A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

GDCh

www.angewandte.org

Accepted Article

Title: Light-driven intramolecular C-N cross-coupling via a long-lived photoactive photoisomer complex

Authors: Ke Zheng, Dong Jing, Cong Lu, Zhuo Chen, Songyang Jin, Lijuan Xie, Ziyi Meng, and Zhishan Su

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201906112
Angew. Chem. 10.1002/ange.201906112

Link to VoR: http://dx.doi.org/10.1002/anie.201906112
http://dx.doi.org/10.1002/ange.201906112

WILEY-VCH

10.1002/anie.201906112

WILEY-VCH

RESEARCH ARTICLE

Light-driven intramolecular C-N cross-coupling via a long-lived photoactive photoisomer complex

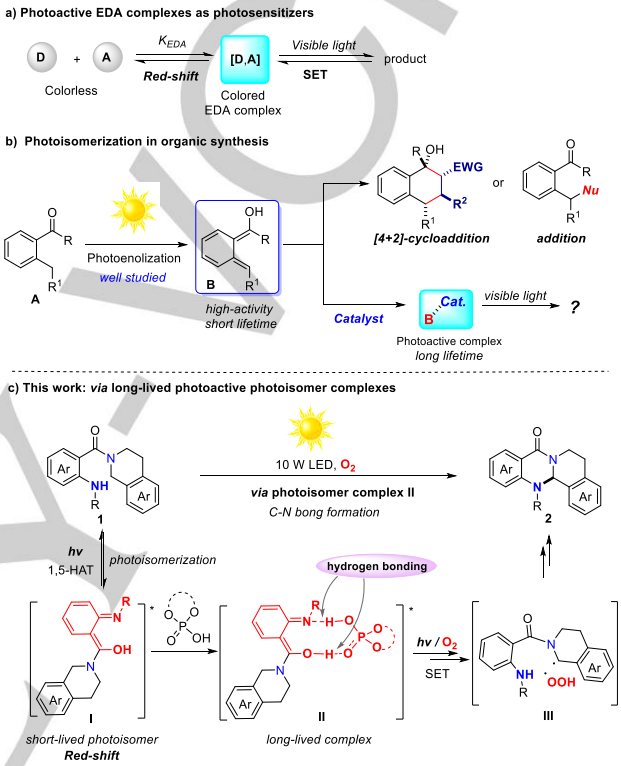
Dong Jing[#], Cong Lu[#], Zhuo Chen, Songyang Jin, Lijuan Xie, Ziyi Meng, Zhishan Su and Ke Zheng[*]

Abstract: We report herein a visible-light-driven intramolecular C-N cross-coupling reaction under mild conditions (metal & photocatalyst free, at room temperature) via a long-lived photoactive photoisomer complex. This strategy is applied by rapidly preparing the *N*-substituted polycyclic quinazolinone derivatives with a broad substrate scope (>50 examples) and further exploited to synthesize the natural products tryptanthrin, rutaecarpine, and their analogues. The success of gram-level synthesis and solar-driven transformation, as well as promising tumor-suppressing biological activity, proves the potential of this strategy for practical applications. Mechanistic investigation, including control experiments, DFT calculations, UV-vis spectroscopy, EPR, and X-ray single-crystal structure of the key intermediate, provides insight into the mechanism. We expect this report will provide new opportunities to perform photoredox transformations under more environmentally friendly photocatalyst-free conditions.

Introduction

Over the past decade, the field of photochemistry has attracted considerable attention from the chemistry community for the development of sustainable bond-forming platforms.[1] Visible-light photoredox catalysis has been proven to be a powerful and environmentally friendly tool to initiate a variety of organic reactions.[2] However, due to the weak interaction of simple organic molecules with visible light, most synthetic strategies rely upon the use of photoredox catalysts (PCs), such as Ru-complexes,[3] Ir-complexes,[4] organic dyes,[5] as well as other photosensitizers.[6] Most recently, the Melchiorre group and other groups developed a visible-light-induced organic reaction that relied on the formation of EDA complex[7,8] or excited state of organocatalytic intermediates[2e,9], which enabled radical transformations to develop under photocatalyst-free conditions (Scheme 1a).

Since first reported by Lifschitz in 1919,[10a] photochromism[10] has attracted considerable attention for its wide application in materials and life science, such as data storage,[11] cargo



Scheme 1. a) Photoactive EDA Complexes as Photosensitizers; b) Photoisomerization in Organic Synthesis; c) C-N Bond Formation via Long-lived Photoactive Photoisomer Complexes.

delivery,[12] sensing,[13] fluorescent probes and photoregulated biological functions.[14] The unique chemical property of photochromic units is their ability to reversibly transform between colored and colorless states upon light irradiation.[15] This offers an opportunity to attempt to enable photoexcitation with visible light, even though starting molecules have no absorbance in the visible region. Actually, photoisomerization of suitable organic molecules is an important strategy in photochromism, which has been used in photochemical synthesis for more than 50 years.[16] As a representative, the highly reactive hydroxy-o-quinodimethanes **B**, generated upon photoenolization of 2-alkyly benzophenones **A**, have been well studied in various fields.[17] In fact, since Yang and Rivas's work in 1961, there have only been a small number of reports (including [4+2]-cycloaddition, Michael addition, trifluoromethylation, and CO_2-carboxylation) utilizing the photochemical properties of photoisomers **B** in organic synthesis (Scheme 1b).[18] Most recently, the Melchiorre and Bach groups have described that the transformation of the photoisomers **B** could be performed with an enantioselective approach.[19] As far as we know, one of the major issues limiting the application of this versatile intermediate is the characteristically short lifetime of

[*] Prof. K. Zheng, D. Jing, C. Lu, S. Jin, L. Xie, Z. Meng, Z. Su
Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China
E-mail: kzheng@scu.edu.cn
Z. Chen
Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China Department
[#] These authors contributed equally to this work.
Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201906112

photoisomers, which quickly and efficiently convert back to the starting molecule.[18d, 20] Early in 1977, the Wirz group demonstrated that the unstable photoisomers could be stabilized by using hydrogen-bond acceptor solvents, which might raise its possibility for the application in organic synthesis.[21] Moreover, Jacobsen and other chemists[22] have shown that organocatalysts can accelerate reactions via hydrogen-bonding with substrates. Inspired by these pioneering works, we hypothesized that in the presence of a suitable catalyst (hydrogen-bonding acceptor/donor) the coordination of the catalyst to the unstable photoisomer might retard the intramolecular hydrogen back-transfer, thus affording a long-lived complex (**B**···*Cat*, Scheme 1b). If so, it should be possible to design a photo-chemistry processing system from a long-lived photoactivate complex.

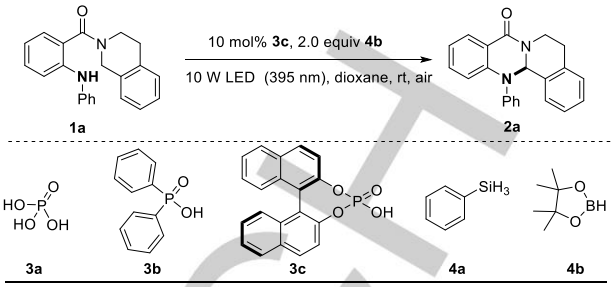
Quinazolinone is an attractive scaffold which plays an extensive role in pharmaceutical chemistry and provides a privileged structure in medicinal chemistry.[23] The intramolecular C-N cross-coupling reaction has proven to be an efficient strategy for the synthesis of such species.[24] In particular, Toste and Sigman reported an asymmetric synthesis of quinazolinone derivatives by an intramolecular C-N bond formation using chiral triazole-containing phosphate anions as catalysts, wherein a bidentate binding model was proposed for the interaction of the catalyst and reactive intermediate through a multidimensional correlation analysis.[25] In this report, we reveal that a long-lived photoactivate photoisomer can, in fact, trigger a photochemical catalytic radical process that enables intramolecular C-N cross-coupling reactions with high yields under irradiation of visible light. Using this strategy, more than 50 fused *N*-substituted polycyclic quinazolinone derivatives are constructed under mild conditions. Notably, most of these represent new chemical entities and have never been reported before. This study offers the demonstration of using a long-lived photoactivate photoisomer in synthetic applications.

Results and Discussion

Reaction Optimization. Scheme 1c depicts our design for utilizing the photoactivity of the long-lived photoisomer complex. First, photoirradiation of the starting material 2-aminobenzamide **1** forms the highly-energetic colored photoisomer **I** via the Norrish Type II photoisomerization. We envisioned that the newly-formed short-lived photoisomer **I** could be stabilized by the coordination of the phosphoric acid via hydrogen bonding, creating the photoisomer complex **II** (Supported by the results of the DFT calculation; for more detail see SI). The resulting long-lived photoisomer complex **II** might induce a SET process, affording the contact radical pair **III**. Finally, the *N*-substituted polycyclic quinazolinone products **2** was produced by the intramolecular C-N cross-coupling.

To evaluate the feasibility of this concept, the 2-(phenylamino)benzamide **1a** was selected as the model substrate for demonstrating the practicability of intramolecular C-N cross-coupling reactions under irradiation by 10 Watt, 395 nm light. Initial optimization studies revealed that using a catalytic amount of phosphoric acid ((*R*)-BPA **3c** as a catalyst with 2 equiv. PinBH as a reductant in dry 1,4-dioxane) under irradiation of purple LED (395 nm) for 2 hours in the ambient atmosphere gave the best

Table 1: Screening of the Reaction Conditions[a]

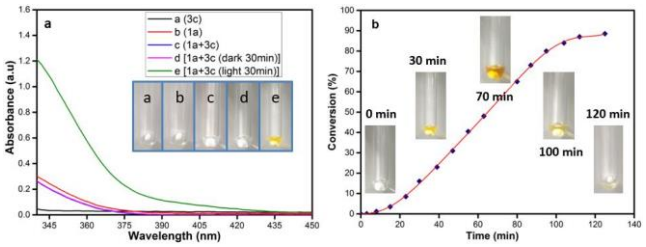


entry	variation from the "standard conditions"	t (h)	yield (%)[b]
1	None	2	94
2	K_2HPO_4 instead of **3c**	10	NR
3	**3a** instead of **3c**	10	43
4	**3b** instead of **3c**	10	52
5	without **3c**	24	trace
6	**4a** instead of **4b**	6	86
7	without **4b**	10	68
8	under N_2	10	NR
9	without light	10	trace

[a]Reaction conditions: (0.075mmol) **1a**, solvent (0.5 mL), air, irradiation with 10 W purple LED (395 nm) at rt. [b]Isolated yield. (*R*)-BPA = (*R*)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate.

yield for the desired product **2a** (94% yield; Table 1, entry 1).[26] It is worth noting that using (*R*)-BPA **3c** was critical for achieving the high yield. Lower yields were observed when using K_2HPO_4, H_3PO_4 **3a**, or diphenylphosphinic acid **3b** as catalysts (Table 1, entries 2-5). A brief survey of solvents showed that the dioxane could give the best result (more details see SI, Table S3). A reducing agent was added to inhibit the oxidation by-product and pinacolborane **4b** proved to be the most effective at facilitating transformation (Table 1, entries 6-7). The control experiments indicated that O_2 and light were crucial for this reaction (entries 8-9).

During our investigations, we noticed that a marked yellow color appeared when the colorless solution was under irradiation for 30 min. As shown in Scheme 2a, the UV-vis absorption spectra showed that both (*R*)-BPA **3c** (curve a) and **1a** (curve b), as well as the combination of them (curve c), displayed no absorbance around 395 nm**.** Therefore, this showed the possibility that the substrate and (*R*)-BPA **3c** worked as a photosensitizer, or that the



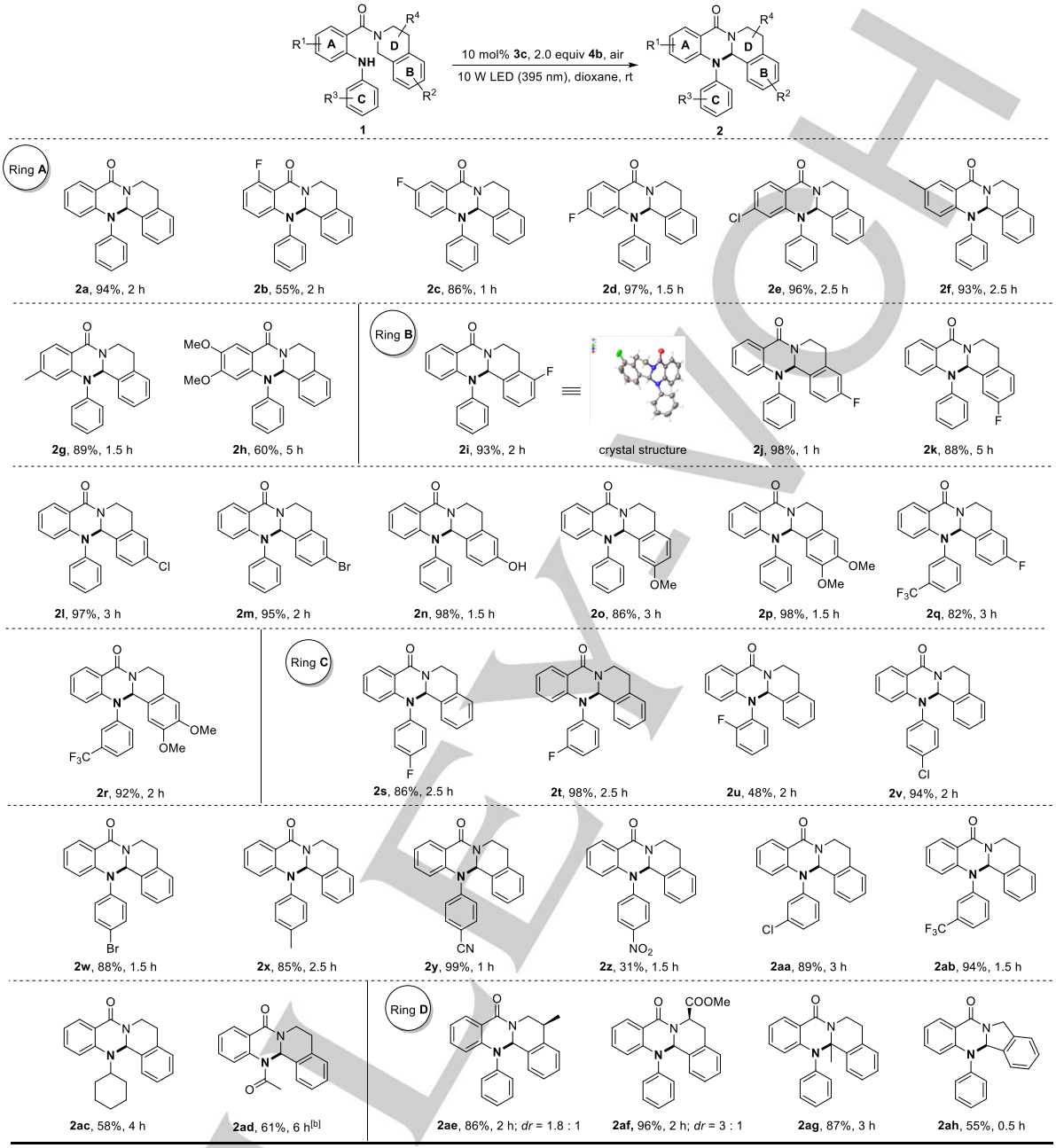
Scheme 2. a) UV−Vis Absorption Spectra. All the experiments were carried out under 5×10^{-4} M; b) Reaction Profile.

10.1002/anie.201906112

WILEY-VCH

RESEARCH ARTICLE

Table 2: Substrates Scope for the Synthesis of *N*-substituted Quinazolinone Derivatives[a]



[a]Reactions were performed with substrate **1** (0.075 mmol), **3c** (0.0075 mmol, 10 mol%), **4b** (0.15 mmol, 2.0 equiv), 0.5 mL dioxane. The reaction mixture was stirred under 10 W LED (395 nm) at rt. Isolated yield (The average of at least two independent experiments). [b]Without **4b**.

formation of EDA complex was excluded. Compared to no-color-change and no-detected red-shift with the mixture of **1a** and **3c** under dark conditions for 30 minutes, when the mixture was irradiated by light for 30 minutes (curve e) a significant red-shift and a new tailing band from 380 to 420 nm appeared. These results indicated that the long-lived photoactivate photoisomer complex **II** might be generated under the irradiation of light, which was consistent with the mechanism proposed in Scheme 1c. The reaction profile in Scheme 2b further lent support to the hypothesis that the formation of the photoactivate photoisomer complex **II** happens during the reaction course. The time-dependent conversion curve of **2a** illustrates that the transformation rate was slow in the initial stage (first ten minutes) and increased sharply after 20 minutes along with a remarkable color change (from colorless to a marked yellow), which is probably due to the low conversion of colored photoactive species in the initial stage and the accumulation of them after a period of irradiation under light. Moreover, as the reaction progresses, the yellow solution faded and eventually turned to a pale-yellow, suggesting that these colored photoactive species were the key intermediates in the catalytic cycle, and consuming them also accompanied the generation of the product **2a**.

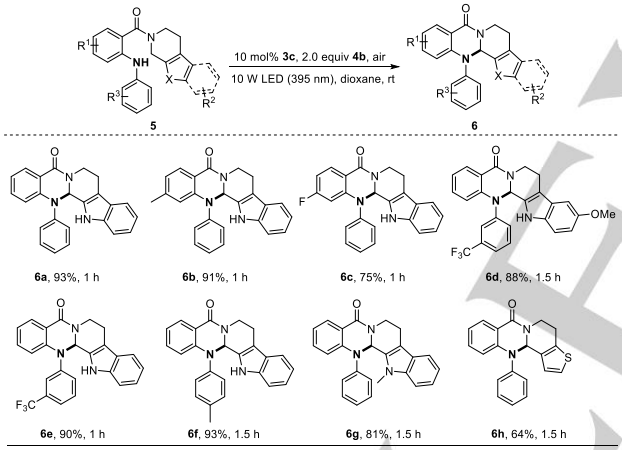
10.1002/anie.201906112

Substrate Scope and Synthetic Applications. Next, with optimal conditions in hand, the substrate scope was extended. As summarized in Table 2, the reaction displayed a broad scope with 2-aminobenzamide **1** and excellent yields were achieved (up to 99% yield). The results indicated this method exhibited excellent functional group tolerance. A wide variety of 2-aminobenzamide bearing different substituents (R^1 or R^2), including F, Cl, Br, Me, OMe, CF_3, and OH on benzene rings **A** & **B,** had been successfully applied to the reaction to produce the desired products with moderate to excellent yields in less than 5 hours (up to 98% yield, **2a**-**2r**). This demonstrated the high efficiency of this protocol. The structure of the product was further confirmed by X-ray diffraction analysis of **2i**. To our delight, for *N*-aryl substituted substrates, a wide range of functional groups (R^3) at different positions on benzene ring **C** was also well tolerated, affording cyclization products in high to excellent yields (up to 99% yield, **2s**-**2ab**). However, the substrate **1z** with nitro group substituent at the 4-position gave lower yield in some cases. We were also pleased to discover that *N*-alkyl substituted substrates **1ac** and **1ad** were also decently tolerated, giving the corresponding products in moderate yields. However, for the substrates with substituted on the amino, the dealkylated products **8a** were obtained as main products. Similar investigations were set up for benzene ring **D**. The substrates with methyl or ester group substituted on ring **D** performed well, finishing the corresponding products in excellent yields (**2ae** and **2af**). To our surprise, the substrates with a methyl group at the reactive site also went smoothly, furnishing the product with a quaternary carbon center in 87% yield (**2ag**). Additionally, the corresponding isoindoline product (**2ah**) could be obtained in good yield under optimal conditions.

To further evaluate the potential of this strategy, we applied it to the synthesis of the natural product rutaecarpine's analogues. A series of benzamides with tetrahydro-1H-pyrido[3,4-*b*]indoleyl (**5a**-**5f**) were proven suitable for this transformation as highlighted in Table 3, and the corresponding *N*-substituted analogues (**6a**-**6f**) were produced with high yields in one and a half hours. Moreover, the benzamides with *N*-methyl indoleyl **5g** and thiopheneyl **5h** were successfully subjected to the reaction, giving the desired products **6g** and **6h** with good to high yields. It should be noted that most of these fused *N*-substituted polycyclic quinazolinone derivatives (**2** and **6**) represent new chemical entities.

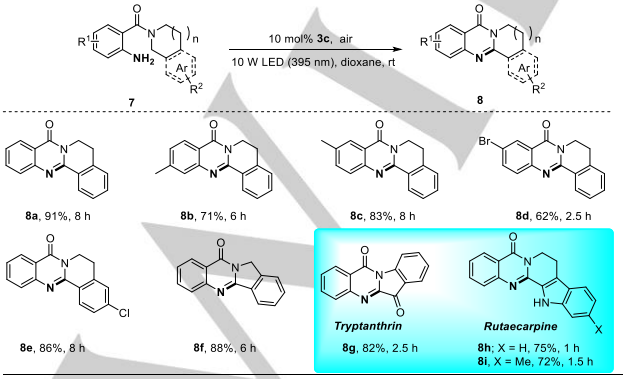
Encouraged by the above results, we further applied this system to the cyclization of 2-aminobenzamides **7** and furnished the corresponding products **8a**-**8f** in high yields without using the reductant pinacolborane (Table 4). Notably, the natural products tryptanthrin, rutaecarpine, and their analogues (**8g**-**8i**) were achieved in up to 82% yields. This strategy proved to be an efficient and easy way to produce these valuable natural products and their analogues. Furthermore, the synthetic utility of this protocol was fully demonstrated by the gram-level synthesis and the product **2a** was obtained with 95% yield in 1.2 hours. With solar being a clean and renewable energy source,[27] results also showed that this transformation could also be driven by sunlight with 86%, thereby demonstrating the potential to make this strategy environmentally friendly (more detail see SI, Scheme S1).

Table 3. The Synthesis of *N*-substituted Rutaecarpine Analogues[a]



[a]Reactions were performed under standard conditions. Isolated yield (The average of at least two independent experiments).

Table 4. Substrates Scope for 2-Aminobenzamides **7**[a]



[a]Reactions were performed with substrate (0.075 mmol), **3c** (0.0075 mmol, 10 mol%), 0.5 ml dioxane. The reaction mixture was stirred under 10 W LED (395 nm) at rt. Isolated yield (The average of at least two independent experiments).

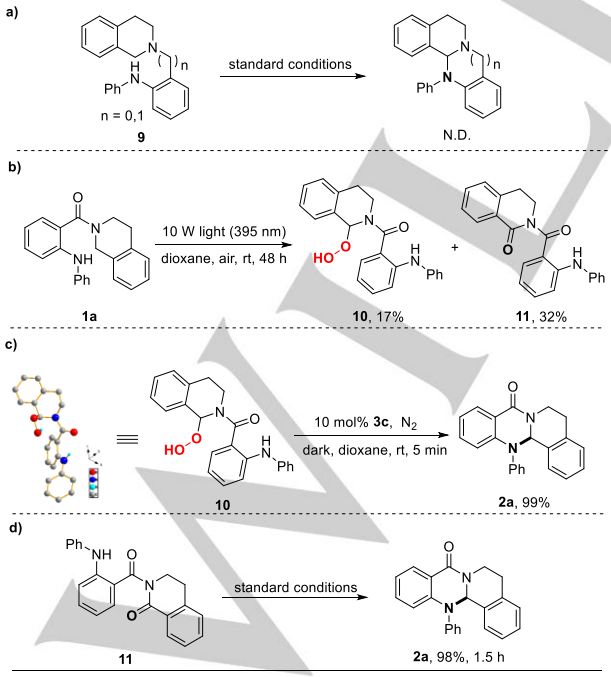
Biological activity. To demonstrate the biological application of this strategy, the obtained polycyclic quinazolinones were assayed for growth inhibitory activities on human cancer cell lines H3122 (lung cancer), MDA-MB-231 (breast cancer), and RS4;11 (leukemia) using the CCK8 assay. Most of them exhibited anti-tumor effects against these human cancer cell lines (more data see SI). Interestingly, compared to quinazolinone **8a**, significant improvement of anti-tumor activity was observed for the new *N*-substituted polycyclic quinazolinone scaffolds **2a** and **6a**. Introduction of a methoxy group on ring B (compound **2o**) led to H3122 (IC_{50} = 0.31 μM), and RS4;11 (IC_{50} = 0.05 μM) cell lines. These preliminary results suggest that these new *N*-substituted polycyclic quinazolinone scaffolds have remarkable medicinal potential in oncology due to their promising features as anti-tumor candidates. Further structural optimization and SAR of these new scaffolds are currently in progress.

Table 5. *In Vitro* Antitumor Activity of the Polycyclic Quinazolinones (IC_{50}, μM)

Compounds	MDA-MB-231	H3122	RS4;11	GES-1
8a	>100	>100	>100	>100
2a	14.64	10.72	2.23	50.3
2o	**0.40**	**0.31**	**0.05**	**>100**
6a	0.46	0.33	0.12	>100
Evodiamine	0.52	0.41	0.08	58.4

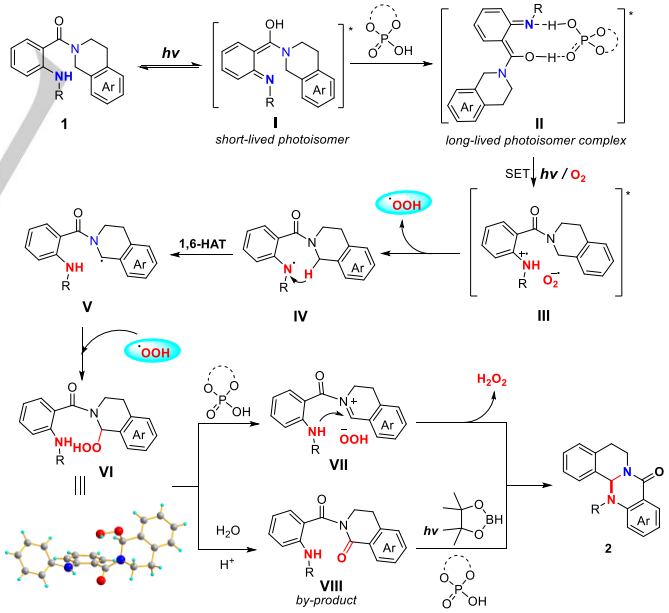
10.1002/anie.201906112

Mechanistic Studies. Several control experiments were performed to gain insights into the nature of this photochemistry strategy. Our proposed mechanism utilizes long-lived photoisomer complexes that are stabilized by the coordination of the ligand BPA via hydrogen bonding (Scheme 1c) as critical intermediates. First, we wanted to verify the mechanics of the hydrogen bonding. The results showed that for the substrates **9** without carbonyl group under standard conditions (Scheme 3a) no cyclization products were observed. Also, NMR spectroscopy of the mixture of **1a** and **3c** revealed that both the NH group and carbonyl group of the **1a** have H-bonding interactions with **3c**, which was consistent with the mechanism proposed in Scheme 1c (More detail see SI, Scheme S7). The results of the control experiments indicated that the absence of either light or O_2 completely suppressed the reaction (Table 1, entries 8 & 9). Moreover, when the reaction proceeded in the absence of both (*R*)-BPA and pinacolborane, moderate conversion of **1a** with oxidation products (**10** & **11**) were observed, even with the reaction time extended to 48 hours (Scheme 3b). These results suggested that the formation of a photoactive photoisomer complex followed by the activation of O_2 was necessary to initiate the photochemistry process. When the reaction was performed in the presence of the photocatalysts (such as Eosin Y, TPP or $Ru(bpy)_3Cl_2$), which produced the singlet oxygen through energy transfer process,[28] low yields were obtained (more detail see SI, Table S8). These results indicate that the excited singlet oxygen could not trigger this photochemical catalytic coupling process and that the pathway including the formation of a radical pair via the SET process was more likely a part of this reaction. Besides the evidence from the UV-vis absorption spectra and the reaction profile in Scheme 2, further support for the formation of the long-lived photoactivate photoisomer complex came from the phenomenon of light on/off experiments. A marked yellow solution, which was formed via the irradiation under light for 30 minutes, would turn back to colorless along with a disappearance of the red-shift under dark condition for two hours (more detail see SI, Scheme S3).



Scheme 3. Control Experiments

To further verify the mechanism of this method, the unstable key intermediate **10** (colorless) and oxidation product **11** (light yellow)[29] were carefully isolated from the reaction mixture by chromatography at a low temperature (-20 ℃). The most infusive result was from the structural identification of the unstable hydroperoxide intermediate **10** (grown by slow evaporation of the solvent at -15 ℃ and under the dark conditions of a glovebox) by the single-crystal X-ray diffraction analysis, which provided direct evidence for the formation of hydroperoxide as a key intermediate in the catalytic cycle. Moreover, the pH-dependent intermediate **10** could be transformed to the final product **2a** with quantitative yield within five minutes in the presence of (*R*)-BPA only, with no need for light, O_2, or pinacolborane (Scheme 3c). These results indicated that the (*R*)-BPA played a key role in the reaction process, either by stabilizing the photoactive photoisomer or by accelerating the cyclization step. Moreover, the oxidation product **11** could be easily transformed to product **2a** by adding pinacolborane as a reductant under standard conditions (Scheme 3d). That is why the increased yield was obtained with adding pinacolborane (from 68% to 94%; Table 1, entry 6). In addition, when radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidine-*1*-oxyl) was added to this reaction, less than 5% **2a** was obtained. The radical capture product was detected by HRMS, and the superoxide radical anion was confirmed by EPR spectroscopy (see SI, Scheme S5). This all suggests a radical process was involved in this reaction.



Scheme 4. Proposed Mechanism

On the basis of the above observations and reported literature,[21, 30] a possible mechanism is presented in Scheme 4. This photocatalyzed intramolecular C-N cross-coupling reaction is initiated by a photoisomerization of **1** upon irradiation with visible light, thereby producing the photoactivate photoisomer **I,** which displays obvious absorbance around 395 nm and has a

short lifetime. The long-lived photoisomer complex **II** is generated by the coordination of (*R*)-BPA **3c** via hydrogen bonding, which can induce the SET process by irradiation of visible light to generate the radical pair **III**. The resulting superoxide radical anion $O_2^{\bullet-}$ abstracts a hydrogen atom from the intermediate **III** to produce the amino radical **IV**, followed by intramolecular 1,6-HAT, thereby generating the carbon-centered radical **V**. Then, the radical recombination of **V** and $HO_2^{\bullet}$ form the key intermediate hydroperoxide **VI**, which is easily converted to the iminium ion **VII** under acidic conditions provided by Brønsted acid **3c** (via a subsequent pH-dependent equilibrium under acidic conditions).[31] Finally, the polycyclic quinazolinone product is formed through intramolecular nucleophilic addition with the release of H_2O_2. As an alternative pathway, the oxidation byproduct **VIII** forms hydroperoxide **VI** and is efficiently converted to product under standard conditions.

Conclusion

In summary, we have developed a novel, visible-light-mediated intramolecular C-N cross-coupling reaction via a long-lived photoactive photoisomer complex. A series of fused *N*-substituted polycyclic quinazolinone derivatives, as well as their natural products, were synthesized under mild conditions. Moreover, this study confirmed the structure of a hydroperoxide intermediate by the single-crystal X-ray characterization, which provided a shortcut to significant insight into the mechanism. It should be noted that, the success of gram-level synthesis and the potential of solar-driven transformation makes this approach very promising with its environmental and economical applications. Our laboratory continues to explore the biological activity capabilities of these new compounds for oncological medicinal applications using asymmetric synthesis.

Experimental Section

Experimental Details. To an oven-dried quartz tube (10 mL) was charged with 0.5 mL dry 1,4-dioxane, 0.075 mmol **1a** (24.3 mg), **3c** 10 mol % (2.6 mg), **4b** 2.0 equiv (22.0 uL), then closed under air. Then put the quartz tube on the photoreactor which is cooled by 25 °C water, the bottom of the tube is 1.0 cm away from the light source (λ_{max} = 395 nm), irradiated for certain time. After the reaction was completed, the product was directly purified by column chromatography.

Acknowledgements

We thank the National Natural Science Foundation of China (Nos. 21602142), and Fundamental Research Funds for the Central Universities. We thank the Xiaoming Feng laboratory (SCU) for access to equipment. We also thank the comprehensive training platform of the Specialized Laboratory in the College of Chemistry at Si-chuan University for compound testing. We appreciate valuable suggesttions from Prof. J. Chruma (Sichuan university).

Keywords: visible light • photoisomer • metal- and photocatalyst-free reaction • quinazolinones derivatives • biological activity

[1] For selected reviews: a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322-5363; b) N. A. Romero, D. A. Nicewicz, *Chem. Rev*. **2016**, *116*, 10075-10166; c) L. Marzo, S. K. Pagire, O. Reiser, B. König, *Angew. Chem. Int. Ed*. **2018**, *57*, 10034-10072; *Angew. Chem.* 2018, 130, 10188-10228.

[2] For selected reviews: a) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035-10074; b) L. Zhang, E. Meggers, *Acc. Chem. Res.* **2017**, *50*, 320-330; c) J. R. Chen, X. Q. Hu, L. Q. Lu, W. J. Xiao, *Chem. Soc. Rev.* **2016**, *45*, 2044-2056; d) Y. Zhao, W. Xia, *Chem. Soc. Rev.* **2018**, *47*, 2591-2608; e) M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41-49.

[3] For selected examples: a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77-80; b) M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886-12887; c) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757;

[4] For selected examples: a) Q. Lu, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 49-51; *Angew. Chem*. **2017**, *129*, 49–51; b) E. C. Gentry, L. J. Rono, M. E. Hale, R. Matsuura, R. R. Knowles, *J. Am. Chem. Soc.* **2018**, *140*, 3394-3402; c) E. D. Nacsa, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2018**, *140*, 3322-3330.

[5] For selected examples: a) W. Ding, L. Q. Lu, Q. Q. Zhou, Y. Wei, J. R. Chen, W. J. Xiao, *J. Am. Chem. Soc.* **2017**, *139*, 63-66; b) H. Huang, C. Yu, Y. Zhang, Y. Zhang, P. S. Mariano, W. Wang, *J. Am. Chem. Soc.* **2017**, *139*, 9799-9802; c) X. Z. Fan, J. W. Rong, H. L. Wu, Q. Zhou, H. P. Deng, J. D. Tan, C. W. Xue, L. Z. Wu, H. R. Tao, J. Wu, *Angew. Chem. Int. Ed.* **2018**, *57*, 8514-8518; *Angew. Chem*. **2018**, *130*, 8650-8654.

[6] For selected examples: a) L. Capaldo, M. Fagnoni, D. Ravelli, *Chem. Eur. J.* **2017**, *23*, 6527-6530; b) A. Hu, J. J. Guo, H. Pan, H. Tang, Z. Gao, Z. Zuo, *J. Am. Chem. Soc.* **2018**, *140*, 1612-1616; c) Y. Li, K. Zhou, Z. Wen, S. Cao, X. Shen, M. Lei, L. Gong, *J. Am. Chem. Soc.* **2018**, *140*, 15850-15858; d) Y. Yin, Y. Dai, H. Jia, J. Li, L. Bu, B. Qiao, X. Zhao, Z. Jiang, *J. Am. Chem. Soc.* **2018**, *140*, 6083-6087; e) X. Zhu, Y. Lin, Y. Sun, M. C. Beard, Y. Yan, *J. Am. Chem. Soc.* **2019**, *141*, 733-738.

[7] For selected examples: a) E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750-756; b) S. R. Kandukuri, A. Bahamonde, I. Chatterjee, I. D. Jurberg, E. C. Escudero-Adán, P. Melchiorre, *Angew. Chem. Int. Ed.* **2015**, *54*, 1485-1489; *Angew. Chem.* **2015**, *127*, 1505–1509; c) Z. Y. Cao, T. Ghosh, P. Melchiorre, *Nat. Commun.* **2018**, *9*, 3274.

[8] For selected examples: a) C. G. S. Lima, T. de M. Lima, M. Duarte, I. D. Jurberg, M. W. Paixão, *ACS Catal.* **2016**, *6*, 1389-1407; b) Y. Cheng, S. Yu, *Org. Lett.* **2016**, *18*, 2962-2965; c) Q. Guo, M. Wang, H. Liu, R. Wang, Z. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 4747-4751; *Angew. Chem*. **2018**, *130*, 4837–4841; d) B. Liu, C. H. Lim, G. M. Miyake, *J. Am. Chem. Soc.* **2017**, *139*, 13616-13619; e) B. Liu, C. H. Lim, G. M. Miyake, *J. Am. Chem. Soc.* **2018**, *140*, 12829-12835; f) V. Quint, F. Morlet-Savary, J. F. Lohier, J. Lalevée, A. C. Gaumont, S. Lakhdar, *J. Am. Chem. Soc.* **2016**, *138*, 7436-7441; g) H. Y. Tu, S. Zhu, F. L. Qing, L. Chu, *Chem. Commun.* **2018**, *54*, 12710-12713.

[9] For selected examples: a) A. Bahamonde, P. Melchiorre, *J. Am. Chem. Soc.* **2016**, *138*, 8019-8030; b) D. Mazzarella, G. E. M. Crisenza, P. Melchiorre, *J. Am. Chem. Soc.* **2018**, *140*, 8439-8443

[10] a) J. Lifschitz, *Ber. deut. chem. Ges.* **1919**, *52B*, 1919-1926; b) L. Chalkley, *J. Opt. Soc. Am.* **1952**, *42*, 387-392; c) Y. Hirshberg, *J. Am. Chem. Soc.* **1956**, *78*, 2304-2312; d) R. N. Macnair, *Photochem. Photobiol.* **1967**, *6*, 779-797.

[11] S. Kawata, Y. Kawata, *Chem. Rev.* **2000**, *100*, 1777-1788.

[12] a) R. Tong, H. D. Hemmati, R. Langer, D. S. Kohane, *J. Am. Chem. Soc*. **2012**, *134*, 8848-8855; b) J. Zhang, J. Wang, H. Tian, *Mater. Horiz*. **2014**, *1*, 169-184.

[13] Y. J. Diaz, Z. A. Page, A. S. Knight, N. J. Treat, J. R. Hemmer, C. J. Hawker, J. R. Alaniz, *Chem. Eur. J*. **2017**, *23*, 3562-3566.

[14] a) K. Li, B. Liu, *Chem. Soc. Rev*. **2014**, *43*, 6570-6597; b) M. Irie, T. Fukaminato, K. Matsuda, S. Kobatake, *Chem. Rev*. **2014**, *114*, 12174-12277.

[15] a) R. Liu, Y. Yang, Q. Cui, W. Xu, R. Peng, L. Li, *Chem. Eur. J*. **2018**, *24*, 17756-17766; b) N. Mallo, E. D. Foley, H. Iranmanesh, A. D. W. Kennedy, E. T. Luis, J. Ho, J. B. Harper, J. E. Beves, *Chem. Sci.* **2018**, *9*, 8242-8252.

[16] a) N. C. Yang, C. Rivas, *J. Am. Chem. Soc*. **1961**, *83*, 2213; b) B. By Elliott, R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, ***1973***, 308-313.

[17] For selected examples: a) M. Winkler, J. O. Mueller, K. K. Oehlenschlaeger, L. Montero de Espinosa, M. A. Meier, C. Barner-Kowollik, *Macromolecules* **2012**, *45*, 5012-5019; b) K. K. Oehlenschlaeger, J. O. Mueller, N. B. Heine, M. Glassner, N. K. Guimard, G. Delaittre, F. G. Schmidt, C. Barner-Kowollik, *Angew. Chem. Int. Ed*. **2013**, *52*, 762-766; *Angew. Chem*. **2013**, *125*, 791-796; c) K. Hiltebrandt, K. Elies, D. R. D'hooge, J. P. Blinco, C. Barner-Kowollik, *J. Am. Chem. Soc*. **2016**, *138*, 7048-7054.

[18] a) K. C. Nicolaou, D. Gray, J. Tae, *Angew. Chem. Int. Ed*. **2001**, *40*, 3675–3678; *Angew. Chem*. **2001**, *113*, 3787–3790; b) K. C. Nicolaou, D. L. F. Gray, J. Tae, *J. Am. Chem. Soc*. **2004**, *126*, 613–627; c) Y. Masuda, N. Ishida, M. Murakami, *J. Am. Chem. Soc*. **2015**, *137*, 14063-14066; d) X. Yuan, S. Dong, Z. Liu, G. Wu, C. Zou, J. Ye, *Org. lett*. **2017**, *19*, 2322-2325; e) T. Ide, S. Masuda, Y. Kawato, H. Egami, Y. Hamashima, *Org. lett*. **2017**, *19*, 4452-4455; f) J. Mateos, A. Cherubini-Celli, T. Carofiglio, M. Bonchio, N. Marino, X. Companyó, L. Dell'Amico, *Chem. Commun*. **2018**, *54*, 6820-6823.

[19] a) B. Grosch, C. N. Orlebar, E. Herdtweck, W. Massa, T. Bach, *Angew. Chem. Int. Ed*. **2003**, *42*, 3693-3696; *Angew. Chem*. **2003**, *115*, 3822-3824; b) L. Dell'Amico, A. Vega-Peñaloza, S. Cuadros, P. Melchiorre, *Angew. Chem. Int. Ed*. **2016**, *55*, 3313-3317; *Angew. Chem*. **2016**, *128*, 3374-3378; c) L. Dell'Amico, V. M. Fernández-Alvarez, F. Maseras, P. Melchiorre, *Angew. Chem. Int. Ed*. **2017**, *56*, 3304-3308; *Angew. Chem*. **2017**, *129*, 3352-3356; d) S. Cuadros, L. Dell'Amico, P. Melchiorre, *Angew. Chem. Int. Ed*. **2017**, *56*, 11875-11879; *Angew. Chem*. **2017**, *129*, 12037-12041.

[20] a) P. Klán, T. Šolomek, C. G. Bochet, A. Blanc, R. Givens, M. Rubina, V. Popik, A. Kostikov, J. Wirz, *Chem. Rev*. **2013**, *113*, 119-191.

[21] R. Haag, J. Wirz, P. J. Wagner, *Helv. Chim. Acta*. **1977**, *60*, 2595-2607.

[22] a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev*. **2007**, *107*, 5713-5743; b) S. M. Banik, A. Levina, A. M. Hyde, E. N. Jacobsen, *Science* **2017**, *358*, 761-764.

[23] a) S. B. Mhaske, N. P. Argade, *Tetrahedron* **2006**, *62*, 9787-9826; b) A. Hameed, M. Al-Rashida, M. Uroos, S. A. Ali, Arshia, M. Ishtiaq, K. M. Khan, *Expert Opin. Ther. Pat*. **2018**, *28*,281-297.

[24] a) Y. Liu, J. Wei, C. M. Che, *Chem. Commun*. **2010**, *46*, 6926-6928; b) A. V. A. Gholap, S. Maity, C. Schulzke, D. Maiti, A. R. Kapdi, *Org. Biomol. Chem*. **2017**, *15*, 7140-7146; c) C. Lu, Z. Su, D. Jing, S. Jin, L. Xie, L. Li, K. Zheng, *Org. Lett*. **2019**, *21*, 1438-1443.

[25] a) A. J. Neel, J. P. Hehn, P. F. Tripet, F. D. Toste, *J. Am. Chem. Soc*. **2013**, *135*, 14044-14047; b) A. Milo, A. J. Neel, F. D. Toste, M. S. Sigman, *Science* **2015**, *347*, 737-743; c) M. Orlandi, F. D. Toste, M. S. Sigman, *Angew. Chem. Int. Ed*. **2017**, *56*, 14080-14084; *Angew. Chem*. **2017**, *129*, 14268-14272.

[26] No ee value was obtained when using (*R*)-BPA **3c** or (*S*)-BPA **3c** as a catalyst, the (*R*)-BPA **3c** is cheaper than (*S*)-BPA **3c** or racemic-BPA **3c**.

[27] X. Fan, X. Gong, M. Ma, R. Wang, P. J. Walsh, *Nat. Commun.* **2018**, *9*, 4936.

[28] a) D. Arian, L. Kovbasyuk, A. Mokhir, *J. Am. Chem. Soc*. **2011**, *133*, 3972-3980; b) M. Pineiro, A. L. Carvalho, M. M. Pereira, A. M. D. A. Rocha Gonsalves, L. G. Arnaut, S. J. Formosinho, *Chem. Eur. J*. **1998**, *4*, 2299-2307; c) A. A. Abdel-Shafi, P. D. Beer, R. J. Mortimer, F. Wilkinson, *J. Phys. Chem. A*, **2000**, *104*, 192–202; d) Q. Q. Zhou, Y. Q. Zou, L. Q. Lu, W. J. Xiao, *Angew. Chem. Int. Ed*. **2019**, *58*, 1586-1604; *Angew. Chem*. **2019**, *131*, 1600–1619; e) F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer, F. Glorius, *Chem. Soc. Rev*. **2018**, *47*, 7190-7202.

[29] No intermediate **10** and oxidation byproduct **11** were detected by HPLC under standard conditions and more detail see SI.

[30] H. Bartling, A. Eisenhofer, B. König, R. M. Gschwind, *J. Am. Chem. Soc.* **2016**, *138*, 11860-11871.

[31] E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317-5325.

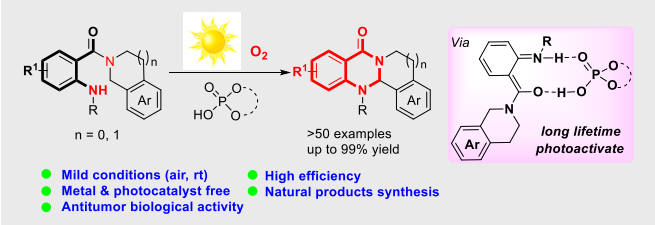
[32] CCDC 1888722 (**2i**) and 1888745 (**10**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

10.1002/anie.201906112

WILEY-VCH

Entry for the Table of Contents

RESEARCH ARTICLE



Text for Table of Contents

Dong Jing[#], Cong Lu[#], Zhuo Chen[+], Songyang Jin, Lijuan Xie, Ziyi Meng, Zhishan Su and Ke Zheng[*]

Page No. – Page No.

Light-driven intramolecular C-N cross-coupling via a long-lived photoactive photoisomer complex