COMMUNICATION

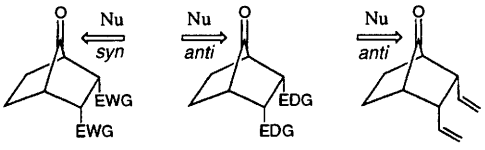
π-Face selectivities in nucleophilic additions to 2-*endo*-arylnorbornan-7-ones: the role of through-space electrostatic interactions

Goverdhan Mehta,*[a] Faiz Ahmed Khan,[a] Narinder Mohal,[a] I. N. Narayan Namboothiri,[b] P. Kalyanaraman[b] and Jayaraman Chandrasekhar*[b]

[a] *School of Chemistry, University of Hyderabad, Hyderabad 500 046, India*
[b] *Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*

Experimental diastereoselectivities in hydride reduction of 2-*endo*-arylnorbornan-7-ones and computed transition state energetics reveal that the facial selectivity in these systems is predominantly determined by repulsions between the approaching nucleophile and the electron cloud of the aryl ring.

The origin of π-face selectivity in nucleophilic additions to sterically unbiased ketones continues to be a topic of experimental and theoretical scrutiny and of intense on-going debate.[1] Numerous *endo*-substituted norbornanones have proved to be valuable substrates for delineating the contributions of electrostatic and orbital interactions at the transition state.[2,3] Studies of nucleophilic additions to norbornan-7-ones **1a,b** bearing different *endo*-substituents have

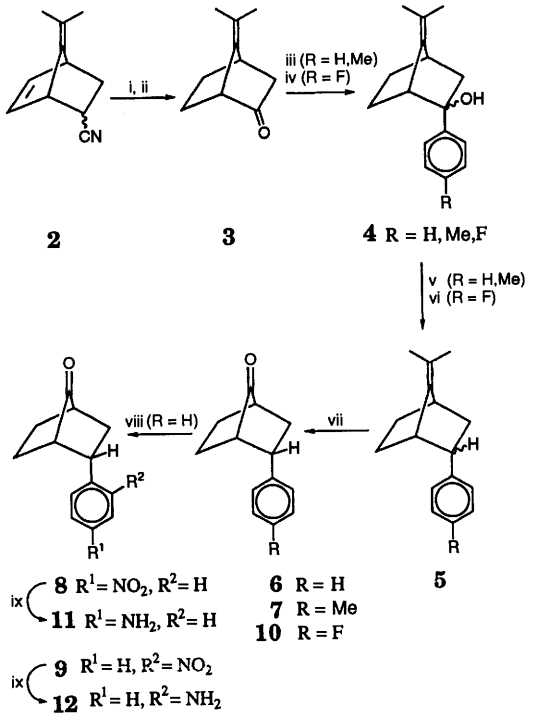


1a **1b** **1c**

shown that, while acceptor groups (EWG) are *syn*-directing, the donor groups (EDG) are *anti*-directing. However, stereoinduction at the C-7 carbonyl through the 2-*endo*-aryl group, which can serve as an important and incisive probe for evaluating stereoelectronic effects, has not been investigated. We reasoned that 2-*endo*-phenylnorbornan-7-one and some of its aryl-substituted derivatives could fine-tune face selectivity through the substituent-induced long-range orbital/electrostatic interactions. In addition, it was of interest to compare the stereoelectronic effect of the *endo*-phenyl group with the *endo*-vinyl group. We have previously shown [2a,c] that the 2-*endo*-vinyl compound **1c** prefers *anti*-face addition, contrary to the prediction based on the Cieplak model,[4] which favoured a *syn*-approach due to the inductively electron-withdrawing nature of the vinyl group. The observed *anti*-selectivity in **1c** could be reconciled in terms of the vinyl group either acting as a donor group [2a] or exercising considerable electrostatic repulsion on the *syn*-face, as revealed by MO calculations,[2c] to direct the nucleophile on the opposite-face.

In this context, the π-face selectivities in the 2-*endo*-aryl derivatives assume special significance and should complement the studies with the vinyl group. We now report the selectivities in nucleophilic additions to a number of 2-*endo*-arylnorbornan-7-ones and interpret the trends using MO calculations.

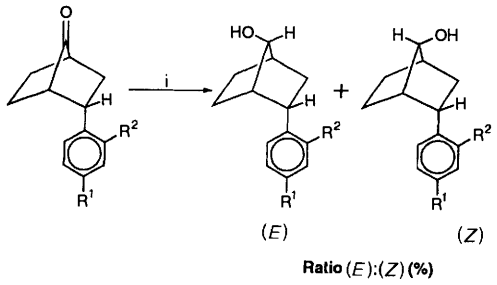
The 2-*endo*-arylnorbornan-7-ones are accessible, and short, straightforward but non-trivial syntheses of the seven substrates **6**–**12** were achieved from the 6,6-dimethylfulvene–acrylonitrile adduct **2** [5] *via* the bicyclic ketone **3** as shown in



Scheme 1 *Reagents and conditions:* i, $H_2NNH_2{\cdot}H_2O$, $CuSO_4{\cdot}5H_2O$, EtOH, room temp., 80%; ii, LDA, THF, O_2, −78 °C, $SnCl_2$–HCl, NaOH, 35%; iii, RC_6H_4Br, Li, THF, ultrasound, room temp., 50%; iv, *p*-FC_6H_4MgBr, THF, *ca.* 5 °C, 94%; v, Li, NH_3, THF, −78 °C, NH_4Cl, 90%; vi, ZnI_2, $NaCNBH_3$, $ClCH_2CH_2Cl$, room temp., 50%; vii, O_3, CH_2Cl_2, −78 °C, Me_2S, 60% for R = H, Me, 12% for R = F; viii, Fuming HNO_3, Ac_2O–$MeNO_2$ (1:1), room temp., 50%; ix, H_2, Pd–C (10%), EtOH–$CHCl_3$ (9:1), 76% for **11**, 70% for **12**

Scheme 1. In the aryl addition (**3** ⟶ **4**) as well as deoxygenation (**4** ⟶ **5**) steps, a *ca.* 3:1 mixture of *endo*:*exo* products was obtained. However, the desired 2-*endo*-arylnorbornan-7-ones **6**, **7** and **10**, obtained as major products, were readily isolated and characterized. Nitration of **6** furnished the *p*-nitrophenyl and *o*-nitrophenyl (2.5:1) derivatives **8** and **9**, respectively, which could also be readily separated. Reduction of **8** and **9** furnished the *p*-aminophenyl and *o*-aminophenyl derivatives **11** and **12**, respectively (Scheme 1). The *endo* stereochemistry of the 2-arylnorbornan-7-ones **6**–**12** was fully secured on the basis of the pronounced shielding of the transannularly poised C-6 carbon resonance by the C-2 substituent in the ^{13}C NMR spectra.

The 2-*endo*-arylnorbornan-7-ones **6**–**12** were subjected to $NaBH_4$ reduction to furnish in each case a mixture of two diastereomeric (*E*)-**6a**–**12a** and (*Z*)-**6b**–**12b** alcohols, respectively, in high yield (Scheme 2). The ratios of the products were determined by integration of the ^1H NMR spectra of the crude



		Ratio (E):(Z) (%)	
6	$R^1 = R^2 = H$	**6a** 45 : 55	**6b**
7	R^1 = Me, R^2 = H	**7a** 45 : 55	**7b**
8	$R^1 = NO_2$, R^2 = H	**8a** 58 : 42	**8b**
9	R^1 = H, $R^2 = NO_2$	**9a** 47 : 53	**9b**
10	R^1 = F, R^2 = H	**10a** 46 : 54	**10b**
11	$R^1 = NH_2$, R^2 = H	**11a** 40 : 60	**11b**
12	R^1 = H, $R^2 = NH_2$	**12a** 43 : 57	**12b**

Scheme 2 *Reagents and conditions:* i, $NaBH_4$, MeOH, 0–5 °C, >90%

reaction mixtures. The stereochemistry of the products in all the cases was determined unambiguously from the ^1H NMR spectra (see Spectroscopic data section) on the basis of greater deshielding (*ca.* 0.3 ppm) of *exo*-benzylic methine protons in (*Z*)-**6b–12b** alcohols compared with the corresponding (*E*)-**6a–12a** alcohols, for which there is ample precedence.[2] These experimental results indicate a small variation in face selectivities, but a definitive trend is discernible. While for **6**, **7** and **9–12** *anti*-approach leading to (*Z*)-alcohols is preferred, for the *p*-nitrophenyl derivative **8** *syn*-approach leading to (*E*)-alcohol dominates. It is significant that the *p*-nitrophenyl **8** and *o*-nitrophenyl derivative **9** exhibit opposite face-selectivities.

To understand the factors contributing to the observed trends, transition state structures for *syn*- and *anti*-addition of LiH to the ketones **6–12** were examined using semi-empirical MO theory. The structures with vanishing gradients and a single imaginary frequency for the vibrational mode corresponding primarily to hydride addition were determined at the MNDO[6] level. Similar calculations were also carried out for LiH addition transition states for the ketones **6–9** at *ab initio*[7] (3-21G basis) level. The energies of the latter geometries were also computed using the 6-31G* basis set at the Hartree–Fock and MP2 levels.

The face selectivity for **6** and **7** is not fully reproduced at the 3-21G level (Table 1). However, the direction of energy changes in the nitro derivatives is in agreement with the observed trends. The energy differences are overestimated throughout. Single point 6-31G* calculations lead to significantly reduced energy differences. Electron correlation corrections at the MP2 level do not lead to significant changes in the relative energies. Transition state optimization using the larger basis set is evidently needed to obtain reliable energy differences.

Remarkably, the computed relative energies of the *syn*- and *anti*-transition states at the MNDO level are in complete agreement with the experimental trends in face-selectivity (Table 1). For the phenyl derivative **6**, *anti*-face addition is predicted to be preferred. Introduction of a methyl, fluoro or amino substituent at the *para*-position has only marginal effect on the face selectivity. In contrast, the *para*-nitro group reverses the facial preference. The Boltzmann distribution corresponding to the small computed energy differences is also consistent with the magnitude of the observed stereoselectivities in these systems.

The computed preferences at the MNDO level were further probed using the computational model proposed earlier and designed to help interpretation.[2c] Energies of model transition states with a point negative charge placed at 1.4 Å from the carbonyl carbon (deliberately chosen to highlight preferences resulting from electrostatics) lead to a large *anti* preference (2.38 kcal mol^{-1}) for **6**. Use of a hydride ion as a probe to include orbital effects leads to the same preference but with a smaller energy difference (0.25 kcal mol^{-1}). Evidently, electrostatic repulsion between the electron-rich phenyl group and the negative charge approaching from the *syn*-face compete and overwhelm Cieplak-type hyperconjugative interactions which would favour *syn*-addition in the case of an inductively electron-withdrawing phenyl substituent. A similar interpretation was considered for the vinyl derivative earlier.[2] The present study provides further insights. It is possible to modulate the repulsion due to the electron-rich aryl group through remote substitution. At the distal *para*-position, the nitro group can reduce the electrostatic repulsion offered by the phenyl ring, so that Cieplak-type orbital interactions can dictate the facial selectivity. Additional evidence for the direct electrostatic repulsion between the nucleophile and the *endo* substituent comes from the result for the *o*-nitro derivative. Although the aryl ring is depleted of electron density, the large negative charge on the oxygen atoms deters the *syn*-approach of the nucleophile leading to the observed *anti*-face preference. However, the *p*- and *o*-aminophenyl derivatives **11** and **12** exhibit selectivities in concordance with the expectation that

Table 1 MNDO heats of formation, *ab initio*[a] total energies (Hartree) and *syn–anti* differences of transition states of LiH addition to 2-*endo*-arylnorbornan-7-ones

		Heats of formation/kcal mol^{-1}		
Substrate	Level	*syn* (*Z*)	*anti* (*E*)	*E*(*syn* − *anti*)/kcal mol^{-1}
6	MNDO	23.91	23.70	0.21
	HF/3-21G	−580.061 33	−580.060 38	−0.59
	HF/6-31G*	−583.294 32	−583.294 25	−0.04
	MP2/6-31G*	−585.157 36	−585.157 03	−0.21
7	MNDO	16.00	15.80	0.20
	HF/3-21G	−618.881 99	−618.881 14	−0.53
	HF/6-31G*	−622.331 17	−622.331 25	−0.05
	MP2/6-31G*	−624.328 05	−624.327 84	−0.13
8	MNDO[b]	39.70	39.86	−0.16
	HF/3-21G	−782.356 00	−782.354 02	−1.24
	HF/6-31G*	−786.759 88	−786.758 93	−0.59
	MP2/6-31G*	−789.168 00	−789.166 93	−0.67
9	MNDO[b]	53.83	52.65	1.18
	HF/3-21G	−782.336 55	−782.348 87	7.73
	HF/6-31G*	−786.739 50	−786.748 81	5.84
	MP2/6-31G*	−789.155 59	−789.163 60	5.03
10	MNDO	23.65	23.38	0.27
11	MNDO	28.36	28.06	0.30
12	MNDO	−23.23	−23.42	0.19

[a] Using geometries optimized at the 3-21G level. [b] The nitro group was constrained to be in the plane of the phenyl ring.

the more electron-rich aromatic ring will generate enhanced electrostatic repulsion on the *syn*-face.

The above interpretations are also consistent with the contrasting face-selectivities observed for **6** and 5-phenyladamantanone and point to the subtleties associated with long range electronic effects. The observed *syn*-selectivity in 5-phenyladamantanone (58:42) is the opposite of that observed for 2-phenylnorbornanone (45:55). In 5-aryladamantanones, the substituent is one bond further removed from the reaction centre. Hence, through-space repulsion from the phenyl group towards the reagent approaching from the *syn*-face would be less effective. Cieplak-type hyperconjugative interactions expected from the inductively electron-withdrawing phenyl group would then lead to the observed *syn*-selectivity.[8] In consonance with this interpretation, the *p*-nitrophenyladamantanone shows enhanced *syn*-face preference.

In summary, the variations in the face selectivities during hydride addition to 2-*endo*-arylnorbornyl derivatives **6–12** are best interpreted in terms of subtle changes induced in the direct electrostatic response of the distal aryl substituent to the approaching nucleophile.

Spectroscopic data

All new compounds were characterized on the basis of ^1H and ^{13}C NMR and mass spectral/elemental analyses data.

Compound 6a. ^1H NMR (200 MHz, $CDCl_3$): δ 7.41–7.20 (m, 5 H), 4.27 (s, 1 H), 3.33–3.22 (m, 1 H), 2.30–2.26 (m, 1 H), 2.21–1.85 (series of m, 2 H), 1.72–1.25 (series of m, 5 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 142.59, 128.36 (2 C), 128.05 (2 C), 125.75, 80.65, 46.80, 41.95, 41.50, 32.03, 27.05, 20.11 (Calc. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.79; H, 8.50%).

Compound 6b. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5 H), 4.27 (s, 1 H), 3.83–3.66 (m, 1 H), 2.42–2.10 (series of m, 3 H), 1.71–1.20 (series of m, 5 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 142.92, 128.33 (2 C), 128.03 (2 C), 125.56, 81.60, 46.60, 42.09, 41.59, 31.42, 27.08, 20.59; *m/z* 188 (M^+) (Calc. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.85; H, 8.54%).

Compound 7a. ^1H NMR (200 MHz, $CDCl_3$): δ 7.12–7.03 (m, 4 H), 4.26 (s, 1 H), 3.29–3.21 (m, 1 H), 2.37 (s, 3 H), 2.36–1.21 (series of m, 8 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 139.49, 134.97, 128.8 (2 C), 127.91 (2 C), 80.66, 46.58, 41.68, 41.58, 32.16, 27.09, 20.90, 20.10.

Compound 7b. ^1H NMR (200 MHz, $CDCl_3$): δ 7.26–7.09 (m, 4 H), 4.26 (s, 1 H), 3.77–3.66 (m, 1 H), 2.37 (s, 3 H), 2.36–2.09 (series of m, 3 H), 1.67–1.25 (series of m, 5 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 139.78, 135.03, 128.79 (2 C), 128.27 (2 C), 81.67, 46.60, 41.70, 41.61, 31.60, 27.13, 20.93, 20.62; *m/z* 202 (M^+).

Compound 8a. ^1H NMR (200 MHz, $CDCl_3$): δ 8.19–8.15 (d, *J* 8,† 2 H), 7.35–7.31 (d, *J* 8, 2 H), 4.30 (s, 1 H), 3.42–3.30 (m, 1 H), 2.35 (m, 1 H), 2.21–1.19 (series of m, 7 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 150.84, 146.30, 128.77 (2 C), 123.35 (2 C), 80.37, 46.62, 42.19, 41.40, 32.17, 27.03, 20.21; *m/z* 233 (M^+).

Compound 8b. ^1H NMR (200 MHz, $CDCl_3$): δ 8.19–8.15 (d, *J* 8.0, 2 H), 7.43–7.39 (d, *J* 8.0, 2 H), 4.30 (s, 1 H), 3.88–3.80 (m, 1 H), 2.50–2.13 (series of m, 3 H), 1.76–1.10 (series of m, 5 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 151.64, 146.02, 129.05 (2 C), 123.30 (2 C), 81.24, 46.60, 42.57, 41.57, 31.66, 27.05, 20.60; *m/z* 233 (M^+).

Compound 9a. ^1H NMR (200 MHz, $CDCl_3$): δ 7.72–7.30 (m, 4 H), 4.28 (s, 1 H), 3.65–3.60 (m, 1 H), 2.40 (m, 1 H), 2.15 (m, 1 H), 2.10–1.21 (series of m, 6 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 151.42, 136.24, 131.53, 129.45, 126.78, 124.09, 80.61, 46.48, 41.20, 37.77, 32.41, 26.89, 20.29.

Compound 9b. ^1H NMR (200 MHz, $CDCl_3$): δ 7.71–7.33 (m, 4 H), 4.29 (s, 1 H), 4.20–4.01 (m, 1 H), 2.45–1.21 (series of m, 8 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 151.76, 136.74, 131.40, 129.74, 126.58, 124.06, 81.56, 46.44, 41.31, 38.07, 32.13, 26.80, 20.75; *m/z* 216 ($M^+ + 1 - H_2O$).

Compound 10a. ^1H NMR (200 MHz, $CDCl_3$): δ 7.25–6.90 (m, 4 H), 4.20 (s, 1 H), 3.35–3.19 (m, 1 H), 2.25–1.20 (series of m, 8 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 161.2, 138.12, 129.28 (2 C), 114.79 (2 C), 80.55, 46.81, 41.49, 41.26, 32.36, 27.03, 20.00; *m/z* 206 (M^+).

Compound 10b. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–6.90 (m, 4 H), 4.27 (s, 1 H), 3.75–3.69 (m, 1 H), 2.41–1.20 (series of m, 8 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 161.13, 138.49, 129.36 (2 C), 114.74 (2 C), 81.53, 46.60, 41.58, 41.42, 31.81, 27.08, 20.46; *m/z* 206 (M^+).

Compound 11a. ^1H NMR (200 MHz, $CDCl_3$): δ 6.99–6.95 (d, *J* 8.0, 2 H), 6.68–6.64 (d, *J* 8, 2 H), 4.23 (s, 1 H), 3.20–3.05 (m, 1 H), 2.15–1.20 (series of m, 8 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 144.17, 132.59, 128.82 (2 C), 115.06 (2 C), 80.68, 46.95, 41.53, 41.18, 32.27, 27.08, 20.02 (Calc. for $C_{13}H_{17}NO$: C, 76.66; H, 8.43; N, 6.89. Found: C, 76.78; H, 8.44; N, 6.82%).

Compound 11b. ^1H NMR (200 MHz, $CDCl_3$): δ 7.07–7.03 (d, *J* 8.0, 2 H), 6.69–6.65 (d, *J* 8.0, 2 H), 4.25 (s, 1 H), 3.79–3.62 (m, 1 H), 2.29–1.20 (series of m, 8 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 144.04, 132.79, 129.10 (2 C), 115.09 (2 C), 81.70, 46.65, 41.58, 41.24, 31.69, 27.13, 20.53 (Calc. for $C_{13}H_{17}NO$: C, 76.66; H, 8.43; N, 6.89. Found: C, 76.72; H, 8.40; N, 6.85%).

Compound 12a. ^1H NMR (200 MHz, $CDCl_3$): δ 7.18–7.14 (d, *J* 8.0, 1 H), 7.06 (t, *J* 7.8, 1 H), 6.81 (t, *J* 7.8, 1 H), 6.70–6.66 (d, *J* 8.0, 1 H), 4.35 (s, 1 H), 3.40–3.20 (m, 1 H), 2.39–1.35 (series of m, 8 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 144.78, 127.40, 126.84, 126.04, 118.41, 115.86, 81.03, 46.69, 44.04, 41.36, 37.08, 26.77, 20.47; *m/z* 203 (M^+).

Compound 12b. ^1H NMR (200 MHz, $CDCl_3$): δ 7.26–7.01 (m, 2 H), 6.82–6.65 (m, 2 H), 4.30 (s, 1 H), 3.80–3.60 (m, 1 H), 2.71–1.30 (series of m, 8 H); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 144.80, 127.67, 126.80, 126.67, 118.33, 115.81, 81.85, 43.49, 41.45, 37.00, 30.54, 26.90, 20.91; *m/z* 203 (M^+).

† *J* Values given in Hz.

Acknowledgements

F. A. K. and N. M. thank CSIR for the award of research fellowships. We thank Mr M. Praveen for carrying out some preliminary experiments and Drs S. Lalitha and B. Ganguly for computational help.

References

1 (*a*) Review: B. W. Gung, *Tetrahedron*, 1996, **52**, 5263; (*b*) W. Adcock, J. Cotton and N. A. Trout, *J. Org. Chem.*, 1994, **59**, 1867 and references cited therein.

2 (*a*) G. Mehta and F. A. Khan, *J. Am. Chem. Soc.*, 1990, **112**, 6140; (*b*) G. Mehta and M. Praveen, *Tetrahedron Lett.*, 1992, **33**, 1759; (*c*) B. Ganguly, J. Chandrasekhar, F. A. Khan and G. Mehta, *J. Org. Chem.*, 1993, **58**, 1734; (*d*) G. Mehta, F. A. Khan, B. Ganguly and J. Chandrasekhar, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2275.

3 M. N. Paddon-Row, Y.-D. Wu and K. N. Houk, *J. Am. Chem. Soc.*, 1992, **114**, 10 638.

4 (*a*) A. S. Cieplak, *J. Am. Chem. Soc.*, 1981, **103**, 4540; (*b*) A. S. Cieplak, B. Tait and C. R. Johnson, *J. Am. Chem. Soc.*, 1989, **111**, 8447.

5 K. Alder, R. Ruhmann, *Leibigs Ann. Chem.*, 1950, **566**, 1.

6 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899.

7 GAUSSIAN 92, Revision E.3, M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. DeFrees, J. Baker, J. J. P. Stewart and J. A. Pople, Gaussian Inc., Pittsburgh PA, 1992.

8 The opposite face selectivities observed for 2-*endo* arylnorbornanones and 5-aryladamantanones can also be interpreted in terms of the earlier proposal of through-bond orbital interaction involving the aryl ring and the adjacent σ-bond of the norbornyl unit [ref. 2(*a*)].

Paper 6/05469B
Received 5th *August* 1996
Accepted 24th *September* 1996