saturated natural products into the corresponding amines.

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Dialkylboranes as Consistent Reagents for Steric Control of Reduction in Both Monocyclic and Bicyclic Systems

Sir:

We wish to report that the dialkylboranes exhibit remarkable consistency in directing the reduction of both α-substituted cycloalkanones and bicyclic ketones from the less hindered direction to give predominantly the less stable of the two possible alcohols. Thus these reagents are highly promising both for achieving the preferred synthesis of a given isomer and for establishing the configurations of a pair of epimeric alcohols.

Since their introduction, the complex hydrides, such as lithium aluminum hydride and sodium borohydride, have been exceedingly valuable for the convenient conversion of ketones to alcohols. One aspect of this application, however, has resulted in frustrating ambiguities. The reduction of monocyclic ketones, such as 2-methylcyclopentanone and 2-methylcyclohexanone, appears to involve the attack of the reagent from the side of the methyl group, presumably the more hindered direction, to yield predominantly the more stable of the two possible alcohols (*trans*).[1,2] On the other hand, the reduction of bicyclic systems involves approach of the reagent from the less hindered side of the carbonyl group to yield the less stable of the two possible alcohols.[3]

These results have led to two different generalizations governing the course of such reductions.[1] In the case of relatively flexible monocyclic ketones the steric factor in the transition state will be relatively small and the course of the reduction will be controlled primarily by the stability of the product. On the other hand, in rigid bicyclic ketones, the steric factor will be far greater in the transition state and will exert a dominant role on the course taken by the reduction.[4]

Even in the case of the monocyclic ketones, reduction by lithium aluminum hydride is not consistent! Thus, 2-methylcycloheptanone[5] and the 2-methylcyclooctanone (Table I) yield the *cis* alcohol preferentially. There would be obvious advantages to a reagent which achieves the reduction of both monocyclic and bicyclic ketones with consistent stereochemistry.

Previously, we had observed that disiamylborane and diisopinocampheylborane reduced 2-methylcyclopentanone and 2-methylcyclohexanone to give the *cis* alcohol preferentially.[6] Extension of this study to representative monocyclic and bicyclic derivatives reveals that reduction to give predominantly the less stable of the two possible alcohols is of wide generality.[7]

The results are summarized in Table I.

Table I. Reduction of Representative Ketones by Dialkylboranes at 0°

	Per cent alcohol involving reduction to form the less stable epimer				
Ketone	Lithium aluminum hydride in THF	Diborane in THF	Disiamylborane in THF	Dicyclohexylborane in diglyme	Diisopinocampheylborane in diglyme
2-Methylcyclobutanone[a]	25	41	74	71	83
2-Methylcyclopentanone[a]	21	25	78	80	94
2-Methylcyclohexanone[a]	25	26	79	94	94
2-Methylcycloheptanone[a]	73	74	64	97	98
2-Methylcyclooctanone[a]	73	82	*d*		
Norcamphor[b]	90	98	92	94	94
Camphor[c]	91	52	65[e]	93[e]	100[e]

[a] *cis*-2-Methylcycloalkanol. [b] *endo*-Norborneol. [c] Isoborneol. [d] Very slow reaction. [e] Slow reduction.

The 1-methylcycloalkenes were subjected to hydroboration–oxidation to yield the pure *trans*-2-methylcycloalkanols.[8] A sample was retained for identification purposes and the remainder oxidized to ketone by the chromic acid–ether procedure.[9] The reduction procedures were similar to those previously described.[4,6] The products were analyzed by glpc using a temperature-programmed capillary instrument (Perkin-Elmer Model 226) to establish actual total yields (>85%), as well as the relative yields reported in Table I.

These results are quite promising. They suggest that the dialkylboranes should prove quite valuable in providing consistent steric control of reduction in both flexible monocyclic and in rigid bicyclic systems. We continue to explore the scope of this reduction.

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(2) For an alternative interpretation, see J. C. Richer, *J. Org. Chem.*, 30, 324 (1965).

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(7) On the other hand, where the alkyl substituent is relatively remote from the reaction center, as in 3- and 4-methyl- and -*t*-butylcyclohexanones, the dialkylboranes exert only a minor influence on the direction taken by the reduction—in all cases the product is predominantly the more stable of the two possible epimers. Thus it is quite clear that the 2-methyl substituent in the 2-methylcycloalkanones must be exerting a dominant steric effect on the direction taken in the reductions involving the highly hindered dialkylboranes.

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