# Solvent-Controlled Intramolecular [2 + 2] Photocycloadditions of α-Substituted Enones

**ARTICLE** *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · JULY 2006

Impact Factor: 12.11 · DOI: 10.1021/ja060968g · Source: PubMed

Published in final edited form as:
*J Am Chem Soc*. 2006 June 7; 128(22): 7315–7319. doi:10.1021/ja060968g.

# Solvent-Controlled Intramolecular [2+2] Photocycloadditions of α-Substituted Enones

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## Abstract

The regio- and stereoselectivity of intramolecular [2+2] photocycloadditions of 2′-hydroxyenones are shown to be solvent-dependent. In the presence of aprotic solvents, 2′-hydroxyenones undergo photocyclo-additions in a manner consistent with the presence of an intramolecular hydrogen bond between the carbonyl group and the tether's hydroxy functionality. In protic solvents, intermolecular interactions appear to disrupt the intramolecular hydrogen bond providing products with complementary diastereoselectivity. If the facial accessibility of the α-tethered olefin is limited, the cycloadditions proceed to give head-to-tail or head-to-head regioisomers, depending on the nature of the solvent employed.

## Introduction

Intramolecular [2+2] photocycloadditions between enones and olefins provide rapid and powerful entries into complex polycyclic ring systems.[1] While numerous examples of selective photocycloaddtions have been presented,[2] there are only a few examples of solvent-controlled [2+2] photocycloadditions,[3] particularly involving intramolecular hydrogen bonds that can direct the course of the reaction. Bach and coworkers observed high enantioselectivity in intra- and intermolecular [2+2] photocycloadditions in the presence of a chiral host, which hydrogen bonds to a prochiral substrate or guest.[4] Likewise, Crimmins and coworkers have demonstrated important solvent effects on diastereoselective intramolecular [2+2] photocycloadditions through intramolecular hydrogen bonds with β-dicarbonyl compounds (Scheme 1).[5] The γ-hydroxyl group was proposed to hydrogen bond with the exocyclic carbonyl moiety and direct the facial selectivity, based on choice of solvent. This strategy was used in the total synthesis of gingkolide B.[6]

In a study of intramolecular photocycloadditions of functionalized cyclobutenes, we noted a solvent-dependant intramolecular [2+2] photocycloaddition of 2′-hydroxyenone **1** (Scheme 2).[7] Photocycloadditions of **1** in protic solvents, such as acetone/water led to a preference of the "head-to-head" (straight) coupling product **2** over the "head-to-tail" (crossed) cycloadduct **3** in a 7:1 ratio.[8] Alternatively, when the photocycloaddition was carried out in an aprotic solvent, such as methylene chloride, the crossed product was favored by a 10:1 ratio. It was speculated that an intramolecular hydrogen bond between the enone carbonyl and the 2′-hydroxy group in this substrate was responsible for this solvent-controlled regioselectivity.

Unfortunately, the role of 2′-substituents in these [2+2] photocycloadditions is unclear. In an approach to the guanacastepenes, Sorensen observed a highly selective intramolecular [2+2] photocycloaddition of a 2′-substituted system (eq 1).[9] In this case, only one diastereomer was

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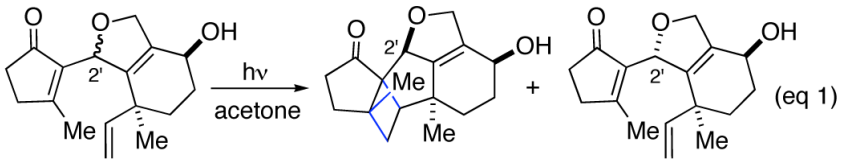
a competent substrate in the [2+2] photocycloaddition. Given these observations, we sought to explore the role of 2′-functionalization in these cycloadditions. We were particularly interested in examining the generality of solvent effects on intramolecular [2+2] photocycloadditions of 2′-hydroxyenones. Accordingly, the regio- and stereochemical results of photochemical cycloadditions of 2′-hydroxyenones in protic and aprotic solvents are described herein.




(eq 1)

## Results and Discussion

As illustrated in Scheme 3, enones with acyclic 2′-hydroxy-containing tethered olefins were synthesized in order to observe the role that steric effects and hydrogen bonding play in the regio- and stereochemical preference of intramolecular [2+2] photocycloadditions. Enones **5** and **8** were prepared in a straightforward manner from either cyclopentenyl bromide **4** or cyclohexenyl bromide **7** (Scheme 3).[10] Lithium-halogen exchange of **4** or **7** occurred after addition of *n*-BuLi at -78 °C, at which time 4-pentenal was added, followed by acidic workup to afford enone **5** and **8**, respectively, in a 60-80% yield. Enone **5** was further transformed to methyl ether **6** using Trost's methylation conditions.[11] This substrate should provide insight into the [2+2] photocycloaddition for systems lacking an intramolecular hydrogen bond.

In a similar fashion, enones **10** and **12**, with one-carbon longer olefin tethers, were also generated. The addition of Weinreb amide **13**, which was readily prepared from 5-hexenoic acid, to the respective vinyl lithium reagent derived from five- or six-membered rings afforded products **9** and **11** in moderate yields. Luche reduction,[12] followed by acidic workup provided substrates **10** and **12** in >80% yields.

With functionalized 2′-hydroxyenones in hand, we examined the photocycloaddition of these systems in a variety of solvents. As shown in Table 1, enone **5** was irradiated with a 450-Watt medium pressure lamp through Pyrex filters in various solvents to yield mixtures of cycloadducts **14a** and **14b**. Resubjection of either cycloadduct to the photolysis conditions did not lead to formation of the other diastereomer; an observation indicating that the products were not equilibrating under the photolysis conditions. The ratio of cycloadducts obtained in these photocycloadditions suggested that an intramolecular hydrogen bond between the 2′-hydroxy group and the enone carbonyl can influence the facial selectivity of the interacting π-systems.[13]

The results summarized in Figure 1 point to a role that solvent may play in controlling these intramolecular photocycloadditions. In aprotic solvents, such as methylene chloride, an intramolecular hydrogen bond between the 2′-hydroxyl and the carbonyl groups can orient the enone and pendent olefin to provide a particular facial selectivity between the two reactive π-systems leading to adduct **14b**. In protic solvents, however, hydrogen bonding with the solvent competes effectively with the intramolecular interaction, affording the opposite facial selectivity between the enone and tethered olefin. This orientation leads to diastereomer **14a**. As indicated in entry 2 of Table 2, [2+2] photocycloaddition of methyl ether **6** provides only cycloadduct **15** regardless of the solvent employed. The relative stereochemistry of this photoproduct is similar to adduct **14a**, where the intramolecular hydrogen bond is not present.

The transformations described in entries 3-5 of Table 2 explore the scope of the solvent-controlled photocycloadditions with 2′-hydroxyl-containing substrates with larger cyclic enones and longer tethered olefins. In all cases, the two reactive π-systems interact in a "head-to-head" fashion, where their facial selectivity is dictated by the presence or absence of an intramolecular hydrogen bond.[14] Cyclohexenone **8**, shown in entry 3 for example, reacted in a very similar manner to substrate **5**. Protic solvents favored photoadduct **18a**, while aprotic solvents led to **18b** as the major product. The results of photocycloadditions of substrates with an additional methylene group in the pendent olefin are shown in entries 4 and 5. In these examples, the solvent-dependent facial control improved in protic and aprotic solvents, however, the overall efficiency of the photocycloaddition appeared to suffer as indicated by the lower yields.[15]

Conformation of the structures for cycloadducts **14a** and **14b** was accomplished through the correlation studies illustrated in Scheme 4. Compounds **14a** and **14b** were shown to be diastereomers through oxidation of both secondary alcohols to the same diketone **17**. Derivatization of **14a** to bromobenzoate **16** allowed for confirmation of relative stereochemistry for diastereomer **14a** through X-ray crystallographic studies. The structures and stereochemistry of the remaining cycloadducts were confirmed in a related fashion. As shown in Scheme 4, photoadducts **18a**, **18b**, **19a**, and **19b** could all be transformed into the same diketone **21**. Likewise, the diastereomeric relationship between adducts **20a** and **20b** was demonstrated through a PCC oxidation to diketone **22**. These studies, combined with additional X-ray crystallographic information,[16] allowed for the unambiguous structural assignment for each of the photoadducts.

These diastereoselective cycloadditions differ from the solvent-dependent straight and crossed photocycloadditions observed with enone **1**. We suspect this disparity arises from structural constraints imposed by compound **1**'s polycyclic ring system. That is, regardless of solvent, only one face of the isolated olefin is available to the excited enone. For substrate **5**, the presence or absence of an intramolecular hydrogen bond dictates the facial selectivity of both the isolated olefin and enone; however, only the enone facial selectivity is influenced in substrate **1**. The generality of these solvent-controlled regio- and diastereoselective photocycloadditions was probed with substrates that limit olefin accessibility.

As illustrated in Figure 2, substrate **23**, with a tethered cyclopentenyl ring, offers a system that restricts the pendent olefin's accessibility. As shown in eq 2, conditions that allow an intramolecular hydrogen bond between the enone and 2′-hydroxyl group should lead to photoadduct **24**, with a head-to-head coupling between the enone and accessible face of the tethered olefin. If the intramolecular hydrogen bond is broken through intermolecular interactions, the stereogenic center on the cyclopentenyl ring prohibits the other face of the enone from interacting (in a low energy manner) with the opposite face of the tethered olefin (eq 3), as was observed with substrate **5**. Instead, the opposite face of the enone interacts with the accessible face of the attached olefin to yield the head-to-tail (crossed) product **26** shown in eq 4. To test this hypothesis, enones **27** and **28** were prepared and studied in intramolecular [2+2] photocycloadditions in protic and aprotic solvents.

As outlined in Scheme 5, enones **27** and **28** were generated in three steps from enantiopure acid **29**.[17] Weinreb amide **30** was prepared employing Scheffer's protocol.[18] Addition of the lithium reagent derived from cyclopentene **4** to Weinreb amide **30** then yielded substrate **31** in 51% yield. CBS reductions using each antipode of the catalyst, followed by mild hydrolysis produced the diastereomeric enones **27** and **28** in >10:1 diastereomeric purity as determined by chiral HPLC analysis.

Enone **27** underwent an intramolecular photochemical cycloaddition in an aprotic solvent ($CH_2Cl_2$) to give the head- to-head cycloadduct **32** as the major product, albeit in low yield (Table 3). In contrast, using an acetone/water mixture as solvent to disrupt the intramolecular hydrogen bond in **27** forced the cycloaddition to go in a head-to-tail fashion to provide compound **33** as the major isolable product, again with low efficiency. These results follow the reactivity trends discussed in Figure 2.

Likewise, when diastereomer **28** was subjected to the same set of reaction conditions, a similar, but less pronounced selectivity trend was observed. Irradiation of enone **28** in a protic environment afforded mainly the head-to-head cycloadduct **35** in 64% yield. Switching the solvent to $CH_2Cl_2$ generated more of the head-to-tail regioisomer **36**, but still in a minor amount compared to **35**. While the regioselectivity in this series is influenced by the presence or absence of an intramolecular hydrogen bond, there are also other factors,[19] such as steric effects that play an important role in dictating the facial and regioselectivity in these intramolecular [2+2] photocycloadditions.[8]

As with the previous substrates, the diastereoisomeric relationship between photoadducts **32** and **35**, as well as **33** and **36**, was demonstrated by oxidation to the same diketones. This information, coupled with X-ray crystallographic studies summarized in Figure 3 allowed for unambiguous assignment of relative stereochemistry of these cycloadducts.

## Summary

There has been a longstanding interest in the factors influencing [2+2] photocycloadditions of cyclic enones.[20] For 2′-hydroxyenones, the regio- and diastereoselective outcome of intramolecular [2+2] photocycloadditions can be dictated by solvent. An intramolecular hydrogen bond between the carbonyl and 2′-hydroxyl group can govern the facial selectivity between the two interacting π-systems under photochemical [2+2] conditions. Changing the tether to a conformationally restricted olefin, however, limits one π-system affording complementary regioselective cycloadditions in protic and aprotic media.

## Experimental Section

### Representative procedure for the intramolecular [2+2] photocycloaddition

To a thick-walled, flame-dried, Pyrex reaction tube was added the α,β-unsaturated ketone (1 equiv) and solvent [3.7 mM]. The solution was degassed by bubbling $N_2$ through the solution for 15 min and then irradiated through a 4 mm barrier of Pyrex with a 450 W medium pressure Hanovia mercury lamp until the reaction was deemed finished by TLC analysis. The reaction was concentrated under reduced pressure, and purified through silica gel flash chromatography.

### Representative procedure for the oxidation of photocycloadducts

To a stirred solution of the photocycloadduct (1.0 equiv) in $CH_2Cl_2$ [0.1-0.01 M] was added pyridinium chlorochromate (PCC 20% on basic alumina, 2.0 equiv). The reaction was stirred at room temperature until the starting material was deemed consumed by TLC analysis. The reaction mixture was filtered through a plug (1 cm) of celite and the filtrate was washed with a solution of saturated $CuSO_4$ (2 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation.

### Representative procedure for the derivatization of the [2+2] photocycloadducts

To a solution of cycloadduct (1 equiv) in $CH_2Cl_2$ [0.1 M] cooled to 0 °C was added 4-bromobenzoic acid (1.1 equiv), 4-dimethylaminopyridine (DMAP, 0.5 equiv), and *N*,*N*'-dicyclohexylcarbodiimide (DCC, 1.1 equiv). The reaction was warmed slowly to room

temperature. After the reaction was deemed finished by TLC analysis, the mixture was diluted with $CH_2Cl_2$ and dried with $MgSO_4$. The solution was filtered, concentrated, and purified through silica gel chromatography. The product was then recrystallized under the appropriate conditions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgment

We thank the National Institute of General Medical Sciences (National Institutes of Health, GM62824) for financial support. We are grateful to Schering-Plough for X-ray facility support, and Keith Griswold, Wayne Lo, and Dr. Richard J. Staples for substantial assistance with X-ray crystallographic studies.

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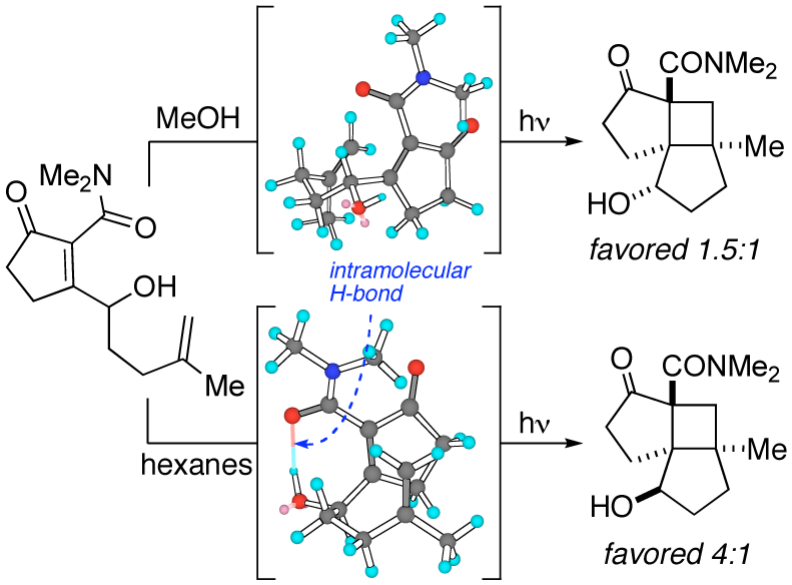
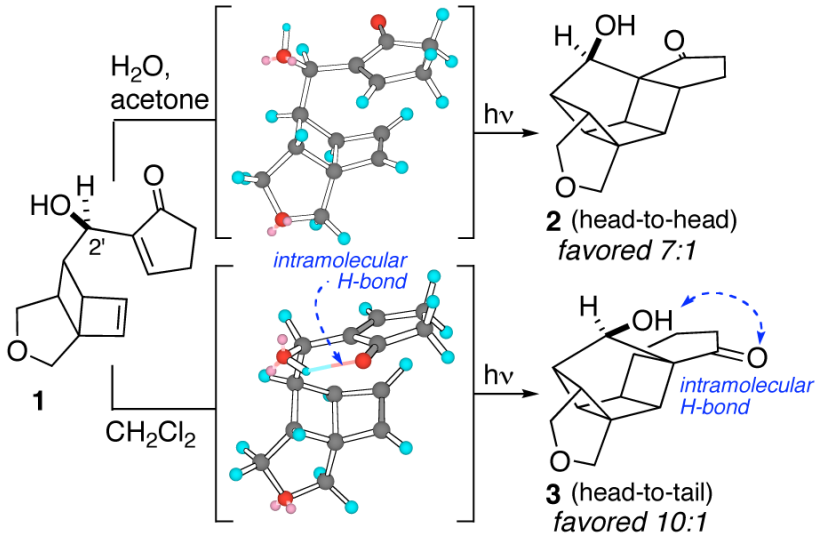
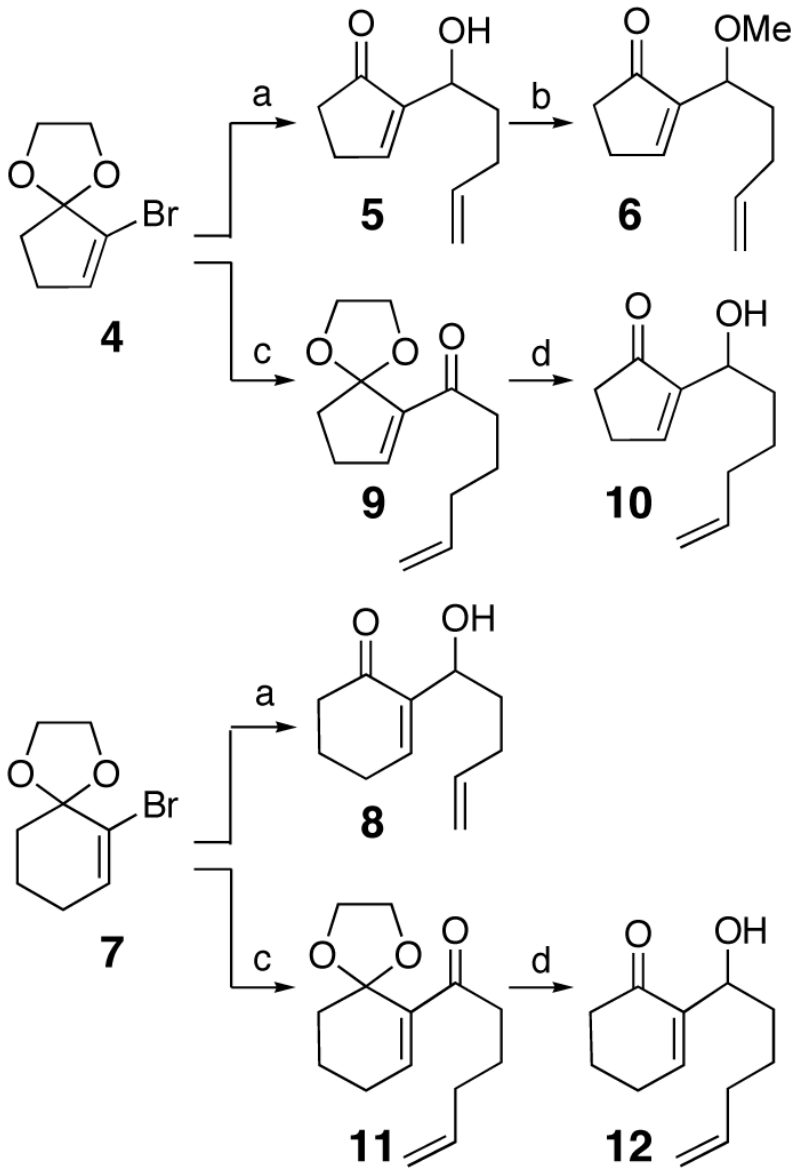



**Scheme 1.**
Crimmins' solvent-dependant intramolecular [2+2] photocycloadditions.



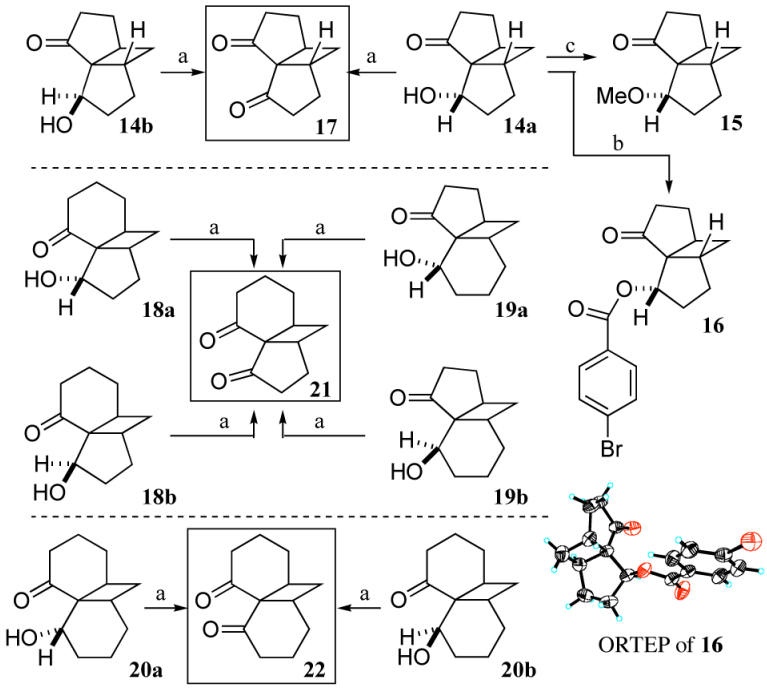

**Scheme 2.**
Solvent-dependant regioselective intramolecular [2+2] photocycloadditions.




**Scheme 3.**

Synthesis of 2′-hydroxyenones.

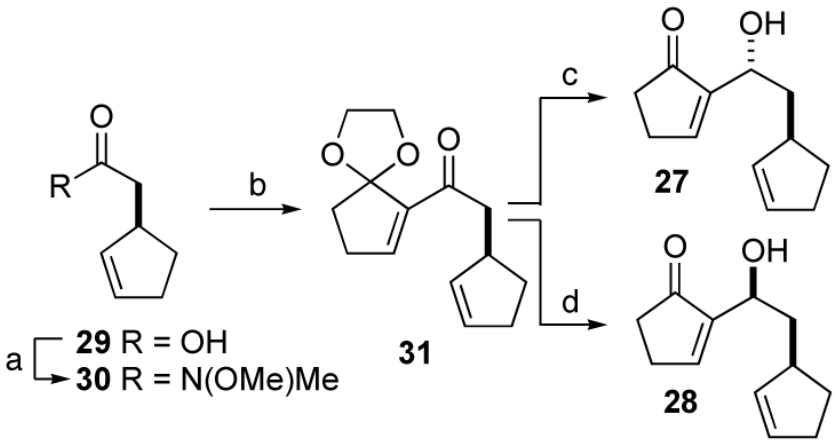
(a) 1. *n*-BuLi, -78 °C, THF 2. 4-pentenal, 1M HCl (60-80% over 3 steps). (b) $Ag_2O$, MeI, 58 °C, 48 hrs (60-70%). (c) 1. *n*-BuLi, -78 °C, $Et_2O$. 2. *N*-methoxy-*N*-methylhex-5-enamide **13** (57%, 2 steps). (d) 1. $CeCl_3$, $NaBH_4$, MeOH, 0 °C. 2. 1M HCl (80% 2 steps).




**Scheme 4.**

Structural confirmation of photocycloadducts.

(a) PCC (20% on basic alumina), $CH_2Cl_2$ (75-85%). (b) DMAP, DCC, *p*-bromobenzoic acid, $CH_2Cl_2$ (60%). (c) $Ag_2O$, MeI, $CH_3CN$ (67%).




**Scheme 5.**

Synthesis of diastereomers **27** and **28**.

(a) N,O-dimethylhydroxylamine hydrochloride, CDI, $CH_2Cl_2$, 0 °C (79%). (b) **4**, *n*-BuLi, -78 °C, THF (51%). (c) (R)-1 methyl-3,3 diphenyl-1H,3H pyrrolo[1,2-c][1,3,2]-oxasaborole, $BH_3$-THF, Toluene, 0 °C; then 1M HCl (50-70%). (d) (S)-1 methyl-3,3 diphenyl-1H,3H pyrrolo [1,2-c][1,3,2]oxasaborole, $BH_3$-THF, toluene, 0 °C; then 1M HCl (50-70%).

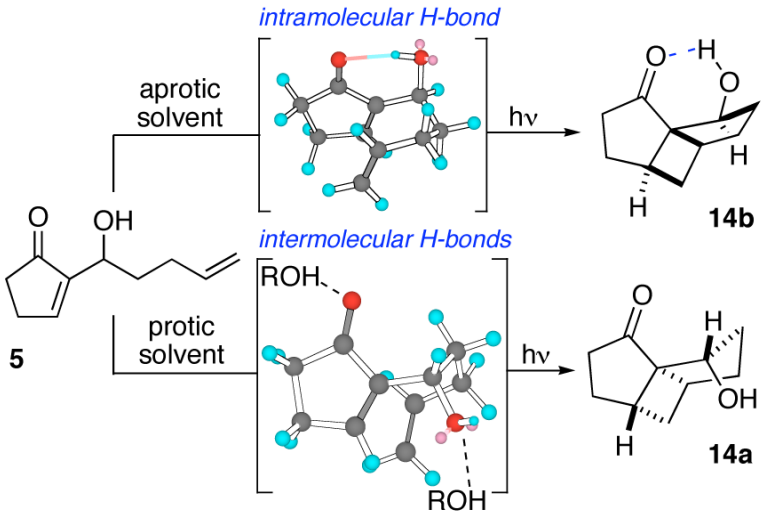



**Figure 1.**
Photocycloaddition facial selectivity controlled by intra- and intermolecular hydrogen bonding.

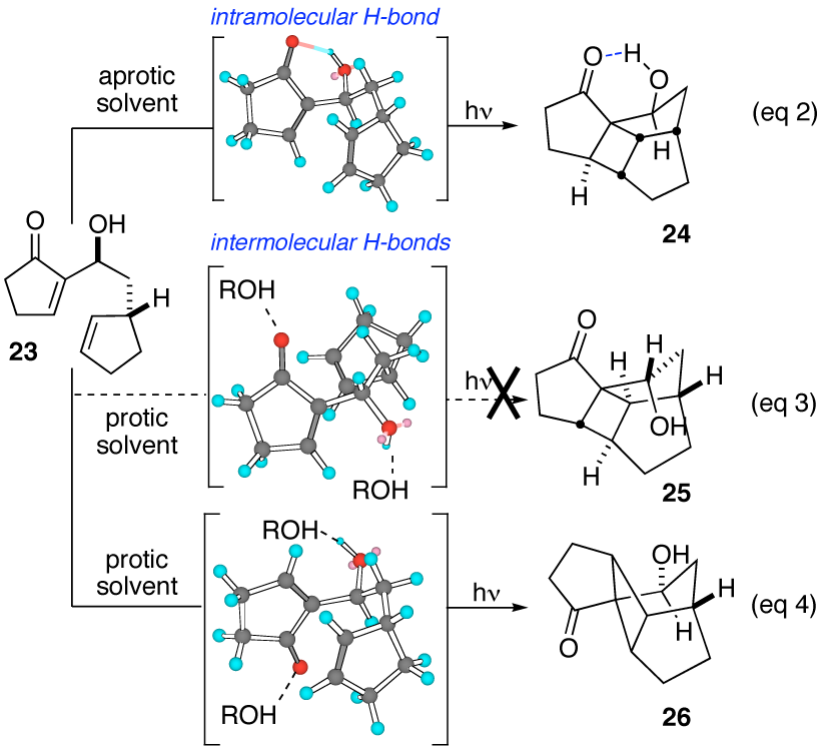



**Figure 2.**
Regioselectivity controlled by hydrogen bonding and olefin accessibility in [2+2] photocycloaddition.

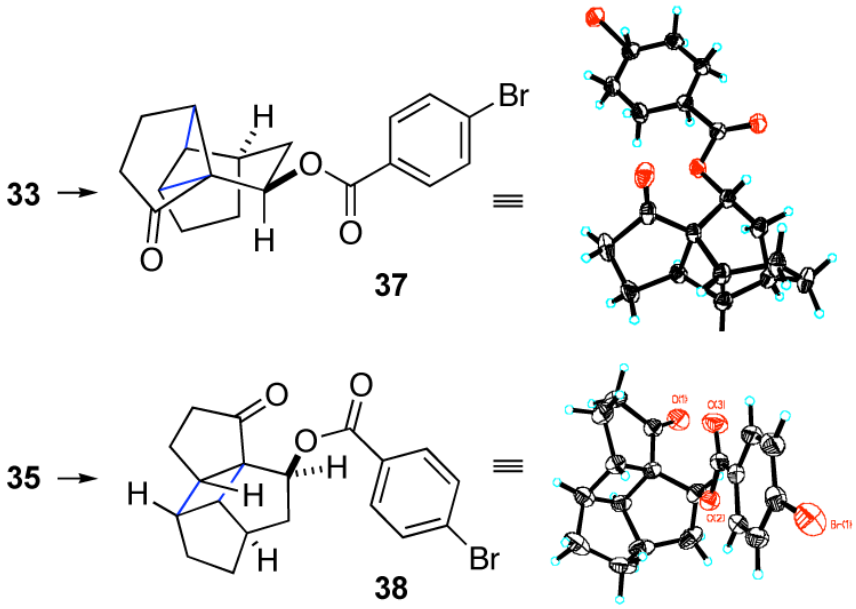
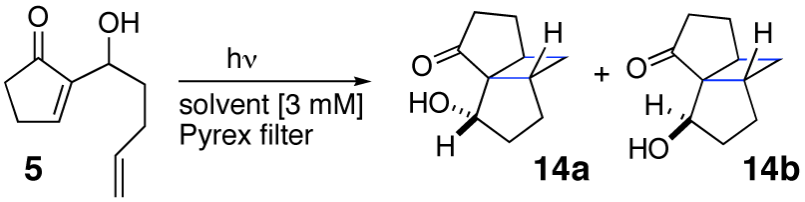



**Figure 3.**
ORTEPs of *p*-bromobenzoic esters of photoadducts **33** and **35**.

**Table 1**

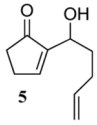
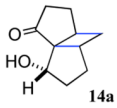
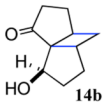
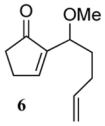
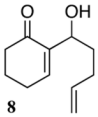
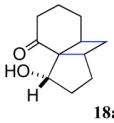
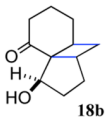
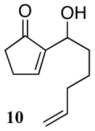
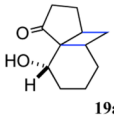
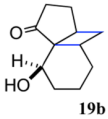
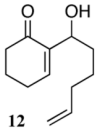
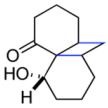
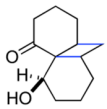
Intramolecular [2+2] photocycloadditions solvent screen




| entry | solvent | 14a | 14b | yield(%) |
|---|---|---|---|---|
| (1) | acetone/$H_2O$ | >20 | 1 | 60 |
| (2) | methanol | >20 | 1 | 65 |
| (3) | acetonitrile | 5 | 3 | 77 |
| (4) | diethyl ether | 2 | 1 | 90 |
| (5) | dichloromethane | 1 | 6 | 80 |
| (6) | pentane | 1 | 2 | 63 |
| (7) | cyclohexane | 1 | 3 | 42 |

**Table 2**

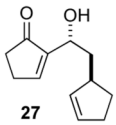
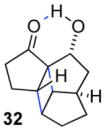
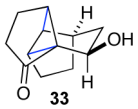
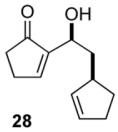
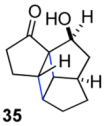
Solvent dependant intramolecular [2+2] photocycloadditions

| entry | enone | products | solvent/yield/ratio |
|---|---|---|---|
| (1) |  **5** |  **14a**  **14b** | $CH_2Cl_2$ 80% **14a/14b** (1:6)<br>acetone/$H_2O$ 60% **14a/14b** (>20:1) |
| (2) |  **6** |  **15** | $CH_2Cl_2$ 89% (81% conv.)<br>MeOH 60% (87% conv.) |
| (3) |  **8** |  **18a**  **18b** | $CH_2Cl_2$ 72% **18a/18b** (1:4)<br>acetone/$H_2O$ 74% **18a/18b** (6:1) |
| (4) |  **10** |  **19a**  **19b** | $CH_2Cl_2$ 47% **19a/19b** (>1:20)<br>acetone/$H_2O$ 38% **19a/19b** (>20:1) |
| (5) |  **12** |  **20a**  **20b** | $CH_2Cl_2$ 21% **20a/20b**(1:10)<br>acetone/$H_2O$ 40% **20a/20b** (16:1) |

All reactions: h*v*, Pyrex filter, 3mM in solvent.

## Table 3

[2+2] Photocycloadditions of **27** and **28**

| entry | enone | products | solvent/yield/ratio |
|---|---|---|---|
| (1) |  **27** |  **32**  **33** | $CH_2Cl_2$ 25% **32**/**33** (3:1) acetone/$H_2O$ 25% **32**/**33** (>1:20) |
| (2) |  **28** |  **35**  **36** | $CH_2Cl_2$ 60% **35**/**36** (2:1) acetone/$H_2O$ 64% **35**/**36** (>20:1) |

All reactions: h*v*, Pyrex filter , [3 mM].