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Hydroxy-Directed Hydroaluminations: A Stereoselective Approach to Cycloalkanols From β-Aryl Enones.

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Abstract: **Various aryl substituted enones are reduced using lithium aluminum hydride to afford sterioselectively trans substituted alkanols. Mechanistic studies demonstrate 1,2 addition followed by hydroxy-directed hydroalumination of the conjugated styryl unit.**

The use of an adjacent functional group to influence the stereochemical course of a reaction is a valuable principle in modern synthetic organic chemistry.[1] In this report we describe a method for the reduction of a variety of aryl substituted enones by lithium aluminum hydride with complete control of stereochemistry at the α and/or β position via an intramolecular hydroxy-directed hydroalumination. The hydroalumination of carbon-carbon double bonds was first described by Brown for systems where the olefin was in conjugation with adjacent π systems.[2] Subsequently several papers appeared[3] describing the reduction of cinnamyl acids, aldehydes, ketones and alcohols to the corresponding hydrocinnamyl alcohols, though controversy exists regarding both the mechanism and stereochemistry of this reaction.[4] In our work, we required a stereoselective route to the trans alcohols **2** from various enones exemplified by **1**.

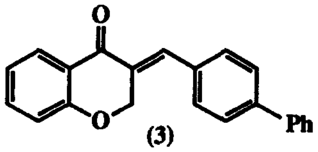
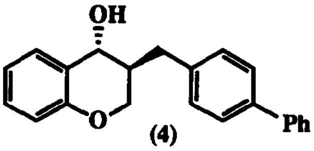
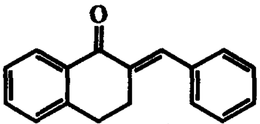
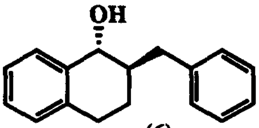
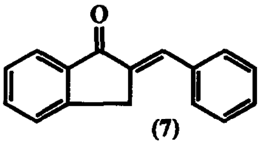
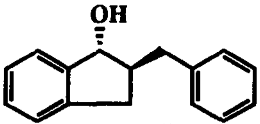
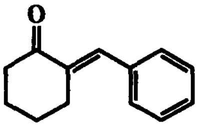
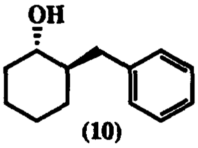
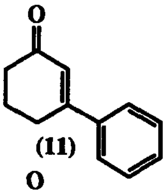
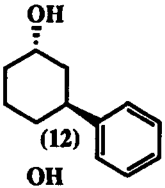
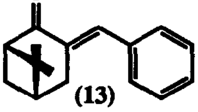
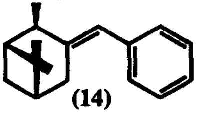
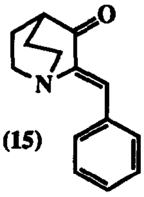
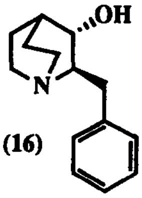
Scheme 1

1 **2**

X = $(CH_2)_n$, O. **R= H, OMe, Ph, F, CF_3**

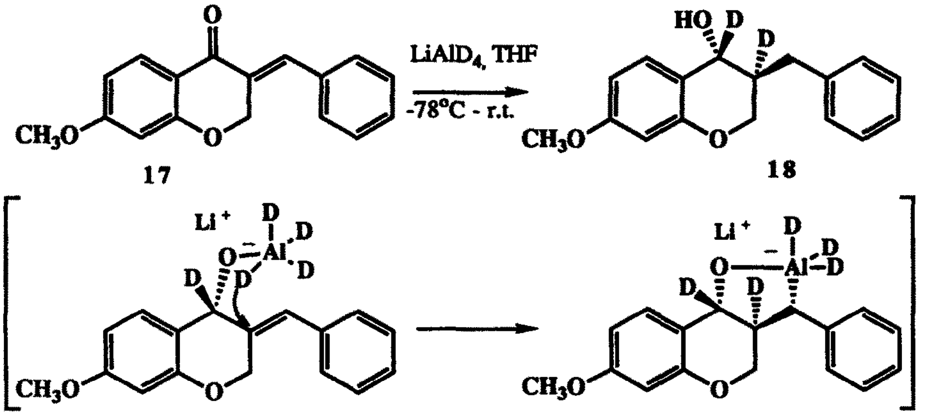
The prerequisite benzylidene ketones were prepared by standard methods.[5] All attempts to prepare **6** in a stereoselective manner by hydrogenation followed by ketone reduction gave predominately the *cis* product.[6] Treatment of **5** with 2.2eq of lithium aluminum hydride in THF at -78°C gave the allylic alcohol derived from 1,2 addition of hydride to the ketone. Upon warming to room temperature and stirring for 10 hours, a 55% yield of the trans product **6** was obtained. No *cis* product was observed by NMR or TLC analysis.[7] Higher yields could be afforded by dropwise addition of a solution of enone **5** into a refluxing mixture of lithium aluminum hydride in THF affording alcohol **6** in 73% yield. Several other enones (Table I) were reduced under these conditions (Method A) to give moderate to excellent yields of the trans alcohols with no *cis* alcohol observed. Of note is the ability to control 1,3 stereochemistry in substrate **11** and the tolerance of the reaction to basic nitrogen containing substrates as exemplified by quinuclidine example **15**.[7]

Table 1

Substrate	Product	Method[11]	Time(hr)	Yield
 (3)	 (4)	A	3.5	89 %
 (5)	 (6)	A	2	73 %
 (7)	 (8)	A	3	59 %
 (9)	 (10)	A	1	76 %
 (11)	 (12)	A	1.5	55 %
 (13)	 (14)	A	24	86 %
(15) 	(16) 	A	1	78 %

To help determine the mechanistic course of this reaction deuterium labeling studies were performed. Reduction of **17** (Method B) afforded the product of 1,2 addition followed by intramolecular directed deuteroalumination across the carbon-carbon double bond to provide **18** exclusively (Scheme 2).[9] Further evidence for the intramolecular nature of this hydroalumination comes from the reaction of enone **13** under standard conditions. While 1,2 addition occurred cleanly, no olefin reduction was observed even upon reflux for 24 hours. In this case, intramolecular delivery of hydride is sterically inhibited by the bridge-head dimethyl group.[10]

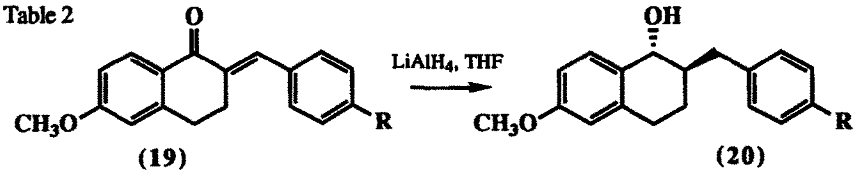
Scheme 2



Further studies to understand the mechanism of this process was performed by low temperature addition of LAH to the substrate then stirring at 22°C for the specified time.[8] As illustrated (Table 2), a correlate exists for an increased rate of olefin hydroalumination with increased electron withdrawing capability of substituents on the aromatic ring (based on the σ constants), with the relative rate order of CF3>Ph~F>H>OMe.

In summary, we have described a useful, stereoselective route to trans-substituted cycloalkanols through directed hydroalumination of the readily available benzylidene ketone precursor. Efforts to trap the final hydroalumination intermediates are currently in progress.

Table 2



	R	Method[12]	Time	Yield (20)
19a	H	B	6 hrs	53 %
19b	Phenyl	B	1.5 hrs	92 %
19c	CF_3	B	<.5 hrs	88 %
19d	F	B	3 hrs	45 %
19e	OMe	B	24 hrs	75 %

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6. Ketone reduction conditions examined included, dissolving metal, Luche, superhydride, L-selectride, Merwein Pondorff, LAH, $Ø_3$SiH, hydrogenation; optimum conditions utilized $NaBH_4$, MeOH at 0°C providing a 60:40 mixture of *cis:trans* adduct.
7. H^1-NMR, C^{13}-NMR, IR, MS and combustion analysis are consistent with the assigned structure.
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9. (a) Borden, W.T. *J. Am. Chem. Soc.* **1970**, *92*, 4898. (b) Wong, M.Y.H.; Gray, G.R. *J. Am. Chem. Soc.* **1978**, *100*, 3548.
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11. **Method A.** To a stirred slurry of lithium aluminum hydride (2.2eq) in refluxing THF (.2M) was added a solution of the substrate enone (1mmole) in THF (.2M) over 30 minutes. The mixture was refluxed for the appropriate time then cooled to 0°C and a saturated aqueous solution of K^+/Na^+ tartrate carefully added (3x volume). The mixture was stirred for 1 hour and the two phase solution extracted 2x with ether. The combined organic extracts were dried over $MgSO_4$, filtered, evaporated and chromatographed over silica gel.
12. **Method B.** 2.2 eq of lithium aluminum hydride in THF (1M) was added to a -78°C solution of enone in THF (.2M) then stirred at room temperature for the appropriate time. Workup was as described for Method A.

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