# Enhanced Stereoselectivity in the Capture of a 5-Substituted 2-Adamantyl Radical by Substitution of C-5 by Negative Boron

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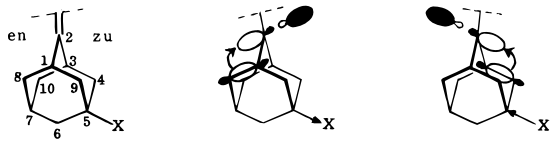
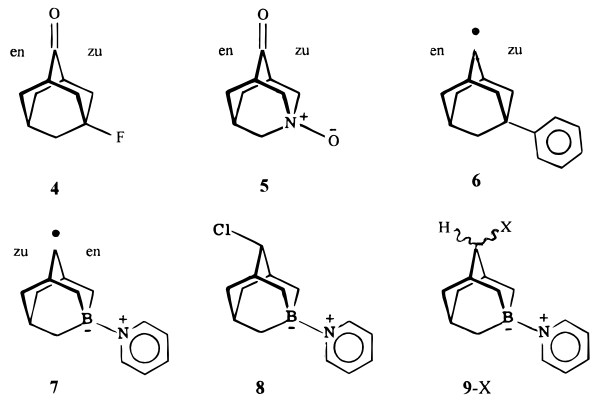
5-Substituted adamantanes **1**-X, provided with a trigonal center at the C-2 site,[1] have proved to be a useful probe in studies of the electronic factor of face selection in addition and elimination.[2] It has been found virtually without exception that if the 5-substituent is electron-withdrawing, it will direct reagents of every description to the *zu* face, by modest but easily measurable margins. Thus, we found[3] that the 5-phenyl-2-adamantyl radical abstracts a bromine atom from molecular bromine to give an *E*/*Z* mixture of bromides in a ratio of 38:62, respectively. While only a few of the readily available substituents are electron donors (compared to hydrogen), we did learn that such donors at C-5 promote capture at (or departure from) the *en* face. To date, we have favored[4] a notion advanced by Cieplak[5] as the explanation of these observations, namely, that transition state stabilization is achieved by hyperconjugation such that the more electron-rich antiperiplanar vicinal bonds function as donors to the $\sigma^*$ component of the incipient (or breaking) bond, as in structures **2** and **3**.




**1**-X **2** **3**

However, our examples have as yet not included any abstractions by a 2-adamantyl radical with a *donor* group as the 5-substituent, and this has become a weakness. Indeed, several groups active in computational chemistry have recently advocated[6] that the observations are best explained by electrostatic effects. As yet, these accounts have not offered calculations based on the simple Westheimer−Kirkwood model[7] in support of this view, nor have solvent effects been reported[8] to strengthen it. The most telling evidence for an electrostatic basis of these effects has been indirect: Adcock[9] reports that a 5-trimethylstannyl substituent, which strongly enhances[10] the solvolytic departure of a leaving group at C-2, completely fails to impart any selectivity in atom abstraction by a C-2 radical site. The radical was generated in a complex reaction, and the yields of abstraction products were moderate (70%) to poor (4%); furthermore, the attribution[11] to "electrostatic steering" as the cause of face selectivity in *all* trigonal species except cations seems a long extrapolation supported only by correlations of NMR chemical shifts. Nevertheless, it became clearly desirable to study an abstraction reaction of a 2-adamantyl radical carrying in the 5-position a functional group with a donating ability substantially stronger than that of trimethylstannyl.

To do so, we harked back to an idea, first used a few years ago,[12] to create a substituent even more powerfully polarizing than fluoro: replacement of C-5−F by an isoelectronic moiety in which, in effect, a proton had been transferred from the fluorine nucleus in 5-fluoroadamantan-2-one **4** to that of the contiguous carbon. Indeed, it was found that the product ratios in carbonyl reduction, methylation, and several additional types of addition[13] to the trigonal site in the resulting amine oxide **5** show the *zu* face now to be favored more strongly by 1 order of magnitude. In an analogous way, "proton transfer" in the opposite direction in the 5-phenyl-2-adamantyl radical **6** would lead to the zwitterionic and isoelectronic radical **7**. By the best of good fortunes, this radical's most reasonable precursor [(*Z*)-2-chloro-5-boraadamantane **8**] as well as the product to be expected from hydrogen abstraction (5-boraadamantane **9**-H) had already been




**4** **5** **6**

**7** **8** **9**-X

reported.[14] Equally fortunately, it is known that the tri-*n*-butyltin hydride reduction of chlorides takes place via

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(1) (a) As in all of our previous papers on this subject, we have for the sake of the reader's convenience used the numbering system shown in **1**, which in fact applies to adamantanone but which is incorrect for some of the compounds described here; **9**-H is actually the pyridine complex of 1- rather than of 5-boraadamantane, for example. (b) Note that with boron lower in priority than carbon, **8** must be designated the *Z*-isomer.

(2) Examples include: (a) Dekkers, A. W. J. D.; Verhoeven, J. W.; Speckamp, W. N. *Tetrahedron* **1973**, *29*, 1691. (b) Bone, J. A.; Pritt, J. R.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1447. (c) le Noble, W. J.; Chiou, D.-M.; Maluszynska, H.; Okaya, Y. *Tetrahedron Lett.* **1977**, 3865. (d) Grob, C. A.; Wang, G.; Yang, C. *Tetrahedron Lett.* **1987**, *28*, 1247. (e) Laube, T.; Stilz, H. U. *J. Am. Chem. Soc.* **1987**, *109*, 5875. (f) Adcock, W.; Coope, J.; Shiner, V. J.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411. (g) Burgess, K.; van der Donk, W. A.; Jarstfer, M. B.; Ohlmeyer, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 6139. (h) Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017. (i) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418. (j) Chung, W.-S.; Wang, N.-J.; Liu, Y.-D.; Leu, Y.-J.; Chiang, M. Y. *J. Chem. Soc., Perkin Trans. 2* **1995**, 307.

(3) Bodepudi, V.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001.

(4) Cheung, C. K.; Tseng, L. T.; Lin, M.-h.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598; **1987**, *109*, 7239.

(5) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(6) For references and discussion, see: Lau, J.; Hung, R.; Gonikberg, E. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421.

(7) See, for example: *Advanced Organic Chemistry*, 3rd ed.; Wheland, G. W., Ed.; Wiley: New York, 1960; Chapter 11.

(8) An exception has been claimed (not in the adamantane series). See: Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.

(9) Adcock, W.; Clark, C. K.; Trout, N. A. *Tetrahedron Lett.* **1994**, *35*, 297.

(10) See ref 2f and Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836 and 3839.

(11) Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867.

(12) Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916.

(13) Reference 6 and Gonikberg, E. M.; le Noble, W. J. *J. Org. Chem.* **1995**, *60*, 7751.

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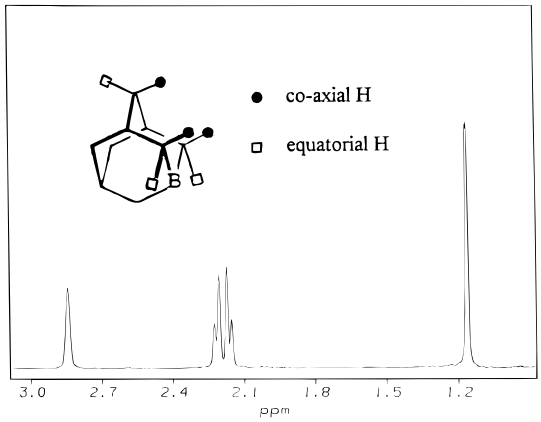


**Figure 1.** $^1$H NMR spectrum of **9**-H. The pyridine portion is not shown.

radicals, with loss of configuration. Thus, both *cis*- and *trans*-α-chlorodecalin are reduced by this hydride to the same mixture of *cis*- and *trans*-decalin;[15] reduction of optically active 1-chloro-1-phenylethane with $Ph_3SnD$ leads to racemic ethylbenzene-α-$d_1$.[16] The 2-adamantyl radical is furthermore known[17] to be planar, so that the question of pyramidality of the trigonal center does not arise.

The donating power of the negative boron atom became at once evident to us from the fact that **8** was found to react instantly with silver nitrate to give a precipitate. Tri-*n*-butyltin hydride reduction with AIBN initiation in refluxing benzene, monitored by means of TLC, cleanly converted **8** into **9**-H in 4 h, and hence it became possible to study the selectivity of the radical by the use of tri-*n*-butyltin deuteride; however, to do so, we first needed to analyze the $^1$H NMR spectrum of **9**-H.

This spectrum was measured in hexadeuteriobenzene; it is shown in Figure 1. The 3-fold (B−N) axis of the tricyclic skeleton leads to four signals in a ratio of 6:3:3:3. The singlets at $\delta$ 1.16 and 2.85 are due to the six equivalent boron-bound methylene protons and the three bridgehead protons, respectively; the leaning pair of doublets at $\delta$ 2.16 and 2.22 with $J = 12$ Hz represents the remaining six protons. The latter group is divided into three equatorial and three coaxial atoms, and the question to be settled is: Which doublet corresponds to which group of three? This was decided in two independent ways. The first method rested on a 2QF COSY spectrum, which showed the protons represented by the $\delta$ 2.22 signal to be coupled with the high-field methylene protons. This is consistent with the *W*-configuration connecting each of the three coaxial protons with a pair of the high-field protons in this rigid structure. The second method consisted of a 2D NOESY spectrum, which showed the presence of a through-space interaction between each of the three equatorial protons with a pair of the high-field protons. The results of these experiments are shown in Figure 2. Both approaches support the conclusion that the $\delta$ 2.22 doublet must be ascribed to the three coaxial protons, and the $\delta$ 2.16 doublet to the three equatorial ones. With these two signals assigned, we could then determine the isotopimeric product ratio in the deuterium abstraction, simply by integrating them.

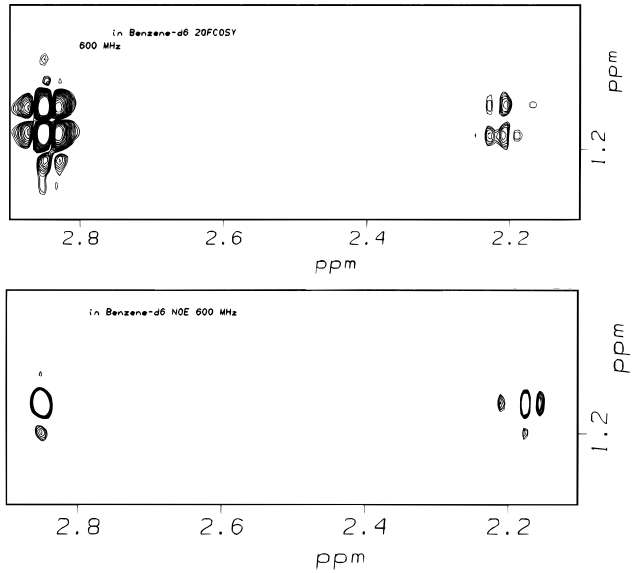


**Figure 2.** A partial NOESY spectrum of **9**-H showing the interaction between the equatorial hydrogens at C-2,8,10 and those at C-4,6,9 (top) and a partial COSY spectrum of the same compound showing *W*-coupling of the coaxial hydrogens at C-2,8,10 with those at C-4,6,9 (bottom).

The reduction was carried out in hexadeuteriobenzene and followed via the disappearance of the C-2-proton signal of **8**. The methylene proton signals of the two boraadamantane complexes **9**-D are nicely separated from those of the excess tin compound. It will be noted that, in the case of complete stereospecificity, the two signals at $\delta$ 2.2 would be in a 3:2 ratio; furthermore, the CHD proton signal would be expected to be broadened because of H−D coupling. The actual spectrum clearly revealed the presence of both isomers, and equally clearly, that the amounts differed (see Figure 3, part a). $^1$H NMR integration showed the product ratio to be 62:38, with the product of attack *anti* to the boron predominant; this ratio is just about the exact opposite of that observed with **6**.

The $^2$H NMR spectrum furnished independent confirmation of this result as shown in Figure 3, parts b and c. Part b show the expected pair of signals, and integration gave a 60:40 ratio, again with the *Z*-isomer[1b] in excess. Proton decoupling narrowed these signals, separated them more cleanly, and produced a 65:35 ratio (part c). Finally, the $^{13}$C NMR spectrum (part d) showed the expected 1:1:1 triplet for C-2 (common for both isomers), shifted upfield somewhat from a multiplet which under sine bell conditions proved itself to be the result of three contributors: a minor peak for C-2,8,10 of the D-free compound present as a minor impurity and the C-8,10 signals of the two deuterioboranes. These latter two peaks are clearly of unequal intensity, but they could not be independently integrated or assigned; their appearance is consistent with the other assays, however.

The magnification of the isomer ratio by resorting to the zwitterionic isoelectronic species is not as large as it was in the case of nucleophilic addition to **4** and **5**, which gave an enhancement by a factor of about 10, as noted. The present comparison *inverts* the ratio in radical capture, from 1.63 for **6** to about 0.61 for **7**; thus, the

(14) (a) Michailov, B. M.; Baryshnikova, T. K. *Bull. Acad. Sci. USSR, Chem. Sci.* **1979**, 1358 and 2361. (b) Michailov, B. M.; Cherkasova, K. L. *J. Organomet. Chem.* **1983**, *246*, 9.
(15) Greene, F. D.; Lowry, N. N. *J. Org. Chem.* **1967**, *32*, 882.
(16) Kuivila, H. G. *Synthesis* **1970**, 499.
(17) Kira, M.; Akiyama, M.; Ichinose, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 8256.

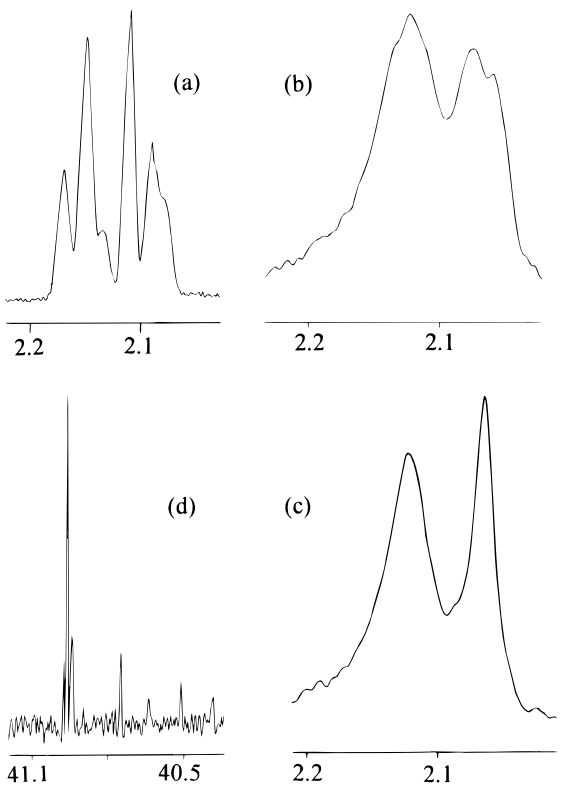


**Figure 3.** (a) The $\delta$ 2.2 portion of the $^1$H NMR spectrum of the reaction mixture of **8** and tri-*n*-butyltin deuteride. Some broadening has occurred, and the two doublets are clearly no longer equal in intensity (compare Figure 1). (b) The same portion in the $^2$H NMR spectrum, with protons coupled. (c) Same as (b), with $^1$H decoupling. (d) Partial $^{13}$C NMR spectrum of the reaction mixture, showing the C-2 signal under sine bell conditions. This improves resolution at the cost of a lower signal-to-noise ratio. The main peak at $\delta$ 41.0 is resolved into three components. From left to right: a trace of **9**-H (C-2,8,10), C-8,10 of *Z*-**9**-D and C-8,10 of *E*-**9**-D (this assignment was not confirmed independently); it is followed by unreacted **8** and the 1:1:1 triplet representing C-2 in both isomers.

effect amounts to an increase in selectivity by a factor now close to 3. However, reduced dependence on neighboring group assistance as compared to reactions of a more cationic character is expected.[18] In any case, the experiment clearly demonstrates that a sufficiently strong donor *does* exert the directive effect that Adcock *et al.* were unable to find in their researches in this area.

We also take note here of the occasional claims that a degree of pyramidality may characterize adamantanones, and thus favor one approach over the other. Most recently, a paper by Gung[19] reported calculations leading him to conclude that **5** is distorted and that this deformation accounts for the large preference of *syn* approach of sodium borohydride in the formation of the alcohols. The same calculations were said to show a lesser distortion to be present in the parent azaadamantanone, which is indeed reduced by this reagent with a smaller preference for *syn* approach. One might extrapolate this reasoning to radical **7**: if it is also distorted and in the opposite sense, one should expect preferred *anti* approach, as observed.

Gung's thesis is not convincing, however. Most blatantly, it ignores the fact, stated in our paper,[12] that a different nucleophile (methyllithium) attacks the parent azaadamantanone preferably from the *anti* direction. Transition state hyperconjugation easily accounts for this fact, as hydrogen bonding in methanol reduces the ability of the nitrogen unshared pair to function as a donor in the borohydride reduction. This explanation is supported strongly by a paper by Senda,[20] who found that the isomer ratio in that reaction is linearly related to the solvent acidity and that the use of THF even leads to a reversal of this ratio.

## Experimental Section

NMR spectra were recorded by means of an AMX-600 and/or an AC-250 spectrometer in hexadeuteriobenzene. The pyridine complexes of 5-boraadamantane (**9**-H) and of 2-chloro-5-boraadamantane (**8**) were prepared according to ref 14a,b. Although these compounds are stable, all of our attempts to convert **8** into either 2-hydroxy-5-boraadamantane (**9**-OH) or 5-boraadamantan-2-one led to cleavage of the boron−carbon bonds and to the total loss of the adamantane skeleton.

**Reduction of 2-Chloro-5-boraadamantane (8).** A solution of the pyridine complex of **8** (18 mg, 0.08 mmol) and AIBN (2 mg) in hexadeuteriobenzene (0.5 mL) was mixed with a solution of tri-*n*-butyltin deuteride (Aldrich, 0.1 mL, 0.25 mmol) in the same solvent (0.25 mL) under nitrogen, and the resulting mixture was heated to reflux for 4 h. The reaction was monitored by means of TLC and the final mixture analyzed with NMR as described in the text.

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**Supporting Information Available:** COSY spectra of boraadamantane (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(18) Bartlett, P. D.; McBride, J. M. *J. Am. Chem. Soc.* **1965**, *87*, 1727. As a reviewer has noted, the comparison is of two reactions in which a different atom is abstracted (bromine by **6** and hydrogen by **7**). Unfortunately, **8** is unstable to bromine, and 1-phenyladamantane does not lend itself to the NMR analysis described here. The stereochemistry is not expected to be affected by this difference, however.

(19) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 232.

(20) Senda, Y.; Morita, M.; Itoh, H. *J. Chem. Soc., Perkin Trans. 2* **1996**, 221.