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π-Stacking Effect on Levoglucosenone Derived Internal Chiral Auxiliaries. A Case of Complete Enantioselectivity Inversion on the Diels−Alder Reaction

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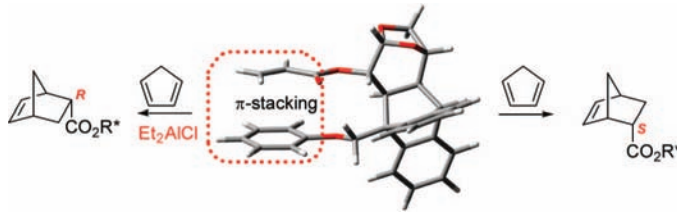
ABSTRACT



Detailed quantum chemical calculations, experimental evidence, and NMR data rationalize the participation of π-stacking interaction in the highly asymmetric Diels−Alder reaction using levoglucosenone derived internal chiral auxiliaries, including the appealing effect of inversion of the enantioselectivity by coordination of the substrate with Et_2AlCl.

Noncovalent interactions between aromatic rings or other unsaturated systems are claimed to be responsible for different phenomena in organic and biological chemistry.[1] Thus, it is well documented that π−π overlap may account for highly selective transformations in the field of asymmetric synthesis. Nevertheless, the indisputable evidence for the participation of such an interaction in controlling the stereoselectivity of organic processes has been presented only in a few cases.[2,3] In the context of our ongoing interest in the development of new tools for asymmetric synthesis derived from biomass, we have recently reported the

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(2) (a) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475. (b) Ma, L.; Jiao, P.; Zhang, Q.; Du, D. M.; Xu, J. *Tetrahedron: Asymmetry* **2007**, *18*, 878.

(3) Noncovalent π−π stacking interactions have been proposed to influence the selectivity of Diels−Alder cycloadditions. See. (a) Miller, G. P.; Briggs, J. *Tetrahedron Lett.* **2004**, *45*, 477. (b) Briggs, J.; Miller, G. P. C. R. *Chemie* **2006**, *9*, 916. (c) McNeil, A. J.; Muller, P.; Whitten, J. E.; Swager, T. M. *J. Am. Chem. Soc.* **2006**, *128*, 12426.

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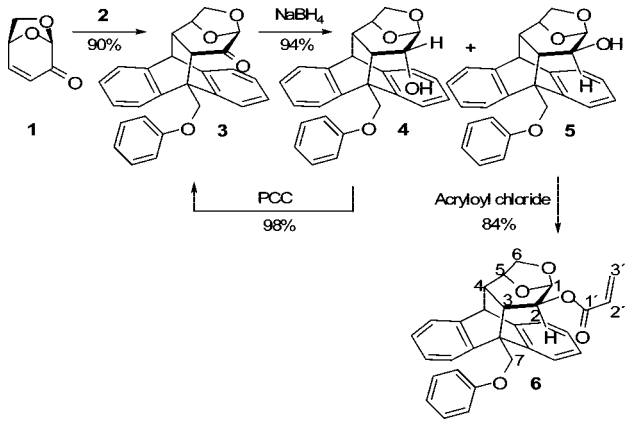
synthesis of different chiral auxiliaries starting from levoglucosenone (**1**)[4] and their use in Diels−Alder reactions.[5] The facial selectivity of these reactions is very sensitive to the pendant side chain group of the acrylates like **6**.[5b] Should this pendant substituent be the origin of the selectivity of these reactions, compound **6** will offer a paramount opportunity to determine the role of the π-stacking in the asymmetric induction, by using the Diels−Alder reaction of acrylate **6** and cyclopentadiene. The computational and spectroscopic evidence for this effect are reported herein.

The synthetic approach toward the preparation of compound **6** started with the cycloaddition reaction between **1** and 9-phenoxymethylanthracene (**2**) yielding only the ortho adduct **3** under thermally driven conditions (Scheme 1). The

Scheme 1. Synthesis of Acrylate **6**



reduction ($NaBH_4$, CH_2Cl_2−MeOH, 0 °C) of ketone **3** led to the formation of two diastereomeric alcohols **4** and **5** (40:60), which were easily separated by flash chromatography. Acrylate **6** was obtained by the reaction of acryloyl chloride with alcohol **5** in the presence of Et_3N at 0 °C. All attempts to synthesize the corresponding acrylic ester from **4** failed, probably due to the steric hindrance surrounding the alcohol position. Therefore, alcohol **4** was recycled by oxidation with PCC regenerating the ketone **3** in excellent yield and increasing the overall yield of acrylate **6**.

The possibility of interaction between the acrylate moiety and the pendant phenyl ring was examined by NMR.[6] The vinylic protons of compound **6** (6.1−5.4 ppm in $CDCl_3$) were shielded between 0.40 and 0.60 ppm compared to those of analogous acrylates having pendant nonaromatic substituents (6.5−5.9 ppm).[5] This shielding effect on the hydrogen atoms of the double bond caused by the aromatic ring due to the anisotropy phenomena pointed to a π-stacking interaction between the aromatic group and the acrylate double bond.[1,2] The close proximity between the phenoxy group and the enoate moiety was further confirmed by NOE experiments. Irradiation of olefinic protons (H-2′, H-3′*cis*, and H-3′*trans*) resulted in enhancement of *ortho*-hydrogens of the phenoxy group.[6] Additionally, a variable-temperature NMR study was carried out between 300 and 230 K.[6] Upon cooling, the chemical shifts of the enoate hydrogens moved upfield by 0.24 (H-2′), 0.11 (H-3′*trans*), and 0.9 ppm (H-3′*cis*). Some authors have claimed that this effect could be interpreted in terms of a conformational equilibrium that is shifted toward the *s-trans* conformer at lower temperatures.[7] However, the spectrum at 230 K did not exhibit the two groups of signals expected for both possible conformers of **6**. This observation suggests that the barrier between the *s-cis* and *s-trans* conformations of the α,β-unsaturated system **6** is <5 kcal/mol and both conformations are in fast exchange on the NMR time scale in the range of temperatures used.

Quantum chemical calculations were used to have a better understanding about this dynamic process. Since most popular DFT methods often fail to describe noncovalent interactions,[8] we carried out a detailed conformational study of **6** at the RI-MP2/def2-SVP level of theory.[9] The two more stable conformations are depicted in Figure 1 being **6**-*s-cis*

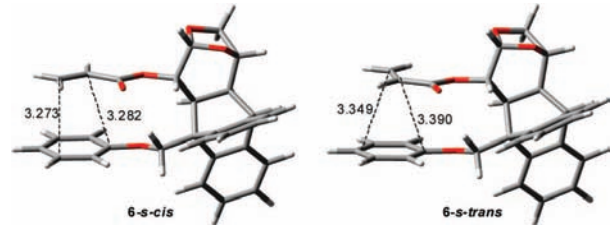


Figure 1. RI-MP2/def2-SVP-fully optimized structures of **6**. C−C bond lengths are given in Å.

0.5 kcal/mol lower in energy than **6**-*s-trans*. In both optimized geometries, the acrylate and the phenoxy ring approximately lie parallel to each other, and the distances between them are ca. 3.2−3.3 Å.[10] The H···H distances for both isomers were consistent with the NOE experiments performed (see Supporting Information). Similar geometries and energy differences were computed at the M05-2X/def2-SVP level (ΔE = 0.5 kcal/mol), which was recently recommended by Truhlar[11] to describe noncovalent interactions. The calculated barrier for the *s-cis*⇆*s-trans* interconversion is low (7.1 kcal/mol at M05-2X/def2-SVP level), which accounts for the failure to detect separate NMR signals for the two conformers at any attainable temperature. However, this barrier is higher than that computed for the

(6) See NMR studies in Supporting Information.

(7) (a) Mezrhab, B.; Dumas, F.; d′Angelo, J.; Richie, C. *J. Org. Chem.* **1994**, *59*, 500. (b) Dumas, F.; Mezrhab, B.; d′Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293. (c) Dussault, P. H.; Woller, K. R.; Hillier, M. C. *Tetrahedron* **2004**, *50*, 8929.

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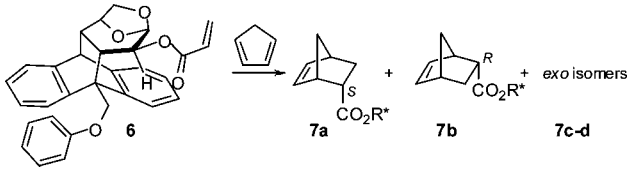
(10) Similar C−C distances have been found in other π-stacked systems. See: Yamada, S. *Org. Biomol. Chem.* **2007**, *5*, 2903.

(11) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.

analogous system where the CH_2═CH group in **6** is replaced by a saturated ethyl group (1.9 kcal/mol at the M05-2X/def2-SVP level), which is fully consistent with the π-stacking proposed above.[12] NBO analysis on **6**-*s*-*cis* (at the M05-2X/6−311+G*//RI-MP2/def2-SVP level) supports the proposed π-interaction showing a two-electron stabilizing donation from the π(C═C, phenoxy ring) orbital to the π*(C═C, acrylate) orbital (associated second-order energy of −1.27 kcal/mol) as well as the donation from the π(C═C, acrylate) to the π* C═C phenoxy ring orbital (associated second-order energy of −1.10 kcal/mol).

Acrylate **6** and cyclopentadiene were reacted in the diverse reaction conditions compiled in Table 1. All cycloadditions

Table 1. Thermal and Lewis Acid Promoted Cycloaddition Reactions of **6** and Cyclopentadiene



entry	Lewis acid (equiv)	solv.	t (°C)	t (h)	yield (%)[a]	*endo*/*exo*[b]	*endo* *R*/*S*[b]
1	−	PhMe	110	1.5	88	69:31	21:79
2	−	PhMe	25	48	92	73:27	16:84
3	−	CH_2Cl_2	25	48	91	78:22	13:87
4	$EtAlCl_2$ (2)	CH_2Cl_2	0	1	92	93:7	92:8
5	$EtAlCl_2$ (2)	CH_2Cl_2	−40	1	93	95:5	94:6
6	$EtAlCl_2$ (2)	CH_2Cl_2	−80	1.5	85	97:3	95:5
7	Et_2AlCl (2)	CH_2Cl_2	0	1	84	92:8	96:4
8	Et_2AlCl (2)	CH_2Cl_2	−40	1	81	95:5	97:3
9	Et_2AlCl (2)	CH_2Cl_2	−80	1	82	96:4	97:3

[a] Yield corresponds to isolated products. [b] Determined by HPLC.

were *endo* diastereoselective, as predicted by the Alder *endo* rule.[13] The existence of two conformers in the acrylate **6** reflects the moderate selectivity in its Diels−Alder reaction with cyclopentadiene, which increases as the temperature of the reaction decreases. The reaction profile calculated for both conformers of compound **6** is depicted in Figure 2. The π-stacking with the pendant phenoxy group blocks one of the faces of the double bond in both conformers.[14] This interaction vanishes along the reaction coordinate because the acrylate double bond participates in the cycloaddition. Therefore, calculations at the B3LYP level can be safely used.[15] The system follows a typical Curtin−Hammett profile. The lowest activation barrier is found for the

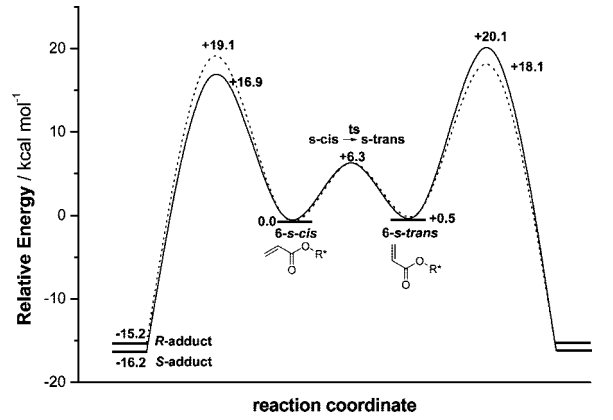


Figure 2. Calculated reaction profile (B3LYP/def2-SVP+ΔZPVE) for the reaction between **6** and cyclopentadiene. Solid lines and dotted lines correspond to the pathways leading to the *S*- and *R*-cycloadducts, respectively.

transformation **6**-*s*-*cis*→*S*-adduct (1.2 kcal/mol lower than the barrier for the transformation **6**-*s*-*trans*→*R*-adduct), in very good agreement with the experimental findings.

The reaction between **6** and cyclopentadiene was carried out next in the presence of Lewis acids. These reactions produced the reversal of the stereoselectivity provided that more than 1 equiv of aluminum Lewis acids was used in the cycloaddition reaction (see Table 1, entries 4−9 and Supporting Information).

To explain this result (with the concomitant increase in the *endo*/*exo* diastereoselectivity), an extensive NMR study was undertaken (see Supporting Information). Spectra of **6** in $CDCl_3$ solution show a significant deshielding of H-5 (from 4.72 ppm in the absence of additive to 4.95 ppm in the presence of 1.5 mol of Et_2AlCl) and H-6 (from 3.77 ppm in the absence of additive to 3.93 ppm in the presence of 1.5 mol of Et_2AlCl). An analogous downfield shift is observed for all the vinylic hydrogens. These findings can only be explained by the formation of a chelated species involving the acryloyl oxygen and the oxygen of the 1,6-anhydro bridge. Two effects derived from this chelation must be expected: (a) the inversion of the faces of each conformer accessible to the diene, (b) a considerable increase in the barrier of the isomerization of the *s*-*cis*⇆*s*-*trans* conformers by the effect of the Al coordination.

To rationalize these results, the potential energy surface of the model complex **[6-Al]**$^+$ was computed. RI-MP2/def2-SVP calculations showed that the most stable isomers of this species are again the complexes **[6-Al-*s*-*cis*]**$^+$ and **[6-Al-*s*-*trans*]**$^+$, with the latter being 1.3 kcal/mol higher in energy (Figure 3). Both isomers present the NMR-predicted coordination mode between **6** and the Lewis acid.[16] Moreover, the high value of the computed isomerization barrier at the

(12) The computed dissociation energy of the $\pi-\pi$ complex between anisole and methyl acrylate at the RI-MP2/def2-SVP level is 9.8 kcal/mol. This value may be used to roughly estimate intramolecular π-stacking in compound **6**.

(13) The sense of asymmetric induction was ascertained by hydrolysis of the adduct **7b**. The absolute configuration of the 5-norbornene-2-carboxylic acid isolated corresponded to the 2-*R*-enantiomer: Chang, H.; Zhou, L.; McCargar, R. D.; Mahmud, T.; Hirst, I. *Org. Process Res. Dev.* **1999**, *3*, 289.

(14) See fully optimized geometries in the Supporting Information.

(15) M05-2X and B3LYP calculations were carried out using the Gaussian03 (rev. E.01) suite of programs, Frisch M. J. et al. (Full reference is given in the Supporting Information).

(16) **[6-Al-*s*-*cis*]**$^+$ is ca. 20 kcal/mol more stable than the corresponding monocoordinated complex.

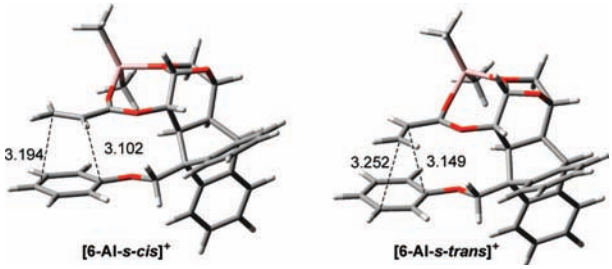


Figure 3. RI-MP2/def2-SVP-fully optimized structures of **[6-Al]**$^+$. C−C bond lengths are given in Å.

M05-2X/def2-SVP level (8.8 kcal/mol) is also in good agreement with the conformational preference toward *s-cis* for **[6-Al]**$^+$, making this chelated species the preferred. Therefore, **[6-Al-*s-cis*]**$^+$ is now the reactive species which leads to the almost exclusive formation of the *R*-isomer, especially at low temperatures that secured the single conformation state of the substrate **[6-Al]**$^+$.

The calculated Diels−Alder reaction profile of **[6-Al]**$^+$ and cyclopentadiene shows that the pathway which leads to the *endo*-*R*-adduct from **[6-Al-*s-cis*]**$^+$ is kinetically favored, even over the *s-cis*⇆*s-trans* isomerization (Figure 4). Again, the stereochemical outcome of the reaction can be explained in terms of the attack of the diene from the less sterically hindered (*si*) enoate π-face in its *s-cis* conformation, which is the inverted face compared to that of the metal-free **6-*s-cis*** analogue. As expected, the computed reaction barriers are clearly lower compared to those for the uncatalyzed processes. These results are in very good agreement with the lower temperatures and reaction times required for these cycloadditions (Table 1).

In summary, we have presented an appealing effect of inversion of the enantioselectivity of the Diels−Alder reaction by coordination of the substrate with Et_2AlCl and explained this effect by a combination of NMR and computational methodologies. To the best of our knowledge, this is the first report on detailed quantum chemical calculations, experimental evidence, and NMR data that provides a key basis to rationalize the participation of a π-stacking interaction, which sterically blocks one of the faces of the double bond involved in the cycloaddition, in a highly asymmetric chemical transformation.

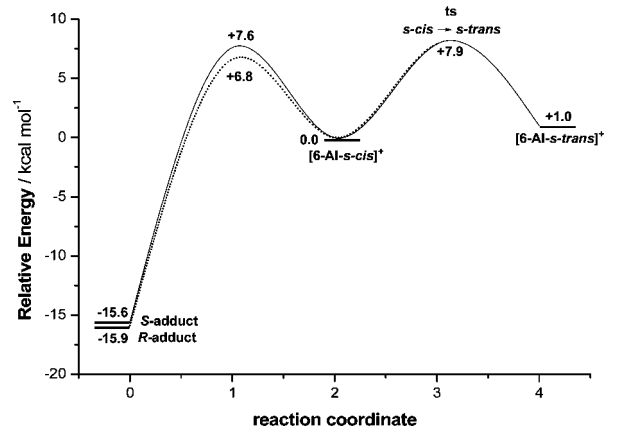


Figure 4. Calculated reaction profile (B3LYP/def2-SVP+ΔZPVE) for the reaction between **[6-Al]**$^+$ and cyclopentadiene. Solid lines and dotted lines correspond to the pathways leading to the *S*- and *R*-cycloadducts, respectively.

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Supporting Information Available: Computational calculation data and experimental procedures for the synthesis of all compounds, characterization data, and copies of ^1H and ^{13}C NMR spectra of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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