

Cite this: *Chem. Sci.*, 2019, **10**, 688

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Received 17th September 2018
Accepted 27th October 2018DOI: 10.1039/c8sc04134b
rsc.li/chemical-science

Introduction

Selective $C(sp^3)$ -H functionalization of easily accessible aliphatic alcohols could streamline the synthesis of alcohols of complex structures. Radical-mediated reactions based on the 1,5-hydrogen atom transfer (1,5-HAT) of an alkoxy radical intermediate have been widely used to functionalize the remote $\delta C(sp^3)$ -H bond of alcohol derivatives even in complex molecular settings.^{1,2} While great success has been achieved using various pre-activated derivatives of alcohols,³ the corresponding reactions of free alcohols are more desirable but pose a significant challenge due to the strong O-H bond (~ 105 kcal mol⁻¹).⁴ A few exciting advances featuring new catalysis strategies have emerged recently (Scheme 1A). Notably, Zuo demonstrated δ C-H amination of primary alcohols with azodiformate using a cerium photocatalyst.⁵ Jiao reported a δ C-C bond forming reaction with sulfonyl oxime ether using a Ag(I) catalyst and $K_2S_2O_8$ oxidant.⁶ Zhu reported a δ C-H Minisci-type heteroarylation of alcohols using a $PhI(OTFA)_2$ (PIFA) oxidant and LED light irradiation.⁷ In Zhu's report, 5 equiv. of alcohols are typically required and the δ C-H bonds of alcohols are limited to unactivated secondary and tertiary C-H. Herein, we report an efficient and economical protocol for δ $C(sp^3)$ -H heteroarylation of free aliphatic alcohols with various N-heteroarenes using a perfluorinated hydroxybenziodoxole (PFBI-OH) oxidant under photoredox catalysis (Scheme 1C).

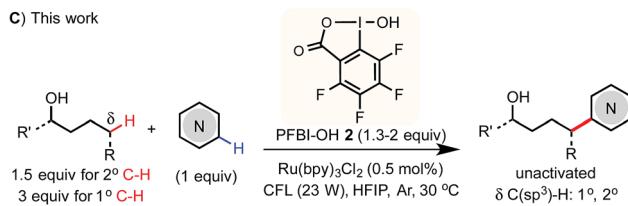
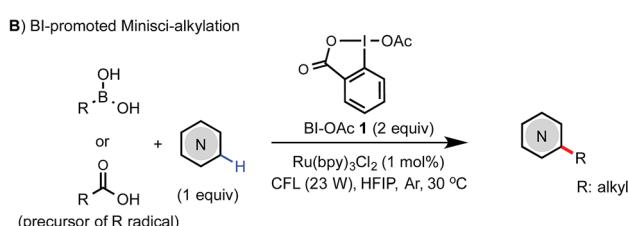
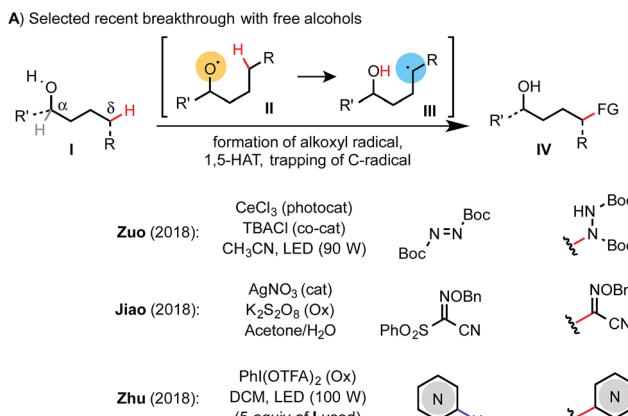
Photoredox-mediated remote $C(sp^3)$ -H heteroarylation of free alcohols†

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We report an efficient and economical method for remote δ $C(sp^3)$ -H heteroarylation of free aliphatic alcohols using a hypervalent iodine PFBI-OH oxidant under photoredox catalysis. The reaction sequence involves *in situ* alcoholysis of PFBI-OH with alcohol, generation of an alkoxy radical intermediate by SET reduction, 1,5-HAT, and Minisci-type C-C bond formation. This method uses a slight excess of alcohols, can facilitate reaction at δ methyl and methylene positions, and has been successfully applied to modification of complex drug molecules.

Results and discussion

The Minisci reaction *via* radical pathways offers a convenient strategy to access complex heteroarenes from simple precursors.^{8,9} In our previous studies, we discovered that benziodoxole



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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8sc04134b

Scheme 1 Radical-mediated remote $C(sp^3)$ -H functionalization of free alcohol.



reagent BI-OAc **1**, a cyclic hypervalent iodine(III), can promote C–H alkylation of various electron-deficient N-heteroarenes with alkyl boronic acid and alkyl carboxylic acid under photoredox catalysis (Scheme 1B).^{10,11} Interestingly, these two reactions proceed through different mechanisms.

The I–OAc bond of BI-OAc **1** can be activated by single electron transfer (SET) reduction by photoexcited Ru(II)* to form an acetate anion and BI radical (see fluorinated analog **35** in Scheme 4E), which reacts with boronic acid ($\text{RB}(\text{OH})_2$) to generate an alkyl radical intermediate following deboronation.¹⁰ In contrast, carboxylic acid (RCO_2H) can undergo ester exchange with BI-OAc to form BI-O₂CR, which can be activated by SET reduction to generate a BI anion and carboxyl radical, which provides an R radical following decarboxylation.¹¹ Encouraged by the BI-OAc-mediated activation of carboxylic acid and a recent study by Chen on BI-mediated β C–C scission reactions of cycloalkyl alcohols under photoredox catalysis,¹² we began to test whether common aliphatic alcohols can react with a suitable BI reagent to generate an alkoxyl radical, which can be trapped with N-heteroarenes to give useful products.^{13–15} As shown in Table 1, we were pleased to find that the reaction of pentanol **3** (1.5 equiv.) with 4-chloroquinoline **4**

(1 equiv.) gave alkylation product **4a** with an exclusive δ regioselectivity in 80% isolated yield using 1.35 equiv. of PFBI-OH **2** and 0.5 mol% of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ in hexafluoroisopropanol (HFIP) solvent at 30 °C under irradiation with a 23 W compact fluorescent lamp (CFL).¹⁶ In comparison, the use of BI-OAc **1**, BI-OH **5**, and other benziodoxoles bearing different aromatic substituents gave considerably lower yield (entries 2–4). Reaction with acyclic I(III) reagents including PhI(OTFA)₂ **7** or PhI(OAc)₂ also proceeded in low yield under our optimized conditions (entries 5 and 7). Other important observations regarding the reaction optimization include the following: (1) no α -heteroarylation product **4a'** was obtained.¹⁷ Little butyl-substituted product **4a''** (<2%) *via* the β -scission pathway of a pentoxy radical intermediate was obtained.¹⁸ (2) HFIP solvent is critical for obtaining high yield (entries 12 and 13). (3) While the use of 1 equiv. of alcohol **3** gave 42% yield of **4a**, increasing the amount of **3** from 1.5 to 2 equiv. only slightly improved the yield (entries 15 and 16). (4) The reaction yield is sensitive to the amount of **2** used (entries 17 and 18). (5) A reaction conducted under a CFL in the absence of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ gave no product (entry 11). (6) Pre-stirring of **3** and **2** is unnecessary.

Table 1 Heteroarylation of **3** with **4**

Entry	Change from the standard conditions, reagents (equiv.)	Yield of 4a ^a (%)
1	Standard conditions	84 (80 ^b)
2	2 → BI-OAc 1	25
3	2 → BI-OH 5	3
4	2 → PFBI-OAc 6	30
5	2 → PhI(OTFA) ₂ 7	4
6	2 → PhI(OTFA) ₂ 7 (2.3), CFL → blue (LED, 100 W), HFIP → CH_2Cl_2 , no $\text{Ru}(\text{bpy})_3\text{Cl}_2$	3
7	2 → PhI(OAc) ₂	28
8	$\text{Ru}(\text{bpy})_3\text{Cl}_2$ (0.5 → 1 mol%)	61
9	$\text{Ru}(\text{bpy})_3\text{Cl}_2$ → Ir(ppy) ₃	13
10	$\text{Ru}(\text{bpy})_3\text{Cl}_2$ → $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6$	32
11	No $\text{Ru}(\text{bpy})_3\text{Cl}_2$	<1
12	HFIP → CH_2Cl_2	3
13	HFIP → $\text{CF}_3\text{CH}_2\text{OH}$	38
14	HFIP → HFIP/ CH_2Cl_2 (1/5)	8
15	3 (1.5 → 1)	42
16	3 (1.5 → 2)	86
17	2 (1.35 → 1.5)	70
18	2 (1.35 → 1.2)	63

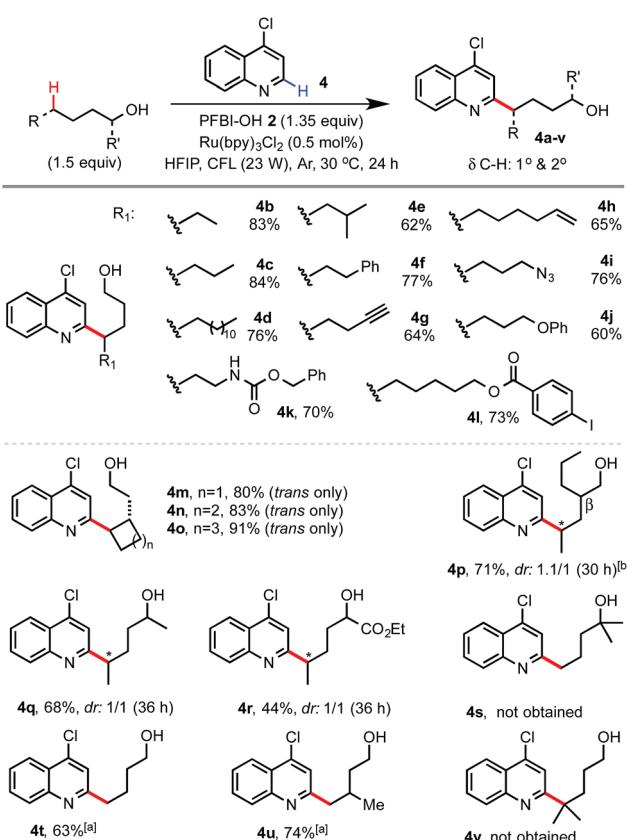
BI-OAc 1: A benziodoxole ring with an acetoxy group (-OAc) at the δ position. BI-OH 5: A benziodoxole ring with a hydroxyl group (-OH) at the δ position. PFBI-OAc 6: A benziodoxole ring with an acetoxy group (-OAc) at the δ position and a trifluoromethyl group (-CF₃) at the α position. PFBI-OH 2: A benziodoxole ring with a hydroxyl group (-OH) at the δ position and a trifluoromethyl group (-CF₃) at the α position. PhI(OTFA)2 7: A benziodoxole ring with a trifluoroacetoxy group (-OTFA) at the δ position.

^a NMR yield. ^b Isolated yield on a 0.4 mmol scale.

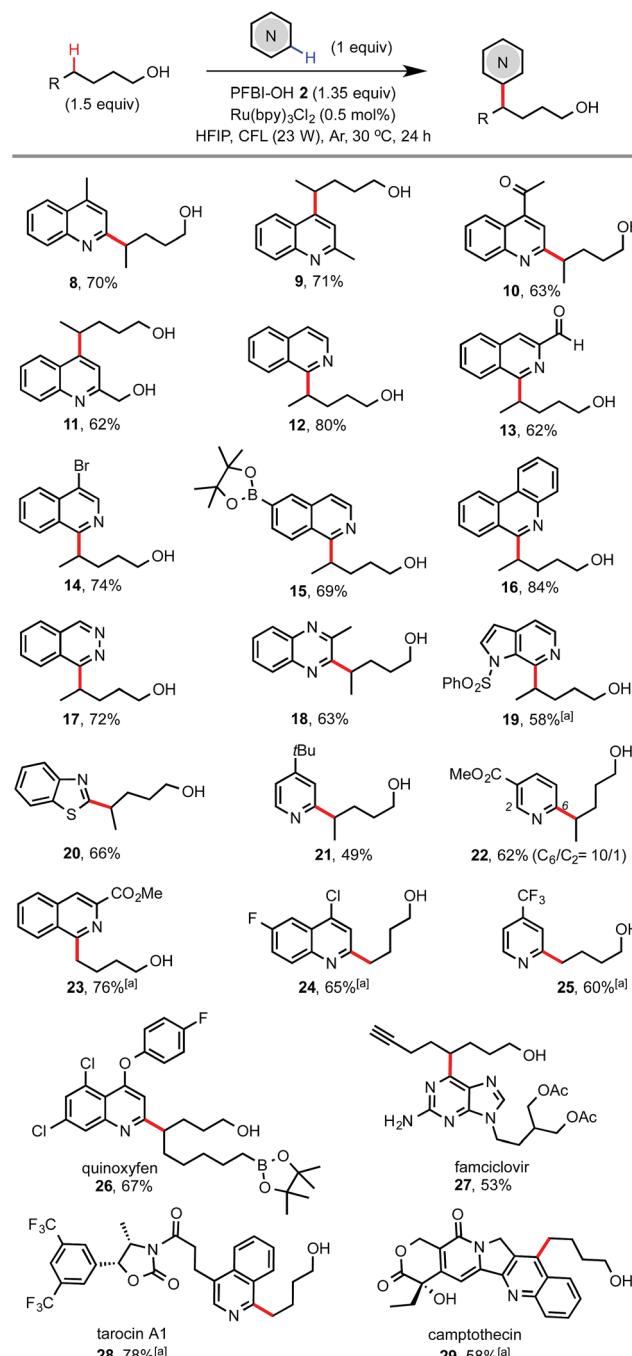


We next examined the scope of alcohols and N-heteroarenes under optimized conditions (Schemes 2 and 3). In general, reaction of primary and secondary alcohols proceeded in good to excellent yield with exclusive δ selectivity. Alcohols bearing relatively weak benzylic (**4f**), allylic (**4h**), α C–H of ether (**4j**), and tertiary (**4e**) $C(sp^3)$ –H bonds also worked well. A wide range of functional groups including terminal alkene and alkyne (**4h** and **4g**), Cbz (**4k**), azido (**4i**), ester (**4l**), aldehyde and ketone (**13** and **10**), halo (**4l**), and even pinacol boronate (**15** and **26**) groups were tolerated. Alcohols without any β -substituent usually gave little β -scission/alkylation side product. As shown in **4p**, a small amount of 4-heptyl substituted byproduct (**16**) was formed with 2-propylpentanol. While the radical functionalization of δ methylene C–H bonds of alcohols and their derivatives has been widely demonstrated in previous studies, we were pleased to find that our reaction at the more challenging δ methyl group also proceeded in good yield (see **4t**, **4u**, **23–25**, **28** and **29**) under slightly more forced conditions with 3 equiv. of alcohols and 2 equiv. of PFBI-OH 2. In comparison, N-heteroarylation at the methide position gave little product (see **4v**) probably due to oxidation of the 3° C-radical to a 3° cation.¹⁹ As shown by **4s**, tertiary alcohols gave little δ functionalization product.²⁰

As shown in Scheme 3, electron deficient N-heteroarenes showed good to excellent reactivity with various alcohols under the standard conditions. Chemoselectivity typical of Minisci reactions was observed for heteroarenes such as



Scheme 2 Scope of alcohols. Isolated yields on a 0.4 mmol scale. ^a3 equiv. of 1-alcohol and 2 equiv. of PFBI-OH were used, 36 h. ^b16% of 4-heptyl substituted side product was obtained.

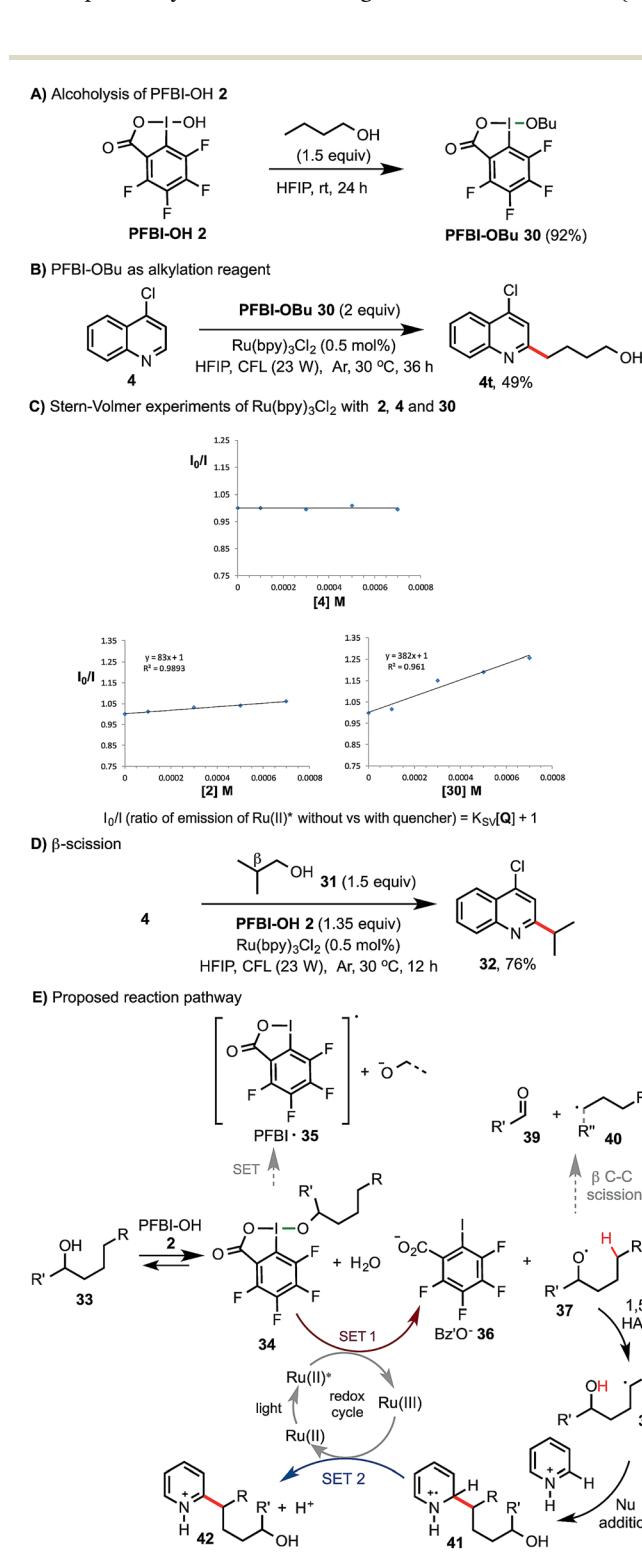


Scheme 3 Scope of N-heteroarenes. Isolated yield on a 0.4 mmol scale. ^a3 equiv. of alcohol and 2 equiv. of PFBI-OH were used, 36 h.

quinolines (**8–11**), isoquinolines (**12–15**), phenanthridine (**16**), phthalazine (**17**), quinoxaline (**18**), azaindole (**19**), and benzothiazole (**20**). Reaction of symmetric phthalazine (**17**) and pyridines (**21** and **25**) mainly gave mono-alkylation products. Reaction of complex N-heteroarene-containing drug molecules also worked well. For instance, reaction of famciclovir with 7-octyn-1-ol gave **27** in 53% yield. Reaction of quinoxifen with 9-boronylnonanol gave **26** in 67% yield. Reaction of tarocin A1 and camptothecin with 1-butanol gave **28** and **29** bearing a simple alkyl alcohol handle in good yield.



Preliminary experiments were carried out to probe the reaction mechanism (Scheme 4). Similar to the ester exchange reaction of BI-OAc **1** with carboxylic acids, PFBI-OH **2** can readily undergo alcoholysis with 1-butanol in HFIP at rt to give PFBI-OBu **30** (Scheme 4A). Reaction of 4-chloroquinoline **4** with **30** under similar photoredox conditions gave product **4t** in comparable yield as with using PFBI-OH **2** and BuOH (63% in Scheme 2).



Scheme 4 Mechanistic study.

in Scheme 2). Stern–Volmer (SV) fluorescence quenching experiments of Ru(bpy)₃Cl₂ showed that the Ru(II)* excited state is quenched by PFBI-OBu **30**, but not by 4-chloroquinoline **4** (Scheme 4C). In comparison, quenching of Ru(II)* by PFBI-OH **2** also occurs but with a much smaller SV quenching constant (K_{SV}) than when using **30** (83 vs. 382), indicating a weaker oxidative quenching ability of **2**.²¹ As shown in Scheme 4D, reaction of **4** with isobutanol **31**, bearing a β substituent but lacking δ C–H bonds, gave product **32** in high yield. This indicated that the corresponding isobutoxy radical is generated and then undergoes β -scission to form an isopropyl radical.¹⁸ Based on these pieces of evidence, we propose that the reaction of alcohol **33** starts with alcoholysis with PFBI-OH **2** to form **34** (Scheme 4E). **34** can be activated by SET reduction by Ru(II)* to give BzO[–] anion **36** and alkoxy radical **37**.²¹ The fluoro substitution on benziodoxole probably makes the iodo center of PFBI-OH **2** more electrophilic for alcoholysis and makes **34** more easily reducible by SET.²² 1,5-HAT reaction of **37** gives C-radical **38**, which reacts with N-heteroarenes to give **41**. SET oxidation of **41** by Ru(III) gives the alkylated product **42** and regenerates Ru(II). Alternatively, **41** could be oxidized by **34** to form **42** and **37**, propagating a radical chain reaction. In principle, alkoxy radical **37** can also undergo β -scission to give **39** and shortened alkyl radical **40**. In our system, we found that this competing pathway was negligible for alcohols bearing no β substituent (see **40**, R'' = H).²³

Conclusions

In summary, we have developed an efficient and economical method for remote C(sp³)–H heteroarylation of free aliphatic alcohols under mild conditions using photoredox catalysis. The reaction sequence involves facile *in situ* alcoholysis of PFBI-OH with alcohol, generation of an alkoxy radical intermediate by SET reduction, 1,5-HAT, and Minisci-type C–C bond formation. The reaction shows broad substrate scope for both alcohols and N-heteroarenes. Importantly, this method uses a slight excess of alcohols, can facilitate reaction at the δ methyl and methylene positions, and has been successfully applied to modification of complex drug molecules. The high electrophilicity of PFBI-OH is critical to achieving high efficiency without the use of a large excess of alcohols. Remote C–H functionalization reactions of other types of substrate using a similar strategy are currently under investigation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully thank the National Natural Science Foundation of China (21672105, 21725204, and 91753124), Natural Science Foundation of Tianjin (18JCZDJJC32800), and Laviana for financial support of this work.



Notes and references

1 For selected recent reviews on alkoxyl radical-mediated reactions, see: (a) L. M. Stateman, K. M. Nakafuku and D. A. Nagib, *Synthesis*, 2018, 1569; (b) J.-J. Guo, A. Hu and Z. Zuo, *Tetrahedron Lett.*, 2018, **59**, 2103; (c) K. Jia and Y. Chen, *Chem. Commun.*, 2018, **54**, 6105.

2 For selected reviews on radical functionalization of sp^3 C–H bonds, see: (a) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362; (b) M. C. White, *Science*, 2012, 335, 807; (c) T. Dohi and Y. Kita, *ChemCatChem*, 2014, **6**, 76; (d) M. Yan, J. C. Lo, J. T. Edwards and P. S. Baran, *J. Am. Chem. Soc.*, 2016, **138**, 12692; (e) D. Ravelli, S. Protti and M. Fagnoni, *Chem. Rev.*, 2016, **116**, 9850; (f) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016.

3 For selected examples of remote $C(sp^3)$ –H functionalization of alcohols using pre-activated derivatives, see: (a) D. H. R. Barton, J. M. Beaton, L. E. Celler and M. M. Pechet, *J. Am. Chem. Soc.*, 1960, **82**, 2640; (b) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed.*, 1964, **3**, 525; (c) J. I. Concepción, C. G. Francisco, R. Hernández, J. A. Salazar and E. Suárez, *Tetrahedron Lett.*, 1984, **25**, 1953; (d) A. L. J. Beckwith and B. P. Hay, *J. Am. Chem. Soc.*, 1988, **110**, 4415; (e) R. Kundu and Z. T. Ball, *Org. Lett.*, 2010, **12**, 2460; (f) J. Zhang, Y. Li, F. Zhang, C. Hu and Y. Chen, *Angew. Chem., Int. Ed.*, 2016, **55**, 1872; (g) C. Wang, K. Harms and E. Meggers, *Angew. Chem., Int. Ed.*, 2016, **55**, 13495.

4 Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, FL, 2007.

5 A. Hu, J.-J. Guo, H. Pan, H. Tang, Z. Gao and Z. Zuo, *J. Am. Chem. Soc.*, 2018, **140**, 1612.

6 Y. Zhu, K. Huang, J. Pan, X. Qiu, X. Luo, Q. Qin, J. Wei, X. Wen, L. Zhang and N. Jiao, *Nat. Commun.*, 2018, **9**, 2625.

7 During the preparation of this manuscript, the following work by Zhu was published online. X. Wu, H. Zhang, N. Tang, Z. Wu, D. Wang, M. Ji, Y. Xu, M. Wang and C. Zhu, *Nat. Commun.*, 2018, **9**, 3343.

8 (a) F. Minisci, E. Vismara and F. Fontana, *Heterocycles*, 1989, **28**, 489; (b) M. A. J. Dunton, *Med. Chem. Commun.*, 2011, **2**, 1135.

9 For selected recent examples of Minisci alkylation of N-heteroarenes, see: (a) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. D. Bel and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 3292; (b) G. A. Molander, V. Colombel and V. A. Braz, *Org. Lett.*, 2011, **13**, 1852; (c) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95; (d) A. P. Antonchick and L. Burgmann, *Angew. Chem., Int. Ed.*, 2013, **52**, 3267; (e) J. Jin and D. W. C. MacMillan, *Nature*, 2015, **525**, 87; (f) L. Fang, L. Chen, J. Yu and L. Wang, *Eur. J. Org. Chem.*, 2015, 1910; (g) D.-C. Wang, R. Xia, M.-S. Xie, G.-R. Qu and H.-M. Guo, *Org. Biomol. Chem.*, 2016, **14**, 4189; (h) M. C. Quattrini, S. Fujii, K. Yamada, T. Fukuyama, D. Ravelli, M. Fagnoni and I. Ryu, *Chem. Commun.*, 2017, **53**, 2335.

10 G.-X. Li, C. A. Morales-Rivera, Y. Wang, F. Gao, G. He, P. Liu and G. Chen, *Chem. Sci.*, 2016, **7**, 6407.

11 J. Wang, G.-X. Li, G. He and G. Chen, *Asian J. Org. Chem.*, 2018, **7**, 1307.

12 (a) K. Jia, F. Zhang, H. Huang and Y. Chen, *J. Am. Chem. Soc.*, 2016, **138**, 1514; (b) K. Jia, Y. Pan and Y. Chen, *Angew. Chem., Int. Ed.*, 2017, **56**, 2478.

13 For selected reviews on photoredox-mediated organic reactions, see: (a) J. M. R. Narayanan and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (c) M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898.

14 For selected reviews on hypervalent iodine chemistry, see: (a) T. Wirth, *Angew. Chem., Int. Ed.*, 2005, **44**, 3656; (b) A. Yoshimura and V. V. Zhdankin, *Chem. Rev.*, 2016, **116**, 3328; (c) Y. Li, D. P. Hari, M. V. Vita and J. Waser, *Angew. Chem., Int. Ed.*, 2016, **55**, 4436.

15 For selected examples of using benziodoxole reagents in visible light-mediated reactions, see: (a) H. Huang, G. Zhang, L. Gong, S. Zhang and Y. Chen, *J. Am. Chem. Soc.*, 2014, **136**, 2280; (b) Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2015, **54**, 11196; (c) F. Le Vaillant, T. Courant and J. Waser, *Angew. Chem., Int. Ed.*, 2015, **54**, 11200; (d) Y. Wang, G.-X. Li, G. Yang, G. He and G. Chen, *Chem. Sci.*, 2016, **7**, 2679.

16 For the original report of PFBI-OH 2, see: R. D. Richardson, J. M. Zayed, S. Altermann, D. Smith and T. Wirth, *Angew. Chem., Int. Ed.*, 2007, **46**, 6529. PFBI-OH can be readily prepared on the gram scale in 2 steps from a cheap precursor (2,3,4,5-tetrafluorobenzoic acid, <\$250 per kg).

17 Previously reported Minisci alkylation reactions with alcohols mainly take place on the weak α -C(sp^3)-H bond of alcohols; for selected examples, see: (a) F. Minisci, A. Citterio and E. Vismara, *Tetrahedron*, 1985, **41**, 4157; (b) C. A. Correia, L. Yang and C.-J. Li, *Org. Lett.*, 2011, **13**, 4581; (c) T. D. Neubert, Y. Schmidt, E. Conroy and D. Stamos, *Org. Lett.*, 2015, **17**, 2362.

18 For selected examples of radical reactions facilitated by β -C–C scission of alcohols, see: (a) R. Ren, Z. Wu, Y. Xu and C. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2866; (b) D. D. Bume, C. R. Pitts and T. Lectka, *Eur. J. Org. Chem.*, 2016, **26**; (c) A. Nikolaev, C. Y. Legault, M. Zhang and A. Orellana, *Org. Lett.*, 2018, **20**, 796; (d) X. Wu, M. Wang, L. Huan, D. Wang, J. Wang and C. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 1640.

19 G.-X. Li, C. A. Morales-Rivera, F. Gao, Y. Wang, G. He, P. Liu and G. Chen, *Chem. Sci.*, 2017, **8**, 7180.

20 Alcoholysis of PFBI-OH 2 with tertiary alcohol is probably hampered by sterics.

21 HFIP is a weak acid. We suspect that proton-coupled electron transfer may be involved in SET reduction of **34**, forming **Bz'OH** and **37**. In comparison, formation of PFBI radical **35** via SET reduction of **34** is possibly less favoured due to the weaker basicity of the alkoxyl O on **34**. PFBI-OH



2 could also be activated by SET reduction to generate PFBI radical 35. The use of slightly more alcohol than PFBI-OH 2 (1.5 vs. 1.35 equiv.) might help suppress the formation of 35.
22 Our previous study showed that PFBI radical 35 is more electrophilic for H-abstraction than the corresponding plain BI radical (ref. 19).

23 Even reactions with butanol gave little propyl-substituted side products (see 4t). As seen with isobutanol 31, some β -substituted alcohols can readily undergo β -scission to form more stabilized C-radical 40, which can be effectively engaged in the subsequent Minisci reaction. Detailed study of this transformation will be reported in a future paper.

