

Importance of steric factors in face-selective cycloadditions: 1,6-annulated cyclohexa-1,3-dienes

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Abstract—Diastereotopically nonequivalent π -facial 1,6-annulated-1,3-cyclohexadienes have been explored as probe molecules to assess the face-selectivities in cycloadditions. Steric factors have been found to be important in controlling the face-selectivities with these dienes. Studies with the hitherto unexplored diene **5** were also consistent with the order C–H > C–C for hyperconjugative stabilization of the transition state.

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Evaluation of the effects that influence π -facial diastereoselection in [4+2] cycloadditions has been the subject of important discussion in recent years.^{1,2} Several factors, both steric as well as electronic, have been suggested to explain the face selectivity in cycloadditions with dienes and dienophiles where at least one of the components contains nonequivalent π -faces. As a means for predicting such face-selectivity, Mehta and Uma gave the following qualitative hierarchy of stereoelectronic effects: steric > through space electrostatic repulsion or attraction stabilizing orbital interactions > hyperconjugation > ground-state orbital distortion.^{2b} Such facial diastereoselection in [4+2] cycloadditions has been extensively studied with dissymmetric cyclopentadienes. Amongst the dissymmetric 1,3-cyclohexadienes, polycyclic and 5,6-cage-annulated derivatives with minimum conformational ambiguities have been studied extensively.² Amongst the simple dissymmetric cyclohexadienes, primarily masked *o*-benzoquinones have been explored for such selectivity.³ We report in this letter, the cycloaddition reactions of 1,6-annulated 1,3-cyclohexadienes **1** and **5** bearing diastereotopically nonequivalent

π -faces. The investigation reveals how the steric effect becomes the primary factor in controlling the face-selectivity in such reactions.

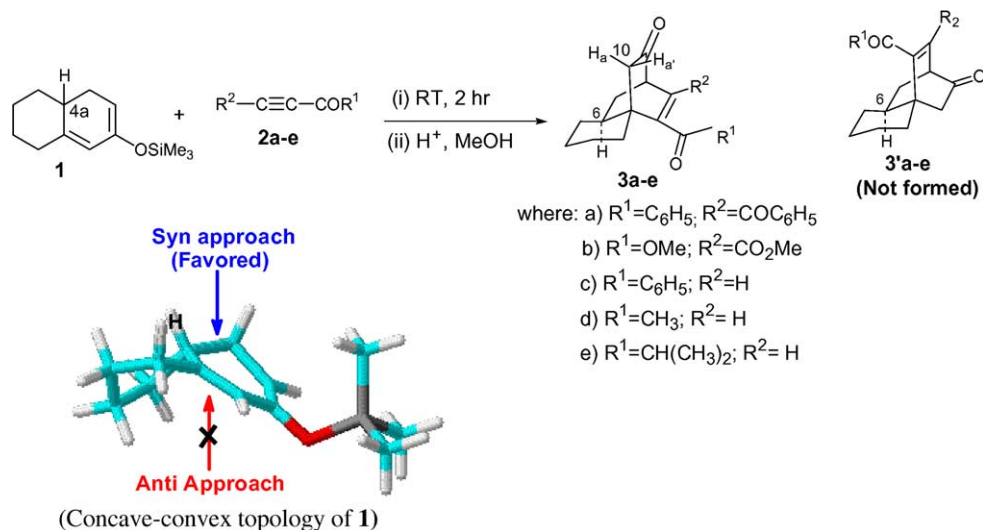
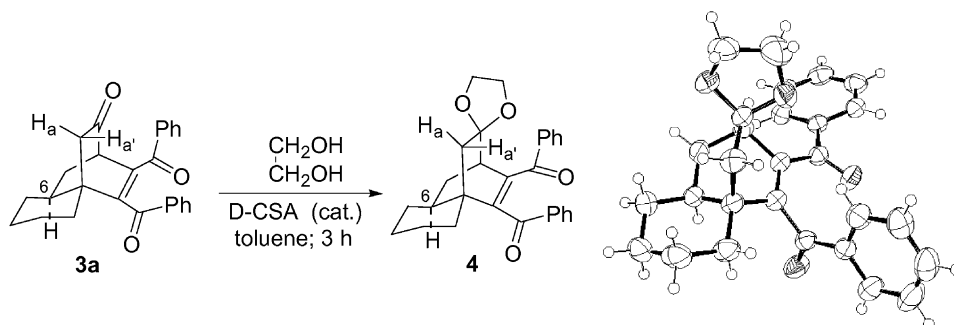
Earlier, in describing cycloadditions of acetylenic ketones **2a–e** to one of the title dienes namely, (4,4a,5,6,7,8-hexahydronaphthalene-2-yloxy)-trimethylsilane, **1**, we reported exclusive face-selective additions of the dienophiles yielding the diastereomers **3a–e**.⁴ The other diastereomers **3'a–e** could not be identified from any of the reactions (Scheme 1). The topology of diene **1** clearly showed a preferential *syn* approach by a dienophile to the C–H bond at the C4a asymmetric center of the diene in view of its concave–convex topology. This topology shields any approach of the dienophiles from the concave face favoring an exclusive diastereoselective adduct formation. Similar steric factors were also found to be operative in steroidal dienes.⁵

The stereochemistry of these adducts at C6 has now been established from the X-ray data of **4**.⁶ This ketal was best synthesized (78%) by refluxing 11,12-dibenzoyl-tricyclo[6.2.2.0^{1,6}]dodec-11-en-9-one **3a** and ethylene glycol in toluene using a catalytic amount of *D*-camphorsulfonic acid (CSA) for 3 h (Scheme 2).

In order to explore the power of such steric factors in controlling the π -facial selectivity steric effects in the

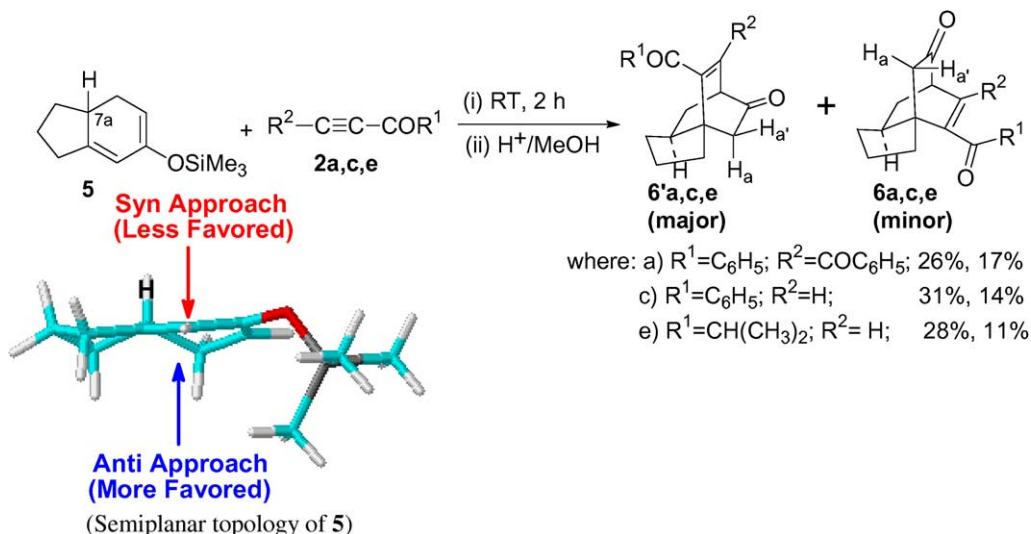
Keywords: Cycloaddition; π -Facial selectivity; Annulated cyclohexadienes.

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Scheme 1. Adduct formation from **1**.Scheme 2. Ketalization of **3a** and ORTEP diagram of **4**.

diene were minimized by using the diene trimethyl-(2,3,7,7a-tetrahydro-1*H*-inden-5-yloxy)-silane, **5**, with semiplanar topology (Scheme 3). Although several cycloadditions have been reported with the 7a-methyl derivative of **5**,⁹ additions to the parent molecule have

remained unexplored till now. The favored approach of acetylenic dienophiles **2a,c,e** to **5** was found to be *anti* to the C–H bond at the C7a asymmetric center of the diene giving **6'a,c,e** in major proportions. Minor quantities of the other diastereomers **6a,c,e** were also formed

Scheme 3. The adduct formation from diene **5**.

by the corresponding *syn* approach of the dienophiles (Scheme 3). The overall yields from these reactions were only moderate (~40%) and the mixture of isomers were separated with difficulty. The structures of the products were confirmed from their analyses and spectroscopic data (Table 1 in Supplementary data).¹⁰ The structure of **6'a** was confirmed by its X-ray crystallographic data (Fig. 1).⁶

While in facially biased dienes like **1** the steric effect controlled the selectivity in the sterically less biased diene **5** other effects influenced the diastereoselection. This was further confirmed from the addition of *N*-phenylmaleimide (NPM) to dienes **1** and **5** (Scheme 4). While in both the cases only the *endo*-adducts were obtained, diastereoselection led to **7** from **1** but **8** from **5**. The principle of hyperconjugative stabilization of a transition state was applicable in all these diastereoselective dienophile additions to **5**.^{1d,11} In the transition state, stabilization of the σ_{CC}^* orbital of the newly forming bond by the differential hyperconjugative effect of the σ orbital of one of the anti-periplanar allylic bonds (C–H or C–C) led to diastereoselection where, additions of *anti* to the C7a–H bond (Fig. 2B) were found to be always preferred over C7a–C bond (Fig. 2A). The relative electron donating ability of a σ_{C-H}^* bond vis-a-vis a σ_{C-C}^* bond in such transition state has long been a subject of debate.^{1,7,8} Our results are consistent with Cieplak's

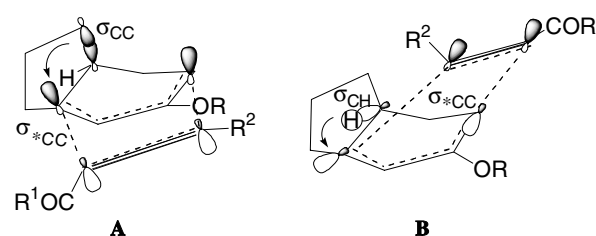


Figure 2. Hyperconjugative stabilization picture in the transition state of cycloaddition of **5**.

model of intrinsic C–H > C–C order of hyperconjugation.^{1d} While with the linear geometry of acetylenic ketones, additions *anti* to the C7a–C bond could give the less preferred adducts **6a,c,e**, the trigonal geometry of an ethylenic dienophile like NPM probably exerted more steric hindrance forming only **8** by preferred attack from the *anti*-side of the C7a–H bond of **5** and the formation of the other diastereomer was disfavored. In the case of diene **1**, its steric congestion led to adduct **7**.

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Supplementary data

Table with important ¹H NMR data, ¹H and ¹³C NMR spectra, and analytical data of the new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.129.

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- Because of the difficulty in obtaining a single crystal of **3a**, a single crystal of its ketal derivative, **4**, was used for obtaining the X-ray crystal data. X-ray data for both **4**

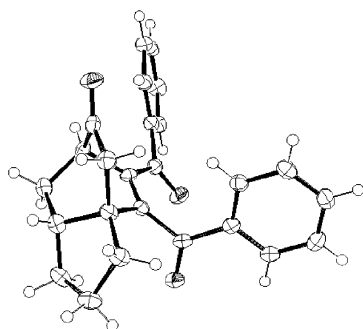
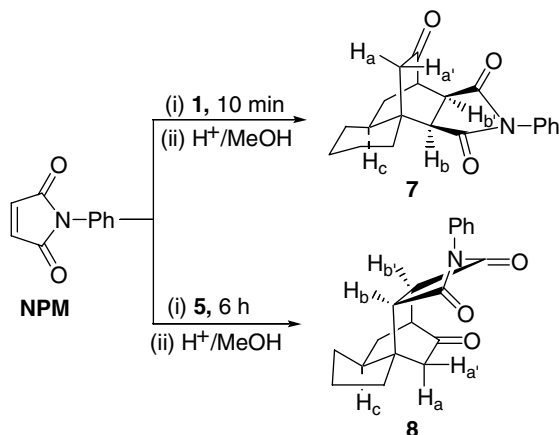


Figure 1. ORTEP diagram of **6'a**.



Scheme 4. Additions of NPM with **1** and **5**.

and **6'a** were collected at 293(2) K on a Bruker SMART-CCD diffractometer with graphite monochromated Mo-K α radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods (SHELXS-97). Crystals of **4** are colorless, of size: $0.50 \times 0.50 \times 0.10$ mm³, triclinic, space group *P*-1, $a = 9.186(2)$ Å, $b = 11.417(4)$ Å, $c = 12.118(3)$ Å, $\alpha = 73.302(6)^\circ$, $\beta = 73.658(4)^\circ$, $\gamma = 66.352(4)^\circ$, $V = 1094.9(5)$ Å³, $Z = 2$. Crystals of **6'a** are colorless, of size: $0.45 \times 0.30 \times 0.10$ mm³, monoclinic, space group *P*2₁, $a = 6.1243(3)$ Å, $b = 14.4240(8)$ Å, $c = 10.7673(5)$ Å, $\alpha = 90.0^\circ$, $\beta = 104.165(2)^\circ$, $\gamma = 90.0^\circ$, $V = 922.3(8)$ Å³, $Z = 2$. Crystallographic data (excluding structure factors) for these structures have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 275903, **4** and CCDC 275904,

6'a. Copies of the data can be obtained free of charge, on application to CCDC, 12, Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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