Tetrahedron Letters, Vol. 33, No. 47, pp. 7107-7110, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

A MECHANISTIC AND STRUCTURAL ANALYSIS OF THE BASIS FOR HIGH ENANTIOSELECTIVITY IN THE OXAZABOROLIDINE-CATALYZED REDUCTION OF TRIHALOMETHYL KETONES BY CATECHOLBORANE

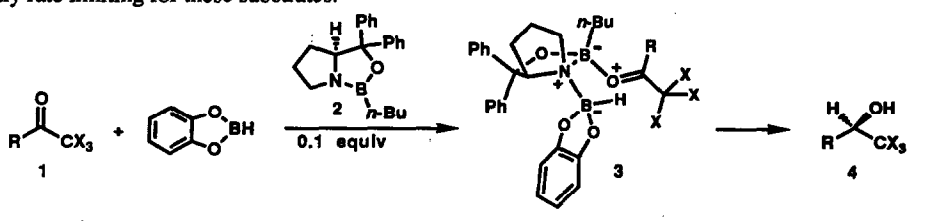
E. J. Corey, John O. Link, and Raman K. Bakshi

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: *The rates and enantioselectivities of the reduction of a series of trihalomethyl ketones under catalysis by oxazaborolidine 2 can be explained in terms of structural and mechanistic analyses which are detailed herein and which have predictive value.*

The reduction of a series of trihalomethyl ketones, $RCOCX_3$ (**1**), by catecholborane[1] in toluene is strongly catalyzed by the chiral oxazaborolidine **2** and provides trihalomethyl carbinols **4** with excellent enantioselectivity.[2] The absolute stereochemical course of the reduction is consistent with structure **3** as the preferred activated assembly on the pathway to **4**. In **3** the catalyst is coordinated to the carbonyl lone pair which is *syn* to the group R and *anti* to the trihalomethyl group, which implies that the latter group is the bulkier of the two. This preferential coordination geometry then should translate into enantioselectivity either if the formation of **3** is rate limiting or if **3** and the alternative minor diastereomeric complex, in which coordination occurs *syn* to the CX_3 group, are converted to product at nearly the same rate. This paper addresses several issues which are of interest in connection with the enantioselective conversion **1** → **4** : (1) the rate-enhancing effect of halogen on the reduction; (2) the reason for the greater effective bulk of CX_3 as compared with groups such as *tert*-butyl, mesityl and 9-anthryl; and (3) the consequences of intramolecular steric compression, restricted rotation and gearing effects on the level of enantioselectivity.

In order to obtain information on the electronic effect of substituents on the rate of enantioselective reduction of ketones the relative rates of reduction of acetophenone and its *p*-nitro- and *p*-methoxy derivatives were determined using the B-methyl analog of **2** as catalyst and borane in tetrahydrofuran as stoichiometric reductant at 23 °C. Equimolar amounts of each of the three possible pairs of these ketones were reduced with 10 mole % of borane and **2** and the ratios of reduction products were measured by gas chromatographic analysis. In this way the relative rates of reduction for acetophenone, its *p*-nitro- and *p*-methoxy derivatives were found to be 1.0, 3.4 and 1.8 respectively. The simplest interpretation of this small rate difference with a minimum rate for acetophenone is that neither ketone-catalyst coordination nor hydride transfer to carbonyl steps are strictly rate limiting for these substrates.[3]



The ^1H–^2H kinetic isotope effect (k_H/k_D) for the hydride transfer step was measured by using an excess of a 1 : 1 mixture of B^1H_3 and B^2H_3 (6 mole equiv of each) in tetrahydrofuran with 2 equiv of the B-methyl analog of **2** and 1 equiv of acetophenone. The ratio of ^1H to ^2H in the reduction of product, 1-phenylethanol,

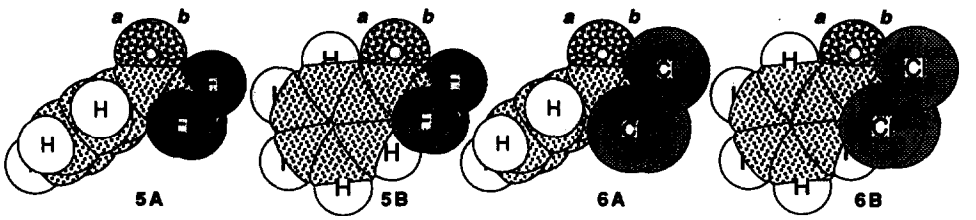
was determined mass spectrometrically to be 1.7 which is then the approximate value of k_H/k_D. This low value is indicative of an early transition state for the highly exothermic step in which hydride is transferred to carbonyl.

Since α,α,α-trifluoro and α,α,α-trichloroacetophenone are comparable in reactivity to acetophenone in oxazaborolidine-catalyzed reduction, it is apparent that for the trihalomethyl ketones the increased electrophilicity of the carbonyl carbon compensates for the lower Lewis basicity and greater steric shielding of the carbonyl oxygen. That is, the rate constant for hydride transfer is increased, perhaps even to the point that complexation is rate limiting for these substrates. In this event the enantioselectivity would depend directly on the relative rates of complexation of trihalomethyl ketone **1** at the lone pairs which are *syn* or *anti* to the trihalomethyl group, the latter being favored. Supporting evidence for this possibility has been obtained from an experiment in which α,α,α-trifluoroacetophenone was treated with a 1 : 1 mixture of catecholborane–^{1}H and catecholborane–^{2}H (10 equiv of each) and catalyst **2** (1 equiv) in CH_2Cl_2 at -78 °C. The product was found to be a 1 : 1.1 mixture of deuterated and non-deuterated trihalomethyl carbinol, as would be consistent with a rate limiting association of ketone with the catecholborane complex with **2** followed by hydride transfer which is fast.

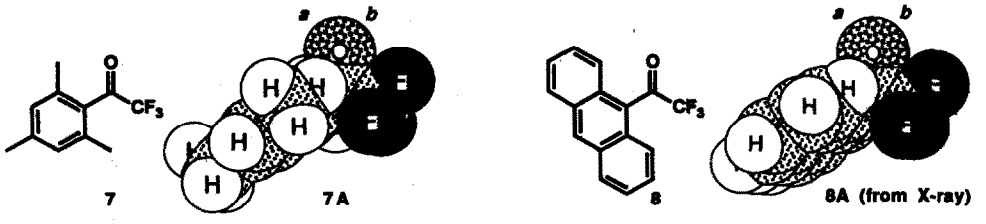
The relative sizes of three of the trihalomethyl groups are in fact in the expected order $CBr_3 > CCl_3 > CF_3$ as indicated by the following reductions of acetophenones by catecholborane in toluene under catalysis by 10 mole % of **2** to give *R* trihalomethyl carbinols with the *R/S* enantioselectivities shown:

Ketone:	**5**, $C_6H_5COCF_3$	**6**, $C_6H_5COCCl_3$	**7**, $C_6H_5COCBr_3$
R/S:	95 : 5 (-78°)	98 : 2 (-23°)	99 : 1 (-23°)

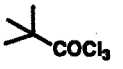
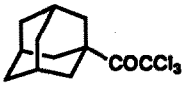
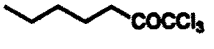
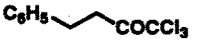
In each of these substrates it is reasonable that phenyl is effectively the smaller group. With the phenyl group of **6** oriented perpendicular to the $C_\alpha COC_{\alpha'}$ plane (**6A**), the trichloromethyl group can rotate quite freely and it is obvious that lone pair *a* is more accessible. In **6B** (phenyl in the $C_\alpha COC_{\alpha'}$ plane), the phenyl and CCl_3 groups are geared and lone pairs *a* and *b* are both strongly obstructed.



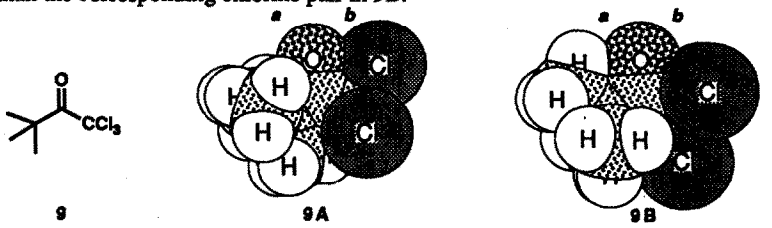
In the case of mesityl trifluoromethyl ketone (**7**) the reduction by catecholborane and **2** shows >99.5 : 0.5 *R/S* enantioselectivity, and with 9-anthryl trifluoromethyl ketone (**8**) the reduction shows 97 : 3 *R/S* enantioselectivity. In each of these cases the substrate is locked firmly in the conformations **7A** or **8A** respectively (analogous to **6A**) favoring catalyst coordination at lone pair *a*. The lower enantioselectivity in the reduction of phenyl trifluoromethyl ketone **5** as compared with the mesityl and 9-anthryl analogs **7** and **8** deserves comment. To the extent that conformation **5B** contributes to the rotomeric population distribution, coordination to lone pair *a* and formation of the *R* carbinol becomes relatively less favorable than for **5A**, or the analogs **7A** and **8A**. Thus, because of the possibility of rotation of phenyl in **5**, the molecular geometry **5B** is possible in which phenyl more strongly screens lone pair *a* than is the case for mesityl or 9-anthryl which are locked non-conjugated rotomers analogous to **5A**. In this sense it is possible for a phenyl group to exert greater screening than a mesityl or 9-anthracenyl group.



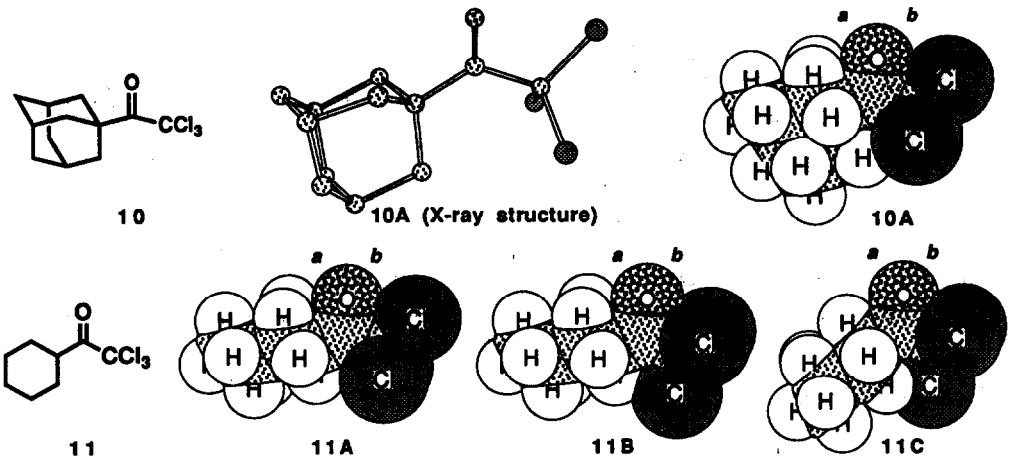
A similar superficial anomaly has been observed in the catecholborane reductions catalyzed by 10 mole % of **2** in toluene for the series of trichloromethyl ketones, *tert*-butyl (**9**), adamantyl (**10**), cyclohexyl (**11**), *n*-amyl (**12**) and 2-phenylethyl (**13**) for which the following *R/S* enantioselectivities were measured experimentally:

	9, 	**10**, 	**11**, 
R/S	99 : 1 (-20°)	99 : 1 (-20°)	96 : 4 (-20°)
	12, 	**13**, 	
R/S	97.5 : 2.5 (-60°)	97.5 : 2.5 (-78°)	

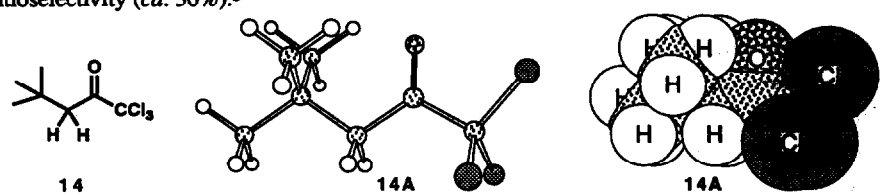
In each of the above cases the trichloromethyl group is the stronger with regard to screening of the carbonyl lone pair. This may be due in part to an electrostatic destabilization of the complex in which negatively charged boron is attached to oxygen at the lone pair *syn* to the electron rich CCl_3 group, as pointed out previously.[2c] However, even granting this effect, it might be surprising that the reductions of **9** and **10** are as enantioselective as they are and, indeed, somewhat more enantioselective than those of **11**, **12** and **13**. In the case of *tert*-butyl trichloromethyl ketone (**9**), in which the two groups attached to carbonyl are geared and can rotate in phase, coordination with catalyst **2** must be considered for two conformers, **9A** and **9B**. The 99 : 1 observed enantioselectivity, corresponding to preferential complexation at lone pair *a* in **9A** over *b* in **9B**, may be due in part to the ability of the two methyl groups closest to oxygen in **9A** to rotate into a position in which they screen less effectively than the corresponding chlorine pair in **9B**.



Adamantyl trichloromethyl ketone (**10**) is locked by intramolecular steric compression in conformation **10A** and the counterpart of **9B** is energetically too unfavorable.[4] In consequence coordination to lone pair *a* is favored 99 : 1 even though the adamantyl group is too rigid to allow the kind of relaxation of β-hydrogens which is possible for **9A**. Cyclohexyl trichloromethyl ketone (**11**) undergoes somewhat less selective reduction (97.5 : 2.5) possibly because coordination to lone pair *a* in **11A** is less favorable than in **9A**, because the cyclohexane ring prevents deflection of the β-hydrogens by internal C–C rotation; approach of catalyst to lone pair *b* in **11B** or **11C** is essentially equivalent to lone pair *b* in **9B**. Finally, the lack of gearing and greater rotational mobility in substrates **12** and **13** may slightly increase the proportion of **9B**-like rotomer and coordination of catalyst **2** to the *b* lone pair, resulting in slightly diminished (97.5 : 2.5) enantioselectivity.



As a result of the foregoing analysis it was predicted that neopentyl trichloromethyl ketone (**14**) would represent an exceedingly unfavorable case for enantioselective reduction by catecholborane under catalysis by **2**. It is apparent that the intramolecular steric compression between trichloromethyl and *tert*-butyl would compel these groups to be antiperiplanar about the CH_2—CO bond as shown in **14A**. In this conformation one of the oxygen lone pairs is strongly screened by *tert*-butyl and the other by trichloromethyl. Experimentally it was found that **14** undergoes reduction only exceedingly slowly (only 30% conversion at -20 °C after 56 h) and with poor enantioselectivity (*ca.* 30%).[5]



We believe that the mechanistic insights described herein will help to define the scope of chiral oxazaborolidine-catalyzed reduction of trihalomethyl and other highly substituted ketones.[6]

References and Notes:

1. (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611-614. (b) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209-1216.
2. (a) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Letters* **1991**, *32*, 6835-6838; (b) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A. *Tetrahedron Letters* **1991**, *32*, 6839-6842; (c) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906-1908; (d) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1992**, *33*, 3431-3434. In general higher enantioselectivities are observed with catecholborane/C_7H_8 than with BH_3•THF for the oxazaborolidine catalyzed reduction of trihalomethyl ketones.
3. If the formation of complex (such as **3**) were rate limiting the order of reactivity of the *p*-substituted acetophenones is expected to be *p*-OMe > *p*-H > *p*-NO_2 whereas the reverse order is expected for rate-limiting hydride addition to carbonyl.
4. Conformation **10A** is indicated clearly by the X-ray crystallographic study reported in the preceding paper, this issue.
5. For another "worst case" situation see De Ninno, M. P.; Perner, R. J.; Lijewski, L. *Tetrahedron Letters* **1990**, *31*, 7415-7418.
6. This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

(Received in USA 20 July 1992)