# Intramolecular [2+2] Cycloaddition of Isocarbostyrils Catalyzed by an Iridium Visible-light Photocatalyst

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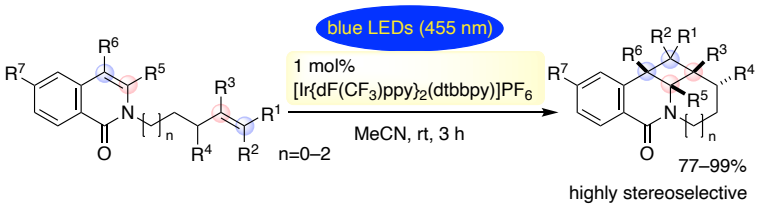
*Supporting Information Placeholder*




**ABSTRACT:** Irradiation on *N*-(ω-alkenyl)isocarbostyrils in the presence of an iridium photocatalyst by LEDs emitting 455 nm light gave the corresponding cyclobutane-fused benzo[*b*]quinolizine derivatives stereoselectively in high yields. Loading 1 mol% of the catalyst was enough to obtain high yields of the products in convenient reaction time in many cases. The reaction likely proceeds through stepwise [2+2] cycloaddition via a triplet biradical intermediate.

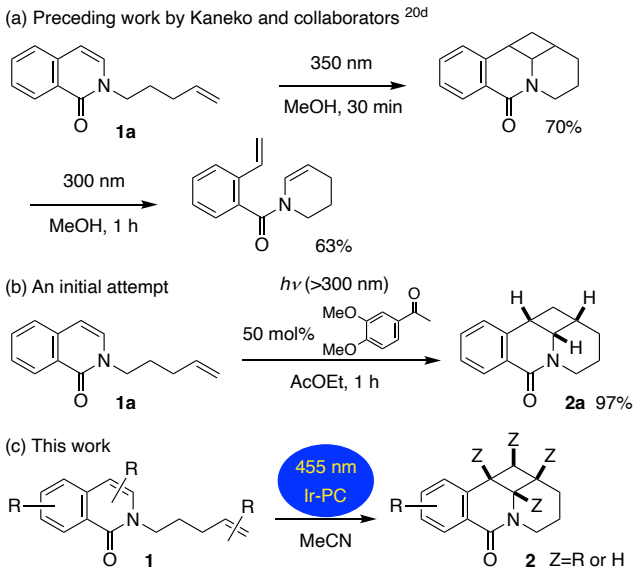
Isoquinoline alkaloids constitute a group of natural compounds with wide scaffold diversity and multi-target potential for the treatment of complex diseases.[1–5] Some studies have suggested multi-modal capacity of isoquinoline alkaloids, promoting the polypharmacological research of these molecules, especially in the neurodegenerative diseases and cancer.[6–8] These backgrounds make isoquinoline alkaloids typical structural motifs in pharmaceuticals. In conjunction with a recent trend in drug discovery, i.e., "escape from flatland" concept,[9] conformationally constrained small-ring-fused compounds have attracted much attention in modern medicinal chemistry.[10,11] In this context, cyclobutanes have interested researchers in drug discovery due to the growing demand for less lipophilic conformationally restricted analogues of known scaffolds rather than the rigid aromatic compounds.[12,13] Thus, novel small-ring-fused isoquinoline frameworks are expected to provide new pharmaceutical candidates in various bioactive screening.[14,15] To date, a number of synthetic methods have been reported for isoquinoline derivatives,[16,17] whereas there has been much less exploration regarding small-ring-fused, especially cyclobutane-fused isoquinoline derivatives.

The photochemical [2+2] cycloaddition reaction is one of the most popular and facile methods of constructing 4-membered cyclic compounds.[18] The [2+2] photocycloaddition of isocarbostyril, which is one of typical photo-reactive isoquinoline derivatives, with alkenes has been known since almost fifty years ago.[19] Extensive studies by a research group of Kaneko, Bach, and others have contributed to the development of this research field.[20–23] The reaction is known to proceed by direct irradiation or under the catalysis of a photosensitizer to give cyclobutane-fused 1-oxo-1,2,3,4-tetrahydroisoquinolines in moderate to high yields. Intramolecular cycloadditions have also been developed to build up a nitrogen-containing poly-cyclic framework.[20c,d,21b,d] Enantioselective intramolecular [2+2] cycloaddition of isoquinolones using well-designed chiral photosensitizer reported by Bach is noteworthy.[21c–e] However, almost all of these reactions required high energy UV irradiation, which occasionally caused undesirable side reactions exemplified by ring-opening reaction that gives a formal metathesis product (Scheme 1a).[20d] Exceptionally, Bach and collaborators have reported an example of intermolecular enantioselective cycloaddition of isocarbostyril under purple light irradiation (419 nm) with the assistance of a chiral thioxanthone template.[22] In this context, the realization of the [2+2] photocycloaddition of isocarbostyrils under visible light irradiation, which has lower energy than UV, would provide much milder alternatives.[24,25]

In our continuing work on the photochemistry of heteroaromatic compounds,[26] it has been recently found that 1-(ω-alkenoyl)indoles or 3-(ω-alkenyl)indoles show an excellent reactivity in the intramolecular [2+2] photocycloaddition sensitized by 3',4'-dimethoxyacetophenone (diMeOAP), which is a sensitizer of choice in this kind of reactions, to afford the corresponding cyclobutane-fused products in good yields.[26a,b] Inspired by these results, a reaction of *N*-(4-pentenyl)isocarbostyril (**1a**) under sensitization with diMeOAP was carried out according to the typical conditions in our previous reports, and it was found that a [2+2] adduct **2a** was produced in nearly quantitative yield (Scheme 1b). This result prompted us to conduct the reaction by using a visible-light photocatalyst (PC) that have relatively high triplet excitation energy ($E_T$) enough to cause energy transfer to **1a**, to find that

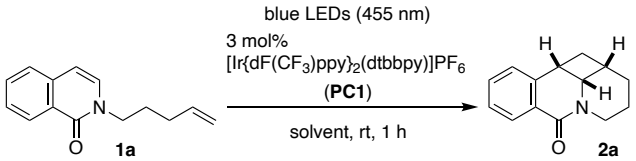
the reaction does proceed under sensitization with some iridium PCs, giving the [2+2] products in high yield with excellent stereoselectivity (Scheme 1c).[25] I would like to report herein the detail of the investigation.

**Scheme 1. Intramolecular [2+2] Photocycloaddition of *N*-(ω-Alkenyl)isocarbostyril**




An iridium photocatalyst, [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (**PC1**, $E_T$=60.8 kcal/mol),[27] was chosen for the initial solvent screening (Table 1). The reactions were carried out by irradiating **1a** with blue LEDs (455 nm) in the presence of **PC1** in a series of solvents. The solvents were thoroughly degassed by freeze-thaw cycles before use. The reactions were conducted at room temperature and discontinued in 1 h irrespective of the consumption of **1a**. Because so little compound was found other than **1a**, **2a**, and **PC1** in $^1$H NMR spectra of the crude mixtures, the reaction was estimated by comparing **1a**/**2a** ratio without strict quantification (see, Fig. S1). The reaction proceeded moderately in alcoholic solvents that have been reported to improve the efficiency of the energy transfer process by reducing the triplet energy of the indole derivatives by the formation of hydrogen bonds (entries 1 and 2).[25d] In our cases, non-hydrogen bonding polar solvents or halogenated solvents turned out to be suitable for the reaction, affording good yields of **2a** (entries 3–6). Ethereal solvents gave moderate results (entries 7 and 8). Although the influence of solvents on the reaction is not fully understood, superiority of MeCN or $CH_2Cl_2$ has been reported in the literature.[28] The stereochemistry of **2a** was determined by conventional NOE experiments after isolation (see the Supporting Information). When isolated **2a** was irradiated under the reaction conditions in acetonitrile, it was recovered unchanged almost quantitatively. Based on these results, acetonitrile was chosen as the best solvent because it gave the highest yield of **2a** and the cleanest reaction.

**Table 1. Solvent Screening**[a]

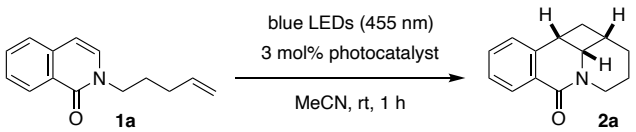



| Entry | Solvent | **1a** : **2a**[b] |
|---|---|---|
| 1 | MeOH | 47 : 53 |
| 2 | HFIP | 61 : 39 |
| 3 | AcOEt | 32 : 68 |
| 4 | MeCN | 7 : 93 |
| 5 | $CH_2Cl_2$ | 11 : 89 |
| 6 | $C_6H_5CF_3$ | 26 : 74 |
| 7 | MTBE | 41 : 59 |
| 8 | THF | 44 : 56 |

[a] All reactions were carried out in a Pyrex test tube by external irradiation with blue LEDs emitting 455 nm light at a concentration of 10 mM. [b] Estimated by the $^1$H NMR integral ratio of the crude mixture.

Next, a series of visible-light photocatalysts that have absorption around 455 nm were examined (Table 2). MesAcrClO$_4$ (**PC2**) and 4CzIPN (**PC5**) showed no conversion and the starting material **1a** was recovered without change (entries 1 and 4). The reaction was hardly proceeded in the presence of [Ru(bpy)$_3$](PF$_6$)$_2$ (**PC3**) or Ir(ppy)$_3$ (**PC4**), whereas [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ (**PC6**) and **PC1** catalyzed the reaction nicely to give **2a** in 75% and 86 yield, respectively (entries 2, 3, 5, and 6). Considering the $E_T$ of the photocatalysts shown in the table, these results clearly indicate that a photocatalyst that has an $E_T$ larger than 60–61 kcal/mol is required for this reaction to proceed smoothly, though the $E_T$ of **1a** is not known in the literature. The $T_1$–$S_0$ energy gap of a simplified molecule, *N*-methylisocarbostyril, was estimated as about 62 kcal/mol by theoretical calculations.[31] The reaction did not proceed at all without photoirradiation (entry 7). When the reaction was conducted in the presence of 1,3-cyclohexadiene, a typical triplet quencher ($E_T$=53 kcal/mol),[32] significant inhibition was observed, and the yield of the product largely decreased (entry 8). This result suggests that the reaction likely proceeds through triplet sensitization of **2a** by **PC1**. No reaction occurred in the absence of the photocatalyst (entry 9).

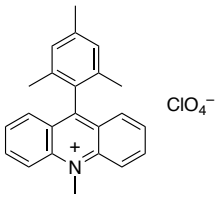
**Table 2. Choice of Photocatalysts**[a]



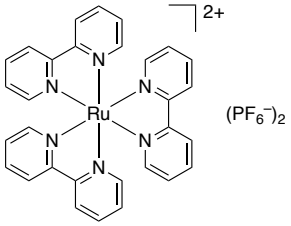

| Entry | Photocatalyst | $E_T$ (kcal/mol) | Conv. (%)[b] | **2a** (%)[b] |
|---|---|---|---|---|
| 1 | MesAcrClO$_4$ (**PC2**) | 44.7 [c] | 0 | 0 |
| 2 | [Ru(bpy)$_3$](PF$_6$)$_2$ (**PC3**) | 46.5 [c] | 3 | 0 |
| 3 | Ir(ppy)$_3$ (**PC4**) | 57.8 [c] | 2 | 0 |

| | | | | |
|---|---|---|---|---|
| 4 | 4CzIPN (**PC5**) | 58.3 [d] | 0 | 0 |
| 5 | [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ (**PC6**) | 60.4 [e] | 79 | 75 |
| 6 | [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)] PF$_6$ (**PC1**) | 60.8 [c] | 94 | 86 |
| 7 [f] | **PC1** | 60.8 [c] | 0 | 0 |
| 8 [g] | **PC1** | 60.8 [c] | 52 | 46 |
| 9 | none | | 0 | 0 |

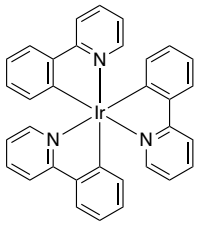
[a] All reactions were carried out in a Pyrex test tube by external irradiation with blue LEDs emitting 455 nm light at a concentration of 10 mM. [b] Determined by the $^1$H NMR integral ratio using 1,3,5-trimethoxybenzene as an internal standard. [c] Ref 27. [d] Ref 29. [e] Ref 30. [f] In the dark. [g] In the presence of 10 equivalents of 1,3-cylcohexadiene.



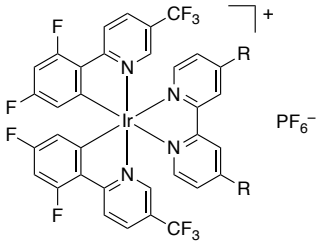

MesAcrClO$_4$ (**PC2**)



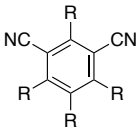

[Ru(bpy)$_3$](PF$_6$)$_2$ (**PC3**)



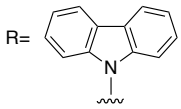

Ir(ppy)$_3$ (**PC4**)




R=H: [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ (**PC6**)
R=*t*-Bu: [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (**PC1**)

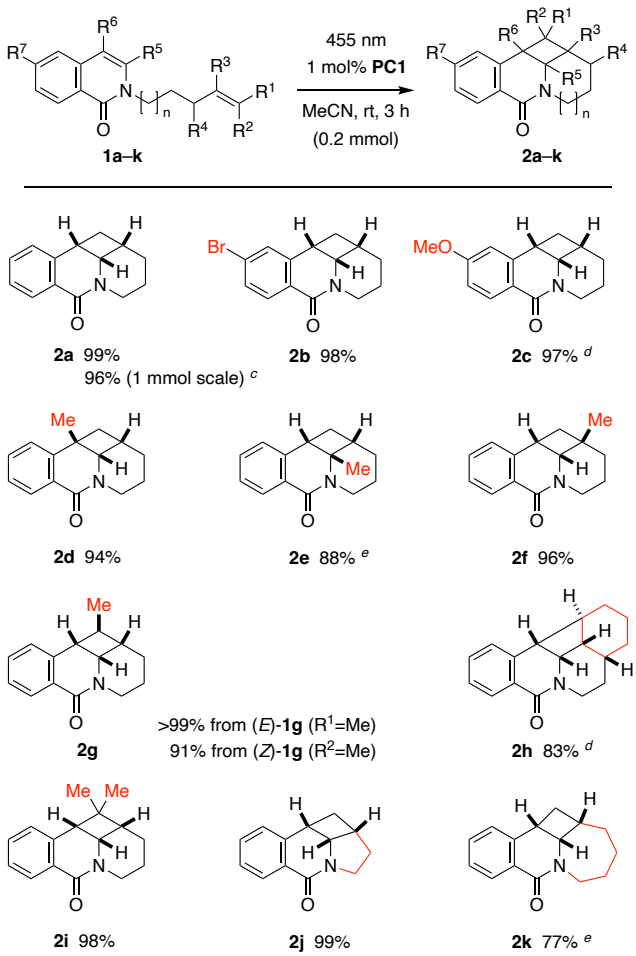



4CzIPN (**PC5**)




With the optimized photocatalyst and solvent in hand, the reaction using a variety of isocarbostyril derivatives was explored next (Scheme 2). The reactions shown in Scheme 2 were carried out in 0.2 mmol scale in a Pyrex round-bottomed flask. The reactions were discontinued as soon as possible after consumption of the starting materials. In the reaction of **1a**, the amounts of **PC1** could be reduced to 1 mol% by prolonging the irradiation time to 3 h, affording **2a** in 99% yield. Accordingly, the following reactions were conducted in the presence of 1 mol% **PC1** for 3 h in principle. It was easy to scale up the reaction of **1a** with little sacrifice of the yield of **2a** (96%). The substituents at the benzene ring of the isoquinolone moiety turned out to have influence on the reaction rate. The reaction of **1b** (6-Br) gave comparable yields of the cyclized product **2b** (98%) in the standard rection conditions, while the reaction of **1c** (6-MeO) was somewhat retarded. Longer reaction time was required to complete the reaction, though the yield of **2c** was comparable (97%). The reactions with Me-substituted substrates **1d** (R$^6$=Me), **1e** (R$^5$=Me), and **1f** (R$^3$=Me) gave the corresponding products that have a quaternary carbon at the ring junction around the cyclobutane moiety in high yields. The slow reaction of **1e** would be attributable to a steric factor in the first ring closure discussed below (see, Scheme 4). Interestingly, when the reaction was carried out by using (*E*)- or (*Z*)-**1g**, the same product **2g** was obtained irrespective of the geometry of the alkene moiety. This observation was interpreted as a result of stereochemical inversion at the terminal alkene carbon to avoid locating the methyl group at sterically congested concave site. Similarly, irradiation of **1h**, which has a cyclohexenyl side chain, cycloadduct **2h** was obtained in 83% yield through the *trans*-addition to the cyclohexenyl moiety. The relative configuration of **2h** was unambiguously determined by X-ray crystallographic analysis (Fig. 1, CCDC 2226849). The reaction also worked well in the case of more sterically demanding substrate **1i**, giving the product **2i** in excellent yield. In addition to that, the variation of the length of the *N*-alkyl side chain led to the formation of five- and seven-membered cycloaddition product (**2j**, 99%, **2k**, 77%), though the reaction rate was slowed in the reaction of **1k**.

**Scheme 2. Substrate Scope**[a,b]




[a] All reactions were carried out in a Pyrex round-bottomed flask by external irradiation with blue LEDs emitting 455 nm light at a concentration of 10 mM. [b] Yields of isolated product. [c] Reaction time, 5 h. [d] Reaction time, 6 h. [e] Reaction time, 9 h.

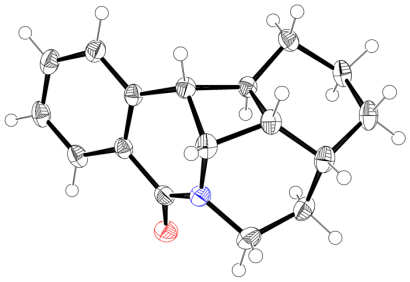
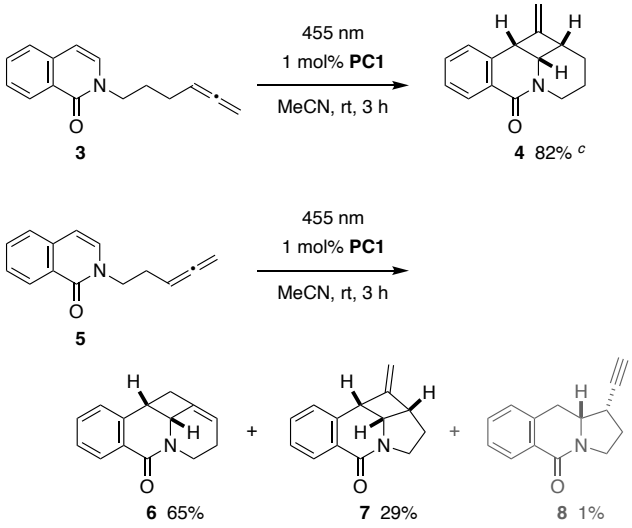


**Figure 1.** ORTEP drawing of **2h**.

This reaction worked well when the alkene terminal was replaced with an allene moiety. When *N*-4,5-hexadienyl isocarbostyril **3** was irradiated under the typical conditions shown in Scheme 2, the cycloaddition products with *exo*-methylene cyclobutane **4** was obtained in 82% (Scheme 3). Unfortunately, the separation was quite difficult in this case, the product contained small amounts of un inseparable unknown compound. The reaction of **5**, which has a side chain shorter than **4**, gave three types of the adducts, including **6** via distal [2+2] addition, **7** via proximal [2+2] addition, and very small amounts of tentatively assigned terminal alkyne **8** via 1,5-hydrogen transposition. The mechanism underlying the formation of the alkyne was discussed in our previous work.[26b]

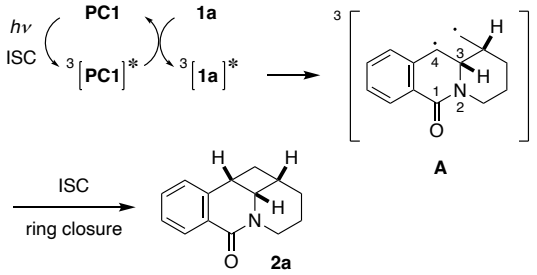
**Scheme 3. Reaction of a Substrate with an Allenyl Side Chain**[a,b]




[a] All reactions were carried out in a Pyrex round-bottomed flask by external irradiation with blue LEDs emitting 455 nm light at a concentration of 10 mM. [b] Yields of isolated product. [c] The product contained small amounts of an inseparable unknown compound (approximately 5%).

Concerning the mechanism of the reaction, we presume that the reaction pathway is as shown in Scheme 4 based on the results discussed above and information from the literatures. Triplet **1a**, which is generated by energy transfer from the triplet **PC1**, makes a carbon-carbon bond between the 3-position of the isocarbostyril and the alkene moiety to form the tricyclic biradical intermediate **A**, followed by the ring closure accompanied by intersystem crossing (ISC), giving the [2+2] adduct **2a**. The mechanism underlying this type of radical bond formation has been well established in the photoreaction between indoles and alkenes,[28] as well as the intermolecular [2+2] cycloaddition of isocarbostyrils under UV irradiation.[21c] The reaction path through the triplet state was also supported by inhibitory effect in the presence of a triplet quencher (Table 2, entry 8). The SET mechanism would be ruled out based on the electrochemical data. The $E_{1/2}^{ox}$ of *N*-methylisocarbostryril is estimated at +1.4~1.5 V (vs. SCE) in the literature,[33] whereas $E_{1/2}$(**PC1***/**PC1**($Ir^{II}$)) is known as +1.21 V (vs. SCE).[27] This means that the reductive quenching of **PC1*** by *N*-alkylisocarbostyrils is unlikely.[34] Though the reduction potential of *N*-alkylisocarbostryril seems unknown, if the reaction proceeds through the oxidative quenching of **PC1***, more reducing **PC4*** ($E_{1/2}$(**PC4**($Ir^{IV}$)/**PC4***) = –1.73 V (vs. SCE), $E_{1/2}$(**PC1**($Ir^{IV}$)/**PC1***) = –0.89 V (vs. SCE))[27] should promote the reaction, but actually **PC4*** did not (Table 2, entries 3 and 6).

**Scheme 4. Plausible Reaction Pathway**




In summary, an unprecedented [2+2] photochemical cycloaddition reaction of isocarbostyril derivatives catalyzed by blue-light (455 nm) photocatalysts has been developed. [Ir{dF($CF_3$)ppy}$_2$(dtbbpy)]$PF_6$ is a catalyst of choice in this reaction. With appropriate substrates, the reaction proceeds almost quantitatively in the presence of 1 mol% of the catalyst within a few hours. It should be noted that the diastereoselection in this reaction is quite high. A plausible reaction pathway is proposed based on some experiments and information from the literature.

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Figure S1–S3, experimental procedures, spectral data, and property of the LED light source. (PDF)

FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds [**1a**–**k**, **2a**–**k**, **3**, **4**, **5**, **6**, **7**].

CCDC 2226849 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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### Notes

The author declares no competing financial interest.

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