

The Intramolecular Diels–Alder Reactions of Photochemically Generated *trans*-Cycloalkenones

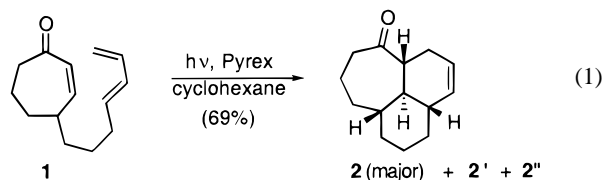
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The construction of complex, polycyclic molecules continues to pose a fundamental challenge to organic chemists. One of the most powerful methods for the rapid synthesis of such molecules involves the use of a thermal, often Lewis acid-catalyzed, Diels–Alder reaction, particularly its intramolecular variant.¹ Many years ago, it was reported that *cis*-cycloheptenone² and *cis*-cyclooctenone³ isomerize to their highly strained *trans* isomers upon irradiation with UV light (>300 nm). The *trans* enones were found to be excellent dienophiles, readily undergoing thermal Diels–Alder reactions to form the corresponding *trans* fused Diels–Alder adducts in very high yields.⁴ Despite their remarkable reactivity, the chemistry of such deformed *trans* enones remains little explored.⁵ In particular, the intramolecular Diels–Alder reactions of these *trans* enones have never been reported. We report here the first examples of the intramolecular Diels–Alder reactions of photochemically generated *trans*-cycloalkenones. These cycloadditions produce a variety of novel, highly complex, polycyclic systems containing exclusively the *trans* ring juncture, a topology that is unavailable via the standard thermal cycloaddition reaction and would be inaccessible by almost any other available synthetic method.

The 4-substituted cycloheptenone **1**^{6,7} underwent a facile intramolecular Diels–Alder reaction upon irradiation (eq 1).⁸ The



starting material was completely consumed (by TLC) after only 30 min of irradiation and afforded the product in 69% isolated yield as a 3:2:1 mixture of three diastereomers, with **2** predominating.^{9,10}

(1) (a) Ciganek, E. *Org. React.* **1984**, *32*, 1–374. (b) Roush, W. R. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 513–550. (c) Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proced. Int.* **1990**, *22*, 131–165.

(2) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1964**, *86*, 2087–2088.

(3) (a) Corey, E. J.; LaMahieu, R. *J. Am. Chem. Soc.* **1965**, *87*, 2051–2052. (b) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1965**, *87*, 2052–2054.

(4) For an excellent summary of the early work, see Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50–57.

(5) See for example: (a) Crandall, J. K.; Haseltine, R. P. *J. Am. Chem. Soc.* **1968**, *90*, 6251–6253. (b) Noyori, R.; Inoue, H.; Katō, M. *J. Chem. Soc., Chem. Commun.* **1970**, 1695–1696. (c) Shinozaki, H.; Arai, S.; Tada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 821–822. (d) Dunkelblum, E.; Hart, H.; Suzuki, M. *J. Am. Chem. Soc.* **1977**, *99*, 5074–5082. (e) Mintas, M.; Schuster, D. I.; Williard, P. G. *Tetrahedron* **1988**, *44*, 6001–6012. (f) Ghosh, S.; Roy, S. S.; Saha, G. *Tetrahedron* **1988**, *44*, 6235–6240.

(6) (a) Bloomfield, J. J.; Nelke, J. M. *Organic Syntheses*; John Wiley & Sons: New York, 1988; Collect. Vol. VI, pp 167–172. (b) Pirrung, M. C.; Webster, J. G. *J. Org. Chem.* **1987**, *52*, 3603–3613. (c) Reingold, I. D.; Beckmann, G.; Grannas, A. M.; Williams, B. D.; Lovell, S.; Kahr, B. E. *Org. Prep. Proced. Int.* **1998**, *30*, 235–238.

(7) (a) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776. (b) Dai, W.; Katzenellenbogen, J. A. *J. Org. Chem.* **1993**, *58*, 1900–1908.

(8) In a typical procedure, a 0.015 M solution of the cycloheptenone **1** (0.50 mmol) in cyclohexane was degassed and irradiated through Pyrex at room temperature under an argon atmosphere. The solvent was removed and the product ketone isolated by flash column chromatography (15:1 hexane/ethyl acetate). The diastereomers were separated by preparative HPLC.

The stereochemical outcome of this reaction can be rationalized by considering the transition states for the reaction. The photoisomerization of **1** to the *trans* form creates a new element of chirality, so as to produce two diastereomeric *trans* enones (**A** or **B**), each capable of reacting with the diene with endo/exo selectivity, for a total of four possible diastereomeric products.



The major product of the cycloaddition was the all *trans* compound **2**, arising from a transition state in which all three rings are in a chairlike conformation (Figure 1). The other two diastereomers isolated are formed from transition states that deviate from the ideal all-chair arrangement.

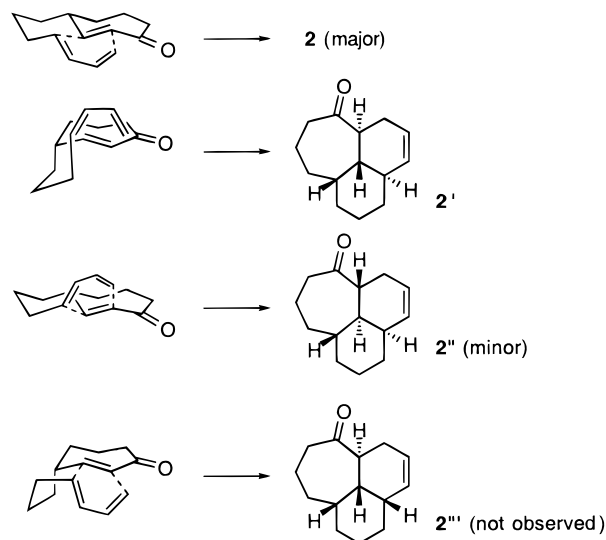
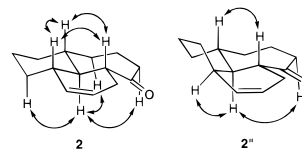


Figure 1. Diastereomeric Outcome of Irradiation of **1**.

We have examined the reactivity of several diene-substituted cycloheptenones and cyclooctenones in the intramolecular “photo” Diels–Alder reaction, and the results are summarized in Table 1. These enones cleanly underwent the intramolecular Diels–Alder reaction to produce intricate, polycyclic systems in good yields. The stereoselectivity of each entry in Table 1 is completely analogous to the first example (eq 1), with the major diastereomer arising from an approach in which all three rings adopt chairlike

(9) Compounds **2** and **2'** were fully characterized by ¹H, ¹³C, HMQC, HMBC, COSY, and NOESY spectroscopy. The relative stereochemistry was determined by NOESY spectra, and some of the relevant NOE interactions are shown below (see Supporting Information). The structure assigned to **2'** should be considered tentative, since, while it is consistent with the NMR data, it is not incontrovertible.



(10) The *cis* enone is considerably less reactive than the *trans* enone. In the absence of light, the thermal intramolecular Diels–Alder reaction of **1** did not take place even upon heating a xylene solution of **1** to 80 °C for 2 h. Indeed, the cycloaddition proceeded only in refluxing xylenes (24 h), which afforded a 10:2:1 mixture of cycloadducts in 45% yield along with a small amount of recovered starting material and a considerable amount of decomposed (polymerized) material. The three cycloadducts of the above reaction were, as expected, structurally different from compounds **2**, **2'**, and **2''**.

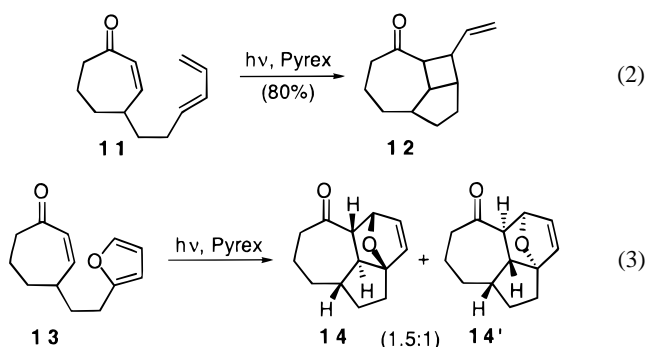
Table 1. Intramolecular Photo Diels-Alder Reactions

entry	starting material	products	% yield ^a (diastereomer ratio) ^b
1			69 (3:2:1)
2			80 (1.25:1)
3			66 (1.2:1)
4			70 (5:1)

^a Isolated yields. Relative stereochemistry not established for diastereomers not shown.¹¹ ^b Ratios based on NMR.

conformations in the transition state. Table 1 illustrates the wide range of structures that can be prepared from this cyclization.^{8,11}

In contrast to the examples above, irradiation of cycloheptenone **11**, having a two carbon linker rather than three, gave a mixture of cycloadducts of which only ~15% (by NMR) comprised the 4+2 adduct (eq 2). The major product was a single diastereomer of the 2+2 adduct (**12**), which was isolated in 80% yield. Interestingly, substitution of the butadiene unit with a cyclic diene completely favored the expected Diels-Alder adduct, which was formed cleanly as a 1.5:1 mixture of diastereomers **14** and **14'**, with no evidence of a 2+2 adduct (eq 3).¹²



(11) A combination of spectroscopic techniques was used to assign the structures of the products shown in the table. Compounds **4**, **4''**, **6**, **6'**, **14'**, and **14''** were characterized using a variety of NMR techniques, particularly NOESY spectroscopy. Single-crystal X-ray analysis established the structure assigned to cycloadduct **10**.¹³ The stereochemistries of compounds **4'**, **8**, **8'**, and **10'** were assigned by comparison of their spectra with that of analogous compounds obtained in this study. See Supporting Information for the spectroscopic data.

Table 2. Light Filter and Temperature Effects on Yields and Diastereoselectivity

entry	substrate	rxn temp	Pyrex filter yield	uranium filter yield	products ratio
1	1	rt	69%	88%	3:2:1
2	7	rt	66%	80%	1.2:1
3	1	-75 °C	39%	77%	10:-:1

We have found that the yield of the photocycloaddition reaction can be improved substantially by using a uranium glass filter instead of Pyrex, as shown in Table 2. The observed higher yields can be understood by considering the spectral cutoff regions for the two types of glasses. Unlike Pyrex, which is reported to cut off light below ~285 nm, uranium glass cuts off light around 340 nm, making Norrish-type photochemistry of the ketone products unlikely.

The diastereoselectivity of the reaction was dramatically improved by lowering the reaction temperature. Irradiation of compound **1** at -75 °C (±5 °C) in methylene chloride afforded a 10:1 ratio of diastereomers **2** and **2''**, but in only 39% yield. Again, the use of the uranium filter significantly improved the yield, giving the same 10:1 mixture of diastereomers, but now in 77% yield.

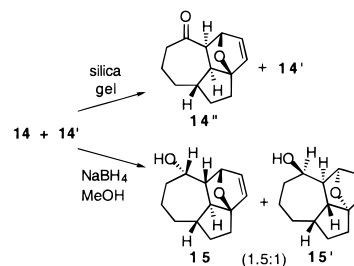
In conclusion, we have shown that photochemically generated *trans*-cyclic enones can be trapped intramolecularly through a thermal Diels-Alder reaction, which provides a new, powerful method for the rapid preparation of complex polycyclic structures from relatively simple precursors. A wide variety of novel compounds containing exclusively the *trans* ring juncture have been prepared in good yields. The use of low temperature for the reaction in conjunction with a uranium glass filter afforded the cycloadducts in high yields and with good diastereoselection. Further investigation of the chemistry of photochemically generated *trans*-cycloalkenones is currently in progress in our laboratories.

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Supporting Information Available: General experimental procedures and ¹H NMR and ¹³C NMR of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) The products of the reaction shown in eq 3 proved difficult to isolate due to the facile epimerization of the major cycloadduct (**14**) to the corresponding *cis* compound (**14''**) on silica gel. This problem was overcome by directly subjecting the crude reaction mixture to reduction with NaBH₄, which yielded the expected alcohols **15** and **15'**, each formed as single diastereomers (72% overall). The relative stereochemistry of **15** was unambiguously assigned using X-ray structure determination.¹³



(13) We thank Professor Robin D. Rogers (University of Alabama) for the X-ray crystal structure determinations. The details of the crystal structures will be reported in due course.