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Photoredox-Catalysed Decarboxylative Alkylation of *N*-Heteroarenes with *N*-(Acyloxy)phthalimides

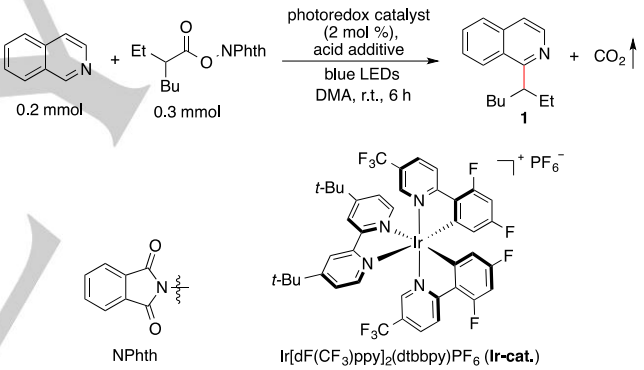
Wan-Min Cheng, Rui Shang,* [§] Ming-Chen Fu, and Yao Fu*[a]

Abstract: An iridium-photoredox catalyst in combination with either a stoichiometric amount of Brønsted acid or a catalytic amount of Lewis acid is capable of catalysing regioselective alkylation of N-heteroarenes with N-(acyloxy)phthalimides at room temperature under irradiation. A broad range of N-heteroarenes can be alkylated using a variety of secondary, tertiary, and quaternary carboxylates. Mechanistic studies suggest that an Ir(II)/Ir(III) redox catalytic cycle is responsible for the observed reactivity.

Direct C–H alkylation of *N*-heteroarenes[1] using available carboxylic acids[2] is a transformation of considerable interest in the pharmaceutical industry due to the prevalence of functionalized *N*-heteroarenes found in medicinal compounds.[3] The well-established Minisci reaction is a useful tool to accomplish this task, in which a protonated *N*-heteroarene is nucleophilically attacked by an alkyl radical generated through radical decarboxylation under strong oxidative conditions (Ag salts and persulfates).[4] The excess amount of strong oxidant is responsible for the generation of an alkyl radical and rearomatization to deliver alkylated *N*-heteroaromatic compounds. However, the presence of a strong oxidant makes the reaction incompatible with functionalities that are easily oxidized, and always generates a variety of radical-addition by-products.[5] Decarboxylative alkylation[6] of *N*-heteroarene using aliphatic carboxylate under mild redox-neutral conditions has not been satisfactorily achieved. Inspired by a recent seminal report on photoredox-catalyzed Minisci alkylation of *N*-heteroarenes using alcohols by MacMillan and co-workers,[7] we conceived that *N*-(acyloxy)phthalimide, which is easily prepared from carboxylic acid and *N*-(hydroxyl)phthalimide,[8] may deliver alkyl radicals controllably through decarboxylation in the presence of a photoredox catalyst[9] to alkylate *N*-heteroarenes and generate phthalimide as the only by-product without using any external oxidant. *N*-(acyloxy)phthalimides have been used as a platform to utilize aliphatic carboxylic acids in Ru-[8,10] and organophotoredox-[11] catalysed decarboxylation, halogenation,[11b] 1,4-addition,[8,10b,11c] and recently elegantly used in abundant-metal-catalysed cross-couplings by Baran and co-workers,[12] but its application in Minisci-type alkylation remains unachieved.

We report in this work that, by using an iridium-photoredox catalyst[13] in combination with an acid additive, *N*-(acyloxy)phthalimides serve as redox-neutral alkylation reagents to alkylate *N*-heteroarenes. Either a stoichiometric amount of Brønsted acid or a catalytic amount of Lewis acid[14] can be used as an additive to give comparable reaction efficiency. A broad scope of *N*-heteroarenes, as well as alkyl carboxylic acids, can be used. Functionalities that are sensitive to strong oxidants and radicals, such as aldehyde, alkene, and sulfide, can be tolerated The reaction adds a new example to the synthetic application of *N*-(acyloxy)phthalimides[15] and also to the expanding repertoire of photoredox-catalysed decarboxylative couplings.[16]

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Additive	Yield [%][b]
1	**Ir-cat.**	200 mol % TFA	**90 (88)**[c]
2	*fac*-Ir(ppy)$_3$	200 mol % TFA	78
3	Ru(bpy)$_3$(PF$_6$)$_2$	200 mol % TFA	12
4[d]	Eosin Y	200 mol % TFA	10
5	none	200 mol % TFA	N.D.
6	**Ir-cat.**	none	< 5
7	**Ir-cat.**	10 mol % B(C$_6$F$_5$)$_3$	75
8	**Ir-cat.**	10 mol % In(OTf)$_3$	**82 (80)**[c]
9	**Ir-cat.**	10 mol % AlCl$_3$	74
10	**Ir-cat.**	10 mol % Zn(OTf)$_2$	57
11	**Ir-cat.**	10 mol % Sc(OTf)$_3$	55

[a] Reaction conditions: isoquinoline (0.2 mmol), redox active ester (0.3 mmol), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2 mol %), (TFA 200 mol %), DMA (2 mL), irradiated under 36 W blue LEDs at room temperature for 6 h under an argon atmosphere. [b] Yields based on GC analysis. [c] Yields based on isolation. [d] Using green LEDs instead of blue LEDs. DMA = *N*,*N*-dimethylacetamide.

We chose the reaction between isoquinoline and 2-(ethylhexanoyl)phthalimide as a model reaction (Table 1). After screening a variety of photoredox catalysts and acid additives, we found the optimized reaction conditions described in Table 1, entry 1. A Schlenk tube charged with isoquinoline (0.2 mmol), 2-(ethylhexanoyl)phthalimide (150 mol %),

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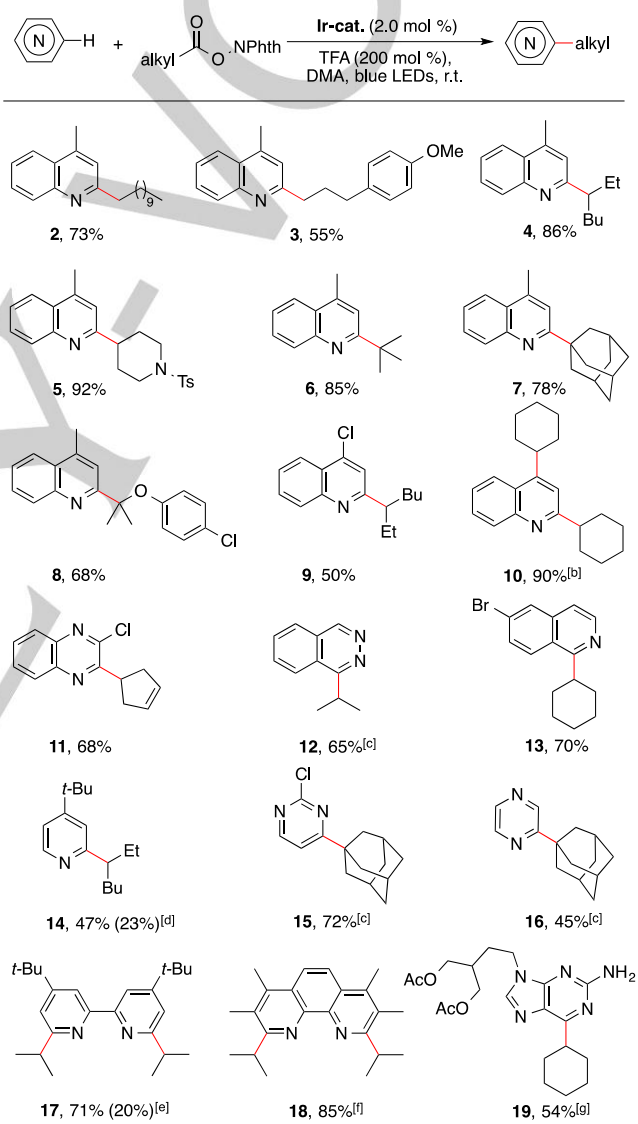
$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mol %), and trifluoroacetic acid (TFA, 200 mol %) in DMA solvent was exposed under irradiation at room temperature under argon. After irradiation for 6 h, the alkylated isoquinoline was isolated in 88% yield after column chromatography. Using *fac*-$Ir(ppy)_3$, a photoredox catalyst with shorter excited-state lifetime, gave the product in lower yield (entry 2). Other photoredox catalysts, such as $Ru(bpy)_3(PF_6)_2$ and Eosin Y, are inefficient as catalysts (entries 3, entry 4). A control experiment showed that a photoredox catalyst is essential for this reaction to proceed (entry 5). The reaction requires an acid additive, as the reaction does not proceed well in the absence of an acid additive (entry 6). We discovered during the optimization that a Lewis acid could be used as a co-catalyst instead of an excess amount of TFA to achieve comparable efficiency. We screened various Lewis acids as co-catalysts, and found that indium(III) triflate served as the best co-catalyst (entry 8). Other Lewis acids, such as $B(C_6F_5)_3$, $AlCl_3$, $Zn(OTf)_2$, and $Sc(OTf)_3$ are less effective. Using Lewis acid co-catalysts may offer an alternative method for substrates that are susceptible to a stoichiometric amount of strong Brønsted acid.

With the optimized reaction conditions in hand, we first investigated the reaction scope using TFA as the additive (Table 2). The reaction has a broad scope of amenable substrates. For *N*-heteroarenes, quinoline (**2**), quinoxaline (**11**), phthalazine (**12**), isoquinoline (**13**), pyridine (**14**), pyrimidine (**15**), pyrazine (**16**), bipyridine (**17**), phenanthroline (**18**), and purine (**19**) are all suitable substrates. A variety of *N*-(acyloxy)phthalimides synthesized from the corresponding aliphatic carboxylic acids can be used to introduce primary, secondary, and tertiary alkyl groups. The alkylation took place on the most electrophilic positions of the *N*-heteroarene in accord with the radical nucleophilic attack mechanism of the Minisci reaction.[17] Quinoline was dialkylated at the C2 and C4 positions when an excess amount of *N*-(acyloxy)phthalimide was used (**10**). The reaction using 4-(*tert*-butyl)-pyridine delivered a mixture of mono- and dialkylation products, in which monoalkylation gives the major product (**14**). For *N*-heteroarenes having two identical reaction sites, using an excess amount of *N*-heteroarenes led to selective monoalkylation (**12, 15, 16**). The reaction is useful for the modification of commercially available ligands such as bipyridine and phenanthroline, as demonstrated by the selective diisopropylation of 4,4'-di-*tert*-butyl-2,2'-bipyridine and 3,4,7,8-tetramethyl-1,10-phenanthroline in good yields (**17, 18**). The applicability of this reaction to functionalize complex drug molecules was demonstrated by the selective alkylation of the antiviral drug, famciclovir, at the C6 position of the purine ring (**19**).

We also studied the scope of the reaction using a Lewis acid as co-catalyst (Table 3). Using a Lewis acid as co-catalyst offers an alternative choice especially when the substrate is susceptible to an excess amount of strong Brønsted acid. The reaction using photoredox/Lewis acid co-catalysis[18] also shows good substrate scope. Besides the various amenable *N*-heteroarenes shown in Table 2, phenanthridine (**33**) and quinazoline (**34**) were also shown to be suitable substrates. Functional groups such as ether (**3, 26**), terminal and internal alkene (**21, 24**), aryl chloride (**9, 32**), alkyl bromide (**22**), tosylamide (**5**), ester (**19, 23**), free amine (**19**), aldehyde (**27**), Boc-protected α-amino acid ester (**28**), and sulfide (**29**) are all tolerated. Methylation is feasible, although the yield is low (**30**). Substrates possessing functional groups sensitive to strong oxidant and an excess amount of radicals, such as aldehyde, sulfide, and alkene are rarely demonstrated as successful examples in Minisci-type reactions using an excess amount of oxidant for radical generation.

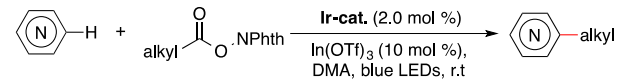
Table 2. Scope of photoredox-catalysed Brønsted acid promoted alkylation of *N*-heteroarenes.[a]

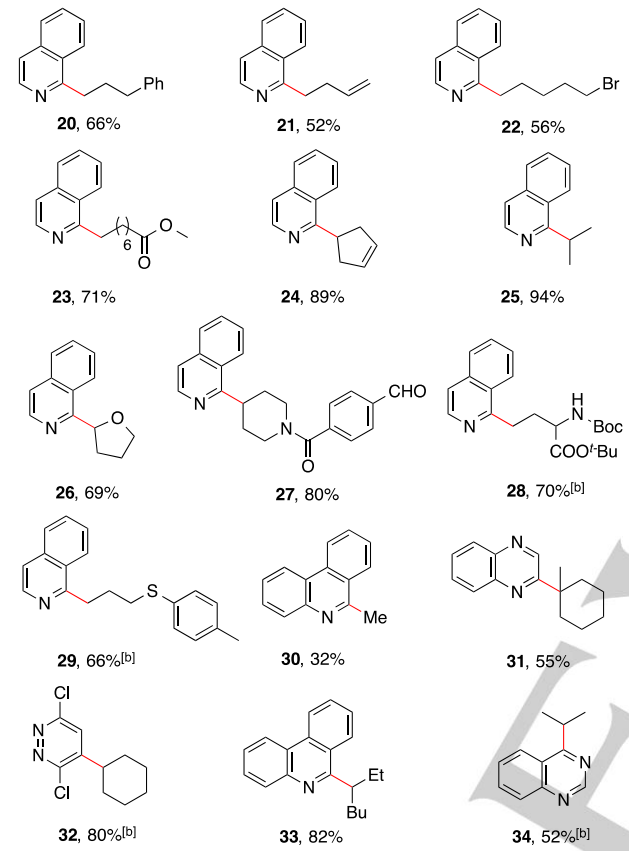


[a] Reaction conditions: heteroarene (0.2 mmol), *N*-(acyloxy)phthalimide (0.3 mmol), **Ir-cat.** (2 mol %), TFA (200 mol %), in DMA (2 mL), irradiation by 36 W blue LEDs for 6 h under Ar. [b] Quinoline (0.2 mmol), *N*-(acyloxy)phthalimide (0.4 mmol), **Ir-cat.** (3 mol %), TFA (200 mol %), in DMA (2 mL). [c] Heteroarene (0.4 mmol), redox active ester (0.2 mmol), **Ir-cat.** (2 mol %), TFA (300 mol %), in 2 mL DMA. Yields based on *N*-(acyloxy)phthalimide. [d] Yield of dialkylation product shown in parentheses. [e] Using 1.0 mmol redox active ester, **Ir-cat.** (3 mol %), TFA (400 mol %), 12 h, yield of monoalkylation product shown in parentheses. [f] Using 0.8 mmol redox active ester, **Ir-cat.** (3 mol %), TFA (400 mol %), 14 h. [g] 0.2 mmol redox active ester and 0.3 mmol

famciclovir.

Table 3. Scope of photoredox/Lewis acid co-catalysed alkylation of *N*-heteroarenes.[a]





[a] Reaction conditions: 0.2 mmol heteroarene, *N*-(acyloxy)phthalimide (0.3 mmol), **Ir-cat.** (2 mol %), In(OTf)$_3$ (10 mol %), in DMA (2 mL), irradiated by 36 W blue LEDs for 6 h under Ar. [b] 0.4 mmol heteroarene, 0.2 mmol *N*-(acyloxy)phthalimide. Yields based on *N*-(acyloxy)phthalimide.

Mechanistic studies were carried out to understand further this photoredox-catalysed C–H alkylation reaction. Although *N*-(acyloxy)phthalimide has been applied in photoredox catalysis, as for ruthenium-catalysed 1,4-addition[8,10b] and organophotoredox-catalysed protonation[11c] and halogenation,[11b] its application in iridium-photoredox catalysis[19] is relatively rare.[19c] From the reactivity and selectivity observed in the scope study, we believe the mechanism of this reaction involves the homolytic aromatic substitution of electron-deficient arene by an alkyl radical generated through radical decarboxylation (Figure 1, **B** to **D**). However, the photoredox cycle of the iridium catalyst to enable this reaction is yet to be clarified. By analysing the redox potentials of the photoredox catalysts and reactants, it is found that *N*-(acyloxy)phthalimide is thermodynamically unfavorable to oxidize Ir(III) to Ir(IV) (Figure 1, dashed pale arrow),[20] while it is reasonable for the oxidation of Ir(II) to Ir(III) [the redox potential of *N*-(acyloxy)phthalimide, $E_{1/2}$ = –1.26 to –1.37 V vs SCE, the redox potential of Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ $E_{1/2}^{*III/II}$ = +1.21 V vs SCE, $E_{1/2}^{III/II}$ = –1.37 V vs SCE; $E_{1/2}^{IV/*III}$ = –0.89 V vs SCE, $E_{1/2}^{IV/III}$ = +1.69 V vs SCE].[8,9b] Considering the low redox potential of the α-alkyl radical adjacent to the nitrogen atom, the excited triplet state *Ir(III) may facilely oxidize the radical cation (**D**) to deliver alkylated product (**E**). Thus, we propose an Ir(III)/Ir(II) redox cycle, in which Ir(II) reduces *N*-(acyloxy)phthalimide to deliver an alkyl radical, followed by oxidation/rearomatization of the radical cation (**D**) by *Ir(III) to regenerate Ir(II), completing the catalytic cycle (Figure 1, black arrow). It is worth to mention that in this mechanism Ir(II) is the active catalyst initiating this photoredox catalytic cycle while Ir(III) was used as pre-catalyst. We rationalize this by some off-cycle processes to reduce *Ir (III) to Ir(II), such as oxidation of solvent (*N*,*N*-dimethylacetamide) or carboxylate anion[13a] generated via decomposition of *N*-(acyloxy)phthalimides. Since radical chain process as well as photosensitizer mediated energy transfer process also accompany in photoredox catalysis. [21,22,23] We also considered the possibility of a photoredox-initiated radical chain mechanism that *N*-(acyloxy)phthalimide (**A**) oxidizes radical cation (**D**) through single-electron transfer as the propagation step.[10a,10b] Although a "light/dark" experiment showed that the product only formed under continuous irradiation (See the Supplementary Information), measurement of quantum yield revealed a value of Φ = 8.8. In addition, the desired product of the model reaction in Table 1 was detected in 19% yield under UV irradiation in the absence of the photoredox catalyst. The results of these experiments suggest that radical chain propagation, probably initiated by photoredox catalyst, is concomitant (Figure 1, pale arrow).

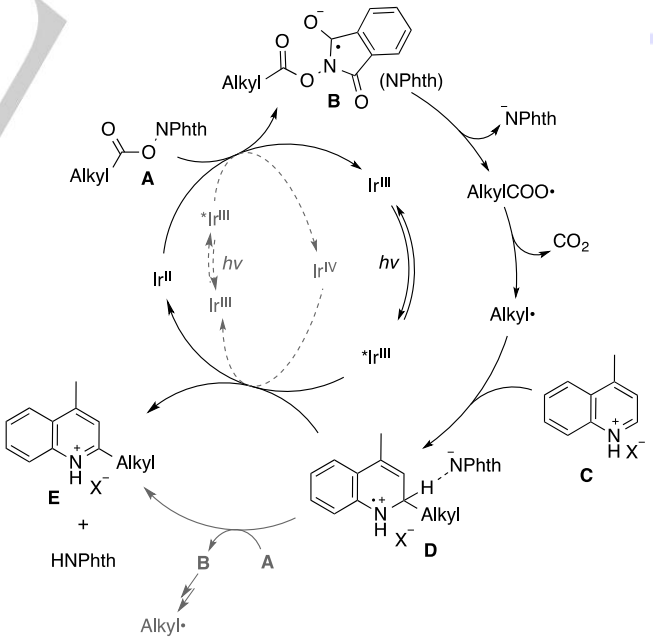


Figure 1. Mechanistic discussion.

In conclusion, we describe herein a photoredox-catalysed redox-neutral Minisci-type alkylation using *N*-(acyloxy)phthalimides as alkylation reagents under mild

irradiation conditions. We also discovered that besides the stoichiometric amount of Brønsted acid as an additive, a catalytic amount of Lewis acid could also be applied as a co-catalyst to achieve comparable efficiency in this reaction. Various primary, secondary, and tertiary alkyl groups can be smoothly introduced to a broad range of *N*-heteroaromatic compounds. The iridium-photoredox catalyst enables controllable radical generation from *N*-(acyloxy)phthalimide without the need of a stoichiometric amount of oxidant, thus rendering a broad scope that includes alkyl carboxylate possessing a functional group incompatible in the traditional Minisci reaction. Analysis of the redox potentials of reactants and catalyst suggests the reaction proceeds through an Ir(III)/Ir(II) mechanism rather than an Ir(IV)/Ir(III) cycle.

Experimental Section

General Procedure for alkylation of *N*-Heteroarenes with trifluoroacetic acid: *N*-heteroarene (1.0 equiv., 0.2 mmol) (if solid), redox active ester (1.5 equiv., 0.3 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.0 mol %, 4.4 mg) were placed in a transparent Schlenk tube equipped with a stirring bar. The tube was evacuated and filled with argon (three times). To these solids, *N*-heteroarene (1.0 equiv., 0.2 mmol) (if liquid), anhydrous N,N-dimethylacetamide (DMA, 2.0 mL) and trifluoroacetic acid (TFA) (2.0 equiv. 0.4 mmol) was added via a gastight syringe under argon atmosphere. The reaction mixture was stirred under the irradiation of a 36 W Blue LEDs (distance app. 3.0 cm from the bulb) at room temperature for 6 h. After 6 h, the mixture was quenched with 0.1 mL triethylamine and 10 mL water, then extracted with ethyl acetate (3 x 10 mL). The organic layers were combined and concentrated under vacuo. The product was purified by flash column chromatography on silica gel (ethyl acetate : petroleum ether=20:1~5:1).

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Keywords: alkylation • decarboxylation • *N*-(acyloxy)phthalimides • *N*-heteroarenes • photocatalysis

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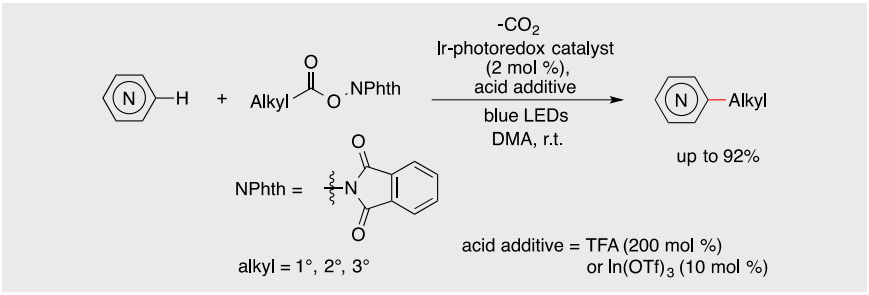

Enabled by merging an iridium-photoredox catalyst with a stoichiometric amount of Brønsted acid or a catalytic amount of Lewis acid, decarboxylative alkylation of *N*-heteroarenes with *N*-(acyloxy)phthalimides was achieved under mild conditions. Mechanistic studies suggest an Ir(II)/Ir(III) redox catalytic cycle is responsible for the observed reactivity.

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