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Studies of the Stereochemistry of [2+2]-Photocycloaddition Reactions of 2-Cyclohexenones with Olefins

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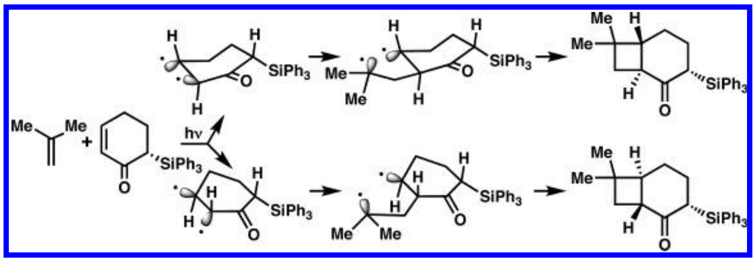
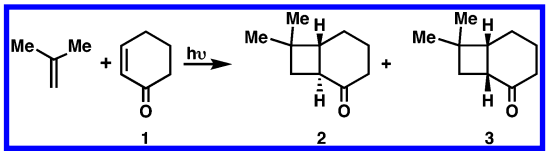
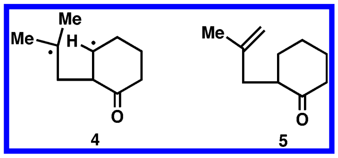
ABSTRACT



Stereochemical studies of the photocycloaddition of a chiral α,*β*-enone and isobutylene lead to a working hypothesis for the geometry of the $^3(\pi-\pi^*)$ excited state of the enone.

Ultraviolet irradiation of 2-cyclohexenone (**1**) at 300−320 nm to effect an n → *π** transition generates an electronically excited species that is sufficiently long lived to be trapped by isobutylene to form as major products the *cis*- and *trans*-fused [4.2.0]-bicyclooctanones **2** and **3**, with the *trans* isomer predominating.[1,2] It is now generally accepted that this reaction proceeds via the diradical **4**, for which there is much experimental evidence, including not only the formation of byproduct **5** (which can result from **4** by 1,5-H migration) but also direct trapping experiments with H_2Se.[3] In addition, it is now clear that the photoreaction involves intersystem crossing of the initially formed n → *π** singlet to an n → *π** triplet which then relaxes to a less energetic $\pi-\pi^*$ triplet, $^3(\pi-\pi^*)$. Reaction of this triplet with isobutylene would be expected to provide the triplet diradical **4** which could be rapidly transformed via the singlet diradical **4** into the products **2**, **3**, and **5**.[4]Assuming this pathway is actually followed, it becomes of some interest to inquire as to the three-dimensional geometry of the $^3(\pi-\pi^*)$ state. All the evidence available suggests that this state involves twisting about the α,*β*-bond of the α,*β*-enone chromophore. First of





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(2) For related studies, see: (a) Büchi, G.; Goldman, I. M. *J. Am. Chem. Soc.* **1957**, *79*, 4741−4748. (b) Cookson, R. C.; Crundwell, E. *Chem. Ind.* **1958**, 1004−1004. (c) deMayo, P.; Takeshita, H.; Sattar, A. B. *Proc. Chem. Soc.* **1962**, 119−119. (d) Eaton, P. E. *J. Am. Chem. Soc.* **1962**, *84*, 2344−2348, 2454−2455.

(3) Maradyn, D. J.; Weedon, A. C. *Tetrahedron Lett.* **1994**, *35*, 8107−8110.

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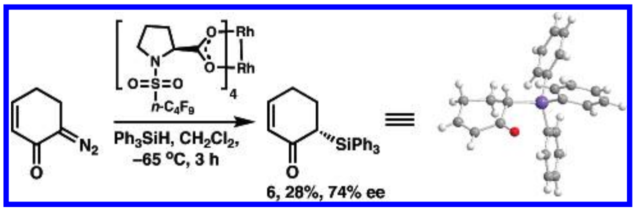
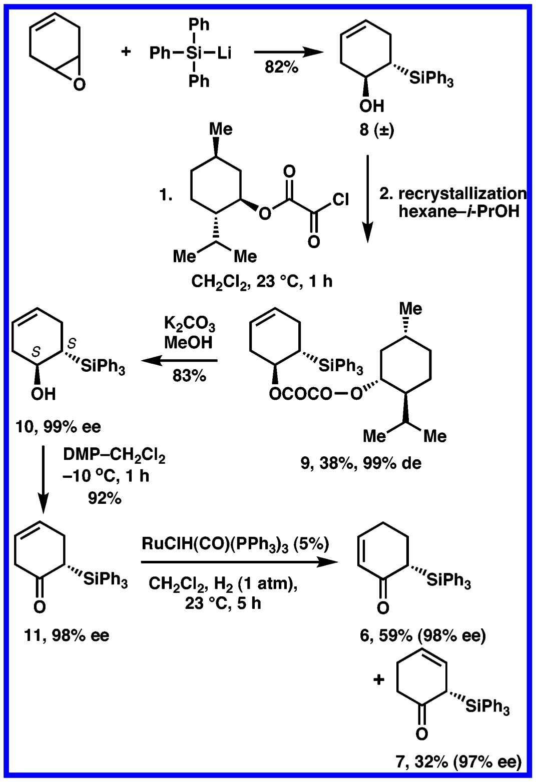
all, it is widely accepted that the lowest triplet of ethylene is the structure in which the two CH_2 planes are at an angle of 90°.[5] Second, the well-known *E* to *Z* photoisomerization of acyclic α,β-enones is most readily understood on the basis of the twisted geometry of the electronically excited state. In the case of *acyclic* α,β-enones, this α,β-twisting and rotation provides a mechanism for rapid dissipation of energy that explains the fact that these photoexcited substrates do not live long enough to be trapped by olefinic partners. 2-Cycloheptenone and 2-cyclooctenone undergo $Z \rightarrow E$ isomerization and cannot be trapped by simple olefins,[6] whereas 2-cyclopentenone and 2-cyclohexenone, which are unlikely to give *E*-isomers, do undergo photocycloaddition with olefins, paralleling **1** → **2** + **3**. The formation of the highly strained and thermodynamically less stable *trans* adduct **2** from **1** and isobutylene provides another argument for a twisted $^3(\pi-\pi^*)$ precursor.[7] Various theoretical and physical studies also lend support to the α,β-twisted structure as the minimum-energy geometry for the 2-cyclohexenone $^3(\pi-\pi^*)$ state.[4] However, the three-dimensional geometry of that state is still unclear. The present study was initiated with two major objectives: (1) to learn more about the preferred minimum-energy conformation(s) of the $^3(\pi-\pi^*)$ excited state and (2) to find a methodology for exerting effective enantiocontrol of the [2+2]-photocycloaddition reactions of cyclic α,β-enones and olefins, such as the reaction **1** → **2** + **3**. Complimentary studies in this laboratory have explored nonphotochemical approaches to the enantioselective synthesis of compounds such as **3** from α,β-enones with some success.[8]

The particular 2-cyclohexenone on which we have focused is the chiral 6-(*S*)-triphenylsilyl-2-cyclohexenone (**6**). Two syntheses of this substrate were developed. The choice of the triphenylsilyl group at the chiral center was based on a number of considerations including: (1) subsequent ease of removal from the attached carbon, (2) large effective steric size, and (3) the unusually high crystallinity of triphenylsilyl-containing molecules (apparently not previously appreciated). The latter effect would seem to be a consequence of the availability of the 6-fold phenyl embrace binding motif for tight crystal packing first noticed with triphenylphosphino compounds.[9] The excellent crystallinity of **6** was confirmed by an initial synthesis using the enantioselective methodology recently developed in these laboratories,[10] specifically, the reaction of triphenylsilane and 6-diazo-2-cyclohexenone[10] in the presence of H. M. L. Davies' chiral rhodium(II) catalyst.[10] Even though this process provided access to **6**, the yield could not be raised above 28% and the enantiopurity of the product was only 74%. Nonetheless, the product was nicely crystalline and could be recrystallized from hexane to give **6** in 98% ee.



The second synthetic pathway to **6**, shown in Scheme 1, was more practical for the synthesis of gram amounts.

Scheme 1. Synthesis of 6-(*S*)-Triphenylsilyl-2-cyclohexenone



Reaction of 1,4-cyclohexadiene oxide with triphenylsilyllithium (from triphenylchlorosilane and lithium in THF at 23° for 3 h)[11] proceeded smoothly to form *trans*-(±)-2-triphenylsilyl-4-cyclohexen-1-ol (**8**) which was converted to a diastereomeric mixture of esters with the monooxalic ester of levorotatory menthol. As we had hoped, as single crystalline diastereomer (**9**) could be obtained by simple recrystallization (from hexane-isopropyl alcohol). Base-catalyzed hydrolysis of **9** to **10** followed by oxidation with the Dess−Martin periodinane reagent afforded the β,γ-enone **11** in excellent yield. The isomerization of **11** to the chiral α,β-enone **6** was attempted under a wide variety of basic

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[5] El-Taher, S.; Hilal, R. H.; Albright, T. A. *Int. J. Quantum Chem.* **2001**, *82*, 242−254 and refs cited therein.

[6] Corey, E. J.; Tada, M.; LaMahieu, R.; Libit, L. *J. Am. Chem. Soc.* **1965**, *87*, 2051−2052. Although *E*-2-cycloheptenone does not add to simple olefins because it rapidly reverts to the *Z*-isomer, it can be trapped by cyclopentadiene to give a (nonphotochemical) Diels−Alder adduct.

[7] In the case of the photocycloaddition of 2-cyclohexenone to tetramethylethylene, the *trans*-fused adduct predominates heavily. See: Nelson, P. J.; Ostrem, D.; Lassila, J. D.; Chapman, O. L. *J. Org. Chem.* **1969**, *34*, 811−813.

[8] Liu, D.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 8160−8161.

[9] Dance, I.; Scudder, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1039−1040.

[10] Ge, M.; Corey, E. J. *Tetrahedron Lett.* **2006**, *47*, 2319−2321.

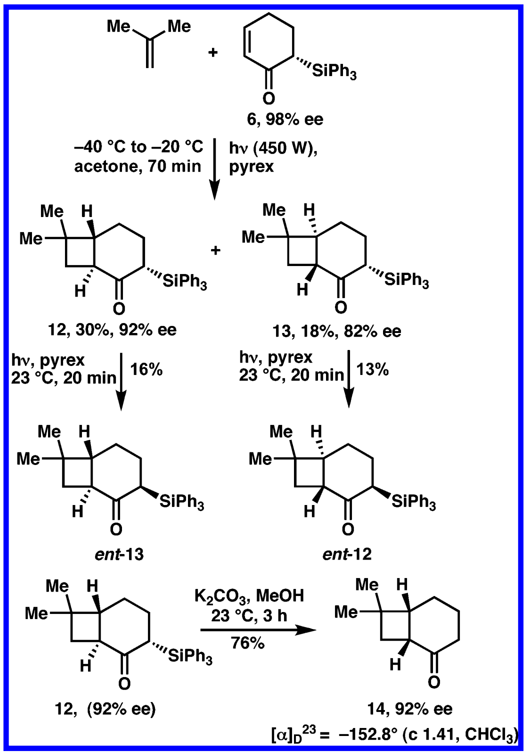
[11] Gilman, H.; Aoki, D.; Wittenberg, D. *J. Am. Chem. Soc.* **1959**, *81*, 1107−1110.

conditions but was unsatisfactory due to concomitant racemization. However, chiral **6** of 98% ee could be obtained under neutral conditions using 5 mol % of RuClH(CO)-$(PPh_3)_3$ in CH_2Cl_2 at 23 °C under an atmosphere of H_2.[12] The isomeric byproduct **7** was also formed in the isomerization of **11** to **6** but was readily separable by chromatography.

The structure and absolute configuration of **6**, mp 109−111 °C, were fully supported by X-ray single-crystal diffraction which revealed the structure shown above and also confirmed the close packing of phenyl groups both with one another and with the 2-cyclohexenone ring, as shown in the Supporting Information. It is interesting that the 2-cyclohexenone subunits also stack face to face along the crystal *a*-axis (see Supporting Information).

The photocycloaddition reaction of **6** and isobutylene was complicated by the occurrence of photoracemization of the [2+2]-cycloaddition products at a rate competitive with their formation (see below). It was best conducted in acetone as solvent for a minimal reaction time, as summarized in Scheme 2. The two principal products of the photoreaction were the *trans*-fused bicyclo[4.2.0]octanones **12** and **13** which were formed in ca. 2:1 ratio. Further irradiation of **12** converted it to *ent*-**13**, whereas irradiation of **13** produced *ent*-**12**. These isomerization reactions can be interpreted as Norrish type-1 processes[13] involving the reversible cleavage of the bond between the carbonyl group and the attached silylated α carbon.

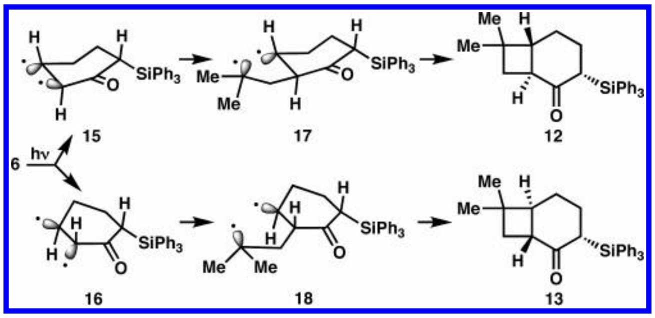
Scheme 2



Treatment of the *trans*-fused bicyclic ketone **12** of 92% ee with K_2CO_3−MeOH gave the *cis*-fused isomer **14** of 92% ee, as expected. The absolute configuration of **14** follows not only from the method of synthesis but also from comparison with a sample of the same chiral compound that was recently prepared in these laboratories.[8]

We believe that the photochemical results shown in Scheme 2 can be used to illuminate the three-dimensional geometry of the $^3(\pi-\pi^*)$ excited state of the α,β-enone **6**. To this end, we advance the following working hypothesis which is outlined in Scheme 3. If we make the reasonable assumption that spin density of the $\pi-\pi^*$ triplet enone is mainly concentrated at C(α) and C(β) *with the spin-paired electrons in orthogonal orbitals* and that the C(α)- and C(β)-hydrogens are *trans* to one another, two structures emerge as possibilities. These are shown in stereoformulas **15** and **16** as two different conformers of this kind of $^3(\pi-\pi^*)$ state in which the triphenylsilyl substituent is equatorial. Attack of isobutylene at C(α) then would generate the 1,4-diradicals **17** from **15** and **18** from **16**. Rapid ring closure of **17** would give **12**, whereas the direct cyclization of **18** would give **13**. It is clear from the inspection of the stereostructures **17** and **18** that the equatorial triphenylsilyl group would have little influence on the face of C(α) which is attacked by isobutylene. The preference for initial attachment to C(α) may arise from the inductive effect of the attached carbonyl that renders C(α) more electron deficient and reactive than C(β). If the chairlike conformer **15** were to predominate somewhat over the twist-boat-like conformer **16**, the 2:1 predominance of adduct **12** over **13** would be easy to understand.

Scheme 3. Working Hypothesis for the Photocycloaddition of **6** and Isobutylene



We believe that this mechanistic model, the proposed conformations of the $^3(\pi-\pi^*)$ state of a 2-cyclohexenone, and the question of whether the unpaired electrons are significantly localized *in spatially orthogonal orbitals* deserve further experimental and theoretical investigation.

Supporting Information Available: Experimental procedures for the reactions described herein and characterization data. Details for the X-ray crystallographic analysis of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Bingham, D.; Webster, D. E.; Wells, P. B. *J. Chem. Soc., Dalton* **1974**, 1519−1521.

[13] Hwu, J. R.; Chen, B.-L.; Liu, C.-F.; Murr, B. L. *J. Organomet. Chem.* **2003**, *686*, 198−201.