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[2 + 2] Photocycloadditions between the Carbon−Nitrogen Double Bonds of Imines and Carbon−Carbon Double Bonds

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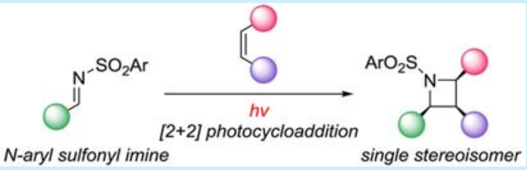
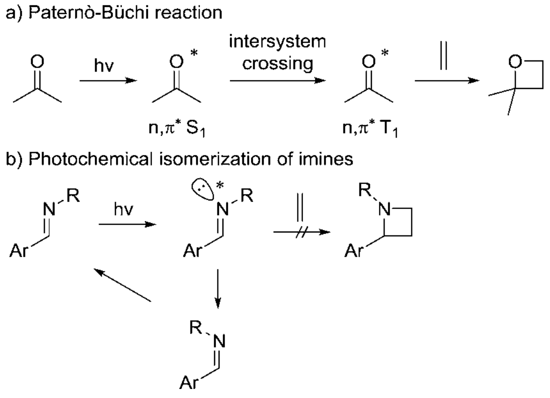
Supporting Information

ABSTRACT: In contrast to the well-known [2 + 2] photocycloadditions between C═O and C═C bonds, the participation of C═N bonds in such reactions is relatively rare. In this paper, the unprecedented UV-light-induced [2 + 2] cycloadditions between *N*-arylsulfonylimines and styrene derivatives or benzofurans are described. This photolytic reaction allows the highly stereoselective construction of azetidine derivatives under ambient conditions.

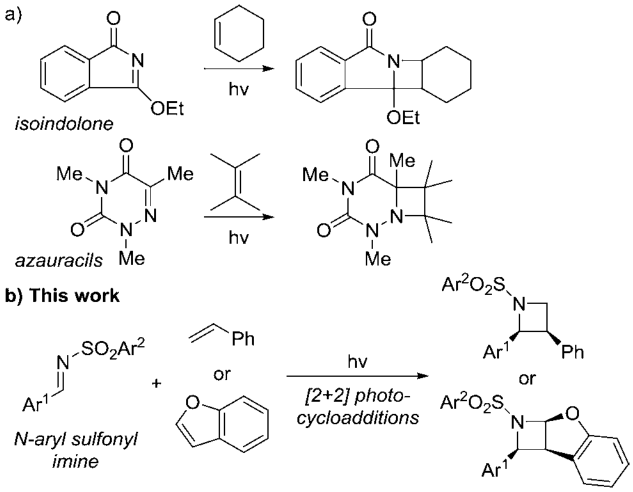


[2 + 2] Photocycloadditions between two double bonds represent a powerful strategy for the construction of four-membered rings in a single step.[1] In particular, [2 + 2] photocycloadditions between carbon−oxygen double bonds (C═O) and carbon−carbon double bonds (C═C), the so-called Paternò−Büchi reactions, have been widely used for the synthesis of oxetanes.[2] In contrast, [2 + 2] photocycloadditions between the carbon−nitrogen double bonds (C═N) of, e.g., imines and C═C bonds are less frequently encountered, even though they may provide facile access to azetidine derivatives.[3,4] One of the reasons that could explain the different photoreactivity between C═O and C═N bonds in such reactions is the difference in preferred relaxation pathways for each exited state (Scheme 1). In a typical Paternò−Büchi reaction, the photoinduced excitation of the carbonyl group into a singlet state is followed by an intersystem crossing to a carbonyl triplet state, which reacts with the C═C bond to afford an oxetane (Scheme 1a).[2] Conversely, photochemical isomerizations between *syn*- and *anti*-isomers of the C═N bond may be considered as potentially major relaxation pathways from the exited to the ground state of the C═N bond and, thus, account for the observed lack of photoreactivity (Scheme 1b).[5] Thus, previous examples of [2 + 2] photocycloadditions between C═N and C═C bonds have so far been accomplished only for cyclic C═N bonds with electron-withdrawing groups (EWGs) as in, e.g., isoindolones[3g] or azauracils[3f] (Scheme 2a). Herein, we report unprecedented [2 + 2] photocycloadditions between the C═N bonds of noncyclic imines and C═C bonds (Scheme 2b), which result in the highly stereoselective formation of azetidine derivatives.[6]

Scheme 1. Photoreactivity Differences between C═O and C═N Bonds



Scheme 2. [2 + 2] Photocycloaddition between C═N and C═C Bonds



During our recent studies on the development of novel photoreactions,[7] we unexpectedly discovered that irradiation of a mixture containing the *N*-tosylimine of 2-naphthaldehyde (**1a**) and benzofuran with UV light (λ = 365 nm) afforded azetidine **2a** as a single stereoisomer in 96% yield (Scheme

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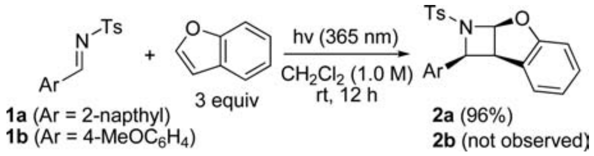
3).[8−10] This result surprised us, as [2 + 2] photocycloadditions between the C═N bonds of noncyclic imines and C═C bonds to afford azetidines have, to the best of our knowledge, not yet been reported. Furthermore, nonphotolytic [2 + 2] cycloadditions between the C═N bonds of imines and C═C bonds also remain quite rare, with the exception of ketenes in the Staudinger reaction.[11,12] Therefore, we further investigated [2 + 2] photocycloadditions between the C═N bonds of imines and C═C bonds. Subsequently, we attempted the reaction between the *N*-tosylimine of *p*-anisaldehyde (**1b**) and benzofuran. However, the formation of targeted product **2b** was not observed after 12 h of irradiation with UV light (Scheme 3).

Scheme 3. [2 + 2] Photocycloadditions between the *N*-Tosylimine 1 and Benzofuran



The differences of photoreactivity between **1a** and **1b** might be explained by measuring their UV−vis spectra (Figure 1a).

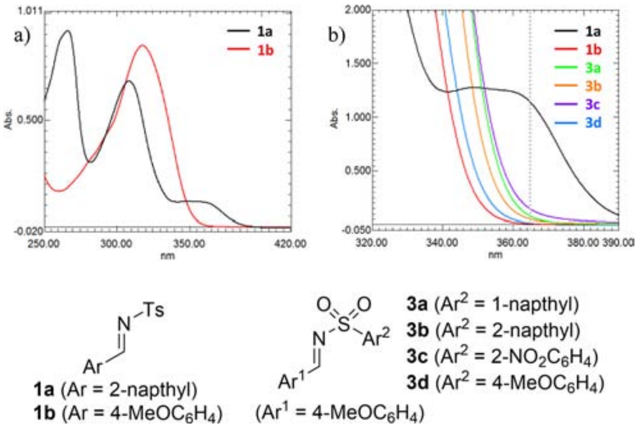
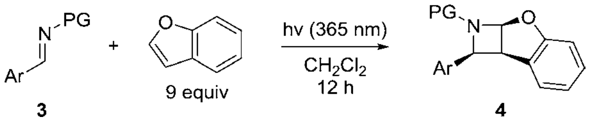


Figure 1. (a) UV−vis spectra of **1a** and **1b** in CH_2Cl_2 (c = 0.025 mM). (b) UV−vis spectra of **1** and **3** in CH_2Cl_2 (320−390 nm; c = 0.25 mM).

While the UV−vis spectrum of **1a** exhibits a strong absorption band at λ = ∼365 nm, for the *N*-tosylimine of *p*-anisaldehyde (**1b**), the absorption at λ = ∼365 nm was not observed. Thus, we then prepared several sulfonylimines of *p*-anisaldehyde (**3a**−**d**) and investigated the UV−vis absorption of them in CH_2Cl_2 (Figure 1b; 320−390 nm; c = 0.25 mM).[13−15] Consequently, the introduction of a naphthyl moiety (**3a** and **3b**) or 2-nitrophenyl moiety (**3c**) on the sulfonyl group resulted in the observation of an absorption at λ = ∼365 nm. On the other hand, the UV−vis spectrum of the (*p*-methoxyphenyl)sulfonyl group (**3d**) did not reveal an absorption at λ = 365 nm, even though a slight bathochromic shift of the longest wavelength absorption band was observed.

Next, we tested the photocycloaddition of imines **3a**−**d** with benzofuran under irradiation by UV light (Table 1). The reactions of **3a**−**c** with benzofuran furnished corresponding azetidines **4a**−**c** (entries 1−3). In contrast, use of **3d**, of which the UV−vis spectrum did not exhibit absorpition band at λ = ∼365 nm, did not afford even a trace amount of the desired product (entry 4). Further modifications of the naphthyl moiety with electron-donating or -withdrawing substituents were tested and revealed that the introduction of an acetoxy group afforded a slightly increased yield (entry 6).[16] The product yield of **4b** can be increased substantially (85%; entry 7) by a prolongation of the reaction time (72 h).

Table 1. Optimization of the Reaction between the *N*-(Arylsulfonyl)imine of *p*-Anisaldehyde (4) and Benzofuran[a]



entry	3 (PG)	yield[b] (%) of 4
1	**3a** (1-naphthyl-SO_2)	11 (**4a**)
2	**3b** (2-naphthyl-SO_2)	33 (**4b**)
3	**3c** (Ns)	3 (**4c**)
4	**3d** (4-$MeOC_6H_4$-SO_2)	not observed (**4d**)
5	**3e** (6-MeO-2-naphthyl-SO_2)	7 (**4e**)
6	**3f** (6-AcO-2-naphthyl-SO_2)	38 (**4f**)
7[c]	**3b**	85[d] (**4b**)

[a] Unless otherwise specified, reactions were conducted in CH_2Cl_2 (1.0 M) at room temperature in the presence of **3** (0.1 mmol) and benzofuran (9.0 equiv) under irradiation by UV light (365 nm). [b] The yield was determined by ^1H NMR spectroscopy using DMF as an internal standard. [c] Reaction time: 72 h. [d] Isolated yield.

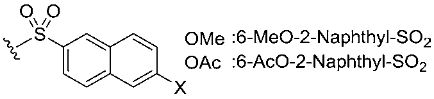
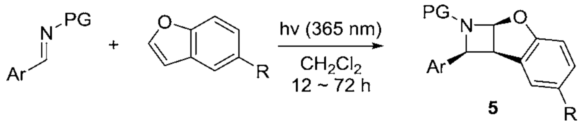


Table 2 summarizes the scope of this [2 + 2] photocycloaddition. Reactions between the *N*-tosylimine of 2-naphthaldehyde (**1a**) and 5-substituted benzofurans (R = Me or Br) afforded the desired azetidines **5a** and **5b** in 73% and 83% yield, respectively (entries 1 and 2), while the corresponding *N*-tosylimine of 1-naphthaldehyde afforded **5c** in 73% yield (entry 3). The reactions between the *N*-(2-

Table 2. Scope of Substrates[a]



entry	Ar	PG	R	yield[b] (%) of 5
1	2-naphthyl	Ts	Me	73 (**5a**)
2	2-naphthyl	Ts	Br	83 (**5b**)
3	1-naphthyl	Ts	H	73 (**5c**)
4	4-$MeOC_6H_4$	naphths	Me	20[c] (**5d**)
5	4-$MeOC_6H_4$	naphths	Br	44 (**5e**)
6[d]	C_6H_5	naphths	H	40 (**5f**)
7[d]	C_6H_5	AcO-naphths	H	50 (**5g**)
8[d]	4-BrC_6H_4	naphths	H	45 (**5h**)

[a] Unless otherwise specified, reactions were conducted in CH_2Cl_2 (1.0 M) at room temeperature in the presence of imine (0.1 mmol) and benzofuran (9.0 equiv) under irradiation by UV light (365 nm). [b] Isolated yield. [c] The yield was determined by ^1H NMR spectroscopy using DMF as an internal standard. [d] An HPML was used instead of a UV lamp. Naphths = 2-naphthyl-SO_2, AcO-naphths = 6-AcO-2-naphthyl-SO_2

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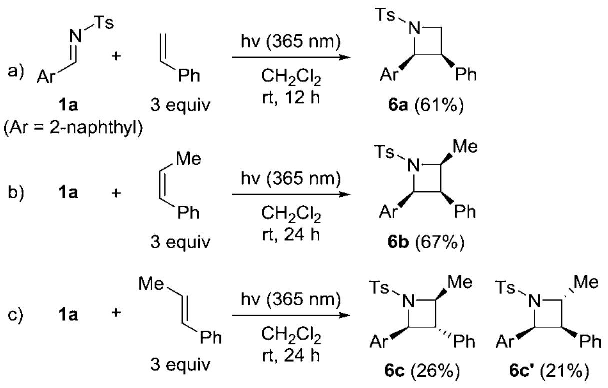
naphthylsulfonyl)imine of *p*-anisaldehyde and 5-substituted benzofurans furnished the corresponding products in low to moderate yield (entries 4 and 5). In the case of the *N*-(2-naphthylsulfonyl)imine of benzaldehyde, irradiation with a high-pressure mercury lamp (HPML; λ = 300−600 nm) was required in order to obtain **5f** in 40% yield (entry 6).[17] The use of the *N*-(6-acetoxy-2-naphthylsulfonyl) group instead of the *N*-(2-naphthylsulfonyl) group provided a higher product yield (cf. entries 6 and 7). The reaction of a 4-bromobenazldehyde-derived imine with benzofuran also afforded **5h** in 45% yield, although HPML irradiation was required. All of these reactions provided only one stereoisomer, while other diastereo- or regioisomers could not be detected.

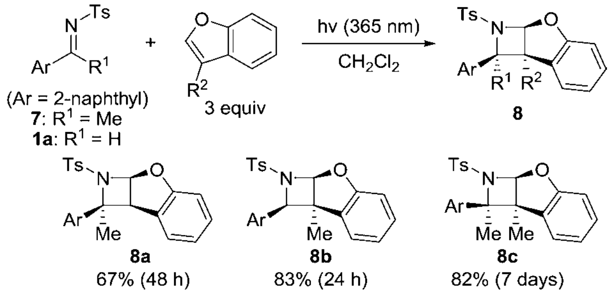
Additionally, the reaction between **1a** and styrene afforded the desired azetidine **6a** in 61% yield as a single diastereomer (Scheme 4a).[18] While the reaction between **1a** and *cis*-β-methylstyrene afforded **6b** in 67% yield as a single stereoisomer (Scheme 4b), the corresponding reaction with *trans*-β-methylstyrene afforded the two diastereoisomers **6c** and **6c′** in almost equal yield (Scheme 4c).

Scheme 4. [2 + 2] Photocycloadditions between the *N*-Tosylimine of 2-Naphthaldehyde (1a) and C═C Bonds



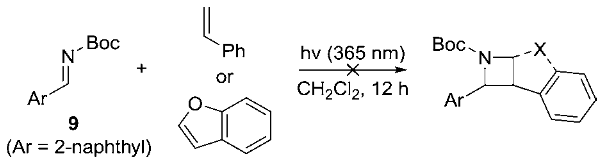
This photocycloaddition could also be successfully employed for the construction of sterically hindered azetidines with a quaternary carbon center (Scheme 5). Exposing a mixture of ketimine (**7**) and benzofuran to irradiation with UV light for 48 h afforded **8a** in 67% yield. When **1a** was treated with 3-methylbenzofuran (R^2 = Me), **8b** was obtained in 83% yield after 24 h. Furthermore, a [2 + 2] photocycloaddition between **7** and 3-methylbenzofuran furnished **8c**, which contains two consecutive quaternary carbon centers in 82% yield as a single stereoisomer.

Scheme 5. [2 + 2] Photocycloadditions between Imines and Benzofurans To Generate Azetidines with a Quaternary Carbon Center



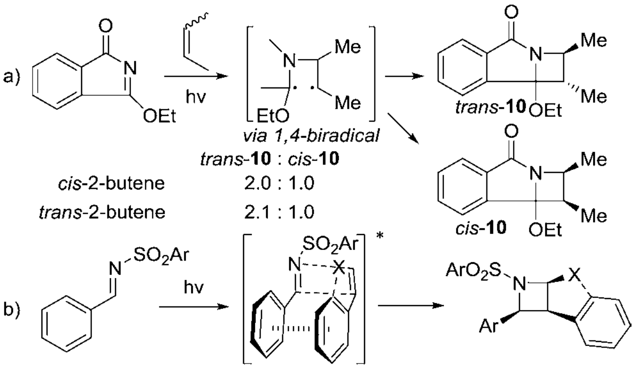
Interestingly, the reactions of 2-naphthaldehyde-derived *N*-Boc (*tert*-butoxycarbonyl) imine (**9**) with styrene or benzofuran did not afford the desired products (Scheme 6), even though the UV−vis spectrum of **9** also reveals an absorption at λ = 365 nm.[13] These results suggest that both the nature of the sulfonyl protecting group of the imine, as well as the presence of an absorption band at λ = ∼ 365 nm, should be of critical importance for this [2 + 2] photocycloaddition.

Scheme 6. [2 + 2] Cycloadditions between 9 and Benzofuran and/or Styrene



Previous reports on the [2 + 2] photocycloaddition between the C═N bond of isoindolones and the C═C bonds of *cis*- or *trans*-2-butene have described the loss of stereochemistry on the olefin moiety, indicating that 1,4-biradical intermediates should be formed during the reaction, similar to a typical Paternò−Büchi reaction (Scheme 7a).[2,3g] However, in the present case, the stereochemistry of the styrene moiety is retained within the products (Scheme 4b,c). Based on these results, we tentatively assigned a mechanism for the present [2 + 2] photocycloaddition, which is based on a concerted pathway involving a singlet state of the imine and a singlet exciplex with a sandwich-type structure between the aryl moieties of the imine and the olefin. This singlet exciplex intermediate should control the direction of the substrates and result in the observed formation of a single product as illustrated in Scheme 7b.[3i,j,19]

Scheme 7. Possible Reaction Intermediates of [2 + 2] Photocycloadditions Involving C═N Bonds



In summary, we have discovered unprecedented UV-light-induced [2 + 2] photocycloadditions between the C═N bond of *N*-arylsulfonylimines and the C═C bond of styrene or benzofuran derivatives at room temperature that afford azetidines in high stereoselectivity. Investigations regarding details of the underlying mechanism, as well as an expansion of the substrate scope and the development of other related photoreactions with imines, are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03003.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(13) For details of UV−vis spectra and emission spectra of imines, benzofuran, and a mixture of them, see the Supporting Information.

(14) In the case of the mixture of imine and benzofuran, the absorption at ∼365 nm almost remained unchanged.

(15) While the fluorescent spectrum of **1a** revealed an emission around λ = ∼430 nm, that of **3a** was found to be very weak, possibly because of a radiationless process such as isomerization of C═N bond.

(16) Due to the synthetic effort involved in the synthesis of **3f**, further optimization of the reaction was examined using **3b**.

(17) Irradiation with UV light (365 nm) to the mixture of the *N*-2-naphthylsulfonylimine of benzaldehyde with benzofuran in CH_2Cl_2 afforded a complex mixture of unknown products, while the formation of azetidine were not observed. While *N*-2-naphthylsulfonylimine of benzaldehyde did not show an absorption at λ = ∼365 nm, an absorption at λ = ∼330 nm was observed. This result may explain the necessity for the use of an HPML (300−600 nm) for [2 + 2] photocycloadditions of *N*-2-naphthylsulfonylimine.

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