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Photoredox-mediated remote C(sp³)-H heteroarylation of free alcohols†

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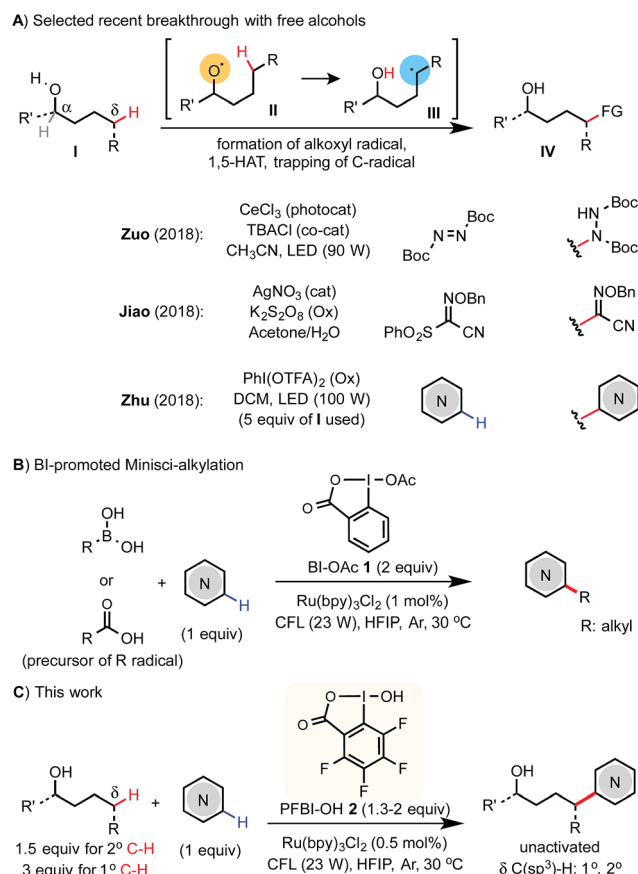
We report an efficient and economical method for remote δ C(sp³)-H heteroarylation of free aliphatic alcohols using a hypervalent iodine PFBI-OH oxidant under photoredox catalysis. The reaction sequence involves *in situ* alcoholysis of PFBI-OH with alcohol, generation of an alkoxy radical intermediate 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.

Introduction

Selective C(sp³)-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 δ C(sp³)-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 K₂S₂O₈ 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(sp³)-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.^{8,9} In our previous studies, we discovered that benziodoxole



Scheme 1 Radical-mediated remote C(sp³)-H functionalization of free alcohol.

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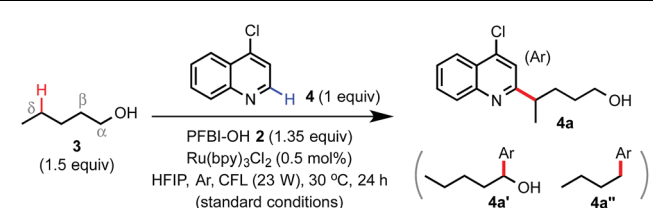


reagent BI-OAc **1**, a cyclic hypervalent iodine(III), can promote C–H alkylation of various electron-deficient N-heteroarenes with alkyl boronic acid and alkyl carboxylic acid under photo-redox catalysis (Scheme 1B).^{10,11} Interestingly, these two reactions proceed through different mechanisms.

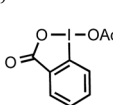
The I–OAc bond of BI-OAc **1** can be activated by single electron transfer (SET) reduction by photoexcited Ru(II)* to form an acetate anion and BI radical (see fluorinated analog **35** in Scheme 4E), which reacts with boronic acid (RB(OH)₂) to generate an alkyl radical intermediate following deboronation.¹⁰ In contrast, carboxylic acid (RCO₂H) 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**

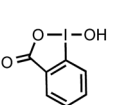
(1 equiv.) gave alkylation product **4a** with an exclusive δ regioselectivity in 80% isolated yield using 1.35 equiv. of PFBI-OH **2** and 0.5 mol% of Ru(bpy)₃Cl₂ in hexafluoroisopropanol (HFIP) solvent at 30 °C under irradiation with a 23 W compact fluorescent lamp (CFL).¹⁶ In comparison, the use of 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 pentoxyl 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 Ru(bpy)₃Cl₂ gave no product (entry 11). (6) Pre-stirring of **3** and **2** is unnecessary.

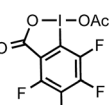
Table 1 Heteroarylation of **3** with **4**

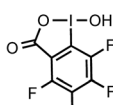


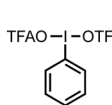
Entry	Change from the standard conditions, reagents (equiv.)	Yield of 4a ^a (%)
1	Standard conditions	84 (80 ^b)
2	2 → BI-OAc 1	25
3	2 → BI-OH 5	3
4	2 → PFBI-OAc 6	30
5	2 → PhI(OTFA) ₂ 7	4
6	2 → PhI(OTFA) ₂ 7 (2.3), CFL → blue (LED, 100 W), HFIP → CH ₂ Cl ₂ , no Ru(bpy) ₃ Cl ₂	3
7	2 → PhI(OAc) ₂	28
8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


BI-OH 5


PFBI-OAc 6


PFBI-OH 2

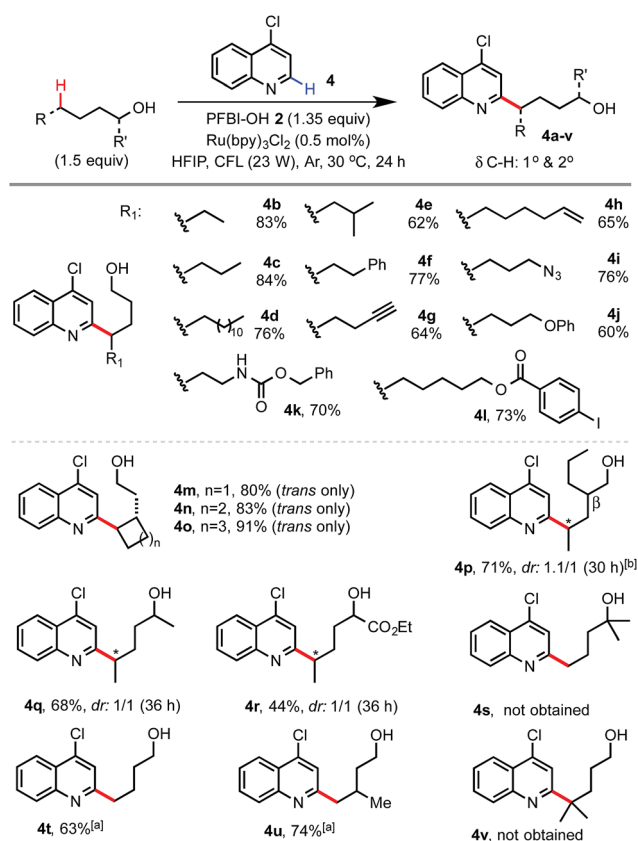

PIFA 7

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

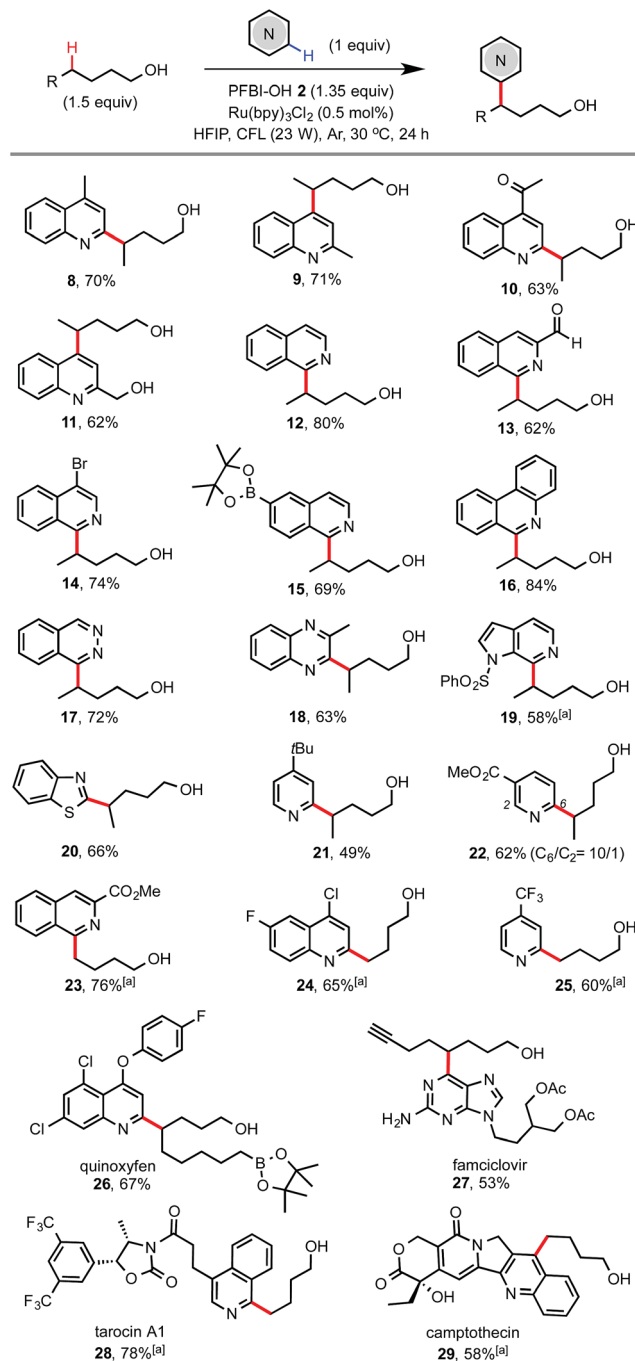


We next examined the scope of alcohols and N-heteroarenes under optimized conditions (Schemes 2 and 3). In general, reaction of primary and secondary alcohols proceeded in good to excellent yield with exclusive δ selectivity. Alcohols bearing relatively weak benzylic (**4f**), allylic (**4h**), α C–H of ether (**4j**), and tertiary (**4e**) C(sp³)–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.

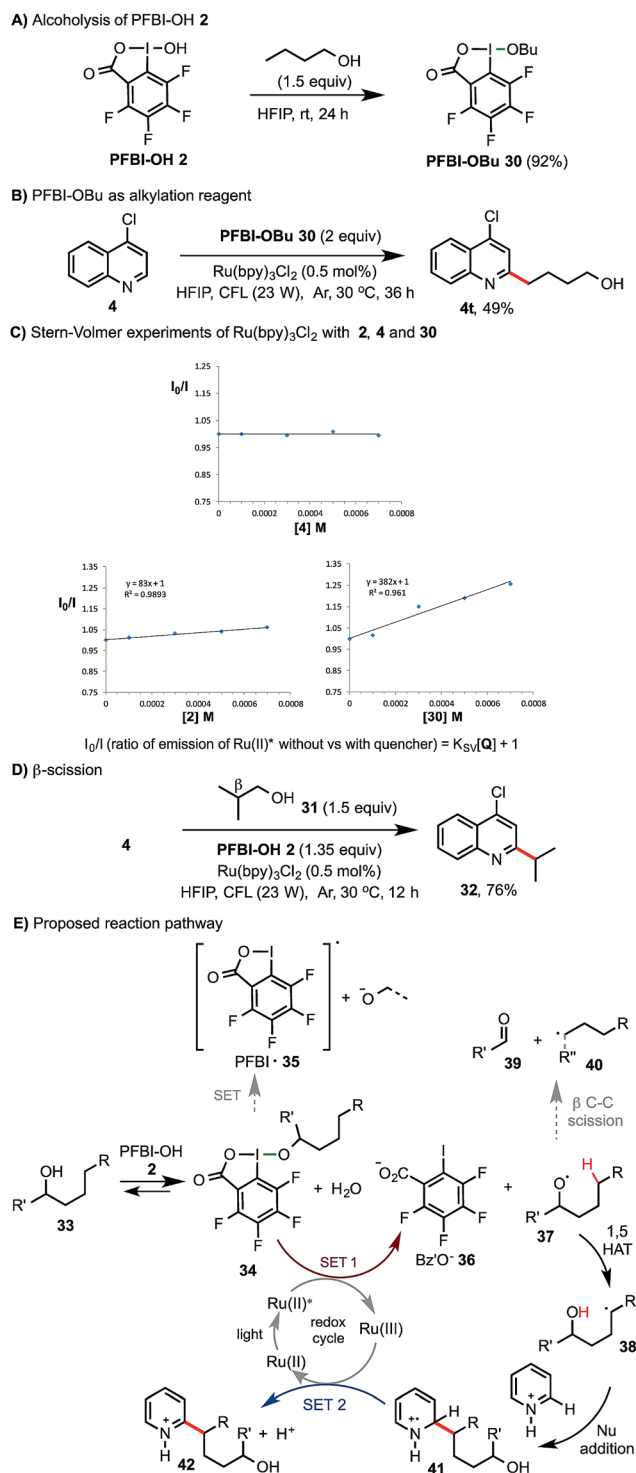


Scheme 3 Scope of N-heteroarenes. Isolated yield on a 0.4 mmol scale. ^a3 equiv. of alcohol and 2 equiv. of PFBI-OH were used, 36 h.

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-borylnonanol 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). 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 Bz'O[−] 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



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 Bz'O[−] 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

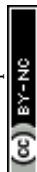
In summary, we have developed an efficient and economical method for remote C(sp³)–H heteroarylation of free aliphatic alcohols under mild conditions using photoredox catalysis. The reaction sequence involves facile *in situ* alcoholysis of PFBI-OH with alcohol, generation of an alkoxy radical intermediate 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

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- 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 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.

