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Phosphoric Acid Mediated Light-Induced Minisci C–H Alkylation of *N*-Heteroarenes

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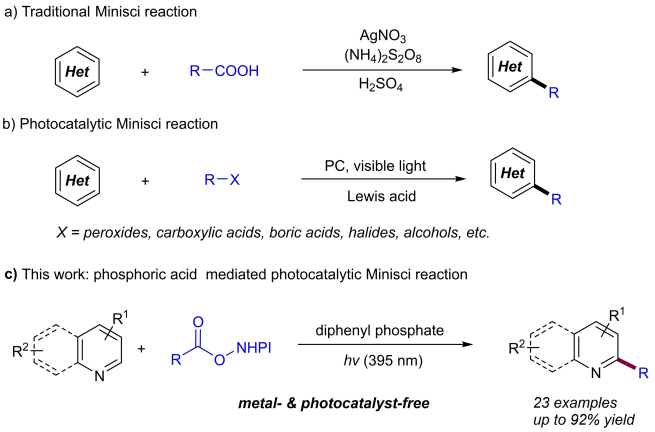
Herein, we report an environmentally-friendly light-induced Minisci alkylation of *N*-heteroarenes with a broad substrate scope using diphenyl phosphate as catalyst under metal- and photocatalyst-free conditions. The radical precursor redox-active esters (RAEs) were introduced as alkylating reagents for the functionalization of *N*-heteroarene derivatives including pyridine, quinoline, and isoquinoline. Mechanistic studies suggested that diphenyl phosphate played a key role via hydrogen bonding in the catalytic cycle.

The functionalization of *N*-heteroarenes has always been a transformation of great interest in organic chemistry due to their omnipresence in varieties of pharmaceuticals and biologically active molecules.[1–2] As a versatile method for the derivation of *N*-heteroarenes, the Minisci reaction, which has been developed since 1970s, has matured into a powerful strategy for C–H functionalization of diverse *N*-heteroarenes.[3–4] The primal methods were implemented using Ag salts and stoichiometric

amounts of persulfates as oxidants and an excess amount of alkyl carboxylic acids as radical precursors (Scheme 1a).[5] Over the past decade, photo-redox organocatalysis has undergone a dramatic development and shown its broad application in organic synthesis.[6–8] As an efficient and environmentally friendly method to produce carbon radicals, the photochemistry was also applied in Minisci-type reactions,[9] where a diverse set of radical precursors such as peroxides,[10] alkyl halides,[11] boric acids or salts,[12] alcohols[13] and ethers,[14] etc. has been utilized in light-induced Minisci-type reactions (Scheme 1b). Despite significant advances that have been made in this field, the existing methods usually require stoichiometric or excess amount of strong acids or oxidants, or with limited substrate scope, using expensive catalysts, and so on. Thus, the development of efficient, environmentally-friendly, and facile approach for Minisci C–H alkylation of *N*-heteroarenes is still highly desired.

As one of the most diverse organic compounds, the carboxylic acids were employed as radical precursors in the



Scheme 1. Methods for Minisci reaction.

light-induced Minisci reactions in 2017 by Glorius group.[15] Over recent years, carboxylic acids and the redox-active esters (RAEs, derived from carboxylic acids) serving as alkylating agents were applied in light-induced Minisci reactions by several groups,[16–18] as well as in asymmetric fashion.[18g–h] Our continuing pursuit of the discovery of new methods under photocatalyst-free conditions has led us to explore a new photochemical protocol for Minisci alkylation to construct the functionalized *N*-heteroarenes. Herein, we report an environmentally-friendly light-induced Minisci-type reactions of *N*-heteroarenes with good functional group tolerance under mild conditions (metal- and photocatalyst-free, at room temperature). A series of functionalized *N*-heteroarenes were synthesized in high yields by employing redox-active esters (RAEs) as radical precursors.

We began our optimization by choosing lepidine (**1a**) and pivalic acid-derived RAE (**2a**) as the model substrates in the presence of 20 mol% diphenyl phosphate (**PA**) under the irradiation of 10 W 395 nm LEDs (Table 1). To our delight, this transformation could proceed smoothly in 1,4-dioxane to give the desired product in excellent yield (92% yield, entry 1). Other solvents such as DCM and THF led to lower yields (entries 2–3). A brief survey of catalyst loading showed that 20 mol% diphenyl phosphate could give the best outcome, lower yields were obtained under higher or lower catalyst loading (entries 4–5). Meanwhile, reducing the equivalents of RAE gave a slightly decreased yield (entry 6). A series of control experiments indicated that the diphenyl phosphate and purple light were crucial to facilitate this transformation (entries 7–9).

With optimized reaction conditions in hand, the generality of this strategy was investigated. Several commercially available

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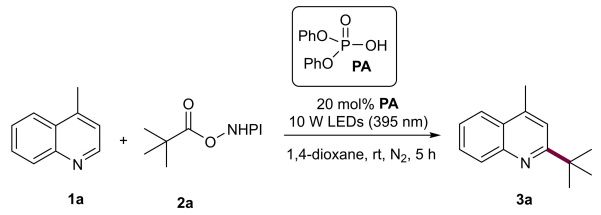
Table 1. Optimization of reaction conditions.[a]



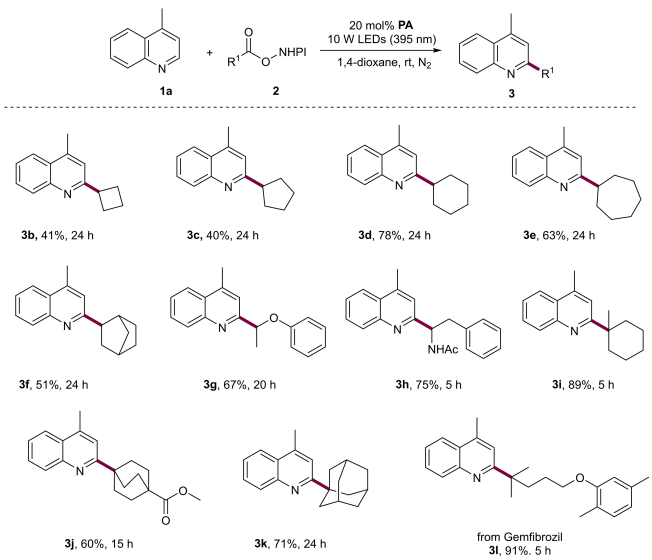
Entry	Deviation from standard conditions	Yield [%][b]
1	none	92
2	DCM as solvent	42
3	THF as solvent	87
4	10 mol% **PA**	67
5	30 mol% **PA**	81
6	1.1 equiv. **2a**	76
7	no phosphoric acid	0
8	no light	0
9	460 nm LEDs	0

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), **PA** (0.02 mmol), 395 nm LEDs (10 W), nitrogen atmosphere, rt = room temperature. [b] Isolated yields.

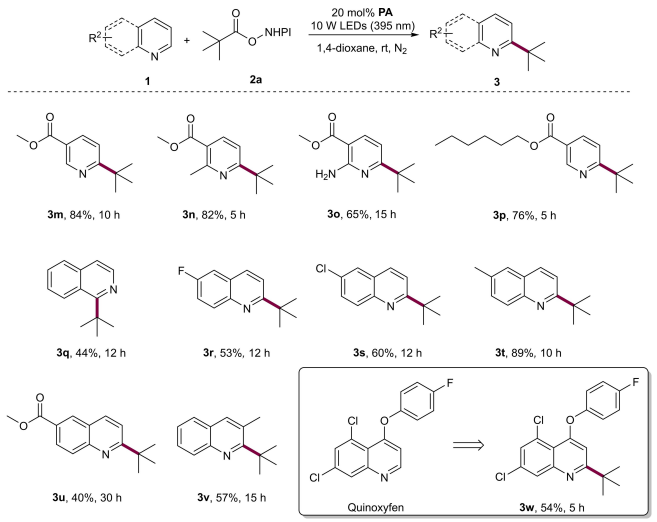
secondary and tertiary aliphatic acids-derived RAEs were subjected to the reaction as alkyl radical precursors. As shown in Scheme 2, a range of cyclic-alkylated products was obtained in moderate to high yields when the RAEs with four-, five-, six-, seven-membered ring were used as radical precursors (**3b**–**e**), where the six-membered ring gave the best result among these analogs (**3d**, 78% yield). Furthermore, a bridged-ring substituent also underwent smooth radical coupling to produce the corresponding product in high yield (**3f**). The amino acid- and phenoxyacetic acid-derived RAEs were also compatible, yielding the desired coupling products in high efficiencies (**3g**, 67% yield and **3h**, 75% yield). Various tertiary alkyl radicals with functional groups were also tolerable, finishing the target products with better outcomes comparing to the secondary alkyl radicals (**3i**–**3l**). It was noted that this method could be applied to late-stage functionalization of the bioactive molecules. The RAE derived from fenofibrate acid, which was used as antihyperlipidemic drug, was well-tolerable to this protocol, affording the desired product in excellent yield (**3l**, 91% yield). Unfortunately, the primary alkyl radicals were not suitable coupling partners in this reaction.

Next, a series of *N*-heteroarenes with various functional groups were subjected to this protocol. To our delight, the substrate scope could be expanded to the pyridine rings. As depicted in Scheme 3, the methyl nicotinate (**3m**, 84% yield) and its analogs with methyl- and amino-groups could proceed smoothly to give corresponding products in moderate to good yields (**3n**, 82% yield; **3o**, 65% yield). The hexyl nicotinate could also conveniently convert to the product in high yield (**3p**, 76%). For the scope of quinolines, isoquinoline reacted successfully to furnish **3q** in 44% yield. The quinolines with diverse substituents at the C6-position were next investigated. The quinolines with halides (**3r-s**), methyl (**3t**), and electron-withdrawing group (**3u**) were well tolerated, giving the corresponding products in good yields with high regioselectivities (alkylation occurred at C2-position exclusively). Similarly, 3-methyl quinoline was used successfully to deliver the mono-substituted product (**3v**, 57% yield). In addition, quinoxyfen, which is used as bactericide, was amenable to this protocol, the product **3w** was obtained in 54% yield.

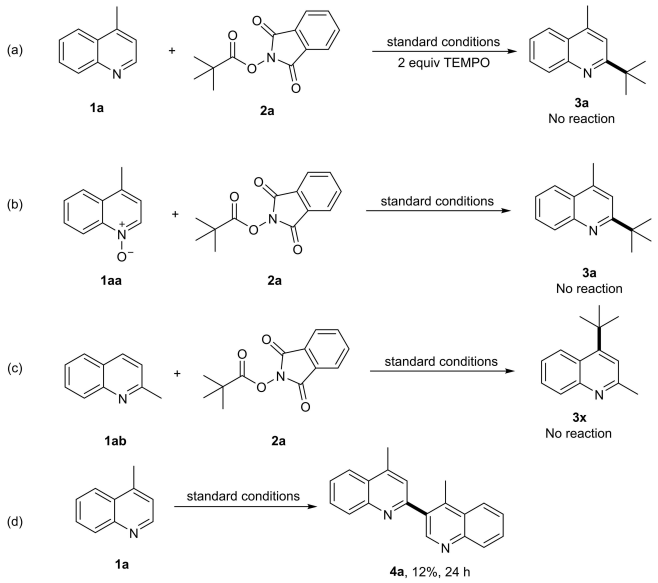
To gain insights into the mechanism, several control experiments were performed. As depicted in Scheme 4, when 2 equivalents of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added into the standard reaction, the transformation was suppressed completely, which indicated that a radical process was involved in this reaction (Scheme 4a). Unlike the traditional light-induced Minisci-type reaction, there



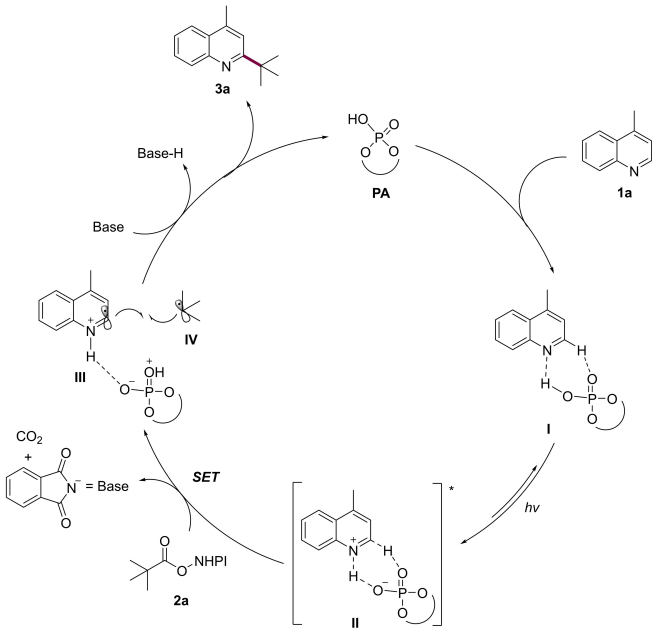
Scheme 2. Substrate scope for the RAEs. [a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), **PA** (0.04 mmol, 20 mol%), 1,4-dioxane (2.0 mL), 10 W LEDs (395 nm), rt, N_2. [b] Isolated yields.



Scheme 3. Substrate scope for the *N*-heteroarenes. [a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), **PA** (0.04 mmol, 20 mol%), 1,4-dioxane (2.0 mL), 10 W LEDs (395 nm), rt, N_2. [b] Isolated yields.



Scheme 4. Control experiments.



Scheme 5. Proposed mechanism.

was no photocatalyst serving as oxidant or reductant to produce radicals in this protocol. We envisioned that the *N*-heteroarene **1a** might coordinate with the diphenyl phosphate via hydrogen bonding to form a photosensitive intermediate, which could absorb light to trigger this transformation. To gather direct evidence for this conjecture, several control experiments were conducted. As shown in Scheme 4b and Scheme 4c, no desired products were obtained when *N*-oxide **1aa** or 2-methylquinoline **2ab** (H atom on C2-position was replaced by methyl group) were used as substrates, which indicated that the diphenyl phosphate was coordinated with substrate **1a** via double hydrogen bonding. Moreover, when **1a** was subjected to the standard conditions without **2a**, the self-coupling product was observed via a radical pathway (Scheme 4d), indicating the aromatic radicals could arise directly from the irradiation of the mixture of **1a** and **PA**.[19] Moreover, the UV – Vis spectroscopic measurements were performed on various combinations of **1a**, **2a**, and catalyst **PA**. The results showed an obvious redshift of absorption onset when the substrate **1a** was mixed with **PA**, tailing into the wavelength range of 400 nm (in SI, Figure S2). These results indicated that a photosensitive intermediate might formed from **1a** and **PA** in our system.

Based on the above mechanistic results, a proposed mechanism was depicted in Scheme 5. First, a photosensitive intermediate **I** is generated by the coordination of **PA** and **1a** via double hydrogen bonding, which was irradiated with visible light to form the excited state **II**. The excited state **II**, which acts as a strong reducing reagent, transfers an electron to the redox-active esters **2a**, leading to the corresponding alkyl radical **IV** along with the aromatic radical **III**.[19] We considered that, as the most favorable pathway, the radical-radical coupling was occurred to deliver the final product **3a** and regenerate the **PA** in the presence of the resultant base (produced from the SET step). Additionally, the traditional radical propagation started from the addition of alkyl radical **IV** to the substrate **1a** was also considered as an alternative pathway to produce the desired product **3a** (more detail see SI, Figure S4).

In conclusion, we have developed a light-induced Minisci alkylated reaction under metal- and photocatalyst-free conditions. A series of functionalized *N*-heteroarenes were synthesized by employing redox-active esters (RAEs), derived from the commercially-available carboxylic acids, as radical precursors. Mechanism studies suggested that a key photosensitive intermediate was formed by the coordination of diphenyl phosphate and *N*-heteroarene via hydrogen bondings and the transformation undergo radical pathway. Further application of this strategy in asymmetric Minisci reaction is underway.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkylation · Heterocycles · Lewis acids · Light-induced · Radicals

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