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LETTERS

A head-to-head comparison of α- and β-alkoxy effects on stereoselectivity. Nucleophilic additions to a cyclohexanone substituted with five axial C–O bonds

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Abstract

The stereochemical course of the hydride reduction and of the 1,2-addition of allylmagnesium bromide as well as the Normant reagent to **1** has been determined.

Keywords: addition reactions; chelation; cyclohexanones; ethers; steric effects.

The appreciable stereoselectivity for hydride addition to unhindered cyclohexanones from the axial direction is most often interpreted in terms of torsional effects as originally recognized by Felkin,[1] although the differential interaction of the carbonyl group with adjacent σ bonds is also believed to impact on the favored reaction trajectory.[2] Most organometallic reagents attack alternatively from the equatorial π-surface because steric contributions presumably gain importance. When polar groups are positioned α or β to the cyclohexanone carbonyl, the factors determinative of the stereochemical outcome are less obvious. The role of α hetero substituents on the relative transition state energies has been attributed most frequently to interactions involving the antiperiplanar allylic bonds.[3,4] In Anh's view, a critical role is played by that interaction involving the incipient bonding orbital and the antibonding orbital(s) of the antiperiplanar bond(s). According to the Cieplak hypothesis, transition state stabilization is achieved by electron donation into the vacant orbital associated with the incipient bond. In addition to field and inductive effects,[2c] chelation has been strongly emphasized when operative. 2-Alkoxy cyclohexanones have been most intensely scrutinized for this behavior.[5] Lesser attention has been accorded to 3-oxygenated derivatives.[5d,e,6] Much useful synthetic information has emerged from all of these investigations.

Despite the extensiveness of the prior work, we are unaware of efforts designed to examine cumulative effects in cyclohexanones carrying two or more alkoxy substituents. In order to determine whether the unsymmetrical distribution of electronic and steric influences around a carbonyl group plays a

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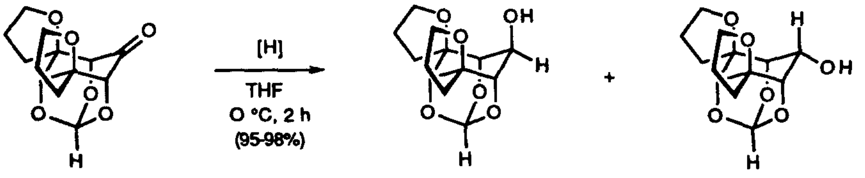
significant, predictable role in selectivity, we have prepared **1** from *myo*-inositol.[7] The C_2 symmetry of this compound and its rather rigid superstructure present several interesting features.[8] On the axial face, steric hindrance between the entering nucleophile and the axial C–O bonds of the spirotetrahydrofuran rings should be a deterrent unless chelation can override this strain. Indeed, the axial predisposition of both β-oxygen atoms is particularly conducive to chelation control. As the size of the R group entering into the axial position is increased, the steric hindrance to nucleophilic attack becomes progressively more severe. If approach occurs from the equatorial side, the highly puckered nature of the central six-membered ring should result in a nicely staggered disposition about the newly formed carbinol center.

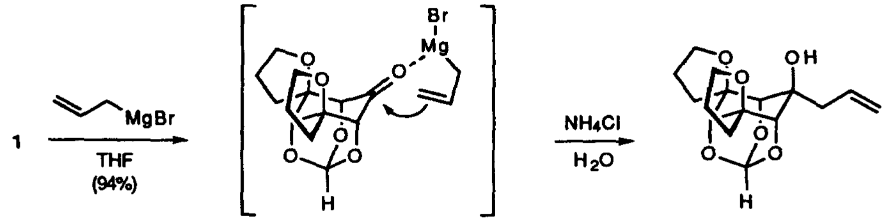


1

	2	**3**
$NaBH_4$	>97%	<3%
$LiAlH_4$	>97%	<3%
$Zn(BH_4)_2$	>97%	<3%

Reduction of **1** with $NaBH_4$ and $LiAlH_4$ gave rise exclusively to **2**, the product of equatorial hydride attack on a 3,5-diaxial-substituted cyclohexanone, and simultaneously, axial attack on a 3,5-dioxolane (which always favors axial attack).[9] This stereochemical outcome, which is completely opposite to the customary response of cyclohexanones, can be interpreted to be a reflection either of the steric contributions of the two axial β-oxygen atoms or of the interplay of hyperconjugative influences arising from the α substituents. The neighboring axial C–O bonds (which are conducive to axial delivery) must be less effective than the C2–C3 and C5–C6 C–C bonds (which favor equatorial delivery), in agreement with established electron-donating ability (C–H>C–C>C–O).[4] Since reduction with $Zn(BH_4)_2$ gave the same result, no chelation appeared to be operative in this instance.[5d]

In similar fashion, addition of allylmagnesium bromide to **1** gave rise exclusively to **4**, the structural assignment of which was corroborated by X-ray crystallographic analysis (Fig. 1).[10] Evidently, approach from the less sterically demanding equatorial face as in **A** was kinetically favored to a high level.



A **4**

When the addition of the Normant reagent[11] to **1** was examined, the stereochemical bias was almost completely reversed. Under entirely comparable reaction conditions, a 10:1 ratio of **5**:**6** was reproducibly obtained. These highly polar products were characterized by direct cyclization via their primary monotosylates. The minor trispiro tetrahydrofuran exhibited spectral properties fully consistent with the highly symmetric C_{3v} isomer. The source of this remarkable reversal was considered to be the coordinated complex **B** whose intervention would direct bond formation to the axial surface in the manner shown. That this species may well be the origin of the phenomenon was suggested by the results of a complementary experiment in which 5 equiv. of $LiClO_4$ was added to **1** in advance of the Normant

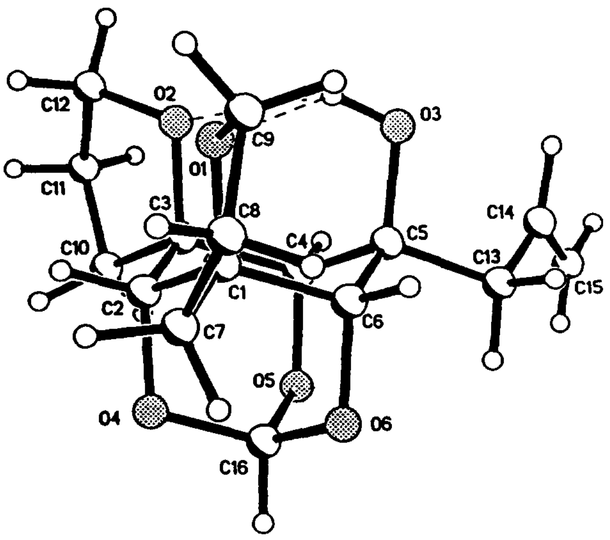
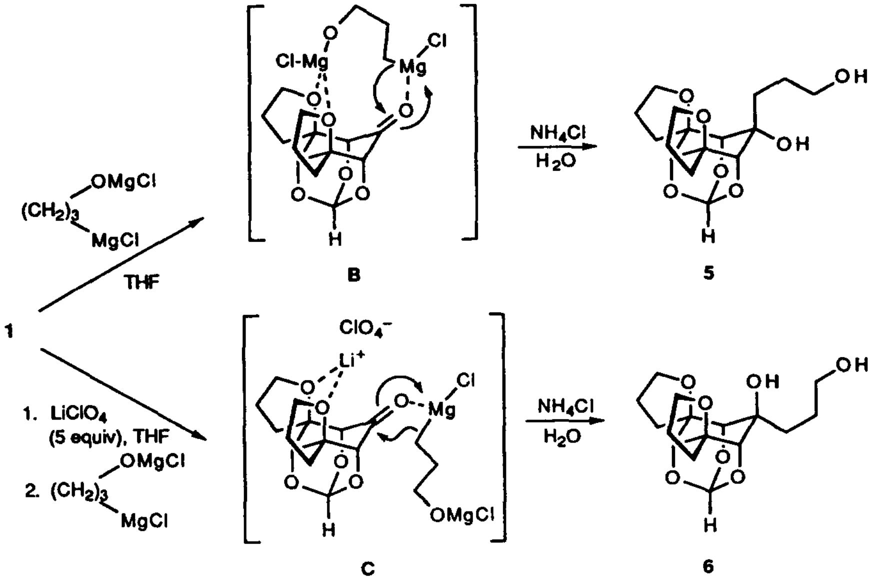


Figure 1. ORTEP diagram of 4

reagent. The intent was to take advantage of the high capacity of compounds of this general class to bind to Li$^+$.[12] With the preformation of complex C,[13] attack by the Grignard should now be relegated totally to the equatorial π-surface. Experimentally, only **6** was produced in high yield.



The capability to employ metal ion chelation as in C for the control of stereoselectivity holds obvious attraction. The hypothetical transition states A–C point to the importance of the chemical environment of the metal in its capability to guide product distribution.[14] For example, the Mg atom present in allylmagnesium bromide and at the C-terminus of the Normant reagent exhibits little or no obvious capacity for engaging in intermolecular coordination to **1**. In the latter instance, it is clearly the more ionic RO$^-$ $^+$MgCl terminus of the chain that is responsible for eventual axial attack by the tethered C–MgCl functionality. Without the benefit of this anchoring, the counterbalancing forces favor equatorial approach as in A and C.

Acknowledgements

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