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ASYMMETRIC TRANSFER OF DIASTEREOTOPIC HYDROGENS IN THE GRIGNARD REDUCTION OF KETONES

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Some years ago Mosher reported the stereochemical result of a ketone reduction with a γ-asymmetric, acyclic Grignard reagent.(1) Methyl t-butyl ketone was allowed to react with the Grignard reagent from (+)-1-chloro-3-methylpentane. The small amount of methyl-t-butylcarbinol obtained had a negligible rotation. Understandably, this result has been interpreted(2) as evidence that, with acyclic Grignard reagents, asymmetric reduction is to be expected only when there is hydrogen transfer from an asymmetric carbon β to magnesium, i. e., when the asymmetric carbon can be one of the six atoms in a presumably nearly planar, cyclic transition state.

Theoretically, however, hydrogen transfer from a β-asymmetric carbon is only a sufficient, not a necessary condition for such asymmetric reductions. The necessary condition is that the Grignard reagent be chiral and the ketone be unsymmetrical, i. e., have enantiotopic faces, so that transition states for reduction are diastereomeric. A γ-asymmetric Grignard from an optically active halide can reduce an unsymmetrical ketone _via_ four diastereomeric transition states. Even though some of the nonbonded interactions (called primary interactions in Fig. 1) appear to be the same, these transition states are not enantiomeric; they are diastereomeric. Therefore, in principle, they have different energies. It is thus theoretically possible that optically active alcohols will result from such reductions.

We have found, in fact, that Grignards from R-(-)-1-chloro-3-phenylbutane and R-(-)-1-chloro-3-phenylpentane reduce isobutyrophenone to optically active alcohol. Reaction of the Grignard reagent from optically pure R-(-)-1-chloro-3-phenylbutane with isobutyrophenone gave, in addition to a substantial amount of 2-methyl-3,6-diphenyl-3-heptanol (Grignard addition), a 9% yield of isopropylphenylcarbinol, $[\alpha]_D$ +11.7; this corresponds to 62.5% R-(+)- and 37.5% S-(-)-isopropylphenylcarbinol (25% asymmetric reduction). Grignard reagent from R-(-)-1-chloro-3-phenylpentane (98% enantiomerically pure) gave an 11% yield of isopropylphenylcarbinol, $[\alpha]_D$ +13.1, 29% asymmetric reduction (corrected for Grignard enantiomeric purity). Thus, in these systems there exist, not only in theory but also in practice, sufficient conditions for preferential hydrogen transfer to one of the enantiotopic faces of the ketone. The asymmetric bias is surprisingly high.

When an unsymmetrical ketone reacts with a γ-asymmetric Grignard from an optically active halide there are three asymmetric centers in the transition states possible for reduction: (1) The asymmetric carbon γ to magnesium, (2) an incipient asymmetric carbinol carbon, and (3) The meso carbon from which hydrogen is transferred. The last two centers may each assume two mirror image configurations, since the ketone has enantiotopic faces and the meso carbon becomes asymmetric when either H_A or H_B is the hydrogen being transferred.(3) The configuration of the asymmetric carbon γ to magnesium is fixed. Hence the four diastereomeric transition states, I-IV, are generated. We believe that asymmetric reduction may be best explained using such transition states* and the hypothesis that there is preferential transfer of one of the two diastereotopic hydrogens on the meso carbon β to magnesium. Since they are diastereotopic, these hydrogens (H_A and H_B in Fig. 1) can, in principle, be transferred at different rates, even if the ketone being reduced is symmetrical (in this event two diastereomeric transition states would be possible). If the reduction is assumed to proceed mainly via II and III, the lowest energy transition states on the basis of what are termed primary interactions, the observed stereochemistry can be rationalized by a preferential of transfer H_A in II rather than H_B in III. On the basis of symmetry arguments alone one can establish that this kinetic inequality should be an intrinsic property of the Grignard reagent, but the nature of the groups on the asymmetric carbon and the structure of the ketone could influence its magnitude.

Vavon and Angelo have reported the asymmetric reduction of ketones with a bicyclic Grignard from isobornyl chloride.(4) With this Grignard reagent, hydrogen is also transferred from a nonasymmetric carbon β to magnesium. In this case activation energy differences for reaction pathways giving enantio-

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*Of the various conformations that retain the primary interactions described, only one is shown for each transition state representation.

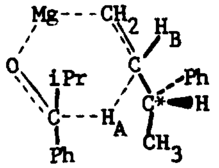
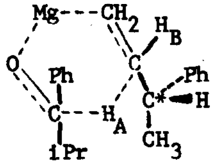
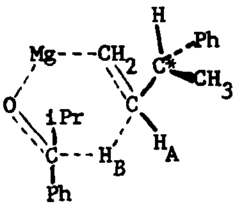
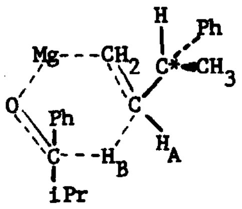
	Primary Interactions	Configuration of Carbinol Produced
 I	iPr *vs.* H Ph *vs.* C*	S
 II	Ph *vs.* H iPr *vs.* C*	R
 III	iPr *vs.* C* Ph *vs.* H	S
 IV	Ph *vs.* C* iPr *vs.* H	R

Figure 1. Diastereomeric transition states for reduction of isopropyl phenyl ketone with Grignard from R-(-)-1-chloro-3-phenylbutane.

meric alcohols could be magnified by the rigid molecular framework of the Grignard reagent which freezes the diastereotopic β-hydrogens in rather disparate environments.* Mosher and LaCombe's acyclic Grignard from (+)-1-chloro-3-methylpentane lacks the rigidity of Vavon's bicyclic Grignard reagent, and it should be less conformationally biased than our 3-phenylbutyl or 3-phenylpentyl reagents. Thus the environments of the two diastereotopic hydrogens, and consequently their rates of transfer, might be more nearly the same.

The observed asymmetric reduction does not require preferential transfer of one of the diastereotopic hydrogens. In terms of the percentage contribution of the four diastereomeric transition states to the enantiomeric composition of the product (3-phenylbutyl Grignard case) all that is required is that $II_A + IV_B = 62.5$ and $I_A + III_B = 37.5$ (subscript designates hydrogen being transferred). If equal transfer is assumed, it follows that $I_A + II_A = III_B + IV_B = 50$. Many sets of percentage contribution values satisfy these equations simultaneously. Similar equations apply if unequal transfer is assumed. Again, many sets of values satisfy these equations, but some are unreasonable if primary interactions are considered.

Experiments designed to determine the ratio of H_A to H_B transfer, and to more precisely define the necessary and sufficient conditions for related asymmetric reductions are in progress.

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*Bicyclic Grignards are, in several respects, rather special cases. In the above example, for instance, the magnesium is attached to an asymmetric center. Furthermore, it may be *exo* or *endo* and it is possible that only one of these interconvertible orientations characterizes an effective reducing Grignard reagent. We are investigating such systems. See also Ref. (5).

References

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