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CONSTRUCTION OF UNIQUE HETEROCYCLIC FRAMEWORKS BY PHOTOCHEMICAL REACTION OF 5- AND 6-MEMBERED HETEROAROMATICS

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Abstract – Photochemical reaction is an attractive synthetic method since it enables peculiar transformations that are not achievable under thermochemical reaction conditions. Construction of heterocyclic frameworks is one of the largest research fields in synthetic organic chemistry, but the utilization of photochemical reactions for heterocyclic-framework construction is limited to such reactions as typical [2+2] cycloaddition reaction, dye-sensitized generation of singlet oxygen, and photochemical radical generation. In this review, we focus on novel methods for the construction of unique molecular frameworks by means of photochemical reactions of heteroaromatic cyclic compounds, including mainly 5-membered heteroaromatics, furans, thiophenes, thiazoles, and oxazoles, as well as several 6-membered compounds. In some cases, heteroaromatic compounds act as acceptors of other photochemically excited molecules, such as ³(n-π*) of carbonyl compounds, and in other cases the heteroaromatic compounds themselves are excited to generate reactive species that participate in the unique bond-forming reactions.

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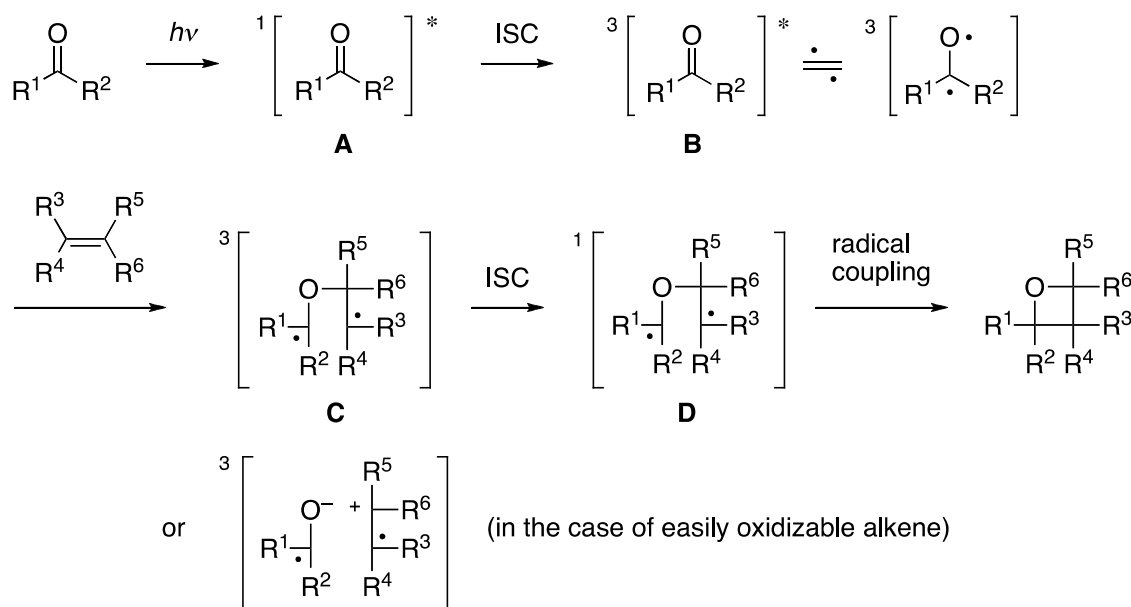
1. INTRODUCTION

Heterocyclic frameworks are a common structural motif in biologically active natural products, pharmaceuticals, and agrochemicals.¹ Accordingly, organic chemists have very actively pursued the development of preparative methods for heterocyclic compounds as well as the characterization of their specific properties.² Among the numerous methods for constructing heterocycles, photochemical cyclization and cycloaddition form a conspicuous category of reactions because they often yield unusual architectures that are hardly accessible by means of ground state chemistry.³ This feature of the photochemical construction of heterocyclic frameworks is of much interest, especially from a standpoint of diversity oriented synthesis. Compounds bearing a peculiar heterocyclic core formed by photochemical cyclization or cycloaddition could provide clues to unexplored biological activities and chemical properties. While typical photoreactions that include isomerization, [2+2] cyclobutane formation, Paternò-Büchi oxetane construction, photochemically initiated radical cyclization, and so on, are frequently employed in the preparation of heterocycles and have been well reviewed,⁴ direct use of the intrinsic photochemical properties of heterocyclic compounds to build up heterocyclic skeletons is less common. This short review is not comprehensive, but is intended to provide readers with recent examples of the construction of unique heterocyclic frameworks by means of photochemical reaction of several 5- and 6-membered heterocycles, along with their typical photochemical behaviors. We include a few results done by our own group.

2. FURAN

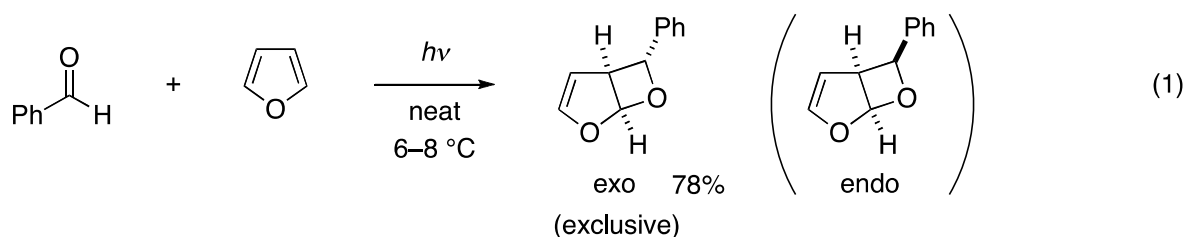
Furans are known as common substrates for a number of photochemical reactions, including photoisomerization,^{5,6} photooxidation with singlet oxygen,^{7,8} and cycloaddition reaction.^{3,9-13} Among these reactions, photochemical oxetane formation with carbonyl compounds (Paternò-Büchi reaction) is perhaps the most widely studied.^{14,15} Those regio- and stereoselectivities of these reactions have been extensively studied. The generally accepted mechanism of the reaction is depicted in Scheme 1.^{3,16} The carbonyl group absorbs light to generate the singlet excited state **A**, which is rapidly converted to its triplet state **B** through an intersystem crossing (ISC) process. Usually, irradiation with >300 nm UV is employed for the excitation. The excited carbonyl group reacts with alkene to give an intermediary triplet 1,4-diradical **C** or radical ion pair **C'** depending on the relative relationship between the redox potential of

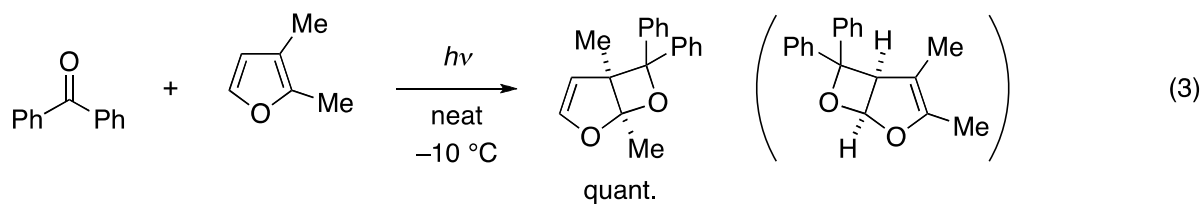
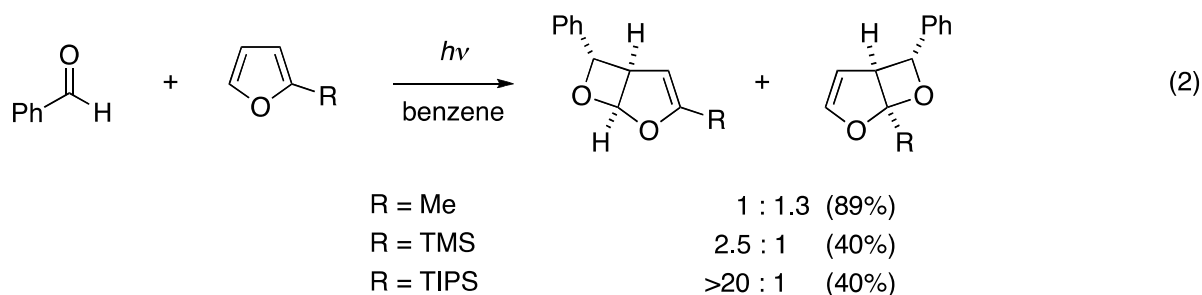
the ketone and that of the alkene. Intramolecular coupling of the singlet biradical **D** produced by ISC affords an oxetane.



Scheme 1. Mechanism of the Paternò-Büchi reaction

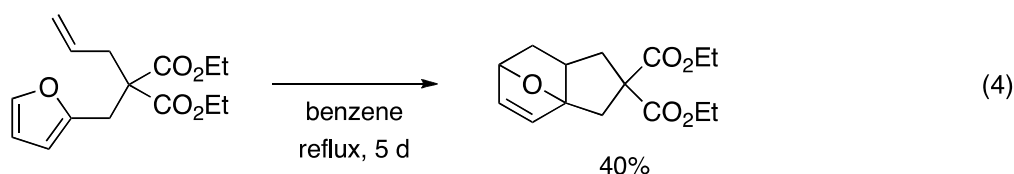
It should be noted that the oxygen atom in the excited carbonyl has an electrophilic character and the first C–O bond formation occurs preferentially at the alkene carbon with a larger HOMO coefficient. The photochemical cycloaddition reaction between furans and carbonyl compounds gives the corresponding oxetanes in moderate to high yield, but the site- and stereoselectivities are rather complicated. The reaction between simple furan and benzaldehyde gave oxetane with almost perfect stereoselectivity (Eq. 1).¹⁷ However, in the reaction of unsymmetrically substituted furans with benzaldehyde, it was reported that the site-selectivity was difficult to control though the stereoselectivity was completely exo-selective (Eq. 2).¹⁸ Thus, an almost 1 : 1 mixture of products was obtained in the reaction with 2-methylfuran. But the site selectivity could be nicely controlled by using a substituent bulky enough to give the less-crowded product. In the case of the reaction between unsymmetrical furans and benzophenone, the oxetane formation preferentially took place at the position bearing the alkyl substituent (Eq. 3).¹⁹



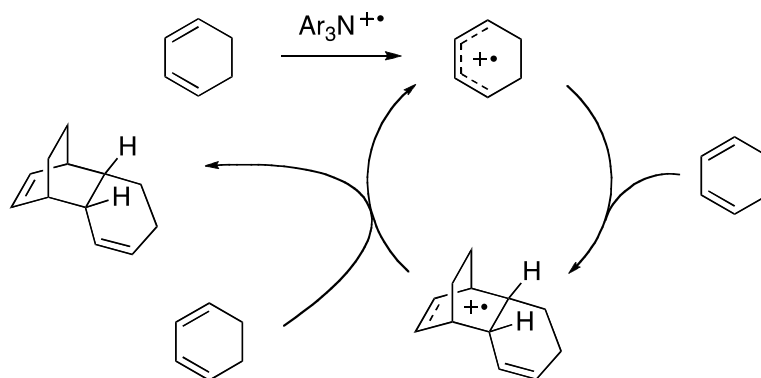
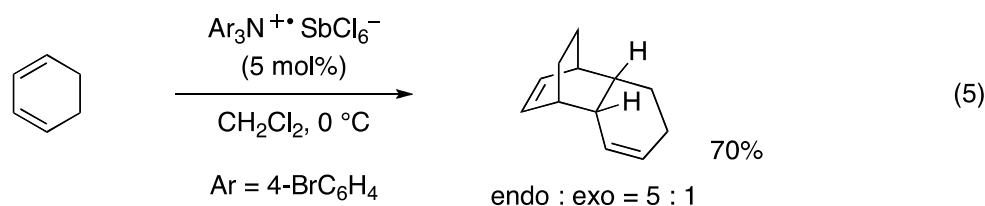


More recently, Abe and collaborators pointed out that the conformational distribution in the intermediary triplet 1,4-diradicals is important when considering the mechanism of stereo- and regioselectivity in the Paternò-Büchi reaction of furan derivatives with aromatic carbonyl compounds.²⁰

Diels-Alder reaction of furans in their ground state is known as a powerful synthetic tool for the construction of a 6-membered ring system with oxygen functionality.²¹ Intramolecular Diels-Alder reaction of furans is a particularly attractive method, since two or more ring systems can be constructed in a single stroke in a highly regio- and stereoselective manner.^{22,23} However, Diels-Alder reactions between furans and electron-rich dienophiles are known to proceed with difficulty even under harsh reaction conditions, whereas the reactions with electron-deficient dienophiles proceed smoothly (Eq. 4).²⁴⁻²⁶

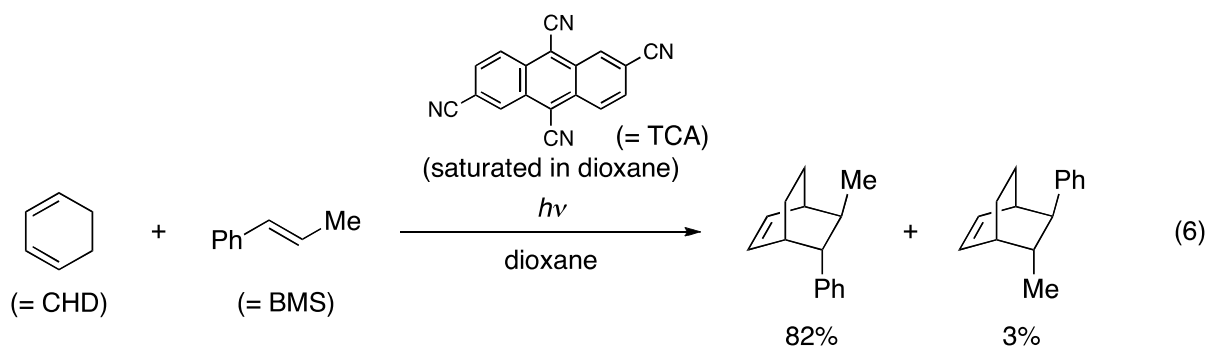


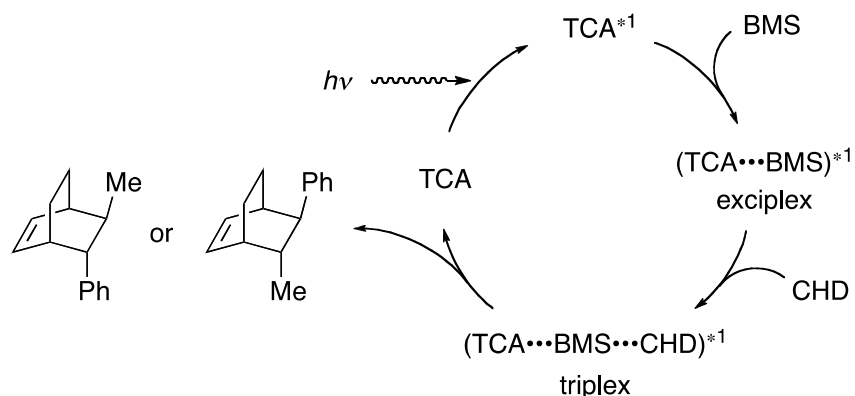
To circumvent this problem, some modified methods have been reported.²⁷⁻³⁰ The cycloaddition reaction through radical ions or excited states is also known as an effective method for making the Diels-Alder reaction between electron-rich dienes and alkenes proceed more easily. Bauld and co-workers reported that Diels-Alder-type dimerization of 1,3-cyclohexadiene and other electron-rich dienes proceeded well via single electron transfer with triarylamminium salts.^{31,32} A radical cation chain process was proposed for these reactions (Eq. 5, Scheme 2).³²



Scheme 2. Proposed mechanism of the [4+2] cycloaddition via cation radical

Several research groups described that the [4+2] cycloaddition reactions of 1,3-cyclohexadiene and related compounds with electron-rich dienophiles were catalyzed by cyanoarenes under UV irradiation (Eq. 6).³³⁻³⁵ Schuster and co-workers proposed that these reactions proceed through intermediary excited-state ternary complexes (triplex) (Scheme 3).^{34,35}

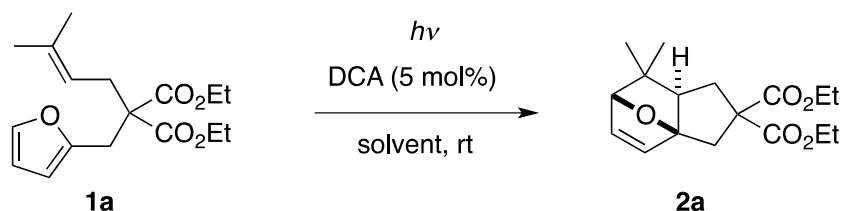




Scheme 3. Proposed mechanism of the triplex Diels-Alder reaction

We investigated the intramolecular Diels-Alder reaction of furans under photosensitized conditions and found that the reactions with appropriately designed furyl alkenes proceeded in high yield with excellent stereoselectivity.³⁶ In order to find the most appropriate solvent, we first examined the photocycloaddition reaction of **1a** in a series of solvents in the presence of 9,10-dicyanoanthracene (DCA).

Table 1. Solvent effect on the photocycloaddition of **1a**^a



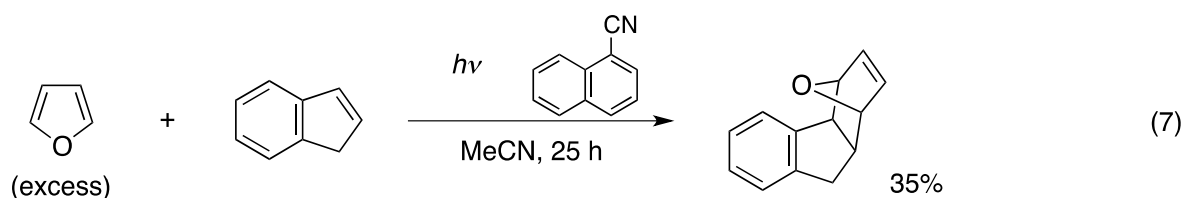
Entry	Solvent	Time (h)	Yield of 2a (%) ^b	Recovery of 1a (%) ^b
1	benzene	8	36	61
2	toluene	8	21	78
3	THF	8	25	71
4	DME	8	31	63
5	1,4-dioxane	8	31	65
6	AcOEt	8	40	58
7	MeCN	9	2	87
8	MeOH	9	0	94
9	benzene	84	89 (79) ^c	2

^a The reaction was conducted under the following conditions: initial concentration of **1a**, 0.04 M; DCA, 5 mol%; temperature, 20 °C; carried out in a Pyrex tube under irradiation with a high-pressure mercury lamp. ^b Estimated by ¹H NMR integration by using pyrazine as an internal standard. ^c Isolated yield in parentheses.

As shown in Table 1, the reaction proceeded well in non-polar solvents (Entries 1, 2), as well as medium polar ones (Entries 3–6). The cyclized product **2a** was obtained in diastereomerically pure form, judging from the ^1H NMR spectrum. The relative configuration was determined by an NOE experiment. We confirmed the quantitative recovery of **2a** without change after irradiation of isolated **2a** under the same conditions. In contrast to the results in entries 1–6, the reactions in highly polar solvents hardly proceeded and resulted in recovery of **1a** (Entries 7, 8). These results strongly suggest that the electron transfer mechanism producing charged species $\mathbf{1a}^{+\bullet}$ and $\text{DCA}^{\bullet-}$ is less likely for the cycloaddition of **1a**, but that the formation of a non-charged exciplex between **1a** and DCA is more likely, as proposed by Schuster and co-workers.^{34,35} We also obtained the following results which support the above consideration. (1) No reaction occurred after irradiation of **1a** in benzene for 15 h without DCA, resulting in quantitative recovery of **1a**. (2) Treatment of **1a** with $(4\text{-BrC}_6\text{H}_4)_3\text{N}^+(\text{SbCl}_6^-)$, a typical one-electron oxidizing reagent, in CH_2Cl_2 resulted in the recovery of **1a** without the production of **2a**.

In the above investigation, benzene was chosen as the most suitable solvent, since the yield of **2a** was relatively high and the sensitizer was less decomposed during the reaction (Entry 2). We next tried the reaction in benzene for a prolonged time and found that the yield of **2a** increased to a synthetically useful level (89%, Entry 9). We carried out the reaction under the condition of high DCA loading, hoping for an increase in the reaction rate. The cyclized product **2a** was obtained with a yield as high as that in Entry 9, but the expected acceleration was not observed.

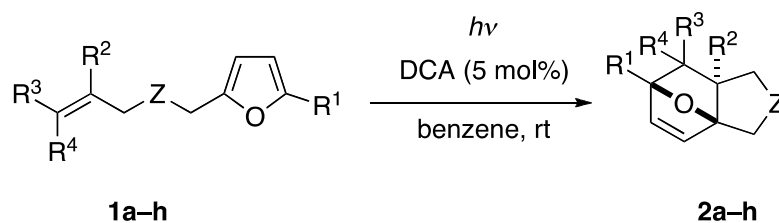
Mizuno, Otsuji, and collaborators reported that a reaction between excess furan and indene mediated by 1-cyanonaphthalene under UV irradiation gave the [4+2] cycloaddition product in 35% yield (Eq. 7).³⁷ They also described that reactions with other alkenes afforded little or no addition product. This pioneering work appeared to leave room for improvement in terms of the reaction efficiency and generality.



Next, the reaction was applied to various substrates by changing substituents around the alkene and the tether moiety. The results are summarized in Table 2. The structure around the olefinic moiety turned out to have a pronounced effect on the product yields. In contrast to **1a** (Entry 1), neither the simple allyl substrate **1b**, methallyl type **1c**, or trisubstituted substrate **1d** underwent cyclization under the standard reaction conditions, and thus all the starting materials were recovered (Entries 2–4). Only tetrasubstituted

alkene **1e** afforded the sterically congested product **2e** in 35% yield (Entry 5). It is quite interesting that only the most bulky substrate could afford the product. Although the reason for this finding was not clarified, both electronic and steric factors might be involved. On the other hand, the tether moiety was less critical for the cyclization. That is, alkenyl furan tethered by amine linkage (**1f**) cyclized under the standard reaction conditions to give the product **2f** in moderate yield with complete stereoselectivity (Entries 6, 7). With regard to **1f**, dioxane gave a better yield than benzene. The diester moiety can be replaced with other functionalities. For instance, diether **1g** also afforded the corresponding cyclized product **2g** in good yield (Entry 8). Substitution on the furan ring did not have an inhibitory effect on the reaction. Thus, when the 5-methyl derivative **1h** was employed as a substrate, the cyclized product **2h** was obtained in high yield and exclusive stereoselectivity (Entry 9). It should be noted that the trimethyl-substituted oxabicyclo[2.2.1]heptane moiety with high steric hindrance was constructed by a simple operation, as well as **2e**.

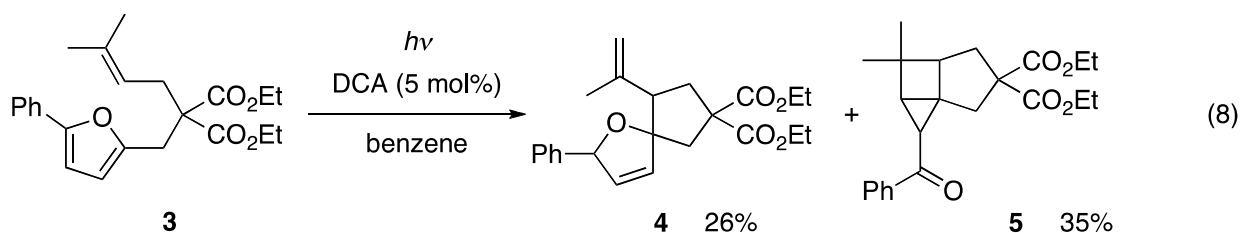
Table 2. Substituent effect on the photocycloaddition



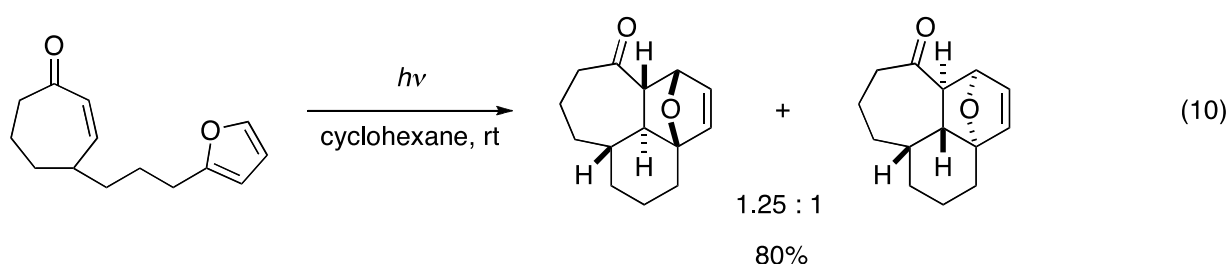
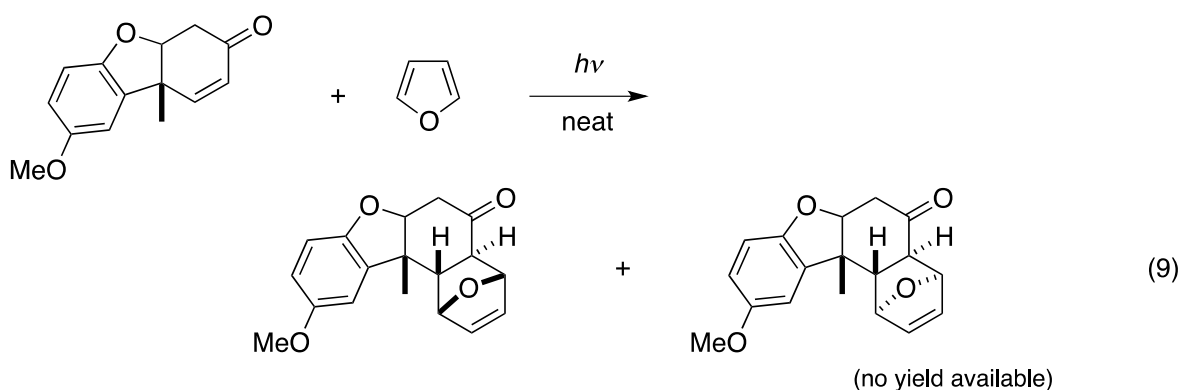
Entry	Subst.	R ¹	R ²	R ³	R ⁴	Z	Yield (%) ^a
1	1a	H	H	Me	Me	C(CO ₂ Et) ₂	79
2	1b	H	H	H	H	C(CO ₂ Et) ₂	0
3	1c	H	Me	H	H	C(CO ₂ Et) ₂	0
4	1d	H	Me	Me	H	C(CO ₂ Et) ₂	Trace
5	1e	H	Me	Me	Me	C(CO ₂ Et) ₂	35 ^b
6	1f	H	H	Me	Me	NBoc	38 ^b
7 ^c	1f	H	H	Me	Me	NBoc	55 ^b
8	1g	H	H	Me	Me	C(CH ₂ OMe) ₂	82
9	1h	Me	H	Me	Me	C(CO ₂ Et) ₂	82

^a Isolated yield. ^b Contains small amounts (approx. 2–3%) of inseparable DCA. ^c 1,4-Dioxane was used as solvent.

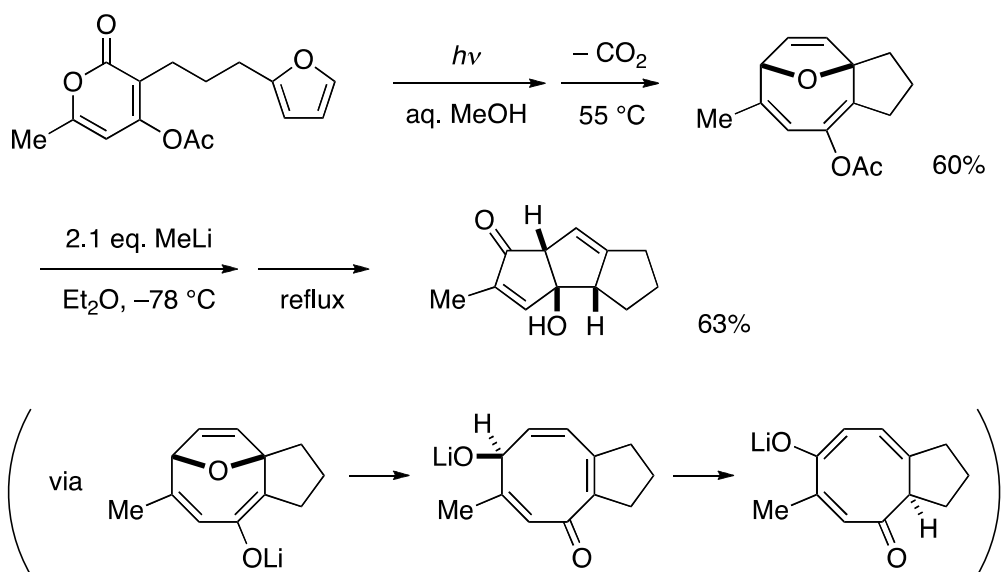
Interestingly, substitution at the 2-position by a phenyl group changed the reaction course dramatically. Irradiation of **3** under the conditions described above did not give the [4+2]-type products, but two new compounds, spirocyclic **4** and tricyclic **5** (Eq. 8).



Diels-Alder reaction between cycloalkenones with fewer than nine ring members and activated furans proceeds readily to give the products with a cis ring juncture, because the geometry of the alkene moiety must be cis due to the ring constraint in their ground state.³⁸ By utilizing photochemically generated twisted triplet cycloalkenones, a cycloaddition reaction yielding trans-fused products was carried out (Eq. 9).³⁹ A similar approach to the trans ring juncture was reported through photochemical isomerization of cis-cycloalkenones to highly strained trans-cycloalkenones (Eq. 10).⁴⁰

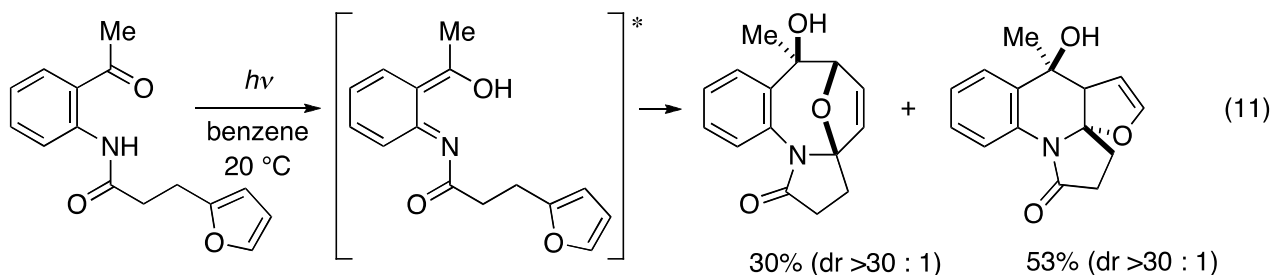


West and collaborators found that ether-bridged cyclooctatrienes were obtained via intramolecular [4+4]-photocycloaddition of pyran-2-ones bearing pendent furans followed by thermal decarboxylation. Treatment of this cyclic ether with excess MeLi furnishes triquinane ring systems via an apparent sequence of β -elimination, 1,5-hydrogen shift, and transannular aldolization (Scheme 4).⁴¹ Triquinanes were afforded cleanly as a single diastereomer by this transformation, though the pathway appeared to be sensitive to triene substitution.



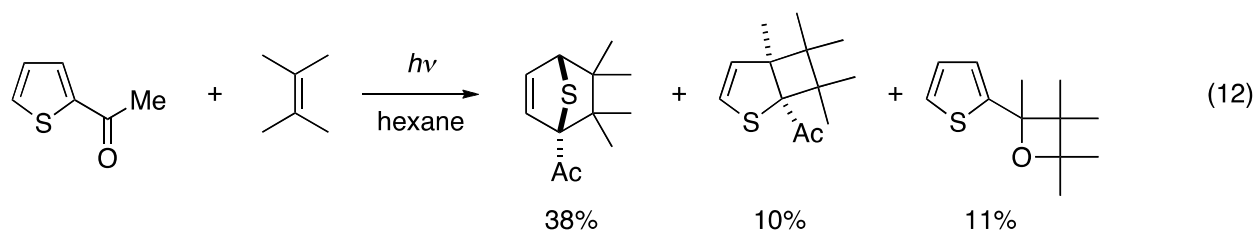
Scheme 4. Intramolecular [4+4]-photocycloaddition between furan and pyran-2-one

The preparation of a polycyclic system was reported by using [4+2] or [4+4] intramolecular cycloaddition between photochemically generated azaxylylenes via excited state intramolecular proton transfer (ESIPT) and furan moieties (Eq. 11).^{42,43} Both the chemo- and diastereoselectivity were largely dependent on the structure of the linker moiety and the dienophile moiety.

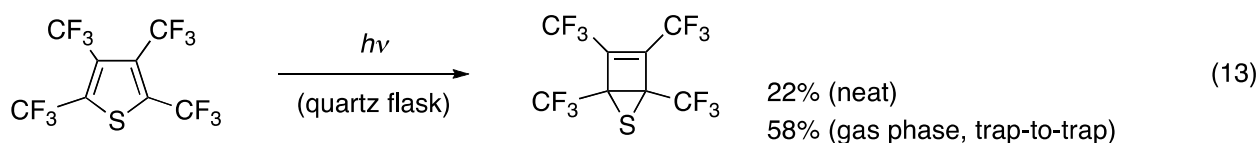


3. THIOPHENE

Though the fundamental photochemical properties of thiophenes have been well studied, the application of their photochemistry to organic synthesis seems to have been rather limited.^{44–46} As in the case of furan derivatives, thiophenes are used as a substrate for photochemical cyclobutane or oxetane formation. However, the extension to ring formations other than 4-membered rings has been much less explored. Cantrell reported that irradiation of 2-acetylthiophene in the presence of 2,3-dimethyl-2-butene gave mainly a [4+2] addition product, whereas irradiation of 3-acetylthiophene under similar conditions afforded no oxetane or other cycloadducts (Eq. 12).⁴⁷



An interesting example of the isolation of Dewar thiophene was reported, though it is not categorized as a cycloaddition reaction (Eq. 13).⁴⁸



As described in Chap. 2, in the photochemical intramolecular cycloaddition of furans, introduction of a phenyl group at the 2-position changed the reaction path dramatically. This finding prompted us to try the reaction by employing thiophene derivatives instead of furans.

When a solution of thiophene derivative **6a** in degassed benzene was irradiated by a high-pressure mercury lamp in a Pyrex glass vessel for 2 h at ambient temperature (around 25 °C), to our surprise, an unexpected compound **7a** was obtained in high yield as a single diastereomer (Eq. 14).⁴⁹ The structure of **7a** was determined unambiguously by X-ray crystallographic analysis (Figure 1).

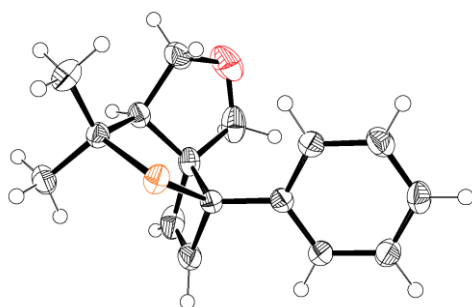
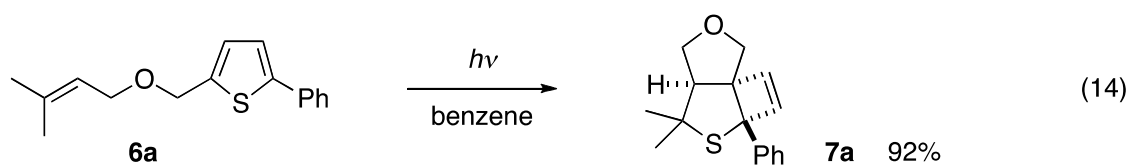
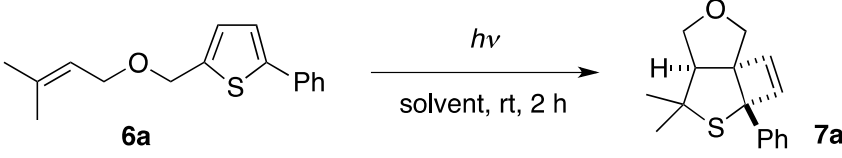


Figure 1. ORTEP drawing of **7a**

This extraordinary cycloaddition reaction proceeded in a range of solvents, but less polar solvents such as hydrocarbons or ethers gave better results (Table 3, Entries 1–7). The reaction in benzonitrile gave a

somewhat inferior result with recovery of only a small amount of **6a** (Entry 8). The reaction rate in acetone was relatively slow, resulting in the product in 62% yield with a recovery of **6a** (28%) (Entry 9). This retardation seemed to have been caused mainly by absorption by acetone rather than quenching of the excited species with acetone, though the detailed reaction mechanism is not clear.

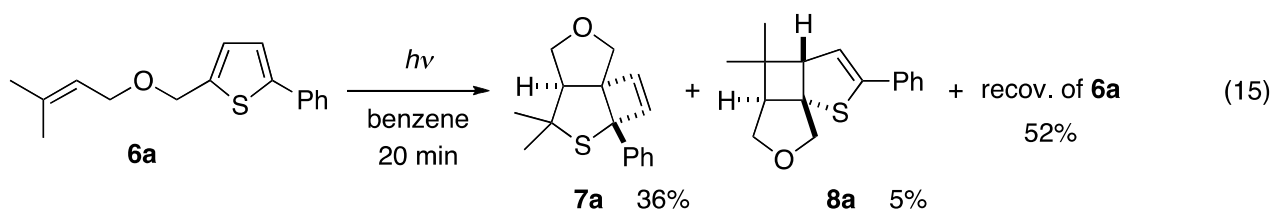
Table 3. Solvent effect on the photocycloaddition of **6a**^a

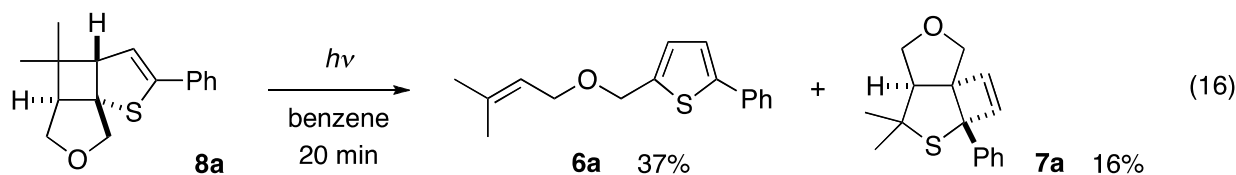


Entry	Solvent	Yield of 7a (%) ^b	Recovery of 6a (%) ^b
1	benzene	92	0
2	hexane	89	0
3	1,4-dioxane	90	0
4	THF	91	0
5	AcOEt	85	1
6	MeCN	84	0
7 ^c	MeOH	84	0
8	C ₆ H ₅ CF ₃	76	4
9	acetone	62	28

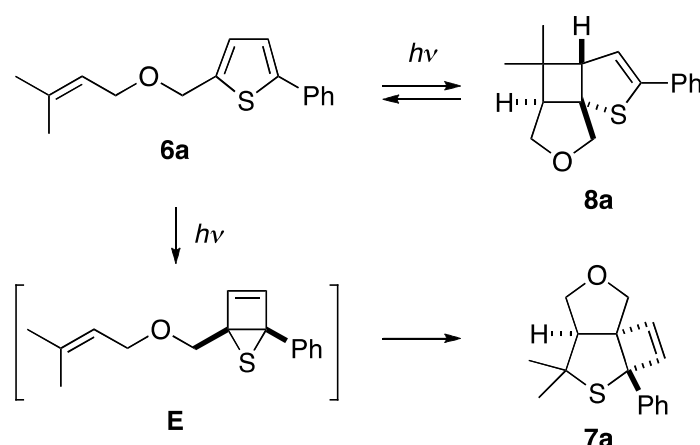
^a All reactions were carried out in a Pyrex test tube by external irradiation at a concentration of 5–6 mM. ^b Determined by ¹H NMR integral ratio using 1,1,2,2-tetrachloroethane as an internal standard. ^c Small amount of unidentified compound was detected.

When the irradiation was stopped in 20 min, a small amount of the [2+2] addition product **8a** was detected (Eq. 15). When isolated **8a** was irradiated under the same reaction conditions, **6a** was formed as a major product with the concomitant formation of **7a** in low yield (Eq. 16). In contrast, irradiation of **7a** under the identical conditions resulted in quantitative recovery of **7a**. These results suggested that the [2+2] cycloaddition of **6a** forming **8a** was reversible, and the adduct **8a** is not likely an intermediate of the transformation to **7a**.





Considering these experimental results and reported observations in the literature,^{5,44,45,50–52} the reaction seems to proceed mainly via the singlet excited state of **6a** followed by the formation of non-charge-separated reactive species. A plausible reaction pathway is proposed in Scheme 5. Photoexcitation of **6a** could cause a 4π electrocyclic reaction to give a Dewar thiophene (5-thiabicyclo[2.1.0]pent-2-ene)-type intermediate **E** (see, Eq. 13). Then the thiirane moiety in **E** could react with the pendant alkene to afford the product **7a**. In addition, a portion of **6a** would undergo reversible formation of **8a**.



Scheme 5. Plausible reaction pathway

This unprecedented cycloaddition of thiophenes could be applied to a variety of substrates with different alkenyl groups and linker moieties. The results are listed in Table 4. This reaction could be conducted under the preparative conditions to give the product **7a** in high isolated yield by using the typical substrate **6a** (Entry 2). The following examples were carried out on a small scale for convenience. Replacement of the phenyl group with a 4-methoxyphenyl group afforded **7b** in 63% yield accompanied by the formation of unidentified by-products (Entry 3). A substrate with a 4-chlorophenyl group **6c** gave the product in good yield (Entry 4). The reaction with a methyl-substituted compound **9** gave no cyclized product with the recovery of most of **9** (entry 5). This result shows that the aromatic ring at the α position plausibly plays an important role in the stabilization of intermediates that leads to the formation of the tricyclic compound. The substituents at the alkene moiety showed notable effects on the reaction (Entries 6–8), though the reaction with the simple allylic compound **6g** resulted in a low yield of the product

(Entry 9). Linker moieties other than ether bonds were also employable. Thus, compounds linked with NBoc or sp^3 -carbon (**10** and **11**) gave the corresponding products in high yields (Entries 10 and 11).

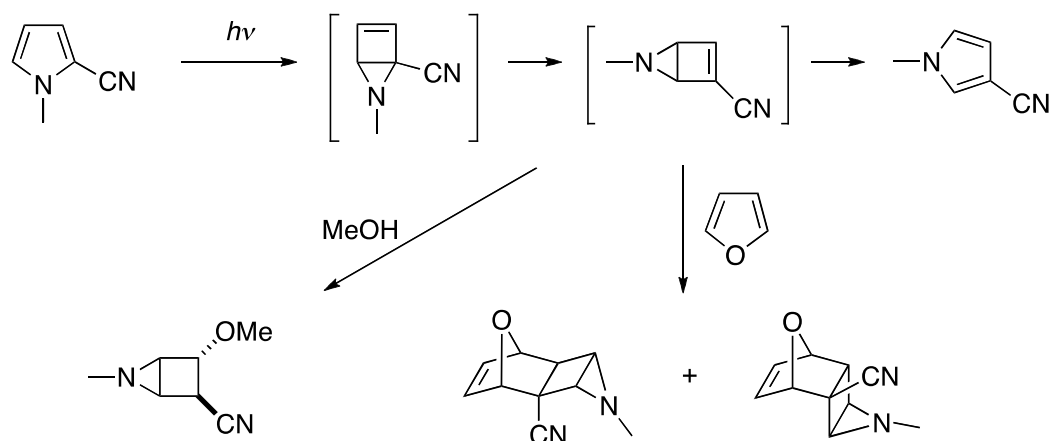
Table 4. Substrate scope^a

Entry	Substrate	Product	Yield (%) ^b	Entry	Substrate	Product	Yield (%) ^b
1 ^c 2 ^e			92 ^d 86	7			76 ^g
3			63	8			50
4			88	9			20
5		f	f	10			68
6			48	11			75 ^h

^a All reactions were carried out by internal irradiation through a Pyrex glass jacket at a concentration of 5–6 mM, until the starting material (0.2 mmol) was completely consumed (typically 2–5 h). ^b Isolated yield. ^c The reaction was carried out in a Pyrex test tube by external irradiation at a concentration of 5–6 mM. ^d Determined by ¹H NMR integral ratio using 1,1,2,2-tetrachloroethane as an internal standard. ^e The reaction was carried out by using 2 mmol of **6a** at a concentration of 0.1 M. ^f No cyclized product was obtained, and unreacted **9** was recovered (91%). ^g Obtained as a diastereomeric mixture (7:3). ^h The sample contained small amounts of inseparable impurities.

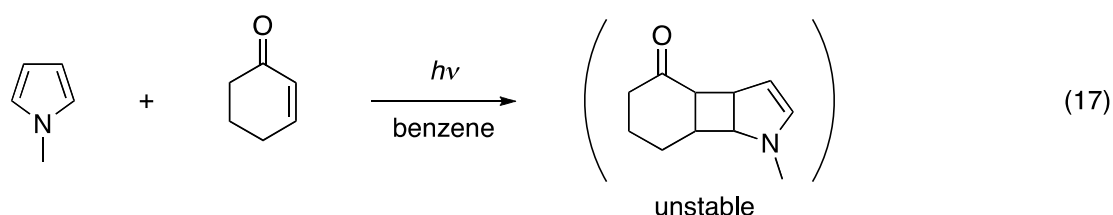
4. PYRROLE

The photochemical isomerization of pyrroles has also been well studied since the early days of the pyrrole photochemistry. Irradiation of a solution of 2-cyanopyrrole in degassed methanol in a quartz tube by low pressure mercury lamps gave 3-cyanopyrrole in 55% yield.⁵³ This isomerization was considered to occur via Dewar pyrrole intermediates that were trapped by co-existing methanol or furan (Scheme 6).⁵⁴

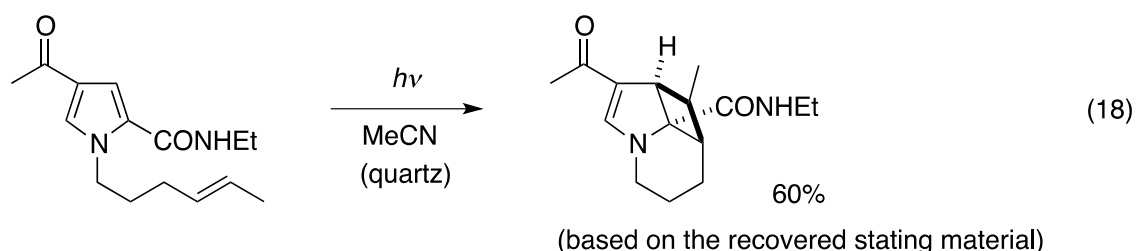


Scheme 6. Rearrangement of 2-cyano-1-methylpyrrole

An attempt to employ 1-methylpyrrole as a substrate for photochemical cyclobutane formation was carried out, but the expected adduct was too unstable to isolate (Eq. 17).⁵⁵



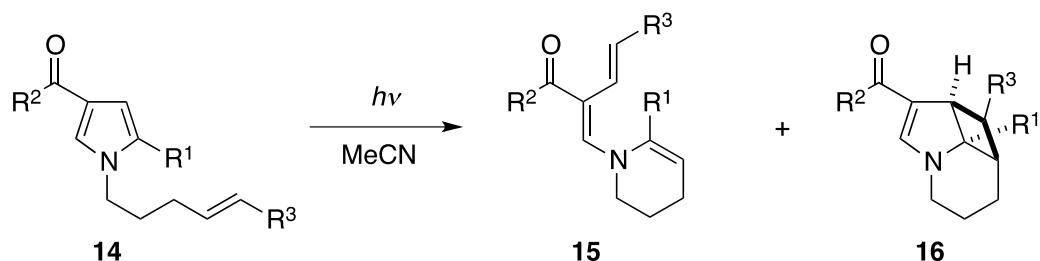
More recently, Booker-Milburn and collaborators reported that intramolecular [2+2] cycloaddition reaction of pyrroles substituted with electron-withdrawing groups at the 2- and 4-positions afforded the corresponding adducts in moderate yield (Eq. 18).⁵⁶



The outcome of the reaction was largely dependent on the type of substituent and the irradiation conditions, and the products produced by formal metathesis of the pendent alkene with the C2–C3 bond of the pyrrole in other cases (Table 5). Specific short wavelength irradiation led to a predominant formation of the cyclobutene product, confirming it as the initially formed intermediate in the reaction sequence. Generally, the yields of the photometathesis products were maximized using Method A.

However, products **15** suffered photodegradation on prolonged irradiation. Although high mass balances were obtained using Method B, conversion to **15** was incomplete even on prolonged irradiation time.

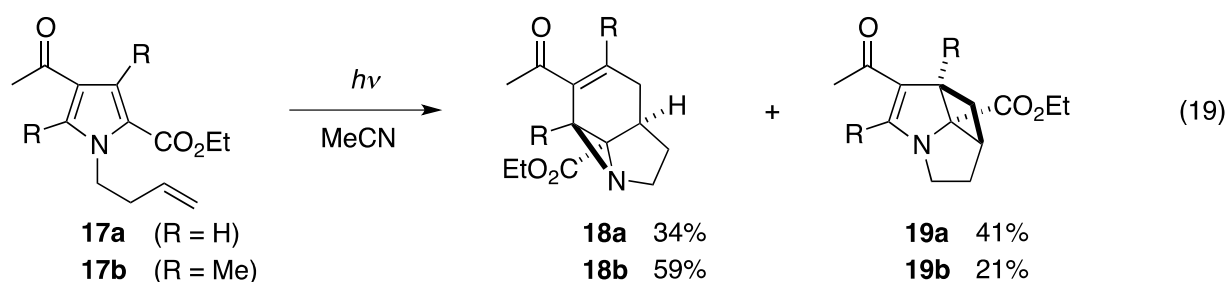
Table 5. Photometathesis of 1-pentenyl-2,4-disubstituted pyrroles **14**⁵⁶



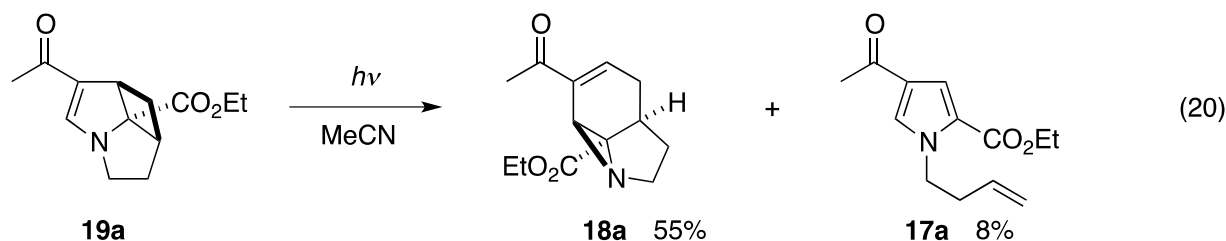
Entry	R ¹	R ²	R ³	Method ^a	Yield of 15 (%)	Yield of 16 (%)
1	CO ₂ Et	H	H	A	45	
2	CO ₂ Et	H	Me	A	45	23
3	CONHEt	H	Me	A	40	11
4	CONHEt	H	Me	B	34	47
5	CONHEt	H	Me	C	34	47
6	CN	H	Me	A	25	28
7	CN	H	Me	B		32
8	CONHEt	Me	Me	A	26 ^b	38 ^b
9	CONHEt	Me	Me	B		60 ^b

^a Method A: 125 W medium-pressure Hg-lamp, Vycor immersion well. Method B: 6 W low-pressure Hg-lamp, quartz immersion well. Method C: laser irradiation at 222 nm, quartz cuvette. ^b Based on recovered **14**.

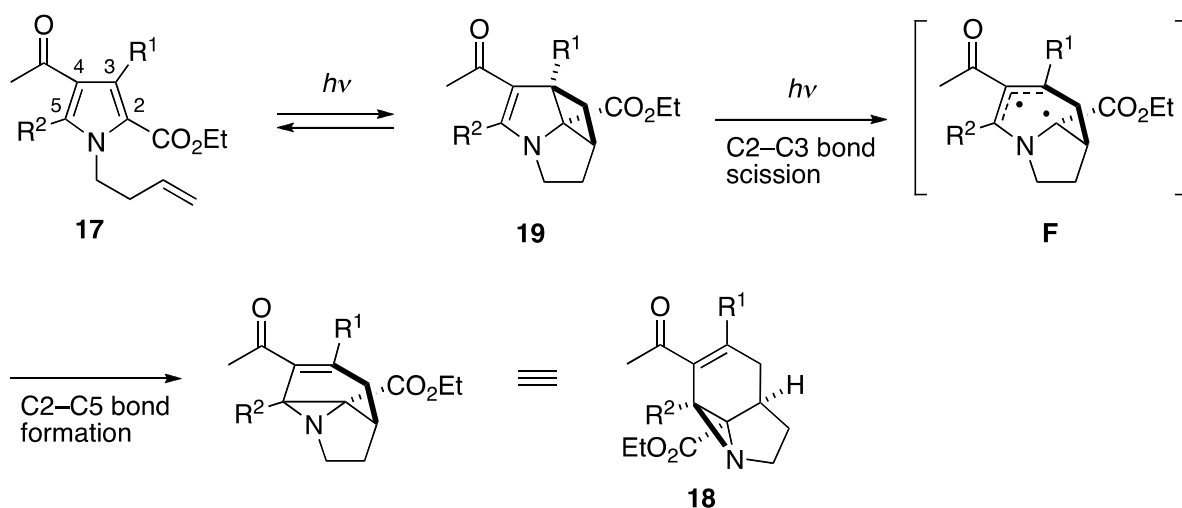
Interestingly, when they employed 1-butenylpyrroles **17** instead of 1-pentenylpyrroles **14**, they obtained a completely different products **18** accompanied with the expected [2+2] adducts **19** (Eq. 19). 3,5-Dimethyl derivative **17b** gave the aziridine product **18b** with a much improved yield.



To obtain insight into the reaction mechanism, isolated **19a** was irradiated with a low-pressure phosphor-coated UVB lamp with the maximum emission centered at 312 nm. The starting material **19a** was completely consumed in 2 h, to give aziridine **18a** (55%) and pyrrole **17a** (8%) (Eq. 20).



This result clearly indicates that **19a** is rearranged mainly to aziridine **18a**, and then reverts to a small amount of original pyrrole **17a**—namely, the first step of cyclobutane formation is reversible. The proposed mechanism of the aziridine formation is shown in Scheme 7. Excitation of pyrrole **17** substituted by an electron-withdrawing group at C2 with a 254 nm low-pressure mercury lamp results in the initial [2+2] cycloaddition across the C2–C3 bond to give cyclobutane **19**. In cyclobutanes bearing an acyl group at C4, further excitation leads to the biradical **F** by way of a C2–C3 bond cleavage. This biradical then undergoes C2–C5 bond formation to form the azirine ring in the final product **18**.

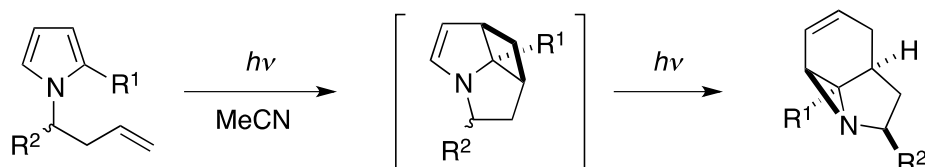


Scheme 7. Proposed mechanism of the aziridine formation

When a substituent was introduced adjacent to nitrogen on the butenyl side chain, an unusually high level of diastereoselectivity was observed (Table 6).⁵⁷ The high level of stereocontrol was maintained for a range of alkyl and alkoxy α -substituents (Entries 1–6). However, on switching from an amide activating group to nitrile, a significant drop in diastereoselectivity was observed (Entry 7). When an optically active

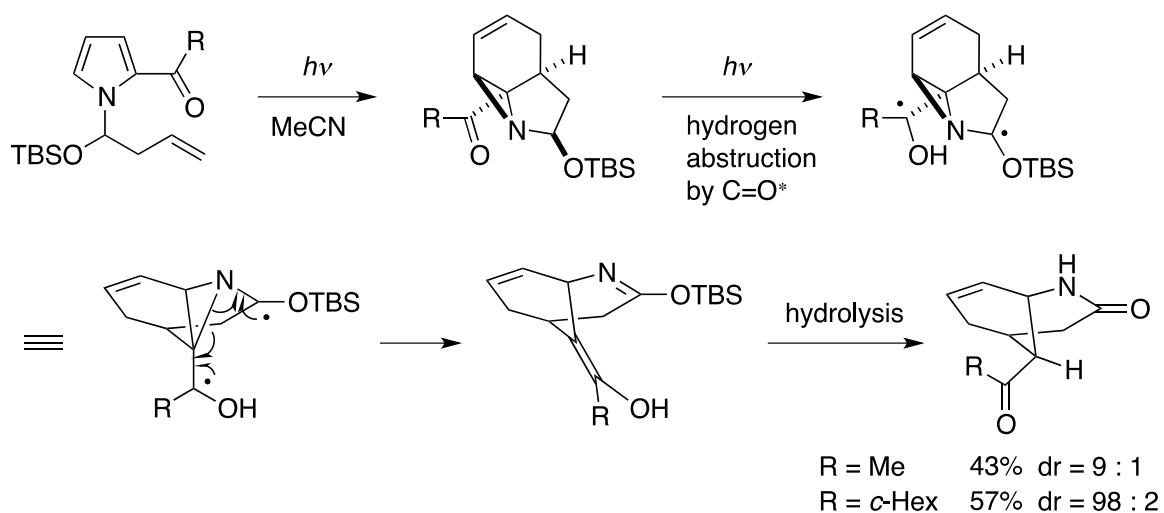
substrate was employed, the photochemical process was nicely performed without a decrease in the optical purity.

Table 6. Substituent effect on the stereocontrol during the photochemical rearrangement of 1-butenylpyrroles⁵⁷



Entry	R ¹	R ²	Yield (%)	dr
1	CONHEt	Me	39	>98 : 2
2	CONHEt	Et	51	>98 : 2
3	CONHEt	Pr	46	>98 : 2
4	CONHEt	<i>i</i> -Bu	60	>98 : 2
5	CONHEt	<i>i</i> -Pr	38	>98 : 2
6	CONHEt	OTBS	70	>98 : 2
7	CN	OTBS	39	8 : 1

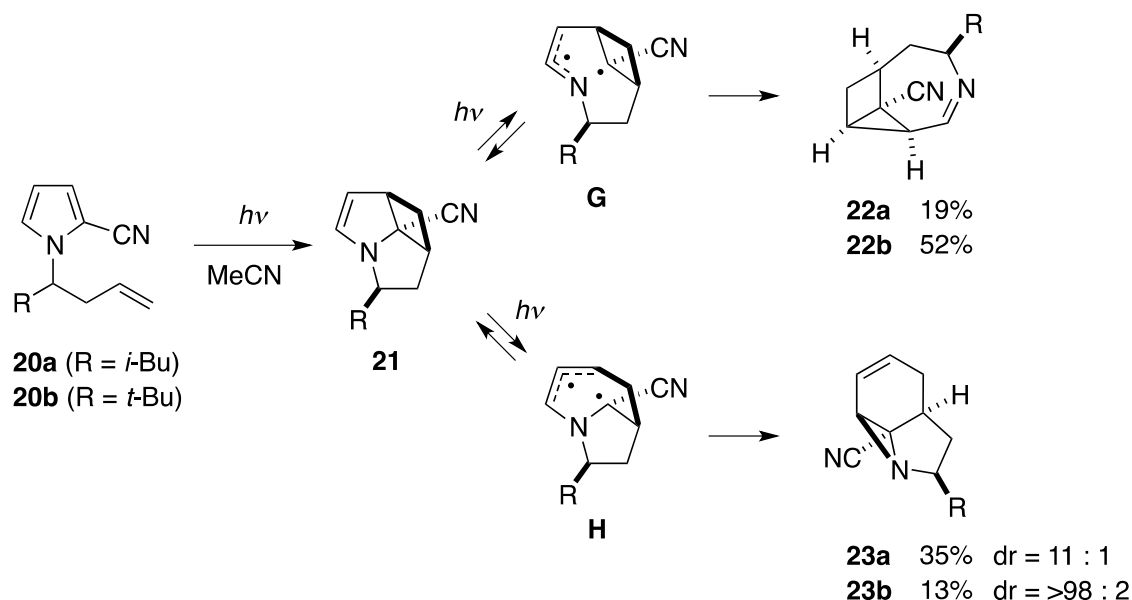
More interestingly, unprecedented stereoselective rearrangement to an azabicyclo[3.3.1]nonane framework was observed under prolonged irradiation when the activating group at the 2-position was replaced with a ketonic group (Scheme 8).



Scheme 8. Conversion of 1-butenylpyrroles to bicyclic lactams and proposed mechanism

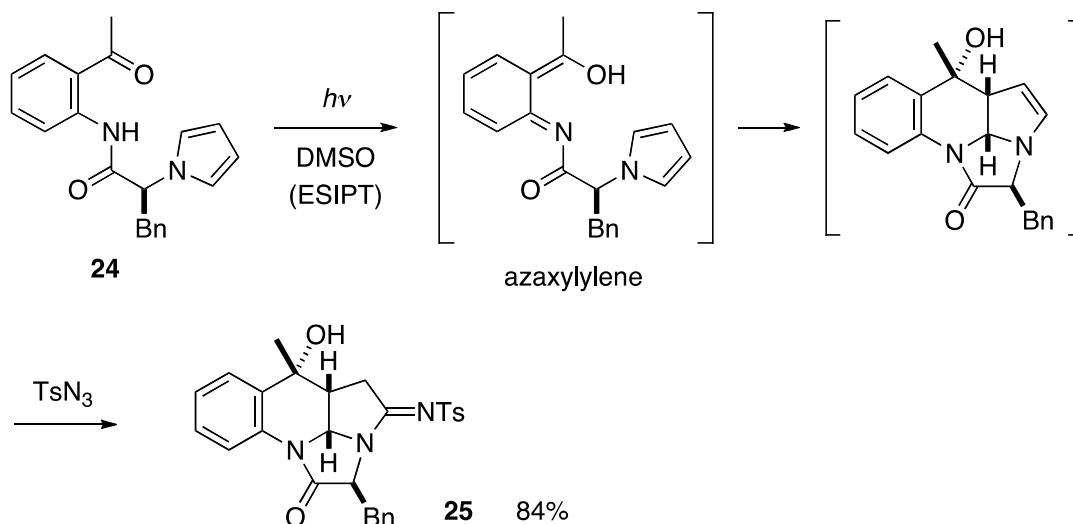
A larger substituent at the ketonic moiety gave superior diastereoselectivity. As the resulting ketone proved stable to epimerization during isolation, the stereoselectivity was likely determined by a kinetic protonation to the intermediary enolate.

Booker-Milburn and collaborators also discovered that substitution at the 2-position by a cyano group partially changed the fate of the initially formed cyclobutane through rearrangement (Scheme 9). When 2-cyanopyrrole **20a** was irradiated by a low-pressure mercury lamp, tricyclic imine **22a** was obtained in 19% yield with concomitant formation of the above-mentioned aziridine **23a** (35%). Replacing the substituent with a bulky group (**20b**) led to the predominant formation of the imine. They explained that the large R group exerted a degree of conformational control that favored fragmentation of **21** to the imine biradical **G** that cyclizes to **22**, rather than fragmentation to the biradical **H**.



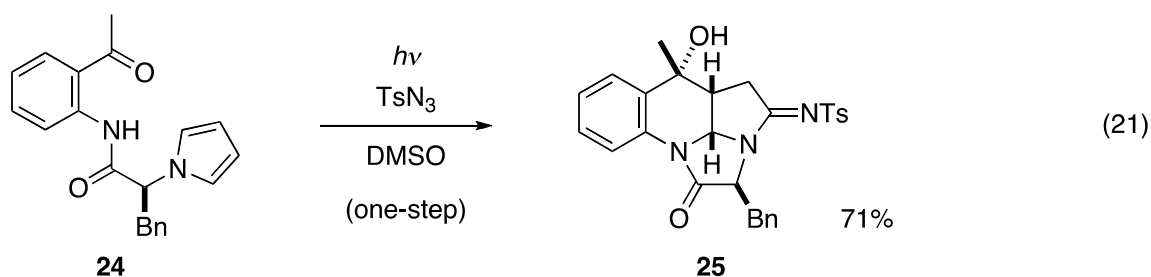
Scheme 9. Conformationally controlled cycloaddition/rearrangement sequence

Kutateladze and collaborators reported that azaxylylene, photochemically generated via the excited state intramolecular proton transfer (ESIPT) in aromatic *o*-amidoketones, could be trapped intramolecularly by tethered pyrrole moieties.⁵⁸ Irradiation of a DMSO solution of **24** by a UV-LED (365 nm) followed by treatment with tosyl azide afforded photocycloaddition product **25** in 84% yield (Scheme 10).



Scheme 10. Construction of pyrrolo[2,3-*b*]quinoline framework via photochemically generated azaxylylene

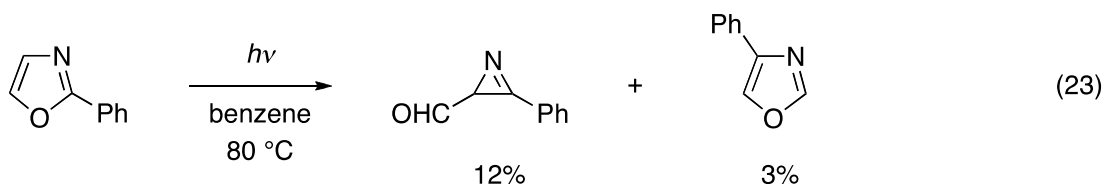
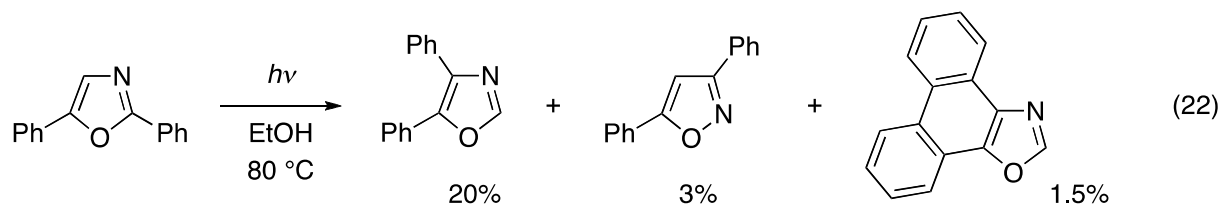
It was also possible to carry out the reaction in the presence of TsN_3 , because the sulfonyl azide does not absorb much above 350 nm. Thus, the two-step, one-pot transformation shown in Scheme 10 could be performed in one-step, one-pot fashion with only a slight loss of the yield (Eq. 21).



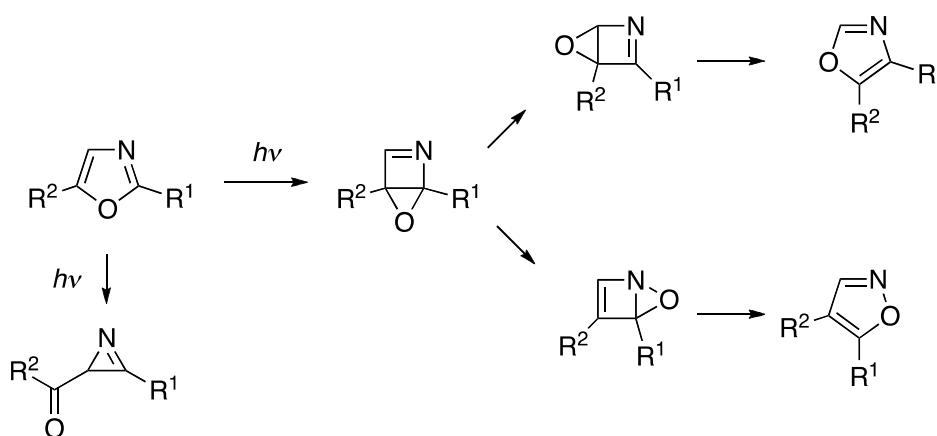
DMSO is not a common solvent for photochemical reaction, but it is known to stabilize the ESIPT species due to its hydrogen bonding ability.⁵⁹ This property extends the lifetimes of the excited states, and therefore enhances the reactivity of photogenerated azaxylylenes.

5. OXAZOLE

The skeletal reorganization of photo-excited oxazoles was well investigated in the early literature. Irradiation of 2,5-diphenyloxazole in ethanol at 80 °C under N_2 by a high-pressure mercury lamp through a Pyrex filter gave mainly 4,5-diphenyloxazole (Eq. 22).⁶⁰ On the other hand, irradiation of a benzene solution of 2-phenyloxazole afforded an azirine derivative and a small amount of isomerized oxazole (Eq. 23).⁶¹

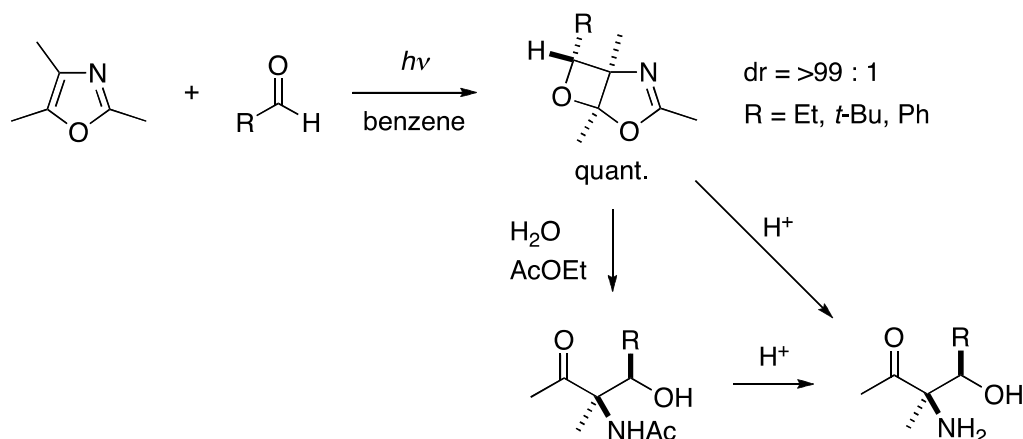


These rearrangements are considered to proceed via an internal cyclization-isomerization mechanism as shown in Scheme 11 based on the theoretical calculations.^{5,62} The 2,4-transposition is caused by the sigmatropic shift of an oxygen atom when a bicyclic intermediate is formed with the disrotatory ring closure, while 1-azirine is formed from the lowest $^1(n-\pi^*)$ state of oxazole with the out-of-plane distortion.



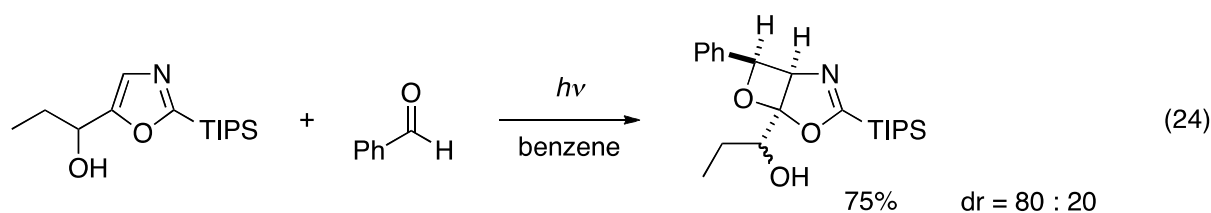
Scheme 11. Proposed mechanism of photochemical isomerization of oxazole

In contrast to these examples, the utilization of oxazoles in photo-cycloaddition reactions has been much less explored: most of the relevant studies have explored the Paternò-Büchi oxetane formation.^{63–65} Griesbeck and collaborators reported that the photocycloaddition of a range of aldehydes with 2,4,5-trimethyloxazole proceeds highly regio- and diastereoselectively to give bicyclic oxetanes. Subsequent hydrolytic cleavage of these adducts gives selectively erythro α -amino, β -hydroxy methyl ketones (Scheme 12).^{66–68}

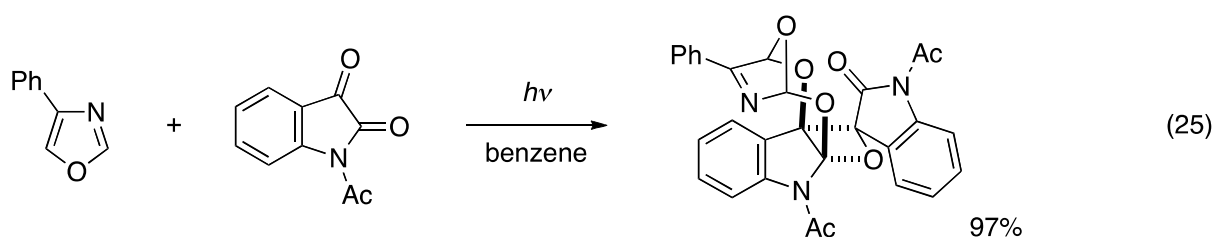


Scheme 12. Photocycloaddition of aldehydes with 2,4,5-trimethyloxazole

More recently, D'Auria et al. showed a hydroxyl directing effect on this type of cycloaddition of 5-(1-hydroxyalkyl)oxazole derivatives. According to their report, the reaction of aromatic aldehydes proceeded with unusual endo stereoselectivity (Eq. 24).⁶⁹ The relative configuration at the hydroxy-position was not determined.

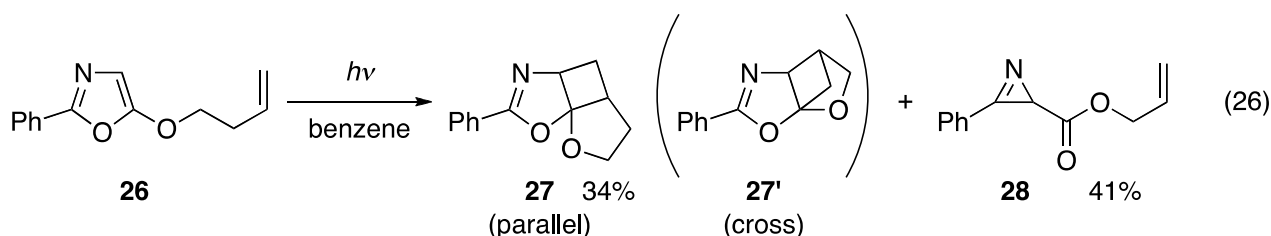


An exceptional [4+4] cycloaddition is known to occur between oxazoles and 1,2-dicarbonyl compounds (Eq. 25).⁶⁵ The product distribution was largely dependent on the substitution pattern on the oxazoles. These regioselective and diastereoselective [4+4] photocycloadditions were explained by estimating the stability of the intermediary diradicals.

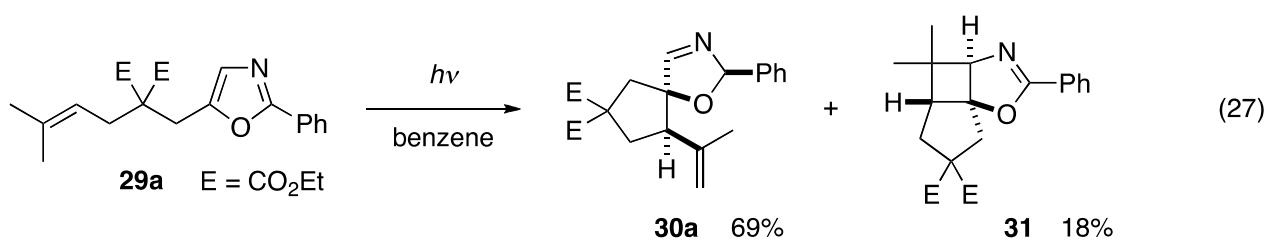


Concerning the cyclobutane ring formation, Padwa and Cohen reported that irradiation of oxazole **26** in benzene by a mercury arc lamp through a Pyrex filter gave the parallel-type intramolecular [2+2] cycloaddition product **27** accompanied by the formation of azirine **28** (Eq. 26).⁷⁰ They observed no

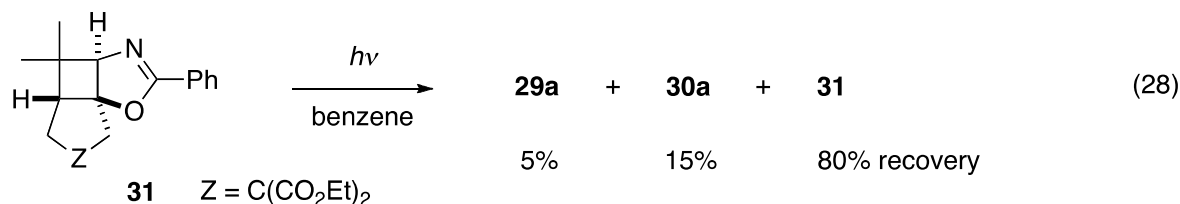
evidence for the formation of cross-addition products **27'**. They ascribed this result to the conformational stability in which the π bonds of the oxazole and olefinic system can easily approach in parallel relationship.



As can be seen in the above examples, the oxazole ring was converted to a masked 1,2-amino alcohol moiety through the dearomatization in this transformation. The 1,2-amino alcohol moiety is an important functionality that frequently appears in useful compounds such as pharmaceuticals, agrochemicals, natural products, and so on. Our above-described experiences with the thiophene photochemistry prompted us to carry out a similar reaction using oxazole derivatives. External irradiation of a benzene solution of **29a** in a Pyrex test tube by a high-pressure mercury lamp afforded an unexpected cyclized product **30a** in moderate yield with concomitant formation of the [2+2] addition product **31** (Eq. 27).⁷¹ It was quite surprising that the unusual spirocyclic compound **30a** was preferably produced over the conventional [2+2] adduct **31**.⁷⁰ More importantly, the reaction proceeded stereoselectively to give **30a** as a single diastereomer with a *cis*-configured alkenyl group and oxygen.

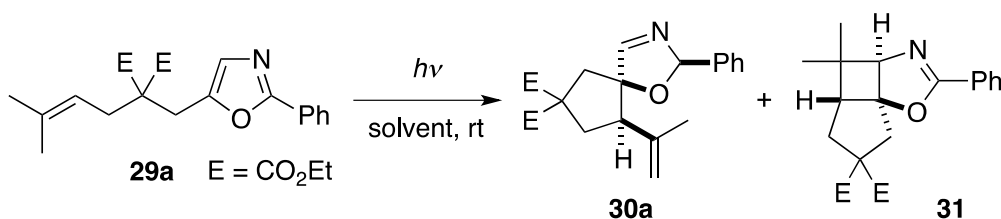


The spirocyclic compound **30a** was stable under the photochemical reaction, based on the fact that irradiation of isolated **30a** caused no decomposition. In contrast, when isolated **31** (containing small amounts (<5%) of unidentified impurities) was irradiated under the same conditions, **30a** and **29a** were slowly produced to give a mixture consisting of **29a**:**30a**:**31** = 5:15:80 (Eq. 28). These results suggest that the [2+2] cycloaddition of **29a** forming **31** is reversible and the adduct **31** is not likely an intermediate of the formation of **30a**.



To find the most suitable reaction conditions, we tried the reaction in a series of solvents (Table 7). The reaction proceeded in 1,4-dioxane, MTBE, and ethyl acetate as well as in benzene (Entries 1–4), whereas the reaction in hexane, acetonitrile, and methanol gave an inferior yield of **30a** with 8–20% recovery of the starting material **29a** (Entries 5–7).

Table 7. Solvent effect on the photocycloaddition of **29a**^a



Entry	Solvent	Yield (%) ^b		Recovery of 29a (%) ^b
		30a	31	
1	benzene	69	18	0
2	1,4-dioxane	53	26	7
3	MTBE	53	21	1
4	AcOEt	61	7	3
5	hexane	40	17	8
6	MeCN	50	30	20
7	MeOH	42	24	10
8	acetone	0	<1	47
9	C ₆ H ₅ CF ₃	38	0	0

^a All reactions were carried out in a Pyrex test tube by external irradiation for 3–3.5 h at a concentration of 2.7–2.9 mM. ^b Determined by ¹H NMR integral ratio using 1,1,2,2-tetrachloroethane as an internal standard.

The formation of **30a** was completely inhibited in acetone (Entry 8). In benzotrifluoride, though **29a** was consumed completely, **30a** was obtained in only 38% yield with the formation of an uncharacterizable mixture (Entry 9).

Selecting benzene as a suitable solvent for this reaction, the reaction was investigated using a range of oxazole derivatives (Table 8). The reactions shown in Table 8 were performed in a photochemical reaction vessel for the internal irradiation. A higher yield of **30a** than that by external irradiation was achieved (Table 8, Entry 1 vs. Table 7, Entry 1).

Table 8. Substrate scope of the photocycloaddition of oxazoles^a

Entry	Substrate, Z	R ¹ , R ² , R ³	Product, Yield (%) ^b	Entry	Substrate, Z	R ¹ , R ² , R ³	Product, Yield (%) ^b
1	29a C(CO ₂ Et) ₂	Me Me H	 30a 83% (70%)	6	32	Me Me H	 33 69% (71%)
2	29b C(CO ₂ Et) ₂	Me Me Me	 30b 76% (43%)	7	34 O	Me Me H	 35 55% (40%)
3	29c C(CO ₂ Et) ₂	Me or H (<i>E:Z</i> = 83:17)	 30c 11% (6%)	8	36a NBoc	Me Me H	 37a 50% (42%)
4	29d C(CO ₂ Et) ₂	Et Et H	 30d 58% (57%)	9	36b NMoc ^c	Me Me H	 37b 54% (52%)
5	29e C(CO ₂ Et) ₂	-(CH ₂) ₅ - H	 30e 52% (46%)	10	36c NMs	Me Me H	 37c 51% (46%)

^a All reactions were carried out in a Pyrex reaction vessel for photochemical reaction by internal irradiation at a concentration of 2.6–5.0 mM.

^b Determined by the ¹H NMR integral ratio using 1,1,2,2-tetrachloroethane or pyrazine as an internal standard. The numbers in parentheses are the isolated yields. ^c Moc = Methoxycarbonyl.

Although **30a** was somewhat susceptible to hydrolytic decomposition during the usual chromatographic purification, we could isolate the compound in pure form with only a slight loss of the yield. The substituents at the alkene moiety showed a notable effect on the reaction. The reaction of **29b** with a tetra-substituted alkenyl group revealed that the bulkiness of the alkene moiety did not much affect the reaction (Entry 2). It should be noted that neighboring quaternary carbon centers were created stereoselectively, suggesting the high potential of this reaction for the preparation of organic molecules

with a congested structure. Irradiation of **29c**, which has an (*E*)-crotyl side chain instead of prenyl, gave vinyl-substituted cyclopentane, but the yield was much decreased (Entry 3). This detrimental effect on the yield will be discussed later. Linker moieties other than diethyl malonate derivatives were also employable (Entries 4–8). Thus, compounds linked with oxygen or protected nitrogen (**34** and **36a–c**) gave the corresponding products, substituted tetrahydrofuran and pyrrolidine, in moderate yields (Entries 7 and 8–9). 2-Methyl- and 2-unsubstituted oxazole derivatives gave no cyclized product with nearly quantitative recovery of the starting materials.

The reaction with 4-bromobenzenesulfonamide derivative **36d** gave the crystalline spiro product **37d** and [2+2] cycloadduct **38** (Eq. 29). We could obtain single crystals of each compound that were suitable for X-ray crystallographic analysis and confirmed the structures of **36d** and **38** with relative stereochemistry unambiguously (Figure 2).

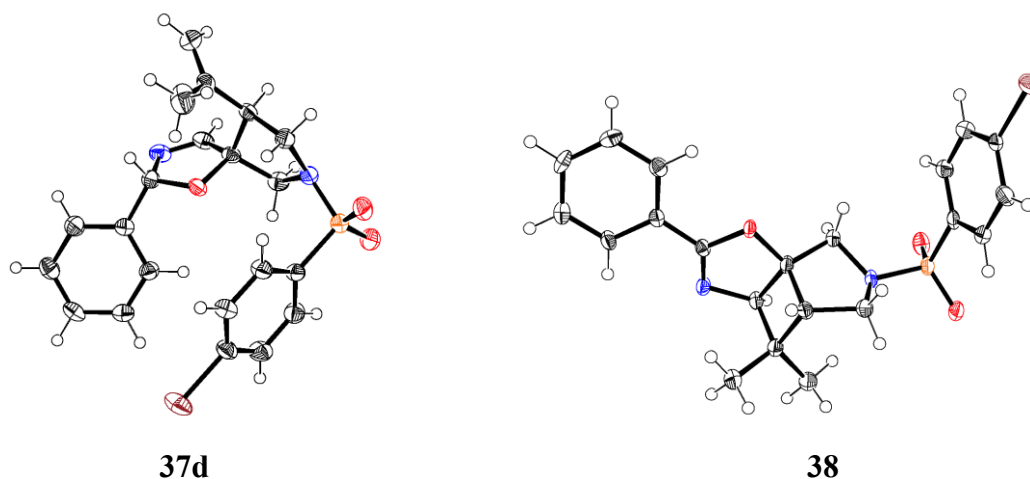
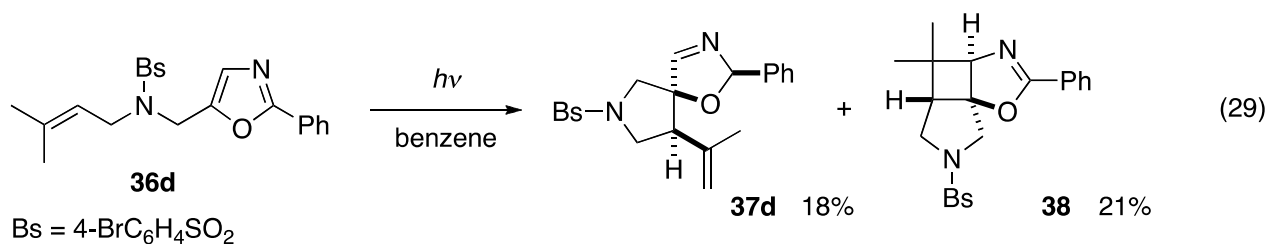
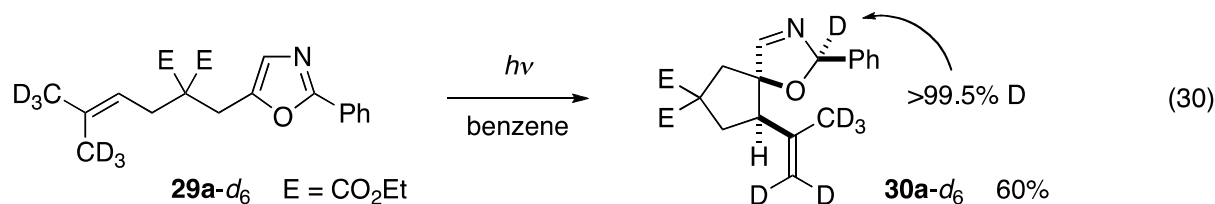
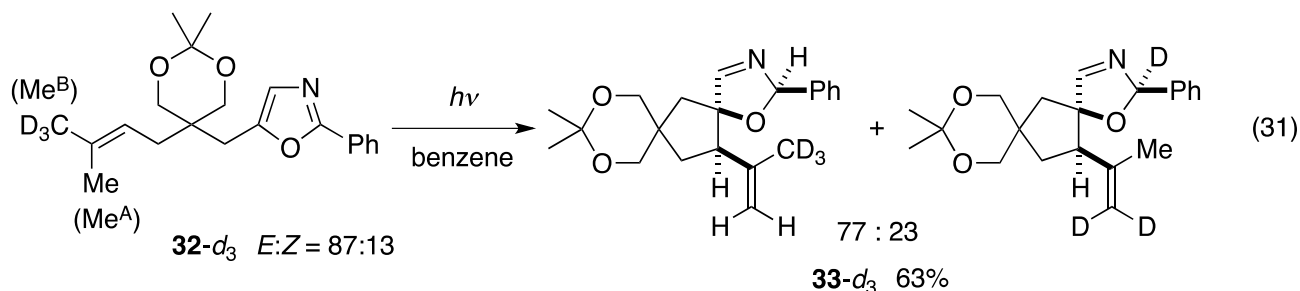


Figure 2. ORTEP drawings of **37d** and **38**

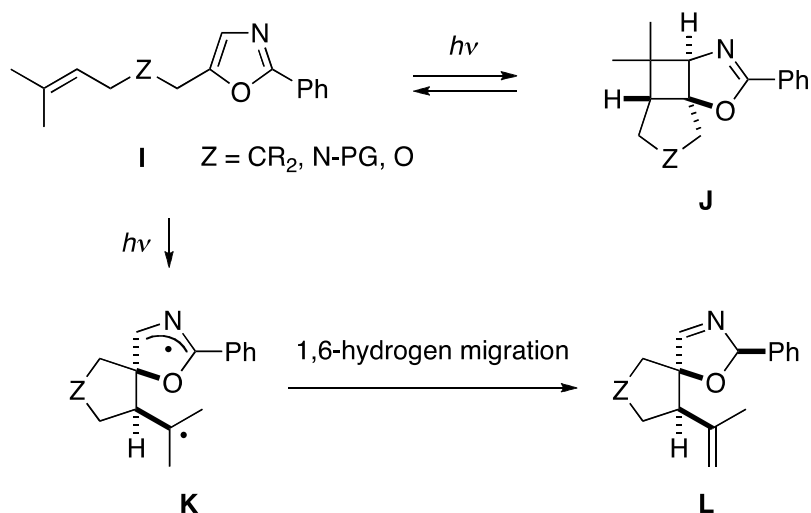
To obtain insights into the reaction mechanism, we carried out the reaction using a deuterium-labeled compound. When **29a-d₆** was irradiated under typical conditions, **30a-d₆** was exclusively produced (Eq. 30). This result clearly shows that the hydrogen at the benzylic methine comes from either methyl of the prenyl moiety.



When labeled compound **32-d₃** (*E:Z* = 87:13) was irradiated in the same manner, the cycloaddition product **33-d₃** with an H/D ratio of 23:77 was obtained (Eq. 31). As clearly seen in Eq. 30, the benzylic hydrogen was derived exclusively from one of the prenyl methyls. The result shown in Eq. 31 indicates that approximately 93% of the benzylic hydrogen comes from Me^A, and 7% comes from Me^B. This observation is consistent with the low yield in the reaction of **29c** that has an (*E*)-enriched crotyl side chain (Table 8, Entry 3).



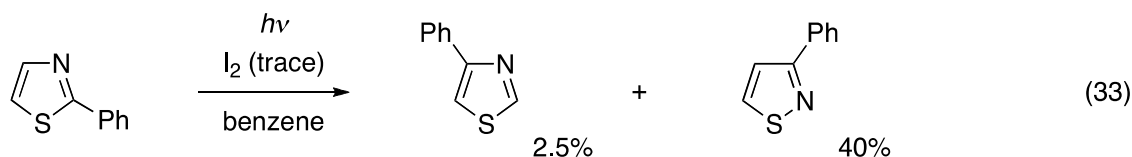
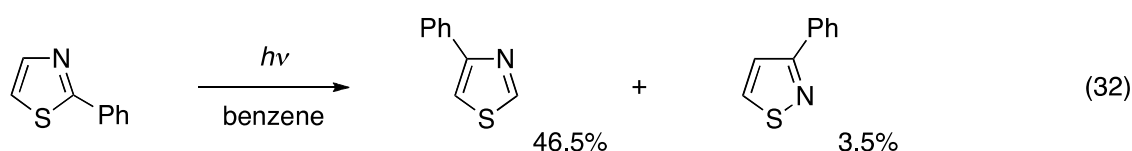
Though the detailed mechanism should be disclosed by further investigation, we surmise that the pathway is as shown in Scheme 13 based on the observations described above. Photoexcited **I** would cyclize to a biradical intermediate **K** via the formation of a carbon-carbon bond between the 5-position of oxazole and the alkene moiety, followed by 1,6-hydrogen migration,^{35,72} to give the spiro product **L**. As described before, the starting material **I** reversibly formed the [2+2] adduct **J**. Although direct formation of **L** from **J** can not be ruled out completely, it seems less likely because photoabsorption of **J** in the range of Pyrex-filtered UV is much less effective than that of **I**.



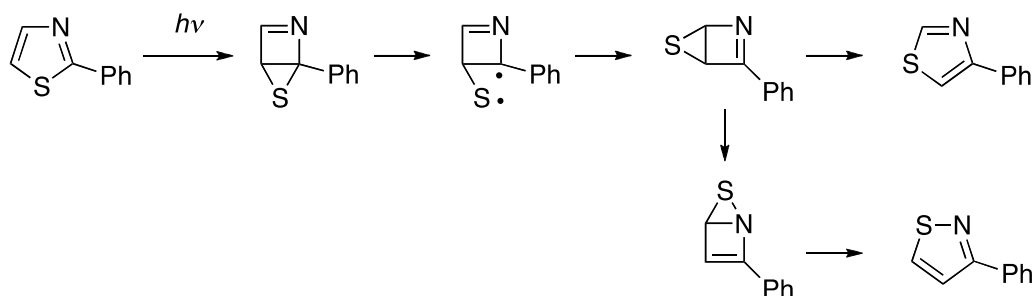
Scheme 13. Plausible reaction pathway of the photochemical cycloaddition of oxazoles

6. THIAZOLE

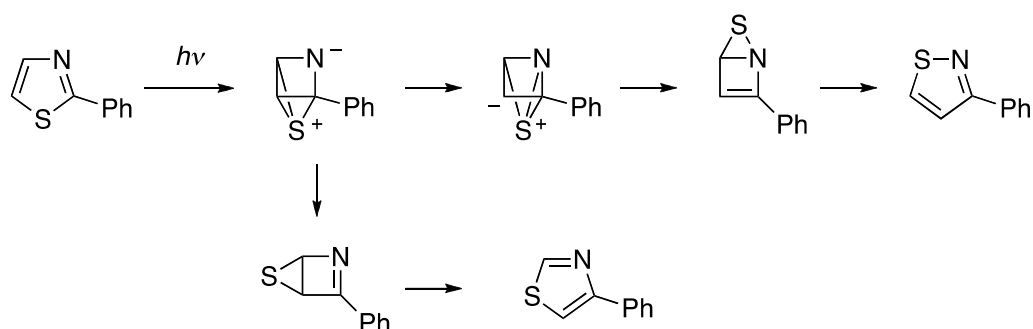
Though the photochemical transposition reaction of thiazoles has been widely studied, like the corresponding reaction in oxazoles, bond-forming reactions via cycloaddition are quite rare. Typically, 2-phenylthiazole isomerized mainly to 4-phenylthiazole by photoirradiation in benzene accompanied with the formation of a small amount of 3-phenylisothiazole (Eq. 32).⁷³ Interestingly, the product distribution was inverted by carrying out the reaction in the presence of a catalytic amount of iodine (Eq. 33).⁷³



The role of iodine is believed to facilitate the intersystem crossing and/or the opening of the Dewar intermediate (Scheme 14).^{5,74} Other authors proposed the intermediacy of a tricyclic sulfonium ion as depicted in Scheme 15.⁷⁵

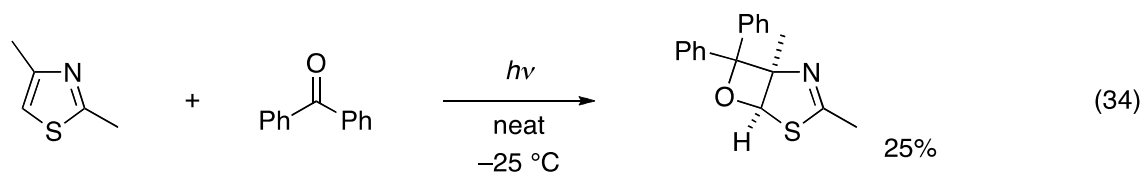


Scheme 14. Photoisomerization of thiazole

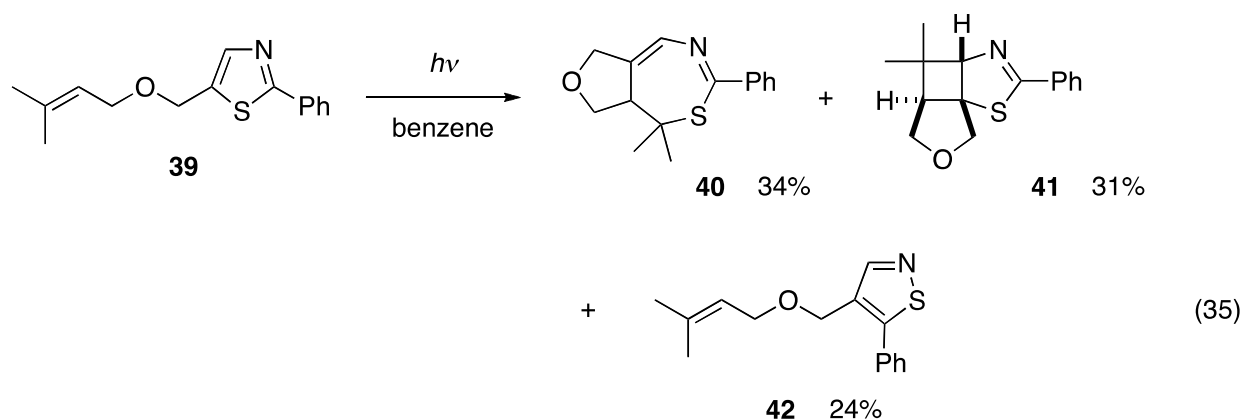


Scheme 15. Photoisomerization of thiazole via tricyclic sulfonium ion

On the other hand, few reports can be found on the photochemical cycloaddition of thiazoles.^{76,77} When a mixture of 2,4-dimethylthiazole and benzophenone was irradiated, the Paternò-Büchi-type cycloaddition proceeded to give the oxetane (Eq. 34).⁷⁶



In the course of our study on the photoreaction of the sulfur-containing 5-membered heteroaromatic compounds described in the previous chapter, we found that 2-arylthiazole derivatives under photoirradiation exhibited interesting behaviors that were completely different from those of thiophenes.⁷⁸ Irradiation of a solution of **39** in benzene at room temperature through Pyrex glass gave the unexpected thiazepine **40** in moderate yield, accompanied by the [2+2] addition product **41** and isomerized isothiazole **42**, with small recovery of **39** (2%) (Eq. 35).



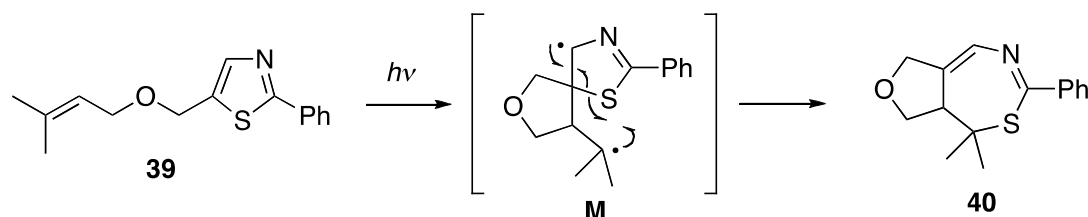
As shown in Table 9, the product distribution was hardly affected by solvents other than acetone. The reaction proceeded somewhat sluggishly in acetone likely due to competitive absorption by the solvent.

Table 9. Solvent effect on the photocyclization of **39**

Entry	Solvent	Conversion (%)	Yield (%) ^a		
			40	41	42
1	benzene	98	34	31	24
2	hexane	91	28	31	29
3	1,4-dioxane	90	30	32	23
4	AcOEt	90	30	32	25
5	MeCN	97	24	32	20
6	acetone	70	25	13	13

^a Estimated by ¹H NMR integrals using pyrazine as an internal standard.

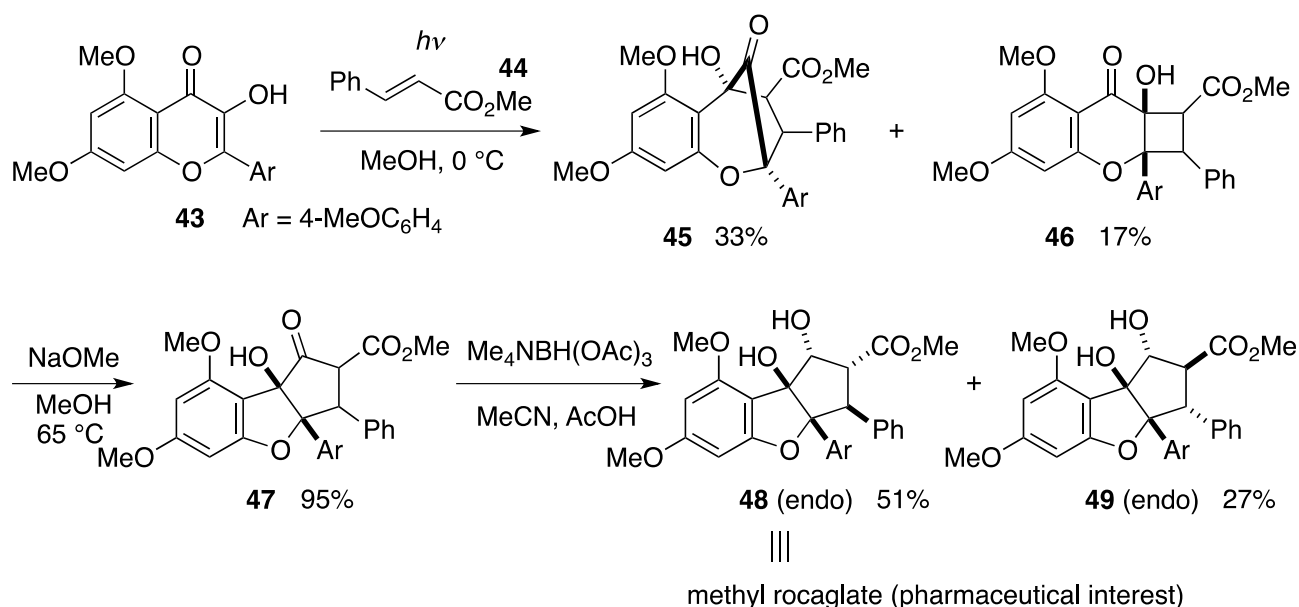
Though the mechanism of the reaction was not clarified, thiazepine **40** was likely formed via the biradical species **M** followed by successive [1,3]-transposition of sulfur by analogy of the oxazole photocycloaddition depicted in Scheme 9 (Scheme 16).



Scheme 16. Plausible pathway for the formation of thiazepine

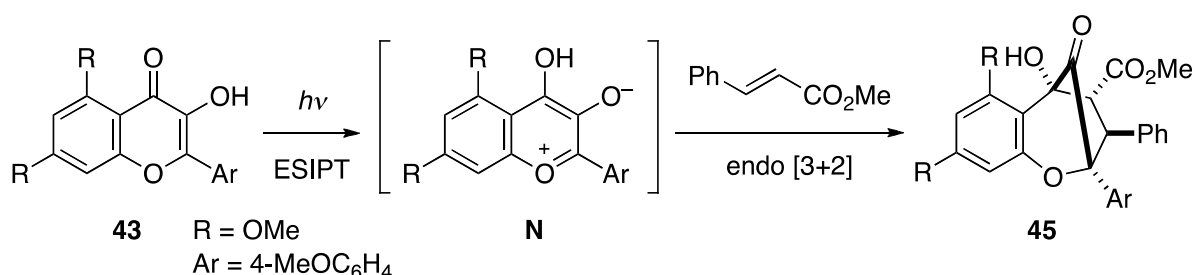
7. PYRONE, QUINOLONE

Both pyrones and quinolones are known to be common substrates for a wide range of photoreactions, including electrocyclization and cycloaddition.^{12,41,79,80} Here, we focus on the construction of a complex ring system using photo [3+2] cycloaddition through excited state intramolecular proton transfer (ESIPT). Porco and collaborators reported that irradiation of 3-hydroxyflavone derivative **43** and electron-deficient alkene **44** by a medium-pressure mercury lamp with a uranium filter (>350 nm) gave the cycloaddition products **45** and **46** as a mixture of endo/exo isomers, respectively (Scheme 17).⁸¹ Compounds **45** and **46** were in equilibrium during silica gel purification due to an acid-mediated ketol shift. Basic treatment of these compounds afforded the rearranged product **47**, which was stereoselectively reduced to (±)-methyl rocaglate **48** and its stereoisomer **49**.



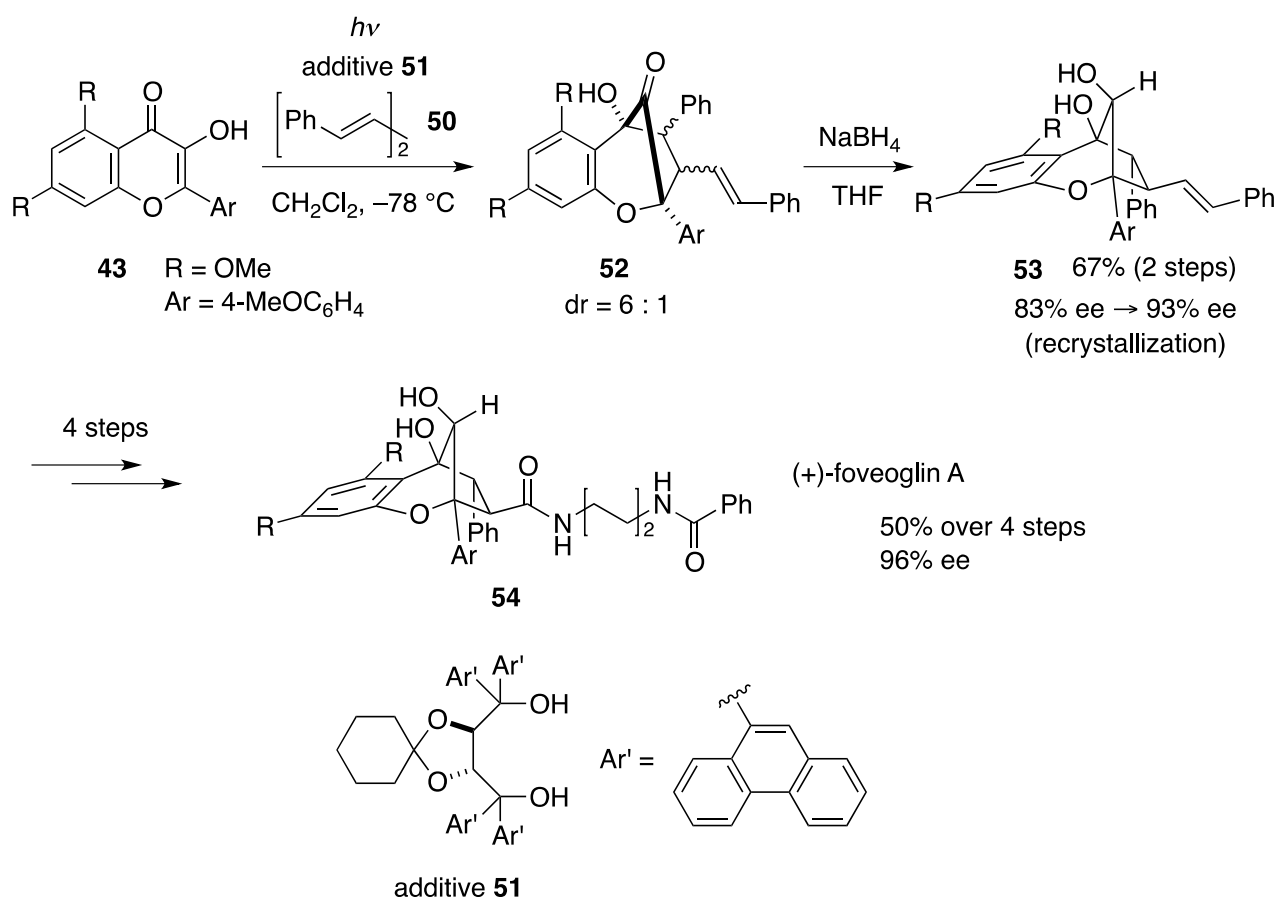
Scheme 17. Photochemical [3+2] cycloaddition of flavone derivative through ESIPT

This [3+2] cycloaddition proceeded through an oxidopyryllium intermediate **N** that was generated by ESIPT of photoexcited **43** (Scheme 18).



Scheme 18. Presumed [3+2] cycloaddition via photochemically generated oxidopyryllium

More recently, this reaction was extended to an asymmetric synthesis using a TADDOL derivative as a stoichiometric additive by the same authors.⁸² When a solution of the flavone derivative **43** and diene **50** in dichloromethane was irradiated by UV-LED (365 nm) in the presence of TADDOL derivative **51** at $-78\text{ }^{\circ}\text{C}$, the cycloaddition products endo- and exo-**52** were obtained as a 6 : 1 mixture. These compounds were treated with NaBH_4 in THF to give **53** in 67% (2 steps) and 83% ee (Scheme 19). The optical purity was enhanced to 93% ee after recrystallization. (+)-Foveoglin A(**54**) was synthesized from compound **53** after 4-step transformations.



Scheme 19. Asymmetric synthesis of (+)-foveoglin A via enantioselective ESIPT photocycloaddition

The asymmetric induction was presumed to come from the interaction between **43** and **51** through hydrogen bonding as depicted in Figure 3.

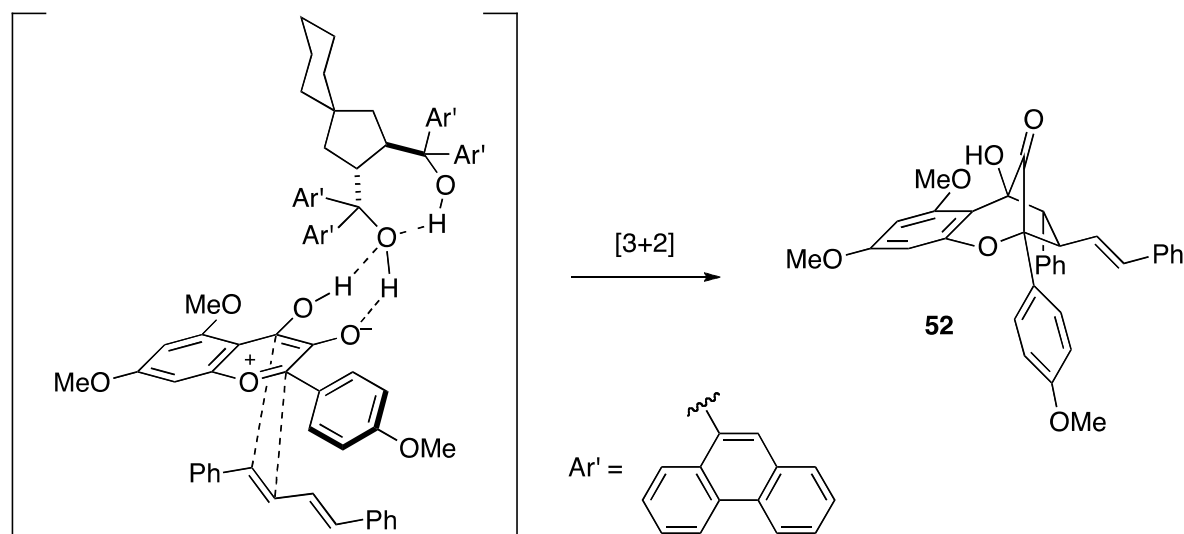
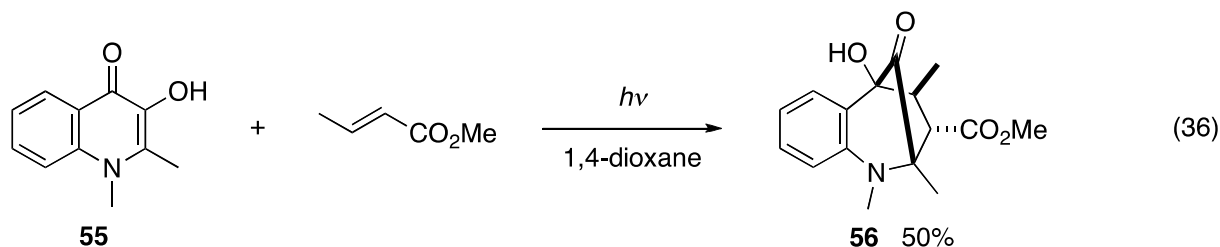
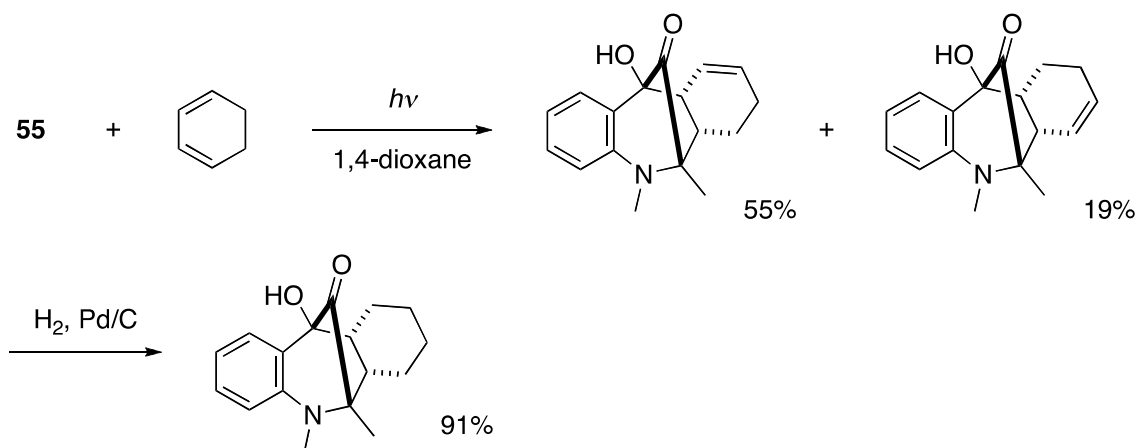


Figure 3. Presumed model for the asymmetric induction

This type of ESIPT-mediated photocycloaddition can be applied to 3-hydroxyquinolines as well as pyrones. In fact, Porco et al. showed that irradiation of hydroxyquinoline derivative **55** in the presence of alkene gave a cycloadduct **56** with an aza-bicyclo[3.2.1]octane framework in moderate yield (Eq. 36).⁸³



It is important to choose an appropriate reaction partner alkene for the successful ESIPT-mediated photocycloaddition. To find suitable alkenes for the reaction, Porco et al. investigated the photophysical property of **55** in detail and utilized the fluorescence quenching of excited **55** (**55***) by a range of dipolarophiles.⁸³ The quenching behavior can be roughly considered as an indicator of the reactivity in the photoreaction. It is naturally expected that poor quenchers would not be likely to show photocycloaddition reactivity. Interestingly, they found that strong and moderate quenchers did not always show the reactivity. For example, methyl fumarate, which is known as a good dipolarophile, did not afford the photocycloadduct at all. They hypothesized that the lack of reactivity may be attributed to quenching via charge-transfer mechanisms in which photoexcited **55*** serves as a charge donor to the quencher. In addition to methyl crotonate in Eq. 36, methyl butynoate or several conjugated alkenes were found to give the corresponding photocycloadducts (Scheme 20).



Scheme 20. ES IPT photocycloaddition between **55** and 1,3-cyclohexadiene followed by hydrogenation

8. CONCLUSION

This short review deals with the application of photochemical reactions of selected 5- and 6-membered ring heteroaromatics to the construction of unique frameworks. Though the photochemical properties of 5- and 6-membered ring heteroaromatics have been investigated since early years of photochemistry, their reactions have not been fully employed in synthetic chemistry, especially as a tool for carbon-carbon bond-forming cycloadditions. As described in the previous sections, photochemical reaction can often provide a complex polycyclic structure in a single step that is hardly available by the ground state chemistry. In recent years, LED light sources that have a narrow range of emission have become more common, enabling the selective excitation of a specific functionality or compound without affecting other functional groups. Many organic photoreactions do not require toxic heavy metal reagents and have an advantage from an environmental point of view. In this context, the development of synthetic organic photochemistry might take on a new urgency. This research field is expected to make further advances.

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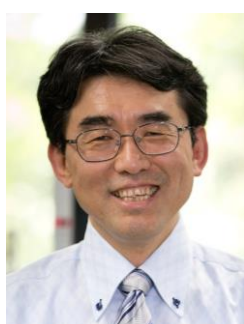
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