JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

# Direct β-Alkylation of Aldehydes via Photoredox Organocatalysis

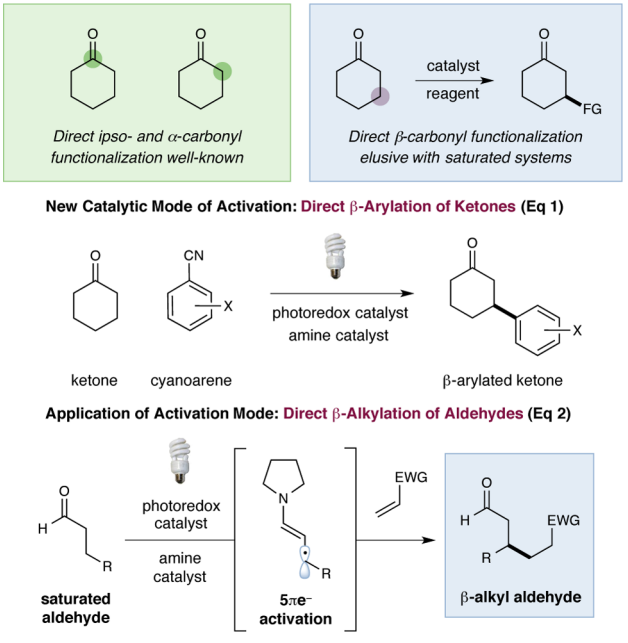
Jack A. Terrett, Michael D. Clift, and David W. C. MacMillan*

Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States

Supporting Information

**ABSTRACT:** Direct β-alkylation of saturated aldehydes has been accomplished by synergistically combining photoredox catalysis and organocatalysis. Photon-induced enamine oxidation provides an activated β-enaminyl radical intermediate, which readily combines with a wide range of Michael acceptors to produce β-alkyl aldehydes in a highly efficient manner. Furthermore, this redox-neutral, atom-economical C−H functionalization protocol can be achieved both inter- and intramolecularly. Mechanistic studies by various spectroscopic methods suggest that a reductive quenching pathway is operable.

Direct β-functionalization of saturated carbonyls has recently become an important goal within the field of new reaction invention.[1] While chemical methods that induce bond formations at the *ipso*- and α-positions of C=O moieties have long been established within organic synthesis,[2,3] it is remarkable that the β-functionalization of esters, ketones, aldehydes, and amides has been effectively limited to the addition of soft nucleophiles to α,β-unsaturated systems. Recently, our laboratory introduced a unique 5πe$^-$ carbonyl activation mode utilizing the synergistic merger of organocatalysis and photoredox catalysis[4] to accomplish the direct β-arylation of saturated ketones and aldehydes (eq 1).[1f] This strategy employs two catalytically generated radical species—a β-enaminyl radical formed via oxidation and β-deprotonation of an enamine, and a radical anion generated by photocatalytic reduction of a cyanoarene—that couple to form β-aryl carbonyl products. Furthermore, we recently demonstrated the generality of this activation platform via direct β-aldol reaction of ketones with transiently generated aryl ketyl radicals to form γ-hydroxyketone adducts.[1i] Here we translate this generic activation mode to direct β-alkylation of saturated aldehydes with Michael acceptors. This formal "homo-Michael" transformation delivers β-alkyl aldehydes by a combination of photoredox and amine catalysis (eq 2), further emphasizing the utility of this novel 5πe$^-$ carbonyl activation mode for a broad range of previously unknown transformations.



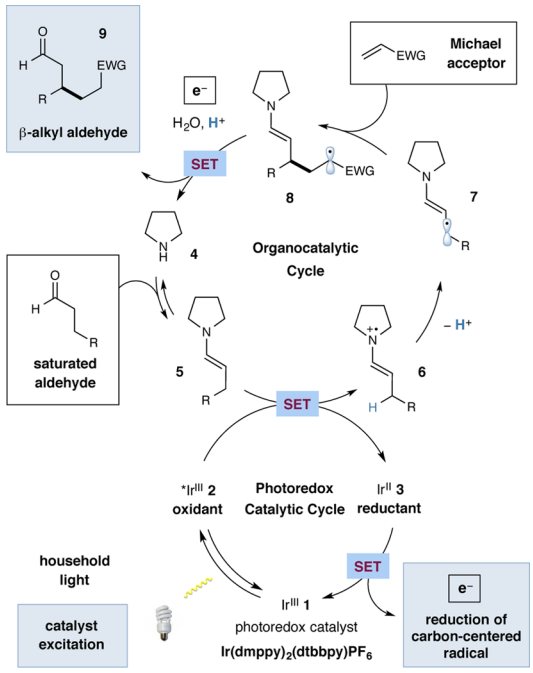

Within the discipline of organic chemistry, the Michael reaction is among the most prevalent and commonly employed strategies to couple electrophilic olefins with enolates or enamines to deliver α-carbonyl alkylated products.[5] While 1,4-conjugate addition of α-carbonyl nucleophiles is a well-established transformation,[5,6] an analogous "homo-Michael" reaction, in which the β-position of a fully saturated carbonyl species functions as the nucleophile, is essentially unknown.[1g] Indeed, current methods for installing alkyl groups at the β-position of carbonyls typically require the use of unsaturated carbonyl substrates and stoichiometric organometallic reagents, such as organocuprates.[7] Based on the insight gained over the course of our β-arylation program,[1f] we hypothesized that a transiently generated 5πe$^-$ β-enaminyl radical intermediate (formed via an enamine oxidation/deprotonation sequence) could be intercepted by a Michael acceptor, prior to a terminal reduction step.[8] Most importantly, this organocatalytic, redox-neutral, and atom-economical approach would provide direct access to a diverse range of β-alkyl aldehydes via a single chemical transformation, requiring no substrate preactivation or use of stoichiometric transition metals.

Based on our previous work in organocatalysis and visible light-promoted photoredox catalysis,[9] we propose the β-Michael mechanism outlined in Scheme 1. Initial excitation of heteroleptic Ir(III) photocatalyst $Ir^{III}(dmppy)_2(dtbbpy)PF_6$ (dmppy = 2-(4-methylphenyl)-4-methylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) (**1**) by visible light produces the photoexcited $*Ir^{III}$ state **2**, which can act as both a strong oxidant ($E_{1/2}^{*III/II}$ = +0.55 V vs SCE in MeCN) and reductant ($E_{1/2}^{IV/*III}$ = −0.87 V vs SCE) in a single-electron transfer (SET) event with an appropriate substrate quencher.[10] Concurrent condensation of a secondary amine catalyst **4** onto an aldehyde forms the enamine intermediate **5**. Based on the analysis of standard

**Received:** March 14, 2014
**Published:** April 22, 2014

   dx.doi.org/10.1021/ja502639e | J. Am. Chem. Soc. 2014, 136, 6858−6861

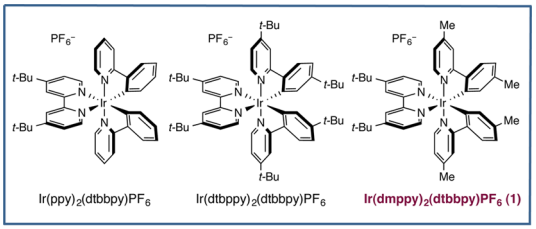
**Scheme 1. Proposed Mechanism of the $\beta$-Alkylation Reaction**

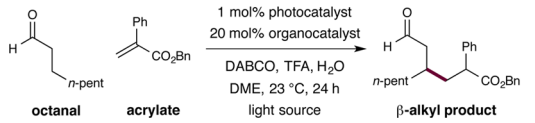



reduction potentials, we hypothesized that *$Ir^{III}$ **2** should readily oxidize the catalytically generated electron-rich enamine **5**[11] to form the respective radical cation **6** and the reduced Ir(II) photocatalyst **3**. Given the substantial increase in acidity of the $\beta$-C−H following enamine oxidation, we presumed that deprotonation of the $\beta$-methylene of the radical cation **6** would be facile, forming nucleophilic $\beta$-enaminyl radical intermediate **7** ($5\pi e^-$-activated intermediate).[1f] This transiently generated $5\pi e^-$ system could be rapidly intercepted by an electrophilic Michael acceptor, forging the desired C−C bond while producing the $\alpha$-acyl radical adduct **8**. Reducing this $3\pi e^-$ species **8** ($E^{red}_{1/2}$ = −0.59 to −0.73 V vs SCE)[12] with the available $Ir^{II}$ species **3** ($E^{III/II}_{1/2}$ = −1.52 V vs SCE)[10] would then return the photocatalyst to its ground state **1**, completing the photoredox catalytic cycle. Finally, protonating the enolate along with enamine hydrolysis (thereby completing the organocatalytic cycle by regenerating amine **4**) would then deliver the $\beta$-alkylated product **9**.

We initiated our examination of the proposed $\beta$-alkylation protocol using benzyl 2-phenyl acrylate as the electrophilic coupling partner and octanal as the saturated carbonyl component. To our delight, we observed the desired $\beta$-alkylation product (albeit in a modest 7% yield) using $Ir(ppy)_3$ as photocatalyst and diisobutylamine as the amine organocatalyst (Table 1, entry 1). From an early stage we identified that the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) as an organic base and DME as solvent was essential for the desired bond formation to be realized. Early comparisons of photocatalysts revealed noticeable improvements in efficiency when switching to more oxidizing photocatalysts, such as $Ru(bpy)_3Cl_2$ and $Ir(ppy)_2(dtbbpy)PF_6$ (cf. entries 1−3). Tuning the light source to the maximum absorption wavelength of the photocatalyst ($\lambda_{max}$ = 450 nm)[10] via the use of blue LEDs resulted in further improvements in efficiency (entry 4). At this point, we next examined the influence of the organocatalyst in this $\beta$-alkylation protocol. As might be expected, employing a more nucleophilic amine catalyst dramatically diminished reaction yields due to a competing 1,4-heteroconjugate addition with the acrylate

**Table 1. Initial Studies toward the $\beta$-Alkylation Reaction**




| entry | photocatalyst | organocatalyst | light source | yield[a] (%) |
|---|---|---|---|---|
| 1 | $Ir(ppy)_3$ | *i*-$Bu_2NH$ | 26 W CFL | 7 |
| 2 | $Ru(bpy)_3Cl_2$ | *i*-$Bu_2NH$ | 26 W CFL | 50 |
| 3 | $Ir(ppy)_2(dtbbpy)PF_6$ | *i*-$Bu_2NH$ | 26 W CFL | 52 |
| 4 | $Ir(ppy)_2(dtbbpy)PF_6$ | *i*-$Bu_2NH$ | blue LEDs | 64 |
| 5 | $Ir(ppy)_2(dtbbpy)PF_6$ | pyrrolidine | blue LEDs | 6 |
| 6 | $Ir(ppy)_2(dtbbpy)PF_6$ | *i*-$Pr_2NH$ | blue LEDs | 77 |
| 7 | $Ir(ppy)_2(dtbbpy)PF_6$ | $Cy_2NH$ | blue LEDs | 80 |
| 8 | $Ir(dtbppy)_2(dtbbpy)PF_6$ | $Cy_2NH$ | blue LEDs | 56 |
| 9[b] | $Ir(dmppy)_2(dtbbpy)PF_6$ | $Cy_2NH$ | blue LEDs | 84 |
| 10[c] | $Ir(dmppy)_2(dtbbpy)PF_6$ | $Cy_2NH$ | blue LEDs | 0 |
| 11 | $Ir(dmppy)_2(dtbbpy)PF_6$ | $Cy_2NH$ | none | 0 |
| 12 | none | $Cy_2NH$ | blue LEDs | 0 |
| 13 | $Ir(dmppy)_2(dtbbpy)PF_6$ | none | blue LEDs | 0 |

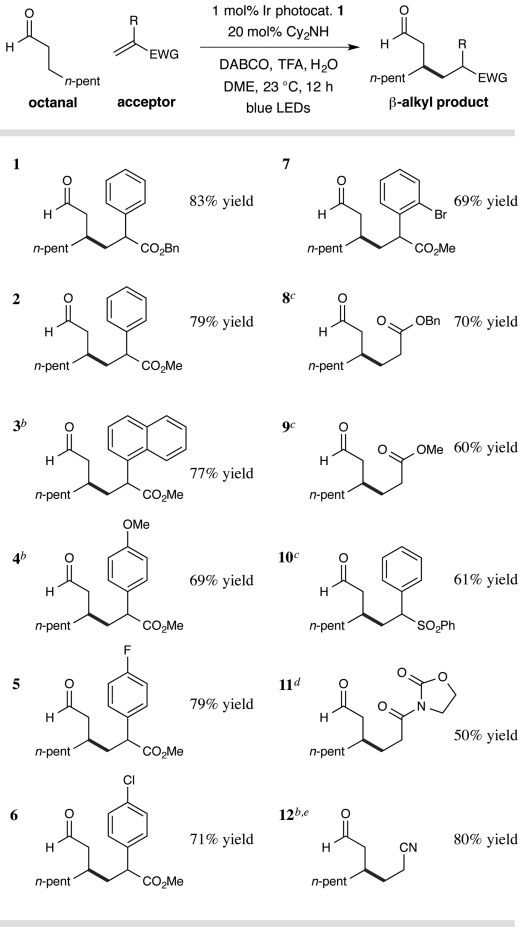
[a]Yield determined by $^1H$ NMR analysis using methyl benzoate as internal standard. Reactions performed with 2.0 equiv of octanal and 1.0 equiv of DABCO. [b]Reaction complete after 12 h. [c]Reaction performed in the absence of DABCO. CFL = compact fluorescent light.

electrophile (entry 5), a problem that is commonly confronted in prototypical Michael reactions with organocatalysts.[13] In contrast, increasing the steric bulk on the secondary amine catalyst by installing $\alpha$-branched alkyl groups adjacent to the nitrogen position provided superior efficiency (entries 6 and 7). Indeed, the use of the modified photocatalyst $Ir(dmppy)_2(dtbbpy)PF_6$ with dicyclohexylamine was found to be optimal, providing the $\beta$-alkylated product in 84% yield (entry 9). Last, control experiments revealed the requirement for base, light, photocatalyst, and organocatalyst in this new $\beta$-alkylation protocol (entries 10−13).

With the optimal $\beta$-alkylation conditions in hand, we sought to determine the generality of this direct $\beta$-Michael addition. As shown in Table 2, we identified a broad range of electrophilic olefin acceptors as effective alkylation partners for this protocol. Notably, aryl substitution at the $\alpha$-position of acrylate olefins proved highly effective for both benzyl and methyl ester systems (entries 1 and 2, 83% and 79% yield), presumably due to formation of a benzylic radical in the key C−C bond-forming step (radical **8**, Scheme 1). Sterically demanding arenes are readily accommodated on the acrylate coupling partner (entry 3, 77% yield). Electron-rich and electron-deficient arenes on the olefin are also tolerated (entries 4 and 5, 69% and 79% yield), including a series of halogen-substituted phenyl rings (entries 5−7, 69−79% yield). Importantly, unsubstituted acrylates, vinyl sulfones, acryloyl oxazolidinones, and acrylonitriles are also competent electrophiles in this direct $\beta$-alkylation reaction (entries 8−12, 50−80% yield). Interestingly, highly electrophilic

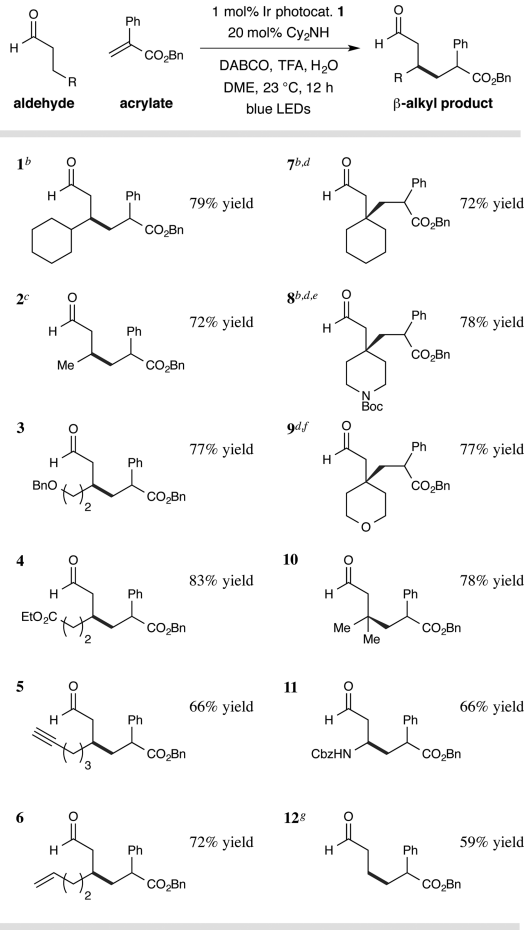

dx.doi.org/10.1021/ja502639e | J. Am. Chem. Soc. 2014, 136, 6858−6861

**Table 2. Scope of the Michael Acceptor Coupling Partner**[a]




[a]Isolated yields, see SI for experimental details. Diastereomeric ratios (dr) 1−1.3:1, determined by $^1$H NMR analysis. [b]Reaction time = 24 h. [c]5.0 equiv of DABCO and 3.0 equiv of octanal for 30 h. [d]5.0 equiv of DABCO, 5.0 equiv of octanal, 40 mol% $Cy_2NH$, and HOAc instead of TFA. [e]3.0 equiv of octanal.

**Table 3. Scope of the Aldehyde in the β-Alkylation Reaction**[a]




[a]Isolated yields, see SI for experimental details. Diastereomeric ratios 1−2:1, determined by $^1$H NMR analysis. [b]Reaction time = 24 h. [c]5.0 equiv of butanal. [d]3.0 equiv of aldehyde. [e]HOAc used instead of TFA. [f]Reaction time = 36 h. [g]10 equiv of propionaldehyde.

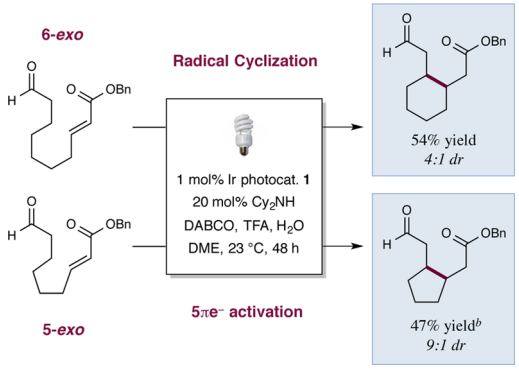
Michael acceptors such as alkylidene malonates do not participate in this β-coupling reaction. Remarkably, these reaction partners form aldehyde α-alkylation products exclusively, a regiochemical outcome that is not observed for other Michael acceptors shown in Table 2 (e.g., acrylates, vinyl sulfones, and acrylonitriles).[14]

We next focused our attention on the scope of the aldehydic coupling partner, as exemplified in Table 3. Aliphatic aldehydes function broadly, regardless of the inherent steric bulk positioned around the reactive β-C site (entries 1 and 2, 79% and 72% yield). Importantly, a variety of functional groups are tolerated on the alkanal system, including ethers, esters, alkynes, and alkenes (entries 3−6, 66−83% yield). Perhaps most notably, quaternary C centers can be formed in a facile manner utilizing this new transformation, with rapid alkylation of β-sites that are found within cyclic (tetrahydropyran and piperidine) and acyclic (*gem*-dimethyl) systems (entries 7−10, 72−78% yield). β-Amino aldehydes are competent substrates for formation of stereogenic amines with good levels of reaction efficiency (entry 11, 66% yield). Intriguingly, propionaldehyde undergoes β-alkylation at the terminal methyl site using these photoredox conditions (entry 12, 59% yield), indicating that primary β-enaminyl radicals can be generated in this protocol.

A series of Stern−Volmer fluorescence quenching experiments were performed in an effort to provide evidence for the mechanistic proposal outlined in Scheme 1. Indeed, we have determined that the emission intensity of $*Ir^{III}(dmppy)_2(dtbbpy)PF_6$ is dramatically diminished in the presence of the operating enamine (formed in situ from dicyclohexylamine and octanal), thereby indicating that enamine oxidation is likely the first step in the photoredox cycle.[15] Comparatively, there is no fluorescence quenching when the amine catalyst, aldehyde donor, or benzyl 2-phenyl acrylate acceptor is exposed separately to the photoexcited $*Ir^{III}$ species. In addition, electron paramagnetic resonance (EPR) spectroscopy has revealed the existence of an organic radical ($g_{iso}$ = 1.9858) following excitation of the photocatalyst in the presence of enamine; this signal is absent if either aldehyde or amine is removed.[15] It is important to consider that an alternative catalysis mechanism might involve single-electron reduction of the Michael acceptor prior to coupling with the β-enaminyl radical (a radical−radical combination that would be consistent with our previous β-arylation and β-aldol studies). However, this pathway would depend on a facile reduction of benzyl 2-phenyl acrylate ($E^{red}_{1/2}$ = −1.97 V vs SCE),[10] which is thermodynamically unfavorable for either the $*Ir^{III}$ or $Ir^{II}$ oxidation state of photocatalyst **1**. Indeed, EPR studies indicate that no organic radical is generated with benzyl 2-phenyl acrylate in the presence of either photocatalyst **1**


dx.doi.org/10.1021/ja502639e | J. Am. Chem. Soc. 2014, 136, 6858−6861

**Scheme 2. Intramolecular $\beta$-Alkylation Cyclization Reaction**[a]




[a]Isolated yields, see SI for experimental details. Diastereomeric ratios determined by $^1$H NMR analysis. [b]40 mol% isopropylbenzylamine as organocatalyst for 72 h.

or Ir(ppy)$_3$—a strongly reducing *Ir$^{III}$ complex ($E_{1/2}^{IV/*III} = -1.73$ V vs SCE)[16]—further indicating that acrylate reduction is not likely involved in the catalytic cycle.[15] As such, we conclude that addition of a 5$\pi$e$^-$ $\beta$-enaminyl radical (such as **7**) to the ground state of the Michael acceptor coupling partner (as shown in Scheme 1) is the operating C−C bond-forming step.[17]

Last, to further explore the utility of this new $\beta$-alkylation reaction, we have investigated intramolecular variants as a mechanism to rapidly access ring systems of various formats. As shown in Scheme 2, both 6-*exo* and 5-*exo* cyclizations are accomplished with useful efficiencies and diastereocontrol (47−54% yield, 4−9:1 dr). This provides further evidence that the critical key step does not involve radical−radical coupling, given the low probability of generating two radicals simultaneously on the same molecule.

In summary, through the synergistic combination of organocatalysis and photoredox catalysis, we have accomplished the first direct $\beta$-alkylation of fully saturated aldehydes with Michael acceptors. We have further demonstrated the utility of a 5$\pi$e$^-$ $\beta$-enaminyl activation platform as a general approach to direct $\beta$-functionalization of carbonyls. Importantly, this C−H bond activation method is entirely redox-neutral and atom-economical, and it requires no preactivation of either coupling partner. Mechanistic studies have provided spectroscopic evidence supporting a reductive quenching pathway, in which C−C bond formation occurs by $\beta$-enaminyl radical addition into a ground-state Michael acceptor. Efforts toward expanding the scope of the carbonyl coupling partner as well as developing an asymmetric variant are currently underway and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

dmacmill@princeton.edu

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support was provided by NIHGMS (R01 01 GM093213-01) and gifts from Merck and Amgen.

## ■ REFERENCES

(1) (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (b) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7261. (c) Zhang, S.-L.; Xie, H.-X.; Zhu, J.; Li, H.; Zhang, X.-S.; Li, J.; Wang, W. *Nat. Commun.* **2011**, *2*, 211. (d) Hayashi, Y.; Itoh, T.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3920. (e) Stowers, K. J.; Kubota, A.; Sanford, M. S. *Chem. Sci.* **2012**, *3*, 3192. (f) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593. (g) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835. (h) Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 8588. (i) Petronijević, F. R.; Nappi, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 18323. (j) Huang, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 17747.

(2) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part B: Reactions and Synthesis*; Springer: New York, 2001.

(3) (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (c) Evans, D. A.; Helmchen, G.; Rüping, M. *Asymmetric Synthesis—The Essentials*; Wiley-VCH: Weinheim, 2006.

(4) For reviews on photoredox catalysis, see: (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785. (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (c) Inagaki, A.; Akita, M. *Coord. Chem. Rev.* **2010**, *254*, 1220. (d) Teply, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. (e) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (f) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (g) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 985.

(5) (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *11*, 1701.

(6) Bressy, C.; Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: Weinheim, 2007.

(7) (a) Rossiter, B. E.; Swingle, N. E. *Chem. Rev.* **1992**, *92*, 771. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

(8) For examples of photoredox-catalyzed reductive quenching mechanisms involving radical additions into Michael acceptors, see: (a) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2012**, *48*, 6966. (b) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338. (c) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672.

(9) (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (c) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600. (d) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114. (e) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.

(10) See SI for cyclic voltammetry and UV/vis data.

(11) (a) Schoeller, W. W.; Niemann, J. *J. Chem. Soc., Perkin Trans. 2* **1988**, 369. (b) Renaud, V. P.; Schubert, S. *Angew. Chem.* **1990**, *102*, 416.

(12) Bortolamei, N.; Isse, A. A.; Gennaro, A. *Electrochim. Acta* **2010**, *55*, 8312.

(13) Kano, T.; Shirozu, F.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 16068.

(14) At this stage we have found Michael acceptors bearing $\beta$-substitution to be less competent in the described intermolecular $\beta$-alkylation protocol.

(15) See SI for fluorescence quenching and EPR data.

(16) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143.

(17) When coupling partners that undergo facile single-electron reduction, such as vinyl ketones, are employed, no desired $\beta$-alkylated product is formed, and only dimerization of the coupling partner is observed. This suggests against a radical−radical coupling event in the key C−C bond-forming step of this protocol.