[2 + 2] Photocycloaddition of Cinnamyloxy Silanes

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The [2 + 2] photocycloaddition is a powerful carbon–carbon bond forming reaction. Recently, much attention has been focused on intramolecular [2 + 2] reactions, where selective coordination of different alkenes to a template[1] or covalent bonding to a tether[2] is used to preorganize reactant alkenes. This methodology provides a means for controlling the regio- and stereochemistry of the reaction, as well as minimizing competing reactions, such as cis–trans isomerization.

The temporary silicon connection has been employed in several reactions including radical cyclizations,[3] [4 + 2] cycloadditions,[4] and disaccharide synthesis.[5] We have previously reported the diastereoselective formation of a cyclobutane derivative in high yields from the photocycloaddition of dialkylbis(cinnamyloxy)silanes.[6] Since that time, other [2 + 2] cycloadditions using the silicon tether have been reported.[7] In this paper, we address the synthetic utility and mechanism of the silicon tethered [2 + 2] photocycloaddition with styrene as the chromophore.

In order to investigate the generality of this reaction, we have prepared several silanes having one cinnamyloxy ligand and various alkenyloxy groups attached to the silicon (Scheme 1). Compounds **2a–h** were irradiated and desilylated, and the photoproducts were separated by chromatography. In general, isomerization about the cinnamyl double bond occurs in the absence of cycloaddition. Both the allyl (**2a**) and crotyl (**2b**) irradiations resulted in only trans–cis isomerization of the cinnamyl double bond. Irradiation of the dimethyl-substituted alkene derivative **2c** gave an unexpected product, 6-methyl-3-phenyl-5-heptene-1,4-diol, which we have justified by a mechanism involving hydrogen abstraction (Figure 1).[8] Derivatives **2d**, **2e**, **2g**, and **2h** resulted in good to excellent yields of the desired substituted cyclobutanes **3d–h**. These results are summarized in Table 1.

Generally, only one cyclobutane diastereomer is formed. The stereochemistry of **3e** was previously reported to be

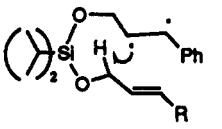
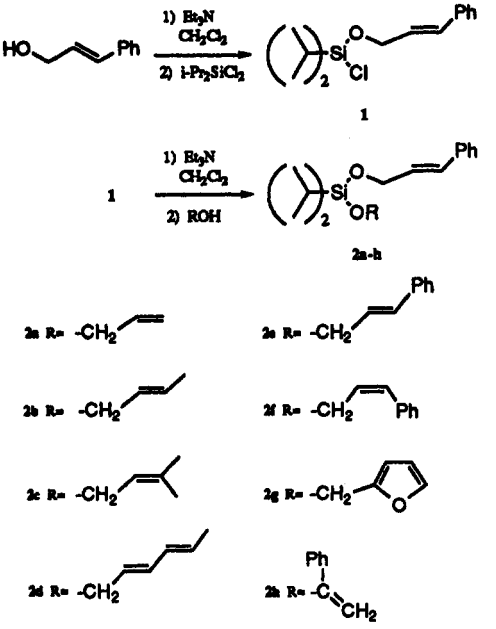


Figure 1.

Scheme 1. Preparation of Silanes



the all trans isomer.[6] Independent synthesis (Scheme 2) has established that **3e** is the β isomer.[9] NMR experiments indicate that the other cyclobutane derivatives have similar stereochemistry, which is consistent with mechanistic information (discussed below).

We believe the cycloaddition proceeds through the excited singlet state for several reasons. First, the observed high diastereoselectivity indicates a very short-lived intermediate. The presence of oxygen has no effect on the yields of cycloaddition. Acetone sensitization results in only trans–cis isomerization of the double bond (no cycloaddition or hydrogen abstraction products). Finally, other workers have shown that styryl systems undergo cycloadditions by way of the singlet excited state.[10]

However, in order to verify that no long-lived radical intermediates are involved, a cyclopropyl-substituted alkene was studied (Scheme 3). The cyclopropylcarbinyl radical opens up at a rate of 1×10^8 s^{-1} at 25 °C.[11] After photolysis at 25 °C and desilylation, **8** gave two diols, the hydrogen abstraction product **9** and cyclobutane **10** in 40 and 55% yields, respectively. As seen in other chemical reactions, the cyclopropyl substitution behaves similarly to a vinyl or phenyl substituent and facilitates the [2 + 2] reaction in our system. No cyclopropyl ring opened products were detected, even at elevated temperatures (82 °C). These results indicate that the reaction does not involve diradical intermediates with lifetimes greater than 10^{-8} s.

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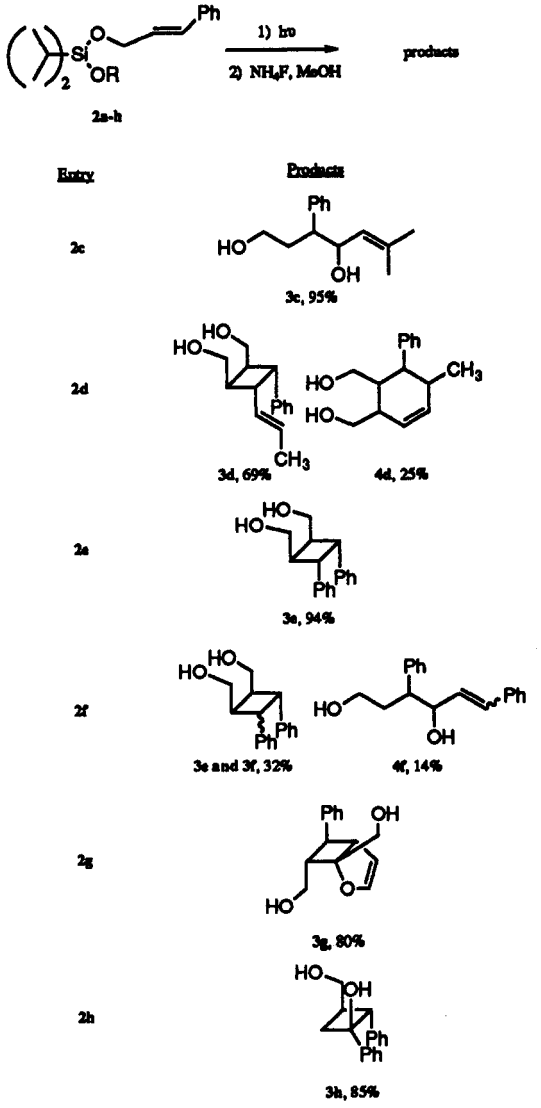
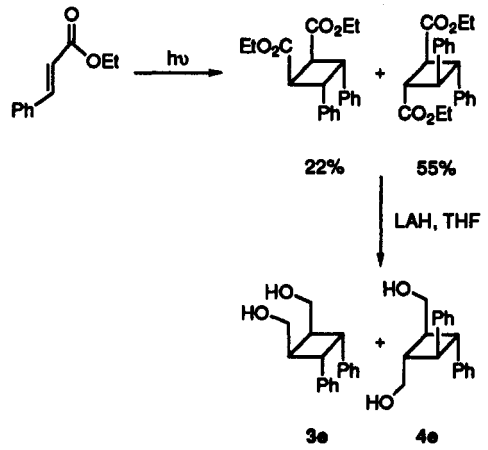
Table 1. Photolysis Results



Scheme 2. Independent Synthesis of Diastereomeric Cyclobutane Diols



With simple alkenes, the [2 + 2] reaction is frequently stereospecific,[12] suggesting a very short-lived intermediate or a concerted reaction. To gain information about the specificity of this [2 + 2] reaction, a stereochemical

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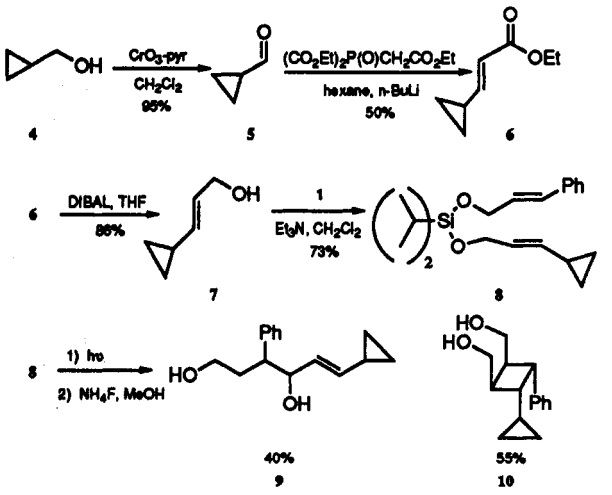
Scheme 3. Preparation and Photolysis of Cyclopropyl Derivative



study was performed. Irradiation of the *cis*-cinnamyl–*trans*-cinnamylsilane **2f** led to the formation of a new cyclobutane, which we have assigned as **3f**, in addition to the β isomer **3e**. We have also irradiated the bis(*cis*-cinnamyloxy)silane derivative. The only cycloaddition products detected were **3e** and **3f** in less than 10% yield. The major pathways were cis–trans isomerization and hydrogen abstraction. Our interpretation of the data is that the [2 + 2] photocycloaddition reaction is stereospecific and that the excited *cis*-cinnamyl moiety does not undergo cycloaddition to any detectable extent. Presumably, **3f** forms only when an excited *trans* molecule reacts with a gound state *cis* molecule. These observations correlate well with the chemistry of stilbene.[13]

The generally accepted mechanism of singlet excited state [2 + 2] cycloadditions involves two steps.[14] First, there is reversible formation of an excited complex (exciplex). The interactions involved in this complex are very weak and generally the most favorable interaction is achieved by maximum overlap of π orbitals. The observed diastereomer **3e** is indeed the adduct that would allow for maximum π overlap. In the second step, the excited complex rearranges to give the pericyclic intermediate, which may go on to cycloadduct. Energetically speaking, the driving force for cycloaddition is the energy minima of the exciplex and pericyclic intermediate. Caldwell's equation[14] has been remarkably successful in predicting whether or not cycloaddition will occur between two alkenes if other processes do not interfere. By his calculation, the reaction of styrene with simple alkenes should be very favorable ($\gamma \sim 15$). However, to our knowledge, no experimental evidence exists for these cycloadditions. Literature examples of styrene cycloadditions include only nucleophilic alkenes.[10] Our results also indicate that cycloaddition does not occur with simple alkenes, but does occur with alkenes that are part of an extended π system. Interestingly, even the cyclopropyl-substituted alkene results in cycloaddition. Lack of cycloaddition between styrene and simple alkenes may be due to either the absence of exciplex formation or ISC of the excited state complexes. We are investigating these possibilities with fluorescence studies.

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Conclusions

Several previously inaccessible cyclobutane derivatives have been synthesized in good yields and high diastereoselectivity. Using the styryl chromophore, the photocycloaddition is efficient with alkenes that are part of an extended π system. Further mechanistic studies are in progress.

Experimental Section

General. NMR spectra were obtained in $CDCl_3$ at 200 MHz (^1H) or 50 MHz (^{13}C) and are reported in ppm from internal standard TMS. Microanalyses were performed by M-H-W Laboratories. All reactions were done under an argon atmosphere, unless noted otherwise. Diisopropyldichlorosilane was purchased from Huls and used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Flash chromatography was conducted with silica gel (200–450 mesh) and the indicated eluents.

Preparation of Diisopropyl(cinnamyloxy)silanes. Triethylamine (0.682 g, 6.75 mmol) and cinnamyl alcohol (0.906 g, 6.75 mmol) were added to an excess of the diisopropyldichlorosilane (5.00 g, 27.0 mmol) at 0 °C in 20 mL of methylene chloride. The reaction was allowed to warm to room temperature and stirred for 10 h. Then the mixture was concentrated, washed with pentane, filtered, and concentrated. Diisopropylchloro(cinnamyloxy)silane (**1**) was isolated (1.8 g, 6.4 mmol, 95% yield) by distillation at 0.25 torr and 200 °C. A second alkoxy group was attached to the silane by adding 1 equiv of triethylamine and the desired alcohol to **1** in 20 mL of methylene chloride. The reaction mixture was stirred for 10 h, concentrated, washed with pentane, and filtered, and the pentane was evaporated off. **2a–h**, **8** were purifed by chromatography (5% EtOAc/95% C_5H_{12} elution). Isolated yields were 75–90%.

General Photolysis Procedure. Irradiations were performed using a Hanovia 450 W medium pressure Hg lamp in a water cooled quartz well with the samples in quartz test tubes at a 1.5 cm distance from the well. The samples were dissolved in acetonitrile and deoxygenated prior to photolysis with nitrogen gas[16] bubbled through the solutions for 20 min. Photolysis concentrations were approximately 0.01 M. Solutions were irradiated until complete conversion of the starting material (1–3 h) was observed by NMR. The solutions were then concentrated and desilylated by refluxing with NH_4F in 10 mL of MeOH for 5–10 h. The reaction mixture was concentrated, a water–chloroform extraction was performed, and the organic layer was concentrated. Chromatography (40% EtOAc/60% C_5H_{12}) gave the pure diols.

1,2-Bis(hydroxymethyl)-3-phenyl-4-(1-propenyl)cyclobutane (3d). The procedure described above gave an oil in 69% yield. Spectral data were as follows: ^1H NMR (D_2O exchange) δ 7.1–7.3 (m, 5H, arom), 5.35 (dq, 1H, alkene), 5.15 (dd, 1H, alkene), 3.95 (m, 2H, OCH_2), 3.70 (m, 2H, OCH_2), 3.35 (dd, 1H, HCPh), 3.15 (m, 1H), 2.85 (m, 1H), 2.65 (m, 1H), 1.5 (d, 3H), CH_3); assignments verified with homonuclear decoupling and COSY experiments. ^{13}C NMR δ 130.8, 128.4, 128.1, 128.0, 126.6, 126.0, 62.6, 62.5, 43.0, 41.8, 41.6, 40.1, 17.8.

1,2-Bis(hydroxymethyl)-3,4-diphenylcyclobutane, β Isomer (3e). In this case, the photolysis time for complete conversion of starting material was only 5 min. The procedure described above gave an oil in 94% yield, based on HPLC analysis. Spectral data were as follows: ^1H NMR (D_2O exchange) δ 7.05 (m, 4H), 7.0 (dd, 2H), 6.95 (d, 4H), 4.1 (dd, 2H), 3.9 (dd, 2H), 3.6 (d, 2H, HCPh), 3.2 (m, 2H); assignments verified by homonuclear decoupling and COSY experiments. ^{13}C NMR δ 139.7, 127.9, 127.8, 125.9, 62.6, 44.1, 40.4.

6,7-Bis(hydroxymethyl)-5-phenyl-1-oxabicyclo[3.2.0]-2-heptene (3g). The procedure described above gave an oil in 80% yield. Based on available information, the stereochemistry has been tentatively assigned. Spectral data were as follows: ^1H NMR (D_2O exchange) δ 7.2–7.4 (m, 5H, arom), 6.39 (bs, 1H, alkene), 4.75 (dd, 1H, alkene), 4.08 (dd, 2H, OCH_2), 3.71 (m, 2H), OCH_2), 3.59 (m, 1H, HCPh), 3.32 (m, 2H); assignments verified by homonuclear decoupling and COSY experiments. ^{13}C NMR δ 147.0, 141.5, 128.2, 127.5, 126.2, 112.3, 89.2, 64.1, 62.1, 52.0, 48.8, 41.1.

1,2-Diphenyl-3-(hydroxymethyl)-1-cyclobutanol (3h). The procedure described above gave a white solid in 85% yield. Spectral data were as follows: ^1H NMR (D_2O exchange) δ 7.0–7.4 (m, 10H, arom), 3.75 (dd, 2H, OCH_2), 3.63 (d, 1H, HCPh), 2.90 (dd, 1H, J = 10 Hz), 2.50 (m, 1H), 2.20 (dd, 1H, J = 10 Hz); regio- and stereochemistry verified by homonuclear decoupling, COSY, and europium shift reagent experiments: ^{13}C NMR δ 127.8, 127.2, 126.3, 65.5, 57.3, 36.4, 32.8, 26.9.

1,2-Bis(hydroxymethyl)-3-phenyl-4-(1-propenyl)cyclobutane, All Trans Isomer (4e). A thin film[17] was prepared by placing *trans*-ethyl cinnamate (0.1 g, 0.57 mmol) between two petri dishes. The film was irradiated for 12 h to give a mixture of cyclobutane esters. The crude mixture was reduced with LAH (18.3 mg, 0.48 mmol), which was added to 5 mL of THF at room temperature. The crude cyclobutane ester mixture was added (0.85 g, 0.24 mmol) and the solution was refluxed for 3 h. The reaction was allowed to cool and then washed with NH_4Cl, $NaHCO_3$, and brine. Chromatography (30% EtOAc/70% C_5H_{12}) gave 10 mg of pure **4e**. The spectral data were as follows: ^1H NMR (D_2O exchange) δ 7.25 (m, 10H), 3.95 (dd, 2H), 3.62 (dd, 2H), 3.19 (d, 2H), 2.4 (m, 2H); ^{13}C NMR δ 142.3, 128.5, 126.8, 126.6, 65.3, 47.5, 47.3.

4-Cyclopropyl-1,2-bis(hydroxymethyl)-3-phenylcyclobutane (10). The procedure described above resulted in complete conversion of **8** to a mixture of **9** and **10**. NMR indicated the mixture was 55% **10**. Repeated chromatography (20% EtOAc/80% C_5H_{12}) gave pure **10**. The spectral data were as follows: ^1H NMR (D_2O exchange) δ 7.1–7.4 (m, 5H, arom), 3.7–4.0 (m, 4H, OCH_2), 3.35 (dd, 1H, HCPh), 3.15 (m, 1H), 2.55 (m, 1H), 1.6 (m, 1H), (–)0.12–0.5 (m, 5H); ^{13}C NMR δ 140.7, 128.7, 128.6, 128.1, 127.9, 127.0, 62.9, 62.6, 44.3, 42.3, 40.9, 39.5, 11.8, 4.1, 2.9.

Cyclopropanecarboxaldehyde (5). Pyridine (26.3 g, 0.33 mol) was added to 420 mL of CH_2Cl_2 at room temperature. Then the CrO_3 (16.7 g, 0.17 mol) was added all at once at rt. The deep burgandy solution was allowed to stir for 15 min. Then alcohol **4** was added (2.0 g, 0.03 mol) and immediately a thick, black precipitate formed. The reaction stirred an additional 15 min. The solution was then washed with 5% NaOH, 5% HCl, $NaHCO_3$, and brine. Most of the CH_2Cl_2 was distilled off a using 24 in. column. On the basis of NMR, there was complete conversion to the aldehyde. The aldehyde was not further purified, but used in the next step as the crude solution. ^1H and ^{13}C NMR were compared with known spectra.

Ethyl 3-Cyclopropyl-2-propenoate (6). Triethyl phosphonoacetate (6.4 g, 0.03 mol) was added to 20 mL of hexane. A 2.5 M solution of *n*-butyllithium in hexanes (11.2 mL, 0.03 mol) was added slowly at 0 °C. Considerable heat evolved and a yellow salt precipitated out of solution. The mixture stirred an additional 5 min and then the crude aldehyde **5** was added slowly (2.0 g, 0.03 mol). The solution was refluxed for 40 min, allowed to cool, quenched with water, and washed with $NaHCO_3$. The solvent was evaporated off and the desired ester isolated by distillation with the Kugelrohr at 100 °C and 1 torr (2.0 g, 0.15 mol, 50% yield).

3-Cyclopropyl-2-propen-1-ol (7). The ethyl ester **6** (1.0 g, 7.1 mmol) was added to 20 mL of freshly distilled THF and the solution cooled to 0 °C. A 1.0 M solution of DIBAL in toluene (14.3 mL, 14.3 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred an additional 5 h. The reaction was then quenched by slowly adding NH_4Cl and then washed with $NaHCO_3$ and H_2O. The desired alcohol was isolated (0.6

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(16) Nitrogen was purified by passing it through an Ace-Burlitch inert atmosphere system containing a column packed with a BASF R3-11 catalyst followed by another column packed with Aquasorb drying agent.

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g, 6.1 mmol, 86% yield) by distillation with the Kugelrohr at 50 °C and 1 torr. ^{1}H NMR was compared with the known spectrum.[18]

Acknowledgment. We thank the Brigham Young University Development Fund for financial support and the National Science Foundation for NMR instrumentation support (Grant No. CHE 8712101).

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra of **3d,e,g,h** and **4e** and ^{1}H NMR spectrum of **10**. Also NMR data for **3c**, **4d**, **4f** (*E* + *Z*), **9**, **1**, **8**, **6**, and **2a−e,g,h**, (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.