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Photoredox-mediated remote C(sp<sup>3</sup>)-H heteroarylation of free alcohols†Guo-Xing Li,<sup>a</sup> Xiafei Hu,<sup>a</sup> Gang He<sup>\*a</sup> and Gong Chen<sup>ID</sup> <sup>\*ab</sup>

We report an efficient and economical method for remote  $\delta$  C(sp<sup>3</sup>)-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  $\delta$  methyl and methylene positions, and has been successfully applied to modification of complex drug molecules.

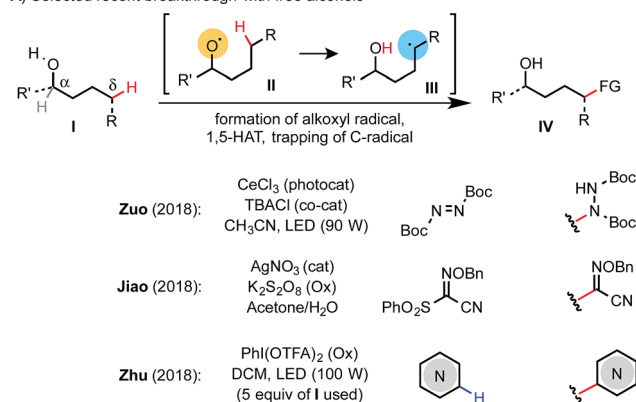
## Introduction

Selective C(sp<sup>3</sup>)-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<sup>3</sup>)-H bond of alcohol derivatives even in complex molecular settings.<sup>1,2</sup> While great success has been achieved using various pre-activated derivatives of alcohols,<sup>3</sup> the corresponding reactions of free alcohols are more desirable but pose a significant challenge due to the strong O-H bond (~105 kcal mol<sup>-1</sup>).<sup>4</sup> A few exciting advances featuring new catalysis strategies have emerged recently (Scheme 1A). Notably, Zuo demonstrated  $\delta$  C-H amination of primary alcohols with azodiformate using a cerium photocatalyst.<sup>5</sup> Jiao reported a  $\delta$  C-C bond forming reaction with sulfonyl oxime ether using a Ag(I) catalyst and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> oxidant.<sup>6</sup> Zhu reported a  $\delta$  C-H Minisci-type heteroarylation of alcohols using a PhI(OTFA)<sub>2</sub> (PIFA) oxidant and LED light irradiation.<sup>7</sup> In Zhu's report, 5 equiv. of alcohols are typically required and the  $\delta$  C-H bonds of alcohols are limited to unactivated secondary and tertiary C-H. Herein, we report an efficient and economical protocol for  $\delta$  C(sp<sup>3</sup>)-H heteroarylation of free aliphatic alcohols with various N-heteroarenes using a perfluorinated hydroxybenziodoxole (PFBI-OH) oxidant under photoredox catalysis (Scheme 1C).

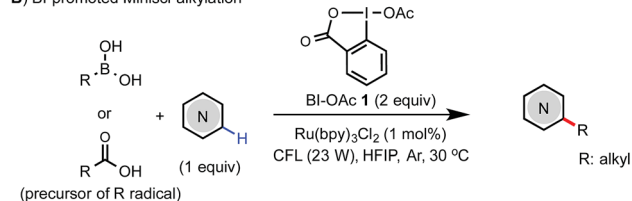
## Results and discussion

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

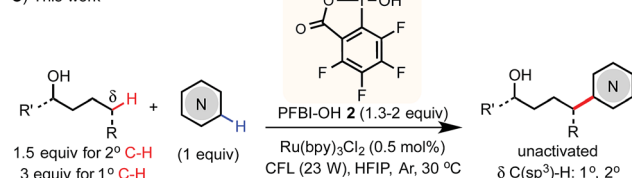
## A) Selected recent breakthrough with free alcohols



## B) BI-promoted Minisci-alkylation



## C) This work



Scheme 1 Radical-mediated remote C(sp<sup>3</sup>)-H functionalization of free alcohol.

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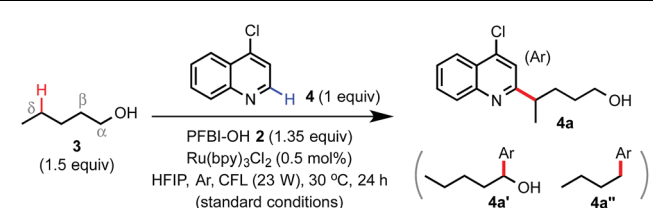
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reagent BI-OAc **1**, a cyclic hypervalent iodine(III), can promote C–H alkylation of various electron-deficient N-heteroarenes with alkyl boronic acid and alkyl carboxylic acid under photoredox catalysis (Scheme 1B).<sup>10,11</sup> Interestingly,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

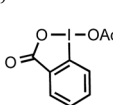
The I–OAc bond of BI-OAc **1** can be activated by single electron transfer (SET) reduction by photoexcited Ru(II)\* to form an acetate anion and BI radical (see fluorinated analog **35** in Scheme 4E), which reacts with boronic acid (RB(OH)<sub>2</sub>) to generate an alkyl radical intermediate following deboronation.<sup>10</sup> In contrast, carboxylic acid (RCO<sub>2</sub>H) can undergo ester exchange with BI-OAc to form BI–O<sub>2</sub>CR, which can be activated by SET reduction to generate a BI anion and carboxyl radical, which provides an R radical following decarboxylation.<sup>11</sup> 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,<sup>12</sup> 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.<sup>13–15</sup> As shown in Table 1, we were pleased to find that the reaction of pentanol **3** (1.5 equiv.) with 4-chloroquinoline **4**

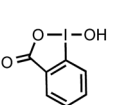
(1 equiv.) gave alkylation product **4a** with an exclusive δ regioselectivity in 80% isolated yield using 1.35 equiv. of PFBI-OH **2** and 0.5 mol% of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> in hexafluoroisopropanol (HFIP) solvent at 30 °C under irradiation with a 23 W compact fluorescent lamp (CFL).<sup>16</sup> 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)<sub>2</sub> **7** or PhI(OAc)<sub>2</sub> 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.<sup>17</sup> Little butyl-substituted product **4a''** (<2%) via the β-scission pathway of a pentoxyl radical intermediate was obtained.<sup>18</sup> (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 Ru(bpy)<sub>3</sub>Cl<sub>2</sub> gave no product (entry 11). (6) Pre-stirring of **3** and **2** is unnecessary.

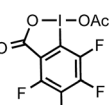
Table 1 Heteroarylation of **3** with **4**

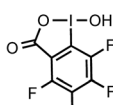


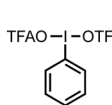
| Entry | Change from the standard conditions, reagents (equiv.)                                                                                                      | Yield of <b>4a</b> <sup>a</sup> (%) |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------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

  
**BI-OAc 1**

  
**BI-OH 5**

  
**PFBI-OAc 6**

  
**PFBI-OH 2**

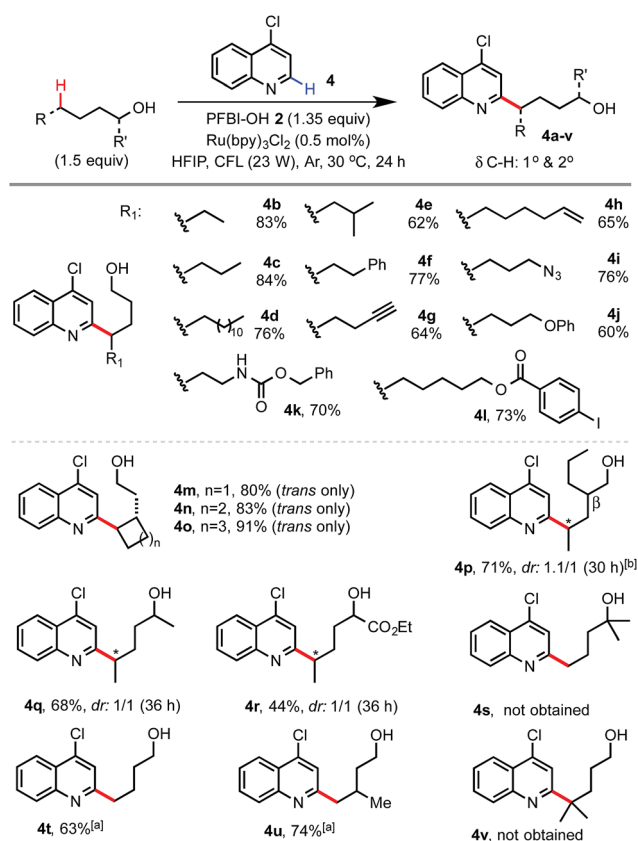
  
**PIFA 7**

<sup>a</sup> NMR yield. <sup>b</sup> Isolated yield on a 0.4 mmol scale.

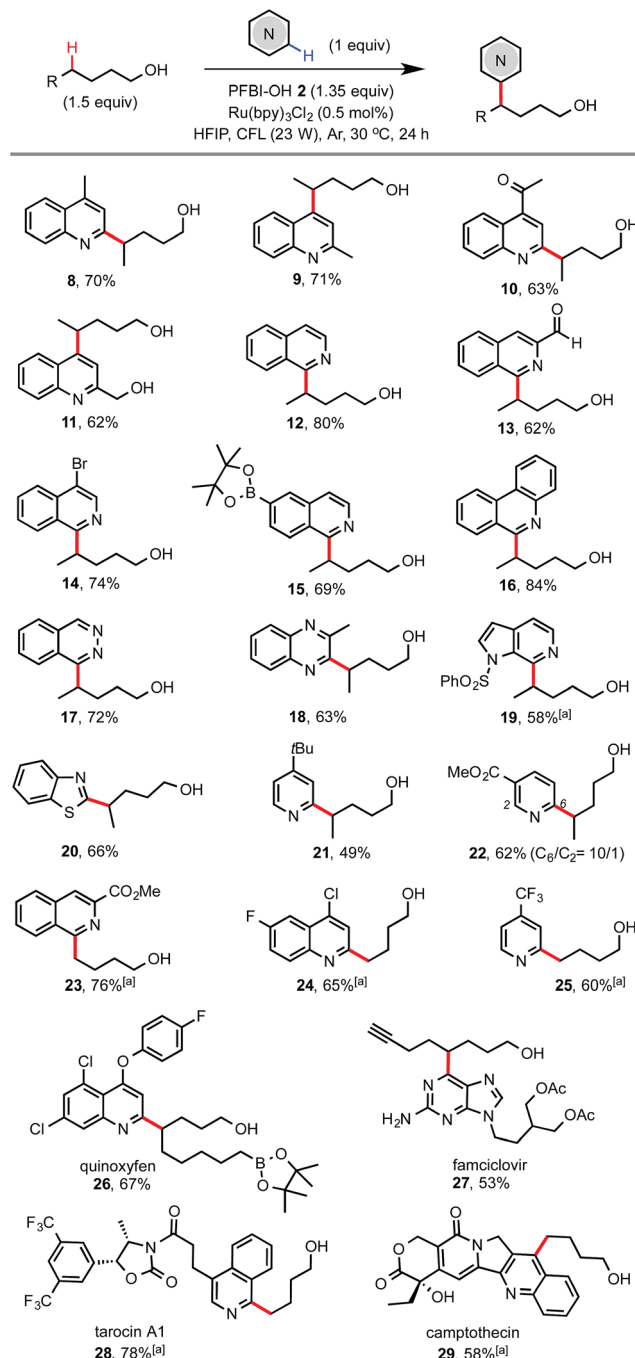


We next examined the scope of alcohols and N-heteroarenes under optimized conditions (Schemes 2 and 3). In general, reaction of primary and secondary alcohols proceeded in good to excellent yield with exclusive  $\delta$  selectivity. Alcohols bearing relatively weak benzylic (**4f**), allylic (**4h**),  $\alpha$  C–H of ether (**4j**), and tertiary (**4e**) C(sp<sup>3</sup>)–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  $\beta$ -substituent usually gave little  $\beta$ -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  $\delta$  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  $\delta$  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.<sup>19</sup> As shown by **4s**, tertiary alcohols gave little  $\delta$  functionalization product.<sup>20</sup>

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. <sup>a</sup>3 equiv. of 1-alcohol and 2 equiv. of PFBI-OH were used, 36 h. <sup>b</sup>16% of 4-heptyl substituted side product was obtained.



Scheme 3 Scope of N-heteroarenes. Isolated yield on a 0.4 mmol scale. <sup>a</sup>3 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-borylnonan-1-ol gave **26** in 67% yield. Reaction of taracin 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). Stern–Volmer (SV) fluorescence quenching experiments of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> 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**.<sup>21</sup> As shown in Scheme 4D, reaction of **4** with isobutanol **31**, bearing a  $\beta$  substituent but lacking  $\delta$  C–H bonds, gave product **32** in high yield. This indicated that the corresponding isobutoxy radical is generated and then undergoes  $\beta$ -scission to form an isopropyl radical.<sup>18</sup> 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 Bz'O anion **36** and alkoxy radical **37**.<sup>21</sup> 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.<sup>22</sup> 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  $\beta$ -scission to give **39** and shortened alkyl radical **40**. In our system, we found that this competing pathway was negligible for alcohols bearing no  $\beta$  substituent (see **40**, R'' = H).<sup>23</sup>

in Scheme 2). Stern–Volmer (SV) fluorescence quenching experiments of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> 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**.<sup>21</sup> As shown in Scheme 4D, reaction of **4** with isobutanol **31**, bearing a  $\beta$  substituent but lacking  $\delta$  C–H bonds, gave product **32** in high yield. This indicated that the corresponding isobutoxy radical is generated and then undergoes  $\beta$ -scission to form an isopropyl radical.<sup>18</sup> 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 Bz'O anion **36** and alkoxy radical **37**.<sup>21</sup> 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.<sup>22</sup> 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  $\beta$ -scission to give **39** and shortened alkyl radical **40**. In our system, we found that this competing pathway was negligible for alcohols bearing no  $\beta$  substituent (see **40**, R'' = H).<sup>23</sup>

## Conclusions

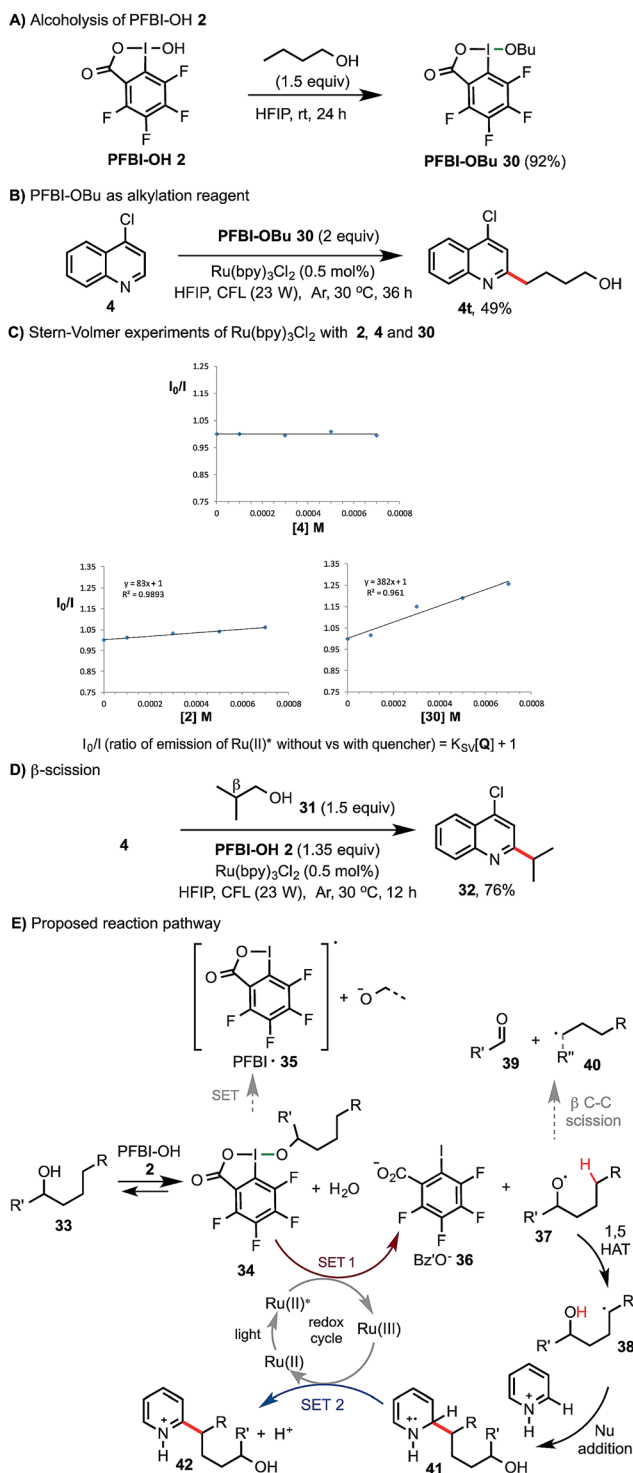
In summary, we have developed an efficient and economical method for remote C(sp<sup>3</sup>)–H heteroarylation of free aliphatic alcohols under mild conditions using photoredox catalysis. The reaction sequence involves facile *in situ* alcoholysis of PFBI-OH with alcohol, generation of an alkoxy radical 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  $\delta$  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

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Scheme 4 Mechanistic study.



## Notes and references

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- 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).
- Previously reported Minisci alkylation reactions with alcohols mainly take place on the weak  $\alpha\text{-C}(\text{sp}^3)\text{-H}$  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.
- For selected examples of radical reactions facilitated by  $\beta\text{-C-C}$  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.
- G.-X. Li, C. A. Morales-Rivera, F. Gao, Y. Wang, G. He, P. Liu and G. Chen, *Chem. Sci.*, 2017, **8**, 7180.
- Alcoholysis of PFBI-OH **2** with tertiary alcohol is probably hampered by sterics.
- 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  $\beta$ -substituted alcohols can readily undergo  $\beta$ -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.

