Tetrahedron Letters No.7, pp. 569-571, 1969. Pergamon Press. Printed in Great Britain.

ASYMMETRIC ORGANIC REACTIONS, III. REACTIONS OF DIASTEREOMERIC ETHER COMPLEXES OF THE GRIGNARD REAGENT FROM (±)-1-CHLORO-2-PHENYLBUTANE

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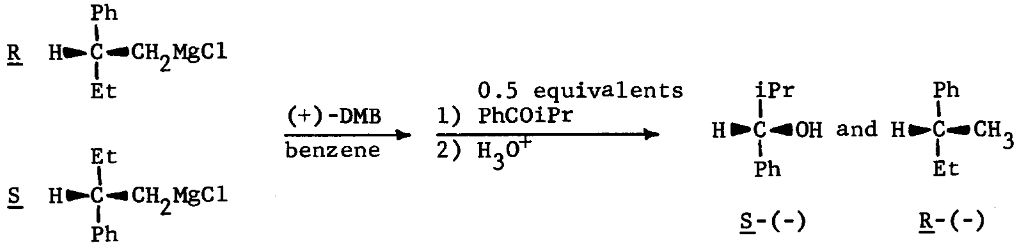
(Received in USA 9 November 1968; received in UK for publication 6 January 1969)

Asymmetric reductions with the Grignard reagent from optically active 1-chloro-2-phenylbutane have been studied by Mosher and coworkers.(1) We wish to report on some asymmetric reactions of the Grignard reagent from racemic 1-chloro-2-phenylbutane in the presence of optically active ethers.

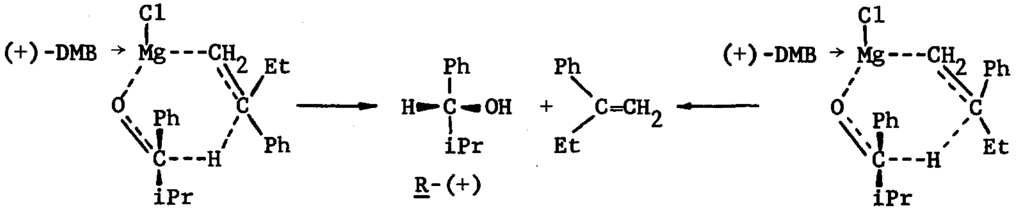
When the Grignard reagent from racemic halide was allowed to react with approximately 0.5 equivalents(2) of phenyl isopropyl ketone in the presence of (2R, 3R)-(+)-2,3-dimethoxybutane ((+)-DMB, 82% enantiomerically pure) there was isolated, after hydrolytic work-up, (-)-phenylisopropylcarbinol ($[\alpha]_D$-2.06 neat, 8.4 per cent excess of the S enantiomer). An optically active addition product was also isolated but its configuration is as yet unknown. Unreacted Grignard reagent was hydrolyzed during the work-up to (-)-2-phenylbutane ($[\alpha]_D$-1.2 neat, 4.9 per cent excess of R enantiomer). These data indicate that an asymmetric reduction of the ketone occurred and that the Grignard reagent was simultaneously partially resolved.



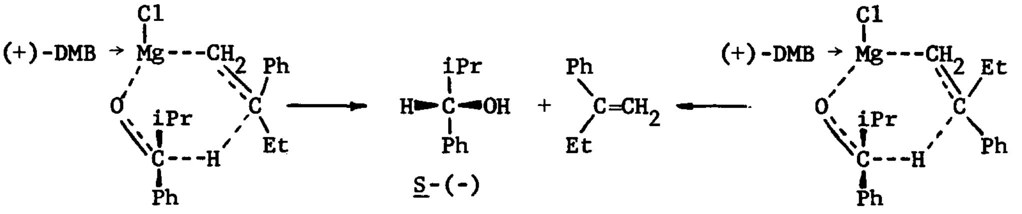
A rationalization of the kinetic resolution is that in the presence of an optically active ether the racemic Grignard forms diastereomeric complexes, R-Grignard-(+)-DMB and S-Grignard-(+)-DMB. These react at different rates with the ketone *via* three possible pathways: addition, reduction, and enolization. The S-Grignard must be consumed more rapidly since the isolation of (-)-2-phenylbutane upon complete hydrolysis shows that the unreacted Grignard was enriched in the R-enantiomer.

In the presence of (+)-DMB four diastereomeric cyclic transition states

(1-4) can be envisaged for reduction rather than the two sets of enantiomeric transition states that would describe reduction in the presence of an achiral ether. It is interesting that if the S-(-)-alcohol is assumed to come primarily from the transition state involving hydrogen transfer to the re face[(3)] of the ketone by the S-Grignard-(+)-DMB complex (as represented by (3), in which



(1) si-face,R-Grignard (2) si-face,S-Grignard



(3) re-face,S-Grignard (4) re-face,R-Grignard

the phenyl-phenyl interaction is minimized) then one is led to the conclusion that the reduction reaction will consume S-Grignard more rapidly than R-Grignard. This correlates with the observation that the unreacted Grignard is enriched in the R enantiomer, although reduction is not the only reaction that can consume the Grignard asymmetrically. It may be, however, that the reduction reaction discriminates more effectively between the enantiomers than do the addition and enolization reactions, since the chiral center of the Grignard is more directly involved in the reduction process. A more detailed rationalization in terms of transition state models that correlate the configuration of the ether and that of the alcohol appears unwarranted at present.

Behavior similar to that described above has also been observed using the monofunctional ether (+)-1-methoxy-2-methylbutane and the tetrafunctional ether (+)-dimethylisosorbide. Partial kinetic resolution has also been achieved by reaction of the Grignard with 0.5 equivalents of benzophenone in chiral ethers. However, the (+)-DMB-phenyl isopropyl ketone system gave products of higher enantiomeric purity.

The reactions described above provide an alternate method for the partial kinetic resolution of an α-asymmetric alkyl magnesium compound. The potential utility of such resolutions has been outlined in the preceeding paper. To our knowledge this is also the first example of asymmetric reduction with diastereomeric Grignard complexes.(4)

Acknowledgement: We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research, and Drs. J. A. Morrison (National Research Council of Canada) and J. W. LeMaistre (Atlas Chemical) for gifts of some of the chemicals used.

References

(1) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson and H. S. Mosher, J. Org. Chem., 29, 37 (1964).

(2) The apparent amount of Grignard reagent used was based on a total base titration and the actual amount may have been slightly lower. Consequently the equivalents of ketone actually used may have been slightly higher.

(3) K. R. Hanson, J. Am. Chem. Soc., 88, 2731 (1966).

(4) See C. Blomberg and J. Coops, Rec. Trav. Chim., 83, 1083 (1964) and references therein, for a description of some reactions of symmetrical Grignard reagents in chiral ethers. Kinetic resolution is, of course, not possible in these systems.