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Diastereofacial Selectivities of Substituted 5-Aza- and 5-Bora-2-adamantanones. Application of the Complexation Model and its ab Initio MO Investigation

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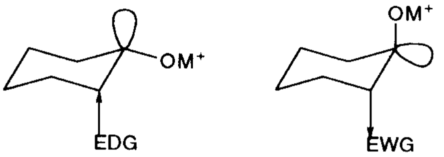
Abstract: N-Substituted 5-aza-2-adamantanones and 5-bora-2-adamantanone have been studied by ab initio MO methods at Becke3LYP level for their diastereofacial selectivities in reactions with nucleophiles by applying the complexation model. The facial predictions are fully consistent with the experiments. This is to be emphasized that in a given substrate there may be centres other than the carbonyl oxygen that may compete for the cation and, thus, contribute to the overall diastereodetermination. Other models such as the Cieplak model, Anh-Felkin model, and Houk model may or may not apply.

Keywords: Adamantanones; cation-complexation; stereoelectronic effects; diastereoselection

Introduction

In 1997, we proposed a cation-complexation model to predict the facial selectivity of substituted cyclohexanones and reported since the first results on 3-oxa-, 3,5-dioxa-, and 3-thia-cyclohexanones,[1a] 3-ax- and 3-eq-halocyclohexanones,[1b] and 4-X-cyclohexanones (X = Cl, F, OR, and SR).[1c] The significant features of the model are: (a) the cation carbonyl complexation precedes the nucleophilic attack, (b) such a complexation causes pyramidalization at the carbonyl carbon, (c) consequent to the pyramidalization, the electron-poor p orbital on the carbonyl carbon ($p_{C=O}$) orients in such a way that it is antiperiplanar to the more electron-donating σ bond or an electron pair orbital at the adjacent carbon, and (d) in the absence of other effects including the torsional strain, the nucleophile is electrostatistically drawn to this p orbital on whichever face (ax/eq) it is to complete the nucleophilic process. In this manuscript, we report on the application of the complexation model to substituted 5-aza- and 5-bora-2-adamantanones and demonstrate that (a) it performs fully consistent with the experimental results and (b) the Cieplak model,[2] Anh-Felkin model[3] and Houk's TS model[4] fail at one or the other substrate. The 5-substituted 2-adamantanones are considered geometrically unbiased and their selectivities have been thoroughly studied experimentally by le Noble[5] to allow us compare our results immediately. The stereoelectronically favored ax- and eq-orientations of the $p_{C=O}$ on cation-complexation are shown below:



Stereoelectronically favored ax- and eq-orientations of $p_{C=O}$ on complexation with a cation M^+. (a) EDG = electron-donating group, EWG = electron-withdrawing group

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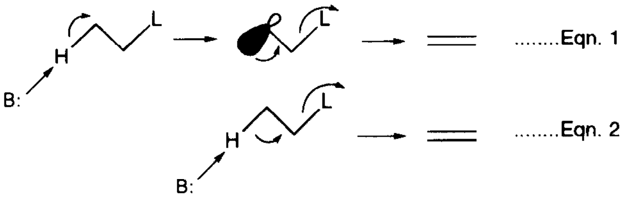
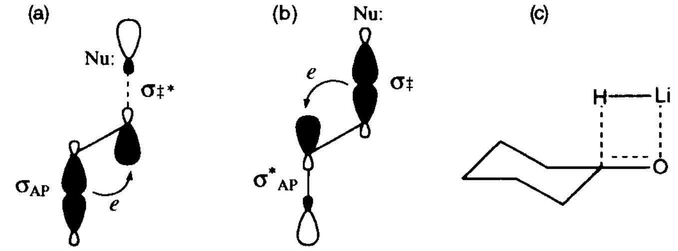
Both the cation carbonyl complexation and it actually taking place in the carbonyl σ plane have been conclusively demonstrated in the literature.[6,7] The notion of an electron-poor orbital antiperiplanar to an electron rich σ bond or an electron pair orbital for an energetically beneficial interaction can be easily gleaned from the TS geometries for E1cB and E2 reactions (Equations 1 and 2, respectively). Thus, the cation complexation model is fully supported by the stereoelectronic effects.[8] Furthermore, the complexation model makes no assumptions as most other models do.



L = an electron attracting leaving group, B = a base

The Cieplak model assumes the TS electron-poor and requires electron-donation from the more electron-rich σ bond at the α carbon to the incipient bond. On the contrary, the Anh-Felkin model requires electron-donation from the incipient bond to an antiperiplanar and electron-poor σ bond on the α carbon because the TS was assumed to be electron-rich. Both these models, therefore, predict opposite diastereoselectivities for the same molecule. The TS model of Houk assumes the simultaneous approach of both the components, the cation and the anion, of a nucleophile to the carbonyl π plane and, thus, ignores the experimentally well documented cation-carbonyl complexation and the consequent geometrical changes in the molecule. Further, the TS model does not explain the variation in diastereoselectivity with the variation in the nature of the cation component of the nucleophile.[9] Like the Cieplak model, the cation-complexation model is also based on the stereoelectronic effects but the methods of its application are different. The complexation model relies upon the ground state geometry after a cation has complexed with the carbonyl oxygen (and other potentially electron-rich centres in the molecule) and gives due significance to the electrostatic attraction between the orbitals that are required for bond formation; a feature that is fundamental to all reactions. Also, unlike the Houk's TS model that considers the setting up of the TS in the π plane of the carbonyl in its ground state, the complexation model considers the setting up of such a TS only after the necessary cation complexation. The pictorial representations of the Cieplak model, Anh-Felkin model and Houk model are given below:



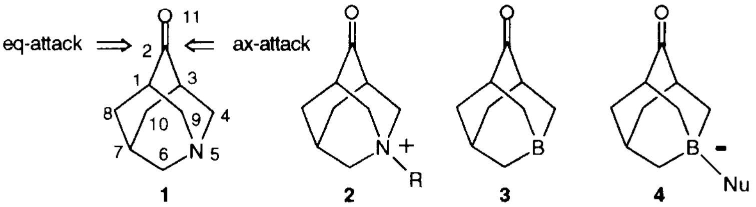
(a) Cieplak model, (b) Anh-Felkin model and (c) Houk model for axial attack on cyclohexanone with LiH as the attacking nucleophile. Nu: = nucleophile

Computational Methods

The geometries and the Natural Bond Orbital (NBO) charges were calculated at Hartree Fock (HF) level using Gaussian 94.[10] Further geometry improvements were achieved from computations at Becke3LYP level. The 6-31G* basis set was used throughout. Though the results from the HF method are qualitatively very similar to those from the Becke3LYP method, we present below the results from the latter only.

Results and Discussion

We have studied 5-aza-2-adamantanone (**1**), N-methyl-5-aza-2-adamantanone (**2**, **R** = **Me**), 5-aza-2-adamantanone N-oxide (**2**, **R** = **O⁻**), 5-bora-2-adamantanone (**3**) and its derivative **4**. The geometrical consequence of an axial-like $p_{C=O}$ orientation on cation-complexation is an increased equatorial-like orientation of the elongated C=O bond. This results in an increase in D1 on the axial face of the heteroatom-containing cyclohexanone ring. Likewise, an equatorial-like $p_{C=O}$ orientation results in an increase in the torsion angle D2 on the equatorial face of the heteroatom-containing cyclohexanone ring. Thus, an increase in the torsion angle D1 and a corresponding decrease in the torsion angle D2 predicts axial selectivity. Likewise, a decrease in D1 and a corresponding increase in D2 predicts the equatorial selection The torsion angles D1 and D2 and the angles A1 and A2 are collected in Table 1. The NBO charges on the selected atoms are collected in Table 2.



D1 = O11-C2-C3-C4, D2 = O11-C2-C3-C10, A1 = O11-C2-C1, A2 = O11-C2-C3
The ax- and eq-attacks shown are with respect to the heteroatom-containing cyclohexanone ring.

Table 1. Selected geometrical parameters of 5-aza- and 5-bora-2-adamantanones and their complexes

1	5-aza-2-adamantanone
	D1 = 120.88; D2 = 122.10; A1 = 124.08; A2 = 124.08
	5-aza-2-adamantanone; C=O...H⁺
	D1 = 108.53; D2 = 137.77; A1 = 118.04; A2 = 124.28
	5-aza-2-adamantanone; C=O...H⁺ and N...H⁺
	D1 = 135.50; D2 = 107.55; A1 = 117.80; A2 = 125.38
2	N-methyl-5-aza-2-adamantanone
	D1 = 123.00; D2 = 117.87; A1 = 124.33; A2 = 124.33
	N-methyl-5-aza-2-adamantanone; C=O...H⁺
	D1 = 135.30; D2 = 107.70; A1 = 117.98; A2 = 125.57
3	5-aza-2-adamantanone N-oxide
	D1 = 123.66; D2 = 117.98; A1 = 124.17; A2 = 124.17
	5-aza-2-adamantanone N-oxide; C=O...H⁺
	D1 = 128.82; D2 = 114.99; A1 = 118.38; A2 = 124.55
4	5-bora-2-adamantanone
	D1 = 118.17; D2 = 122.18; A1 = 123.08; A2 = 123.08
	5-bora-2-adamantanone; C=O...H⁺
	D1 = 123.27; D2 = 119.40; A1 = 117.38; A2 = 123.06
	5-bora-2-adamantone; B...H⁻ and C=O...H⁺
	D1 = 100.91; D2 = 142.88; A1 = 117.52; A2 = 121.37
	H-B-C6-C1 = 179.78; H-B-C9-C8 = 179.64

Table 2. The NBO charges on selected atoms in 5-aza- and 5-bora-2-adamantanones and their complexes

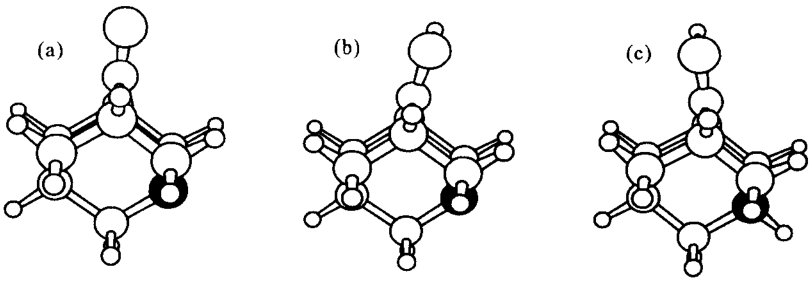
	C2	C3	.C4	.A5[a]	C=O[b]	N-O/B-H[c]
5-aza-2-adamantanone	0.5878	- 0.3620	- 0.2665	- 0.5003	- 0.5417	
5-aza-2-adamantanone; C=O...H+	0.6218	- 0.3725	- 0.2397	- 0.4317	- 0.5831	
5-aza-2-adamantanone; C=O..H+, N..H+	0.7076	- 0.3830	- 0.2587	- 0.4676	- 0.5226	
5-methyl-5-aza-2-adamantone	0.5802	- 0.3661	- 0.2547	- 0.3082	- 0.4719	
5-methyl-5-aza-2-adamantone; C=O...H+	0.7094	- 0.3789	- 0.2555	- 0.3128	- 0.5244	
5-aza-2-adamantanone N-oxide	0.5959	- 0.3703	- 0.2689	0.0286	- 0.5227	- 0.7107
5-aza-2-adamantanone N-oxide; C=O..H+	0.7120	- 0.3720	- 0.2696	0.0248	- 0.5498	- 0.6587
5-bora-2-adamantanone	0.5946	- 0.3237	- 0.8143	0.9247	- 0.5334	
5-bora-2-adamantanone; C=O..H+	0.7179	- 0.3465	- 0.7961	0.9499	- 0.5538	
5-bora-2-adamantanone; C=O..H+, B..H-	0.6811	- 0.3485	- 0.6553	0.1596	- 0.6079	- 0.0058

[a]This is the heteroatom at position 5, [b]This column shows the NBO charges on the carbonyl oxygen, [c]This column shows the NBO charges on the atom attached externally to the 5-heteroatom.

The individual cases are discussed below.

5-Aza-2-adamantanones (1)

The torsion angle D1 was reduced by >12° and D2 enlarged by >15° on protonation of the carbonyl oxygen. This suggests an equatorial orientation of the $p_{C=O}$. An eq-attack will, therefore, be predicted. The C3C4/C1C9 bonds are more electron-rich than the C1C8/C3C10 bonds. This is so particularly because the C3C4/C1C9 bonds are antiperiplanar to the equatorial electron pair orbital on the nitrogen atom. This situation is somewhat similar to those of 5-trimethylsilyl- and 5-trimethylstannyl-2-adamantanones that have been shown to exhibit, respectively, 45:55 and 43.5:56.5 selectivities in favor of equatorial attack in reductions with $NaBH_4$ in isopropanol.[5(a)] This selectivity was slightly higher at 35:65 in reaction of the stannyl derivative with MeLi in Et_2O. Both the C-Si and C-Sn bonds are electron-donors. However, the trend reversed on allowing protonation of the ring nitrogen as well: D1 was enlarged by >14° and D2 reduced by by an equal amount. An ax-attack must, therefore, predominate just as it has been reported by le Noble.[5] The 62:38 ax:eq reduction by $NaBH_4$ in both methanol and water was considered by le Noble to have involved a hydrogen-bonded amine center. The computed 3D geometries of 5-aza-2-adamantanone and its protonated derivatives are shown below:



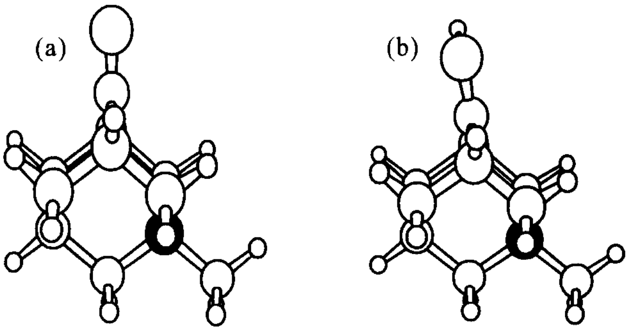
(a) 5-aza-2-adamantanone, (b) 5-aza-2-adamantanone; C=O...H+, (c) 5-aza-2-adamantanone; C=O...H+ and N...H+

From the NBO analysis, the nitrogen atom bears almost as much negative charge as the carbonyl oxygen. As such, a competition between the two heteroatoms for the cation is a genuine possibility. The N-protonation makes the nitrogen electron-attracting which, in turn, renders the C3C4/C1C9 bonds electron-poor. In comparison, the bonds C1C8/C3C10 are less electron-poor and control the $p_{C=O}$ orientation antiperiplanar to them. This leads to an axial orientation of the $p_{C=O}$ and, thus, the observed preference for ax-attack.

The Cieplak model fails because it predicts only equatorial selectivity on taking into account the electron-donating nature of the electron pair orbital on nitrogen. This model, however, will appear to succeed in predicting the observed axial preference if the electron-attracting nature of the C-N bonds were considered. The calculated geometry of the carbonyl-protonated 5-aza-2-adamantanone [structure (b) above] settles beyond doubt that the stereoelectronic effects caused by the electron pair orbital on nitrogen are more significant than the electron-attracting nature of the C-N bonds. The Cieplaka model, therefore, is concluded to fail. The Houk model would appear to fail as well. For the D2 being 1.22° larger than D1, the energy of the eq-TS is likely to be lower than that of the ax-TS and, hence, an equatorial preference for nucleophilic attacks may be predicted. Unfortunately, such TS calculations have not been reported.

N-Methyl-5-aza-2-adamantanone (2, R = Me)

The >12° increase in D1 and >10° decrease in D2 on carbonyl protonation allow us to predict a preference for ax-attack. Further, for the >27° difference of D1 and D2 in the protonated species, a very high axial selectivity may be expected. This is in excellent agreement with the reported experimental results where as high as 96:4 diastereoselection was noted from reduction with $NaBH_4$ in *i*-PrOH.[5(b)] Like the N-protonated 5-aza-2-adamantanone above, the C1C8/C3C10 bonds are less electron-poor than the C3C4/C1C9 bonds. In consequence, the $p_{C=O}$ orients antiperiplanar to the first two bonds and, hence, the observed axial selection. The computed 3D structures of N-methyl-5-aza-2-adamantanone and its protonated derivative are given below:



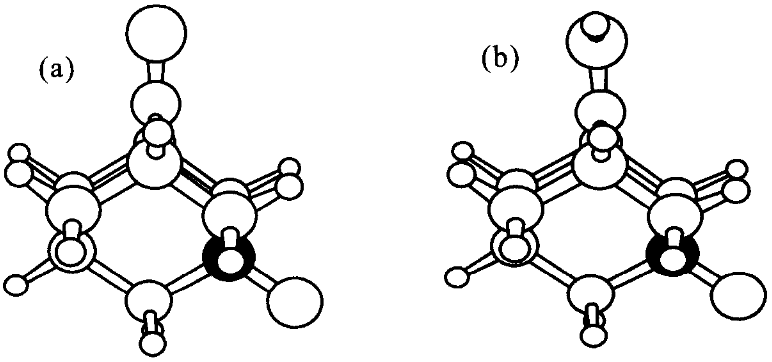
(a) N-methyl-5-aza-2-adamantanone and (b) N-methyl-2-adamantanone; C=O...H^+

The present axial prediction is in accord with the Cieplak model. It requires the nucleophile to approach the carbonyl function from antiperiplanar to the C1C8/C3C10 bonds that are more electron-rich than the C3C4/C1C9 bonds. The Houk model may succeed in as much as the qualitative axial diastereoprediction is concerned. This, however, is likely to fall short of predicting high level of selectivity because D1 is only 5.13° larger than D2 in the unprotonated species and, thus, the energy of the ax-TS may not be all that significantly favored over that of the eq-TS. Such TS calculations, however, have not been reported. The Anh-Felkin model fails because it predicts the equatorial selection for the more electron-deficient nature of the C3C4/C1C9 bonds than those of C1C8/C3C10 bonds.

5-Aza-2-adamantanone N-oxide (2, R = O)

The 5° increase in D1 and the 3° decrease in D2 on carbonyl protonation clearly indicate a preference for axial attack. The 14° difference of D1 and D2 in the protonated species is large enough to cause a considerable torsional strain in the alternate eq-TS. The axial diastereoselection may additionally be supplemented by cation complexation of the equatorially oriented N-oxide oxygen. This appears genuine for the fact that the NBO charge on this oxygen is actually larger than that on the carbonyl oxygen. This will make the C3C4/C1C9 bonds even more electron-poor than those in the only carbonyl protonated N-oxide species and, therefore, result in a more effective diastereocontrol. Overall, a high axial selectivity will be predicted. The is, again, in excellent agreement with the experimental observations.[5(b)] Like the N-methyl-2-adamantanone species above, the observed ax:eq selectivity was as high as 96:4 from reduction with $NaBH_4$ in *i*-PrOH.

The Cieplak model succeeds in predicting the axial attack on 5-aza-2-adamantanone N-oxide but the Anh-Felkin model does not. For the electron-attracting nature of the N^+-O^- bond, the C1C9/C3C4 bonds are rendered more electron-poor than the bonds C1C8/C3C10. Consequently, C1C8/C3C10 favor the $p_{C=O}$ orient antiperiplanar to them and the axial attack is observed. The Anh-Felkin model requires a nucleophile to approach the carbonyl from antiperiplanar to C1C9/C3C4 bonds because they are more electron-poor than the C1C8/C3C10 bonds. The Houk model is likely to succeed as well because D1 is 5.7° larger than D2 in the parent N-oxide. But, again, like the cases of N-methyl-2-adamantanone and 5-aza-2-adamantanone N-oxide above, this model may fall short of predicting high selectivity. The computed 3D structures of 5-aza-2-adamantanone and its carbonyl protonated derivative are shown below:

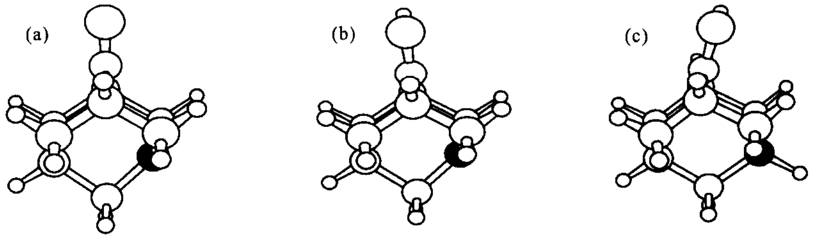


(a) 5-aza-2-adamantanone N-oxide and (b) 5-aza-2-adamantanone N-oxide; C=O...H^+

5-Bora-2-adamantanone (3)

This molecule appeared very appealing to us because under nucleophilic conditions a nucleophile will be expected to add on to the boron atom before any addition to the carbonyl carbon could take place to give **4**.[11] This is so because the boron atom is >1.5 times more electron-poor than the carbonyl carbon from the NBO charges. This will have consequences on the observed diastereoselectivity. We have mimicked the nucleophile by a hydride ion and the cation, as usual, by H^+. The D2 is >40° larger than D1 and, hence, an equatorial attack is predicted. This is in agreement with the results from the 5-pyridyl-5-bora-2-adamantyl radical in its capture of deuterium from *n*-Bu_3SnD; the ax:eq ratio was 35:65.[12] A radical orbital is largely similar to a $p_{C=O}$ because both are electron-poor and, hence, similar stereoelectronic arguments apply. The fact that a nucleophilic attack at boron is indeed very significant stems from the predominant axial prediction if only the carbonyl protonated species were to be considered.

The Cieplak model fails as it predicts axial attack for the electron-attracting nature of the boron atom. For the same reason, the Anh-Felkin model succeeds and it predicts the equatorial selection. The Houk model would also appear to succeed in predicting the equatorial preference. Since D2 is 4° larger than D1 in 5-bora-2-adamantanone, less destabilizing interactions in the eq-TS over those in the alternate ax-TS will be expected. However, the level of the selectivity predicted from the this model may be expected to be much lower than that predicted from the complexation model. For the purposes of the complexation model, the difference of D2 and D1 is ten times larger than that for the Houk model. The computed 3D structures of 5-bora-2-adamantanone and its above derivatives are given below:



(a) 5-bora-2-adamantanone, (b) 5-bora-2-adamantanone; C=O...H^+ and (c) 5-bora-2-adamantanone; C=O...H^+ and B...H^-

Conclusion

We have demonstrated that the complexation model works consistently well for the 5-hetero-2-adamantanones. The ground state geometry after complexation(s) is largely responsible for the observed selectivities. The direction of pyramidalization at the carbonyl carbon is influenced by the electron-releasing or electron-attracting character of the group in 5-position. The more exposed and, hence, the sterically less crowded face of the carbonyl function that has the $p_{C=O}$ is preferred for the nucleophilic attack.

In the application of the model, care must be exercised for the fact that other than the carbonyl oxygen there may be other potentially electron-rich centers in the molecule whose complexation with a cation must also be considered for a realistic diastereoprediction. Further, a centre like boron that is more electron deficient than the carbonyl carbon must be considered for attack by a nucleophile prior to the attack at the carbonyl carbon. The so produced species constitutes the diastereodetermining species.

The other models like the Cieplak model, Anh-Felkin model and Houk model may or may not apply. Even in the examples where the Houk model may appear to succeed, it is expected to fall short of predicting the high level of actually observed diastereoselectivities. It is important to note that the substituted 2-adamantanones are fairly large systems. The TS calculations on these at a reliable level of theory from modern standards will be highly CPU-intensive and, possibly, prohibitive.[13]

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References & Notes

1. (a) Jeyaraj, D. A.; Yadav, A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 4483; (b) Jeyaraj, D. A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 6095; (c) Yadav, V.K.; Jeyaraj, D. A. *J. Org. Chem.* **1998**, *63*, 3474.
2. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540; Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.
3. Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199; Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
4. Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018; Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638; Coxon, J. M.; Houk, K. N.; Luibrand R. T. *J. Org. Chem.* **1995**, *60*, 418; Frenking, G.; Kohler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146.
5. (a) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836; (b) Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916.
6. Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247; Warnhoff, E. W.; R.-Warnhoff, P.; Wong, M. Y. H. *J. Am. Chem. Soc.* **1980**.*102*, 5956; Laube, T.; Stilz, H. U. *J. Am. Chem. Soc.* **1987**, *109*, 5876; Marouka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588; Evans, D. A. *Science* **1988**, *240*, 420; Mackey, M. D.; Goodman, J. M. *J. Chem. Soc. Chem. Commun.* **1997**, 2383; Lecea, B.; Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **1997**, *62*, 6485.
7. The cation complexed to the carbonyl is expected to lie in the nodal plane of the carbonyl π bond as established by X-ray structure of a methylaluminum diaryloxide complex of benzophenone. Power, M. B.; Bott, S. G.; Atwood, J. L.; Barron, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 3446.
8. Deslongchamp, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983.
9. Harada, T.; Nakajima, H.; Ohnishi, T.; Takeuchi, M.; Oku, A. *J. Org. Chem.* **1992**, *57*, 720; Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890; Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
10. All the calculations were performed using the program Gaussian 94, Revision C.2. See, Frish, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez,C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.
11. For CO addition, see Brown, H. C. *Acc. Chem. Res.* **1969**, *2*, 65; For the addition of CN^-, see Pelter, A.; Hutchings, M. G.; Smith, K. *J. Chem. Soc. Chem. Commun.* **1973**, 186; For the addition of 1-lithio-1,1-bis(phenylthio)alkane, see Hughes, R. J.; Neube, S.; Pelter, A.; Smith, K.; Negishi, Ei-chi; Yoshida, T. *J. Chem. Soc. Perkin Trans. 1* **1977**, 1172.
12. Gonikberg, E. M.; Picart, F.; le Noble, W. J. *J. Org. Chem.* **1996**, *61*, 9588; **1997**, *62*, 4885; Adcock, W.; Lunsmann, D.; Trout, N. A. *J. Org. Chem.* **1998**, *63*, 7231.
13. For a recent account of the diastereoselectivities of various systems including the 5-hetero-2-adamantanones, see, Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437.