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MECHANISTIC AND STEREOCHEMICAL ASPECTS OF THE 1,2-3,4 HYDRIDE REDUCTION OF ENONES[1]

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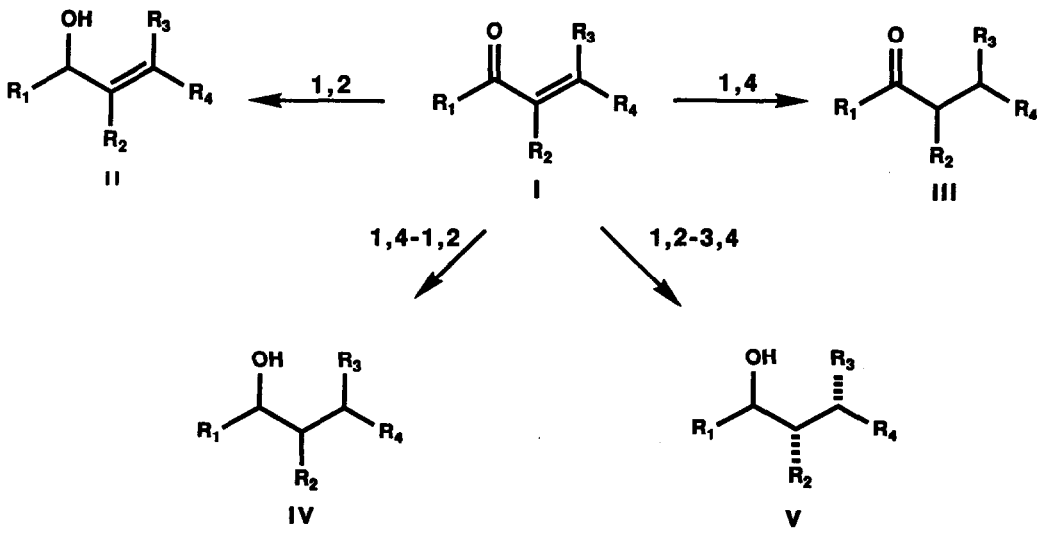
Abstract: A unique mode of metal hydride reduction of unsaturated ketones is described which proceeds with a high degree of regio- and stereocontrol.

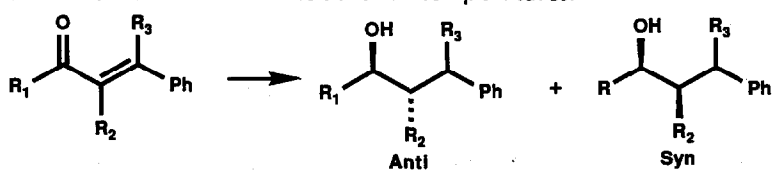
Reduction of α,β-unsaturated carbonyl systems has reached a prominent position in organic synthesis due to the high regio- and stereocontrol associated with the process.[2] Both the regio- and stereochemistry associated with 1,2 reductions[2b] (I → II), 1,4 reductions[2c] (I → III), and reductions leading to fully saturated alcohols[2f,3] (I → IV); 1,4-1,2 reductions) are dependent on both reagent and substrate. While a high degree of stereochemical control has been associated with the 1,2 and the 1,4 modes of reduction[2], the pathway leading to saturated alcohols, usually encountered as byproducts from 1,2 reductions, proceeds with poor stereoselectively and results in a mixture of diastereomeric alcohols.[3] The poor stereoselectivity in this later case is perhaps not surprising since the two step process is influenced by both conformational and electronic factors.

Scheme 1

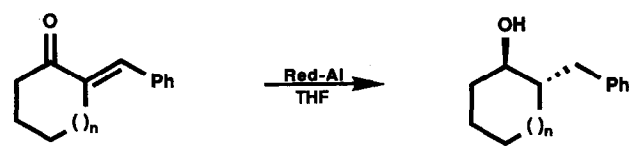


We recently reported two studies on a less familiar mode of hydride reduction, which we call "1,2-3,4 reduction," in which we described reductions of α-oxoketene dithioacetals which proce ded in a regio- and stereospecific manner.[4] In this letter we would like to provide further details on the general nature and understanding of this 1,2-3,4 reduction process and also illustrate its usefulness as a means of establishing up to three consecutive stereocenters (I → V) with a high degree of stereocontrol.

Our results are summarized below. In each case studied, the initial 1,2 reduction occurred rapidly with either $LiAlH(D)_4$ or Red-Al® (sodium bis (2-methoxyethoxy)aluminum hydride) at 0°C in THF.[5,6] The rate of the second reduction (hydroalumination) was found to be dependent on the substitution pattern of the enone. With no substitution (i.e. **1**), or in the case of a small R_1 group (-CH_3: **2**), reduction was complete after an hour at 0°C. As the size of R_1 increased (**1** *vs* **4**), elevated reaction temperatures were required to force the second hydroalumination to completion. Moreover, when R_1 and R_2 (or R_3) were methyl groups (i.e. **5** or **6**), complete reduction to the saturated alcohol required at least three hours at reflux.[9] Reduction of the cyclic benzylidenes **7** and **8** required reaction times of 16-26 hours at reflux temperatures.

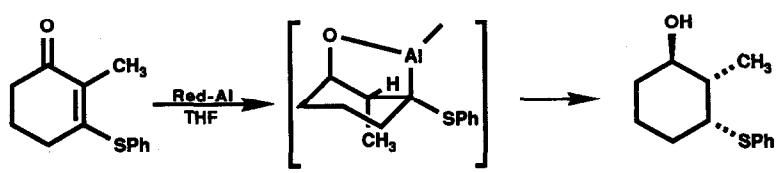


	R_1	R_2	R_3	Rxn. Conds.		Anti/Syn	%Yield
1	H	H	H	$LiAlD_4$	1h/0°C	1/1	78%
2	CH_3	H	H	$LiAlD_4$	1h/0°C	4/1	32%
3	$(CH_3)_2CH$	H	H	$LiAlD_4$	1h/RT	9/1	63%
4	$(CH_3)_3C$	H	H	$LiAlD_4$	1h/Δ	>99/1	71%
5	CH_3	CH_3	H	$LiAlD_4$	6h/Δ	83/17	86%
6	CH_3	H	CH_3	Red-Al	6h/Δ	>99/1	72%



7 n=1 — **9** N=1 >99/1 trans/cis 87%

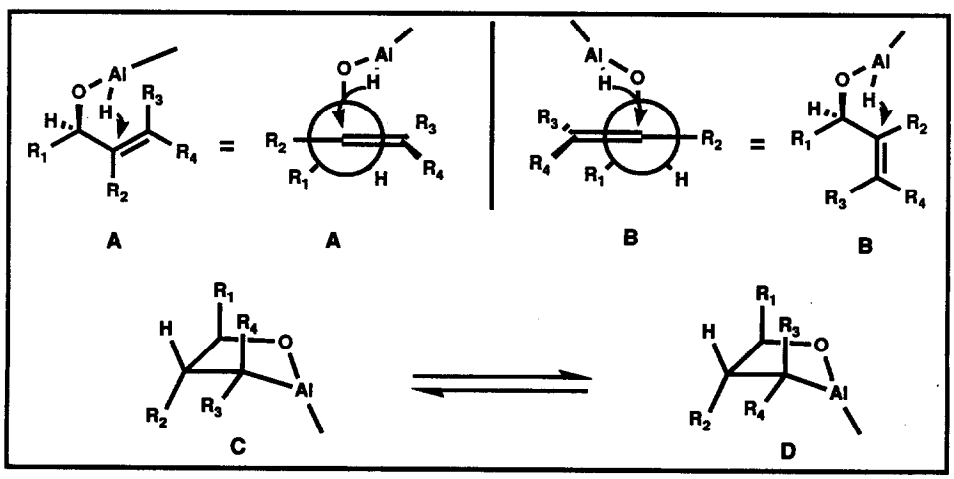
8 n=2 — **10** N=2 87/13 trans/cis 73%



11 **12** **13**

Reduction of unsaturated systems having only an R_1 substituent ($R_2 = R_3 = H$) showed increased stereoselectivity as the size of that substituent increased. Interestingly, while introduction of a methyl group at R_2 had little influence on the diastereomer distribution (compare entries **2** and **5**), there was a marked difference in the reaction rate, the latter reaction requiring 6 hours in refluxing THF. In comparison, methyl substitution at both R_1 and R_3 (i.e. benzylidene **6**) proceeds in a stereospecific fashion with respect to the first two centers and with stereoselectivity (4.5/1 [β/α]) at the third center. Reduction of benzylidenes **7** and **8** proceeded with stereocontrol in the cyclohexane case to give a trans alcohol as the only product, while the cycloheptane system proceeded in a stereoselective fashion to yield a trans/cis mixture.[7] One of the more interesting reductions was conducted with the β-thioarylenone **11**. Reduction of **11** with SMEAH (THF/reflux/16h) afforded the stereochemically pure cyclohexanol **13** in 67% yield.[8] The stereochemical course of this reduction can be rationalized by involvement of the organoaluminate intermediate **12** which undergoes retention of configuration upon protonation.[4]

The stereochemistry associated with 1,2-3,4 reductions can be envisioned as having two origins. The first centers around the relative steric interactions between R_1 and R_2 *vs* R_1 and R_3 in the allylic organoaluminate intermediates **A** and **B**. These interactions contribute substantially to the stereochemical outcome at the first two centers in the reduction; R_1 vs R_2 being favored over R_1 vs R_3. The second element of stereochemical control is related to the cyclic organoaluminate resulting from the hydroalumination of the allylic organoaluminate. Inspection of the two cyclic diastereomeric organoaluminates suggests that the relative steric interactions between R_1 and R_4 in **C** ($R_2 = H$) and R_1 and R_3 in **D** ($R_2 = H$) could be envisioned as controlling elements in establishing the stereochemistry at this final center provided protonation of the carbon-aluminum bond occurs in a stereoselective manner.[10]



This study establishes the feasibility of stereochemical control in the complete saturation of α,β-unsaturated carbonyl systems bearing an anion stabilizing group at the β position by metal hydride reagents. We have gained a better understanding of the contribution the substitution pattern of the enone has on the stereoselectivity observed in 1,2-3,4 reductions, as well as, the reaction rate. The stereochemical outcome of a 1,2-3,4 reduction may be predicted at all three centers based on the substitution pattern present in the enone system.

Acknowledgement. We would like to acknowledge Physical and Analytical Chemistry for spectral determinations and Mary Ferriell for the preparation of this manuscript.

References and Notes

1. Parts of this work were presented at the 101st ACS meeting New York City 1986.
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4. Gammill, R. B.; Gold, P. M.; Mizsak, S. A., J. Amer. Chem. Soc., (1980) **102**, 3095. Gammill, R. B.; Bell, L. T.; Nash, S. A., J. Org. Chem., (1984) **49**, 3039.
5. The regiochemistry of these reductions is clearly defined *via* reduction with $LiAlD_4$ or SMEAH with a deuterium quench (see reference 4).
6. The stereochemistry was established through NMR analysis of rigid derivatives and will be described in detail in the full account of this work.
7. The loss of stereocontrol in the latter case likely reflects the added conformational flexibility available to the allylic organoaluminate in the larger ring system during the second hydroalumination step. In addition, it should be noted, that in contrast to the acyclic system **5**, a second β substitutent was not necessary for complete stereocontrol at the first two centers.
8. The stereochemistry of this compound was established by single crystal x-ray analysis. Space group P2,2,2, Z = 4, a = 5.26(1) Å, b = 13.053(1) Å, c = 17.080(1)Å, 1244 reflections, CuK_α, $C_{13}H_{19}OS$, Final R = 0.030. Coordinates deposited in Cambridge Databank.
9. This result should be compared to that obtained in the α-ketoketene dithioacetal case in which reduction proceeded readily at O°C. This difference in reactivity is presumably due to the greater stabilization offered by the two sulfur β substituents during the hydroalumination of the olefin.
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