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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 heteroaromatics in the presence of the silicates and trifluoroacetic acid produced the corresponding alkylated compounds. The present reaction system does not require any terminal oxidant although the reaction seems to be a formal oxidation reaction. This study 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-dihydropyridines¹² 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.^{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

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

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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, alkylsilicates **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, desulfonyative 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.

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 alkylolithium 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

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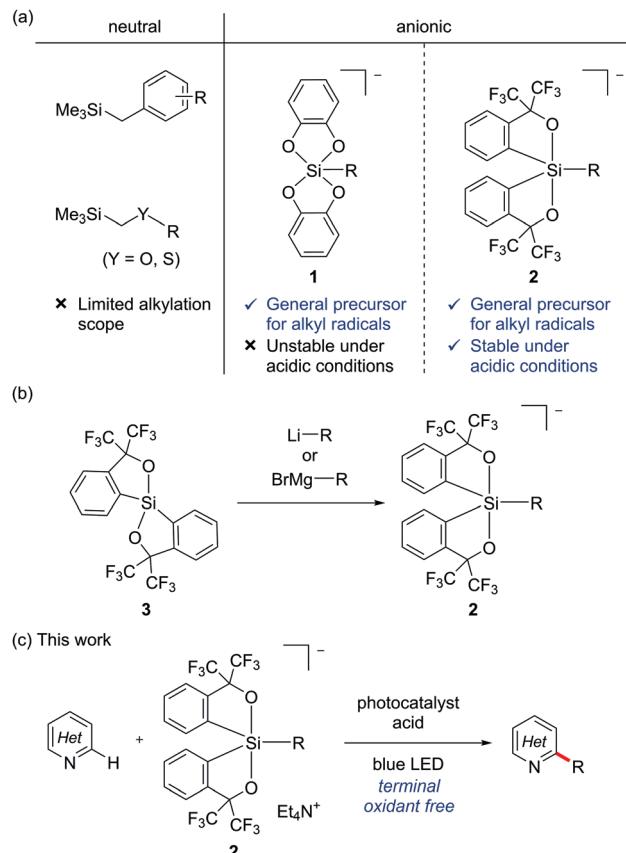
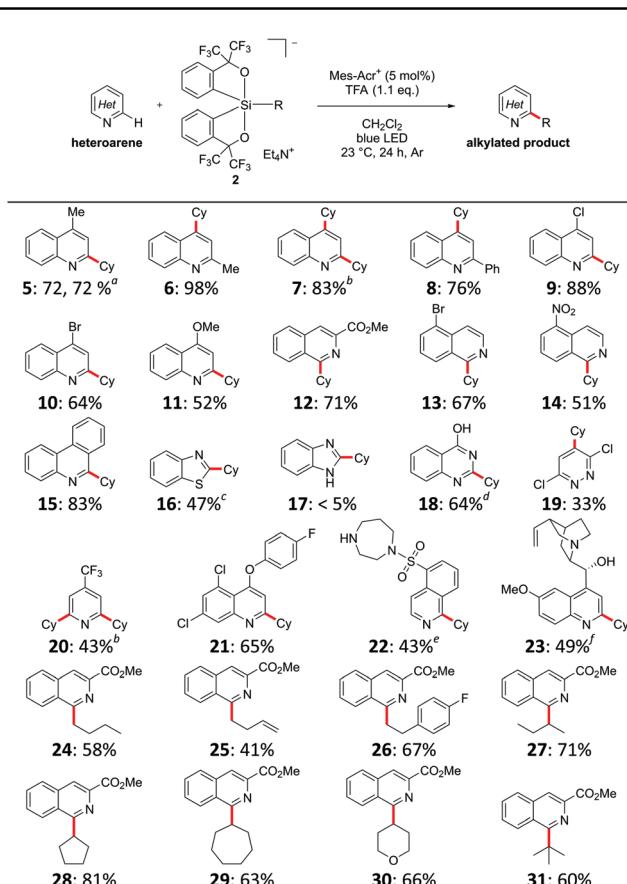


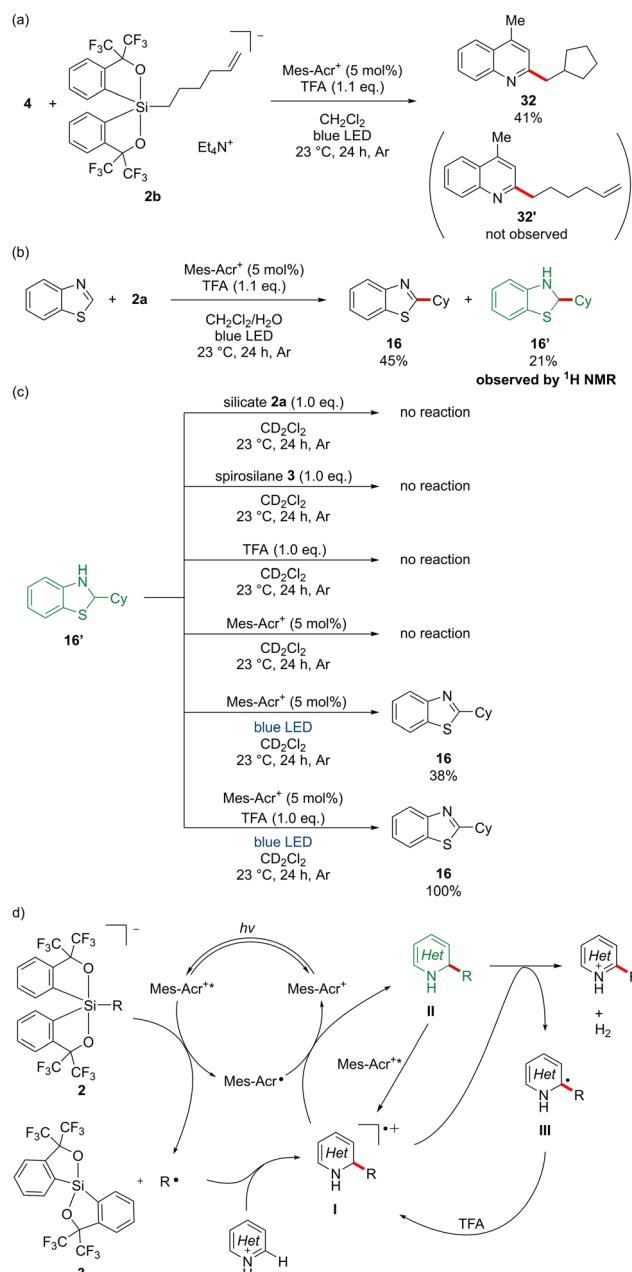
Table 2 Substrate scope for the photocatalytic C–H alkylation reaction



Heteroarene (0.2 mmol), alkylsilicate **2** (0.24 mmol), Mes-Acr⁺ (5 mol%), and TFA (0.22 mmol) were stirred at 23 °C in CH₂Cl₂ (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 CH₂Cl₂/H₂O mixture (1/1). ^d Performed in a CH₃CN/H₂O 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.

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. ¹H 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 CD₂Cl₂ solution of **16'** resulted in no reaction. However, the dehydrogenated product **16** was observed in 38% yield by ¹H 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⁺ ($E_{\text{red}} = +2.06 \text{ V vs. SCE}$)¹⁸ is more positive than the oxidation potential of cyclohexylsilicate **2a** ($E_{\text{red}} = +1.47 \text{ V vs. SCE}$). 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 oxidation of intermediate **II** by the excited state of the photocatalyst would generate **I** (see ESI†). Reaction of **I** and **II** generates radical **III**, hydrogen molecule, and TFA.



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.

Notes and references

- 1 A. F. Pozharskii, A. T. Soldatenkov and A. R. Katritzky, *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, Wiley, Hoboken, 2nd edn, 2011.
- 2 (a) F. Minisci, E. Vismara and F. Fontana, *Heterocycles*, 1989, **28**, 489–519; (b) M. A. J. Duncton, *Med. Chem. Commun.*, 2011, **2**, 1135–1161; (c) R. S. J. Proctor and R. J. Phipps, *Angew. Chem. Int. Ed.*, 2019, **58**, 13666–13699.
- 3 (a) F. Minisci, R. Mondelli, G. P. Gardini and O. Porta, *Tetrahedron*, 1972, **28**, 2403–2413; (b) N. Kaur, X. Lu, M. C. Gershengorn and R. Jain, *J. Med. Chem.*, 2005, **48**, 6162–6165; (c) R. A. Garza-Sánchez, A. Tlahuext-Aca, G. Tavakoli and F. Glorius, *ACS Catal.*, 2017, **7**, 4057–4061; (d) J. Lin, Z. Li, J. Kan, S. Huang, W. Su and Y. Li, *Nat. Commun.*, 2017, **8**, 14353; (e) W.-F. Tian, C.-H. Hu, K.-H. He, X.-Y. He and Y. Li, *Org. Lett.*, 2019, **21**, 6930–6935; (f) X.-L. Lai, X.-M. Shu, J. Song and H.-C. Xu, *Angew. Chem. Int. Ed.*, 2020, **59**, 10626–10632.
- 4 (a) F. Minisci, E. Vismara and F. Fontana, *J. Org. Chem.*, 1989, **54**, 5224–5227; (b) M. A. J. Duncton, M. A. Estiarte, R. J. Johnson, M. Cox, D. J. R. O'Mahony, W. T. Edwards and M. G. Kelly, *J. Org. Chem.*, 2009, **74**, 6354–6357.
- 5 (a) W.-M. Cheng, R. Shang, M.-C. Fu and Y. Fu, *Chem. – Eur. J.*, 2017, **23**, 2537–2541; (b) W.-M. Cheng, R. Shang and Y. Fu, *ACS Catal.*, 2017, **7**, 907–911; (c) M.-C. Fu, R. Shang, B. Zhao, B. Wang and Y. Fu, *Science*, 2019, **363**, 1429–1434.
- 6 D. A. Dirocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway and M. Tudge, *Angew. Chem. Int. Ed.*, 2014, **53**, 4802–4806.
- 7 (a) J. Jin and D. W. C. Macmillan, *Nature*, 2015, **525**, 87–90; (b) S. P. Pitre, M. Muuronen, D. A. Fishman and L. E. Overman, *ACS Catal.*, 2019, **9**, 3413–3418.
- 8 I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, 2010, **132**, 13194–13196.
- 9 (a) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95–99; (b) F. O'Hara, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2013, **135**, 12122–12134; (c) R. Gianatassio, S. Kawamura, C. L. Eprile, K. Foo, J. Ge, A. C. Burns, M. R. Collins and P. S. Baran, *Angew. Chem. Int. Ed.*, 2014, **53**, 9851–9855.
- 10 (a) X. Ma and S. B. Herzon, *J. Am. Chem. Soc.*, 2016, **138**, 8718–8721; (b) J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutiérrez, J. Giacoboni, M. W. Smith, P. L. Holland and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 2484–2503.
- 11 (a) G. A. Molander, V. Colombel and V. A. Braz, *Org. Lett.*, 2011, **13**, 1852–1855; (b) J. K. Matsui and G. A. Molander, *Org. Lett.*, 2017, **19**, 950–953; (c) J. K. Matsui, D. N. Primer and G. A. Molander, *Chem. Sci.*, 2017, **8**, 3512–3522; (d) H. Yan, Z.-W. Hou and H.-C. Xu, *Angew. Chem. Int. Ed.*, 2019, **58**, 4592–4595.
- 12 Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui and G. A. Molander, *J. Am. Chem. Soc.*, 2017, **139**, 12251–12258.
- 13 J. Dong, X. Wang, Z. Wang, H. Song, Y. Liu and Q. Wang, *Org. Chem. Front.*, 2019, **6**, 2902–2906.
- 14 (a) J. Yoshida, T. Maekawa, T. Murata, S. Matsunaga and S. Isoe, *J. Am. Chem. Soc.*, 1990, **112**, 1962–1970; (b) J. Biedermann, H. M. R. Wilkering, F. Uhlig and I. Hanzu, *Electrochem. Commun.*, 2019, **102**, 13–18.
- 15 (a) V. Corcé, L.-M. Chamoreau, E. Derat, J.-P. Goddard, C. Ollivier and L. Fensterbank, *Angew. Chem. Int. Ed.*, 2015, **54**, 11414–11418; (b) M. Jouffroy, D. N. Primer and G. A. Molander, *J. Am. Chem. Soc.*, 2016, **138**, 475–478; (c) C. Lévéque, L. Chenneberg, V. Corcé, C. Ollivier and L. Fensterbank, *Chem. Commun.*, 2016, **52**, 9877–9880; (d) Z.-J. Wang, S. Zheng, J. K. Matsui, Z. Lu and G. A. Molander, *Chem. Sci.*, 2019, **10**, 4389–4393.
- 16 (a) E. F. Perozzi and J. C. Martin, *J. Am. Chem. Soc.*, 1979, **101**, 1591–1593; (b) W. H. Stevenson, S. Wilson, J. C. Martin and W. B. Farnham, *J. Am. Chem. Soc.*, 1985, **107**, 6340–6352; (c) K. C. K. Swamy, V. Chandrasekhar, J. J. Harland, J. M. Holmes, R. O. Day and R. R. Holmes, *J. Am. Chem. Soc.*, 1990, **112**, 2341–2348.
- 17 For application of the spirosilane bearing a pair of the *C,O*-bidentate ligands $[-C_6H_4-2-C(CF_3)_2O-]$: (a) M. Kira, K. Sato and H. Sakurai, *J. Am. Chem. Soc.*, 1988, **110**, 4599–4602; (b) D. A. Dixon, W. R. Hertler, D. B. Chase, W. B. Farnham and F. Davidson, *Inorg. Chem.*, 1988, **27**, 4012–4018; (c) S. K. Chopra and J. C. Martin, *J. Am. Chem. Soc.*, 1990, **112**, 5342–5343; (d) H. Lenormand, J.-P. Goddard and L. Fensterbank, *Org. Lett.*, 2013, **15**, 748–751; (e) F. Medici, G. Gontard, E. Derat, G. Lemière and L. Fensterbank, *Organometallics*, 2018, **37**, 517–520; (f) F. Medici, J. Maury, G. Lemière and L. Fensterbank, *Chem. – Eur. J.*, 2019, **25**, 9438–9442; (g) K. Sakai, K. Oisaki and M. Kanai, *Adv. Synth. Catal.*, 2020, **362**, 337–343.
- 18 K. Ohkubo, K. Mizushima, R. Iwata and S. Fukuzumi, *Chem. Sci.*, 2011, **2**, 715–722.

