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ASYMMETRIC ORGANIC REACTIONS, II. PARTIAL KINETIC RESOLUTION OF THE GRIGNARD REAGENT FROM 1-CHLORO-2-PHENYLBUTANE(1)

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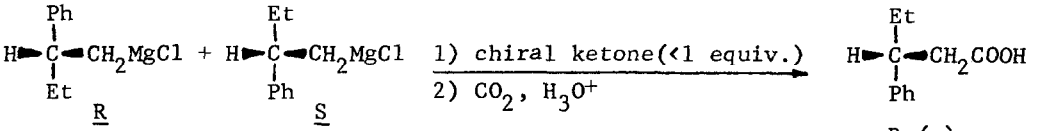
The Grignard reagent from racemic 1-chloro-2-phenylbutane has been partially resolved by allowing it to react with less than one equivalent of one of several readily available chiral ketones. Reaction with approximately 0.5 equivalents(2) of (+)-camphor, (-)-fenchone, (-)-menthone or (+)-3-methylcyclohexanone led to more rapid consumption of the Grignard reagent having the R configuration as evidenced by the fact that carbonation of the unreacted Grignard reagent gave 3-phenylpentanoic acid enriched in the R enantiomer. As expected the enantiomeric purity of the acid increased when the Grignard reagent was allowed to react with 0.75 equivalents(2) of ketone.



Racemic Grignard Reagent

Predominant Enantiomer

Fenchone appears to discriminate between the enantiomers of the Grignard reagent more effectively than the other ketones examined thus far (Table I). A sample that had an apparent enantiomeric purity of only about 39 per cent was, for example, more effective than enantiomerically pure (+)-camphor. This observation is consistent with the hypothesis that asymmetric selection should be maximized when reduction is the primary reaction pathway. Fenchone cannot give enolization products and the relative amount of addition is low due to steric hindrance. Reduction, a more important reaction in the case of fenchone, involves the transfer of hydrogen from the chiral center of the Grignard reagent(3) and the rates at which the enantiomers are consumed *via* reduction may be more disparate than are the rates of enolization or addition. It may even be that the enantiomer of Grignard reagent that is consumed more rapidly *via* reduction is not that which reacts preferentially by one of the alternative reaction pathways. The observation that a reaction

TABLE I

Partial Kinetic Resolution of the Grignard Reagent from Racemic 1-Chloro-2-phenylbutane[a]

Ketone	Per Cent Enantiomeric Excess[b] of (R)-(-)-3-phenylpentanoic Acid[c]
 (1R, 4R)-(+)-Camphor[d]	3.7 5.7[e] 7.7[f]
 (1R, 4S)-(-)-fenchone	8.6 (22)
 (1R,4S)-(-)-menthone	10.4 (11.0)
 (R)-(+)-3-methylcyclohexanone	1.24 (1.39)

(a) Reaction with 0.5 equivalents[(2)] of ketone at room temperature unless otherwise annotated. Acid impurities from carbonation of enolates were removed by decarboxylation and the 3-phenylpentanoic acid was extracted from neutral components as the sodium salt. The final product was free of impurities as determined by g.l.p.c. analysis. (b) Defined as 100 $[\alpha]_D^{obs.}/[\alpha]_D$ max.) where $[\alpha]_D$ max. = -54.2 (benzene)[(4)]. (c) Values in parentheses are corrected for the enantiomeric purity of the ketone. (c) Reaction with (-)-camphor gave S-(+)- acid. (e) Reaction refluxed after addition of camphor. (f) Reaction with 0.75 equivalent[(2)] of camphor.

that was refluxed after addition of (+)-camphor gave R-(-)-3-phenylpentanoic acid with a higher enantiomeric purity than that from a room temperature reaction may reflect a different relative contribution of the various reaction pathways to the overall rate of Grignard reagent consumption under slightly different reaction conditions.

The influence of the multiple asymmetric centers in (-)-menthone is

clarified by comparison with (+)-3-methylcyclohexanone. Both ketones show the same direction of enantiospecificity, but the additional asymmetric center adjacent to the carbonyl group in menthone leads to an eight fold increase in the magnitude of the asymmetric bias.

Aside from its intrinsic interest, this type of kinetic resolution is of potentially greater utility than many others. It provides a method of configurational correlation for a series of derivatives prepared from aliquots of an enantiomerically enriched Grignard reagent. Absolute configurations and maximum specific rotations can be established simultaneously provided the configuration and enantiomeric purity of one member of such a series are known. Using enantiomeric ketones one can quickly prepare enantiomeric derivatives of the Grignard for synthetic purposes or mechanism studies.

Preliminary experiments with 2-butyl and 2-octyl Grignard reagents and (+)-camphor did not lead to optically active acid derivatives. However, under the proper conditions, it may be possible to asymmetrically perturb the equilibrium between the enantiomers of certain secondary Grignard reagents (or other organometallics) and then trap optically active derivatives before re-equilibration. Work is continuing along these lines and with other organometallics that are asymmetric beta to the metal.

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References

(1) Paper I: Tetrahedron Lett., 985 (1968).

(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) J. D. Morrison, "Asymmetric Reduction", Survey of Prog. in Chem., Vol. 3, A. F. Scott (ed.), Academic, New York (1966).

(4) P. A. Levene and R. E. Marker, J. Biol. Chem., 100, 685 (1933); see also M. J. Brienne, C. Ouannes and J. Jaques, Bull. Soc. Chim. Fr., 613 (1967).