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FULL PAPER

Photocatalyzed Intramolecular [2+2] Cycloaddition of *N*-alkyl-*N*-(2-(1-arylvinyl)aryl)cinnamamides

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Supporting information for this article is given via a link at the end of the document.

Abstract: *N*-Alkyl-*N*-(2-(1-arylvinyl)aryl)cinnamamides are converted into natural product inspired scaffolds via iridium photocatalyzed intramolecular [2+2] photocycloaddition. The protocol has a broad substrate scope, whilst operating under mild reaction conditions. Tethering four components forming a trisubstituted cyclobutane core builds rapidly high molecular complexity. Our approach allows the design and synthesis of a variety of tetrahydrocyclobuta[*c*]quinolin-3(1*H*)-ones, in yields ranging between 27-99%, and with excellent regio- and diastereoselectivity. Moreover, it was also demonstrated that the intramolecular [2+2]-cycloaddition of 1,7-enynes - after fragmentation of the cyclobutane ring - leads to enyne-metathesis-like products.

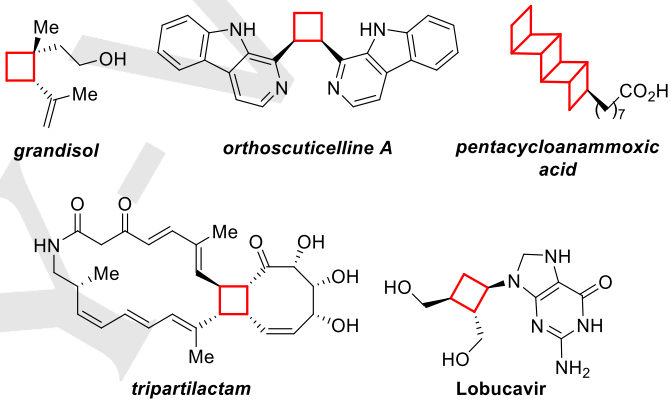

Figure 1. Selected examples of pharmaceuticals and natural products bearing the cyclobutane core moiety

Introduction

Cyclobutane containing molecules are interesting organic molecules, frequently found in pharmaceuticals[1] and biologically relevant natural products (Figure 1).[2] The core structure has been exploited by numerous research groups as key reactive intermediates towards building complex molecular architectures.[3] The synthesis of cyclobutane derived compounds has been achieved through a diverse range of approaches,[4] with [2+2] photocycloadditions being the most versatile and well established strategy.[5] The first examples of cyclobutane synthesis through [2+2] photocycloadditions were reported at the end of the 19th century and since then an immense amount of information has been collected[6] allowing for rationally designed transformations.[7] Beyond a better mechanistic understanding, those studies culminated in exceptional preparative methodologies, with highly stereoselective applications in total synthesis.[5] Nonetheless, until recently, most of the photoinduced protocols require the use of high-energy UVC radiation[8] (ca. λ = 240–265 nm; photon energy 108-120 kcal mol^{-1}), which is not amenable to highly functionalized organic substrates often present in the synthesis of bioactive small-molecules.

In this context, visible-light photocatalysis has emerged as an important tool for the synthesis of complex molecular architectures through [2+2] photocycloadditions under mild and selective redox or energy-transfer processes. Their broad applicability is highlighted by a number of key photocatalytic [2+2] cycloaddition reactions already reported in the literature employing photosensitive metal complexes (ruthenium,[9] iridium,[10] rhodium[11]) and organic dyes.[12] In 2012, Yoon and co-workers showcased the intramolecular [2+2] styrene cycloaddition via a triplet sensitization mechanism mediated by an Ir(III) photocatalyst, affording a range of high value cycloadducts (Scheme 1a).[13] This approach was further expanded to 1,3-dienes,[14] and more recently an enantioselective version was developed using a chiral hydrogen-bonding iridium photosensitizer (on both intra- and intermolecular systems).[15] Meanwhile, Kwon and co-workers elegantly reported [2+2] cycloadditions involving aromatic dienones also employing an iridium-complex photosensitizer.[16] Contrasting with the previous examples of straight [2+2] cycloadditions, a crossed cycloaddition process took place to afford a family of benzobicyclo[3.1.1]-heptanones in good to excellent yields (Scheme 1b). Very recently, adapting the previous works from Mykhailiuk and Cibulka groups to visible-light photocatalytic conditions,[17] Reiser´s and Oderinde´s groups concomitantly reported the synthesis of aryl-3-azabicyclo[3.2.0]-heptanones and aryl-3-azabicyclo[3.2.0]heptanes employing the same photosensitizer as reported in Yoon´s seminal works (Scheme 1a).[18],[19]

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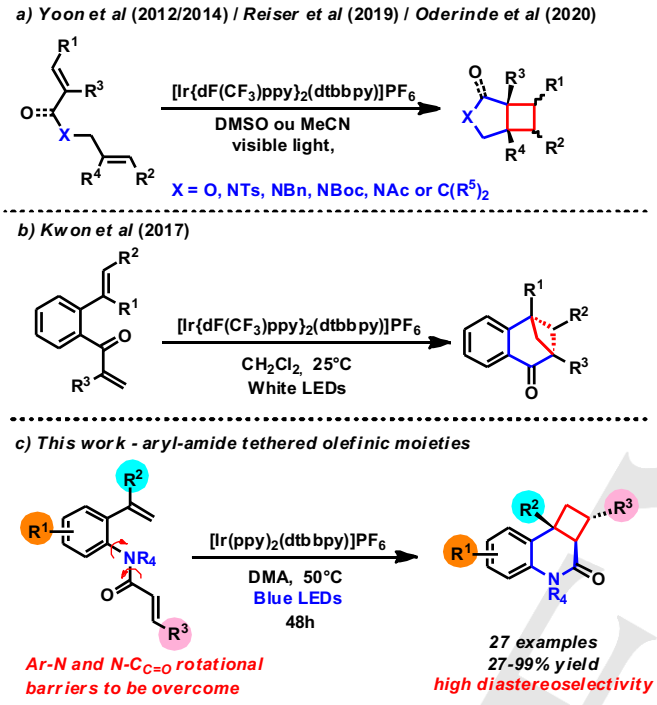
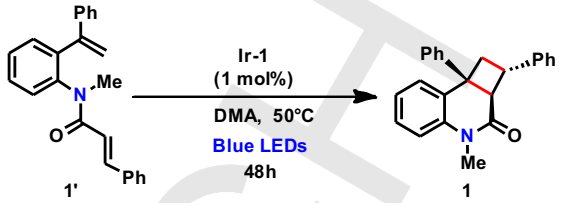
Herein, as part of our ongoing investigations towards the development of photocatalytic strategies for the synthesis of complex heterocyclic compounds,[20] we report our latest findings towards the synthesis of substituted tetrahydro-cyclobuta[*c*]quinolin-3(1*H*)-ones via a highly diastereoselective intramolecular visible-light photocatalyzed [2+2] cycloaddition of *N*-alkyl-*N*-(2-(1-arylvinyl)aryl)cinnamides (Scheme 1c). A distinct feature of our strategy is the fact that the participating olefinic entity is tethered by a rigid aryl-amide moiety restricting the rotation along amide and Ar-N bonds.

Scheme 1. Previous reports on photocatalyzed [2+2] cycloadditions on relevant systems and our protocol.

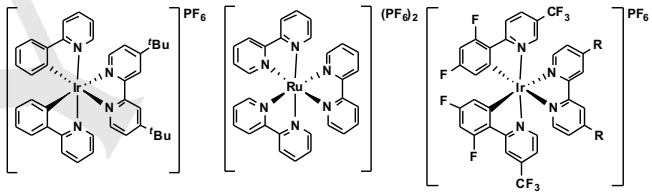


compound **1** was obtained and characterized by X-ray structure analysis (Scheme 2 – See supporting information for more details).

Table1. Optimization of the photocatalyzed [2+2]-cycloaddition



entry	deviation from standard conditions	1 [%]
1	none	97
2	Ru-1 instead of Ir-1	10
3	Ir-2 instead of Ir-1	94
4	Ir-3 instead of Ir-1	93
5	MeCN instead of DMA	36
6	DMSO instead of DMA	90
7	24-36h	83-86
8	no cat or in darkness	nr



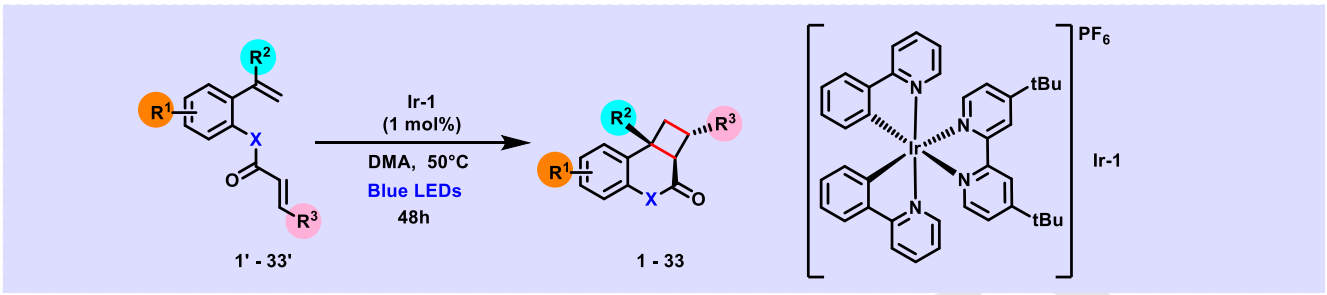
Reaction conditions: **1'** (0.1 mmol) and photocatalyst (1.0 mol%) in solvent (0.5 mL) at T= 50 °C (no fan) under household blue LEDs irradiation (34 W) during 48 h.

Results and Discussion

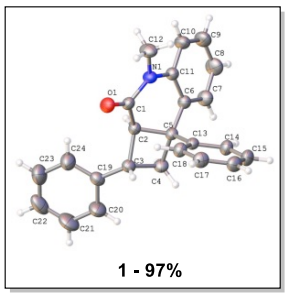
To begin our studies, we chose to optimize the [2+2] cycloaddition reaction conditions starting with substrate **1'** in the presence of 1 mol% of the photocatalyst **Ir-1.** (E_T = 49.2 kcal/mol). Under these conditions, we were pleased to observe that cyclobutane **1** could be accessed in 97% yield and excellent diastereoselectivity (Table 1, entry 1). Changing to the ruthenium-based photocatalyst **Ru-1** (E_T = 46.5 kcal/mol) led to a significant drop in the product yield (10%, entry 2). Using higher triplet energy photocatalysts, **Ir-2** (E_T = 62 kcal/mol) and **Ir-3** (E_T = 61.8 kcal/mol) afforded the desired product in 94% and 93% yield respectively (entries 3 and 4). To further investigate the influence of the polar solvent, dimethyl acetamide was replaced by acetonitrile or dimethyl sulfoxide, but a decrease in yields were observed (entries 5 and 6). Shortening the reaction time from the 48 hours to 24 hours or 36 hours led to a significant drop in yield (83% and 86% respectively, entries 7 and 8). Additionally, control experiments revealed that the combination of both **Ir-1** photocatalyst and blue LED light irradiation is essential for the reaction outcome. In order to determine the structure of the diastereoisomer in this transformation, a crystal structure of

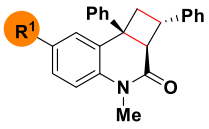
With the optimized conditions in hand, we turned our attention to investigate the substrate scope of the transformation (Scheme 2). Based on the excellent yield obtained for **1**, we first evaluated the influence of different functional groups at the *para* position in the aniline portion (R^1) of the styrene moiety. Gratifyingly, the reaction tolerated a range of functionalities including halides (Cl, Br = **2**, **4**, 76% and 78% yield respectively), and electron donating groups, including methoxy (**3**), methyl (**5**), and thiomethyl (**6**) in yields ranging between 63-80%. When the dimethylamine group (**7**) was introduced however, the target product was accessed in only 23% yield, likely owing to the competing photosensitizer quenching by this functional group under the reaction conditions. Substituents at other positions also gave the desired cyclobutane products. A trimethoxy-derivative was tested, affording the desired product (**8**) in moderate yield (53%). Replacing the aniline moiety by a naphthalen-2-amine group led to a detrimental change in product yield (**9**, 27%).

Next, the phenyl moiety at R^2 was modified to incorporate *para*-halide substituents (**10** and **11**) and a *para*-methyl group (**12**) - the corresponding cyclobutaquinolinones were obtained in 56%, 85% and 84% yield respectively. Replacing the phenyl ring with a thiophenyl or a methyl group were also tolerated, affording the desired products in excellent isolated yields (**13**, 82% and **14**, 80%). When an *ortho*-methyl-phenyl derivative was attempted,

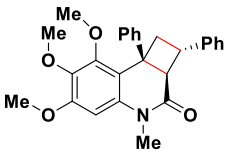


Styrene moiety

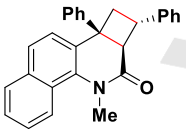




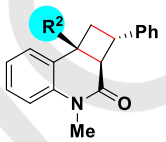
2, R^1 = Cl, 76%
3, R^1 = MeO, 63%
4, R^1 = Br, 78%
5, R^1 = Me, 65%
6, R^1 = SMe, 80%
7, R^1 = $N(Me)_2$, 23%



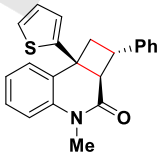
8, 53%



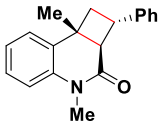
9, 27%



10, R^2 = *p*-ClC_6H_4, 56%
11, R^2 = *p*-FC_6H_4, 85%
12, R^2 = *p*-MeC_6H_4, 84%

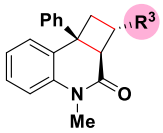


13, 82%

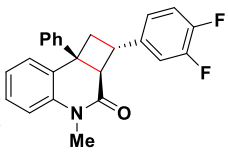


14, 80%

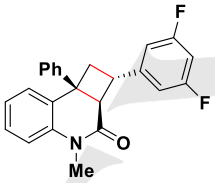
Cinnamic moiety



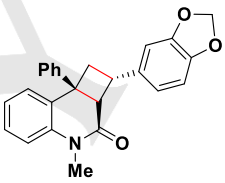
15, R^3 = *p*-$MeOC_6H_4$, 85%
16, R^3 = *o*-$MeOC_6H_4$, 68%
17, R^3 = *p*-MeC_6H_4, 98%
18, R^3 = *o*-MeC_6H_4, 93%
19, R^3 = *p*-BrC_6H_4, 96%



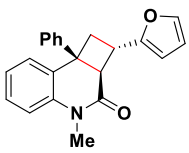
20, 88%



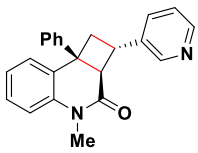
21, 49%



22, 99%

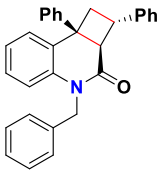


23, 30%

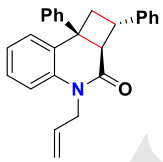


24, 47%

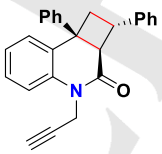
Nitrogen substituents



25, 93%

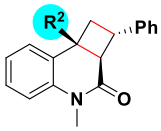


26, 80%

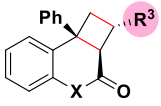


27, 77%

Other limitations:



28, R^2 = *o*-MePh, 0%[b]
29, R^2 = 1-Naphthyl, 0%[b]



30, X = NMe, R^3 = H, 20%, d.r 2:1[c]
31, X = NMe, R^3 = Me, 53%[c]
32, X = O, R^3 = Ph, 0%[d]
33, X = NH, R^3 = Ph, 0%[d]

[a] Reaction conditions: Diene **1'-33'** (0,1 mmol), **Ir-1** (1.0 mol%), DMA (0.5 mL), 50 °C (no fan), irradiation with household blue LEDs (34 W), 48 h.
[b] Only the starting material isomerization product was obtained.
[c] Photocatalyst **Ir-3** was employed in lieu of **Ir-1**.
[d] Decomposition of the starting material was observed.

Scheme 2. Exploring the reaction scope[a]

only the isomerization product was obtained, possibly due to steric hinderance of the *ortho*- donating group. The same replaced by a naphthyl moiety (**29**).

The scope and limitations in terms of the the R^3 substituent on the cinnamide moiety were also investigated. A wide range of functionalities were well tolerated, including *ortho*- and *para*-substituted methoxy, methyl and bromo, as well as di-fluoro and methylenedioxy groups in good to excellent yields between 49-98% (**15-22**). Additionally, heteroaromatics also underwent this transformation, providing the cyclobutaquinolinones **23** and **24** in 30% and 47% yield, respectively. Under the optimized conditions, no product was detected when the cinnamide moiety was replaced by a crotylamide or an acrylamide. However, reactivity could be restored when **Ir-3** was employed in lieu of **Ir-1**, affording the desired products **30** and **31** in 20% and 53% yield, respectively.

To complement the previous substrates, we were successfully able to modify the *N*-methyl group with *N*-benzyl (**26**, 93%), *N*-allyl (**26**, 80%) and *N*-propargyl (**27**, 77%) groups, affording the desired products in high yields (Scheme 2). When attempting to access the cyclobutachromen-3-one **32** and *N*H-cyclobutaquinolinone **33**, only decomposition of the starting materials was observed, highlighting the requirement of an *N*-protected aryl-amide moiety (Scheme 2).

With the success of the styrenyl-derived substrates undergoing a smooth reaction to the desired

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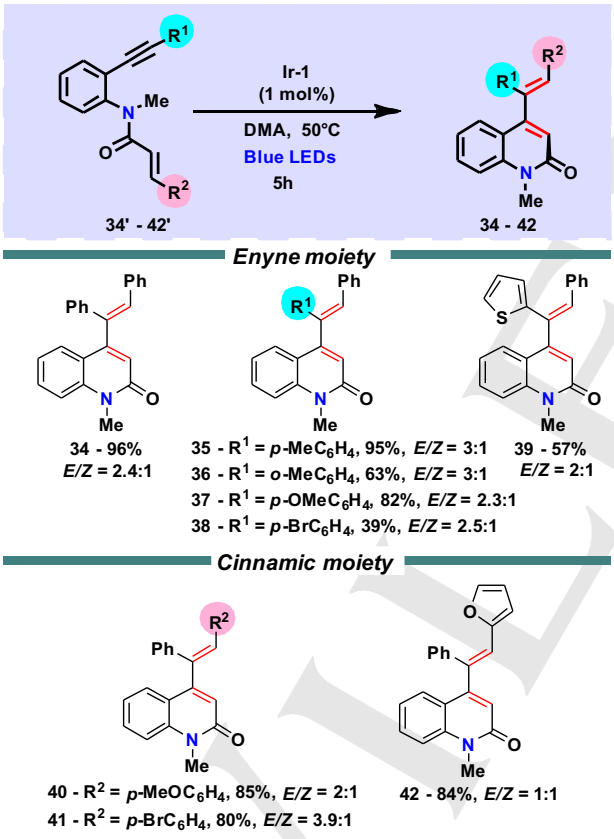
cyclobutaquinolinones, we investigated replacing the pendant alkene functionality with an internal alkyne group **(34')**. To our delight, instead of the expected cyclobutene product, the diene **34** could be accessed in 96% yield using iridium catalyst **Ir-1** (1 mol%) in DMA at 50 °C using blue LEDs for five hours (Scheme 3 – see SI for full table of optimization conditions).[21] Satisfied by this result, we moved onto investigating the scope of the transformation, firstly by modifying the enyne moiety R^2 aryl substituent. Incorporation of an electron rich methyl group at the *para*-position gave the desired diene product **35** in 95% yield, whilst an *ortho*-methyl substituent led to a noticeable drop in yield, presumably due to steric hinderance (**36**, 63%). Methoxy substituents on the aryl ring in the *para*-position were also tolerated in the reaction, giving rise to product **37** in 82% yield; however, incorporation of an electron deficient bromine atom at the *para*-position resulted in a lower yield of 39% for diene product **38**. Furthermore, we were pleased to see that an aryl ring could be replaced with a heteroaryl ring system, a 2-thiophene, which yielded diene **39** in a respectable 57% yield. We then moved onto investigating the scope of the cinnamic moiety – substituted aryl rings incorporating either a methoxy or bromide substituent gave the required diene products **40** and **41** in 85% and 80% yield, showing a good tolerance to electronic changes on this part of the starting materials. A final inclusion of a 2-furan heterocycle, in place of an aryl ring, gave diene **42** in 84% yield.

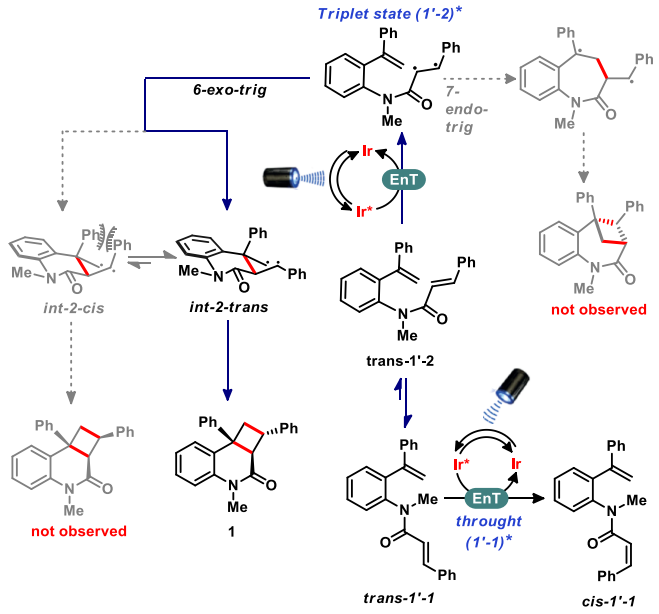


Reaction conditions: Enyne **34'-42'** (0.1 mmol) and **Ir-1** (1.0 mol%) in DMA (0.5 mL) at T= 50 °C (no fan) under household blue LEDs irradiation (34W) during 5h.

Scheme 3. Synthesis of dienes using an Iridium photocatalyzed approach.

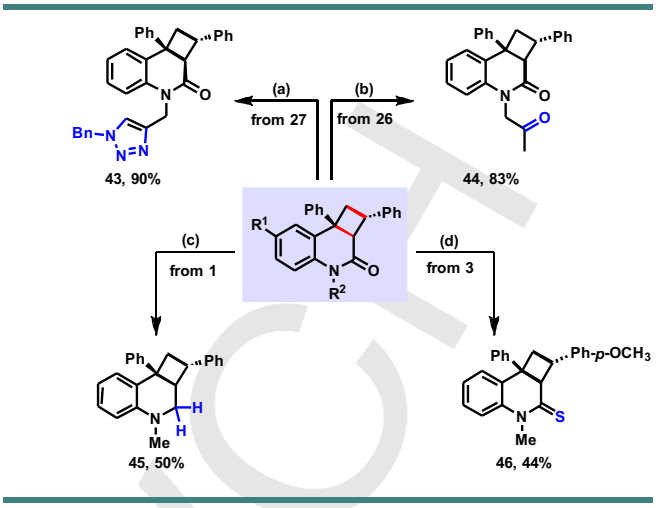
In order to evaluate whether the intramolecular cycloaddition proceeds via EnT or photoinduced electron transfer (PET) mechanism, we performed the cyclic voltammetry of **1'** to determine its redox properties (See supporting information). From these experiments, two reducing potentials were found ($E_{1/2}$= -2.06, -2.49 V vs SCE), which are outside of the reachable redox window of **Ir-1** (supporting information). These findings indicate that the reaction is not triggered by PET, but by an EnT photosensitization. To further corroborate this evidence, a set of additional experiments were performed using different photocatalysts which were selected based on their triplet energies (Table S2, supporting information).[5,22] As observed, catalysts with lower triplet energy than **Ir-1**, such as Eosin Y and $Ru(bpy)_3(PF_6)_2$ were ineffective for the transformation (Table S2, entries 2 and 3, respectively), whilst the photosensitizers with higher triplet energy afforded the corresponding products (Table S2, entries 4-7). When the reaction was performed under aerobic conditions, a decrease to 75% was observed, which could be explained by the quenching of the triplet state of the **Ir-1** by oxygen (Table S2, entry 8). Additionally, it is noteworthy that the reaction also worked in the absence of the photocatalyst in the presence of more energetic radiation (UVA) – (Table S2, entries 9 and 10).

Based on our findings and on previous studies by Reiser and Kwon,[16][18] the mechanistic considerations for the reaction are shown below in Scheme 4. We also considered a strong dependence between the reaction outcome and conformation adopted by the aryl-cinnamide, since the rotational barriers around the amide (15–20 kcal/mol) and the (*ortho*-substituted) Ar–N (~20-30 kcal/mol) bonds need to be overcome to achieve a conformation, in which the olefin moieties are close enough to react (Scheme 4, center).[23] As previously described, we postulate the iridium photocatalyst (**Ir-1**) absorbing blue LED irradiation is excited to the *Ir(III) singlet excited state.[5b] Inter-system crossing converts the singlet into the long-lived triplet-state, [24] which undergoes an intermolecular energy-transfer (**EnT**) process to give a conformationally distinct biradical species, depending on the conformation of the starting substrate. An EnT to conformer ***trans-1'-1***, in which the olefinic moieties are distant from each other, leads to biradical ***1'-1**** (not shown) that can rotate along the C-C bond axis and return to the ground state to afford isomer ***cis-1'-1*** (Scheme 4, bottom right). This pathway is consistent with the results obtained when bulky aryl moieties were placed in R^2 position (**28** and **29**, Scheme 2). On the other hand, an EnT to conformer ***trans-1'-2*** leads to biradical ***1'-2**** (Scheme 4, top-center) that can, due the proximity of the olefinic moieties, undergo two different cyclization pathways. According to the results obtained, the cyclization through a *6-exo-trig* process is faster and two new conformationally distinct biradical species (***int-2-cis*** and ***int-2-trans***) are possible (Scheme 4, left). In order to minimize the repulsion between the aryl moieties, the biradical ***int-2-trans*** is formed exclusively, leading to the observed product **1** through a radical-radical coupling event. Moreover, this mechanistic proposal does not rule out the possibility of the isomerization product ***cis-1'-1*** to adopt a suitable conformation to also undergo the cycloaddition pathway towards **1** after a second photoexcitation event.



Scheme 4. Postulated reaction mechanism for the Iridium-photocatalyzed [2+2] cycloaddition reaction of 1.

To showcase the utility and importance of our cyclobutaquinolinone products, we subjected some of the obtained analogues to late-stage structural modification reactions (Scheme 5). Initially, the cyclobutaquinolinone **27** bearing an *N*-alkynl moiety underwent a copper-catalysed azide-alkyne cycloaddition reaction with phenyl azide, affording the 1,2,3-triazole product **43** in excellent yield (90%).[25] Following this success, *N*-allyl derived cyclobutaquinolinone **26** underwent a smooth palladium-catalysed oxidation of the carbon-carbon double bond, furnishing ketone **44** in 83% chemical yield.[26] To conclude the late-stage structural modifications, we focused on modifying the carbonyl substituent at C2 on the quinolinone core – DIBAL reduction of **1** gave tetrahydroquinoline **45** in acceptable yield (50%),[27] whilst conversion of the carbonyl moiety into a thiocarbonyl group was realized using Lawessons reagent on cyclobutaquinolinone **3**, providing cyclobutaquinolinthione **46** in modest yield (44%).[28]



Reagents and conditions: (a) $CuSO_4.5H_2O$, sodium ascorbate, benzyl azide, DCM/H_2O, 3 h; (b) $PdCl_2$, $CuCl_2$, THF:H_2O (20 equiv.), O_2 (baloon); (c) DIBAL, toluene, reflux; (d) Lawesson's reagent, toluene, reflux

Scheme 5. Late-stage diversification of cyclobutaquinolinones

Conclusion

The synthesis of a broad range of highly substituted and complex cyclobutane-derived dihydroquinoline products has been realized utilizing an iridium photocatalyzed approach. The [2+2] cycloaddition reaction tolerated a diverse range of functional groups at four key positions of the molecular scaffold. The reaction generates tricyclic molecules of high value add, with 29 examples isolated in yields ranging between 19-98%. The mechanism of the reaction was postulated based on some preliminar experiments and recent literature precedents, which suggest that transformation proceeds via an intermolecular energy transfer process (EnT) between the photocatalyst and alkenyl substrate. Moreover, replacing the alkenyl moiety for an alkynyl group in the starting materials, we could extend the scope of the iridium photocatalyzed approach to access diene products. The synthetic utility of these molecules was further demonstrated by five derivatizations in different positions of the heterocyclic scaffold. Current research in our group is looking to expand further on this photocatalytic transformation upon new substrates for the synthesis of complex organic structures.

Experimental Section

Full experimental details along with NMR spectra can be found in the supplementary information.

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Keywords: energy transfer • cycloaddition • photocatalysis • dienes

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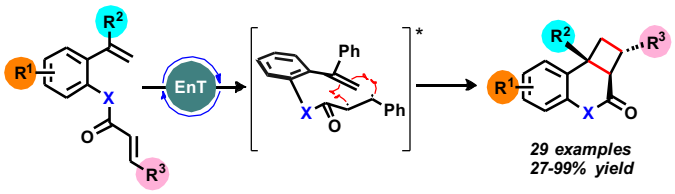

A highly efficient and straightforward photocatalytic strategy for the preparation of tetrahydrocyclobuta[*c*]quinolin-3(1*H*)-ones is reported. The reaction presents a high functional group tolerance and diastereoselectivity. Mechanistic evidence supports an energy-transfer (EnT) pathway. The synthetic utility of these molecules was further demonstrated by derivatizations in different positions of the heterocyclic scaffold.

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