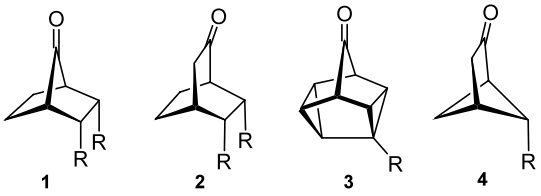
The tricyclo[2.1.0.0^{2,5}]pentan-3-one system: a new probe for the study of π-facial selectivity in nucleophilic additions

Goverdhan Mehta,[a,*] S. Robindro Singh,[a] U. Deva Priyakumar[b] and G. Narahari Sastry[b,*]

[a]*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*
[b]*Molecular Modelling Group, Organic Chemical Sciences, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

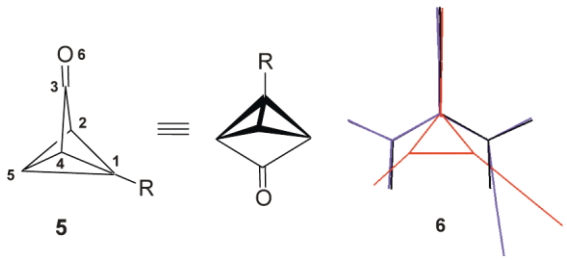
Abstract—Monosubstituted tricyclo[2.1.0.0^{2,5}]pentan-3-one derivatives have been synthesised and subjected to hydride reduction. Quite unexpectedly and in contrast to earlier observations in related systems, *anti*-selectivity has been encountered in these substrates. Computational studies employing various models reproduce the observed facial preference and indicate that the causative factor for the *anti*-preference could be the polarization of the C1–C5 strained σ bond.

Control of diastereoselectivity during nucleophilic additions to carbonyl groups is a key issue in stereogenesis. It is now well recognised that both steric and long range electronic effects can profoundly influence π-face selection during addition to the carbonyl group.[1] While the role of steric effects in determining face-selectivity is quite predictable, the precise nature, effectiveness and predictability of remote electronic effects in determining π-face selectivity is still a matter of ongoing scrutiny and debate.[1,2] Efforts from our group and of others over the past decade have focussed on studying systems where the two faces of the carbonyl group are virtually in an isosteric environment but are amenable to long range electronic perturbation.[3] These approaches have enabled the segregation of steric effects from electronic effects and firmly established the role of the latter in influencing π-face selection.[3,4] For example, we have reported that in *endo* substituted bicyclo[2.2.1]heptan-7-ones **1**[3a,b] and bicyclo[2.2.2]octan-2-ones **2**,[3c] 4-substituted-9-nor snoutanone **3**[3d] and 5-*exo*-substituted-bicyclo[2.1.1] hexan-2-ones **4**,[4] where the carbonyl group is in a sterically neutral disposition, distal substituents (R) can significantly influence the stereochemical outcome (*syn*- versus *anti*-addition). The issue of concern now is the delineation of the precise nature of the electronic effects operating in these systems. Several explanations based on hyperconjugative interactions at the transition state (Cieplak effect), electrostatic effects, various orbital mixing/tilting effects and cation complexation, among others have been proffered to explain the various experimental data.[1–5] A scrutiny of the available experimental and computational data reveals that many of these electronic effects operate simultaneously, within a narrow energy range, either co-operatively or in opposition and their cumulative effect determines the observed π-face selectivities. Thus, elucidation and quantification of the subtle role of the various electronic factors that determine facial selectivity is still a challenge that mandates continued search and study of newer probe systems. As part of our continuing efforts in the area, we introduce tricyclo[2.1.0.0^{2,5}]pentan-3-one **5** as a new probe system wherein π-facial discrimination is introduced through the remote C-1 substituent (R).



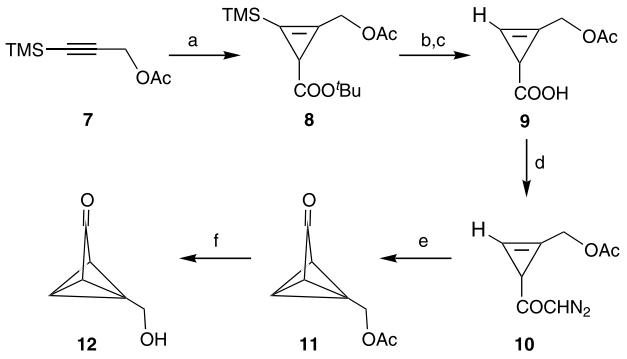
Besides having an isosteric environment around the carbonyl group as revealed by high level calculations and crystal structure data (vide infra), the overlay diagram (**6**) of **5** (R = CN, red) with the parent bicyclo[1.1.1]pentan-2-one (black) and its *endo*-4-cyanobicyclo[1.1.1]pentan-2-one derivative (blue) indicates that the skeleton of **5** is much more strained (cf. **1**–**4**) and the C1 substituent does not come in the way of the trajectory of the approaching nucleophile. Interestingly,

* Corresponding authors. E-mail: gm@orgchem.iisc.ernet.in

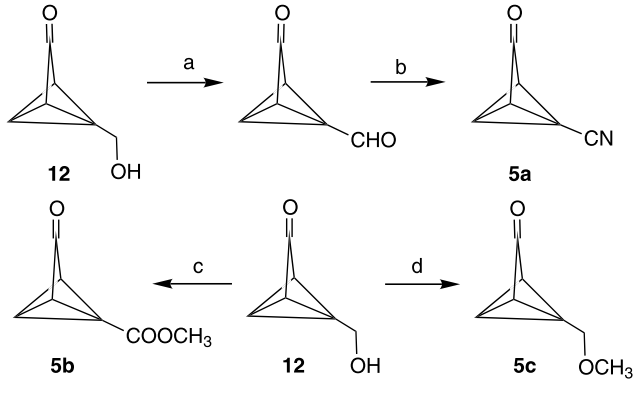


the electronic effects of the C1 substituent in **5** are transmitted through the connecting cyclopropane bonds. Further, the stereo-differentiating C1 and C5 carbons in **5** are connected through a unique bond which is the central bond of the bicyclo[1.1.0]butane moiety embedded in it (see bold). Thus, a study of face selection in derivatives of **5** was of intrinsic interest and we wish to report here the results of experimental and computational studies on this system.

Our initial task was to access derivatives of **5**. However, a literature search revealed that C1 monosubstituted derivatives of tricyclo[2.1.0.$0^{2,5}$]pentan-3-one **5** are not



Scheme 1. *Reagents and conditions*: (a) N_2CHCOO^tBu, $Rh_2(OAc)_4$, rt 50–60%; (b) TBAF, THF, 0°C, 2 h, 75%; (c) TFA, 0°C, 1.5 h, 80%; (d) i. $(COBr)_2$, ether, 0°C, 4 h; ii. CH_2N_2, ether, −78°C, 24 h, 50% (two steps); (e) $Rh_2(OAc)_4$, $CHCl_3$, 60°C, 1 h, 30%; (f) K_2CO_3, MeOH, rt, 4 h, 85%.



Scheme 2. *Reagents and conditions:* (a) PDC, CH_2Cl_2, 4 h, 90%; (b) i. $NH_2OH{\cdot}HCl$, py, CH_2Cl_2, 1 h; ii. TsCl, py, 0°C–rt, 36 h, 50% (two steps); (c) i. RuO_2–$NaIO_4$, acetone–H_2O (1:1), 2 days; ii. CH_2N_2, 0°C, 15 min 50% (two steps); (d) CH_3I, Ag_2O, CH_2Cl_2, 2 days, 85%.

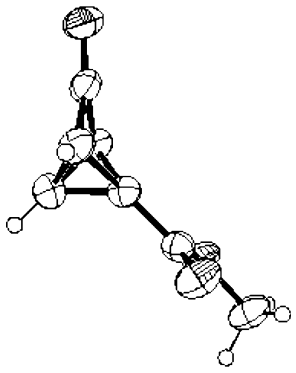
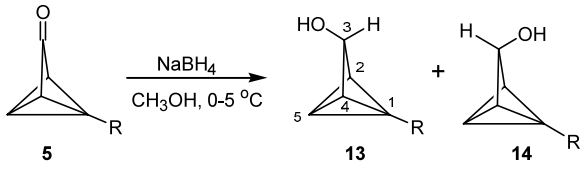


Figure 1. ORTEP diagram of **5b**.



		(E)-	*(Z)*-
a	R = CN	43%	57%
b	R = COOMe	47%	53%
c	R = CH_2OCH_3	35%	65%

Scheme 3.

known.[6] Therefore, a new synthesis of the C1 monosubstituted tricyclo[2.1.0.$0^{2,5}$]pentan-3-ones was developed as shown in Scheme 1 and was based on earlier approaches to this ring system.[7] We selected three monosubstituted derivatives **5a**–**c** for the present study.

Careful addition of *tert*-butyl diazoacetate to an excess of TMS-protected 2-propynyl acetate **7** in the presence of dirhodium(II) tetraacetate catalyst resulted in controlled nitrogen evolution and formation of cyclopropene **8**.[8] Protodesilylation and hydrolysis of the ester group in **8** led to cyclopropene carboxylic acid **9** (Scheme 1). Carboxylic acid **9** was elaborated to the α-diazoketone **10** for an intramolecular [2+1]-cycloaddition. Decomposition of **10** in the presence of the $Rh_2(OAc)_4$ catalyst furnished the tricyclic ketone **11** which was further hydrolysed to the hydroxymethyl derivative **12**[8] (Scheme 1). The hydroxymethyl bearing tricyclic ketone was elaborated to the desired derivatives **5a**–**c** as shown in Scheme 2. These transformations were devised to avoid any carbonyl group protecting manoeuvres in view of the extreme sensitivity and volatility of the substrates. At this stage an X-ray crystal structure determination of **5b** was carried out (Fig. 1)[9] to secure the structures and confirm that the two faces of the carbonyl group were in a near iso-steric environment. Tricyclic ketones **5a**–**c** were subjected to sodium borohydride reduction to furnish (*E*)-**13a**–**c** and (*Z*)-**14a**–**c** alcohols in nearly quantitative yields (Scheme 3). The observed diastereoselectivities (*E*:*Z* ratio) are displayed in the Scheme and were determined through ^{1}H NMR analyses.

The stereostructures of **13a–c** and **14a–c** were unambiguously determined on the basis of the relative deshielding (ca. 0.2 ppm) of the H(5) protons in the (*E*)-alcohols **13a–c** compared to the (*Z*)-alcohols **14a–c**. Additionally, the H(5) proton in (*E*)-**13a–c** appeared as a diagnostic doublet ($J = \sim 7.5$ Hz) due to long range (4 bond) coupling with the *syn*-H(3) proton and could be readily recognised.

The stereoselectivities observed during hydride reduction of **5a–c** exhibit a small preference for the *anti*-face addition but this result is in contrast with the trend observed earlier with related systems.[1–4] We have consistently encountered *syn* face preference of the remote electron withdrawing substituents such as cyano and ester in the systems **1–4**, among others, studied so far.[3] To understand the underlying reasons for this unexpected deviation, tricyclic ketones **5a–c** were studied computationally employing five different models. Orbital and electrostatic effects were assessed employing the hydride and charge models as described earlier, i.e. by placing an H^- ion and a negative point charge, respectively, at a distance of 1.4 Å away from the carbonyl carbon along the trajectory perpendicular to the π-plane.[3b] The LiH transition states (Table 1) were characterized as saddle points through geometry optimizations followed by frequency calculations.[5b] Semiempirical calculations were performed using the AM1 Hamiltonian.[10] The NBO analysis[11] and cation complexation models (Table 2)[5c] were investigated at the B3LYP/6-31G* level of theory.[12] Interestingly, all five models employed in the present study (see Tables 1 and 2) predict addition from the *anti*-face in agreement with the experimental results.

Table 1. The relative energy for *syn* and *anti* face additions calculated using the charge, hydride and LiHTS models at AM1 level of theory.[a] All values are given in kcal/mol

Structure	Charge		Hydride		LiHTS	
	syn	*anti*	*syn*	*anti*	*syn*	*anti*
5a	12.21	0.00	0.61	0.0	1.18	0.00
5b	9.13	0.00	0.76	0.00	1.72	0.00
5c	4.73	0.00	0.06	0.00	0.40	0.00

[a] A value of 0.0 denotes the preference of the corresponding face addition.

Table 2. The principal dihedral angles (in degrees) in the proton complexed reactant[a,b] and interaction energy (kcal/mol) of the σ bond antiperiplanar to the incipient C–H bond in the *syn* and *anti* sides of **5** and the $\pi^*_{C=O}$ of the reactant obtained at the B3LYP/6-31G* level

Comp.	*syn*		*anti*		NBO	
	D1	D2	D3	D4	*syn*	*anti*
5a	123.5	121.2	177.9	175.7	13.80	9.90
5b	119.8	116.6	173.7	171.2	13.32	10.66
5c	119.8	116.0	173.1	170.8	12.11	12.74

[a] D1, D2, D3 and D4 are the dihedral angles ∠6-3-4-1, ∠6-3-2-1, ∠6-3-4-5 and ∠6-3-2-5, respectively.

[b] If D1>D3 and D2>D4, *syn* attack is preferred; if D3>D1 and D4>D2, *anti* attack is preferred.

The unexpected and seemingly contra-intuitive diastereoselection observed in the case of **5a–c** may be attributed to charge polarization induced by an electron-withdrawing substituent on the central σ bond of the bicyclobutane moiety (see bold in **5**). Thus, the polarized C_1–C_5 bond renders a δ^+ on C-5 to facilitate the *anti* attack of the nucleophile.

The high preference for *anti*-selectivity in the charge model (Table 1) may be directly traced to the overriding electrostatic influence, effectively countering the opposing orbital interactions. The LiHTS model and hydride models (Table 1) also reproduce the observed *anti*-selectivity but the small magnitude of such preference is perhaps more realistic. The NBO analysis (except in **5c**) and cation complexation model calculations summarized in Table 2 also support the *anti*-preference observed in **5a–c**.

If the contention that the *anti*-selectivity observed in **5a–c** is due to the polarization of the central cyclobutane bond C1–C5 is valid, then the removal of this bond should restore the commonly observed *syn*-preference. Indeed, we tested all the above computational models with the model compound *endo*-4-cyanobicyclo[1.1.1]pentan-2-one and found complete reversal and prediction of the expected *syn*-selectivity. Efforts are underway to experimentally validate this prediction.[13]

In summary, we have devised a synthesis of 1-substituted tricyclo[2.1.0.$0^{2,5}$]pentan-3-ones **5a–c**, with the carbonyl group positioned in a near iso-steric environment, and introduced these substrates as a new probe system for studying π-face selectivity during nucleophilic additions. The small *anti*-preference observed for the hydride addition to **5a–c** is quite unexpected and a departure from earlier observations in related systems. Computational studies reproduce the observed selectivities and indicate that polarization of the C1–C5 bond and the resulting electrostatic interaction as the possible causative factor.

Acknowledgements

R.S. and U.D.P. thank CSIR and UGC, respectively, for the award of research fellowships.

References

1. For recent reviews on diastereoselection, see a thematic issue: (a) *Chem. Rev.* **1999**, *99*, 1069–1480; (b) Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437.
2. Mehta, G.; Khan, F. A. *Tetrahedron Lett.* **1992**, *33*, 3065.
3. (a) Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140; (b) Ganguly, B.; Chandrasekhar, J.; Khan, F. A.;

Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734; (c) Mehta, G.; Khan, F. A.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1711; (d) Mehta, G.; Ravikrishna, C.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1997**, 75; (e) Mehta, G.; Ravikrishna, C.; Kalyanraman, P.; Chandrasekhar, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1895; (f) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690; (g) Ohwada, T. *J. Am. Chem. Soc.* **1992**, *114*, 8818; (h) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 117678; (i) Fraser, R. R.; Faibish, N. C.; Kong, F.; Bednarski, F. *J. Org. Chem.* **1997**, *62*, 6164; (j) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199; (k) Mehta, G.; Gagliardini, V.; Priyakumar, U. D.; Sastry, G. N. *Tetrahedron Lett.* **2002**, *43*, 2487.

4. Mehta, G.; Singh, S. R.; Gagliardini, V.; Priyakumar, U. D.; Sastry, G. N. *Tetrahedron Lett.* **2001**, *42*, 8527.
5. (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540; (b) Paddow-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638; (c) Jeyaraj, D.; Yadav, A. A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 4483.
6. Levin, M. D.; Kaszynski, P.; Michl, J. *Chem. Rev.* **2000**, *100*, 169.
7. (a) Doering, W.v. E.; Pomerantz, M. *Tetrahedron Lett.* **1964**, *5*, 961; (b) Maier, G.; Resinauer, H. P.; Freitag, H. A. *Tetrahedron Lett.* **1978**, *19*, 121; (c) Dowd, P.; Garner, P.; Schappert, R.; Irngartinger, H.; Goldman, A. *J. Org. Chem.* **1982**, *47*, 4240; (d) Irngartinger, H.; Reimann, W.; Garner, P.; Dowd, P. *J. Org. Chem.* **1988**, *53*, 3046.
8. All new compounds reported here were fully characterized on the basis of complementary spectroscopic (IR, ^{1}H and ^{13}C NMR and MS) and analytical data. Except in the case of the **13c**, all the diastereomers were separated and individually characterized. Selected spectral data. **8**: IR (cm^{-1}) 1751, 1722; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (1/2ABq, $J=16$ Hz, 1H), 5.02 (1/2ABq, $J=16$ Hz, 1H), 2.10 (s, 4H), 1.37 (s, 9H), 0.20 (s, 9H); ^{13}C (75 MHz, $CDCl_3$): δ 175.0, 170.3, 122.1, 108.2, 79.5, 59.4, 28.0, 22.5, 20.7, −1.7; Mass: m/z 241 (M^+–Ac), 211 (M^+–$SiMe_3$). **9**: IR (cm^{-1}) 3148, 1784, 1743, 1698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H), 5.06 (brs, 2H), 2.33 (s, 1H), 2.12 (s, 3H); ^{13}C (75 MHz, $CDCl_3$): δ 181.5, 170.3, 110.3, 97.8, 57.5, 20.5, 20.0; Mass: m/z 111 (M^+–CO_2H), 114 (M^++1–Ac). **11**: IR (cm^{-1}) 1782, 1744; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.04 (s, 2H), 4.17 (s, 1H), 2.22 (s, 2H), 2.11 (s, 3H); ^{13}C (75 MHz, $CDCl_3$): δ 182.5, 170.7, 56.2, 40.1 (2C), 20.7, 11.0, 3.4; Mass: m/z 153 (M^++1). **12**: IR (cm^{-1}) 3401, 1763; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.65 (s, 2H), 4.15 (s, 1H), 2.20 (s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 183.5, 54.7, 39.2 (2C), 13.6, 3.6; Mass: m/z 111 (M^++1). **5a**: IR (cm^{-1}) 2241, 1805; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74 (s, 1H), 2.8 (s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 177.3, 111.7, 46.6 (2C), 29.6, 7.6. **5b**: IR (cm^{-1}) 1794, 1729; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.53 (s, 1H), 3.85 (s, 3H), 2.68 (s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 179.7, 166.1, 52.8, 44.0 (2C), 10.6, 8.6; Mass: m/z 107 (M^+–OMe). **5c**: IR (cm^{-1}) 1778; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.43 (s, 2H), 4.14 (s, 1H), 3.45 (s, 3H), 2.2 (s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 183, 63.7, 58.4, 39.5 (2C), 10.5, 2.9; Mass: m/z 147 (M^++Na). **14a**: IR (cm^{-1}) 3397, 2226; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (d, $J=10.2$ Hz, 1H), 4.0 (s, 1H), 2.76 (d, $J=10.2$ Hz, 1H), 2.64 (s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 116.1, 86.4, 40.1 (2C), 13.19, 8.77; Mass: m/z 130 (M^++Na). **14b**: IR (cm^{-1}) 1714, 3415; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11 (s, 1H), 3.75 (s, 3H), 3.69 (s, 1H), 2.69 (s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 170.9, 84.3, 51.9, 40.1 (2C), 24.4, 16.3; Mass: m/z 141 (M^++1). **13a**: IR (cm^{-1}) 3394, 2226; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.48 (t, $J=7.5$ Hz, 1H), 4.17 (d, $J=6.6$ Hz, 1H), 2.61 (s, 2H), 2.44 (d, $J=9.3$ Hz, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 115.6, 86.9, 39.2 (2C), 25.5, −2.78; Mass: m/z 130 (M^++Na). **13b**: IR (cm^{-1}) 1714, 3414; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.3 (m, 1H), 3.85 (d, $J=7.5$ Hz, 1H), 3.76 (s, 3H), 2.63 (s, 2H), 2.32 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 169.6, 86.0, 52.0, 39.2 (2C), 28.0, 12.8; Mass: m/z 141 (M^++1). **14c**: IR (cm^{-1}) 3398; ^{1}H NMR (300 MHz, $CDCl_3$), δ 4.1 (s, 3H), 3.5 (s, 3H), 3.2 (s, 1H), 2.0 (s, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 85.2, 68.1, 58.17, 32.9 (2C), 27.2, 4.5.
9. Crystal data for **5b**: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. Crystal system: triclinic, space group: P-1, cell parameters: $a=5.6956(22)$, $b=7628(30)$, $c=7.8045(30)$ Å, $\alpha=70.62(0)$, $\beta=88.50(1)$, $\gamma=87.93(1)°$, $V=325.27(22)$ Å^3, $Z=2$, ρ(calcd) $=1.4103$ g cm^{-3}, $F(000)=144$, $\mu=1.117$ mm^{-1}, $\lambda=0.71073$ Å. Total number of l.s. parameters $=115$. $R_1=0.0371$ for $F_o>4\sigma(F_o)$ and 0.0427 for all 1286 data. $wR_2=0.1016$, GoF $=1.052$, Restrained GoF $=1.052$ for all data. An ORTEP drawing of compound **5b** with 50% ellipsoidal probability has been displayed. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre (Reference number 203637).
10. Dewar, M. J. S.; Zoebisch, Z.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
11. NBO Version 3.1: Glendening, E. D.; Reed, A.; Carpenter, J. E.; Weinhold, F.
12. Gaussian 98, Revision A.11.2, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Rega, N.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 2001.
13. Unpublished results.