# Photocatalysis

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# Stereoselective Synthesis of Cyclohepta[b]indoles by Visible-Light-Induced [2+2]-Cycloaddition/retro-Mannich-type Reactions

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**Abstract:** A novel method for the concise synthesis of cyclohepta[b]indoles in high yields was developed. The method involves a visible-light-induced, photocatalyzed [2+2]-cycloaddition/ retro-Mannich-type reaction of enaminones. Experimental and computational studies suggested that the reaction is a photoredox process initiated by single-electron oxidation of an enaminone moiety, which undergoes subsequent cyclobutane formation and rapidly fragmentation in a radical-cation state to form cyclohepta[b]indoles.

**C**yclohepta[*b*]indoles (Figure 1) bearing an all-carbon quaternary stereogenic center at the indole C3 are motifs existed in a variety of natural products (Figure 1, **1**–6).<sup>[1]</sup> These natural products display a broad spectrum of biological activities, for example, alstonlarsine A (**3**) exhibits DRAK2 inhibitory activity,<sup>[1e]</sup> and ajmaline (**6**), a voltage-gated Na<sup>+</sup> channel blocker, is a class Ia antiarrhythmic drug.<sup>[2]</sup> Much effort has therefore been devoted to their syntheses.<sup>[3]</sup>

In 2018, Hiersemann's group<sup>[4]</sup> reported that cyclohepta [*b*]indole **8** could be synthesized via a  $[2+2]/4\pi$  electrocyclic ring-opening reaction under excitation by a light source (254 nm) in a quartz tube (Scheme 1 a). In 1975, Tamura's group<sup>[5]</sup> developed a [2+2]/retro-Mannich strategy involving structurally diverse 2-azabicyclo[2.1.1]hexane rings as intermediates (Scheme 1 b). This method has been widely used to synthesize nitrogen-containing molecules.<sup>[6]</sup> Since 2019, You et al.,<sup>[7]</sup> Dhar et al.,<sup>[8]</sup> Fu et al.,<sup>[9]</sup> and Koenig et al.<sup>[10]</sup> independently developed methods for synthesizing cyclobutane-fused polycyclic indoles via energy transfer to the indole moiety (Scheme 1 c).

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With this chemistry in mind, we envisaged that the enaminone<sup>[11]</sup> motif in substrate **14** (Scheme 1 d) could be activated via electron transfer. The resultant radical cation<sup>[12]</sup>



Figure 1. Cyclohepta[b]indole and associated indole alkaloids.

a) Hiersemann's work (2018)



b) Tamura's work (1975)



c) You's work (2019)



d) This work



Scheme 1. [2+2]-based cycloaddition reactions.

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could participate in an indole-based dearomative redox [2+2]annulation<sup>[13]</sup> and a subsequent retro-Mannich-type reaction<sup>[14]</sup> to afford a series of tetracyclic cyclohepta[b] indoles 15. Here, we report our recent efforts to develop a novel and concise method for the stereoselective synthesis of structurally diverse tetracyclic cyclohepta[b]indoles via a singleelectron-transfer (SET)-initiated process.

We explored the synthetic feasibility with enaminone 14 as the substrate, which was readily synthesized with a new one-pot protocol via condensation of tryptamine with 1,3cyclopentanedione and selective *t*-butyloxycarbonyl (Boc) protection.<sup>[14d,e]</sup> We initially used Ir-based blue phosphorescent materials,<sup>[15]</sup> namely FIrpic,<sup>[16]</sup> PhFIrpic,<sup>[17]</sup> and FCNIrpic,<sup>[18]</sup> as photocatalysts in the proposed annulation reaction (Table 1, entries 1-7) because of their high energy triplet states.<sup>[19]</sup> These compounds catalyzed the desired annulation. Product 15 was obtained in 93% yield when the reaction was performed in the presence of FCNIrpic in CH<sub>3</sub>CN at room temperature for 24 h. The relative stereochemistry of 15 was confirmed by X-ray diffraction (XRD; see Supporting Information).<sup>[20]</sup> When we performed the same reaction without visible-light irradiation or without a catalyst, no reaction occurred (Table 1, entries 8 and 9). This

#### Table 1: Optimization of reaction conditions.[a]

|       | Boc O L4   | st<br>LEDs<br>, 24 h<br>Boc H<br>15 | N Co                     |
|-------|--|-------------------------------------|--------------------------|
| Entry | Catalyst   | Solvent                             | Yield [%] <sup>[b]</sup> |
| 1     | FIrpic   | DCM                                 | 13                       |
| 2     | PhFIrpic   | DCM                                 | 20                       |
| 3     | FCNIrpic   | DCM                                 | 67                       |
| 4     | FCNIrpic   | DCE                                 | 58                       |
| 5     | FCNIrpic   | MeOH                                | 58                       |
| 6     | FCNIrpic   | Acetone                             | 80                       |
| 7     | FCNIrpic   | CH₃CN                               | 93                       |
| 8     | FCNIrpic   | CH₃CN                               | N.R. <sup>[c]</sup>      |
| 9     | _  | CH₃CN                               | N.R.                     |
| 10    | Ru(bpy) <sub>3</sub> Cl <sub>2</sub> ·6 H <sub>2</sub> O         | DCM                                 | N.D.                     |
| 11    | $Ru(bpz)_3(PF_6)_2$  | DCM                                 | N.D.                     |
| 12    | fac-Ir(ppy) <sub>3</sub>   | DCM                                 | N.D.                     |
| 13    | Ir(ppy)2(dtbbpy)PF6  | DCM                                 | N.D.                     |
| 14    | Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub> | DCM                                 | N.D.                     |
| 15    | $Mes-Acr^+ \cdot ClO_4^-$  | DCM                                 | N.D.                     |

[a] Reaction conditions: substrate 14 (0.1 mmol) and catalyst (5 mol%) in the stated solvent (2 mL) were irradiated by 18 W blue LEDs  $(\lambda_{max} = 460 \text{ nm})$  at room temperature under argon for 24 h. [b] Yields determined from <sup>1</sup>H NMR spectra with *p*-dinitrobenzene as internal standard. [c] Control experiment conducted in the dark. LEDs = lightemitting diodes. DCM = dichloromethane. DCE = 1,2-dichloroethane. N.D. = desired product not detected.



indicates that the annulation was photocatalyzed. We also tested that other photocatalysts (Table 1, entries 10-15) could not afford the desired annulated products.

We then synthesized substrates 16a-16s to investigate the substrate scope. The annulation results obtained under the optimized reaction conditions are shown in Table 2. Annula-



[a] Reaction conditions: substrates 16a-16s (0.2 mmol) and FCNIrpic (5 mol%) in CH<sub>3</sub>CN (4 mL) were irradiated by 18 W blue LEDs at room temperature under argon for 24 h. d.r. = diastereomeric ratio.

tions performed with substrates bearing electron-donating or -withdrawing groups at the indole C4, C5, and C6 positions gave the desired cyclohepta[b]indoles in good to excellent vields. However, when the indole ring was substituted at C7 with a methoxy group, the yield was low, presumably because of the steric effect. We prepared substrates 16n and 16o, which exhibited a methyl or benzyl group at the indole C2, and investigated the construction of vicinal quaternary centers. The desired annulation proceeded and products were obtained in moderate yields. For substrate bearing a bromide group at the C2 position, an intramolecular coupling product was obtained (see Supporting Information). A substrate bearing a chiral amino acid ester at the linker motif (16p) gave 17p diastereoselectively in 67% yield. When the enone motif in substrate 14 was replaced with a lactone (16q) or lactam (16r) moiety, the [2+2] cycloaddition reaction afforded products 17q and 17r in 49% and 52% yields, respectively, without a retro-Mannich ring-opening reaction. The relative stereochemistry of 17q was confirmed by XRD (see Supporting Information).<sup>[20]</sup> Acyclic 1,3-diketone product 17s can also be generated in moderate yield, which is a synthetic precursor for polycyclic indoline-based natural products<sup>[14d,i]</sup> (see Supporting Information for details).

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Then we turned our attention to the reaction mechanism. We identified the segment of the substrate that interacts with FCNIrpic by performing luminescence-quenching experiments on **18** and **19**, and comparing the results (Figure 2a): the fluorescence of the photocatalyst FCNIrpic was quenched by enaminone **18**, while almost no quenching was observed when FCNIrpic was mixed with indole **19**. This indicates that excited-state FCNIrpic activates the substrate solely by interacting with the enaminone moiety. To prove that the enaminone was activated via single electron oxidation<sup>[13a-p]</sup> instead of energy transfer,<sup>[21]</sup> we synthesized compound **20**, and performed a comparative experiment (Figure 2b). It shows that although the fluorescence of FCNIrpic could be quenched by enaminone **20**, no reaction occurred when **20** 





**Figure 2.** a) Luminescence-quenching experiments performed with 10  $\mu$ M FCNIrpic solution mixed with given concentration of **18** or **19**. Substrate background was measured with 0.025 mol L<sup>-1</sup> of **18** or **19** without an Ir catalyst. b) Outcome of control experiments and luminescence-quenching experiment result with **20**. Both reactions were performed in MeCN for 24 h at r.t. The quenching was measured with 10  $\mu$ M FCNIrpic solution mixed with given concentration of **20**. Background caused by direct excitation and florescence of **20** was subtracted from the spectrum (see the Supporting Information).

was irradiated with blue LEDs in the presence of FCNIrpic. Conversely, when we irradiated enaminone **20** with a highpressure Hg lamp in the absence of FCNIrpic, the annulation product **21** was obtained in 77% yield, indicating that once triplet state **20**\* is formed, it should undergo [2+2]/retro-Mannich-type process.<sup>[4a,14j]</sup> Thus, single electron oxidation (**20**→**20**<sup>+</sup>) is a more plausible explanation for the nonproductive luminescence-quenching. Electrochemical studies performed in CH<sub>3</sub>CN also show that it is thermodynamically feasible for the excited photocatalyst ( $E_{p/2}^{III*/II}$  =+1.24 V vs. Ag/AgCl) to oxidize substrate **14** ( $E_{p/2}^{ox}$  =+1.18 V vs. Ag/ AgCl) via SET.

The reaction mechanism was further investigated compu-

tationally (Figure 3).<sup>[22]</sup> Stationary points for the organic species were located at ωB97M-V/def2-QZVP//ωB97X-D/def-TZVP level,<sup>[23]</sup> which was chosen to better describe the radical-cation species.<sup>[24]</sup>
 Rates and thermodynamic properties for SET processes were estimated according to Marcus-Hush theory using PBE0 functional with LANL2TZ(f) basis set and pseudopotential for Ir atoms and def-TZVP basis sets for others.<sup>[23d,25]</sup> The functional was chosen to better describe the transition-metal species.<sup>[26]</sup> SMD method was used for solvation effects, including those involved in external reorganization energies.<sup>[27]</sup> The energies mentioned below are all Gibbs free energies with solvation effects.

This reaction is probably initiated by singleelectron oxidation of substrate **14** to its radical cation **IM1** by excited-state FCNIrpic ([Ir<sup>III</sup>]\*). This process releases 1.1 kcalmol<sup>-1</sup> of free energy, which is consistent with the electrochemical analysis ( $\Delta E_{ox} = +0.06 \text{ eV}$ , ca. 1 kcalmol<sup>-1</sup>). The effective activation Gibbs free energy for the SET process, was estimated to be a reachable 11.9 kcal mol<sup>-1</sup> according to the Marcus-Hush theory. Electronic structure analysis confirmed that the spin density of **IM1** is located almost exclusively at the enaminone moiety (see Supporting Information), which is consistent with the luminescence-quenching experiments.

Aided by a favorable  $\pi$ - $\pi$  stacking interaction, the oxidized enaminone moiety in IM1 readily undergoes radical addition to the indole ring, with a barrier of only 5.9 kcal mol<sup>-1</sup> (via **TS1**), to form IM2. Subsequent addition of the benzylic radical to the iminium moiety requires a barrier of 18.9 kcalmol<sup>-1</sup>. The resulting radical-cation intermediate IM3 is unstable and has a natural tendency to either fragment back to IM2 (breaking bond a) or forward to IM4 (breaking bond b). The regiochemistry of the fragmentation is coupled to the out-of-plane bending vibration of the N-H bond; when N-H vibrates so that the unbonded single electron is mainly situated in a position antiperiplanar to bond b (TS3, Figure 3), IM4 can be readily reached, with a barrier of only 2.0 kcal  $mol^{-1}$ . **IM4** can then be reduced by previously



*Figure 3.* Calculated energy profile. The solvated Gibbs free energies are referenced to a combined system of 14 and the excited-state FCNIrpic photocatalyst  $[Ir^{III}]^*$ .

generated  $[Ir^{II}]^{-}$  species to zwitterion **IM6**, which can be converted to product **15** via intermolecular proton transfer.

An alternative route might involve initial generation of the [2+2] reaction product IM5 via single-electron reduction of IM3, and a subsequent closed-shell retro-Mannich reaction. We estimated that the effective activation Gibbs free energy for SET between **IM3** and [Ir<sup>II</sup>]<sup>-</sup> is only 0.8 kcal mol<sup>-1</sup>. However, this bimolecular process is probably diffusion controlled, and the overall rate would be slower than the transformation of IM3 to IM4 via TS3, which is an intramolecular process with a barrier of only 2.0 kcalmol<sup>-1</sup>. Furthermore, we could not identify a low-energy pathway for the subsequent retro-Mannich reaction of IM5 in neutral solution. For example, direct fragmentation of the neutral species IM5 to IM6 is endothermic and involves an insurmountable 24.1 kcalmol<sup>-1</sup> barrier (TS4). Other processes involving activation of IM5 via intermolecular proton transfer of the amine or ketone moiety were also determined to have high barriers (see Supporting Information for details).

On the basis of the computational and experimental results, we propose that the mechanism of this reaction involves single-electron oxidation of the substrate by an excited photocatalyst, and subsequent stepwise cyclization to form an unstable cyclobutene species. Fragmentation of the radical cation then occurs and a seven-membered ring is formed, which then undergoes single-electron reduction and proton transfer to form the product.

In conclusion, we have developed a formal photoredoxcatalyzed [2+2]/retro-Mannich-type cycloaddition for the synthesis of cyclohepta[b]indoles, with FCNIrpic as a visible-light photocatalyst. A plausible mechanism was proposed on the basis of luminescence-quenching of model substrates, comparative experiments, and a computational study. We found that this reaction, unlike those reported in previous studies, was initiated by single-electron oxidation of an enaminone moiety, and followed by subsequent nucleophilic indole addition to form a cyclobutane structure, which rapidly fragmented in a radical-cation state to form cyclohepta-[b]indoles. The active intermediate, an enaminone radicalcation, is different from that in traditional UV-light-excitation and energy-transfer processes. This leads to different reactivities and substrate scopes. Further studies to expand this photoredox catalytic method are currently underway in our laboratory.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** [2+2]/retro-Mannich-type cycloaddition · amine radical cation · cyclohepta[*b*]indole · photoredox catalysis

For selected examples, see: a) T.-S. Kam, Y.-M. Choo, *Tetrahedron Lett.* 2003, 44, 1317; b) T.-S. Kam, Y.-M. Choo, *Helv. Chim. Acta* 2004, 87, 991; c) T.-S. Kam, Y.-M. Choo, *Phytochemistry* 2004, 65, 2119; d) S. Siddiqui, R. H. Siddiqui, *J. Indian Chem. Soc.* 1931, 8, 667; e) X.-X. Zhu, Y.-Y. Fan, L. Xu, Q.-F. Liu, J.-P. Wu, J.-Y. Li, J. Li, K. Gao, J.-M. Yue, *Org. Lett.* 2019, 21, 1471; f) T. R. Govindachari, K. Nagarajan, H. Schmid, *Helv. Chim. Acta* 1963, 46, 433; g) C.-A. Geng, X.-K. Liu, *Fitoterapia* 2013, 89, 42; h) P. F. Rosales, G. S. Bordin, A. E. Gower, S. Moura, *Fitoterapia* 2020, 143, 104558; for a review on cyclohepta-

[b]indole, see: i) E. Stempel, T. Gaich, Acc. Chem. Res. 2016, 49, 2390.

- [2] M. Lei, L. Wu, D. A. Terrar, C. L.-H. Huang, *Circulation* 2018, 138, 1879.
- [3] For selected examples, see: a) K. Lee, D. L. Boger, J. Am. Chem. Soc. 2014, 136, 3312; b) Y.-G. Zhou, H. N. C. Wong, X.-S. Peng, J. Org. Chem. 2020, 85, 967; c) L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, Angew. Chem. Int. Ed. 2017, 56, 3703; Angew. Chem. 2017, 129, 3757; d) M. Lounasmaa, P. Hanhinen, The Alksloids: Chemistry and Biology, Vol. 55, Elsevier, 2001, pp. 1–87; e) C. R. Edwankar, R. V. Edwankar, S. Rallapalli, J. M. Cook, Nat. Prod. Commun. 2008, 3, 1839; f) S. E. Lewis, Tetrahedron 2006, 62, 8655.
- [4] a) D. Tymann, D. C. Tymann, U. Bednarzick, L. Iovkova-Berends, J. Rehbein, M. Hiersemann, *Angew. Chem. Int. Ed.* **2018**, *57*, 15553; *Angew. Chem.* **2018**, *130*, 15779; b) D. C. Tymann, L. Benedix, L. Iovkova, R. Pallach, S. Henke, D. Tymann, M. Hiersemann, *Chem. Eur. J.* **2020**, *26*, 11974.
- [5] Y. Tamura, H. Ishibashi, M. Hirai, Y. Kita, M. Ikeda, J. Org. Chem. 1975, 40, 2702.
- [6] For selected reviews, see: a) M. D. Kärkäs, J. A. Porco, C. R. J. Stephenson, *Chem. Rev.* 2016, *116*, 9683; b) J. D. Winkler, C. M. Bowen, F. Liotta, *Chem. Rev.* 1995, *95*, 2003.
- [7] a) M. Zhu, C. Zheng, X. Zhang, S.-L. You, J. Am. Chem. Soc. **2019**, 141, 2636; b) M. Zhu, X.-L. Huang, H. Xu, X. Zhang, C. Zheng, S.-L. You, CCS Chem. **2020**, 2, 652; c) M. Zhu, X. Zhang, C. Zheng, S.-L. You, ACS Catal. **2020**, 10, 12618.
- [8] a) M. S. Oderinde, E. Mao, A. Ramirez, J. Pawluczyk, C. Jorge, L. A. M. Cornelius, J. Kempson, M. Vetrichelvan, M. Pitchai, A. Gupta, A. K. Gupta, N. A. Meanwell, A. Mathur, T. G. M. Dhar, J. Am. Chem. Soc. 2020, 142, 3094; b) M. S. Oderinde, A. Ramirez, T. G. M. Dhar, L. A. M. Cornelius, C. Jorge, D. Aulakh, B. Sandhu, J. Pawluczyk, A. A. Sarjeant, N. A. Meanwell, A. Mathur, J. Kempson, J. Org. Chem. 2021, 86, 1730.
- [9] Z. Zhang, D. Yi, M. Zhang, J. Wei, J. Lu, L. Yang, J. Wang, N. Hao, X. Pan, S. Zhang, S. Wei, Q. Fu, ACS Catal. 2020, 10, 10149.
  [10] A. B. Rolka, B. Koenig, Org. Lett. 2020, 22, 5035.
- [10] A. D. Kolka, D. Koellig, Org. Lett. 2020, 22, 5055.
- [11] Y. Li, D. Wang, L. Zhang, S. Luo, J. Org. Chem. 2019, 84, 12071.
- [12] For selected examples on photogenerated amine radical cations, see: a) S. A. Morris, J. Wang, N. Zheng, Acc. Chem. Res. 2016, 49, 1957; b) J. Hu, J. Wang, T. H. Nguyen, N. Zheng, Beilstein J. Org. Chem. 2013, 9, 1977; c) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, Chem. Soc. Rev. 2016, 45, 2044.
- [13] For selected examples on redox [2+2] photocycloaddition, see: a) M. A. Ischay, Z. Lu, T. P. Yoon, J. Am. Chem. Soc. 2010, 132, 8572; b) M. A. Ischay, M. S. Ament, T. P. Yoon, Chem. Sci. 2012, 3, 2807; c) M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, J. Am. Chem. Soc. 2008, 130, 12886; d) J. Du, T. P. Yoon, J. Am. Chem. Soc. 2009, 131, 14604; e) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, Science 2014, 344, 392; f) S. Farid, S. E. Shealer, J. Chem. Soc. Chem. Commun. 1973, 677; g) Y. Takahashi, O. Okitsu, M. Ando, T. Miyashi, Tetrahedron Lett. 1994, 35, 3953; h) M. Riener, D. A. Nicewicz, Chem. Sci. 2013, 4, 2625; i) E. L. Tyson, E. P. Farney, T. P. Yoon, Org. Lett. 2012, 14, 1110; j) S. Lin, S. D. Lies, C. S. Gravatt, T. P. Yoon, Org. Lett. 2017, 19, 368; k) X. Wang, C. Chen, Tetrahedron 2015, 71, 3690; l) X. Wang, Y. Gao, Z. Ma, R. A. Rodriguez, Z.-X. Yu, C. Chen, Org. Chem. Front. 2015, 2, 978; m) J. Kollmann, Y. Zhang, W. Schilling, T. Zhang, D. Riemer, S. Das, Green Chem. 2019, 21, 1916; n) K. Tanaka, Y. Iwama, M. Kishimoto, N. Ohtsuka, Y. Hoshino, K. Honda, Org. Lett. 2020, 22, 5207; o) C. Yang, R. Li, K. A. I. Zhang, W. Lin, K. Landfester, X. Wang, Nat. Commun. 2020, 11, 1239; p) R. Li, B. C. Ma, W. Huang, L. Wang, D. Wang, H. Lu, K. Landfester, K. A. I. Zhang, ACS Catal. 2017, 7, 3097; For selected examples on visible-light-mediate dearomative [2+2] cycloaddition, see: q) M. Okumura, D. Sarlah, Eur. J. Org. Chem. 2020, 1259; r) S. Stegbauer, C. Jandl, T. Bach, Angew.

Chem. Int. Ed. 2018, 57, 14593; Angew. Chem. 2018, 130, 14801;
s) N. Hu, H. Jung, Y. Zheng, J. Lee, L. Zhang, Z. Ullah, X. Xie,
K. Harms, M.-H. Baik, E. Meggers, Angew. Chem. Int. Ed. 2018, 57, 6242; Angew. Chem. 2018, 130, 6350; t) M. J. James, J. L. Schwarz, F. Strieth-Kalthoff, B. Wibbeling, F. Glorius, J. Am. Chem. Soc. 2018, 140, 8624; u) F. Strieth-Kalthoff, C. Henkel, M. Teders, A. Kahnt, W. Knolle, A. Gómez-Suárez, K. Dirian, W. Alex, K. Bergander, C. G. Daniliuc, B. Abel, D. M. Guldi, F. Glorius, Chem 2019, 5, 2183; v) J. Ma, F. Schäfers, C. Daniliuc, K. Bergander, C. A. Strassert, F. Glorius, Angew. Chem. Int. Ed. 2020, 59, 9639; Angew. Chem. 2020, 132, 9726.

- [14] For selected examples on [2+2]-photocycloaddition/retro-Mannich reaction, see: a) F. M. Schell, P. M. Cook, J. Org. Chem. 1984, 49, 4067; b) A. Amougay, J.-P. Pete, O. Piva, Tetrahedron Lett. 1992, 33, 7347; c) J. D. Winkler, C. L. Muller, R. D. Scott, J. Am. Chem. Soc. 1988, 110, 4831; d) J. D. Winkler, R. D. Scott, P. G. Williard, J. Am. Chem. Soc. 1990, 112, 8971; e) J. D. White, Y. Li, D. C. Ihle, J. Org. Chem. 2010, 75, 3569; f) C. S. Swindell, B. P. Patel, S. J. deSolms, J. P. Springer, J. Org. Chem. 1987, 52, 2346; g) J. D. White, D. C. Ihle, Org. Lett. 2006, 8, 1081; h) J. D. Winkler, J. M. Axten, J. Am. Chem. Soc. 1998, 120, 6425; i) J. D. White, Y. Li, Heterocycles 2014, 88, 899; j) A. J. A. Roupany, J. R. Baker, RSC Adv. 2013, 3, 10650; k) Y.-S. Kwak, J. D. Winkler, J. Am. Chem. Soc. 2001, 123, 7429; 1) J. D. Winkler, J. R. Ragains, Org. Lett. 2006, 8, 4031; m) G. Lutteke, R. AlHussainy, P. J. Wrigstedt, B. T. B. Hue, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, Eur. J. Org. Chem. 2008, 925
- [15] K. S. Yook, J. Y. Lee, Adv. Mater. 2012, 24, 3169.
- [16] C. Adachi, R. C. Kwong, P. Djurovich, V. Adamovich, M. A. Baldo, M. E. Thompson, S. R. Forrest, *Appl. Phys. Lett.* 2001, 79, 2082.
- [17] V. N. Kozhevnikov, Y. Zheng, M. Clough, H. A. Al-Attar, G. C. Griffiths, K. Abdullah, S. Raisys, V. Jankus, M. R. Bryce, A. P. Monkman, *Chem. Mater.* 2013, 25, 2352.
- [18] a) M. E. Thompson, P. I. Djurovich, R. Kwong, WO2004/016711,
   2004; b) M. E. Thompson, P. Djurovich, R. Kwong, Y.-J. Tung,
   D. B. Knowles, J. Brooks, R. W. Walters, US2004/0121184, 2004.
- [19] Since FIrpic, PhFIrpic, and FCNIrpic have higher E<sub>0.0</sub> than typical photocatalysts like *fac*-Ir(ppy)<sub>3</sub>, Ru(bpy)<sub>3</sub><sup>2+</sup>, and so on, they typically have both stronger oxidative and reductive ability, which presumably is the key to the success of the reaction. For selected papers using FIrpic in organic synthesis, see: a) H. Zhou, P. Lu, X. Gu, P. Li, Org. Lett. 2013, 15, 5646; b) Q. Liu, F.-P. Zhu, X.-L. Jin, X.-J. Wang, H. Chen, L.-Z. Wu, Chem. Eur. J. 2015, 21, 10326; c) F. M. Hörmann, T. S. Chung, E. Rodriguez, M. Jakob, T. Bach, Angew. Chem. Int. Ed. 2018, 57, 827; Angew. Chem. 2018, 130, 835; d) Q.-B. Zhang, Y.-L. Ban, P.-F. Yuan, S.-J. Peng, J.-G. Fang, L.-Z. Wu, Q. Liu, Green Chem. 2017, 19, 5559; e) A. Das, T. Banerjee, K. Hanson, Chem. Commun. 2016, 52, 1350.
- [20] Deposition numbers 2065412 and 2065413 (derivatives of 15 and 17q) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
- [21] For selected reviews on energy transfer, please see: a) Q.-Q.
  Zhou, Y.-Q. Zou, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2019**, 58, 1586; *Angew. Chem.* **2019**, 131, 1600; b) F. Strieth-Kalthoff, F. Glorius, *Chem* **2020**, 6, 1888.
- [22] Gaussian 09 and ORCA 4.2.0 program packages are used for computational study. a) M. J. Frisch, G. W. Trucks, H. B. Schlegel, et al. Gaussian 09, Revision D.01, *Gaussian, Inc.*, 2009 (For a complete list of authors, please see the Supporting Information); b) F. Neese, *WIREs Comput. Mol. Sci.* 2018, 8, e1327.
- [23] a) N. Mardirossian, M. Head-Gordon, J. Chem. Phys. 2016, 144, 214110; b) J.-D. Chai, M. Head-Gordon, Phys. Chem. Chem. Phys. 2008, 10, 6615; c) F. Weigend, R. Ahlrichs, Phys. Chem.

Angew. Chem. Int. Ed. 2021, 60, 11211-11216





Chem. Phys. 2005, 7, 3297; d) A. Schäfer, C. Huber, R. Ahlrichs, J. Chem. Phys. 1994, 100, 5829.

- [24] S. N. Steinmann, C. Corminboeuf, J. Chem. Theory Comput. 2012, 8, 4305.
- [25] a) R. A. Marcus, Pure Appl. Chem. 1997, 69, 13; b) C. Adamo, V. Barone, J. Chem. Phys. 1999, 110, 6158.
- [26] a) Y. A. Aoto, A. P. de Lima Batista, A. Köhn, A. G. S. de Oliveira-Filho, J. Chem. Theory Comput. 2017, 13, 5291; b) Y. Minenkov, E. Chermak, L. Cavallo, J. Chem. Theory Comput.

**2016**, *12*, 1542; c) T. Weymuth, E. P. A. Couzijn, P. Chen, M. Reiher, J. Chem. Theory Comput. **2014**, *10*, 3092.

[27] A. V. Marenich, C. J. Cramer, D. G. Truhlar, J. Phys. Chem. B 2009, 113, 6378.

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