A Paradigm for Diastereoselectivity in Electrophilic Attack on Trigonal Carbon adjacent to a Chiral Centre: the Methylation and Protonation of Some Open-chain Enolates†

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Methylation of the enolates (**3**), and protonation of the enolates (**4**), are diastereoselective in conformity with a recently formulated rule, and are, with one exception, selective in the opposite sense to nucleophilic attack on the corresponding aldehydes (**7**) and ketones (**8**).

Cram's rule was formulated more than thirty years ago[1] to deal with the diastereoselectivity of *nucleophilic* attack, in open-chain structures, on trigonal carbon adjacent to a chiral centre. The diastereoselectivity of *electrophilic* attack, in open-chain structures, on trigonal carbon adjacent to a chiral centre has received much less attention, but recently a rule has been proposed by Houk and his co-workers.[2] The rule is based on similar reasoning to that used by Felkin to explain Cram's rule. Felkin's argument,[3] refined by Anh[4] and by Houk,[2] is summarised in the drawing (**1**). The rule for electrophilic attack is similarly summarised in the drawing (**2**), where, the argument goes, the preferred conformation has the 'small' (S) substituent eclipsing (or partly eclipsing) the double bond, and the electrophile attacking from within the double bond on the less-hindered side, *anti* to the 'large' (L) group. It follows that electrophilic attack should take place from the opposite side to that of the corresponding nucleophilic attack on a carbonyl group, and that the electrophilic rule, other things being equal, should prove to be the opposite of Cram's rule.

Most of the known examples of open-chain diastereoselective electrophilic attack are not properly covered by this rule, because the chiral centre carries an oxygen function, which either delivers the reagent (epoxidation[5] or Simmons–Smith reaction[6] on allylic alcohols) or exerts a substantial, but not entirely consistent, electronic effect (allylic ethers react with osmium tetroxide consistently in one sense,[7] but with hydroborating agents in the other[8]). The alkylation of enolates with a β-oxyanion probably involves a chelate and is not a true open-chain reaction.[9] Halogen attack, although much studied (in halolactonisation for example[10]) presents difficulties in identifying which step—electrophilic attack or opening of the intermediate—is stereochemistry-determining. Hydrobora-

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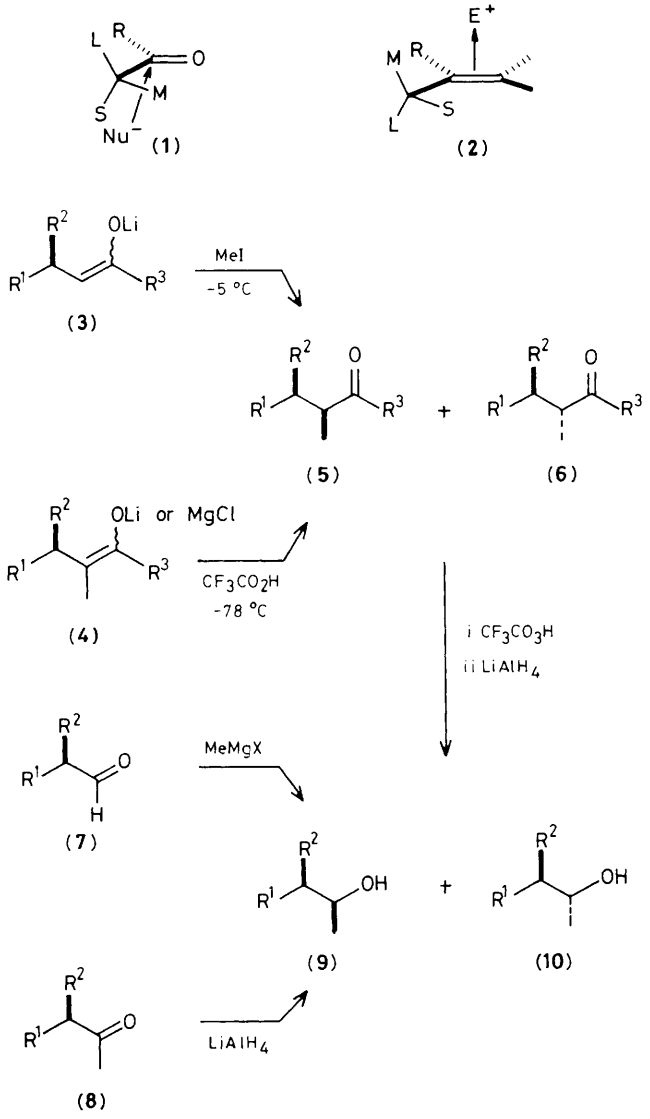

Scheme 1. Reactions were carried out in the optically inactive series; only one enantiomer is drawn.

tion of some alkenes[11] and electrophilic attack on allylsilanes[12] are the best examples of reactions showing high diastereoselectivity in conformity with the rule,[2] as also are our results[13,14] on the alkylation of β-silyl and β-stannyl enolates. However the latter results, with a metallic heteroatom on the chiral centre, might be thought to be rather special cases. We now report results which have been designed to be a paradigm for electrophilic attack on trigonal carbon adjacent to a chiral centre: the methylation and protonation, respectively, of the enolates (**3**) and (**4**), and we compare our results, in the sense of their diastereoselectivity, with the corresponding nucleophilic attacks on the aldehydes (**7**) and the ketones (**8**). Our results are displayed in Scheme 1 and Table 1.

Alkylation and protonation regularly take place in the same sense, with the electrophile attacking from above, as drawn. Thus for alkylation [(**3**) → (**5**) + (**6**)], the major product is (**5**), whereas for protonation [(**4**) → (**5**) + (**6**)], the major product is (**6**). (Presumably, protonation takes place first on oxygen, and the stereochemistry-determining step is the second protonation on carbon; this does not affect the argument.) Because the conjugate additions used to prepare the enolates gave mixtures of geometrical isomers,[15] we were not able, as we were in the silicon series,[13,14] to investigate the effect of double bond geometry on the diastereoselectivity. In the silicon series it is usually, but not quite always,[16] small.‡ The equilibrium ratios for the ketones (**5**) and (**6**) are also listed in Table 1. They regularly fall between the alkylation and protonation ratios, showing that our results, whether purely kinetic or not, are all in the kinetic direction. From the reaction conditions used, it is unlikely that much equilibration had taken place by the time we measured the ratios. Recently, Yamamoto and Maruyama[17] showed that the methylation and protonation of some ester enolates, with the chiral centre carrying a methyl and an n-butyl group, were diastereoselective in the same sense, and to approximately the same degree (methylation, 74 : 26; protonation, 35 : 65), as our results with methyl *vs.* isopropyl. We also examined two other enolate pairs (**3d**,**4d**) and (**3e**,**4e**) (Table 1). The ester enolates (**3d**) and (**4d**) gave very similar results to those of the corresponding methyl ketone enolates (**3a**) and (**4a**). The unselectivity in the methylation of the phenyl ketone enolate (**3e**) is the only sign we have that phenyl ketone enolates might show different diastereoselectivity from other carbonyl derivatives, as suggested by Zimmerman in an early attempt to create an electrophilic rule.[18] However, this difference in a phenyl ketone was not apparent in protonation [(**4e**) → mainly (**6e**)] nor in our results in the silicon series.[13] The change from 60 : 40 in the methyl ketone to 50 : 50 in the phenyl ketone is probably not significant.

With one exception, the corresponding nucleophilic attack takes place in the opposite sense, with the nucleophile attacking from below, as drawn. Thus the aldehydes (**7**) all react with the methyl Grignard reagent to give (**10**) as the major product,[1,19,20] and two of the ketones (**8a**) and (**8b**) give (**9**) as the major product.[1,19] The exception is the ketone (**8c**), for which we could find in the literature no data on hydride reduction. We carried out the reduction and got the highest diastereoselectivity in the whole table, but in the unexpected sense.

Interpretation, especially of the anomalous result, is complicated. There is in the first place considerable doubt about how much of the nucleophilic (Cram) and electrophilic (Houk) attack are controlled by steric and how much by electronic factors. Furthermore, steric effects depend so much upon the precise direction from which a reagent approaches that there can be no single scale for the effective size of a group. The results in the **a** and **b** series are all consistent with Me < Ph and Me < Pr^i, an ordering which seems like a reasonable compromise, based on two measures of size, *A*-values[21] and the 'effective radius'.[22] The problem, not surprisingly, comes in the **c** series, where phenyl and isopropyl are set against each other. The first three results are consistent with Ph < Pr^i, which is also a good compromise order in view of uncertainty in the interpretation of *A*-values. The anomalous result [(**8c**) → mainly (**10**)] now needs explaining. We suggest that the problem stems from the same source that has always made explaining Cram's rule difficult. Because the carbonyl group has no substituent on the oxygen atom, § the ketone can adopt a conformation with any of the three substituents [S, M, or L in (**1**)] eclipsing the carbonyl group

‡ There is one unexplained report (K. Schönauer and E. Zbiral, *Tetrahedron Lett.*, 1983, **24**, 573) of a substantial effect of double bond geometry on the diastereoselectivity in the protonation of an enolate.

§ A Lewis acid is presumably bonded to oxygen, but it is likely to be *trans* to the chiral centre.

Table 1. Ratios of diastereoisomers in the methylation and protonation of the enolates (**3**) and (**4**), and in the corresponding nucleophilic attack on the aldehyde (**7**) and the ketone (**8**).

Substrate	R^1	R^2	R^3	Yield %	Isomer ratios (**5**) : (**6**)[a]	Isomer ratios (**9**) : (**10**)	Equilibrium ratios (**5**) : (**6**)[a]	Ref.
(**3a**)[b]	Ph	Me	Me	58	60 : 40		40 : 60	c
(**4a**)[d]	Ph	Me	Me	85	14 : 86			c
(**7a**)	Ph	Me				33 : 67		1
(**8a**)	Ph	Me				70 : 30		1
(**3b**)[e]	Pr^i	Me	Me	40	75 : 25		65 : 35	c
(**4b**)[f]	Pr^i	Me	Me	74	20 : 80			c
(**7b**)	Pr^i	Me				23 : 77		19
(**8b**)	Pr^i	Me				78 : 22		19
(**3c**)[e]	Pr^i	Ph	Me	54	87 : 13		60 : 40	c
(**4c**)[f]	Pr^i	Ph	Me	77	27 : 73			c
(**7c**)	Pr^i	Ph				45 : 55		20
(**8c**)	Pr^i	Ph		99		3 : 97		c
(**3d**)[g]	Ph	Me	OMe	98	55 : 45[h]		34 : 66	c
(**4d**)[g]	Ph	Me	OMe	81[i]	21 : 79[h]			c
(**3e**)[d,g]	Ph	Me	Ph	93	50 : 50[j]		38 : 62	c
(**4e**)[d,g]	Ph	Me	Ph	91	13 : 87[j]			c

[a] Assigned by Baeyer–Villiger oxidation followed by reduction ($LaAlH_4$) to the alcohols (**9**) and (**10**). Measured by g.l.c. of the mixture of (**9**) and (**10**), so derived; confirmed by ^1H n.m.r. spectroscopy of the mixture of (**5**) and (**6**). [b] Prepared by conjugate addition of Me_2CuLi or Ph_2CuLi to the appropriate enone, trapping the enolate as its silyl enol ether, and regenerating the enolate with MeLi. [c] This work. [d] Prepared by conjugate addition of Me_2CuLi to the enone. [e] Prepared by conjugate addition of Me_2CuLi or Ph_2CuLi to 5-methylhex-3-en-2-one, evaporating off the ether, and replacing it with tetrahydrofuran (THF). [f] Prepared by Cu^I-catalysed addition of Pr^{i}MgCl to the appropriate enone. [g] Prepared from the ester or phenyl ketone with lithium di-isopropylamide. [h] Assigned by methylation of authentic *RS,SR*-acid (A. Theine and J. G. Traynham, *J. Org. Chem.*, 1974, **39**, 153). Determined by ^1H n.m.r. spectroscopy. [i] To guard against the possibility of incomplete formation of enolate, this experiment was a deuteriation result with 81% incorporation of ^2H. [j] Assigned by phenylation of authentic *RS,SR*-acid.

without a high energetic penalty. Furthermore, it has been suggested that a methyl group often prefers to be *gauche* to a phenyl, rather than *anti* to it.[23] This would lead the ketone (**8c**) to adopt a conformation with the isopropyl group eclipsing the carbonyl group, and hence attack from the less hindered direction would occur to give (**10**). We tentatively hazard the prediction that the electrophilic (Houk) rule, in spite of its more recent origin, is likely to prove more reliable than Cram's rule, precisely because the lowest energy conformation (**2**) is more predictable [at least when R in (**2**) is small] than that for aldehydes and ketones.

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