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Decarboxylative C−H Alkylation of Heteroarene *N*-Oxides by Visible Light/Copper Catalysis

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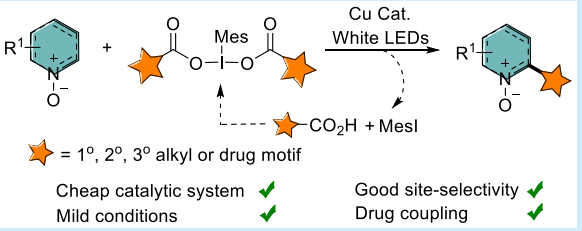
ABSTRACT: This paper reports a highly site-selective alkylation of heteroarene *N*-oxides using hypervalent iodine(III) carboxylates to serve as an alkylating agent in the presence of a cheap copper catalyst under visible light conditions. This mild method proceeds at room temperature in an air atmosphere and can withstand various heteroarene *N*-oxides as well as various primary, secondary, and tertiary alkyl carboxylic acids. It also provides a practical method for enabling the rapid conversion of commercially available raw materials into medically relevant "drug-like" molecules.



Heteroarene *N*-oxides has become privileged pharmacophores in medicinal chemistry,[1] important substrates and intermediates in synthetic chemistry,[2] and useful oxidants in some reactions[3] due to their unique electronic arrangement. In addition, reduction of heteroarene *N*-oxides can afford *N*-heterocycles, both of which are important frameworks in drugs (Figure 1), especially those with heteroaryl aliphatic

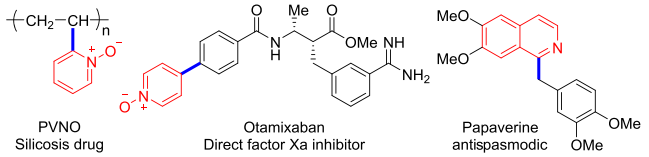


Figure 1. Heteroaryl aliphatic functionality in commercial medicinal agents.

functionality. As a result, for the alkylation of *N*-heterocycles[4] among these reported methods, the use of cheap, abundant carboxylic acids as the starting materials was very attractive for the C−H bond alkylation reaction. Decarboxylative coupling of heterocycles using classical Minisci reactions has been reported by the Minisci group[5] and others[6] (Figure 2a). However, the reaction with unoxidized *N*-heterocycles is difficult to control site-selectively, giving byproducts with multiple-site couplings. Wherefore, seeking a new alternative so that such a reaction produces only a single product has been especially important, and heteroarene *N*-oxides have been demonstrated to be efficient substrates (Figure 2b). In the past reports, several methods for the synthesis of single-site alkylated pyridine *N*-oxide included metal catalysis or photocatalysis.[7] However, harsh catalytic conditions and the use of highly toxic, unstable, difficult-to-obtain alkylating reagents limit the applications of these reactions. Wishing to develop a more attractive synthesis to realize highly site-selective C−H

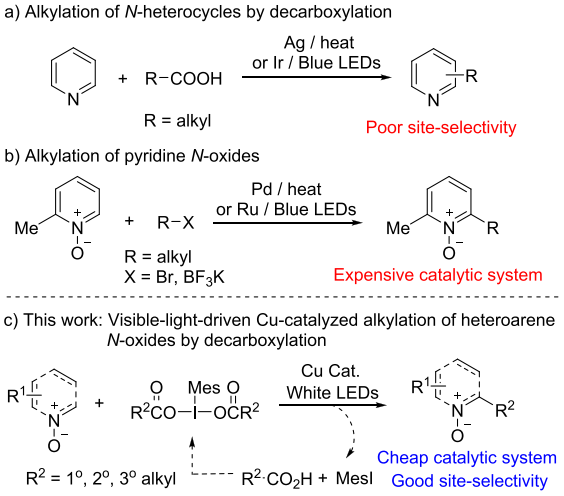


Figure 2. Strategy for the alkylation of heteroaromatics.

alkylation of *N*-heterocycles and their *N*-oxides using abundant and inexpensive alkylating agents for the acquisition of high-value drugs, we were very interested in using hypervalent iodine(III) carboxylates as alkylating agents. This hypervalent iodine(III) carboxylate was easily prepared from carboxylic acid and had been developed into effective reagents for decarboxylative coupling under visible light photocatalysis or transition metal catalysis due to its strong electrophilicity, low

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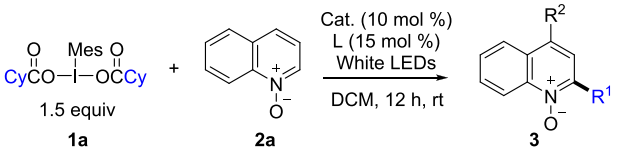
toxicity, and oxidizing activity.[8] Furthermore, the byproducts of carboxylic acid and iodobenzene can be recycled after the decarboxylation coupling.[9] Here, we achieved the *ortho* alkylation of heteroarene *N*-oxides by employing hypervalent iodine(III) carboxylates under copper photocatalysis (Figure 2c). Although the system using a copper complex as a photocatalyst under visible light is still in its infancy, the copper complex has great potential in photocatalysis because it is cheap and abundant on the Earth. Compared to ruthenium or iridium photocatalysts, copper photocatalysts not only have economic advantages but also play a unique role in promoting the transfer of electrons to organic substrates.[10] In this work, we report a highly site-selective C−H functionalization using a copper complex in addition as a photocatalyst.

To optimize this reaction, we chose hypervalent iodine(III) cyclohexanoate **1a** and quinoline *N*-oxide **2a** as the model substrates. At the beginning of the study, we used metal-free photocatalyst $(Acr\text{-}Mes)^+ClO_4^-$ or Eosin Y (Table 1, entry 1 or 2, respectively), and the product 2-cyclohexylquinoline 1-oxide **3a** can be obtained in a yield of 41% or 30%, respectively. At the same time, two byproducts, **3a′** and **3a″**, were detected by GC-MS (entry 3). Then we examined copper salts under the same conditions, and the results showed that divalent copper $CuBr_2$ provided only a trace of the product (entry 4); in contrast, product **3a** can be obtained in a yield of 45% by using monovalent copper CuBr (entry 5). When CuBr was replaced by CuCl, the yield of **3a** increased to 55% (entry 6). For CuI, no desired product was generated (entry 7). As the catalytic amount of CuCl was increased to 20% and that of the ligand BPhen was changed to 30%, the yield of **3a** was directly increased to 77% (entry 8). Finally, other 1,10-phenanthroline ligands, such as 1,10-phenanthroline **L2**, 4,7-dimethoxy-1,10-phenanthroline **L3**, and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline **L4**, were also explored for this transformation, but no further increase in the yield of **3a** was achieved (entries 9−11, respectively). Control experiments in the absence of ligand or visible light were also conducted, and no coupling product could be obtained (entry 12 or 13, respectively). It is noteworthy that this reaction requires only 16 W white light instead of blue light that may irritate eyes and can also react in the air.

Table 1. Optimization of the Reaction Conditions[a]

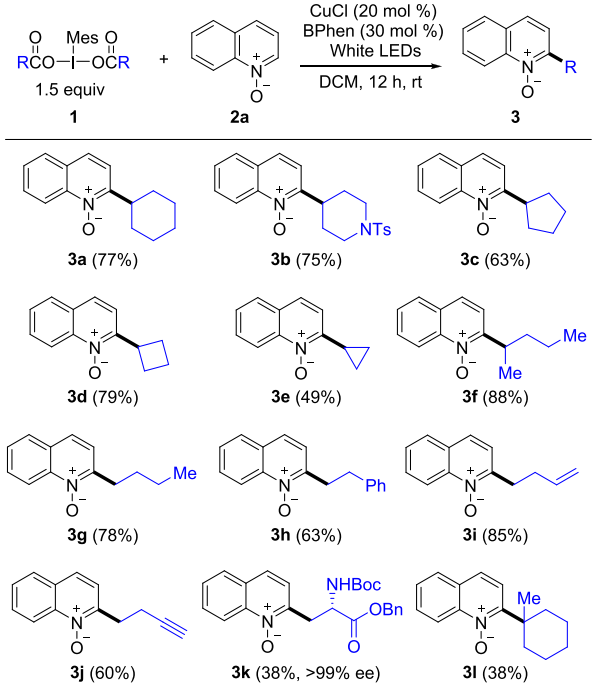


entry	catalyst (equiv)	ligand (equiv)	yield (%) 3a[b]	3a′[c]	3a″[c]
1	$(Acr\text{-}Mes)^+ClO_4^-$ (0.1)	–	41	12	5
2	Eosin Y (0.1)	–	30	6	trace
3	$Cu(OAc)_2$ (0.1)	**L1** (0.15)	40	0	0
4	$CuBr_2$ (0.1)	**L1** (0.15)	trace	0	0
5	CuBr (0.1)	**L1** (0.15)	45	0	0
6	CuCl (0.1)	**L1** (0.15)	55	0	0
7	CuI (0.1)	**L1** (0.15)	0	0	0
8	CuCl (0.2)	**L1** (0.3)	77 (81)[d]	0	0
9	CuCl (0.2)	**L2** (0.3)	45	0	0
10	CuCl (0.2)	**L3** (0.3)	40	0	0
11	CuCl (0.2)	**L4** (0.3)	64	0	0
12	CuCl (0.2)	–	trace	0	0
13[e]	CuCl (0.2)	**L1** (0.3)	0	0	0

[a]Reaction conditions: hypervalent iodine(III) cyclohexanoate **1a** (0.3 mmol, 1.5 equiv), quinoline *N*-oxide **2a** (0.2 mmol), catalyst, ligand in DCM (2.0 mL) under white light-emitting diodes for 12 h at rt. [b]Isolated yields. [c]GC yields. [d]N_2 atmosphere. [e]No light.

After optimizing the reaction conditions for our decarboxylative C−H alkylation of heteroarene *N*-oxides, we next expanded the scope of the hypervalent iodine(III) carboxylates. As shown in Scheme 1, a variety of primary, secondary, and tertiary alkyl decarboxylative couplings with quinoline *N*-oxide **2a** were successful. Hypervalent iodine(III) **1a−c** with the decarboxylative centers in six- and five-membered rings can furnish the desired products **3a−c** in good yields of 77%, 75%, and 63%, respectively. Even with more strained cyclobutyl and cyclopropyl hypervalent iodine(III) carboxylates **1d** and **1e**, the coupling products **3d** and **3e**, respectively, could be obtained in good to moderate yields. Furthermore, general secondary alkyl hypervalent iodine(III) carboxylate **1f** gave target product **3f** in excellent yield. The primary alkyl hypervalent iodine(III) carboxylates **1g−j** were also found to be suitable for the reaction, affording the corresponding products **3g−j**, respectively, in good to excellent yields, and these mild reaction conditions displayed good compatibility with sensitive groups, such as amino, alkenyl, and alkynyl groups. Interestingly, this transformation can also provide an enantiopure amino acid derivative **3k** by employing aspartic

Scheme 1. Scope of Hypervalent Iodine(III) Carboxylates[a]



[a]The reactions were carried out using **2a** (0.2 mmol, 1.0 equiv), **1** (0.3 mmol, 1.5 equiv), CuCl (0.2 equiv), BPhen (0.3 equiv), and DCM (2.0 mL) under white light-emitting diodes for 12 h at rt. Isolated yields based on quinoline *N*-oxides **2a**.

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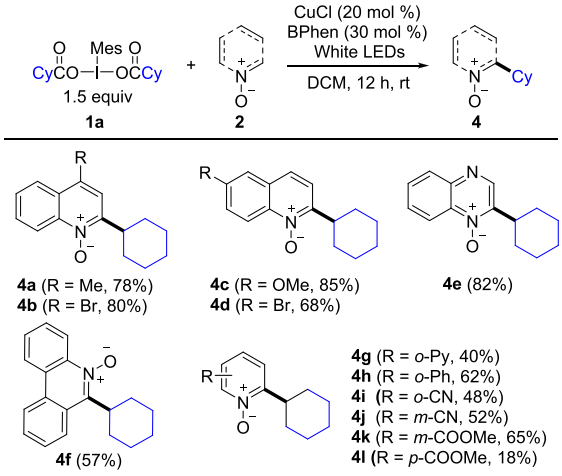
acid-derived hypervalent iodine(III) **1k** as the starting material. Finally, the sterically hindered tertiary alkyl hypervalent iodine(III) carboxylate **1l** can be transformed into the decarboxylative coupling product **3l** in a yield of 38%.

Next, the scope of heteroarene *N*-oxides was explored by using the hypervalent iodine(III) carboxylate **1a** as the model substrate under the standard conditions (Scheme 2). A

Scheme 2. Scope of Heteroarene *N*-Oxides[a]



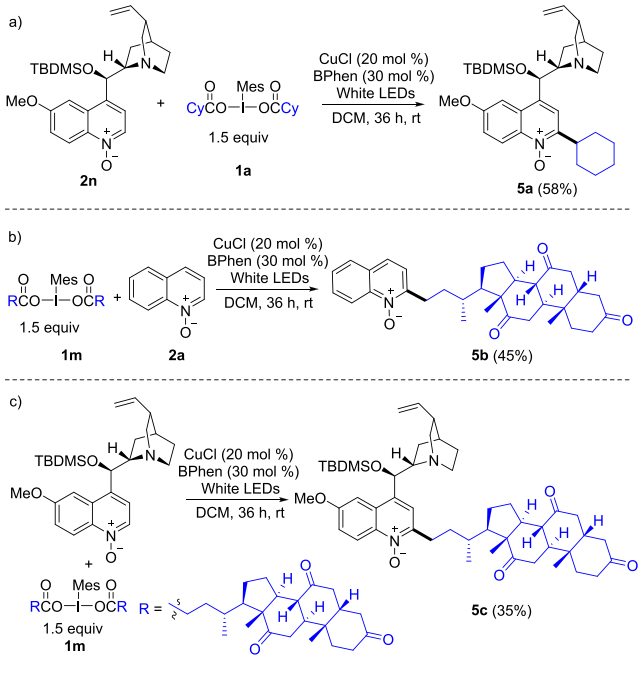
[a]The reactions were carried out using **1a** (0.3 mmol, 1.5 equiv), **2** (0.2 mmol, 1.0 equiv), CuCl (0.2 equiv), BPhen (0.3 equiv), and DCM (2.0 mL). Isolated yields based on heteroarene *N*-oxides.

diversity of quinoline *N*-oxides were proven to be suitable for this transformation, affording the corresponding products **4a**−**d** in good to excellent yields. To our delight, many other heteroarene *N*-oxides, such as quinoxaline *N*-oxide **2e**, phenanthridine *N*-oxide **2f**, and bipyridine *N*-oxide **2g**, reacted well and gave good yields. Furthermore, we observed that pyridine *N*-oxides with a phenyl or cyano group at position C-2 or C-3 were also appropriate substrates, affording the desired products **4h**−**k** in moderate to good yields. When pyridine *N*-oxide with an ester group at position C-4 was used for this reaction, alkylation product **4l** was obtained in a yield of 18%.

To further explore the practicality of this method for synthesizing complex molecules and modifying drug molecules, we conducted the following experiments (Scheme 3). First, we used hydroxy-protected quinine *N*-oxide **2n** to investigate the ability of this method to alkylate *N*-heteroarene drugs. When hypervalent iodine(III) cyclohexanoate **1a** was used as the alkylation reagent, a 58% yield of coupling product **5a** could be obtained and the sensitive group was not affected (Scheme 3a). Next, we tried to make the hypervalent iodine(III) containing drug molecule **1m** through decarboxylation as an alkylating reagent by this strategy. Luckily, we successfully decarboxylated dehydrocholic acid and coupled it with quinoline *N*-oxide **2a** to give the desired product **5b** in 45% yield (Scheme 3b). Finally, a more complicated system with multiple active centers was attempted by the decarboxylation of a drug containing carboxylic acid and coupling with *N*-heteroarene drugs. Gratifyingly, decarboxylation of dehydrocholic acid and coupling with hydroxy-protected quinine *N*-oxide provided the target product **5c** in a yield of 35% (Scheme 3c).

On the basis of relevant reports,[11,12] including photocatalysis by a copper complex with a bidentate nitrogen ligand[12a,f] and our experimental results (Table 1, entries 8, 12, and 13), a

Scheme 3. Diversification of *N*-Heteroarene Drugs



plausible mechanism for copper/photocatalytic decarboxylation coupling is proposed as presented in Figure 3. First, under

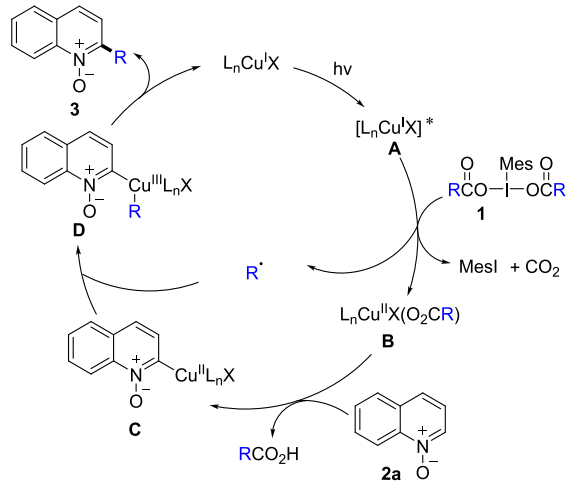


Figure 3. Proposed mechanism for visible light/copper-catalyzed decarboxylation coupling.

visible light irradiation, copper complex $L_nCu^{I}X$ enters the photoexcited $[L_nCu^{I}X]^*$ **A**, which reduces hypervalent iodine(III) carboxylate **1** leading to an alkyl radical ($R^{\bullet}$)[8b,c,9a] and $L_nCu^{II}X(O_2CR)$ **B**[12g,i] through a single-electron transfer (SET) process. Then position C-2 of heteroarene *N*-oxide **2a** preferentially undergoes metallization to generate copper(II) species **C**.[12j] Next, the R radical is captured to provide copper(III) active species **D**. Finally, after reductive elimination, coupling product **3** is obtained and copper(I) complex $L_nCu^{I}X$ is liberated. In addition, a TEMPO trapping experiment supported this radical process (see the Supporting Information for details).

In summary, we have developed a new and practical method for the decarboxylation coupling reaction using copper as a photocatalyst in place of a noble metal photocatalyst, wherein

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the hypervalent iodine(III) carboxylate serves as an alkylating agent. The reaction was suitable for primary, secondary, and tertiary alkyl carboxylic acids and was compatible with sensitive functional groups, such as alkenyl and alkynyl groups. In addition, various heteroarene *N*-oxides, including quinoline, phenanthridine, quinoxaline, bipyridine, and pyridine, were suitable for this reaction, affording the desired product in moderate to excellent yield with high site selectivity. Notably, this method allows coupling of a carboxyl-containing drug molecule to a nitrogen-containing heteroarene drug molecule. It provides a viable solution to the late-stage functionalization of drugs and is expected to provide easy access to new multifunctional drugs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03382.

Synthetic procedures, mechanistic studies, and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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