectivity ought therefore to have been closer to the thermodynamic ratio. This no longer appears to be the explanation. We note only that, in the protonation series, R^3 in (**7**) is a methyl group, and this must disturb the conformation, but we are as yet unable to identify the preferred conformation, let alone the conformation in the transition state. The fact that the conformation (**7**) is indeed preferred when R^3 = H is confirmed by the large coupling constants (10, 11, and 11 Hz) for this hydrogen in three silyl enol ethers we have prepared. A coupling constant of 11 Hz is diagnostic for this conformation in alkenes.[10]

Arrow 3. We have also examined a range of alkyl halides (entries **a** and **j**—**o** in Table 1) and matched them with the corresponding protonation, for which we prepared the appropriate esters (**4j**—**o**) with the alkyl groups already in place. All the alkylations were highly diastereoselective, and all to very much the same extent. In this series, it is the protonations which fall off, especially with the isopropyl (**4l**) and benzyl (**4m**) groups in the molecule, where the diastereoselectivity is even reversed. Again, these groups are in such a position (R^3) that the conformation (**7**) is no longer necessarily the lowest in energy.

Quaternary centres. We have also investigated the diastereoselectivity of alkylation when another group is already in place (Table 2). This creates quaternary centres diastereoselectively (Scheme 3), a subject of current activity.[11] Again, as with protonation, a large group in place (**12h**) seriously impairs the diastereoselectivity. In four cases (**13a**—**d**), we took the β-silyl esters through to the β-hydroxy esters (**14a**—**d**), in order to demonstrate that the quaternary centres, and the terminal double bond, did not interfere with the two-step sequence.

We have proved the relative configuration of a high proportion of the products reported in this paper. The different carbonyl compounds (**2a**—**c** and **2e**) and the nitrile (**2f**) were interconverted by standard chemistry. The ketone (**2d**) and the esters (**5h** and **5i**) were each converted, by the two-step sequence as illustrated for (**2**→**3**) and (**5**→**6**), to give known[12,13] β-hydroxy carbonyl compounds. And the esters (**13a**) and (**13b**) similarly gave alcohols (**14a**) and (**14b**), to which we were able to assign configurations by nuclear Overhauser effect–difference experiments on the cyclic acetals obtained by reduction ($LiAlH_4$) followed by treatment of the diols with 2,2-dimethoxypropane and acid. In view of the uniformly high diastereoselectivity in the alkylation reactions, we feel confident in assigning configurations to the other compounds by analogy.

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