

4-Substituted norsnoutanones: a new probe system for evaluating electronic effects in π -facial selectivity in nucleophilic additions

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Remotely substituted norsnoutanone derivatives show significant and consistent π -face selectivity in nucleophilic additions, revealing the interplay of orbital and electrostatic effects.

Precise and predictable delineation of the various factors that can control π -face selectivities in additions to trigonal carbon centres has been a subject of intense scrutiny in recent years, as the desymmetrization of the two faces of the planar carbonyl/alkene group is a fundamental paradigm of stereoselective synthesis.¹ While the influence of steric factors in π -facial control is fairly well understood, the nature and role of the long range electronic effects (*e.g.* orbital vs. electrostatic) on face-selection is a matter of ongoing debate. In order to segregate the steric and electronic components, various research groups have devised substrates wherein the two π -faces are virtually isosteric with minimal conformational uncertainties and which can be electronically perturbed through distal modifications.^{2–4} Among the systems that have been examined in detail, the sterically unbiased 5-substituted adamantane-2-ones **1**⁴ and *endo*-substituted norbornan-7-ones **2**³ have provided valuable insights into the factors governing the π -face selectivity during nucleophilic additions. Yet the relative importance and subtle interplay of various electronic factors in controlling face-selectivity remains controversial,¹ thus underscoring the need to examine newer systems.

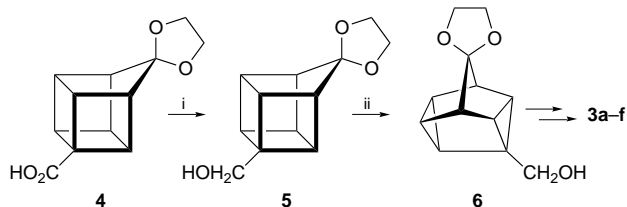
Herein we introduce 4-substituted norsnoutanone **3** (pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonan-9-one), a substrate with sterically unbiased π -faces and a distal substituent to desymmetrize and exert long range electronic perturbation, as a probe to study electronic control of face-selectivity. The pentacyclic system **3** has some interesting features and, in some ways, can be regarded as a hybrid of **1** and **2**. As the overlay diagram of the energy minimized **1–3** (R = CN) indicates, the substituent in **3** is farthest removed from the stereoinduction centre. Furthermore, the substituent at the 4-position in **3** is three bonds away (*cf.* three- and two-bond separation in **1** and **2**, respectively) from the C(9) carbonyl group, but it is linked through cyclopropane bonds which are expected to be better transmitters of electronic effects. Here we disclose our findings that in **3**, the C(4) substituent indeed exerts a dominant influence on the face-selectivity during nucleophilic additions. We also provide the results of calculated transition-state energetics for hydride addition to 4-substituted norsnoutanones that aid in the interpretation of the observed face-selectivities.

We have synthesized six derivatives **3a–f** for the present study from the homocubane-4-carboxylic acid ketal **4**. LAH reduction to **5** and Ag^I mediated rearrangement furnished the

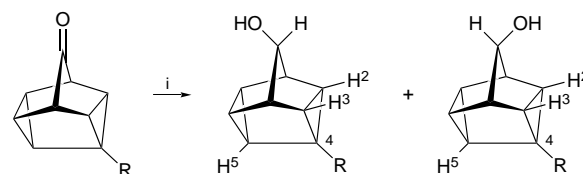
required framework **6**.⁵ The hydroxymethyl functionality in **6** was elaborated through unexceptional but multi-step functional group modifications to furnish **3a–f** (Scheme 1).⁶

Pentacyclic ketones **3a–f** were subjected to hydride reduction with sodium borohydride to furnish (*E*)-**7a–f** and (*Z*)-**8a–f** alcohols in near quantitative yield; the diastereoselectivities are shown in Scheme 2.⁶ The observed *E*:*Z* ratios were determined through ¹H NMR analyses and remained insensitive to changes in the reaction solvent. The stereostructures of **7a–f** and **8a–f** have been unambiguously deduced on the basis of (i) the deshielding (*ca.* 0.3 ppm) of H(5) in *E*-alcohols compared to *Z*-alcohols, (ii) the relative deshielding of the H(2) and H(3) protons in *Z*-alcohols compared to *E*-alcohols, and (iii) the deshielding (7–8 ppm) of the quaternary C(4) carbon resonances in the *Z*-series compared to *E*-series. These observations were further fortified through selected shift reagent (LIS) studies.

The observed diastereoselectivities (Scheme 2) indicate a profound effect and consistent trend in the face-selectivity induced by the remote C(4) substituent. While strong electron-withdrawing groups (*e.g.* cyano, ester) exhibit marked preference for the *syn*-face approach of the hydride to furnish the (*E*)-alcohols, such preference is diminished in the moderately electron-withdrawing substituents present in **3c–e**. In the case of the alkyl-substituted derivative **3f** there is a marginal preference for *anti*-face addition. While these observations are generally similar to those reported for the adamantane **1** and the norbornane **2** derivatives, there are two notable features. There is a marked increase in the face-selectivity in **3** (*cf.* for



Scheme 1 Reagents and conditions: i, LiAlH₄, THF, 82%; ii, Ag^I, MeOH, heat, 88%



3a R = CO ₂ Me	(<i>E</i>)- 7a 79%	(<i>Z</i>)- 8a 21%
b R = CN	b 84%	b 16%
c R = C≡CH	c 76%	c 24%
d R = CH=CH ₂	d 60%	d 40%
e R = CH ₂ OMe	e 56%	e 44%
f R = Et	f 48%	f 52%

Scheme 2 Reagents and conditions: i, NaBH₄, MeOH, 0–5 °C

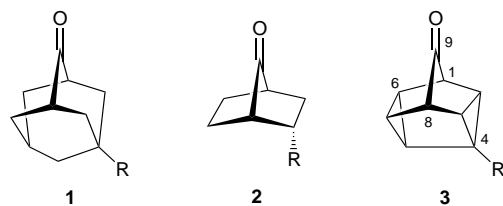


Table 1 MNDO Heats of formation, *ab initio* total energies and relative energies of LiH addition transition states to the *syn*- and *anti*- faces

	Heat of formation/kcal mol ⁻¹	<i>ab initio</i> Energy/E _h			
		MNDO	HF/3-21G	HF/6-31G*	MP2/6-31G*
		//MNDO	//HF/3-21G	//HF/3-21G	//HF/3-21G
3b (<i>anti</i>)	95.0	517.09150	519.98802	521.61734	
(<i>syn</i>)	94.5	517.09315	519.98947	521.61899	
Relative energy ^a /kcal mol ⁻¹	0.5	1.0	0.9 (0.4)	1.0 (0.5)	
3d (<i>anti</i>)	80.3	502.32468	505.13354	506.74174	
(<i>syn</i>)	80.2	502.32483	505.13358	506.74155	
Relative energy ^a /kcal mol ⁻¹	0.1	0.1	0.0 (0.2)	-0.1 (0.1)	

^a A positive value indicates *syn*-face addition transition state is more stable. Values in parentheses correspond to relative energies obtained by replacing LiH by a point charge at the location of the hydride.

Table 2 MNDO Relative energies for *syn* and *anti* face addition calculated using the charge and hydride models as well as with LiH addition transition state geometries for substituted adamantanonones, norbornanonones and norsnoutanonones^a

Substrate	Relative energy/kcal mol ⁻¹			Experimental <i>syn</i> : <i>anti</i> ratio ^b
	Charge	Hydride	Transition state	
1 R = CN	1.3	0.9	0.2	68:32
2 R = CN	1.8	1.4	0.5	88:12
3 R = CN	3.5	1.7	0.5	84:16
1 R = CH=CH ₂	-1.0	0.0	0.0	—
2 R = CH=CH ₂	-2.8	-0.4	-0.2	36:64 ^c
3 R = CH=CH ₂	1.0	0.5	0.1	60:40

^a A positive value indicates preference for *syn*-face addition. ^b For reduction with NaBH₄ or LiAlH₄. ^c For the divinyl derivative.

R = CO₂Me, *E*:*Z* ratios: 57:41 for **1**, 68:32 for **2** and 79:21 for **3**) despite the distal nature of the substituent. Another significant difference is that while the *endo*-vinyl and methoxymethyl substituents in the case of the norbornyl system **2** are, contrary to expectation based on Cieplak model, *anti*-directing, they are *syn*-directing in **3**, in keeping with the inductively withdrawing nature of these substituents.

To test some of the commonly used computational procedures for predicting face-selectivity and to interpret the observed results, transition-state energetics for LiH addition to two representative substrates **3b** and **3d** were calculated. Structures with vanishing gradients and a Hessian of 1 were optimized using MNDO⁷ and *ab initio* (3-21G basis)⁸ methods. Energies were also computed at HF and MP2 levels with the 6-31G* basis set.

At all levels of theory, the 4-cyano substituent in **3b** is correctly predicted to induce a clear *syn*-face selectivity for nucleophilic attack (Table 1). The energy differences are consistent with the observed product ratio. Much smaller relative energies (generally favouring *syn*-face addition) are computed for the vinyl derivative **3d**. The consistency of the MNDO procedure becomes evident when the results for **3d** are compared with those obtained for the *endo*-vinyl substituted norbornanone (Table 2). In the latter, *anti*-face addition is predicted to be favoured by 0.2 kcal mol⁻¹, as is indeed found experimentally.^{3a}

Two procedures were used to examine the electrostatic effects in these systems. The LiH unit in the *ab initio* optimized transition state was replaced by a point negative charge (magnitude the same as the Mulliken charge) at the hydride location. The corresponding relative energies computed with the 6-31G* basis set reflect the differences in the electrostatic response between the nucleophile and the substrate at the transition state. These values for **3b** are smaller than the transition state energy differences but, significantly, are in the

same direction (Table 1). Similar results were earlier obtained for the norbornanonones.⁹ An alternative approach^{3b} to modelling electrostatic effects through a point negative charge and a hydride ion at an assumed distance from the ground state geometry of the substrate provides further insights. Due to the inherent assumptions in these models, unambiguous but exaggerated energy differences are obtained. In all the derivatives considered, the hydride model yields the same facial-selectivity as the transition state relative energies (Table 2), while the charge model reproduces the general trends.

The observed and calculated results can be understood by considering three factors. Cieplak-type hyperconjugative interactions¹⁰ should favour *syn*-face addition in all the substrates with electron-withdrawing groups. Since these groups polarize the adjacent carbon atoms as well as the nearby *exo*-face hydrogen atoms, electrostatic interactions with the nucleophile would reinforce the *syn*-face preference. However, a direct through-space repulsive interactions between the nucleophile and the substituent is also possible, favouring *anti*-face approach. In the norbornanonones, all three factors are important and their relative contributions determine the observed *syn*-face preference for the cyano and *anti*-face attack in the vinyl derivatives. All the interactions are reduced in the adamantanone series. Interestingly, the direct interaction between the nucleophile and the substituent is effectively eliminated in the norsnoutanonones for geometric reasons. Hence, residual electrostatic and orbital effects favour *syn*-face approach in both **3b** and **3d**.

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