U. Erdenebileg et al.

Visible-Light Photocatalytic Double C–H Functionalization of Indoles: A Synergistic Experimental and Computational Study
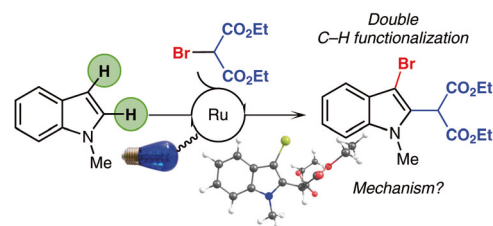
Uranbaatar Erdenebileg[a]
Taye B. Demissie[b]
Jørn H. Hansen*[a]

[a] Department of Chemistry, UiT The Arctic University of Norway, Hansine Hansens veg 54, 9037 Tromsø, Norway
jorn.h.hansen@uit.no
[b] Centre for Theoretical and Computational Chemistry (CTCC), Department of Chemistry, UiT The Arctic University of Norway, 9037 Tromsø, Norway

Abstract Herein is disclosed a novel visible-light photocatalytic double C–H functionalization of indoles. The reaction affords 2,3-difunctionalized indoles in up to 84% yield, but the reaction rate depends strongly on electronic substituent effects. Mechanistic DFT studies and control experiments suggest that the secondary functionalization occurs through an independent photocatalytic oxidation of bromide ions formed during the reaction to generate molecular bromine capable of electrophilic C-3 bromination.

**Key words** photocatalysis, C–H functionalization, indoles, DFT, reaction mechanism

C–H functionalization of heterocycles has become a major area of research in chemical synthesis.[1–4] The prevalence of heterocycles in medicinal and biologically relevant molecules underscores the need for novel chemical methods to achieve complex and efficient transformations.[5–11] Late-stage functionalization is becoming a leading strategy for efficient introduction of specific functional groups,[5] or to generate chemical libraries, for complex bioactive molecules.[5,7,10,12,13]

Visible-light photocatalysis (VLPC) has recently emerged as a powerful manifold for late-stage C–H functionalization.[1–4,7,8,14] An excellent example is the recent protocol reported by DiRocco and co-workers,[6] exemplified by the selective methylation of the antifungal agent voriconazole (Scheme 1), which was achieved in overall 75% yield to produce a mixture of mono- and dimethylated products via iridium photocatalysis. Considering the number of C–H sites available for functionalization, and the presence of other potentially interfering functional groups, this is an impressive achievement. These results truly underscore the potential for design of late-stage functionalization strategies using VLPC.


Jørn H. Hansen received his PhD in organic chemistry from Emory University (Atlanta, GA) in 2010, followed by postdoctoral research at Princeton University, before joining UiT The Arctic University of Norway as an Associate Professor of Chemistry in 2012. His research interests range from development and applications of novel late-stage functionalization methods, chemical library design with bioactive and functional heterocycles, via computational mechanistic analysis to chemical education.

One of the first examples of selective intermolecular C–H functionalization of heterocycles using VLPC came from Stephenson and co-workers,[7] who showed that indoles and other heteroaromatics readily underwent C–H malonation under photocatalytic conditions with diethyl bromomalonate and using 4-methoxy-N,N-diphenylaniline as base. For example, the C-2 malonation of N-methylindole was achieved in 82% yield using 1 mol% of ruthenium(II) trisbipyridine dichloride as the photocatalyst (Scheme 1).[7] In this letter, we describe our recent discovery of a photocatalytic double C–H functionalization process using indoles and diethyl bromomalonate. Our experimental efforts to understand the mechanism and scope, and to advance further development of this process, are detailed herein. Moreover,

U. Erdenebileg et al.

Scheme 1 Photocatalytic C–H functionalization of biologically interesting heterocycles
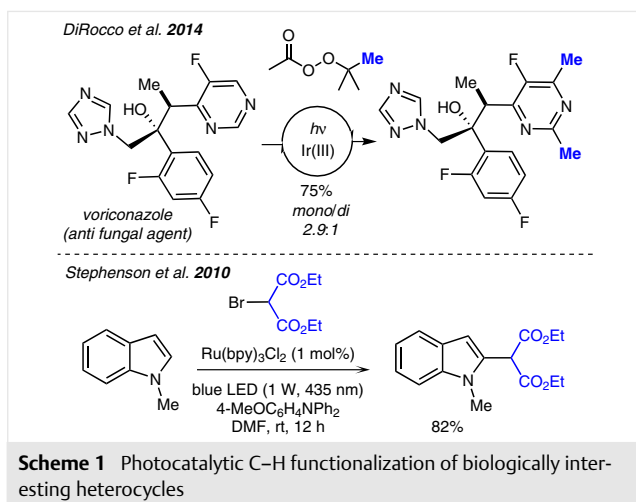
we have synergistically employed density functional theory calculations to assess a likely mechanism for the transformation.

Our work commenced with surveying reactions available in the literature. We attempted to reproduce the result by Stephenson and co-workers in which they achieved C-2 malonation of *N*-methylindole (Scheme 1).[7] We obtained a somewhat lower yield of 68% after 12 hours, but observed that the chemical yield appeared to decrease over time. After 48 hours reaction time, a new species was observed as the major product and identified as the 2,3-difunctionalized indole **2**, in which the C-2 position contained the malonyl group, and the C-3 position was functionalized with bromine (Scheme 2). An ultra-high performance liquid chromatography (UPLC) study of the reaction progress revealed that product **1** is formed initially with a peaking concentration after ca. 10 hours (Figure 1). The difunctionalized indole **2** steadily grows in, reaching the maximum yield region after ca 24 hours. An 84% isolated yield of **2** was

Scheme 2 Observed products in the model reaction
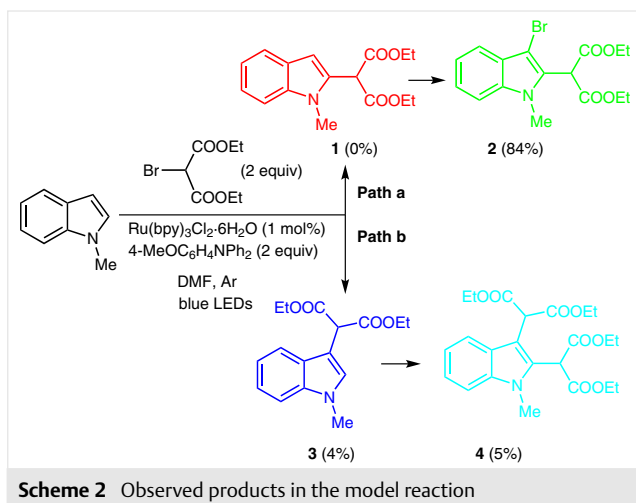
observed after 48 hours reaction time, consistent with Figure 1. As shown in Scheme 2 and Figure 1, **1** and **2** are produced via the main reaction path a.
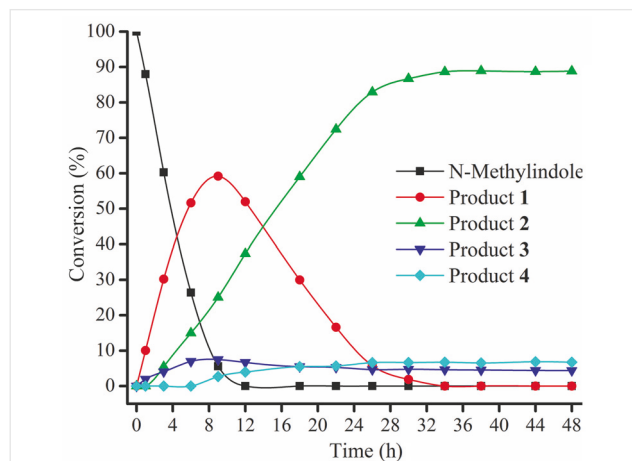

Figure 1 Product distribution as function of time for model reaction

On the other hand, reaction path b is operating, although slow compared to a, and yields C3-malonated product **3**, which is a precursor for the formation of **4**. Figure 1 shows that **1** and **3** are formed in parallel, but that the formation of **1** is much faster. Moreover, the conversion study demonstrates that formation of **4** comes exclusively from **3**. Finally, we have confirmed that **1** and **3** convert exclusively into **2** and **4**, respectively, by control experiments in which pure **1** and **3** were separately subjected to the reaction conditions.

The influence of reaction conditions was surveyed to identify parameters of importance to control the product distribution in favor of compound **2** (Table 1). The reaction works with different common photocatalysts, although ruthenium(II) trisbipyridine hexahydrate afforded the largest amount of **2** after 48 hours reaction time. The reaction also worked in different solvents such as dichloromethane and acetonitrile, but the highest yield of **2** was observed in DMF. The base is a crucial factor, and only the triaryl base 4-MeOC$_6$H$_4$NPh$_2$ was effective at affording high yields of the desired product. The reactions are conducted using two equivalents of diethyl bromomalonate, which afforded a satisfactory reaction rate according to Figure 1. However, when one equivalent of diethyl bromomalonate was employed, much slower conversion was observed, but product **2** was still formed as the major product after ca. 4–5 days. This result strongly suggests that both the bromine and the malonyl group in the final product come from the same equivalent of substrate. For a general procedure and representative analytical data, see reference 15.[15]

To investigate the generality of the newly discovered double C–H functionalization process, various substrates were studied under the best reaction conditions from Table 1. Table 2 shows the isolated yields of C-2 malonated het-

Table 1 Influence of Reaction Variables[a]

| Entry	Catalyst	Base	Solvent	Yield (%)[b]			
				1	2	3	4
1	Ru(bpy)$_3$(PF$_6$)$_2$	4-MeOC$_6$H$_4$NPh$_2$	DMF	4	81	7	8
2	fac-Ir(ppy)$_3$	4-MeOC$_6$H$_4$NPh$_2$	DMF	6	78	6	10
3	Ir(ppy)$_2$(dtbbpy)PF$_6$	4-MeOC$_6$H$_4$NPh$_2$	DMF	5	77	7	11
4	Ru(bpy)$_3$Cl$_2$·6H$_2$O	4-MeOC$_6$H$_4$NPh$_2$	CH$_2$Cl$_2$	2	84	6	8
5[c]	Ru(bpy)$_3$Cl$_2$·6H$_2$O	4-MeOC$_6$H$_4$NPh$_2$	toluene	19	7	1	3
6	Ru(bpy)$_3$Cl$_2$·6H$_2$O	4-MeOC$_6$H$_4$NPh$_2$	MeCN	11	74	4	11
7	Ru(bpy)$_3$Cl$_2$·6H$_2$O	4-MeOC$_6$H$_4$NPh$_2$	DMF	0	84[d]	4[d]	5[d]
8[c,e]	Ru(bpy)$_3$Cl$_2$·6H$_2$O	4-MeOC$_6$H$_4$NPh$_2$	DMF	57	26	5	5
9[c]	Ru(bpy)$_3$Cl$_2$·6H$_2$O	Et$_3$N	DMF	1	2	3	2
10[c]	Ru(bpy)$_3$Cl$_2$·6H$_2$O	DIPEA	DMF	0	0	0	0
11[c]	Ru(bpy)$_3$Cl$_2$·6H$_2$O	pyridine	DMF	0	0	0	0
12[c]	Ru(bpy)$_3$Cl$_2$·6H$_2$O	DBU	DMF	0	0	1	3

[a] Unless otherwise stated, the reaction conditions were: N-methylindole (0.5 mmol), diethyl bromomalonate (1.0 mmol, 2.0 equiv), photocatalyst (0.005 mmol, 1.0 mol%), base (1.0 mmol, 2.0 equiv), and solvent (2 mL), argon atmosphere, 1 W blue LED light (for ruthenium-based catalysts) or 1 W white LED strips (for iridium-based catalysts) at r.t., 48 h.
[b] Unless otherwise stated, yields were calculated on the basis of UPLC analysis of the crude products.
[c] N-Methylindole was not fully consumed after 48 h.
[d] Isolated yields.
[e] With only 1 equiv of diethyl bromomalonate.

Table 2 Isolated Yields of Mono- and Disubstituted Derivatives from Indoles, Benzofuran and Benzothiophene after 48 Hours of Reaction[a]
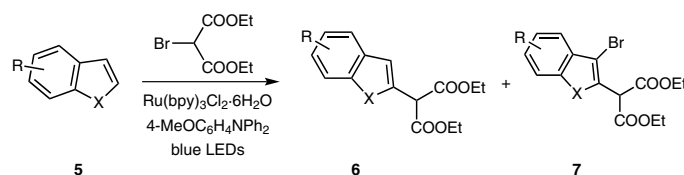
Entry	Substrate	Product	Yield (%)	Product	Yield (%)
1	**5a** X = NH; R = H	**6a**	20	**7a**	63
2	**5b** X = NH; R = 4-Br	**6b**	38	**7b**	27
3	**5c** X = NH; R = 5-Br	**6c**	17	**7c**	58
4	**5d** X = NH; R = 7-Br	**6d**	14	**7d**	52
5	**5e** X = NH; R = 5-MeO	**6e**	0	**7e**	0
6	**5f** X = NH; R = 5-NC	**6f**	22	**7f**	17
7	**5g** X = NH; R = 5-O$_2$N	**6g**	0	**7g**	0
8	**5h** X = N(CH$_2$)$_3$CO$_2$Me; R = H	**6h**	27	**7h**	60
9	**5i** X = N-Boc; R = H	**6i**	82	**7a**[b]	11
10	**5j** X = O, R = H	**6j**	86	**7j**	0
11	**5k** X = S, R = H	**6k**	31	**7k**	0
12	6- and 7-azaindoles	no reaction observed			

[a] Reaction conditions: heterocyclic substrate (0.5 mmol), diethyl bromomalonate (1.0 mmol, 2.0 equiv), tris(bipyridine)ruthenium(II) chloride hexahydrate (0.005 mmol, 1.0 mol %), 4-methoxy-N,N-diphenylaniline (1.0 mmol, 2.0 equiv), and DMF (2 mL), argon atmosphere, 1 W blue LED strips at r.t., 48 h.
[b] The Boc group was lost spontaneously during the reaction.

erocycles **6a–k** and doubly functionalized products **7a–k**. For most substrates, full conversion to difunctionalized product was not observed after 48 hours reaction time.

The reaction rates appeared very sensitive to the substituents, and in several cases, byproducts were also formed from other pathways (Figure 2). As such, reaction time is a crucial and very substrate-specific parameter. Unsubstituted indole (**5a**) afforded **7a** in 63% yield, with 20% of **6a**, indicating that slightly less electron-rich indoles require longer reaction times to be converted fully into the desired product. In a series of brominated indoles **5b–d**, the difunctionalized product **7b** was minor in the case of 4-bromoindole (27% **7b** vs. 38% of **6b**). Moreover, the formation of the C3 homodimer **8** (Figure 2) was observed in 18% yield. In this case, the combined substituent effects of the 4-bromo and 2-malonyl groups must have rendered **6b** amenable to photooxidation and subsequent homodimerization. In 5- and 7-substituted indoles the yields of difunctionalized products were similar (58% and 52%, respectively). 5-Bromo substitution appeared to more favor path b, as the products **9** and **10** were isolated in overall 21% yield (Figure 2). 7-Bromoindole (**5d**) also afforded a small amount of dimalonated product **11** in 18% yield, consistent with increased π-nucleophilicity at C-4 in this system. The π-electron-donating methoxy substituent in the 5-position did not afford any desired product, but rather underwent dimalonation as well as homodimerizations to give a range of products **12–14** (Figure 2). Too electron-rich π-systems lead to reaction pathways involving oxidation of the indole with subsequent side reactions over the bromination. 5-Cyanoindole (**5f**) gave approximately equimolar amounts of **6f** (22%) and **7f**

(17%), in addition to C-3 malonation (8% of **15**); with the major product being C-3 brominated product **16** formed in 32% yield. 5-Nitroindole (**5g**) did not yield any desired product, but afforded C-3 brominated indole **17** in 45% yield (Figure 2). These interesting observations suggest that the bromination can occur independently from the malonation and that electron-poor substrates favor the former over the latter process. The N-substituted indole **5h** afforded 60% of **7h**, suggesting that inductive electron-withdrawing effects of N-substituents also cause reduced conversion rates to the desired difunctionalized product. In this case, the C-3 malonated product **18**, arising from path b, was also observed in 6% yield. Boc-protected indole **5i** afforded 11% of deprotected product **7a**, consistent with the above-mentioned electronic effects. The deprotection occurs spontaneously under the reaction conditions. Attempts to extend the chemistry to benzofuran (**5j**), benzothiophene (**5k**) and azaindoles failed to produce any difunctionalization. In the cases of **5j** and **5k** the C-2 monofunctionalized products were observed exclusively in 86% and 31% yields, respectively. No conversion was observed for the azaindoles.

We next attempted to extend the difunctionalization chemistry to more basic heterocycles such as pyrrole (**19a**), furan (**19b**), and thiophene (**19c**) (Table 3). In these cases, we did not observe any bromination, only mixtures of mono- (**20a–c**) and dimalonated (**21a–c**) products.

In order to understand our newly discovered double C–H functionalization process, and to obtain mechanistic information to develop the chemistry further, we studied various mechanistic possibilities using contemporary DFT
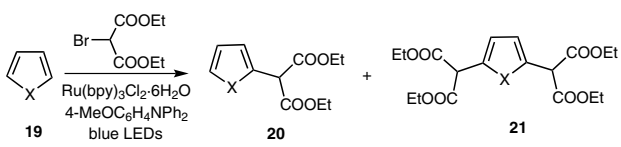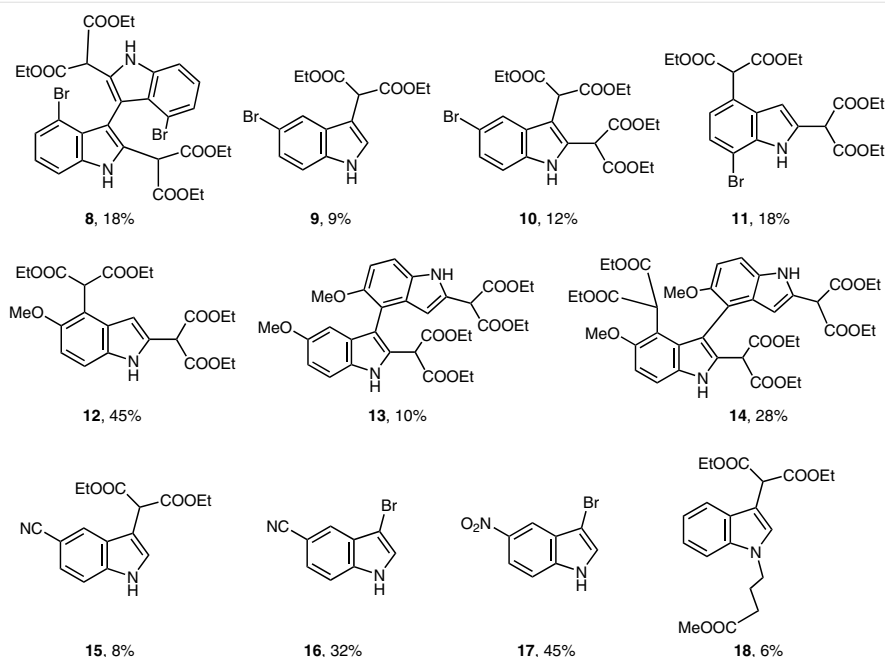

Figure 2 Characterized byproducts and their isolated yields

techniques in conjunction with experimental control experiments. A major goal was to try to understand how the C–H bromination occurs.

Table 3 Isolated Yields of Mono- and Dimalonated Derivatives from Pyrrole, Furan, and Thiophene[a]

Entry	Substrate	Product	Yield (%)	Product	Yield (%)
1	**19a**, X = NH	**20a**	51	**21a**	33
2	**19b**, X = O	**20b**	20	**21b**	72
3	**19c**, X = S	**20c**	54	**21c**	19

[a] Reaction conditions: heterocyclic substrate (0.5 mmol), diethyl bromomalonate (1.0 mmol, 2.0 equiv), tris(bipyridine)ruthenium(II) chloride hexahydrate (0.005 mmol, 1.0 mol%), 4-methoxy-*N*,*N*-diphenylaniline (1.0 mmol, 2.0 equiv), and DMF (2 mL), argon atmosphere, 1 W blue LED strips at r.t., 48 h.

We have recently disclosed two DFT studies of photocatalytic C–H functionalization processes, in one of which the C-2 malonation of indoles was studied in detail (see the Supporting Information).[16,17] Herein, we discuss our proposed mechanism for double C–H functionalization of *N*-methylindole (Scheme 3) with energies calculated at the B3LYP-D3BJ/6-311+G(d,p)/DMF(IEF-PCM) level of theory.
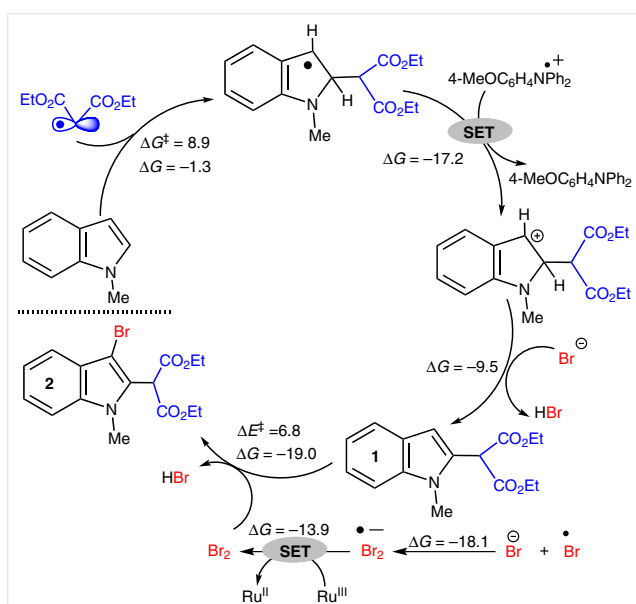
Scheme 3 Experimentally supported, proposed reaction mechanism for the photocatalytic double C–H functionalization of 1-methylindole, calculated using B3LYP-D3BJ/6-311+G(d,p)/DMF(IEF-PCM)

The C-2 addition is the kinetically favored pathway with an energy barrier of 8.9 kcal/mol in the addition step, compared to 10.2 kcal/mol barrier for C-3 addition, consistent with the observed product distribution in Figure 1.

The computed and experimental product distributions are in good agreement in this case and provide the rationale for our choice of computational methodology (see the Supporting Information for comparison with alternative method). The addition step is followed by exergonic single-electron transfer (SET, –17.2 kcal/mol) and subsequent elimination of bromide ion (–9.5 kcal/mol) to form **1**. For the bromination we assessed different possibilities (see the Supporting Information for details). Inspired by recent work by Meyer and co-workers,[18] we hypothesized that the reaction could involve electrophilic bromination by small amounts of Br_2, formed via photocatalytic oxidation of bromide ions that are generated throughout the reaction. Examples of mild bromination of C-2-substituted indoles in DMF exist in the literature,[19] and this was also found to be feasible both computationally and by a control experiment. In the control experiment, **1** was treated with Br_2 in DMF and was shown to convert fully into **2**. Finally, the HBr salt of the triaryl base was prepared independently and could be shown to effect the bromination of **1** under the photocatalytic reaction conditions. These observations strongly support our mechanistic proposal. The photocatalyst can oxidize bromide ions to radicals,[20] which then react with bromide ions exergonically to form $Br_2^{\bullet-}$ (–18.1 kcal/mol), consistent with the Meyer study.[18] The $Br_2^{\bullet-}$ can then become oxidized by the ruthenium(III) photocatalyst to molecular bromine, which was also found to be exergonic by –13.9 kcal/mol. We were unable to obtain a proper transition state for the bromination of **1** with Br_2, but a PES scan revealed an approximate potential energy barrier of 6.8 kcal/mol for this reaction. Followed by HBr elimination, the transformation from **1** to **2** was exergonic by –19 kcal/mol.

In conclusion, we have demonstrated a novel photocatalytic double C–H functionalization of C-2 and C-3 positions of indoles. Moreover, we have studied mechanistic details of the transformation by DFT and by careful examination of the reaction progress and byproduct formation. The results suggest that two independent photocatalytic processes occur to produce the observed difunctionalization and that the secondary reaction occurs through oxidation of bromide ions formed during the reaction progress. This can generate molecular bromine amenable to C-3 bromination. The high sensitivity of the chemical yields toward electronic effects underscores the challenges involved in achieving selective C–H multifunctionalizations. Studies to develop the photocatalytic C–H bromination chemistry further are under way and will be disclosed in the near future.

Acknowledgment

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588719. Detailed experimental procedures, characterization and spectra, as well as computational details and xyz-coordinates, are included.

References and Notes

(1) Fagnoni, M.; Dondi, D.; Ravelli, D.; Albini, A. *Chem. Rev.* **2007**, *107*, 2725.

(2) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052.

(3) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. *Angew. Chem. Int. Ed.* **2016**, *55*, 685.

(4) Xuan, J.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2012**, *51*, 6828.

(5) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546.

(6) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 4802.

(7) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104.

(8) Hari, D. P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958.

(9) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854.

(10) O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122.

(11) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960.

(12) Demissie, T. B.; Hansen, J. H. *Dalton Trans.* **2016**, *45*, 10878.

(13) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science* **2015**, *349*, 1326.

(14) Peña-López, M.; Rosas-Hernández, A.; Beller, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 5006.

(15) **General Procedure**

An oven-dried 10 mL round-bottom flask was equipped with a rubber septum and magnetic stirrer and was charged with the heteroaromatic substrate (0.5 mmol, 1.0 equiv), tris(2,2'-bipyridyl)ruthenium(II) chloride hexahydrate (5.0 μmol, 3.70 mg, 1.0 mol%), 4-methoxyphenyl-*N,N*-diphenylamine (1.0 mmol, 0.274 g, 2.0 equiv), diethyl bromomalonate (1.0 mmol, 0.239 g, 2.0 equiv), and DMF (2.0 mL). The mixture was degassed by the freeze-pump-thaw method, and the reaction vessel was filled with argon. A 1 W blue light-emitting diode (LED) strip was placed around the reaction vessel at a distance of approximately 2–4 cm. The reaction was stopped by removing the LED lamps, and the mixture was poured into a separatory funnel containing EtOAc (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated on a rotary evaporator. The residue was purified by preparative HPLC on a C18 column, using water and MeCN eluent systems. Appropriate fractions were collected, frozen and lyophilized to afford the products as pure compounds.

Analytical Data for Compound 2

IR (neat): 3063 (w), 2981 (m) 2937 (m), 1736 (s), 1613 (w), 1467 (s), 1392 (m), 1367 (s), 1344 (m), 1308 (s), 1266 (s), 1240 (s), 1210 (s), 1175 (s), 1150 (s), 1108 (m), 1095 (m), 1031 (s), 946 (m), 853 (w), 739 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.55 (d, *J* = 7.8 Hz, 1 H), 7.34–7.28 (m, 2 H), 7.22–7.18 (m, 1 H), 5.35 (s, 1 H), 4.33–4.21 (m, 4 H), 3.81 (s, 3 H), 1.30 (t, *J* = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.7 (2 CO), 137.3, 128.5, 126.3, 123.3, 120.5, 119.5, 109.7, 93.6, 62.4 (2 CH$_2$), 50.3, 32.0, 14.1 (2 CH$_3$). HRMS: *m/z* calcd for $C_{16}H_{19}O_4NBr^+$ [M + H]$^+$: 368.0492; found: 368.0491.

(16) Demissie, T. B.; Hansen, J. H. *J. Org. Chem.* **2016**, *81*, 7110.

(17) Demissie, T. B.; Ruud, K.; Hansen, J. H. *Organometallics* **2015**, *34*, 4218.

(18) Li, G.; Ward, W. M.; Meyer, G. J. *J. Am. Chem. Soc.* **2015**, *137*, 8321.

(19) Pathak, R.; Nhlapo, J. M.; Govender, S.; Michael, J. P.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2006**, *62*, 2820.

(20) Hering, T.; Meyer, A. U.; König, B. *J. Org. Chem.* **2016**, *81*, 6927.