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Catalytic Alkylation of Remote C-H Bonds Enabled by Proton-Coupled Electron Transfer

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Abstract

Despite significant advances in hydrogen atom transfer (HAT) catalysis,[1–5] there are currently no molecular HAT catalysts capable of homolyzing the strong N-H bonds of *N*-alkyl amides (Figure 1a). The motivation to develop amide homolysis protocols stems from the synthetic utility of the resulting amidyl radicals, which engage in a variety of synthetically useful transformations, including olefin amination[6–11] and directed C-H bond functionalization.[12–16] The latter process, a subset of the well-known Hofmann-Löffler-Freytag (HLF) reaction, relies on a favorable bond strength differential to enable amidyls to abstract H• from unactivated aliphatic C-H bonds (Figure 1b).[17–21] While powerful, these transforms typically require oxidative *N*-prefunctionalization of the amide starting materials to achieve efficient amidyl generation. Moreover, as these *N*-activating groups are often incorporated into the final products, these methods are generally not amenable to the direct construction of C-C bonds. Here we report a new approach that overcomes these limitations by homolyzing the N-H bonds of *N*-alkyl amides through a proton-coupled electron transfer (PCET) event. In this protocol, an excited state iridium photocatalyst and a weak phosphate base cooperatively serve to remove both a proton and an electron from an amide substrate in a concerted elementary step. The resulting amidyl radical intermediates are shown to be competent to promote subsequent C-H abstraction and radical alkylation steps (Figure 1c). As such, this C-H alkylation represents a novel catalytic variant of the HLF reaction that makes use of simple, unfunctionalized amides to direct the formation of new C-C bonds. Given the prevalence of amides in pharmaceuticals and natural products, we anticipate that this method will simplify the synthesis and structural elaboration of amine-containing targets. Moreover, these studies further demonstrate that concerted PCET can enable homolytic activation of common organic functional groups that are energetically inaccessible using traditional HAT-based approaches.

Our initial efforts sought to identify conditions effective for the direct C-H alkylation of model amide **1**, which has a N-H bond dissociation free energy (BDFE) of 107 kcal/mol.[22,23] In analogy to our previous work on *N*-aryl amide activation, we envisioned a

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Supplementary Information is available in the online version of the paper.

Author Contributions

RRK and GJC conceived of the research. GJC, QZ, and DCM carried out experiments and analyzed results with RRK. CJG assisted with substrate synthesis. RRK wrote the manuscript with input from all of the authors.

The authors declare no competing financial interest.

catalytic cycle wherein the phosphate base would first associate via hydrogen bonding to the amide N-H bond of **1** (Figure 2). Oxidation of this H-bond complex by the excited state of an iridium photocatalyst would result in formal homolysis of the strong N-H bond via concerted PCET [24–26] and furnish a reactive amidyl radical. This oxidation would then be relayed via 1,5 H-atom abstraction from a distal aliphatic C-H bond through a cyclic transition state, resulting in site-selective formation of a new alkyl radical. In turn, this open-shell intermediate could engage in a conjugate addition reaction with an electron-deficient olefin partner to furnish a new C-C bond and an α-carbonyl radical. Electron transfer to this electrophilic radical from the reduced Ir(II) form of the photocatalyst would generate an enolate anion that could be promptly protonated by the phosphoric acid to provide the C-H alkylation product **2** and return both catalysts to their active forms.

Using the catalyst system that proved optimal in our previous studies for *N*-aryl amidyl generation – $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ [27] and the tetrabutyl ammonium salt of dibutyl phosphate – we found that the desired C-H alkylation product **2** could be observed in 28% yield when the reaction was carried out in trifluorotoluene (Table 1, entry 1). Seeking to improve on this result, we evaluated a number of related iridium photocatalysts (entries 2–5), and observed that several gave more promising results. The largest increase in reaction efficiency was observed when $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)]PF_6$ (**E**) was employed ($^*E_{1/2}$ = 1.30 V vs Fc/Fc^+ in MeCN), furnishing the desired C-H alkylation product in 82% yield. Control experiments run in the absence of light, photocatalyst, and base all provided no detectable product (entries 6–8). Notably, both lower photocatalyst or olefin acceptor loadings still delivered serviceable yields of product (entries 9 and 10), though the yields decreased when higher concentrations of phosphate were used (entry 11). Finally, the model reaction also proceeds well when the reaction was run at higher concentrations (0.4M) in $PhCF_3$ (entry 12).

With these optimized conditions in hand, we next evaluated the scope of this C-H alkylation protocol (Figure 3a). On preparative scale, model amide **1** delivered alkylated adduct **2** in 78% isolated yield. Related substrates, wherein the abstracted hydrogen originates from carbocycles of various sizes, were also alkylated efficiently to form products **3** and **4**. Notably, this method is not limited to the abstraction of tertiary methine C-H bonds. Secondary methylene-containing substrates were also viable abstraction partners, as demonstrated by the generation of adamantyl derivative **5**. This example also demonstrates that steric bulk adjacent to the amidyl nitrogen can be tolerated in these reactions. In addition, alkylation was possible at secondary methylene sites on linear alkane substrates (albeit with lower efficiency) as demonstrated by the formation of adduct **6**. The fumarate acceptor in this example was chosen to inductively discourage over-alkylation of the product. The reaction was also successful with amides derived from common terpene feedstocks, generating alkylated product **7.** While this substrate contains two electronically similar methine C-H bonds, the alkylation event occurs exclusively at the site proximal to the amide. This selectivity would likely be diminished or reversed using conventional intermolecular H-atom abstractor catalysts, highlighting the utility of this directed approach afforded by amide PCET. Also, it was found that steric bulk adjacent to the abstracted site could be tolerated, such as the neopentyl group of product **8**. More complex products such as

pregabalin derivative **9** and protected amino alcohol **10** can also be accessed using the reported protocol. Similarly, α-amino- and α-oxy C-H bonds were operable sites for abstraction, as shown by the formation of alkylated carbamate **11** and ether **12**. In **11**, the methylenes flanking either side of the *N*-Boc substituent and the methylene adjacent to the amide N-H bond are electronically similar, which would limit the selectivity of HAT reactions carried out using conventional intermolecular abstractors. In contrast, the cyclic transition states required for HLF reactivity ensure that only a single alkylated product is observed. Lastly, we observed that efficient 1,6 abstraction can occur when the 1,5 pathway is precluded, as shown in the formation of **13** in 57% yield using catalyst **D**.

With respect to the olefinic partner in these reactions, both alkyl and aryl enone derivatives could be effectively utilized to furnish adducts such as **2** and **14**. However, reactions with simple acrylate or acrylamide coupling partners provided only traces of C-H alkylation products. We reasoned that this outcome was likely due to the more difficult reduction of the α-carbonyl radical in these systems ($E_{1/2}$ = −1.37 V vs. Fc/Fc$^+$)[28], which is endergonic relative to the reducing capacity of the Ir(II) state of catalyst **E** ($E_{1/2}$ = −1.07 V vs. Fc/Fc$^+$). To overcome this limitation, we found that various dicarbonyl compounds could be employed successfully (**15**–**17**), including those bearing alkyl substituents at the β-position. These compounds are both more reactive acceptors for the alkyl radical and are amenable to subsequent decarboxylation to furnish formal acrylate and acrylamide addition products. We also found that fumarate derivatives could be alkylated efficiently to furnish 1,2-disubstituted dicarboxylic acid derivative **18**. Various olefins bearing α-substituents could be alkylated efficiently, including methacrolein, α-phenyl acrylonitrile, and α-phenyl methacrylate to furnish products **19**–**21**. A number of structurally and electronically distinct benzamide derivatives could be alkylated successfully using α-phenyl acrylate as the olefin acceptor (**21**–**26**). Additionally, we found that aryl sulfonamides could serve as H-atom abstractors using catalyst **D** under otherwise standard conditions, generating **27** in 74% yield. Common *N*-Boc carbamates could also be alkylated, albeit with lower efficiency (**28**). Importantly, this example demonstrates that a conjugated aryl group is not a requirement for amide PCET reactivity.

We were pleased to find that this method could also be adapted for use in intermolecular C-H functionalizations (Figure 3b). Specifically, the comparatively strong C-H bonds in cyclohexane (10 equivalents) could be alkylated with α-phenyl methacrylate in 69% isolated yield using *N*-ethyl-4-methoxybenzamide (**29**) as the abstractor and 2 mol% of Ir catalyst **D** at 60 °C (**30**). The alkylation of tetrahydrofuran and *N*-Boc pyrrolidine also proceeded with good efficiency (**31**, **32**). These results suggest that *N*-alkyl amides have the potential to serve as highly reactive and structurally modular catalysts for radical C-H functionalization.

To evaluate the possible role of PCET in N-H activation, we examined the mechanism of amidyl formation using Stern-Volmer assays and *N*-ethyl-4-methoxybenzamide (**29**) as a model substrate. Dichloromethane was used as a solvent to ensure full solubility of all reaction components. Notably, this is an effective reaction solvent, delivering **21** (Figure 3a) in 80% yield under otherwise standard conditions. These luminescence quenching experiments revealed that **29** (E_p = +1.48 V vs. Fc/Fc$^+$ in MeCN) does not quench the excited state of photocatalyst **E** (*$E_{1/2}$ = +1.30 V vs. Fc/Fc$^+$ in MeCN). However, solutions

containing varying concentrations of **29** and a constant amount of tetrabutyl ammonium dibutyl phosphate resulted in a significant decrease in the emission intensity. The quenching was found to be linear with respect to the amide concentration (k_{SV} = 46 M^{-1}), consistent with a first-order kinetic dependence. These results rule out stepwise activation of the N-H bond by an ET-PT mechanism, as catalyst quenching cannot be effected by the substrate alone.

Next, we observed that the phosphate base alone also quenched the Ir excited state, though the concentration dependence was non-linear and saturates at higher concentrations. Further experiments wherein the phosphate concentration was varied in the presence of a constant amount of amide exhibited similar saturation behavior, but with greater overall quenching efficiency. Seeking to understand these results, we found that the ^{1}H-NMR chemical shift of the C_3 proton of the dCF_3bpy ligand is sensitive to the concentration of added phosphate, undergoing a downfield chemical shift of 1.4 ppm in the presence of equimolar phosphate. This observation was attributed to hydrogen-bonding between the phosphate and the polarized C-H bonds of dCF_3bpy ligand of catalyst **E**. Precedent for such an effect can be found in the recent work of Meyer, who observed similar effects for ruthenium polypyridyl complexes in dichloromethane in the presence of exogenous anions.[29] We further observed that the presence of ten equivalents of phosphate does not significantly alter the Ir(II/III) redox couple or emission maxima of **E**. Based on these observations, it is unlikely base coordination to the photocatalyst significantly impacts its excited state redox properties. The observed decrease in emission intensity can likely be attributed to more facile non-radiative relaxation of the excited state, in analogy to Meyer's findings.

Thermochemical constraints argue strongly against a PT-ET mechanism of amidyl formation. Specifically, based on the pK_a difference between the benzamide substrate and monobasic phosphate (ΔpK_a ~ 20 in MeCN), the rate constant for proton transfer cannot exceed 6.8×10^{-11} $M^{-1}s^{-1}$. As such, this process would not be kinetically competitive with luminescent decay of the Ir(III) excited state ($1/\tau_0 = 3.6 \times 10^6$ s^{-1}). As both stepwise mechanisms can be discounted, we feel that the data presented above is most consistent with a concerted PCET mechanism of N-H bond activation. We also note that when using the catalyst **E**/dibutyl phosphate combination, the N-H scission step is calculated to be only modestly endergonic (effective BDFE = 103 kcal/mol, ΔG° = +4 kcal/mol).[30] Lastly, we determined that the quantum yield of the model reaction converting **1** to **2** is 0.12.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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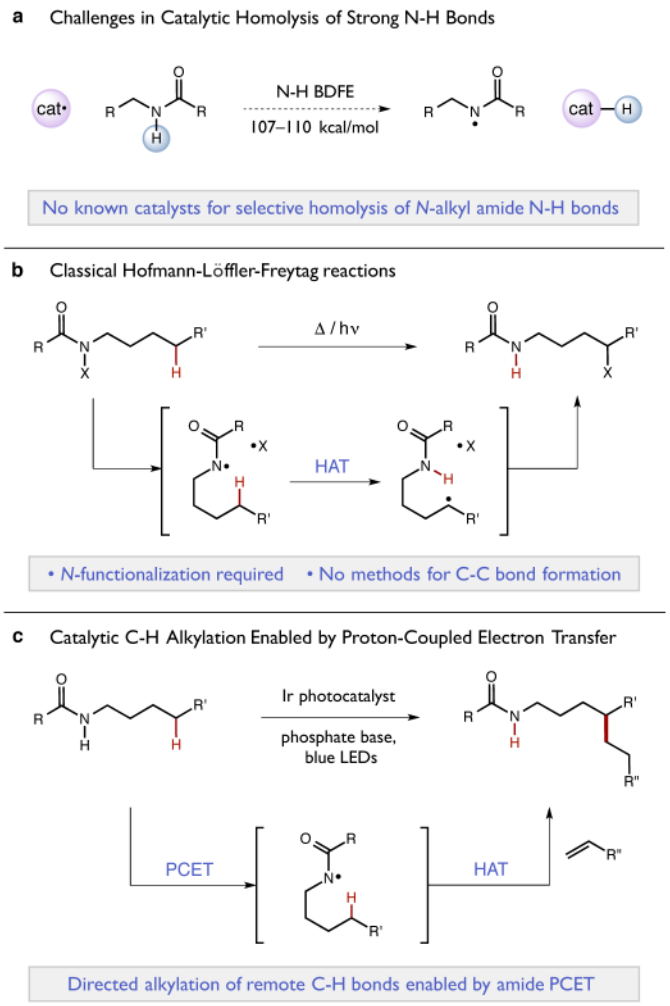


Figure 1. Design and development of a catalytic amidyl-mediated C-H alkylation

a, With bond dissociation free energies (BDFEs) of 107–110 kcal/mol, there are no reported molecular catalysts capable of homolyzing the N-H bonds of *N*-alkyl amides. **b**, The classical Hofmann-Löffler-Freytag reaction enables the selective abstraction of C-H bonds at positions remote from the amidyl radical via hydrogen-atom transfer (HAT). **c**, Proposed direct C-H alkylation of remote C-H bonds via the intermediacy of an amidyl radical generated by concerted oxidative proton-coupled electron transfer (PCET).

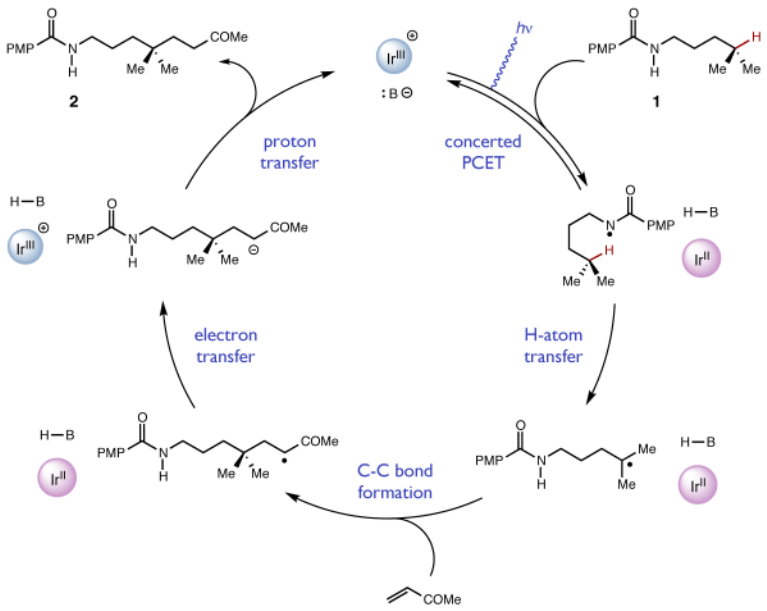


Figure 2. Proposed catalytic cycle

The catalytic cycle begins with an association of the phosphate base (B) via hydrogen bonding to the amide N-H bond of the substrate **1** (*p*-methoxyphenyl = PMP). Oxidative proton-coupled electron transfer generates a neutral amidyl radical. A 1,5 H-atom abstraction then occurs to generate the distal carbon-centered radical. This intermediate undergoes a conjugate addition with an olefin acceptor to furnish a new C-C bond and an α-carbonyl radical. Electron transfer from the reduced Ir(II) catalyst furnishes an enolate. Proton transfer from phosphoric acid produces the product **2** and returns the catalysts to their active forms.

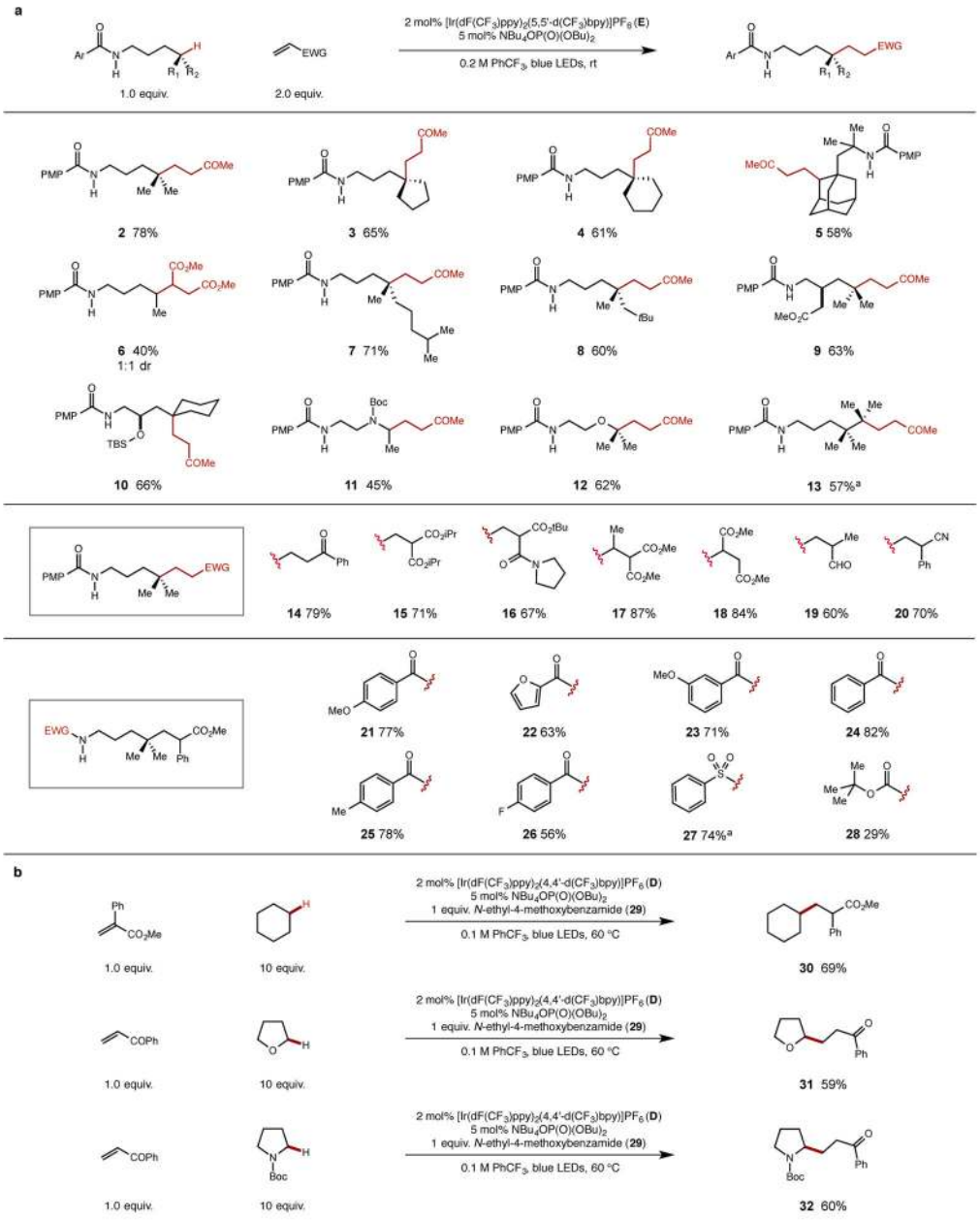


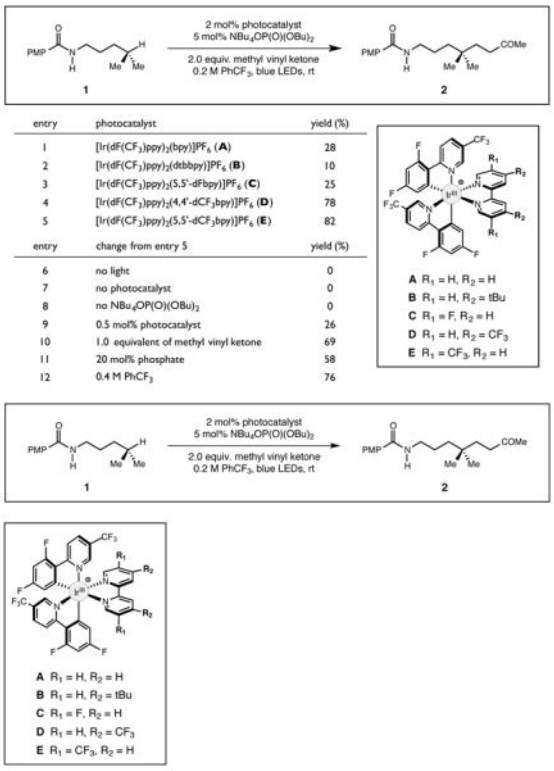
Figure 3. Substrate Scope

a, A range of amide substrates can be alkylated in an intramolecular fashion. The olefin acceptor scope (electron withdrawing group = EWG) illustrates that a variety of common functional groups that can be incorporated into the final alkylated products. A number of structurally and electronically distinct benzamide derivatives can be accommodated, including aryl sulfonamides and *N*-Boc carbamates. [a] Photocatalyst **D** used in reactions to form products **13** and **27. b**, Intermolecular C-H alkylations can also be effected with an excess of the alkane relative to the olefin acceptor. TBS = *tert*-butyldimethylsilyl. Boc = *tert*-butyl carbamate

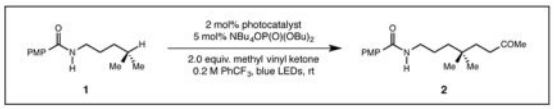
Table 1

Optimization studies

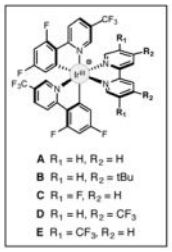
The reaction optimization in trifluorotoluene ($PhCF_3$) shows that [Ir(dF(CF_3)ppy)$_2$(5,5′-dCF_3bpy)](PF_6) offers the highest yield of the desired product. $NBu_4P(O)(OBu)_2$ is the the tetrabutyl ammonium salt of dibutyl phosphate. LEDs are light-emitting diodes. Control experiments show that both catalysts are required for product formation along with the use of visible light. Variations from the standard reaction conditions show decreased reaction efficiencies.



entry	photocatalyst	yield (%)
1	[Ir(dF(CF_3)ppy)$_2$(bpy)]PF_6 (**A**)	28
2	[Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 (**B**)	10
3	[Ir(dF(CF_3)ppy)$_2$(5,5′-dFbpy)]PF_6 (**C**)	25
4	[Ir(dF(CF_3)ppy)$_2$(4,4′-dCF_3bpy)]PF_6 (**D**)	78
5	[Ir(dF(CF_3)ppy)$_2$(5,5′-dCF_3bpy)]PF_6 (**E**)	82
entry	change from entry 5	yield (%)
6	no light	0
7	no photocatalyst	0
8	no $NBu_4OP(O)(OBu)_2$	0
9	0.5 mol% photocatalyst	26

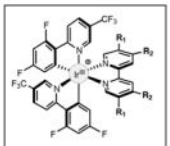


entry	photocatalyst	yield (%)
1	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (**A**)	28
2	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**B**)	10
3	$[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dFbpy)]PF_6$ (**C**)	25
4	$[Ir(dF(CF_3)ppy)_2(4,4'\text{-}dCF_3bpy)]PF_6$ (**D**)	78
5	$[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)]PF_6$ (**E**)	82
entry	change from entry 5	yield (%)
6	no light	0
7	no photocatalyst	0
8	no $NBu_4OP(O)(OBu)_2$	0
9	0.5 mol% photocatalyst	26
10	1.0 equivalent of methyl vinyl ketone	69
11	20 mol% phosphate	58
12	0.4 M $PhCF_3$	76



A $R_1 = H, R_2 = H$
B $R_1 = H, R_2 = tBu$
C $R_1 = F, R_2 = H$
D $R_1 = H, R_2 = CF_3$
E $R_1 = CF_3, R_2 = H$

2 mol% photocatalyst
5 mol% NBu4OP(O)(OBu)2
2.0 equiv. methyl vinyl ketone
0.2 M PhCF3, blue LEDs, rt
PMP
COMe
1
2



A $R_1 = H, R_2 = H$
B $R_1 = H, R_2 = tBu$
C $R_1 = F, R_2 = H$
D $R_1 = H, R_2 = CF_3$
E $R_1 = CF_3, R_2 = H$

entry	photocatalyst	yield (%)
10	1.0 equivalent of methyl vinyl ketone	69
11	20 mol% phosphate	58
12	0.4 M $PhCF_3$	76