The Opposite Diastereoselectivity in the Alkylation and Protonation of Enolates

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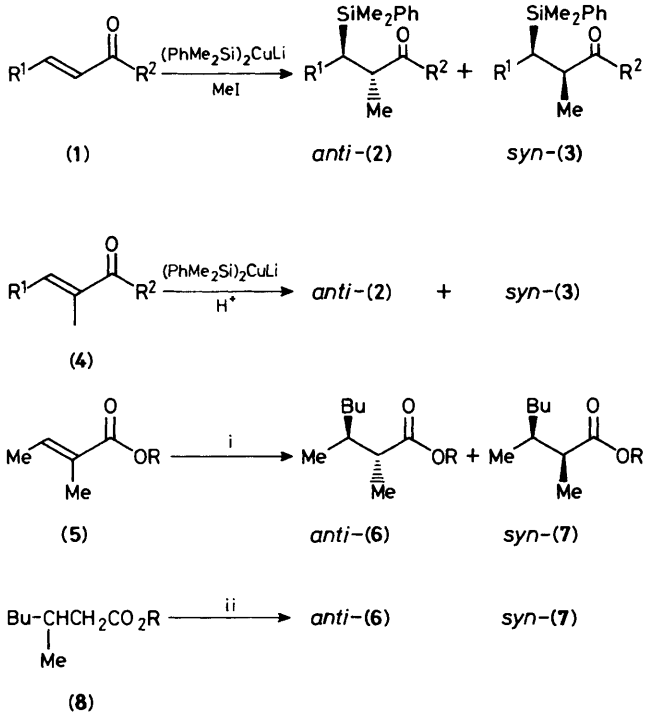
The conjugate addition of $BuCu{\cdot}BF_3$ to the enoate (**5**) produces predominantly the *syn*-isomer (**7**) having the butyl and methyl groups *syn* on the carbon chain, while the methylation of the enolate derived from the ester (**8**) gives preferentially the other diastereoisomer, *anti*-(**6**); the diastereoselectivity can be explained by an eclipsed model.

A recent publication by Bernhard, Fleming, and Waterson[1] on diastereoselectivity in the alkylation of enolates has prompted us to report our own findings in this area. They reported that conjugate addition of the silyl cuprate $(PhMe_2Si)_2CuLi$ to (**1**), followed by methylation, produced predominantly the isomer (**2**) resulting from *trans*-addition of the silyl and methyl groups. Alternatively, similar conjugate addition to (**4**), followed by protonation, gave predominantly the other diastereoisomer (**3**).

In the course of studies on Lewis acid-mediated organocopper reactions,[2] we examined the conjugate addition of $BuCu{\cdot}BF_3$ to the enoates and enoic acid (**5**), followed by protonation. The isomer ratios are summarized in Table 1. Regardless of the substituent R and the quenching temperature, the isomer (**7**) having the butyl and methyl groups *syn*† on the original carbon chain was obtained predominantly. The other isomer (**6**) was produced preferentially in the methylation reaction of the enolate derived from (**8**) (Table 1).

The stereochemistry was determined by comparison with an authentic material prepared independently as shown in Scheme 1. *meso*-2,3-Dimethylsuccinic acid (**9**) was converted into the acid chloride (**10**), which was treated with di-n-propylcopperlithium at −78 °C to give (**11**).[3] The tosylhydrazone of (**11**) was reduced with $NaBH_3CN$[4] to give (**6**) (R = Et).

The stereochemical tendency of our reactions is in good agreement with the observation of Fleming *et al.*[1] They explained the *anti*-selectivity of methylation as shown in Scheme 2. Attack by MeI takes place *anti* to the Si group in the stable conformation (**12**), to produce (**2**). On the other hand, protonation reflects thermodynamic factors to give (**3**). Similarly, the stereochemistry in our reactions can be explained *via* the eclipsed model[5] as shown in Scheme 3.The conjugate addition of $BuCu{\cdot}BF_3$ produces the enolate (**13**),



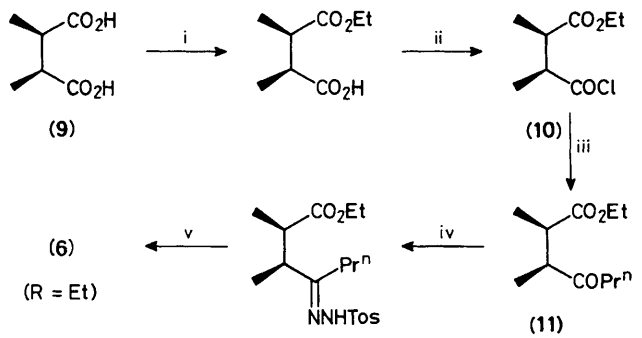
Reagents and conditions: i, $BuCu{\cdot}BF_3$ followed by H^+; ii, lithium di-isopropylamide, −78 °C, followed by MeI, 0 °C.

† The nomenclature *syn* and *anti*, is used to describe the stereochemical situation of the $PhMe_2Si$ and butyl with respect to the incoming groups and is different from the normal usage; S. Masamune and W. Choy, *Aldrichimica Acta*, 1982, **15**, 47.

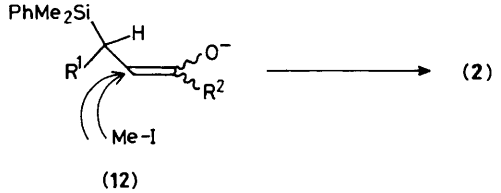
Table 1. Diastereoisomer ratio in the methylation and protonation of (**5**).[a]

Carbonyl compound, R	Quenching temp./°C	Isomer ratio (**6**) : (**7**)
(**5**), Et	−70	26 : 74
	20	36 : 65
(**5**), C_6H_4Me-*p*	0	30 : 70
(**5**), $CH_2OCH_2CH_2OMe$	20	30 : 70
(**5**), H	20	33 : 67
(**8**), Et	0	65 : 35
(**8**), C_6H_4Me-*p*	0	65 : 35

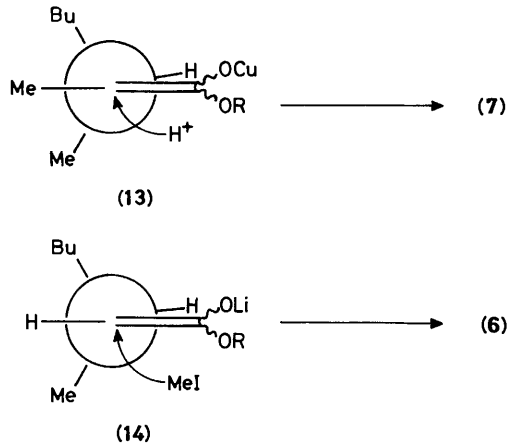
[a] All reactions were carried out on a 1 mmol scale. Excess of $BuCu{\cdot}BF_3$ was used as previously described.[2] Use of $Bu_2CuLi{\cdot}BF_3$ gave somewhat lower diastereoselectivity. The reaction was quenched with MeOH at the indicated temperature, then the ratio was analysed by g.l.c. and/or ^1H n.m.r. spectroscopy.



Scheme 1. *Reagents and conditions:* i, $(MeCO)_2O$, reflux; EtOH, reflux; yield 95%; ii, $SOCl_2$, 20 °C; 97%; iii,Pr^n_2CuLi, −78 °C; 82%; iv, $TosNHNH_2$–EtOH, 20 °C; 85%; v, $NaBH_3CN$–dimethylformamide–sulpholane–H^+, 110 °C; 77%. Tos = *p*-$MeC_6H_4SO_2$.



Scheme 2



Scheme 3

which is attacked by a proton from the less hindered side to give (**7**) predominantly. The methylation of the lithium enolate from (**8**) proceeds *via* (**14**), where the electrophile again attacks from the less hindered side to produce (**6**) preferentially. Taken together, these results indicate that the very high stereoselectivity observed by Fleming and co-workers is due to the steric bulkiness and stereoelectronic effect of the $PhMe_2Si$ group, since even the presence of a butyl group creates a selectivity of *ca.* 7 : 3.

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