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Ligand-Accelerated Iron Photocatalysis Enabling Decarboxylative Alkylation of Heteroarenes

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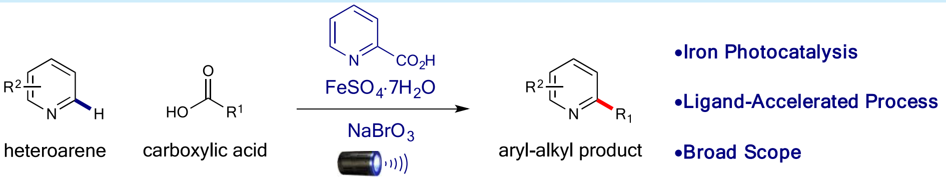
Supporting Information



ABSTRACT: A mild, practical protocol for the decarboxylative alkylation of heteroarenes has been accomplished via iron photocatalysis. A diverse range of carboxylic acids readily undergo oxidative decarboxylation and then couple with a broad array of heteroarenes in this transformation. The photoexcited state lifetimes of iron complexes are typically much shorter than those of iridium and ruthenium complexes. Here we describe our effort on iron photocatalysis by utilizing the intramolecular charge transfer pathway of iron−carboxylate complexes.

Iron is the second most abundant metal on Earth only after aluminum. Iron complexes were the most frequently investigated compounds in the area of photochemistry and photophysics of inorganic compounds prior to the 1970s.[1] However, the attention of photochemists was shifted to the redox-active, luminescent Ru(II) and Ir(III) polypyridyl complexes with long-lived excited states,[2] which provided ample opportunity for photoredox catalysis to activate organic substrates via an intermolecular single-electron transfer pathway.[3] From the green chemistry points of view, there is a long-standing interest in replacing the precious metals in photoactive coordination complexes by more earth-abundant elements.[4] However, the photoexcitable charge-transfer states of most iron complexes are limited by picosecond or subpicosecond deactivation through low-lying metal-centered states, resulting in inefficient electron-transfer reactivity and complete lack of photoluminescence. Recent efforts to increase the excited state lifetimes of iron complexes have focused on increasing the ligand field strength and hence raising the energies of the metal-centered states by the use of strong donor ligands such as *N*-heterocyclic carbenes. Very recently, Wärnmark and co-workers reported an Fe(III) complex with a relatively long-lived (2 ns) doublet ligand-to-metal charge-transfer (^{2}LMCT) state.[5] Together with advances from other groups,[6] it makes iron photoredox catalysis promising. On the other hand, increasing the excited state lifetimes is not the only approach to achieving useful photoreactivity of iron complexes. Chemists are exploring the potential of intramolecular charge-transfer mode by coordination of organic substrates directly to iron, wherein long-lived excited states of iron complexes are not necessarily essential (Figure 1A). The photoinduced reduction of ferrioxalate was first reported by Parker in 1953.[7] The ferrioxalate complex is used widely as an actinometer in quantum yield determinations as a result of its high absorbance and reaction quantum yield. However, the photoreactivity of the Fe(III) carboxylate complexes finds rare application in synthetic organic chemistry so far. We sought to take advantage of this reactivity and use the resulting alkyl

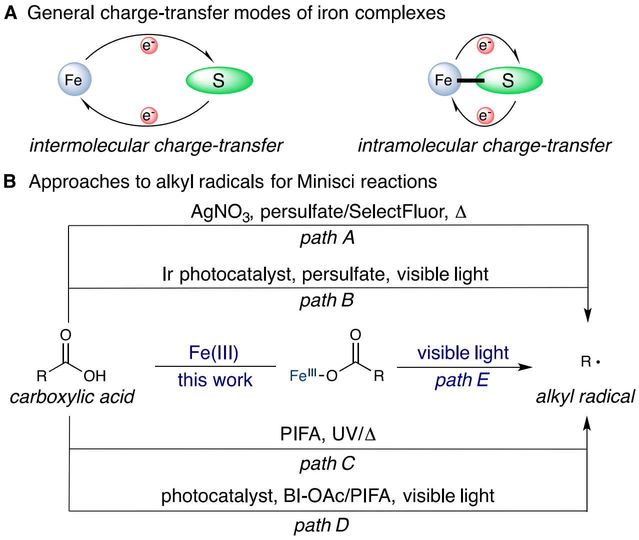


Figure 1. Photochemistry of iron complexes.

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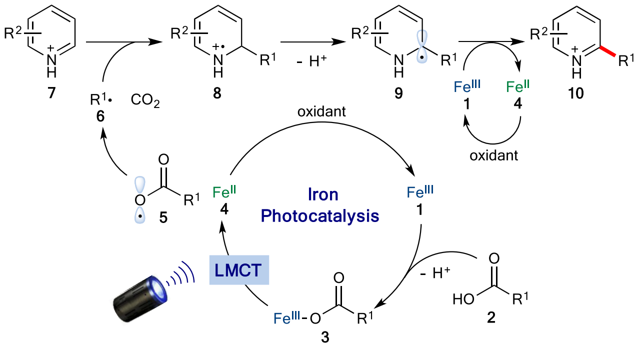
radicals from the oxidative decarboxylation to fulfill alkylation reactions.

In the medicinal chemistry community, there is a growing demand for the direct introduction of alkyl groups to heteroarenes, given their influence on drug metabolism and pharmacokinetic profiles.[8] The open-shell addition of alkyl radical intermediates to heteroarenes, known as the Minisci reaction, has become a mainstay transformation with broad application within modern drug discovery.[9] In few cases, the alkyl radicals are derived from alkanes by a hydrogen atom transfer mechanism,[10] while most of the current methods depend on the use of prefunctionalized reagents as alkyl radical precursors, such as carboxylic acids and derivatives,[11] boronic acids and derivatives,[12] sulfinates,[13] peroxides,[14] alcohols,[15] halides,[16] olefins,[17] 1,4-dihydropyridines,[18] pyridiniums,[19] and sulfones.[20] Radical decarboxylative strategy is appealing since carboxylic acids are inexpensive, stable, and the second largest group of commercially available organic building blocks only after amines (Figure 1B).[21] Minisci and co-workers reported a silver-catalyzed decarboxylative alkylation protocol with the oxidant persulfate under heat conditions,[11a] followed by a modification with Selectfluor as the oxidant recently.[11e] An iridium photoredox catalyst−persulfate system at room temperature was successfully developed more recently.[11h] Hypervalent iodine compounds also witnessed intensive research studies in decarboxylative alkylation since the early report using bis(trifluoroacetoxy)iodobenzene (PIFA) under UV or heat conditions.[11b] Photoredox catalytic methods with acetoxybenziodoxole (BI-OAc) and PIFA made the decarboxylation events happen smoothly by irradiation of visible light.[11i,j] Compared to precious silver and iridium (photo)-catalysts, iron is earth-abundant and nontoxic. Early in 1986, Sugimori reported a light-induced decarboxylative alkylation of heteroarenes using stoichiometric $Fe_2(SO_4)_3$.[22] As our first step toward photochemistry of iron complexes, we developed a catalytic protocol for decarboxylative alkylation of heteroarenes via iron photocatalysis. Notably, the iron catalytic cycle was achieved by the identification of picolinic acid as the ligand, which would lead to further development for iron photocatalysis through ligand modulation. Moreover, in previous methods the expensive organic oxidants (Selectfluor and hypervalent iodine reagents) were typically used, so we sought to find alternative inorganic oxidants with low prices.

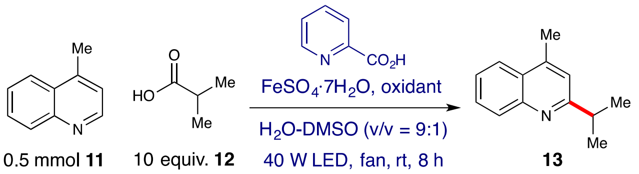
A detailed description of our proposed mechanism for the decarboxylative alkylation is illustrated in Scheme 1. We postulated that coordination of the carboxylic acid **2** to Fe(III) **1** followed by deprotonation would readily form the Fe(III)−carboxylate complex **3**. Photoexcitation of the iron complex **3** should render an intramolecular ligand-to-metal charge-transfer event to generate the reduced Fe(II) **4** and a carboxyl radical **5**, which after CO_2 extrusion would produce the desired alkyl radical **6**. The nucleophilic alkyl radical **6** would then add to the protonated electron-deficient heteroarenes **7** in a Minisci-type pathway to afford the aminyl radical cation **8**. The resulting α-C−H bond of **8** is sufficiently acidic to undergo deprotonation to form the α-amino radical **9**, which could be oxidized by Fe(III) to furnish the desired alkylation product **10**. The terminal oxidant would serve to bring Fe(II) back to Fe(III) to close the catalytic cycles.

Scheme 1. Proposed Mechanism for the Decarboxylative Alkylation of Heteroarenes



We began our investigation into this decarboxylative alkylation of heteroarenes by exposing the water−DMSO solution of lepidine and isobutyric acid to visible light (Kessil 40 W 456 nm LED) in the presence of iron salt for 8 h (Table 1). With 1 equiv of $Fe_2(SO_4)_3$, it afforded the desired aryl-alkyl product **11** in 40% yield (entry 1), while the combination of 5 mol % Fe(III) or Fe(II) with 2 equiv of $NaBrO_3$ gave no desired product (entries 2 and 3). To our delight, a dramatic

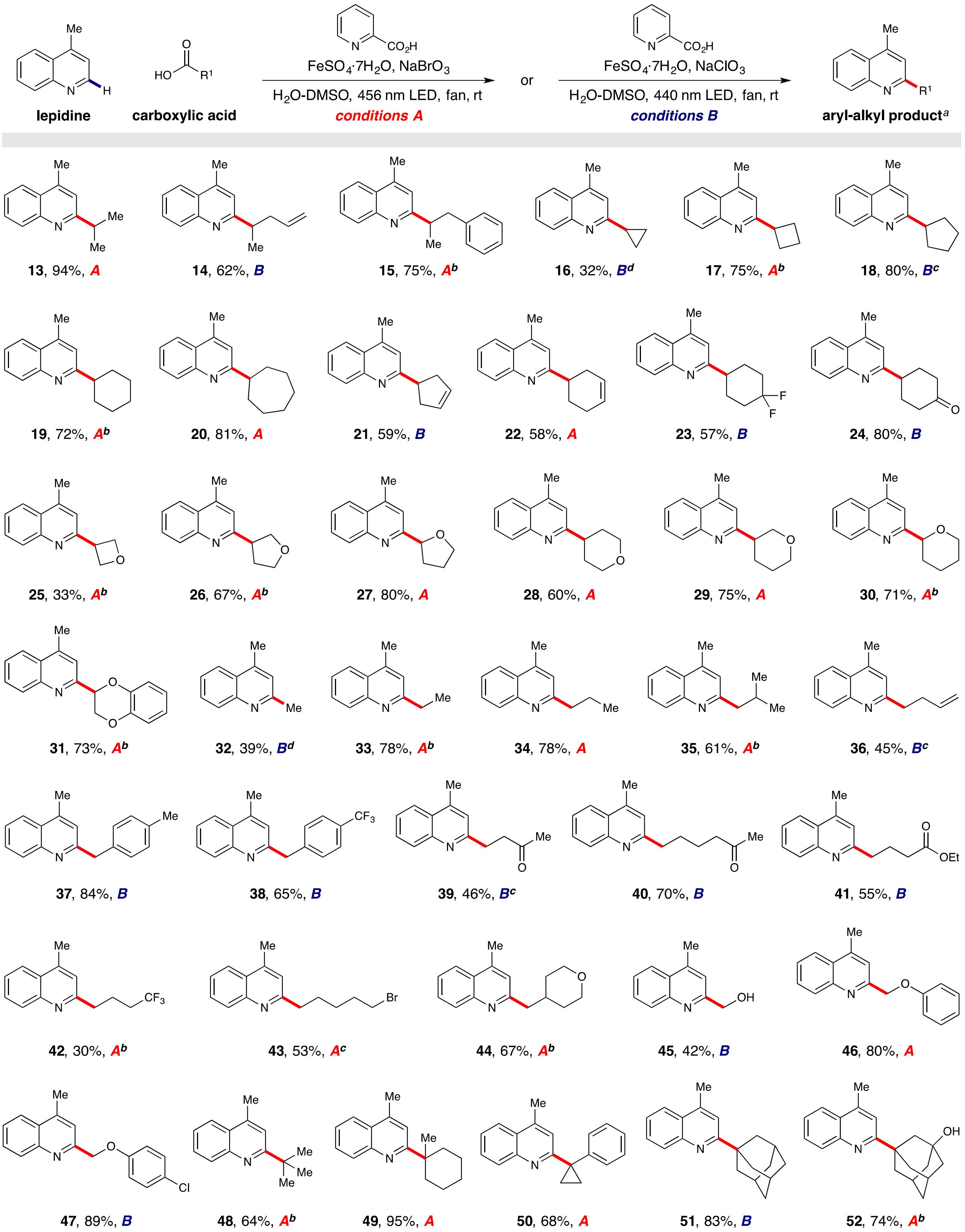
Table 1. Optimization of the Reaction Conditions[a]



entry	iron(II)	picolinic acid	oxidant	wavelength	yield [%]
1[b]	-	-	-	456 nm	40
2[c]	-	-	2 equiv $NaBrO_3$	456 nm	0
3	5 mol %	-	2 equiv $NaBrO_3$	456 nm	0
4	5 mol %	5 mol %	2 equiv $NaBrO_3$	456 nm	60
5	5 mol %	10 mol %	2 equiv $NaBrO_3$	456 nm	94
6	5 mol %	15 mol %	2 equiv $NaBrO_3$	456 nm	85
7	5 mol %	10 mol %	2 equiv $NaBrO_3$	440 nm	85
8	5 mol %	10 mol %	2 equiv $NaBrO_3$	427 nm	83
9	5 mol %	10 mol %	2 equiv $NaBrO_3$	390 nm	49
10	5 mol %	10 mol %	2 equiv $NaClO_3$	456 nm	39
11	10 mol %	20 mol %	3 equiv $NaClO_3$	440 nm	90
12	10 mol %	20 mol %	3 equiv $NaIO_4$	440 nm	80
13	10 mol %	20 mol %	3 equiv KIO_3	440 nm	86
14	-	10 mol %	2 equiv $NaBrO_3$	456 nm	0
15	-	-	-	dark	0
16	5 mol %	10 mol %	2 equiv $NaBrO_3$	dark	0
17	5 mol %	10 mol %	2 equiv $NaBrO_3$	dark, 80 °C	0

[a] Yields determined by ^1H NMR using 1,3-benzodioxole as the internal standard after workup following the general procedure in Supporting Information. [b] 1 equiv of $Fe_2(SO_4)_3$ used. [c] 2.5 mol % of $Fe_2(SO_4)_3$ used. LED = light-emitting diode.

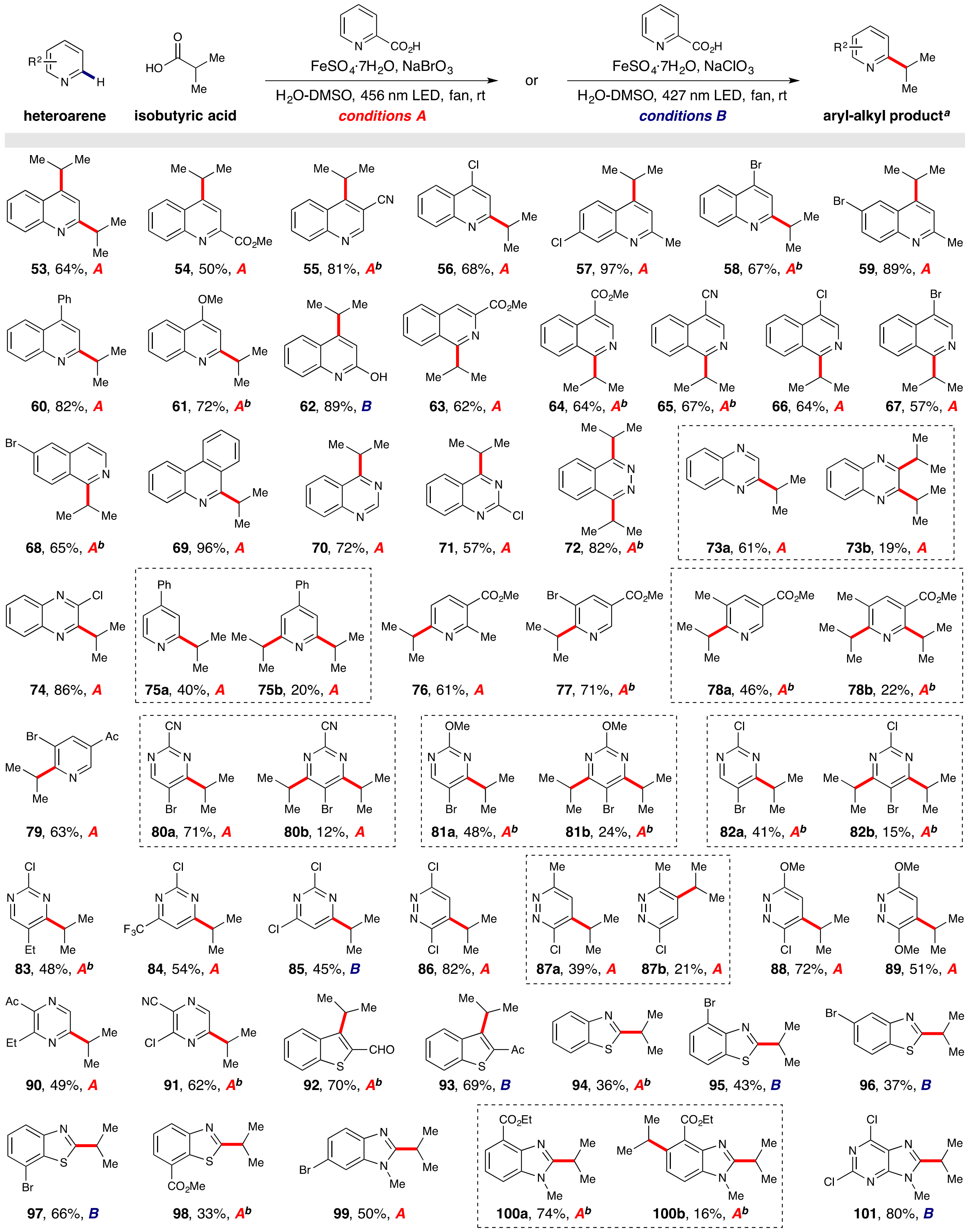
Scheme 2. Scope of the Carboxylic Acids[a]



[a] Isolated yields. See Supporting Information for experimental details. [b] 440 nm LED used. [c] 427 nm LED used. [d] 390 nm LED used.

ligand acceleration effect was observed. The alkylation product **11** could be obtained in 60% yield when picolinic acid was added into the reaction at 1:1 ratio of iron to ligand (entry 4). The yield could reach up to 94% with 2 folds of the ligand (entry 5). Further increase of the amount of picolinic acid led to a slight yield drop (entry 6). A downward trend of the yield

Scheme 3. Scope of the Heteroarenes[a]



[a]Isolated yields. See Supporting Information for experimental details. [b]440 nm LED used.

was noticed as the wavelength of light was changed from 456 to 440, 427, and 390 nm, mainly due to the product decomposition under higher-energy conditions (entries 7−9).

Then we tried out most of the common inorganic oxidants which are metal-free, including but not limited to halogen-containing oxidants, persulfate, hydrogen peroxide, and oxygen. It turned out that sodium chlorate was a compatible oxidant for the reaction, which provided the product **11** up to 90% yield with the irradiation of 440 nm light (entries 10 and 11). Furthermore, periodate and iodate also performed well as the terminal oxidant in the transformation (entries 12 and 13). We speculate that these oxidants have suitable oxidizing ability to turn over the iron catalyst while not being detrimental to the radical process. Indeed, the critical roles of the iron salt and light in the protocol were demonstrated through control experiments. There was no desired product **11** formed in the absence of either iron salt or light, even heated to 80 °C (entries 14−17).

With the optimal conditions in hand, we sought to evaluate the generality of this decarboxylative alkylation protocol. As highlighted in Scheme 2, a wide range of carboxylic acids can serve as alkylating agents in this reaction under the identified conditions A (with $NaBrO_3$ and 456 nm LED) and B (with $NaClO_3$ and 440 nm LED). It is of note that primary, secondary, and tertiary alkyl carboxylic acids are all amenable substrates for the alkylation reaction, with no obvious bias. A variety of functional groups attached to the alkyl radical precursors were well tolerated, including alkenes (**14**, **21**, **22**, and **36**), halides (**23**, **38**, **42**, **43**, and **47**), ketones (**24**, **39**, and **40**), esters (**41**), ethers (**25**−**31**, **44**, **46**, and **47**), and alcohols (**45** and **52**). Cyclic alkyl radicals with different sizes underwent the addition to the heteroarene smoothly (**16**−**31**, **49**−**31**). Moreover, acetic acid was successfully used to deliver the magic methyl group into the product **32**, as well as a number of α-oxy acids for the incorporation of oxyalkyl groups (**27**, **30**, and **45**−**47**).

Next, we explored the scope of the alkylation reaction with respect to the heteroarene component (Scheme 3). A broad array of heteroarenes were coupled oxidatively with isobutyric acid in good to excellent yield under the identified conditions A (with $NaBrO_3$ and 456 nm LED) and B (with $NaClO_3$ and 427 nm LED). Quinolines with electron-withdrawing or -donating substituents (such as ester, cyanide, halides, phenyl, methoxy, hydroxyl groups) were alkylated effectively (**53**−**62**, 50−97% yield). Isoquinolines performed well, including those with nonparticipating functionality (such as ester, cyanide, and halides) (8% yield). Isoquinolines performed well, including those with nonparticipating functionality (such as ester, cyanide, and halides) (**63**−**68**, 57−67% yield), in addition to phenanthridines, quinazolines, phthalazines, and quinoxalines (**69**−**74**, 57−96% yield). Moreover, various pyridine derivatives containing diverse functionality could be converted into the desired aryl-alkyl products in good yield (**75**−**79**, 60−71% yield). It is important to note that pyrimidines are competent substrates for the alkylation protocol, including those with halide substituents (**80**−**85**, 45−83% yield). Substituted pyridazines and pyrazines afforded the alkylated products in useful yield (**86**−**91**, 49−82% yield). We were pleased to find that a variety of 5-membered heteroarenes could participate in the protocol. Benzothiophenes with electron-withdrawing groups at the C2 position reacted at the C3 position regioselectively (**92** and **93**, 70 and 69% yield). Gratifying, benzothiazoles underwent the alkylation predominantly at the C2 position (**94**−**98**, 33−66% yield), as did benzoimidazoles (**99** and **100**, 50 and 90% yield). It is worth mentioning that the decarboxylative alkylation could be extended to the purine derivative (**101**, 80% yield).

Preliminary mechanistic studies have been conducted (see Supporting Information) to support the proposed pathway outlined in Scheme 1. The decarboxylative alkylation is completely shut down by the addition of free radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), indicating a radical mechanism (Figure S1A). The light/dark experiments using alternating intervals of light and dark demonstrate that the constant irradiation of visible light is necessary to drive the alkylation to completion (Figure S1B). The UV−vis spectra show that the iron salt or ligand separately has minimal optical absorption in the visible range. However, the 1:1 solution of iron and ligand exhibits a significantly enhanced absorption of visible light, which is even stronger for the 1:2 solution (Figure S1C). Based on the results, we speculate that the ligand coordination makes Fe(II) more prone to be oxidized after light absorption. Further exploration into the mechanism is being conducted in our lab.

In summary, we have developed a mild and practical protocol for the decarboxylative alkylation of heteroarenes via iron photocatalysis. This new method shows broad scopes with regard to both the carboxylic acids and heteroarene substrates bearing a variety of functional groups. Remarkably, the reaction represents a successful extension of iron photochemistry into synthetic organic chemistry. Although the photoexcited state lifetimes of iron complexes are typically much shorter than those of iridium and ruthenium complexes, they have a huge potential to design diverse transformations via the intramolecular charge transfer pathway of iron−substrate complexes. As such, we anticipate this iron photocatalytic decarboxylation strategy will find more application in both academic and pharmaceutical sciences.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01439.

General experimental procedures, mechanistic studies, reaction setup, characterization data, and spectra for all key compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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