

# Chiral Auxiliaries Promote both Diastereoselective Cycloaddition and Kinetic Resolution of Products in the Ortho Photocycloaddition of Double Bonds to Benzene Rings

Peter J. Wagner\* and Kevin McMahon

Chemistry Department, Michigan State University  
East Lansing, Michigan 48824

Received August 19, 1994

We wish to report that high diastereoselectivity can be achieved in the photoinduced intramolecular ortho cycloaddition of double bonds to triplet benzenes<sup>1</sup> through the use of the same chiral auxiliaries that work well in radical addition reactions. This selectivity is quite unusual in that it is imparted in two separate steps: first during the initial [2 + 2] cycloaddition and later during subsequent electrocyclizations.

We have studied the photochemistry of 2-((3-methyl-3-butenyl)oxy)-5-acetylbenzoic acid **1a** and several derivatives formed from chiral alcohols and amines. Like the simple amide already reported,<sup>2</sup> all these compounds undergo 100% regioselective ortho cycloaddition as depicted in Scheme 1. In all cases, the original cycloadduct **2** converts thermally to **3**, which then photocyclizes to **4** in the stereochemistry shown.<sup>3</sup> The cyclobutene photoproducts **4** all undergo thermal reversion to **3**, in which C-8 is the only permanent new stereocenter created by the cyclization of **1** to **2**. When the compounds bearing chiral auxiliaries were irradiated, <sup>1</sup>H-NMR analysis of products **3** and **4** revealed various ratios of two diastereomers, as listed in the scheme. Each methyl group and each vinyl proton showed clearly distinguishable resonances separated by 0.1–0.4 ppm, whereas in the racemic **3a** and **4a** formed from achiral **1a**, each proton showed a single resonance. Product (8*S*)-**3s** was isolated after one recrystallization as a single diastereomer; its configuration, as revealed by X-ray crystallography, is shown in Figure 1. Both **3p** and **3s** were prepared from racemic **3a** (previously prepared from achiral **1a**); both showed 50:50 ratios of all NMR signals, as compared to the 20:1 ratios observed after irradiation of **1p** and **1s**. The difference between the **3p** and **3s** made by irradiation of **1a** vs those formed by irradiation of **1p** or **1s** establishes that the doubling of NMR signals for **3** and **4** is a true measure of diastereoselectivity at C-8 in the photocycloaddition of **1** and is not due to amide rotations.

The diastereomeric excesses (des) for **3b**, **3m**, and **3p** in methanol and for **3s** in benzene are comparable at high and low conversion. However, in methanol, (8*S*)-**3s** is formed in only 30% de at 20% conversion, but the de increases to 90% as the reaction is completed. The cause for this enhancement of de with conversion was revealed by the following experiment: UV irradiation of the 50:50 mixture of (8*S*)- and (8*R*)-**3s** (formed from racemic **3a** and (*R*)-sultam) very rapidly causes nearly complete epimerization of (8*R*)-**3s** to (8*S*)-**3s**, which slowly cyclizes to **4s**. Exactly the same thing happens with the 50:50 mixture of **3p** prepared from racemic **3a**.<sup>4</sup> The cyclooctatriene diastereomers undergo an uncommon but perfect form of kinetic resolution, whereby one converts into the other faster than either reacts further. The combined findings indicate that diastereoselectivity occurs during the initial formation of

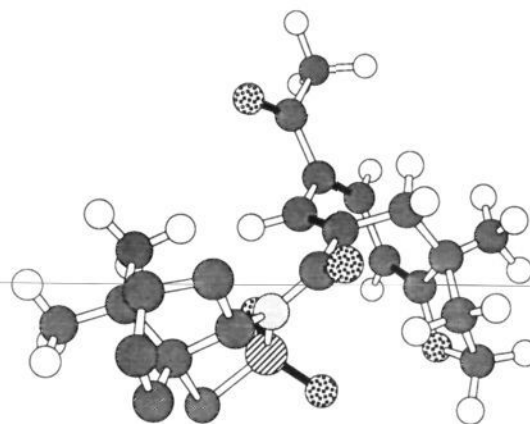
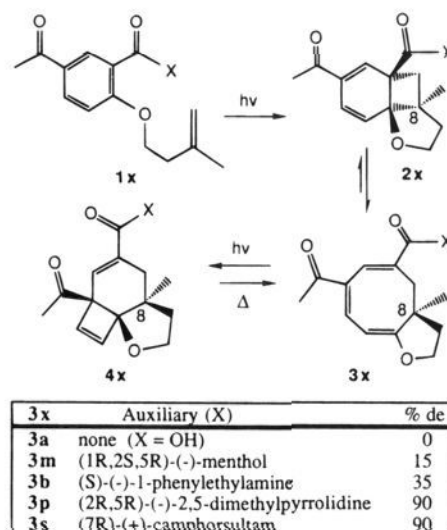


Figure 1. X-ray crystal structure of (8*S*)-**3s**, with hydrogens on sultam deleted.

## Scheme 1



**2** and can be enhanced by a heretofore unrecognized photoepimerization of **3**. We shall first discuss the former.

The small des induced by menthol and (1-phenylethyl)amine are similar to results for [2 + 2] photocycloadditions of enones.<sup>5</sup> The high des for the pyrrolidine and the sultam parallel the results found for the same chiral auxiliaries in free radical additions to acrylic acid derivatives.<sup>6,7</sup> This correlation might at first glance seem to provide further validation of our description of this photocycloaddition as a radical-like addition of the excited triplet benzene ring to a remote double bond to generate a 1,4-biradical,<sup>8,9</sup> but the situation requires more thorough analysis. The radical additions that have been studied involve reaction at either the  $\alpha$  or the  $\beta$  end of a chiral acrylamide,<sup>6</sup> with the former showing significant diastereoselectivity, the latter little. The mechanism that we have proposed for our photocycloaddition portrays triplet **1** as undergoing a hexenyl radical-like cyclization by the  $\beta$ -end of

(5) Inoue, Y. *Chem. Rev.* **1992**, 92, 741.

(6) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, 111, 8309. Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, G.; Lindner, H. J. *Ibid.* **1989**, 111, 8311. Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, 31, 1679.

(7) (a) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, 112, 6738. (b) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *Ibid.* **1990**, 112, 6740. (c) Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *Ibid.* **1990**, 112, 6741.

(8) Wagner, P. J.; Sakamoto, M. *J. Am. Chem. Soc.* **1989**, 111, 8723. Wagner, P. J.; Sakamoto, M. *J. Am. Chem. Soc.* **1989**, 111, 9254.

(9) Cheng, K.-L.; Wagner, P. J. *J. Am. Chem. Soc.* **1994**, 116, 7945.

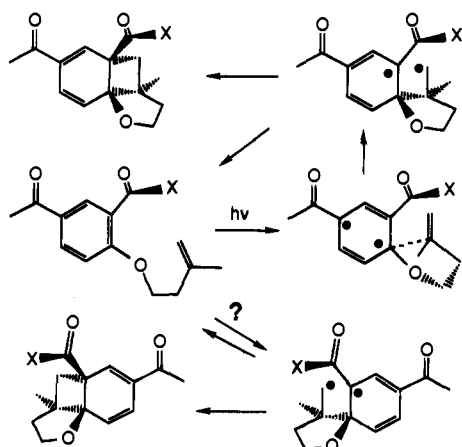
(1) Wagner, P. J.; Nahm, K. *J. Am. Chem. Soc.* **1987**, 109, 6528.

(2) Wagner, P. J.; Sakamoto, M.; Madkour, A. E. *J. Am. Chem. Soc.* **1992**, 114, 7298.

(3) Both NMR and preparative scale irradiations were generally carried out on ~0.01 M methanol solutions in a Rayonet reactor with 300 nm lamps. The de values listed are for complete reaction. Actual product yields averaged 50–60%.

(4) These experiments were conducted on CD<sub>3</sub>OD solutions in an NMR tube and were characterized by the NMR spectral changes.

Scheme 2



an acrylamide. This biradical-forming step, which determines the regio- and stereoselectivity of cycloaddition, is the inverse of the monoradical additions.

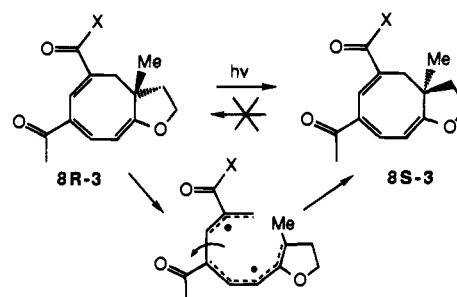
There is a very important and informative difference between these cycloadditions and simple radical additions. The latter involve only two or three centers in each step. This [2 + 2] reaction involves four carbon centers. Its high regioselectivity indicates that both carbons of the remote double bond are involved in determining product selectivity.<sup>2</sup> The high diastereoselectivity now observed demands the same conclusion. Scheme 2 depicts the only approach of the remote double bond to the benzene ring that can produce the observed selectivity. Products are formed only with the end of the double bond pointed toward the amide group and on the face opposite to the chiral auxiliary, with as much as a 95% preference for approach from below the benzene ring (as drawn). Both the regio- and the stereoselectivity are controlled by an as yet undefined combination of preferential exciplex and/or biradical formation and selective partitioning of regio- and stereoisomeric biradicals between cyclization to **2** and reversion to ground state **1**.<sup>10</sup> As in the reactions of enones,<sup>11</sup> cycloaddition is a typical two-step triplet process; both ends of the double bond are involved in product formation, and the stereoselectivity of both  $\alpha$  and  $\beta$  radical reactions is incorporated.

Explaining the observed diastereoselectivity is less straightforward. Both molecular mechanics (MM2) and semiempirical (AM1) computations suggest that the amide groups in **1p** and **1s** are twisted perpendicular to the benzene ring. That explains why strong facial selectivity is observed, but not why (8*S*)- rather than (8*R*)-**3s** is formed preferentially. AM1-level computations do not reveal significant energetic differences between the two diastereomeric **2s** cycloadditions.<sup>12</sup> The products were studied since the major steric interactions with the X group appear to

(10) Tolbert has recognized the importance of both processes in [2 + 2] photocycloadditions: Tolbert, L. M.; Ali, M. B., *J. Am. Chem. Soc.* **1982**, *104*, 1742.

(11) Schuster, D. R.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3.

Scheme 3



involve the methylene next to oxygen and are not important until the benzene carbon to which the tether is attached becomes tetrahedral. The solvent effect on the initial selectivity for **1s** suggests an electrostatic contribution to the sultam-induced selectivity,<sup>13</sup> such that the energy difference between diastereomers depends on solvent polarity.

As regards the kinetic resolution of **3p** and **3s**, AM1 computations predict (8*S*)-**3s** to be 1.5 kcal/mol more stable than (8*R*)-**3s**. Such a difference would explain the thermodynamic preference for (8*R*)-**3s**, but a mechanism for this previously hidden interconversion is required (Scheme 3). The epimerizations of **3p**s reveal a new facet to the already delightfully complex photochemistry of these butenoxy ketones. The cyclooctatrienes **3** apparently open and reclose much more efficiently than they cyclize to cyclobutenes **4**. In fact, concurrent studies have shown that the **3** → **4** conversion proceeds in low (~10%) quantum efficiency.<sup>14</sup> We now know why. Cyclooctatrienes are known to open to tetraenes,<sup>15</sup> but we have never detected one from these ketone reactions. We doubt that ground state tetraenes would recyclize thermally in such high efficiency. We suspect that the acetyl group facilitates intersystem crossing of the excited singlet **3** in competition with cyclization to **4**. Triplet **3** then may initiate a diradical process, in which twisting of the single bond between allyl and pentadienyl subunits of what might be considered the diradical form of triplet tetraene would allow epimerization upon reclosure. There is recent precedent for chiral auxiliaries promoting diastereoselective cyclization of biradicals.<sup>16</sup>

It must be emphasized that the results do not allow us to precisely dissect total selectivity into exact contributions from each of the two stereoselective steps. Future efforts will be directed to doing so.

**Acknowledgment.** This work was supported by NIH Grant No. GM-39821. The NMR spectrometers used were partially funded by NSF Grant CHE88-00770 and NIH Grant RR047550.

(12) A double dihedral driver was applied for rotations around the amide CO-N and CO-C bonds; the resulting lowest energy conformers in each isomer were then individually minimized with no frozen bonds.

(13) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39.

(14) Cheng, K.-L.; Wagner, P. J., unpublished results.

(15) (a) Atkinson, J. G.; Ayer, D. E.; Buchi, G.; Robb, E. W. *J. Am. Chem. Soc.* **1963**, *85*, 2257. (b) Al-Qaradawi, S. Y.; Cosstick, K. B.; Gilbert, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1145.

(16) Wessig, P.; Wettstein, P.; Giese, B.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1994**, *77*, 829.