Photocatalytic alkylation of pyrroles and indoles with α-diazo esters
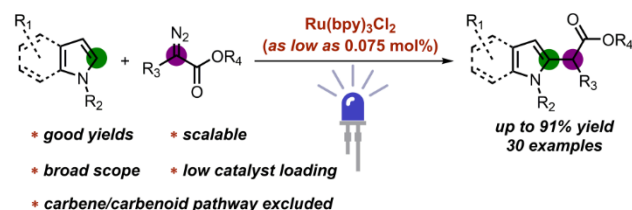
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* good yields   * scalable
* broad scope   * low catalyst loading
* carbene/carbenoid pathway excluded

up to 91% yield
30 examples

ABSTRACT: This article describes direct photoalkylation of electron-rich aromatic compounds with diazo esters. C-2 alkylated indoles and pyrroles are obtained with good yields even though the photocatalyst (Ru(bpy)$_3$Cl$_2$) loading is as low as 0.075 mol %. For substrates bearing electron-withdrawing substituents the addition of a catalytic amount of *N,N*-dimethyl-4-methoxyaniline is required. Both EWG-EWG and EWG-EDG substituted diazo esters are suitable as alkylating agents. The reaction selectivity and mechanistic experiments suggest that carbenes/carbenoid intermediates are not involved in the reaction pathway, instead radical formation is proposed

Five membered heteroaromatic rings are common structural motifs in pharmaceuticals, agrochemicals, and functional dyes.[1] Indoles and pyrroles exhibiting biological activity often possess at least one alkyl substituent attached to the aromatic ring either at 2 or 3 position. Consequently, mild and regioselective methods for C(sp^2)-C(sp^3) bond formation are of high importance.

Classic methods for C-H alkylation of electron-rich heteroaromatic compounds such as Friedel-Crafts type reactions or metallation followed by reaction with electrophiles are suitable for functionalization of simple derivatives, as they often require conditions that are not compatible with many functional groups. Current procedures employing transition metal catalysis broaden the scope, yet due to the character of a catalyst, anhydrous conditions, and elevated temperatures are often required.[2] For indole derivatives usually reactions lead to less challenging C3 alkylation products, if no directing group is present.[3]

In recent years photoredox catalysis emerged as a facile synthetic tool[4] for the formation of C-C bonds, also in alkylation of electron-rich heteroarenes.[5] These reactions relay on ruthenium or iridium complexes which under light irradiation reduce electron-deficient alkyl halides to radicals easily reacting with electron-rich heteroaromatic compounds. Utilization of Au(I) photocatalyst allows similar reaction, yet this process inherently suffers from low selectivity due to instability of radicals.[6] Very recently Glorius *et al.* reported visible light induced C2 alkylation of heteroaromatic compounds using pyridinium salts as radical precursors.[7] However due to utilization of electron-donor-aceptor complexes scope of the method is limited to benzene-fused heteroarenes.

Along this line, thermolysis of ethyl diazoacetate (EDA, **2**) in neat *N*-methylindole (**1**) gives C3 alkylated product resulting from the ring opening of the corresponding cyclopropane intermediates (Scheme 1A).[8] Metal carbenoids as more stable entities insert into indole C-H bond,[2b,3] in this case however selective C2 alkylation is assured by the presence of a directing group at the indole nitrogen atom (Scheme 1B).[9] We have recently reported that under light irradiation diazo esters can act as alkylating agent towards *in situ* formed enamines,[10] later similar approach was also utilized for enantioselective alkylation of 2-acylimidazoles by Meggers *et al.*[11] *We wondered whether and how the*

use of photoredox catalysts would change the reactivity of diazo reagents towards electron-rich heteroarenes.

Herein, we report a new photocatalytic method for C2 alkylation of heteroarenes with diazo compounds (Scheme 1C). The reaction selectivity supported by mechanistic studies suggests that carbene/carbenoid intermediates are not involved in the reaction pathway.

Scheme 1. Reactivity of Diazo Reagents Towards Indoles

A) Manske *et al.*

C3 alkylation

B) Rouping *et al.*

directing group

C) This work

C2 selective, no DG required
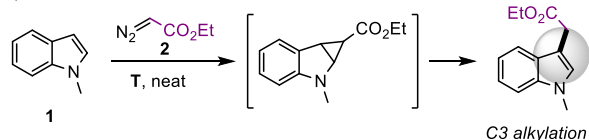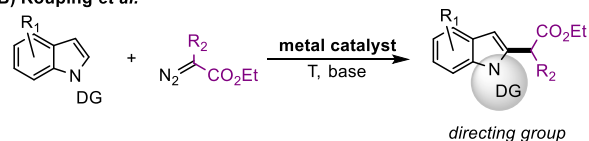
We initiated our studies with performing the model reaction of EDA (**2**) with *N*-methylindole (**1**) catalyzed by Ru(bpy)$_3$Cl$_2$ under light irradiation. Product **3** selectively alkylated at C2 position formed in 30% yield (Table 1). Background experiments revealed that the exclusion of ether the photocatalyst or light irradiation stopped the reaction completely (entries 2-3). Importantly the reaction required anaerobic conditions (entry 4).

Table 1. Background Experiments[a]
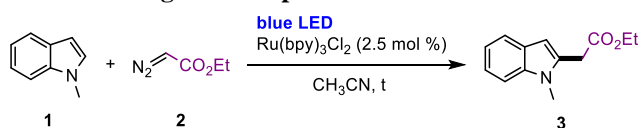
Entry	PC	Solvent	Yield (GC) /%
1	Ru(bpy)$_3$Cl$_2$	CH$_3$CN	30
2	none	CH$_3$CN	nr
3[b]	Ru(bpy)$_3$Cl$_2$	CH$_3$CN	nr
4[c]	Ru(bpy)$_3$Cl$_2$	CH$_3$CN	nr

[a]Reaction conditions: **1** (1.25 mmol, 5 equiv), **2** (0.25 mmol, 1 equiv), Ru(bpy)$_3$Cl$_2$ (2.5 mol %), CH$_3$CN (2.5 mL), blue LED irradiation, 8 h. [b]No light irradiation. [c]Reaction mixture was not degassed.

The proposed mechanism for the alkylation of indoles is shown in Scheme 2. We assumed that the crucial step of this photochemical alkylation involves single electron reduction of diazoethyl acetate. But a detailed mechanistic overview needed further exploration. The addition of TEMPO – a free radical scavenger halted the reaction completely proving that radical species are indeed involved. The Stern-Volmer analysis indicated that only EDA (**1**) quenches luminescence of the Ru-catalyst.

**Scheme 2. Plausible Mechanism for the Alkylation of Indoles**
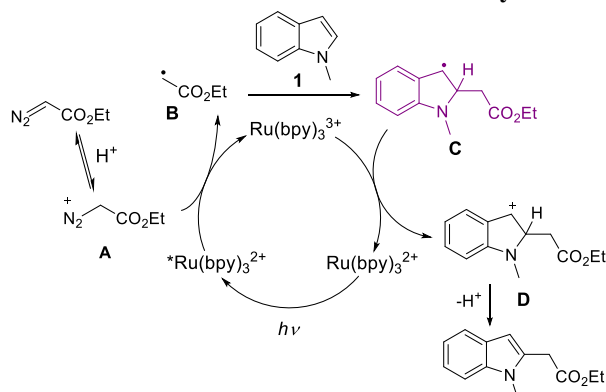
This result supports generation of electron-deficient radical **B** via single electron reduction of diazoethyl acetate. However, EDA (**1**) reduction potential (see SI) is too low to be accessible by any form of the photocatalyst used (*Ru^{2+}/Ru^{3+} *E*= -0.78 V vs SCE),[12] but in protic solvents, particularly in the presence of water, diazo compounds are in equilibrium with their protonated form (**A**),[13] as a result their reduction potential should increase.[14] In fact at pH = 3 emission-quenching rate constant of ethyl diazoacetate slightly increases from k_q = 1.26·10^7 s^{-1} to 1.55·10^7 s^{-1} suggesting that the protonated form **A** of diazo ester may indeed be the actual quencher of the excited catalyst. As a consequence, after extrusion of nitrogen radical **B** is generated which reacts with *N*-methyl indole (**1**) giving radical **C**. Subsequent oxidation with Ru(bpy)$_3$$^{3+}$ allows for the recovery of the catalyst. Deprotonation of cation **D** furnishes the desired alkylated product. The alternative pathway would involve carbene intermediates but both photolysis of benzyl diazoacetate (254 nm) or the reaction with *N*-methylindole in the presence of benzophenone (as a triplet sensitizer) yield only a mixture of O-H insertion, Wolff rearrangement products, and traces of C3 alkylation product suggesting that in our case their presence is not an option.

In the next step we optimized the reaction conditions for the model reaction. None of common organic dyes or metal complexes broadly used in photoredox catalysis but Ru(bpy)$_3$Cl$_2$ were able to catalyze the model reaction (details can be found in SI). The catalyst loading could be as low as 0.075 mol %, however for the scope and limitations studies it was kept at 0.2 mol % level to ensure activity of the catalyst at longer reaction times. The use of protic solvents with the addition of water assured the formation of product **3** with the best result being obtained in a mixture of MeOH/H$_2$O (10:1 *V/V*). With the optimal ratio of *N*-methylindole (**1**) to EDA (**2**) being 4:1, the reaction yielded product in 76% yield. An excess of heteroaromatic compound suppresses the formation of dialkylated product. The process could be scaled up to 5 mmol furnishing product with only slightly diminished yield (68%) after 26 hours, in this case an excessive starting material was recovered (Scheme 3).

With the optimized conditions in hand, we conducted scope and limitations studies. To this end a series of α-diazo esters was synthetized and tested in reaction with *N*-methylindole (**1**) (Scheme 3).

Scheme 3. Reaction of *N*-Me-Indole with Diazo Esters
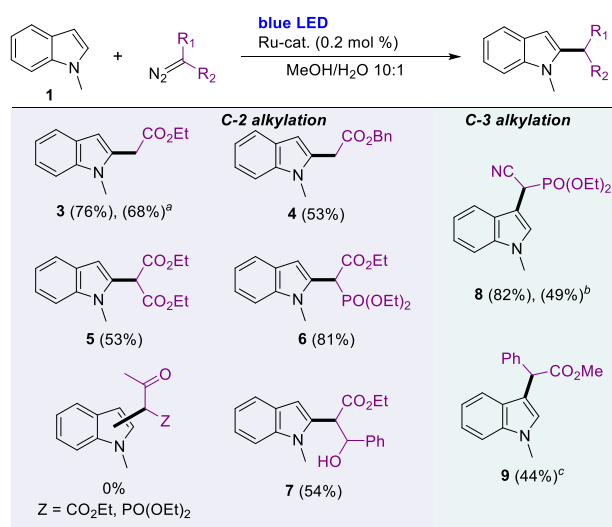
Reaction conditions: **1** (1 mmol, 4 equiv), diazo compound (0.25 mmol, 1 equiv), Ru(bpy)₃Cl₂ (0.5 μmol, 0.2 mol %), MeOH/H₂O (10:1) 2.75 mL, blue LED irradiation, 4.5-8 h. [a] 5 mmol scale, 73% of **1** was recovered, [b] no PC added, [c] MeCN instead of MeOH.

In contrast to our previous reports,[10] disubstituted diazo reagents reacted equally well with the yield and selectivity depending on the substitution pattern and their absorption characteristics. In general, acceptor-acceptor (EWG-EWG) diazo compounds were more reactive towards indole **1** than acceptor-donor (EWG-EDG) substituted compounds. Along this line, triethyl-2-diazophosphonoacetate proved the most reactive giving alkylated derivative **6** in 81% yield. α-Diazo ketones – ethyl 2-diazoacetoacetate and 1-diazo-1-phosphono(diethyl)propan-2-one did not afford corresponding products as prior alkylation the carbonyl group transformed into acetal or hemiacetal hence changing the character of a diazo reagent. These, however, does not mean that all EWG-EDG disubstituted diazo compound are unreactive under developed conditions, ethyl 2-diazo-3-hydroxy-3-phenylpropanoate furnished the corresponding product **7** in 54% yield.

Intriguingly, 2-diazo-2-phosphono(diethyl)acetonitrile and 2-phenyl-2-diazoacetate underwent selective alkylation at C3 position suggesting a possible parallel pathway. In 2018 Davies and coworkers showed that 2-phenyl-2-diazoacetate absorbing at approximately 450 nm (DCM) under blue light irradiation reacts with *N*-Me-indole (**1**) giving C-H insertion products exclusively at C3 position as a result of presumed carbene insertion.[15] We observed that in a mixture of MeO/H₂O C3-alkylation of indole and carbene O-H insertion products also formed. Changing the reaction media to MeCN/H₂O and adding Ru-photocatalyst allowed selective functionalization at C-3 position (**8**, 44%). Similarly, the carbene might be also involved in reaction with 2-phosphono(diethyl)acetonitrile as both Ru-catalyzed and uncatalyzed alkylation gave the same product **9**. Additionally, under blue light irradiation 2-diazo-2-phosphono(diethyl)acetonitrile in MeOH photodecomposed to a mixture of 2-phosphono(diethyl)acetonitrile (66%) and 2-methoxy-2-phosphono(diethyl)acetonitrile (11%) resulting from the reaction of the corresponding carbene with MeOH (see SI). These results corroborate that *once the diazo compound absorbs within the wavelength region of the light used for irradiation, the regioselectivity of the alkylation reaction alters from C2 to C3*, as a consequence of a different operating mechanism.

In the next step, various indole and pyrrole derivatives were tested (Scheme 4). The method worked equally well for unprotected both indoles and pyrroles, giving products **10-12**, **16**, and **19** in high yields. Mild reaction conditions allowed to functionalize even substrate bearing fragile cyclopropyl group at C3 position without ring opening being observed. Electron-deficient heteroarene **14** remained intact

under developed conditions, presumably due to increased oxidation potential of intermediate **C** inaccessible by Ru-photocatalyst.

**Scheme 4. Scope and Limitation Studies - Heteroarenes**[a]
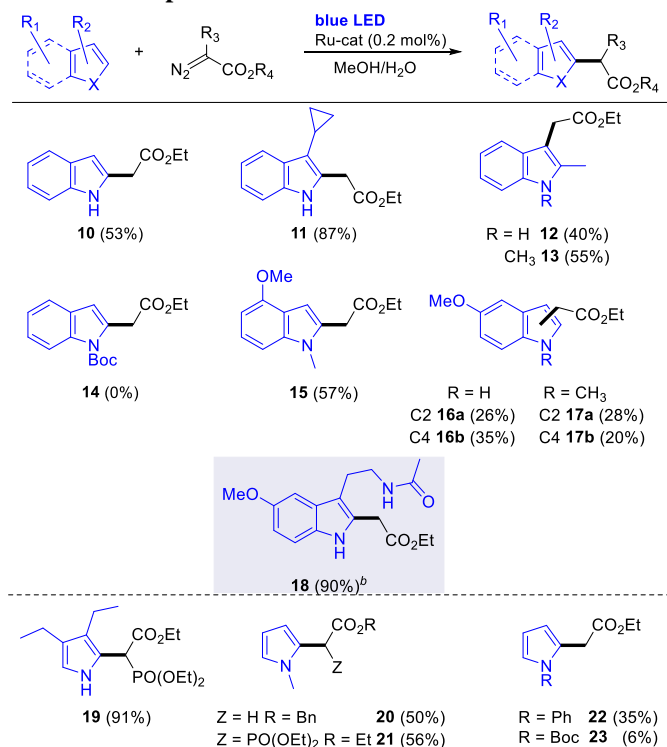
[a]Reaction conditions: heteroarene (1 mmol, 4 equiv), diazo compound (0.25 mmol, 1 equiv), Ru(bpy)$_3$Cl$_2$ (0.5 µmol, 0.2 mol %), MeOH/H$_2$O (10:1) 2.75 mL, blue LED irradiation, 4.5-8 h. [b] 2 equiv. of heteroarene were used.

Not surprisingly, substitution pattern on the phenyl ring has a substantial impact on the reaction regioselectivity. While the reaction of 4-methoxy-1-methyl indole yielded C2 alkylated product **15** selectively, 5-methoxy-derivative furnished a mixture of C4 and C2 regioisomers **16a,b**, **17a,b** in accordance with high nucleophilicity of the corresponding positions in the starting material. The method was also suitable for functionalization of sleep regulating hormone – Melatonin, giving the corresponding product **18** in 91% yield, even though the excess of the starting material was reduced two fold. *N*-Methylpyrrole afforded corresponding alkylated products **20** and **21** in good yields. But once the -Me substituent was replaced with the electron-withdrawing phenyl group the yield diminished substantially.

Puzzled with poor reactivity of heteroarenes with diminished electron density, *N*-Boc-indole (**24**) and *N*-Boc-pyrrole, we wondered whether Ru(bpy)$_3^{3+}$ is sufficiently strong electron acceptor for the oxidation of type **C** radical to the respective cation **D** (Scheme 2). If not, the catalytic cycle cannot close. Therefore, a variety of redox-active additives enabling closing the catalytic cycle were tested (see SI). The addition of a catalytic amount (10 mol %) of 4-methoxy-*N,N*-dimethylanilnie (**25**) facilitated the reaction for indole and pyrrole derivatives with diminished electron density. Quenching rate constant (k_q = 1.46·10^9 s^{-1}) of the fluorescence of the Ru-catalyst by aniline (**25**) was two orders of magnitude higher than for EDA (**2**) indicating that indeed a different mechanistic pathway should operate in this case (Scheme 5). We assumed that the excited state of Ru(bpy)$_3^{2+}$ oxidizes amine **25** to the radical cation generating Ru(bpy)$_3^+$ species. The reduced catalyst is able to generate radical **B** which reacts with heteroaromatic substrate giving radical **C'**. The final step involves hydrogen atom transfer between radical cation of the amine **25** and radical **C'**, what results in formation of the product.

Scheme 5. The Effect of 4-Methoxy-*N,N*-Dimethylanilnie (28) Addition on the Plausible Mechanism
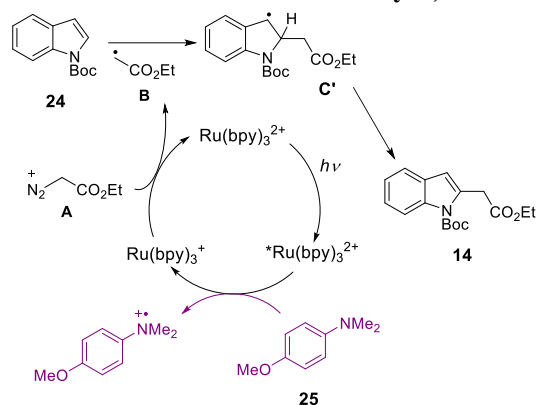
As a consequence, a series of electron-deficient heteroarenes alkylated at C2 position was obtained. *N*-Boc-indole (**24**) which was not reactive under standard conditions, after the addition of amine (**25**) furnished corresponding product **14** in 60% yield (Scheme 6). Other indole derivatives bearing electron-withdrawing substituents are also suitable substrates for this reaction. 5-Bromo-indole provides a mixture of C2 **26a** and C4 **26b** alkylated derivatives while C2 substituted product **27** exclusively formed from the corresponding *N*-methyl-derivative. Regioselectivity increased for indoles bearing strong electron-withdrawing cyano- group, regardless the substitution pattern C2 product **28** was solely obtained. Also, alkylation of L-tryptophan methyl ester gave 67% of corresponding alkylated derivative **29**.

The addition of amine **25** is particularly beneficial for pyrroles where substantial increase in yields was observed. Alkylation of *N*-Boc-protected pyrrole yielded product **23** in high yield (72%) while for *N*-phenylpyrrole the yield increased almost 2.3-fold. Notably, even electron-rich *N*-(dimethylamino)pyrrole afforded product **32** in decent yield.

Scheme 6. Alkylation of Indole and Pyrrole Derivatives in the Presence of Aniline 25
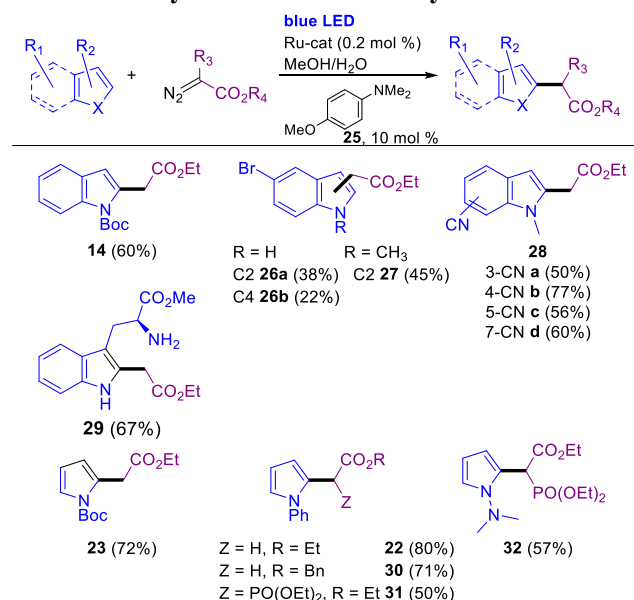
Reaction conditions: heteroarene (1 mmol, 4 equiv), diazo compound (0.25 mmol, 1 equiv), **28** (25 μmol, 10 mol %), Ru(bpy)$_3$Cl$_2$ (0.5 μmol, 0.2 mol %), MeOH/H$_2$O (10:1) 2.75 mL, blue LED irradiation, 4.5-8 h.

In conclusion, a new photocatalytic method for C2 alkylation of indoles and pyrroles has been developed. The method requires unprecedentedly low catalyst loading (0.075 mol %), tolerates variety of functional groups in both heteroaromatic substrates and diazo compounds, and is easily scalable. The

addition of *N,N*-dimethyl-4-methoxyaniline (**25**) enables the synthesis of alkylated derivatives even from electron-deficient indoles and pyrroles.

Mechanistic studies corroborate the proposed reaction pathways involving radical species. However, for diazo compounds exhibiting strong absorption within the wavelength region of the light used for irradiation, the regioselectivity of the alkylation reaction alters from C2 to C3.

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REFERENCES

1. Lednicer, D. *Strategies for Organic Drug Synthesis and Design*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2008.

2. (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173, (b) Li, Y.-P.; Li, Z.-Q.; Zhu, S.-F. *Tetrahedron Lett.* **2018**, *59*, 2307, (c) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603.

3. (a) Gibe, R.; Kerr, M. A. *J. Org. Chem.* **2002**, *67*, 6247, (b) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049.

4. (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322, (b) Hari, D. P.; König, B. *Chem. Commun.* **2014**, *50*, 6688, (c) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075, (d) Douglas, J. J.; Sevrin, M. J.; Stephenson, C. R. J. *Org. Process Res. Dev.* **2016**, *20*, 1134, (e) Staveness, D.; Bosque, I.; Stephenson, C. R. J. *Acc. Chem. Res.* **2016**, *49*, 2295, (f) Yoon, T. P. *Acc. Chem. Res.* **2016**, *49*, 2307, (g) Boubertakh, O.; Goddard, J. P. *Eur. J. Org. Chem.* **2017**, *2017*, 2072, (h) Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2019**, *58*, 3730.

5. (a) Sun, A.; McAtee, R.; McClain, E.; Stephenson, C. *Synthesis* **2019**, *51*, 1063, (b) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368, (c) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104, (d) Jang, H.-L.; Kim, H. T.; Cho, E. J.; Joo, J. M. *Asian J. Org. Chem.* **2015**, *4*, 1386.

6. McCallum, T.; Barriault, L. *Chem. Sci.* **2016**, *7*, 4754.

7. James, M. J.; Strieth-Kalthoff, F.; Sandfort, F.; Klauck, F.; Wagener, F.; Glorius, F. *Chem. – A Eur. J.* **2019**, chem. 201901397.

8. Jackson, R. W.; Manske, R. H. *Can. J. Res.* **1935**, *13b*, 170.

9. Wang, C.; Maity, B.; Cavallo, L.; Rueping, M. *Org. Lett.* **2018**, *20*, 3105.

10. (a) Rybicka-Jasińska, K.; Ciszewski, Ł. W.; Gryko, D. *Adv. Synth. Catal.* **2016**, *358*, 1671, (b) Rybicka-Jasińska, K.; Shan, W.; Zawada, K.; Kadish, K. M.; Gryko, D. *J. Am. Chem. Soc.* **2016**, *138*, 15451, (c) Rybicka-Jasińska, K.; Orłowska, K.; Karczewski, M.; Zawada, K.; Gryko, D. *Eur. J. Org. Chem.* **2018**, *2018*, 6634.

11. Huang, X.; Webster, R. D.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2016**, *138*, 12636.

12. Juris, A.; Balzani, V.; Belser, P.; von Zelewsky, A. *Helv. Chim. Acta* **1981**, *64*, 2175.

13. Albery, W. J.; Bell, R. P. *Trans. Faraday Soc.* **1961**, *57*, 1942.

14. In general protonation lowers both LUMO and HOMO energies, thus increasing the reduction potential in comparison with non-protonated compound. The effect of protonation on reduction potential was observed for aromatic hydrocarbons: Given, P. H.; Peover, M. E. *J. Chem. Soc.* **1960**, 385 and aromatic nitro compounds: Cadle, S. H.; Tice, P. R.; Chambers, J. Q. *J. Phys. Chem.* **1967**, *71*, 3517.

15. Jurberg, I. D.; Davies, H. M. L. *Chem. Sci.* **2018**, *9*, 5112.