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Mechanistic Implications of Stereospecific 1,5–Hydrogen–Atom Transfer in the Formation of an Unusual Allene/Enoate Photoproduct

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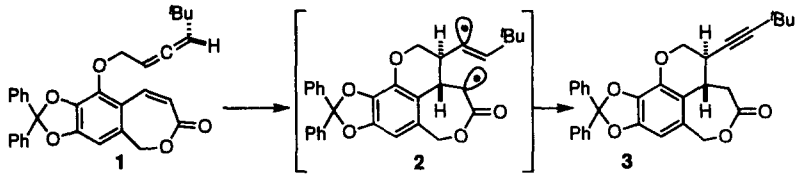
Abstract: Irradiation of allene-enoate **1** affords alkyne **3** as the major photoproduct. Selectively deuterated analog *d*–**1** affords a single diastereomer on irradiation. This result supports a stepwise mechanism for enantioselective [2+2]–photocycloadditions involving a 1,4-biradical intermediate **2** which collapses to products more rapidly than it undergoes reversion to starting material, resulting in the observed high levels of asymmetric induction.

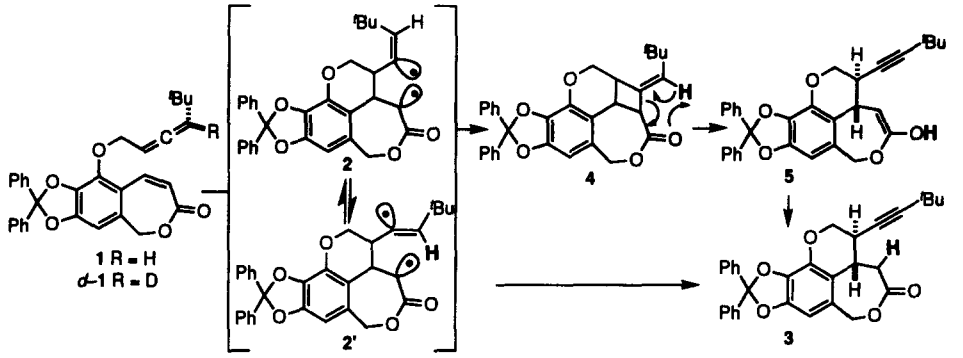
We have previously described asymmetric, intramolecular allene-enone and allene-enoate photocycloadditions which provide access to complex carbocyclic frameworks in enantiomerically pure form.[1] In the course of applying the transformation to the synthesis of several natural products we observed that irradiation of optically active (92% ee) **1** with a medium pressure Hg lamp through a Pyrex filter afforded alkyne **3** (Eq 1) with complete asymmetric induction (92% ee). These results prompted us to scrutinize the reaction with the aim of gaining mechanistic insight into the formation of the unusual alkyne photoproduct. In this communication, we describe an isotopic labeling experiment which supports the intermediacy of a putative 1,4–biradical **2** which fails to undergo ring closure to furnish the expected exoalkylidene cyclobutane and instead preferentially undergoes a rapid, stereospecific 1,5-hydrogen shift.[2]



(1)

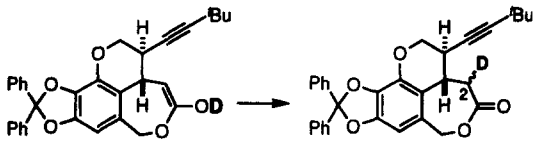
Two distinct mechanistic pathways involving an intermediate 1,4–biradical can account for the formation of alkyne **3** (Scheme 1). Irradiation of the substrate generates an enoate triplet which adds to the proximal terminus of the allene to give an intermediate 1,4-biradical (**2**). In principle, this biradical has three fates following intersystem crossing to the singlet state: (1) ring closure to give exoalkylidene cyclobutane **4**, as would be anticipated for a typical enone-olefin photocycloaddition reaction; alternatively, (2) 1,5–hydrogen transfer to give acetylenic product **3** directly; and (3) reversion to starting material. In the photochemical reactions that we have conducted to date with related substrates that afford alkyne adducts we have failed to observe the intermediacy of ring-closed products such as **4**. Nonetheless, if **4** is transiently formed it could undergo a strain-induced retro–Conia fragmentation[3] to give rise to enol **5** which would tautomerize to afford the observed product **3**. We speculated that a simple experiment utilizing deuterio-labeled allenes would allow these two mechanistic alternatives to be readily distinguished.

Scheme 1

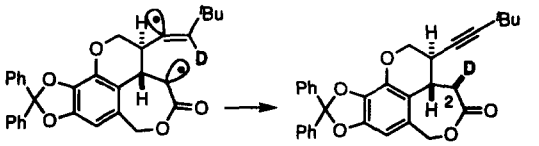


Two limiting experimental outcomes are possible upon irradiation of labeled, racemic allene *d*–**1**.[4] If the formation of products proceeds through enol **6** then tautomerization ought to lead to a diastereomeric mixture of deuterium labeled products **7** (Eq 2). Additionally, when the reaction is conducted in the presence of a protic solvent, exchange of the enolic proton should be faster than tautomerization, leading to unlabeled product **3**. In contradistinction, if the product arises via direct formation of the acetylene by 1,5-hydrogen transfer then, on the basis of molecular modeling,[5] deuterium incorporation at C-2 should occur stereoselectively, giving (2*R*)-**7** (Eq 3). Additionally, conducting the reaction in MeOH should not lead to loss of the deuterium label under the neutral conditions of the reaction.

Irradiation of *d*-**1** in CH_2Cl_2 afforded deuterium-labeled acetylenic product; analysis by ^1H NMR spectroscopy revealed that (2*R*)–**7** had been formed in >20:1 diastereoselectivity (Figure 1).[6] Additionally, irradiation of *d*-**1** in 1:1 CH_2Cl_2:MeOH + 1% N-methyl morpholine furnished the same labeled product (2*R*)–**7** stereospecifically. In order to demonstrate that the enol-keto tautomerization of **6** to **7** would afford a mixture of deuterium stereoisomers, the lithium enolate of **3** was generated and quenched at -78 °C with D_2O to give two diastereomers (2*R*)–**7**/(2*S*)–**7** in a 2.2:1 ratio.[7,8] Collectively these results can only be accommodated by a mechanistic pathway involving biradical intermediate **2** which undergoes a stereospecific 1,5-deuterium shift.



6 (2*R*)–**7** and (2*S*)–**7** (2)



2 (2*R*)–**7** (3)

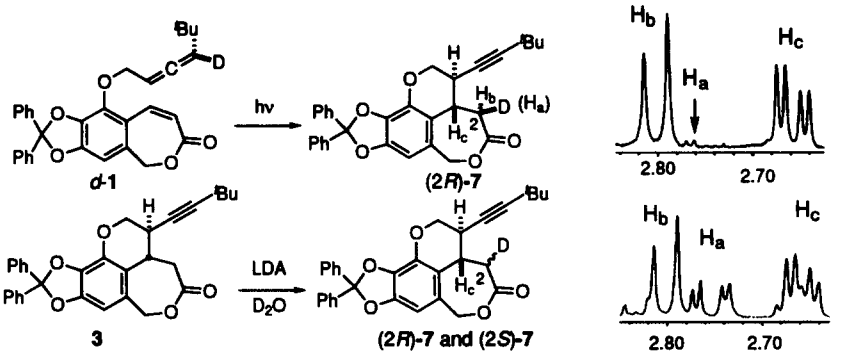
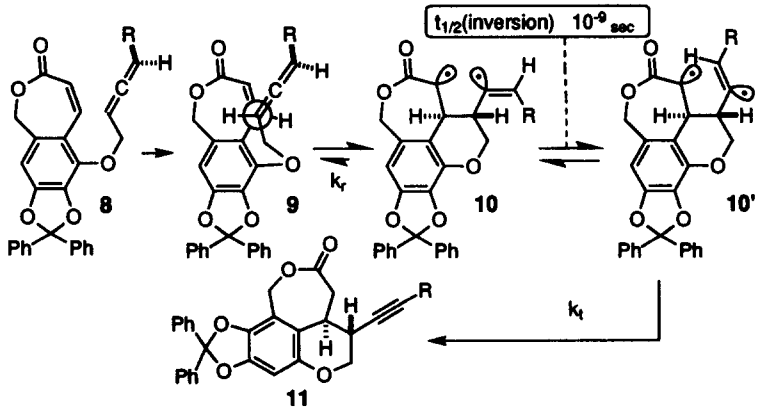


Figure 1. Partial 500 MHz ^{1}H NMR spectra of (2*R*)–**7** and (2*S*)–**7** in C_6D_6 generated under photochemical conditions and by deprotonation with LiN^iPr_2 followed by a D_2O quench.

We have previously proposed a working model that accounts for the high levels of asymmetric induction in photocycloadditions of optically active allenes with cyclic enones and enoates to form cyclobutanes (Scheme 2).[1] The observation of high optical activity in the photoadducts suggests a mechanism in which the stereochemistry of the products is established kinetically upon addition of the enone excited state to the least hindered allene face (**8** → **9** → **10**). Importantly, within the lifetime of the putative 1,4-biradical intermediate **10/10'**, allylic C-C single bond rotation and inversion of the vinyl radical occur (**10** ⇄ **10'**)[9] with consequent loss of olefin geometry.[10,11] The observation of asymmetric induction in the photoaddition that leads to alkyne formation is consistent with a mechanism in which H-atom transfer by the putative 1,4–biradical **10'** is faster than retroaddition, k_t (**10'** → **11**) >>k_r (**10/10'** → **9**).[12] These experiments demonstrate that high optical induction can be expected in [2+2]-photoadditions not only when the biradical can cyclize to a four-membered ring product, but also when other processes are available to this high-energy intermediate that are faster than ring closure, such as 1,5-H transfer.

Scheme 2



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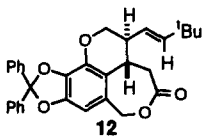
References and Notes

1. (a) Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622-6630. (b) Shepard, M. S.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597-2605.
2. The structural features of the substrate that determine the formation of a cyclobutyl versus alkynyl adduct have not been delineated. We speculate that the strain associated with the putative tetracyclic [2+2] adduct precludes its formation, resulting in the observed preference for 1,5-H shift. The results of further investigations aimed at elucidating the structural parameters that dictate 1,5-H hydrogen transfer will be reported in due course.
3. (a) Rouessac, F.; Beslin, P.; Conia, J.-M. *Tetrahedron Lett.* **1965**, *7*, 3319-3323. (b) Rouessac, F.; Conia, J.-M. *Tetrahedron Lett.* **1965**, *7*, 3313-3318.
4. The deuterated allene was prepared in the following manner:

a) THF, -78 °C, 94%; b) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 70%; c) $NaBD_4$, MeOH, 23 °C, 94%; d) *i.* MsCl, Et_3N, CH_2Cl_2, 0 °C; *ii.* 95:5:1.5 MeCN/HF/H_2O; *iii.* $LiAlH_4$, Et_2O, -78 °C, 88%, three steps.

5. Analysis of Dreiding models of alkene **12** revealed a preference for orientation of the olefinic substituent in a manner that would preclude delivery of the hydride to the α-face. Similar results were obtained by molecular mechanics minimization (MM2) of the same substrate.



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6. It should be noted that the starting *d*–1 is ~97% isotopically pure as determined by analysis of its ^1H NMR spectrum. Thus, the observed 20:1 diastereoselectivity represents a lower limit for stereoselectivity in 1,5–H transfer.
7. The protonation of Li–enolates has been suggested to occur by rapid protonation at oxygen followed by a slow tautomerization, see: Keefe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990; Chapter 7, pp 399–480.
8. The observed ratio of H_b/H_a is 1.6:1 which, after correction for internal return, affords the indicated 2.2:1 ratio. The correction is necessary since it is known that enolates generated with LDA suffer reprotonation by the diisopropylamine which is generated in the course of the reaction and remains associated with the enolate (Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624-1654). The extent of internal return was quantified by comparison of the integrals of H_a and H_b with the integral of H_c. Thus, if the integrals of H_a, H_b, and H_c are I_A, I_B, and I_C, respectively, then % internal return = $(I_A + I_B - I_C)/I_C$, or 26%. The ratio of the two diastereomers (*R*)–7/(*S*)–7 = $(I_C - I_A)/(I_C - I_B)$ = 2.2:1.
9. (a) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147-2195. (b) Kochi, J. K. *Adv. Free Rad. Chem.* **1975**, *5*, 189-317.
10. For mechanistic investigations of alkene–enone photocycloadditions, see: (a) Andrew, D.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 5647-5663. (b) Maradyn, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 5359-5360. (c) Haddad, N.; Abramovich, Z. *J. Org. Chem.* **1995**, *60*, 6883-6887. For computational studies, see: (d) Broeker, J. L.; Eksterowicz, J. E.; Belk, A. J.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 1847-1848.
11. For a [2+2]-photocycloaddition reaction of an alkene with an enone which intercepts the 1,4–biradical, see: Becker, D.; Morlender, N.; Haddad, N. *Tetrahedron Lett.* **1995**, *36*, 1921-1924.
12. For a examples in which retro-addition competes with ring–closure, see: (a) McCullough, J. J.; Ramachandran, B. R.; Snyder, F. F.; Taylor, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 6767-6776. (b) Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8525-8527. (c) Maradyn, D. J.; Sydnes, L. K.; Weedon, A. C. *Tetrahedron Lett.* **1993**, *34*, 2413-2416. (d) Rudolph, A.; Weedon, A. C. *Can. J. Chem.* **1990**, *68*, 1590-1597.

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