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Open chain 1,3-stereocontrol

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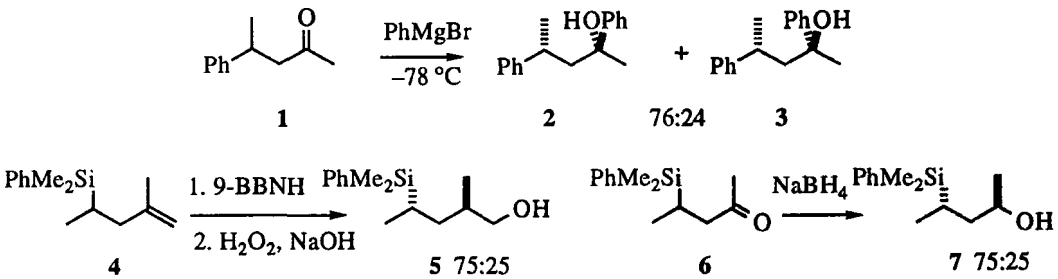
Abstract: Several reactions of nucleophiles with carbonyl compounds and enone systems have been carried out in a search for a rule for open-chain 1,3-stereocontrol.

Cram's rule (1) for nucleophilic attack on a carbonyl group adjacent to a stereogenic centre is well known, and the explanation, successively advanced by Karabatsos, Felkin, and Anh (2), is well accepted. We have pointed out (3) that the corresponding rule for electrophilic attack on a C=C double bond, developed successively by Zimmerman, Barton, and Houk (4), is in one sense the opposite of Cram's rule.

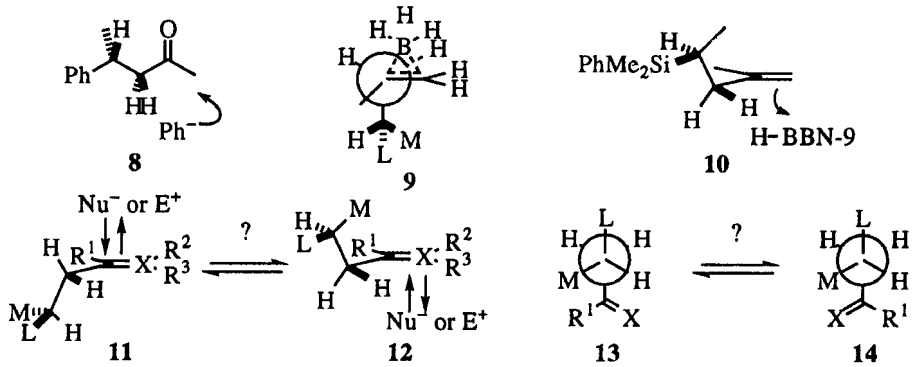
The homologue of these reactions, in which the reaction site and the stereogenic centre are separated by a methylene group, is much less well understood. For good control in this situation, a cyclic substrate or transition structure is usually needed, and there are many such reactions, such as, for example, methods for controlling the relative stereochemistry of 1,3-diols by reduction of β-hydroxyketones (5). In the absence of a ring, it is much more usual to get very low levels of diastereocontrol, as we found in our synthesis of the Prelog-Djerassi lactone, for example, in which lithium phenylacetylide reacted with a ketone having a stereogenic centre at C-3 to give both possible alcohols in equal amounts (6). As it happens, that result was not a disappointment, since the whole point of that synthesis had been to demonstrate how our stereochemically complementary allylsilane syntheses, coupled to the predictably *anti* stereospecific protodesilylation of an allylsilane, allowed us to converge on the correct stereochemistry for C-6 from *both* diastereoisomers.

Nevertheless, it might be much easier if one were not obliged to use round about, multistep sequences to achieve such control. We have now embarked upon a study of this problem, with the aim eventually of finding a rule with which to predict the sense and perhaps even the degree of 1,3-control in open-chain systems. With such a rule, we might be able to identify the features that will lead to high levels of 1,3-stereocontrol, and, if such control is predictable, we can hope to save steps in syntheses.



Cram himself had already started on this route, identifying a reaction **1** → **2** + **3** showing a high level of selectivity (7). Evans found another example of substantial 1,3 selectivity in a hydroboration (8), and we also came across another hydroboration example **4** → **5** and also a ketone reduction **6** → **7** (9). To explain his results, Cram drew a "transition structure" **8**, with the phenyl group attacking from the front surface. Evans drew a rather different looking diagram **9**, and we drew yet another **10**. It is clear that, to make sense of this whole area, we need a uniform presentation of the problem, and a scheme for thinking about what the factors might be. We have chosen to use the drawings **11** and **12** as a basis, and to consider the effect of changing the variables.

We can expect that one of the two hydrogen atoms on the intervening methylene group will more or less eclipse the double bond; we can also expect that the large group L will take up a position in the segment between the two methylene hydrogen atoms. There are then two conformations, **11** and **12**; in the former the top face is more exposed to a reagent and in the latter the bottom face is more exposed. The Newman projections **13** and **14** provide an alternative view, and reveal that the difference is in the segments that the medium-sized group occupies. What we want to know is (i) which, if either, of these conformations is preferred, (ii) how is the position of equilibrium between the conformations affected by changing the variables, and (iii) do the experimental results match the predictions based on these considerations.

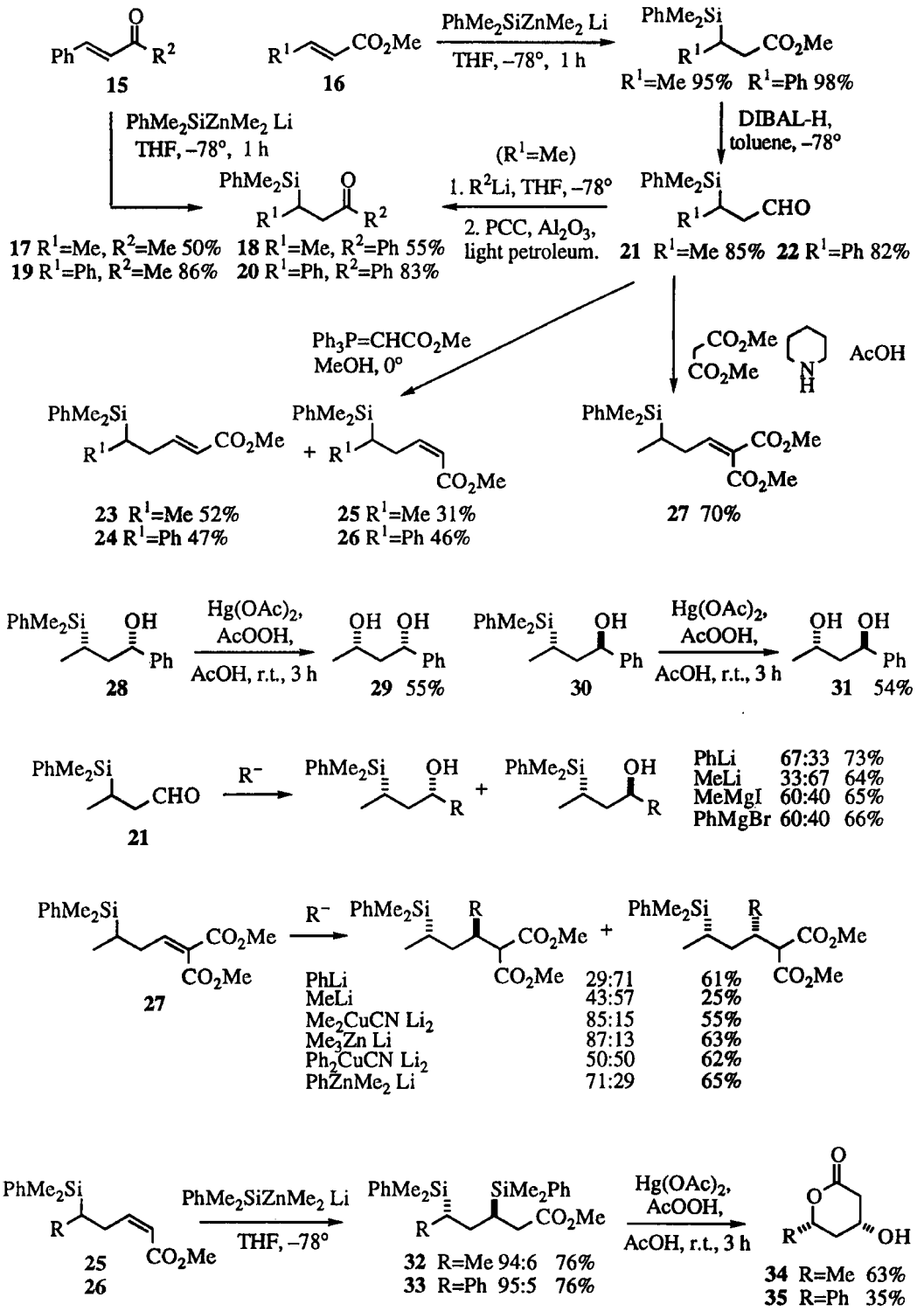


Our immediate problem is the infinite number of possibilities with six structural variables, L, M, R^1-R^3 and X, and a large number of possible reagents, E^+ or Nu^-. To begin with we have chosen to limit ourselves to nucleophilic attack on a carbonyl group (X=O) and on a C=C double bond carrying electron-withdrawing groups (X=C, R^1=H, and R^2 and/or R^3=CO_2Me). We have chosen to use three representative carbon-based groups, namely methyl, phenyl and isopropyl, both as the medium-sized groups M and as the substituent R^1. Perhaps most significantly, and least surprisingly, given that it is we who are doing this work, we have chosen the phenyldimethylsilyl group as the large group L. This particular choice has several virtues. The silyl group is unambiguously *large*, although it may prove to be less *demanding* than we might like. It is unlikely to coordinate to reagents, giving rise to cyclic transition structures. Most important, it can be converted with retention of configuration into a hydroxyl group, which makes it ideal for proving the relative configurations in the products. Thus the reaction **6** → **7** that we had already carried out, had M=R^1=Me, X=O and Nu^-="H^-", and attack took place predominantly in the sense explained by the conformation **12**.

Even with these limitations, there is still a formidable number of possible reactions. We have, so far, carried out those listed in the Table. We prepared the starting materials by silyl-zincation (10) of the ketones **15** and the esters **16**, and by Wittig and aldol reactions on the aldehydes **21** and **22**. We proved the relative configuration of the products, by reactions like those illustrated for the alcohols **28** and **30**. We prepared these alcohols by reduction of the ketone **18** and by phenyllithium or phenyl Grignard attack on the aldehyde **21**, and we separately converted them to the known diols **29** and **31** using one of our one-pot silyl-to-hydroxy conversions (11).

We have used molecular modelling to probe the low-energy conformations of the starting materials, in the hope of finding a correlation between the sense of the selectivity and which surface appears to be the more exposed in the model. We plotted the difference in energy between the lowest-energy conformation predicting attack in the sense **12** and the lowest-energy conformation predicting attack in the sense **11** ($-E_A-E_B$ in the Table) against the observed percent difference between attack in the sense **11** and attack in the sense **12** (A:B in the Table). The result was a disappointingly random scatter. There was essentially no correlation.

One reason for this can be seen in the large variation in the results depending upon the reagent used. Since our modelling, so far, has only looked at the substrate, all reagents are treated as attacking in the same sense and to more or less the same degree. This is rather plainly not the case in practice, as seen by the attack of phenyl- and methyl-lithium on the aldehyde **21**, which take place in the opposite sense to each other, whereas the corresponding Grignard reagents give the same major diastereoisomer. In contrast, phenyl- and



methyl-lithium react with the unsaturated ester **27**, to give the same diastereoisomer, whereas the corresponding cuprates and zincates mostly give the opposite result. Clearly a ground state study, in spite of its success with Cram's rule, cannot deal with this kind of variation.

These are early days yet, and we need more results, but what we can say is that a rule is not going to be as easy to formulate as Cram's rule, which is also a ground-state rule. On the other hand, we do have some interestingly high levels of 1,3-stereocontrol, notably in the conjugate addition of our silyl zincate reagent to the unsaturated esters **25** and **26**, each of which gave the 1,3-disilylated esters **32** and **33**, and hence the β-hydroxylactones **34** and **35** with high selectivity.

Substrate	Nucleophile	A:B[a]	Conditions	$-E_A-E_B$[b]
17	$LiAlH_4$	30:70	ether, –78°	–0.1
	$NaBH_4$	25:75	EtOH, 0°	
18	$LiAlH_4$	79:21	ether, –78°	0.7
	$NaBH_4$	71:29	EtOH, r.t.	
19	$LiAlH_4$	47:53	ether, –55°	3.4
	$NaBH_4$	54:46	EtOH, 0°	
20	$LiAlH_4$	33:67	ether, –55°	–0.2
	$LiAlH_4$	38:62	ether, reflux	
	$NaBH_4$	60:40	EtOH, 0°	
21	PhLi	67:33	THF, –78°	0.6
	PhMgBr	60:40	ether, 0°	
	PhMgOTf	67:33	THF, –78°	
	MeLi	33:67	THF, –78°	
	MeMgBr	55:45	THF, –78°	
	MeMgI	60:40	ether, 0°	
	MeMgOTf	33:67	THF, –78°	
22	PhLi	22:78	THF, –78°	1.7
	PhMgBr	28:72	THF, 0°	
	MeLi	48:52	THF, –78°	
	MeMgBr	53:47	THF, 0°	
23	$(PhMe_2Si)_2Cu$	71:29	THF, –78°	1.9
	$PhMe_2SiZnMe_2$	77:23	THF, –78°	
24	$(PhMe_2Si)_2Cu$	95:5	THF, –78°	3.4
	$PhMe_2SiZnMe_2$	86:14	THF, –78°	
25	$PhMe_2SiZnMe_2$	94:6	THF, –78°	2.5
26	$(PhMe_2Si)_2Cu$	48:52	THF, –78°	–0.8
	$PhMe_2SiZnMe_2$	95:5	THF, –78°	
27	PhLi	29:71	THF, –78°	2.8
	$PhZnMe_2$ Li	71:29	THF, –78°	
	Ph_2CuCN Li_2	50:50	THF, –78°	
	MeLi	43:57	THF, –78°	
	MeMgBr	67:33	THF, 0°	
	Me_3Zn Li	87:13	THF, –78°	
	Me_2CuCN Li_2	85:15	THF, –78°	
	$(PhMe_2Si)_2Cu$	57:43	THF, –78°	
	$PhMe_2SiZnMe_2$	78:22	THF, –78°	
	$PhMe_2SiLi$	55:45	THF, –78°	

[a]The ratio of attack in the sense **11** to that in the sense **12**. [b]The energy difference between the lowest energy conformation predicting attack in the sense **12** and that predicting attack in the sense **11**. Positive numbers predict attack in the sense **11**.

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