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Cram's Rule for Radical Reactions

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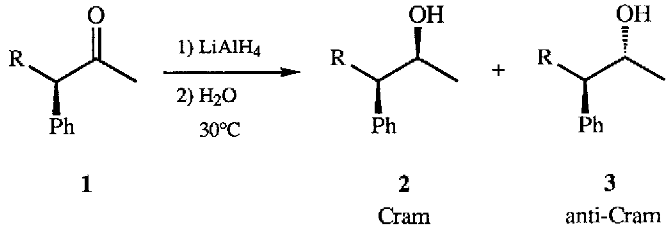
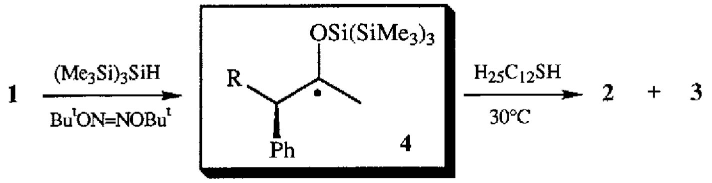
Abstract: Addition of tris(trimethylsilyl)silyl radicals to chiral ketones **1** yields tert. carbon centered radicals **4** that give predominantly Cram products in hydrogen atom abstraction reactions. Analogous sec. acyloxyalkyl radicals undergo radical C,D- and C,C-bond forming reactions that also follow Cram's rule.

Since the classical experiments of Cram,[1] 1,2 asymmetric induction in acyclic systems has been investigated extensively. In contrast to ionic reactions, radical chemistry has only recently reached a level that made studies of chirality transfer possible.[2] Thus, the question arose whether a guideline analogous to Cram's rule exists for radical reactions. We therefore carried out radical experiments with chiral ketones **1** that had been used by Cram[1] and others[3] for hydride ion abstraction from $LiAlH_4$. Reactions of ketones **1** with $(Me_3Si)_3SiH$ and $Bu^tON{=}NOBu^t$ as initiator generated siloxyalkyl radicals **4**.[4] Trapping of these radicals with $C_{12}H_{25}SH$[5] gave products **2** and **3**. Surprisingly, the ratios of Cram:anti-Cram products (**2**:**3**) of hydride ion and hydrogen atom abstraction are very similar.

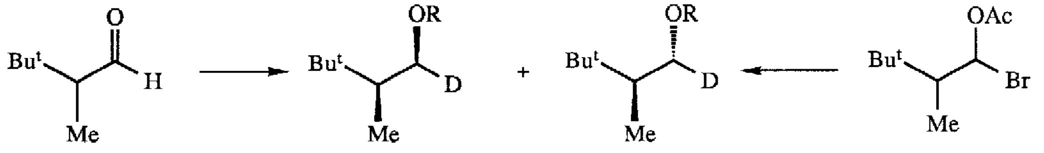


R	2 : 3
a : Me	2.9 : 1
b : Pr^i	13.3 : 1
c : Bu^t	8.3 : 1



R	2 : 3
a : Me	2.9 : 1
b : Pr^i	12.6 : 1
c : Bu^t	5.3 : 1

Qualitatively similar observations were made with aldehyde **5**. Reduction of **5** with $LiAlD_4$ (25°C) provided the Cram:anti-Cram products (**6a**:**7a**) in a ratio of 3.1:1, while reduction with $(Me_3Si)_3SiD$/5% $C_{12}H_{25}SH$ (25°C) gave the two products **6b**:**7b** in a ratio of 2.6:1.[6] Radical reductions of the related bromoacetal **8** with several different deuterium atom donors (25°C) gave similar ratios of **6c**:**7c**, thus indicating that neither the substituent on oxygen (Ac or $(Me_3Si)_3Si$) nor the deuterium donor have very large effects on the stereoselectivity.



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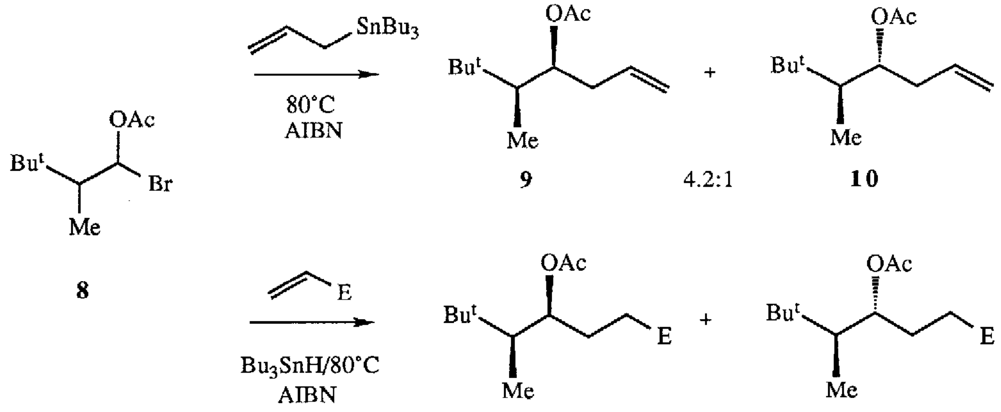
6a R = H
b R = $(Me_3Si)_3Si$
c R = Ac

7a
b
c

8

Precursor	Reductant	Products	Ratio (%D)	% Yield
5	$LiAlD_4$	**6a**:**7a**	3.1:1	—
5	$(Me_3Si)_3SiD/C_{12}H_{25}SH$	**6b**:**7b**	2.6:1	43%
8	$(Me_3Si)_3SiD$	**6c**:**7c**	2.6:1 (57%)	84%
8	$(Me_3Si)_3SiD/C_{12}H_{25}SH$	**6c**:**7c**	2.4:1 (65%)	55%
8	Bu_3SnD	**6c**:**7c**	2.4:1	81%

Starting from bromoacetal **8**, modest levels of 1,2-asymmetric induction can also be achieved in carbon-carbon bond forming reactions. Allylation of **8** under standard conditions (80°C)[7] provided Cram:anti-Cram products (**9**:**10**) in a ratio of 4.2:1. The stereochemistry of these products was assigned by addition of allylmagnesium bromide to **5**, which gave acetates **9** and **10** in a ratio of 4.4:1 after standard acetylation. Similar ratios of products (**11a,b**:**12a,b**) were observed when **8** was added to two electron deficient alkenes under standard reductive conditions (the tin method).[8] The configurations **11** and **12** were assigned by analogy to **9** and **10**. Considering that radical additions give higher selectivities than hydrogen transfers, and that neither type of reaction shows significant electronic effects, a preliminary conclusion is that the size of the trap is more important than its electronic nature in determining the selectivity.



9 4.2:1 **10**

8

11a E = CN, 4.0:1, 63% **12a**
b E = CO_2Et, 3.8:1, 38% **b**

Taking reactions of **1** as representative of **5** and **8**, the formation of Cram products **2** is described by the Felkin-Anh transition state **13**.[9] Because respective radicals **4** abstract hydrogen atoms with similar selectivity to reductions of **1**, it is reasonable that similar transition state geometries are involved. Hydrogen abstraction from a thiol is a very fast reaction[10] (the transition state is early), and the ground state conformations of radicals should be close to transition state conformations. Therefore we have carried out ESR experiments of radical **4b**, generated via silyl radical addition to ketones **1b** (Figure 1).[11]

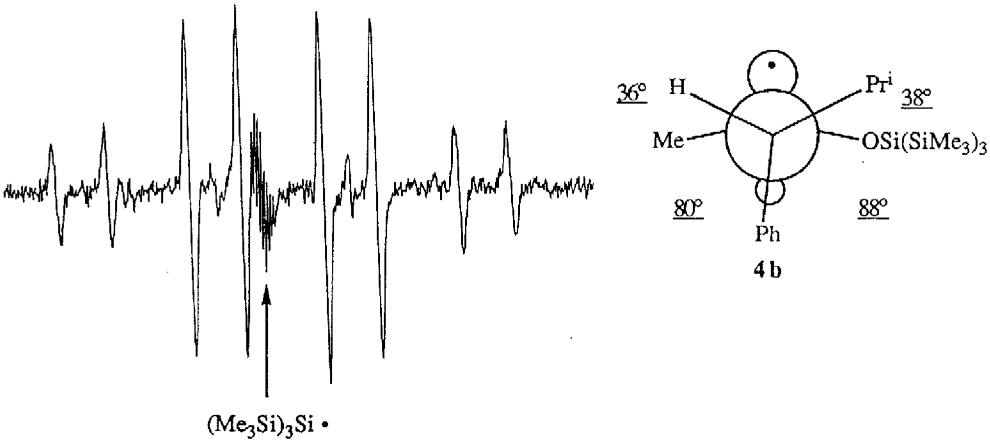
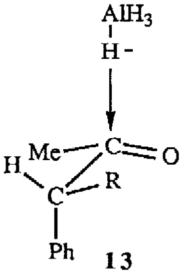


Figure 1. ESR spectrum of radical **4b** and its preferred conformation from AM1 calculations.

Radical **4b** has ß-coupling constants of 20.0 and 7.7 G (T=110°C, g=2.0031). The 20 G coupling represents the average value for several dihedral angles of the hydrogens on the methyl group. In contrast, the 7.7 G coupling demonstrates that a preferred conformation exists for which the dihedral angle between the C,H-bond at the stereocenter and the singly occupied orbital is about 60°.[12] UHF-AM1 calculations[13] support this preferred conformation (Figure 1). The radical is already bent in the ground state by about 10°. On the way to the transition state, this bending increases. UHF/6-31G** calculations for hydrogen atom abstraction from methylthiol by a methyl radical demonstrate that the bond angles between the forming C,H-bond and the C,H-bonds of the methyl radical (angle of attack) are 101° to 103°.[14] Therefore the transition state **14** for the hydrogen atom abstraction by radical **4** and the Felkin-Anh transition state **13** for the hydride ion abstraction are very similar.[15]



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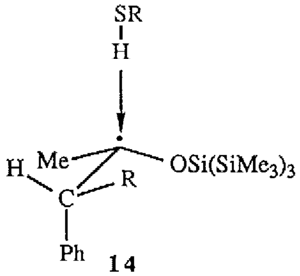

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