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Metal-Free Radical-Mediated C(sp^3)−H Heteroarylation of Alkanes

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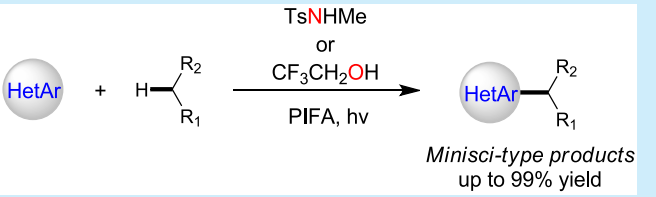
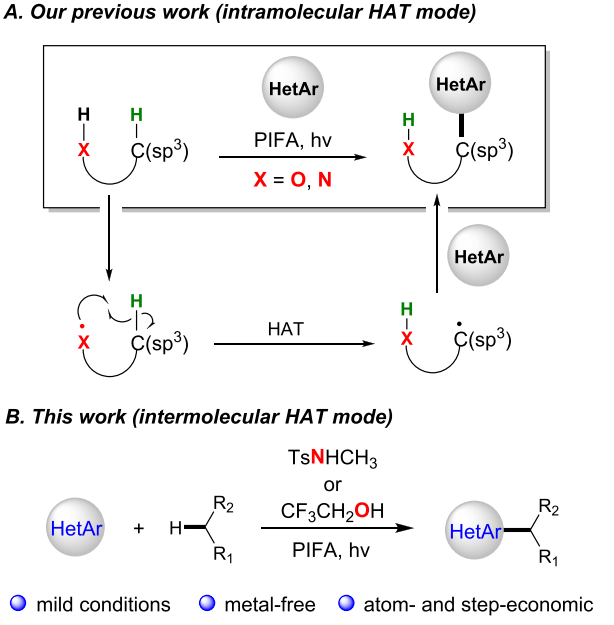
ABSTRACT: Herein we disclose a metal-free, N/O-centered radical-promoted Minisci reaction, in which the coupling of various heteroarenes with simple alkanes proceeds under mild conditions. The reaction conditions are neutral; no extra acid is added to preactivate N-heteroarenes in the Minisci reaction. The N-/O-centered radicals are generated directly from amide (TsNHMe) or alcohol (CF_3CH_2OH) under visible-light irradiation. This green and eco-friendly synthetic process may find potential use in medicinal chemistry.



Heteroaryl moieties are ubiquitous in natural products and artificial molecules, such as ligands of metal complexes, pharmaceuticals, and organic optoelectronic materials.[1] Direct heteroarylative functionalization of abundant C(sp^3)−H bonds through cross-dehydrogenative coupling (CDC) represents one of the most efficient approaches for heteroaryl incorporation, avoiding *de novo* synthesis of the intricate heteroaryl-located compounds.[2] Because of the high atom and step economy, the Minisci reaction provides a robust tool for the late-stage alkylation of N-containing heteroarenes and has attracted broad synthetic interest.[3] For instance, Antonchick[3c] et al. reported a hypervalent iodine-mediated Minisci reaction between alkanes and heteroarenes, in which the in situ generated azido radical was involved in the H-abstraction.

Given the recent surge in the development of diverse reaction modes to abstract C(sp^3)−H bonds intra-/intermolecularly,[4−7] widely available alkanes have proven to be privileged alkyl radical precursors in radical reactions. On the other hand, N- and O-centered radicals are frequently employed for H-abstraction in the hydrogen atom transfer (HAT) process, due to the high bond dissociation energies (BDE) of N−H and O−H bonds. However, the high BDEs also increase the difficulty of generation of N-/O-centered radicals via homolysis of strong N−H/O−H bonds. Among the previous achievements, most of the examples harnessed the prefunctionalized precursors that might be sometimes hard to handle or prepare from alcohols or amides. Therefore, developing efficient methods to directly generate N-/O-centered radicals from N−H/O−H bonds is highly desirable.[8] Recently, we disclosed the radical heteroarylation of remote C(sp^3)−H bonds of unprotected aliphatic alcohols and amides via an intramolecular HAT process (Scheme 1A).[9] The transformations were triggered by N-/O-centered radicals which were delivered by treating alcohols or amides with a hypervalent iodine(III) reagent under mild conditions.

Scheme 1. Radical-Mediated Intra-/Intermolecular C(sp^3)−H Heteroarylation of Alkanes



Stimulated by these findings, we conceive to apply the protocol to the Minisci-type reaction between heteroarenes and general alkenes. The alkyl radicals could be obtained from the intermolecular HAT by using alcohols or amides as H-

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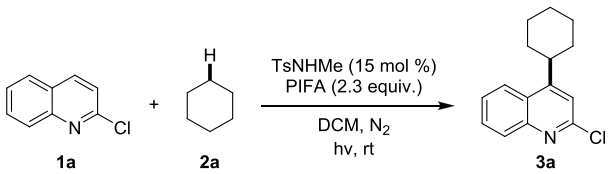
abstracting reagents (Scheme 1B). Herein we report the concrete support for the hypothesis. The reaction of heteroarenes with simple alkanes readily proceeds in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA) under visible-light irradiation. The transformation is promoted either by catalytic TsNHMe or with CF_3CH_2OH as cosolvent. The reaction conditions are mild and neutral, providing a metal-free approach for the Minisci reaction.

At the outset, the reaction of 2-chloroquinoline **1a** with cyclohexane **2a** was investigated to optimize the reaction conditions (Table 1; also see Supporting Information (SI) for details). By using PIFA as oxidant, a catalytic amount of TsNHMe as H-abstracting reagent, and dichloromethane (DCM) as solvent, the corresponding Minisci-type product **3a** was obtained in 95% yield under blue LED irradiation (entry 1). The reaction of **1a** at 1 mmol scale was also conducted, leading to **3a** with the same yield (see SI). When replacing PIFA with other hypervalent iodine oxidants, such as (diacetoxyiodo)benzene (PIDA), 2-iodoxybenzoic acid (IBX), and $NaIO_4$, no desired product was obtained (entries 2–4). It was rationalized that the interaction between TsNHMe and PIFA concomitantly generated the amidyl radical and strong acid trifluoroacetic acid (TFA); the latter could efficiently acidify N-heteroarenes to enhance the electrophilicity and thus facilitate the alkyl radical addition. Afterward, organic solvents were screened, showing that DCM was more effective than other solvents, e.g. $CHCl_3$, benzene, DMSO, etc. (entries 5–7). When using $TsNH_2$ or PhCONH^{t}Bu in lieu of TsNHMe, the desired product was afforded in low yields (entries 8–9). The investigation of light sources showed that, while 30 W blue LEDs and 34 W CFL led to moderate yields of **3a**, the reaction did not occur with 30 W green LEDs (entries 10–12). Control experiments revealed that light and PIFA were necessary for the reaction (entries 13 and 14). The formation of **3a** with 30% yield in the absence of TsNHMe indicated the existence of a secondary HAT pathway, probably attributed to the homolysis of PIFA to generate the CF_3 radical[10] and iodanyl radical[11] that could also abstract an H-atom (entry 15). The reaction under air resulted in a slightly lower yield (entry 16). We next examined other alcohol-based HAT reagents, which could deliver the alkoxy radical to promote the reaction. While with the use of catalytic CF_3CH_2OH instead of TsNHMe the desired product was obtained in 54% yields (entry 17), the reaction resulted in almost quantitative yield by using CF_3CH_2OH as solvent (entry 18). Using CCl_3CH_2OH as solvent gave a 40% yield (entry 19). The reaction afforded the best yield in a mixed solvent (1:1 CF_3CH_2OH/DCM) (entry 20).

Table 1. Reaction Conditions Survey[a]



1a 2a 3a

entry	variation from the standard conditions	yield (%)
1	none	95
2	PIDA instead of PIFA	0
3	IBX instead of PIFA	0
4	$NaIO_4$ instead of PIFA	0
5	$CHCl_3$ instead of DCM	73
6	benzene instead of DCM	34
7	DMSO instead of DCM	0
8	$TsNH_2$ instead of TsNHMe	23
9	PhCONH^{t}Bu instead of TsNHMe	trace
10	30 W blue LEDs as light source	64
11	30 W green LEDs as light source	0
12	34 W CFL as light source	54
13	dark	0
14	without PIFA	0
15	without TsNHMe	30
16	under air	83
17[b]	CF_3CH_2OH instead of TsNHMe	54
18[c]	CF_3CH_2OH instead of DCM	96
19[d]	CCl_3CH_2OH instead of DCM	40
20[e]	CF_3CH_2OH/DCM (1:1)	96

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (5.0 equiv), TsNHMe (15 mol %), and PIFA (2.3 equiv) in solvent (2 mL) under N_2, irradiated with 2 × 50 W blue LEDs at room temperature for 12 h. Isolated yields were given. [b]CF_3CH_2OH (15 mol %). [c]CF_3CH_2OH as solvent (2 mL) without TsNHMe. [d]CCl_3CH_2OH as solvent (2 mL) without TsNHMe. [e]CF_3CH_2OH/DCM (1/1) as mixed solvent (2 mL) without TsNHMe.

With the optimized reaction conditions in hand, we set about assessing the generality of the protocol (Scheme 2). First, we examined the tolerance of various functional groups such as halides, cyano, and ester (**3a**–**3i**). Good to excellent yields were given under both the $TsNHCH_3$ and CF_3CH_2OH mediated conditions, showing good functional group compatibility. Notably, a cyclohexyl group was smoothly incorporated into Quinoxyfen, a pesticide, illustrating the potential of the protocol for the late-stage elaboration of bioactive molecules (**3j**). The alkylation of isoquinoline took place regioselectively at the 1-position (**3k** and **3l**). Pyridines were also suitable heteroarenes (**3m**–**3p**). While the monoalkylated pyridines could be obtained by controlling the amount of cyclohexane (**3m** and **3o**), the use of excess cyclohexane led to the dialkylated pyridine with good yield (**3p**). Of note, this protocol also provided a practical entry to modify *N*,*N*-bidentate ligands such as 4,4′-di-*tert*-butyl bipyridine (**3q**). The reaction with electron-rich benzothiazoles also gave rise to the desired 2-alkylated products in moderate to good yields (**3r** and **3s**). Site-selective alkylation of phenanthridine occurred at the 6-position with high yield under each set of reaction conditions (**3t**).

The transformation also readily proceeded with other valuable heteroarenes containing more than one N atom, e.g., pyrazine, benzopyrazine, pyrimidine, benzopyrimidines, triazine, etc. (**3u**–**3ag**). The dialkylated products could be obtained by using excess alkanes (**3y**, **3ab**–**3ad**). Similarly, the trialkylated 1,3,5-triazine was also furnished in the presence of excess cyclohexane (**3af**). Surprisingly, the alkylated 4-hydroxyquinazoline was not afforded under the TsNHMe-catalyzed conditions, but obtained with good yield by switching to the alcohol-based conditions (**3ae**). Imidazo-[1,2-*a*]pyrazine could be alkylated in moderate yield with unique regioselectivity (**3ag**).

Next, we investigated the scope of simple alkanes. The reaction with linear alkanes normally gave rise to a mixture of positional isomers and showed that the heteroarylation of secondary C(sp^3)–H bonds was superior to that of the primary ones (**3ah** and **3ai**). Interestingly, exclusive selectivity on secondary C–H bonds prior to the more reactive tertiary

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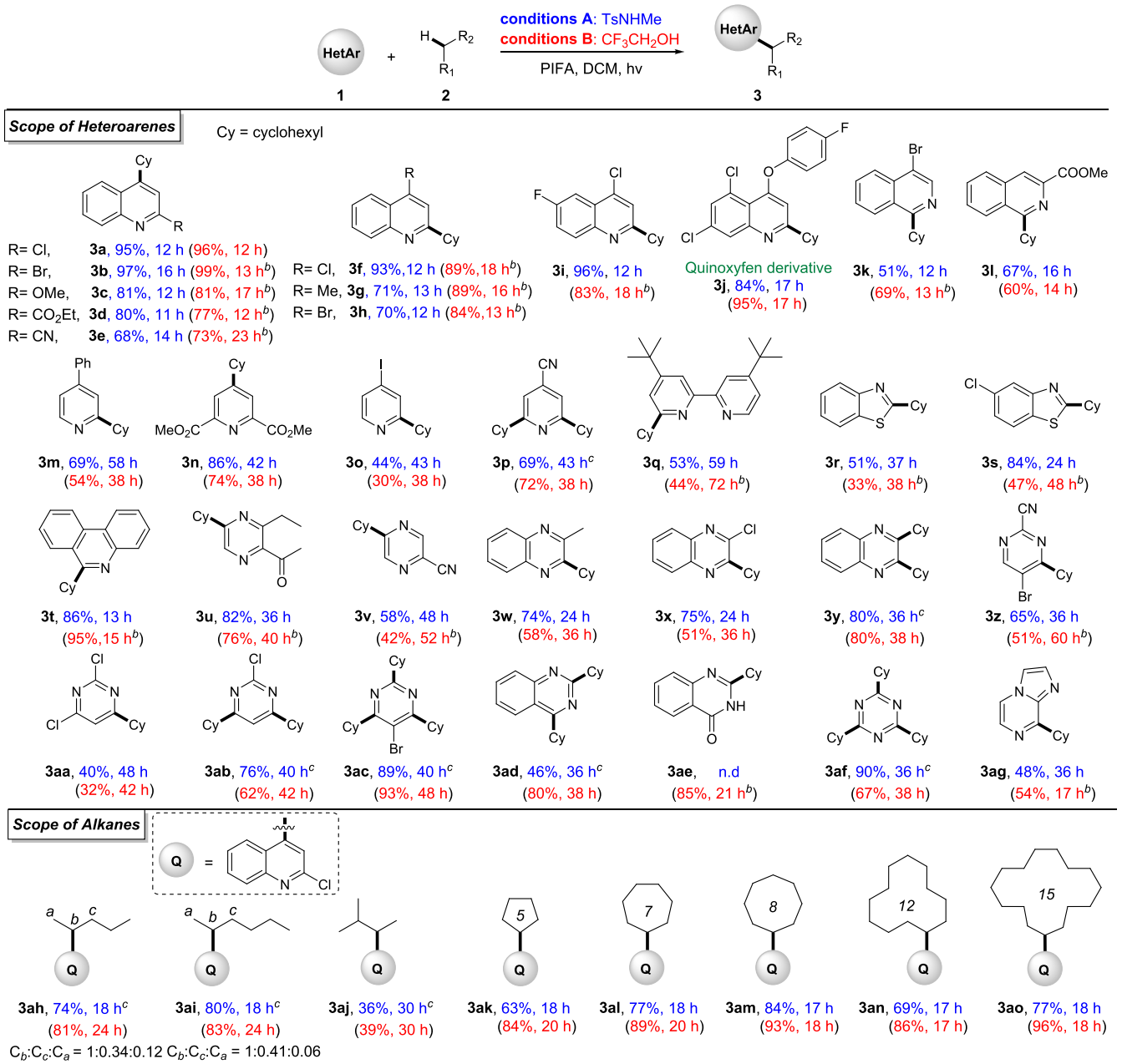
Scheme 2. Scope of Heteroarenes and Alkanes[a]



[a]Reaction conditions A: **1a** (0.2 mmol), **2a** (5.0 equiv), TsNHMe (15 mol %), and PIFA (2.3 equiv) in DCM (2 mL) under N_2, irradiated with 2 × 50 W blue LEDs at room temperature; Reaction conditions B: **1a** (0.2 mmol), **2a** (5.0 equiv), and PIFA (2.3 equiv) in CF_3CH_2OH/DCM (2 mL, v/v 1/1) under N_2, irradiated with 2 × 50 W blue LEDs at room temperature. Isolated yields were given. [b]CF_3CH_2OH (2 mL) instead of CF_3CH_2OH/DCM (2 mL, v/v 1/1) as solvent. [c]aAlkanes (15.0 equiv) and PIFA (5.0 equiv).

C−H bonds was achieved in the heteroarylation of *iso*-pentane, which might be attributed to the steric congestion around the tertiary carbon center (**3aj**). Moreover, a set of cyclic alkanes could be readily coupled with quinoline in moderate to excellent yields (**3ak**−**3ao**). However, ethers and amines were not suitable substrates, probably attributed to the incompatibility of the generated electron-rich α-O-/N-attached alkyl radicals with the oxidative conditions.

To gain deeper insights into the reaction pathways, some mechanistic experiments were performed. When radical scavenger 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was added into the reaction, the conversion was completely inhibited. It might suggest that the reaction went through a radical pathway. In UV−visible spectra, the complex of PIFA-TsNHMe or PIFA-CF_3CH_2OH shows an obvious red shift (see Figures S4−S5). In addition, the quantum yield (8.5%) of the transformation demonstrated that a photochemical process was more likely involved in the Minisci reaction, but a radical chain process is unlikely to be in operation (see Figures S1−S3).

Based on the experimental results and our previous findings,[9] a proposed mechanism was depicted in Scheme 3. Initially, the interaction between PIFA and amide/alcohol generates the intermediate **I**/**II**, which then leads to the corresponding amidyl/alkoxy radical (**III** or **IV**) after homolysis under visible-light irradiation. Meanwhile, an

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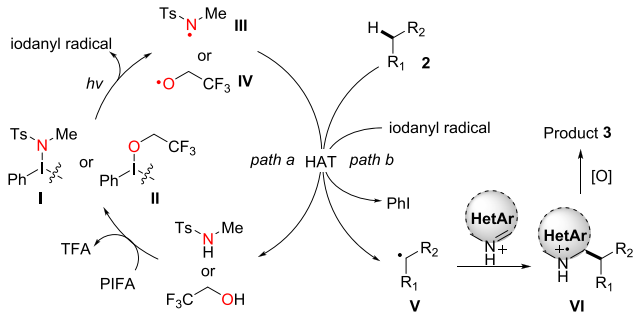
Scheme 3. Proposed Mechanism



iodanyl radical was also formed. The N-/O-centered radical abstracts a H-atom from alkane **2**, affording the alkyl radical **V** (path a). Alternatively, the iodanyl radical may be involved in another possible HAT process (path b).[11] It should be noted that the *in situ* formed TFA preactivates N-heteroarene, thus avoiding the addition of extra acids. Subsequently, the nucleophilic addition of alkyl radical **V** to the acidified heteroarene furnishes the intermediate **VI**, which is oxidized to afford the final product **3**.

In summary, we have described the amidyl/alkoxy radical-promoted metal-free coupling of heteroarenes with simple alkenes. The N-/O-centered radicals are generated directly from TsNHMe or CF_3CH_2OH under visible-light irradiation. The reaction conditions are mild and neutral, offering an efficient approach for the Minisci reaction. The application of this green synthetic process in medicinal chemistry can be anticipated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02475.

Experimental details, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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