π-Facial selectivities in nucleophilic additions to 4-hetero-tricyclo[5.2.1.$0^{2,6}$]decan-10-ones and 4-hetero-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-ones: an experimental and computational study

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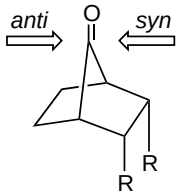
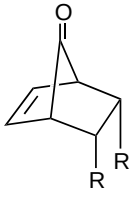
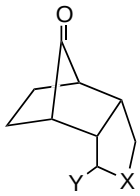
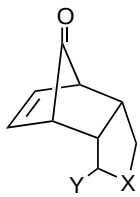
Abstract—Several *endo*-tricyclo[5.2.1.$0^{2,6}$]decan-10-ones and *endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-ones with hetero atom modifications at the distal C-4 position have been subjected to hydride reduction. π-Face selectivities in these systems are largely governed by the same electronic factors that were earlier identified in the case of the norbornyl system. A computational study demonstrates good predictability at the semi-empirical level.

Induction of face-selectivity in addition to the carbonyl group through remote electronic perturbations is an interesting way to achieve diastereoselectivity.[1] In carefully crafted systems, where the carbonyl group is placed in an isosteric environment, electronic modification at distal positions has led to significant levels of diastereoselectivity through face-selection during nucleophilic additions.[1,2] While the role of such electronic effects is now fairly well recognized, the precise nature of the causative factors and predictability remain a matter of debate and ongoing investigation. Explanations based on geometrical and orbital distortions,[3a] electrostatic effects,[3b] different types of specific orbital interactions (Felkin–Anh[3c] and Cieplak type[3d]), among others[3e,3f,3g,3h] have been proffered to explain the range of experimental data. Many of these effects operate









1 a. R=$COOCH_3$
b. R =CH_2CH_3
c. R=CH_2OCH_3

2 a. R=$COOCH_3$
b. R=CH_2CH_3
c. R=CH_2OCH_3

3. X=CH_2 Y=H
4. X=O Y=H
5. X=S Y=H
6. X=  Y=H
7. X=  Y=H
8. X=O Y= =O

9. X=CH_2 Y=H
10. X=O Y=H
11. X=S Y=H
12. X=  Y=H
13. X=  Y=H
14. X=O Y= =O

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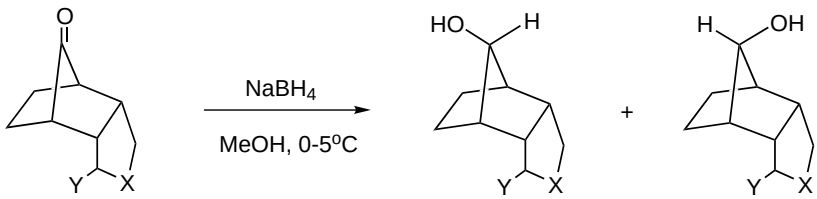
subtly and concurrently, within a narrow energy range, either in concordance or discordance and their cumulative effect determines the final outcome. Thus, prediction of face-selectivity is a difficult task and more experimental probes with subtle distal electronic modulation and convenient, useful models are needed to aid understanding and prediction of face selectivities.

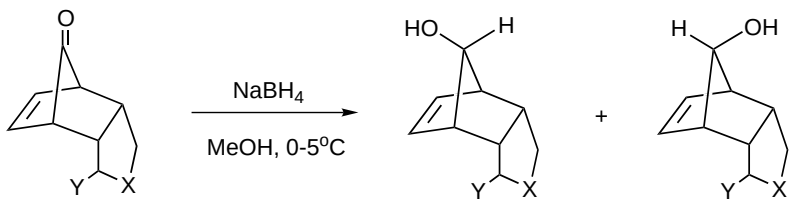
Sometime ago, we had introduced the *endo*,*endo*-disubstituted 7-norbornanone system as an incisive probe to explore face-selectivity and observed that while electron withdrawing substituents as in **1a** favor *syn*-face addition (84:16), alkyl groups as in diethyl derivative **1b** direct addition from the *anti*-face (80:20). In the case of the methoxymethyl derivative **1c**, there is a small preference for the *anti*-face addition (60:40).[2a,2b]

Similar, substituent effects on face selectivity were observed for the 7-norbornenone derivatives **2a**–**c**.[4] To forestall any conformational ambiguity and eliminate the possibility of the substituents in **1** and **2** interacting among themselves, we also studied[5] the rigid, *endo*-tricyclo[5.2.1.$0^{2,6}$]decan-10-one derivative **3**, wherein the *endo*-substituents are locked together and observed that it behaved essentially like the diethyl derivative **1b** with *anti*-selectivity (75:25). This observation spurred us to explore further the *endo*-tricyclo[5.2.1.$0^{2,6}$]decan-10-one system, particularly with heteroatom modification at the distal C-4 position.[6] This position is symmetrically positioned in the plane of the carbonyl group, bisecting the tricyclic framework and lies directly along the trajectory of the approaching nucleophile on the *syn*-face. Thus, it should be possible to detect direct electrostatic interaction, if any, between the nucleophile and the heteroatom in addition to other electronic effects. Herein, we report on the face selectivities exhibited by 4-hetero-*endo*-tricyclo[5.2.1.$0^{2,6}$]decan-10-ones **3**–**8** and the corresponding *endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-ones **9**–**14**.



3.	X=CH_2	Y=H	*E*- **15**	(25	:	75)	*Z*- **21**
4.	X=O	Y=H	**16**	(47	:	53)	**22**
5.	X=S	Y=H	**17**	(44	:	56)	**23**
6.	X=S(O)	Y=H	**18**	(42	:	58)	**24**
7.	X=S(O)	Y=H	**19**	(53	:	47)	**25**
8.	X=O	Y= =O	**20**	(84	:	16)	**26**

Scheme 1.



9.	X=CH_2	Y=H	*E*- **27**	(6	:	94)	*Z*- **33**
10.	X=O	Y=H	**28**	(15	:	85)	**34**
11.	X=S	Y=H	**29**	(10	:	90)	**35**
12.	X=S(O)	Y=H	**30**	(10	:	90)	**36**
13.	X=S(O)	Y=H	**31**	(17	:	83)	**37**
14.	X=O	Y= =O	**32**	(42	:	58)	**38**

Scheme 2.

Substrates **4**–**14** being new, were routinely synthesized following unambiguous, non-trivial routes.[7] Saturated tricyclic ketones **3**–**8** on reduction with sodium borohydride furnished (*E*)-**15**–**20** and (*Z*)-**21**–**26** alcohols in near quantitative yields (Scheme 1).[8] Similarly, the unsaturated counterparts **9**–**14** led to (*E*)-**27**–**32** and (*Z*)-**33**–**38** alcohols on hydride reduction (Scheme 2).[8] The observed diastereoselectivities (*E*:*Z* ratio) are displayed in the schemes and were determined through ^{1}H NMR analyses. All the diastereomers (*E*)-**15**–**20**, (*E*)-**27**–**32** and (*Z*)-**21**–**26**, (*Z*)-**33**–**38** were fully characterized and their stereostructures were unambiguously determined on the basis of NMR analyses, particularly through the relative deshielding of the protons underneath the hydroxyl group.

The stereoselectivities observed during hydride reduction of tricyclic ketones **3**–**14** are generally consistent with the trend observed earlier with the related norbornyl systems.[2a,2b,4] In the saturated series **3**–**8**, while **3** (*anti*-face) and **8** (*syn*-face) exhibit high and opposite stereoselectivity, simple hetero modification at C-4 as in **4**–**7** has only a marginal effect on the face selectivity. Even in the case of diastereomeric sulfoxides **6** and **7** which were specifically crafted to gauge the effect of directionality of the lone pair and oxygen on sulfur, the face selectivity variation is small. The same trend in the effect of distal substituent modification on face selectivities is observed in the case of the unsaturated series **9**–**14** (Scheme 2). While **9** exhibits highest *anti*-face selectivity, it is substantially diminished in the case of **14** and the rest of the substrates **10**–**13** show small reduction in *anti*-face preference compared to **9** (Scheme 2). Once again, these results closely parallel the observations in the saturated analogues (vide supra) and earlier findings with the norbornenone system.[4] Thus, C-4 heteroatom modification has only a modulatory role and is not the main determinant of face-selectivity in these tricyclic systems; its contribution is perhaps submerged among other dominant effects.

We have earlier proposed[2b] the economically attractive semi-empirical MNDO[9] method to discern the role of orbital and electrostatic effects in determining π-face selectivity using the hydride and charge models as well as the LiH transition states. The charge and hydride model calculations were done by placing a point charge and hydride ion, respectively, 1.4 Å away from the carbonyl carbon on both sides along the trajectory perpendicular to the carbonyl face.[3b] The LiH transition states are located on the potential energy surface and characterized as saddle points by the frequency calculations. This model has been found to be fairly reliable in reproducing the observed face selectivities in the norbornyl system and has some predictive value. The experimental data presented here for **3**–**8** provided an opportunity to test further this simple model and the computational results are presented in Table 1. The observed selectivities are correctly reproduced by the hydride model in all cases including the two diastereomeric sulfoxides **6** and **7** where there is a subtle reversal in face selectivity. The LiH transition state model is also in good agreement with the experimental observations. However, the charge model is found to be less consistent (see Table 1) and this to an extent reflects the ascendency of the orbital effects of the kind proposed earlier by us in determining the face selectivities in the norbornyl systems.

Table 1. The relative energies for *syn* and *anti* face additions calculated using the charge, hydride and LiH transition state models at the MNDO level [a]

	Charge model		Hydride model		Transition state	
	Syn	*Anti*	*Syn*	*Anti*	*Syn*	*Anti*
3	6.41	0.00	1.20	0.00	0.47	0.00
4	4.58	0.00	0.25	0.00	0.10	0.00
5	4.05	0.00	0.26	0.00	0.07	0.00
6	3.65	0.00	0.18	0.00	0.19	0.00
7	1.30	0.00	0.00	1.02	0.00	0.49
8	0.76	0.00	0.00	1.35	0.00	0.47

All values are given in kcal/mol.
[a] 0.00 value denotes the preference of face addition.

We have carried out NBO[10] analysis at B3LYP/6-31G* and HF/6-31G* levels to obtain interaction energies between the antiperiplanar σ_{C-C} and $\pi^*_{C=O}$ from the *syn* and *anti* sides in **3**–**8**, and we have also probed the orientation of the carbonyl group after metal ion complexation[3g] at B3LYP/6-31G*. However, both these computational results are substantially less satisfactory than the MNDO model in predicting the observed face selectivities.[11]

In summary, we have shown that distal hetero atom modifications at C-4 in *endo*-tricyclo[5.2.1.0^{2,6}]decan-10-ones and *endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-10-ones do not have a significant bearing on face selectivities during hydride addition. The simple hydride model (as well as the LiH transition state model) at the semi-empirical level constitutes a consistently reliable predictive tool for facial selectivities in these substrates and reinforces our earlier[3b] proposals vis-a-vis the norbornyl system.

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7. Substrates **3**–**14** were prepared from the Diels–Alder adducts of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene with either maleic anhydride or cyclopentadiene through routine but non-trivial functional group transformations. The stereostructures of sulfoxides **6**, **7**, **12**, and **13** were secured through X-ray crystal structure determination of **13** and its correlation with **7**. In the solid state, the C1–C10–C7 bridge of the norbornyl portion of **13** is tilted away from the olefinic side[4b] and the sulfoxide bearing 5-membered ring projects outwards.
8. All new compounds reported here were fully characterized on the basis of complementary spectroscopic (IR, ^{1}H & ^{13}C NMR and MS) and analytical data. ^{13}C NMR δ (75 MHz, $CDCl_3$); **15**: 81.7 (CH), 45.6 (CH), 41.5 (CH), 28.6 (CH_2), 27.0 (CH_2), 19.9 (CH_2). **16**: 81.1 (CH), 68.9 (CH_2), 44.7 (CH), 41.7 (CH), 20.1 (CH_2). **17**: 81.7 (CH), 45.9 (CH), 45.8 (CH), 33.4 (CH_2), 19.4 (CH_2). **18**: (CD_3OD): 53.0 (CH_2), 45.2 (CH), 43.1 (CH), 20.5 (CH_2). **19**: (CD_3OD): 81.7 (CH), 53.6 (CH_2), 45.6 (CH), 39.8 (CH), 20.8 (CH_2). **20**: 178.1 (CO), 80.0 (CH), 68.4 (CH_2), 44.5 (CH), 43.2 (CH), 43.1 (CH), 37.2 (CH), 22.2 (CH_2), 19.0 (CH_2). **21**: 84.9 (CH), 44.8 (CH), 42.2 (CH), 29.6 (CH_2), 26.3 (CH_2), 20.4 (CH_2). **22**: 84.5 (CH), 68.4 (CH_2), 44.4 (CH), 42.1 (CH), 20.4 (CH_2). **23**: 84.9 (CH), 46.6 (CH), 45.4 (CH), 32.7 (CH_2), 19.8 (CH_2). **24** (CD_3OD): 85.6 (CH), 52.7 (CH_2), 44.4 (CH), 44.2 (CH), 21.0 (CH_2). **25**: 82.8 (CH), 52.2 (CH_2), 43.7 (CH), 37.5 (CH), 19.8 (CH_2). **26**: 179.2 (CO), 83.1 (CH), 67.8 (CH_2), 45.1 (CH), 44.3 (CH), 44.2 (CH), 39.1 (CH), 22.5 (CH_2), 19.3 (CH_2). **27**: 133.6 (CH), 89.8 (CH), 52.4 (CH), 44.6 (CH), 43.2 (CH), 28.7 (CH_2), 28.6 (CH_2). **28**: 132.4 (CH), 89.0 (CH), 69.8 (CH_2), 51.8 (CH), 43.9 (CH). **29**: 134.4 (CH), 90.7 (CH), 52.3 (CH), 49.5 (CH), 34.9 (CH_2). **30**: 133.6 (CH), 90.4 (CH), 54.7 (CH_2), 51.5 (CH), 43.6 (CH). **31**: 134.7 (CH), 89.1 (CH), 54.5 (CH_2), 52.3 (CH), 36.4 (CH). **32**: 177.0 (CO), 134.0 (CH), 131.7 (CH), 88.1 (CH), 70.0 (CH_2), 51.8 (CH), 50.4 (CH), 43.7 (CH), 36.0 (CH). **33**: 135.0 (CH), 88.8 (CH), 50.0 (CH), 44.1 (CH), 30.7 (CH_2), 28.0 (CH_2). **34**: 133.4 (CH), 87.8 (CH), 69.3 (CH_2), 49.9 (CH), 45.1 (CH). **35**: 135.6 (CH), 90.3 (CH), 51.0 (CH), 49.6 (CH), 33.6 (CH_2). **36**: 135.2 (CH), 89.2 (CH), 54.3 (CH_2), 49.4 (CH), 45.3 (CH). **37**: 137.2 (CH), 87.9 (CH), 54.8 (CH_2), 51.8 (CH), 38.4 (CH). **38**: 179.0 (CO), 134.9 (CH), 133.3 (CH), 86.7 (CH), 69.5 (CH_2), 50.2 (CH), 49.9 (CH), 45.5 (CH), 37.8 (CH).
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