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Visible Light-Mediated Intermolecular C−H Functionalization of Electron-Rich Heterocycles with Malonates

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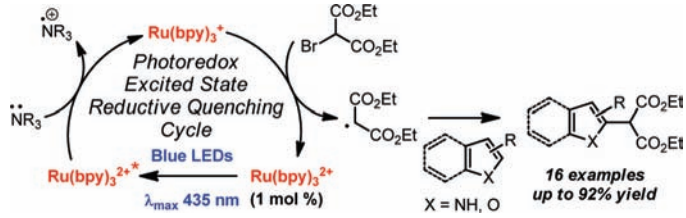
ABSTRACT



The photoredox-mediated direct intermolecular C−H functionalization of substituted indoles, pyrroles, and furans with diethyl bromomalonate is described, utilizing the visible light-induced reductive quenching pathway of $Ru(bpy)_3Cl_2$. An analysis of reductive quenchers and mechanistic considerations has led to an optimized protocol for the heteroaromatic alkylations, providing products in good yields and regioselectivities, as well as successfully eliminating previously observed competitive side reactions. This methodology is highlighted by its neutral conditions, activity at ambient temperatures, low catalyst loading, functional group tolerance, and chemoselectivity.

The direct α-arylation of carbonyl compounds constitutes an important class of reactions for the synthesis of medicinally and biologically relevant molecules. Metal-mediated processes have catapulted progress in this field in terms of efficiency, ease of operation, and functional group tolerance.[1] For example, Kawatsura and Hartwig demonstrated a Pd(0)-mediated intermolecular coupling of substituted aryl halides with malonates, providing high yields of α-arylated products (Figure 1).[2,3] However, an efficient and general method for direct, intermolecular enolate arylations with electron-rich heteroaromatic compounds remains comparatively limited.[4−6] The ubiquity of heterocycle-containing compounds in biologically interesting molecules necessitates further development in this area. We have proposed to accomplish

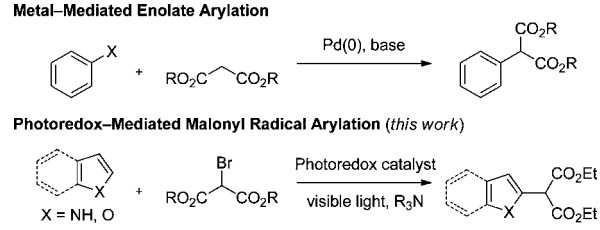


Figure 1. Photocatalytic approach to aromatic malonation.

(1) For an excellent review, see: Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676.

(2) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(3) For selected recent examples, see: (a) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469. (b) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545. (c) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302.

(4) For selected examples of the functionalization of indoles and pyrroles, see: (a) Tsai, A.-I.; Lin, C.-H.; Chuang, C.-P. *Heterocycles* **2005**, *65*, 2381. (b) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (c) Antos, J. M.; McFarland, J. M.; Iavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc.* **2009**, *131*, 6301. (d) Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A. S. C.; Yu, W. Y. *Org. Lett.* **2010**, *12*, 604.

(5) A photoinduced radical substitution of unfunctionalized indoles and pyrroles has previously been described using a 450 W Hanovia lamp using either $(Bu_3Sn)_2$ or $Na_2S_2O_3$ as the initiator in combination with excess of arene (5−15 equiv). See: Byers, J. H.; Campbell, J. E.; Knapp, F. H.; Thissell, J. G. *Tetrahedron Lett.* **1999**, *40*, 2677.

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this goal with the use of visible light photoredox catalysis,[7] an emerging technology in the area of single-electron-transfer (SET) processes.[8]

Trialkylamines are particularly effective reductive quenchers in the photoredox catalytic cycle due to their low oxidation potentials. However, we have observed several undesired side reactions during our previous investigations into the intramolecular malonation of indoles and pyrroles which are compounded in the intermolecular coupling (Figure 2).[9] Specifically, the use of trialkylamines can result in

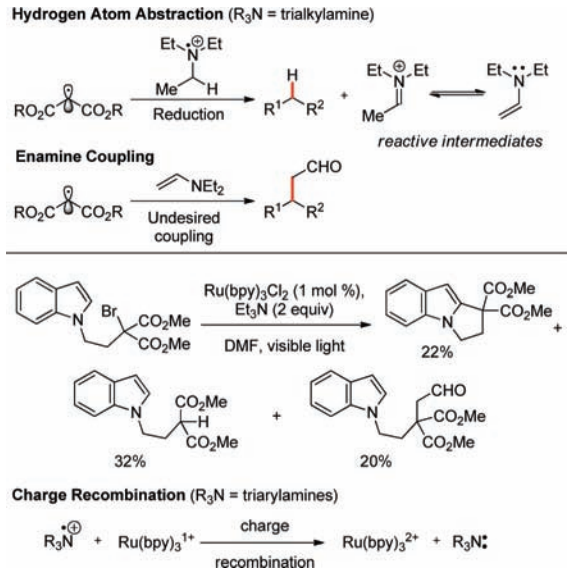
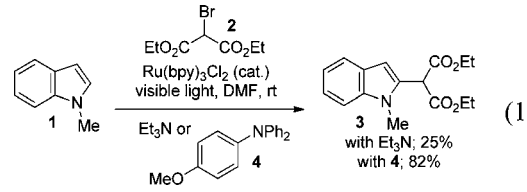


Figure 2. Challenges facing intermolecular photoredox radical chemistry.

competitive hydrogen atom abstraction by the malonyl radical to form the reduced malonate. Indeed, our initial attempts to couple simple indoles with bromomalonate in the presence of Et_3N as an electron donor led to poor isolated yield of the coupling product due to preferential reductive dehalogenation (vide infra). Further complicating the desired intermolecular coupling is the formation of reactive intermediates (iminium ions and enamines) formed as a consequence of this reduction. The enamine undergoes competitive alkylation giving 15−30% yield of the undesired acetaldehyde derivatives. Aromatic amines, in contrast, typically have higher oxidation potentials than trialkylamines but are not capable hydrogen atom donors, thereby relieving some major problems facing successful implementation of intermolecular radical coupling using photoredox catalysis. However, the amine must be chosen carefully such that nonproductive charge recombination does not interfere with the desired radical formation. Herein we report the successful realization of this proposal: coupling of an unactivated heteroaromatic compound and commercially available bromomalonate in the presence of photoredox catalyst $Ru(bpy)_3Cl_2$, visible light, and a suitable tertiary amine electron donor.

Our initial screening focused upon the arylation of **2** with **1**. Using Et_3N as the electron donor, **3** was obtained in only 25% yield after 24 h even when a large excess of **1** or **2** was employed (eq 1).[10] An excess of indole was required with these conditions in order to compete with the undesired reductive dehalogenation. However, the yield remained disappointingly low. Optimization of the reductive quencher led to the discovery of commercially available 4-methoxy-*N*,*N*-diphenylaniline (*p*-$CH_3OC_6H_4NPh_2$, **4**) as a competent electron donor, which cannot act as a hydrogen atom source. The replacement of Et_3N with **4** (2 equiv)[11] provided 82% yield of **3** (Table 1, entry 1). Furthermore, the catalyst loading (1 mol %) and stoichiometry of the reagents (1 equiv **1**, 2 equiv **2**) are improved by using **4** as the electron donor. Similar to the results reported by MacMillan,[8a] the tuning of the light source using blue LEDs (1W, $\lambda_{max} = 435$ nm)[12] was found to accelerate the reaction and complete conversion was achieved after only 12 h.[13] In the absence of $Ru(bpy)_3Cl_2$, light, or **4**, no conversion to **3** was observed.



A series of heteroaromatic compounds were then screened as suitable coupling partners for diethyl bromomalonate using the optimized reaction conditions (Table 1). The reaction generally worked well for substituted indoles, including 5-bromo-7-azaindole, although the yield was moderate (49%,

(6) For selected examples of radical addition to indoles and pyrroles, see: (a) Baciocchi, E.; Muraglia, E. *J. Org. Chem.* **1993**, *58*, 7610. (b) Byers, J. H.; DeWitt, A.; Nasveschuk, C. G.; Swigor, J. E. *Tetrahedron Lett.* **2004**, *45*, 6587. (c) Guadarrama-Morales, O.; Méndez, F.; Miranda, L. D. *Tetrahedron Lett.* **2007**, *48*, 4515. (d) Lindsay, K. B.; Ferrando, F.; Christensen, K. L.; Overgaard, J.; Roca, T.; Bennasar, M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 4181.

(7) For a review on visible light photoredox catalysis and its applications in organic chemistry, see: Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2010**, *39*, DOI:10.1039/b913880n.

(8) For recent examples, see: (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886. (c) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166. (d) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756. (e) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (f) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604. (g) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (h) Tucker, J. W.; Nguyen, J. D.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Chem. Commun.* **2010**, *46*, DOI: 10.1039/c0cc00981d.

(9) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368.

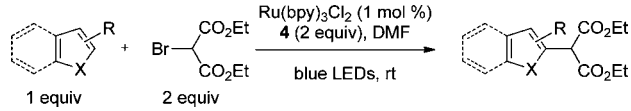
(10) The regioselectivity observed in this reaction (C2 vs. C3) is consistent with a radical process. For a recent example, see: Reyes-Gutiérrez, P. E.; Torres-Ochoa, R. O.; Martínez, R.; Miranda, L. D. *Org. Biomol. Chem.* **2009**, *7*, 1388.

(11) Using 1 equiv of **4** also provided the desired product in comparable yield at the expense of reaction time; however, the use of sub-stoichiometric quantites of **4** did not result in complete conversion. At this time, we believe the excess base is helpful in sequestering HBr. Unreacted **4** could be recovered upon purification on SiO_2.

(12) The blue LEDs have a maximum emission at 435 nm (±15 nm at half-maximum intensity). See the Supporting Information for further details.

(13) Using a 14 W fluorescent light bulb, the reaction was complete in 5 days.

Table 1. Visible Light-Mediated Intramolecular Radical C−H Functionalization of Indoles and Pyrroles



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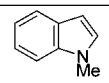
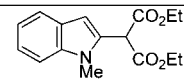
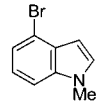
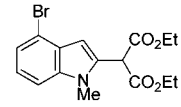
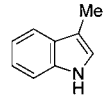
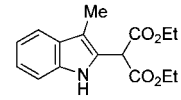
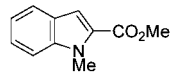
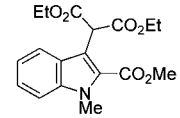
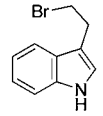
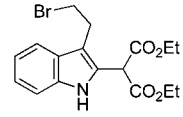
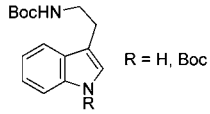
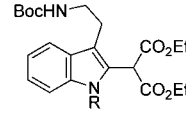
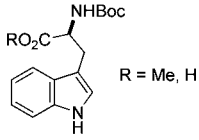
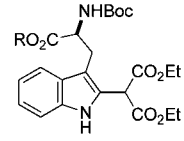
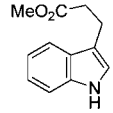
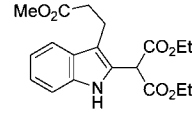
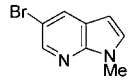
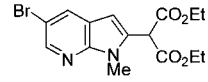
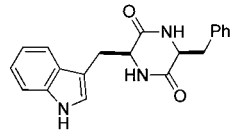
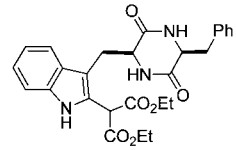
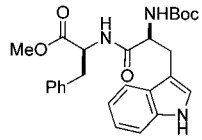
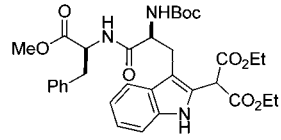
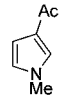
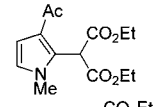
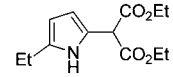
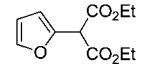
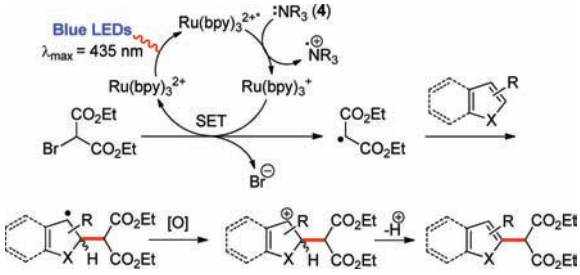
1			82
2			91
3			84
4			92
5			76
6			R = H; 85% (73%)[b] R = Boc; 85%
7			R = Me; 77% R = H; 40%[c]
8			78
9			49
10			70
11			67
12			72
13			68
14			68[d]

[a] Isolated yield after purification by chromatography on SiO_2. [b] 2.0 mmol scale. [c] The reaction was performed in water, and the product was isolated as its methyl ester (yield based upon recovered SM). [d] 5 equiv of furan was used.

entry 9).[14] The functional group tolerance of this reaction is highlighted by the use of unprotected indoles or pyrroles; sensitive functional groups such as alkyl and aryl halides; and acid-labile carbamates, peptides, ketones, and esters. Importantly, these reactions also proceed well on a preparative scale providing the coupled product in comparable yield (entry 6). To further demonstrate the utility of this transformation, furans and pyrroles were also tested and found to work well under the conditions (entries 12−14). Moving from DMF to water, *N*-Boc-tryptophan was also a viable substrate for this reaction, providing the coupled product in 40% yield, despite the solubility issues of both bromomalonate and **4**.

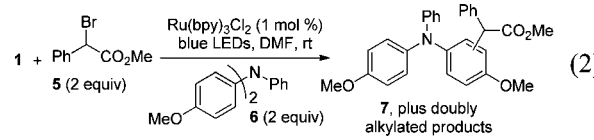
A plausible mechanism based upon these results is shown in Scheme 1. First, $Ru(bpy)_3^{2+}$ is excited by visible light

Scheme 1. Proposed Mechanism



providing $Ru(bpy)_3^{2+}$*, which is then reductively quenched by **4** to produce $Ru(bpy)_3^{1+}$ and the ammonium radical cation. Luminescence quenching experiments indicate that **4** is the only reaction component which quenches the excited state.[12] The Ru^{1+} species in turn performs a single-electron reduction of the activated C−Br bond, regenerating $Ru(bpy)_3^{2+}$ and forming a carbon-centered radical. Coupling of this electron-deficient radical at C2 of the electron-rich arene affords a stabilized radical (benzylic or allylic). Oxidation of the benzylic radical followed by rearomatization provides the observed product.[15]

When a less reactive alkyl bromide such as methyl α-bromophenylacetate (**5**) was treated with **1** under our optimized conditions, no detectable traces of an indole alkylated product were observed, and **5** was recovered. We hypothesized that competitive charge recombination was thwarting the reduction of **5** by $Ru(bpy)_3^{1+}$. To test this hypothesis, we prepared electron-rich amine **6**. Upon treatment of **1** with **5** using **6** as the electron donor, a complex mixture of products resulting from coupling of **5** with the amine **6** was observed (eq 2). Although the use of **6** as the reductive quencher did not afford the desired indole alkylation product, we were pleased to discover that our hypothesis was correct. Indeed, the charge recombination pathway was suppressed, reinvigorating the pathway leading to reduction of **5** by $Ru(bpy)_3^{1+}$, followed by alkylation of the electron-rich triarylamine. At this stage, further optimization of the electron donor, possibly in concert with the photocatalyst, is required to successfully engage less reactive halides such as **5** with the electron-rich arenes in a controlled fashion.



In conclusion, we have developed an efficient method for the direct intermolecular C−H functionalization of indoles, pyrroles, and furans with malonates using visible light photoredox catalysis. This enables rapid access to complex moieties and motifs commonly seen in biologically active natural products. Importantly, the successful functionalization of dipeptide substrates and initial success with reactions conducted in an aqueous environment bode well for future application of this mild reaction in the area of protein modification and bioconjugation chemistries. Efforts are currently underway to achieve these goals and to expand the scope of the coupling reaction by the modification of photocatalyst and electron donor.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Functionalization of azaindoles is generally more challenging than indoles. For a review, see: Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031.

(15) The excited-state Ru(II)* or radical-chain transfer to the benzylic bromide may be responsible for the benzylic oxidation; however, adventitious oxygen or triarylammonium radical cation cannot be ruled out at this time.