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COMMUNICATION

Terminal-oxidant-free photocatalytic C–H alkylations of heteroarenes with alkylsilicates as alkyl radical precursors†

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We report the photocatalytic C–H alkylations of heteroarenes with alkylsilicates bearing *C,O*-bidentate ligands under acidic conditions. Irradiation of heteroaromatic compounds in the presence of the silicates and trifluoroacetic acid produced the corresponding alkylated heteroaromatic compounds. Notably, the present reaction system does not require any terminal oxidant although the reaction seems to be a formal oxidation reaction. This study clearly demonstrates that alkylsilicates can be used in photocatalytic radical chemistry under acidic conditions.

Heteroarenes are important components of natural products and active pharmaceutical ingredients.[1] The radical substitution of a C–H bond of a protonated heteroarene, the Minisci reaction, is a well-known versatile method for derivatizing heteroarenes,[2] and many Minisci-type reactions have been developed over the past several decades. Carboxylic acids,[3] alkyl halides,[4] activated esters,[5] peroxides,[6] alcohols,[7] boronic acids,[8] sulfinate salts,[9] alkenes,[10] alkyltrifluoroborates,[11] and 1,4-dihydropyridines[12] have all been used as radical precursors in these reactions. In addition, although most Minisci-type reactions require stoichiometric amounts of an oxidant, oxidant-free versions, which are expected to serve as mild and clean methods for alkylating heteroarenes, have been developed recently.[3d-3f,11d] Despite great effort, there are only a few examples of Minisci-type reactions that use organosilicon compounds.[13] Only benzylsilanes and silicon compounds bearing single chalcogen atoms at their α-positions have been used as radical precursors in Minisci-type reactions (Fig. 1a) because most silicon compounds, whose carbon–silicon bonding orbitals do not interact with π electrons or lone pairs, have very high oxidation potentials, making it difficult to generate alkyl radicals through oxidation.[14] In this decade, pentacoordinated alkylsilicates **1** bearing pairs of catecholate ligands have turned out to be alkyl radical precursors with low oxidation potentials.[15] Because of lower oxidation potentials, alkysilicates **1** have been used in place of alkyltrifluoroborates that produce toxic boron fluoride byproducts and are poorly soluble in most organic solvents. As one example, desulfonative alkylation of *N*-heteroaryl sulfones using bis(catecholato)silicates under non-acidic conditions was reported.[15d] However, such alkylsilicates, which are unstable to acid, have not been used in reactions under acidic conditions, such as Minisci-type C–H alkylations of heteroarenes.

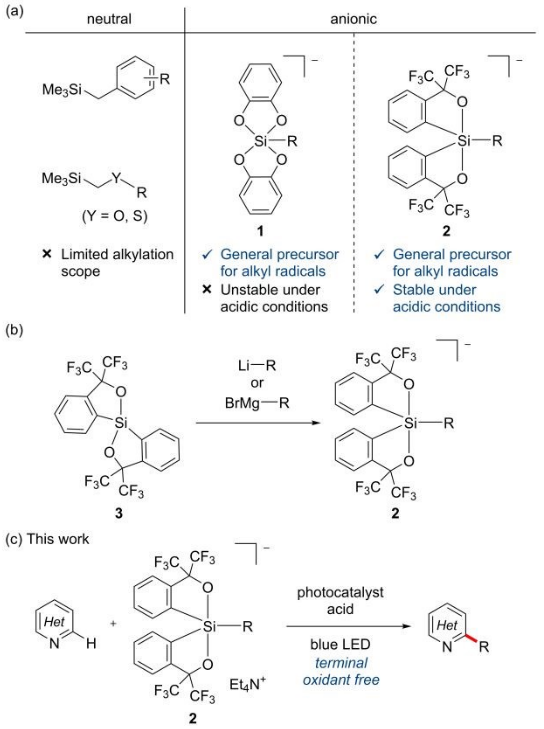

Fig 1. (a) Organosilicon compounds as radical precursors. (b) Synthesis of alkylsilicates 2. (c) This work: C–H alkylation of heteroarenes with alkylsilicates as alkyl radical precursors.

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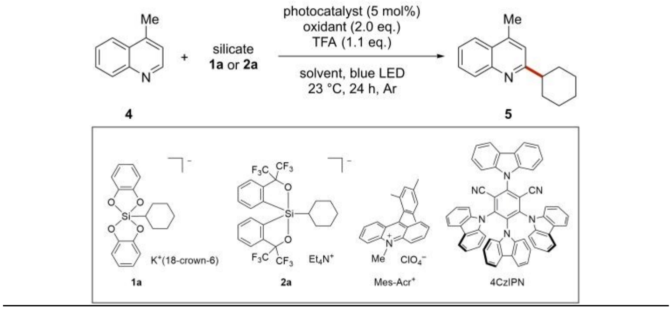
With this background in mind, we focused our attention on alkylsilicates **2** bearing pairs of [-C_6H_4-2-$C(CF_3)_2O$-] *C,O*-bidentate ligands.[16,17] Alkylsilicates **2** can be directly synthesized by the reaction of an alkyllithium or alkylmagnesium bromide with Martin's spirosilane **3** (Fig. 1b).[16a,b] Beneficially, alkylsilicates **2** are stable to water and dissolve well in common organic solvents. Moreover, **2** remain intact under acidic conditions.[16c] Hence, we envisaged that **2** would provide opportunities for the development of new photoredox reactions using organosilicon reagents as radical precursors in acidic media. Herein, we report the photocatalytic C–H alkylation of heteroarenes using alkylsilicates **2** (Fig. 1c). Notably, the present reaction system does not require any terminal oxidant although the reaction seems to be a formal oxidation reaction.

To optimize the reaction conditions, 4-methylquinoline (**4**) and cyclohexylsilicate **2a** were selected as the model substrate and radical precursor, respectively (Table 1). We first carried out the reaction referring to the reaction conditions of photocatalytic Minisci-type reactions using alkyltrifluoroborates as radical precursors.[11c] Irradiation of **4**, **2a**, $(NH_4)_2S_2O_8$, and 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$) as the photocatalyst in CH_3CN/H_2O gave the desired C–H alkylated product **5** in 81% yield (entry 1). Photocatalyst was essential for achieving the alkylation (entries 2 and 3). Surprisingly, the reaction proceeded well in the absence of $(NH_4)_2S_2O_8$ (entry 4), in contrast to the Minisci-type reactions with alkyltrifluoroborates. We considered the possibility that a trace amount of oxygen present in the solution acted as the oxidant, but the desired product was hardly obtained in an oxygen atmosphere (entry 5). Irradiation with blue light, the presence of an acid, and the photocatalyst were all essential for the reaction to progress (entries 6–8). Using CH_2Cl_2 as the solvent improved the yield of **5** (entry 9). As expected, cyclohexylsilicate **1a**, which bears two catecholate ligands, failed to give the desired product (entry 10). The reaction with 4CzIPN as the photocatalyst proceeded, albeit with a slightly lower yield of **5** (entry 11).

Table 1. Optimizing the photocatalytic C–H alkylation reaction.



entry	silicate	photocatalyst	oxidant	solvent	yield [%][a]
1	**2a**	Mes-Acr$^+$	$(NH_4)_2S_2O_8$	CH_3CN/H_2O	81
2	**2a**	none	$(NH_4)_2S_2O_8$	CH_3CN/H_2O	0
3[b]	**2a**	none	$(NH_4)_2S_2O_8$	CH_3CN/H_2O	0
4	**2a**	Mes-Acr$^+$	none	CH_3CN/H_2O	71
5	**2a**	Mes-Acr$^+$	O_2 (1 atm)	CH_3CN/H_2O	trace
6[b]	**2a**	Mes-Acr$^+$	none	CH_3CN/H_2O	0
7[c]	**2a**	Mes-Acr$^+$	none	CH_3CN/H_2O	trace
8	**2a**	none	none	CH_3CN/H_2O	trace
9	**2a**	Mes-Acr$^+$	none	CH_2Cl_2	87
10	**1a**	Mes-Acr$^+$	none	CH_2Cl_2	0
11	**2a**	4CzIPN	none	CH_2Cl_2	73

4-Methylquinoline (**4**, 0.1 mmol), cyclohexylsilicate **1a** or **2a** (0.12 mmol), oxidant (0.2 mmol), photocatalyst (5 mol%), and TFA (0.11 mmol) were stirred at 23 °C in solvent (4 mL) for 24 h and irradiated with blue light. [a] Determined by ^1H NMR spectroscopy. [b] The reaction was carried out in the dark. [c] TFA was not added.

With the optimal conditions in hand, the generality of this Minisci-type C–H alkylation reaction was evaluated. As shown in Table 2, a diverse range of heteroarenes was alkylated under the optimized conditions. The reaction also efficiently produced **5** on the gram scale. 2-Methylquinoline also gave the desired product **6** in high yield, while unsubstituted quinoline gave the 2,4-dialkylated product **7** in 83% yield using 2.2 equivalents of cyclohexylsilicate **2a**. Quinolines with a variety of substituents, including phenyl, chloro, bromo, and methoxy, also gave the corresponding products **8**–**11**. Isoquinolines, as well as unsubstituted phenanthridine and benzothiazole, were also amenable to the protocol to produce **12**–**16**, respectively. As expected, the reaction with benzimidazole resulted in almost no conversion to **17** because of the electron-rich nature of its C2 site,[11c] while quinazolinone and 3,6-dichloropyridazine afforded the desired products **18** and **19**. 4-(Trifluoromethyl)pyridine was converted into the 2,6-dialkylated product **20**. Furthermore, this Minisci-type alkylation protocol was also successfully used to functionalize complex bioactive molecules. For instance, the fungicide quinoxyfen was alkylated at the C2 position of its quinoline ring to give **21** in 65% yield. Fasudil, a potent vasodilator bearing a free NH group, was selectively alkylated at the C1 position to give **22** in 43% yield, which contrasts sharply with the previous photocatalytic Minisci-type alkylation using persulfate as the terminal oxidant that required protection of the NH group.[3c] Quinine gave the corresponding product **23** in 49% yield.

The scope of the silicate was subsequently investigated. Primary alkylsilicates could be used in this reaction to give **24**–**26**, although primary alkyl radicals are less stable than secondary and tertiary alkyl radicals. Both acyclic and cyclic secondary alkylsilicates as well as tertiary alkylsilicates were applicable to the present reaction system to give **27**–**31**.

The following experiments were performed to obtain mechanistic insight into the present reaction. Stern–Volmer quenching experiments revealed that **2a** efficiently quenches the excited state of the photocatalyst, whereas the heteroarene, TFA, the protonated heteroarene, and spirosilane **3** did not (see Supporting Information). These results suggest that oxidation of **2a** is the key initiation step for the C–H alkylation reaction. We next performed a radical clock experiment. Alkylation of **4** with 5-hexenylsilicate **2b** under the

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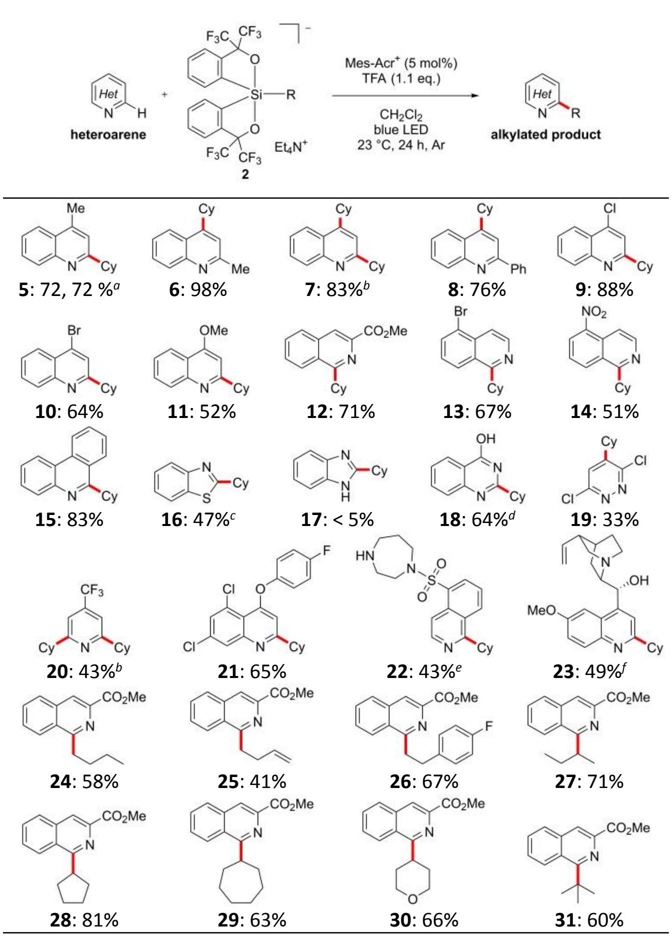
standard conditions gave the ring-closed product **32** without the formation of the linear product **32’** (Scheme 1a), confirming the radical pathway.

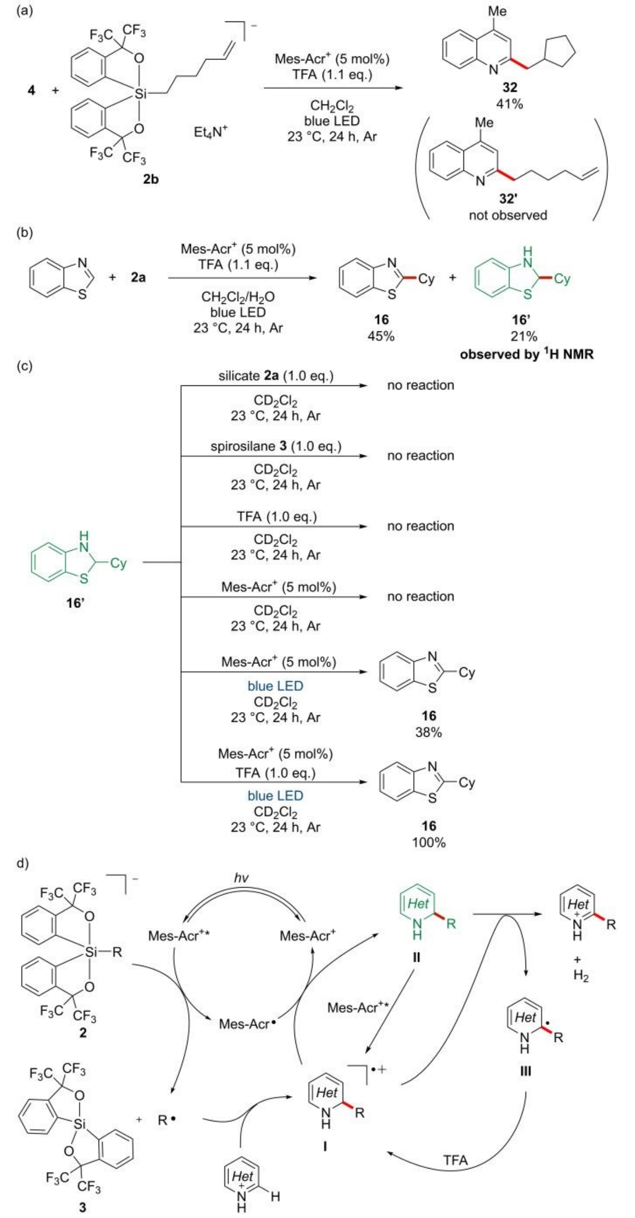
The present method does not require any terminal oxidant, whereas previous oxidant-free Minisci-type reactions include electrochemical oxidation[3f,11d] or hydrogen evolution.[3d,3e] To gain some insight into the alternative oxidative process operating in the present system, we examined the crude products from the reactions of alkylsilicates **2a** with benzothiazole as a substrate. ^{1}H NMR spectroscopy revealed the formation of 2-cyclohexyl-2,3-dihydrobenzo[*d*]thiazole (**16’**) in addition to the desired 2-cyclohexylbenzothiazole (**16**) (Scheme 1b), which suggests that the hydrogenated form of the desired product is a reaction intermediate. To address this possibility, we investigated reaction conditions for the conversion of **16’** into **16** (Scheme 1c). The addition of alkylsilicate **2a**, spirosilane **3**, TFA, or Mes-Acr$^+$ to a CD_2Cl_2 solution of **16’** resulted in no reaction. However, the dehydrogenated product **16** was observed in 38% yield by ^{1}H NMR spectroscopy after irradiation with blue light in the presence of Mes-Acr$^+$. Furthermore, irradiation of **16’** in the presence of both the photocatalyst and TFA produced **16** in quantitative yield, strongly suggesting the intermediacy of **16’** during the formation of **16**.

We propose a possible mechanism for the photocatalytic C–H alkylation reaction (Scheme 1d). First, Mes-Acr$^+$ is excited by visible light and oxidizes alkylsilicate **2**, releasing alkyl radical R• and spirosilane **3**. This process is energetically feasible because the reduction potential of Mes-Acr^{+}***** (E_{red} = +2.06 V vs. SCE)[18] is more positive than the oxidation potential of cyclohexylsilicate **2a** (E_{red} = +1.47 V vs. SCE). The generated alkyl radical R• reacts with the protonated heteroarene to form radical cation **I**. Single electron transfer (SET) from Mes-Acr• to radical cation **I** then forms intermediate **II**. Quenching experiments indicate that the

Table 2. Substrate scope for the photocatalytic C–H alkylation reaction.



Heteroarene (0.2 mmol), alkylsilicate **2** (0.24 mmol), Mes-AcrClO$_4$ (5 mol%), and TFA (0.22 mmol) were stirred at 23 °C in CH_2Cl_2 (4 mL) for 24 h while irradiated with blue light. Yields are isolated yields. ^{a} The reaction was performed on a gram scale. ^{b} 2.2 equiv. of **2a** was used; ^{c} performed in a CH_2Cl_2/H_2O mixture (1/1). ^{d} performed in a CH_3CN/H_2O mixture (1/1); ^{e} 2.1 equiv. of TFA was used and the product was isolated in *N*-Boc protected form. ^{f} 2.1 equiv. of TFA was used and 1,1,1,3,3,3-hexafluoro-2-propanol was used as the solvent.



Scheme 1. Mechanistic studies. (a) A radical clock experiment. (b) Observing the intermediate. (c) The dehydrogenation reaction. (d) Proposed reaction mechanism.

oxidation of intermediate **II** by the excited state of the photocatalyst would generate **I** (see Supporting Information). Reaction of **I** and **II** generates the radical **III**, hydrogen molecule, and protonated desired product, which is deprotonated to give the final product. Protonation of **III** gives **I** again.

In summary, we developed a new protocol for the photocatalytic Minisci-type C–H alkylations of heteroarenes using alkylsilicates as alkyl radical precursors. This method does not require any terminal oxidant, which makes it possible to functionalize various heteroarenes in a mild and clean reaction system. A variety of primary, secondary, and tertiary alkyl groups was directly incorporated into various electron-deficient heteroarenes in an efficient manner. Mechanistic studies suggest that this terminal-oxidant-free alkylation involves the photocatalytic formation of the hydrogenated form of the desired product followed by photocatalytic dehydrogenation. This study clearly demonstrates that alkylsilicates can be used in photocatalytic radical chemistry under acidic conditions.

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Conflicts of interest

There are no conflicts to declare.

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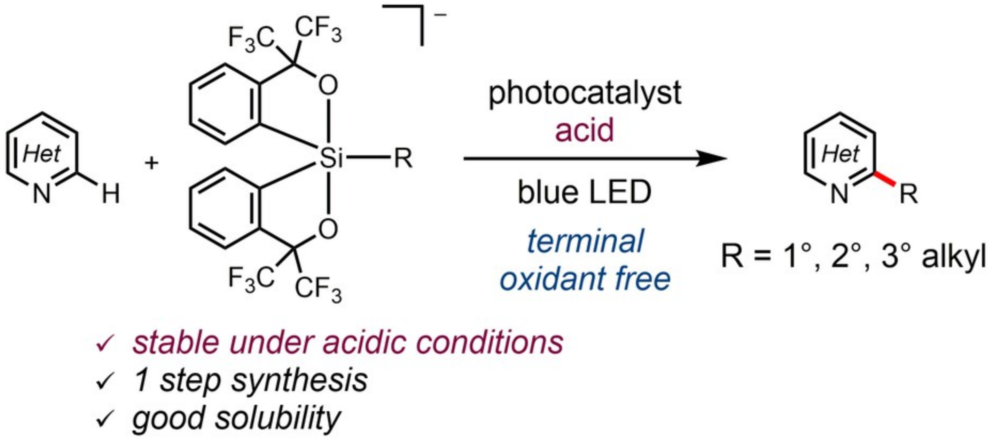

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