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Cobalt-electrocatalytic C–H hydroxyalkylation of *N*-heteroarenes with trifluoromethyl ketones†

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Trifluoromethyl carbinols and *N*-heteroarenes are both prevalent in bioactive molecules. However, access to high-value pharmacophores combining these two functional groups still remains a challenge. Herein, we report an electro-chemical redox-neutral coupling for the synthesis of *N*-heteroaryl trifluoromethyl carbinols from readily available *N*-heteroarenes and trifluoromethyl ketones. The reaction starts with reversing the polarity of ketones to nucleophilic ketyl radicals through an electrocatalytic proton-coupled electron transfer (PCET), followed by radical addition to heteroarenes and rearomatization to afford tertiary alcohol products. Importantly, the merging of paired electrolysis and cobalt catalysis is crucial to this regioselective C–H hydroxyalkylation of heteroarenes, and thus avoids several known competing pathways including the spin-center shift (SCS) process. Collectively, this protocol provides straightforward access to heteroaryl trifluoromethyl carbinols, featuring ideal atom economy, excellent regioselectivity, and paired redox-neutral electrolysis.

Introduction

Both organofluorine compounds[1] and *N*-heterocycles[2] are prevalent in pharmaceuticals, agrochemicals, and other bioactive molecules. In particular, a number of therapeutic drugs contain CF_3-substituted tertiary alcohols[3] or *N*-heteroarenes,[4] as illustrated in Scheme 1A. The combination of these two functional groups, trifluoromethyl carbinols and *N*-heteroarenes, is similarly impactful, expanding the chemical space for drug discovery.[5]

While numerous methods have been developed to generate CF_3-substituted tertiary alcohols,[6] access to *N*-heteroaryl trifluoromethyl carbinols remains underdeveloped.[5c,7] The prevailing approach to CF_3-substituted tertiary alcohols involves nucleophilic addition of a nucleophile, such as organometallic reagents or electron-rich arenes, to the readily available trifluoromethyl ketones (Scheme 1B, left).[6e,8] In contrast, the C–H hydroxyalkylation of electron-deficient *N*-heteroarenes with trifluoromethyl ketones remains unknown, probably due to their mismatched polarity (Scheme 1B, right).

The umpolung strategy, which converts trifluoromethyl ketones to the nucleophilic ketyl radicals,[9] presents an attractive solution for this unprecedented coupling (Scheme 1C), but also raises formidable synthetic challenges. Currently, ketyl radical generation still relies primarily on stoichiometric amounts of Zn, Ti or SmI_2.[10] Alternatively, photoredox catalysis has been proved to be capable of generating ketyl radicals from ketones.[11] However, this method typically requires the use of terminal reductants. Recently, Wang reported a photocatalytic C–H alkylation of heteroarenes with ketyl radicals from ketones.[12] This reaction was achieved by the addition of ketyl radicals to heterarenes *via* a Minisci reaction[13] pathway in combination with a spin-center shift (SCS) process,[14] yielding alkylated products and not hydroxyalkylated adducts. Furthermore, organic electrochemistry[15] has also been demonstrated as a sustainable method for the conversion of ketones to ketyl radicals.[16] However, these protocols commonly require a divided cell setup or a sacrificial anode. Consequently, there remains no general method for accessing tertiary alcohols through the Minisci reaction of ketones and electron-deficient *N*-heteroarenes.

Herein, we report cobalt-electrocatalytic C–H hydroxyalkylation of *N*-heteroarenes with trifluoromethyl ketones for the synthesis of CF_3-substituted tertiary alcohols (Scheme 1D). We envisioned that ketyl radical **I** could be generated from trifluoromethyl ketone **2** *via* a proton-coupled electron transfer (PCET)[17] under mild electroreductive[18] conditions. The desired alcohol product **3** would be constructed through selective radical addition to heteroarene **1** and subsequent anodic oxidation of intermediate **II**. The following competing reaction pathways need to be suppressed. Firstly, a homocoupling of ketyl radical **I** is possible to deliver pinacol **4**. Secondly, the CF_3-substituted ketyl radical **I** may undergo a defluorinative spin-center shift giving radical **5**.[19] Alternatively, **I** may be further reduced to **6**,[20] which can undergo other side reactions. Moreover, the C2/C4 selectivity is also highly challenging.[13c,21] Furthermore, intermediate **II** may be susceptible to SCS

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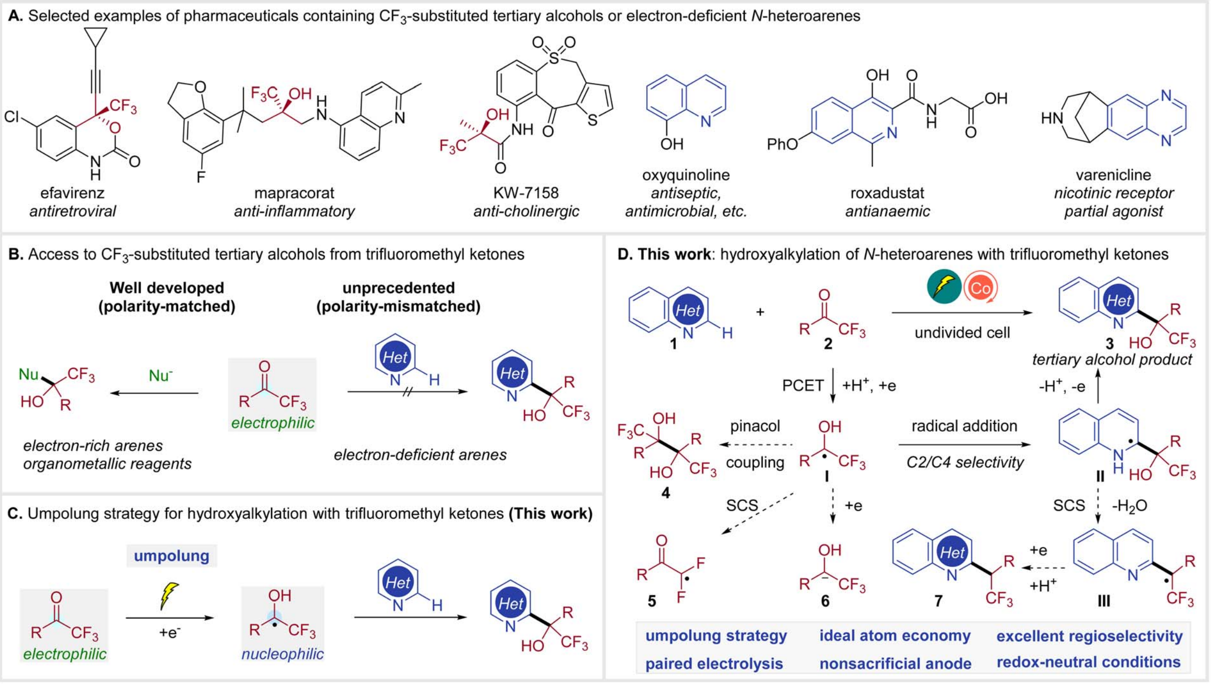


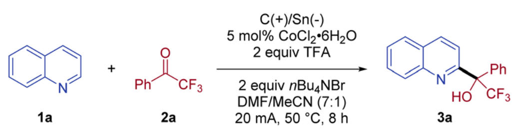
Scheme 1 Context and strategy to access trifluoromethyl tertiary alcohols from trifluoromethyl ketones.

fragmentation[12,22] to generate **III**, which could lead to alkylated side-product **7**, since the α-hydroxy group proved to be active towards elimination of water. These challenges could be addressed *via* identification of a suitable paired electrocatalytic system.[23] This electrocatalytic methodology enables a general, regioselective, and efficient synthesis of heteroaryl trifluoromethyl carbinols from trifluoromethyl ketones and *N*-heteroarenes.

Results and discussion

We commenced our investigation with the coupling of quinoline (**1a**) and 2,2,2-trifluoroacetophenone (**2a**) as the model reaction (Table 1). Pleasingly, the desired alcohol product **3a** was isolated in 76% yield, when the electrolysis was conducted in a DMF/MeCN (7 : 1) solution of **1a** and **2a** at 50 °C in the presence of $CoCl_2·6H_2O$ (5 mol%) as the catalyst, trifluoroacetic acid (TFA) as the acid, and $n$$Bu_4NBr$ as the electrolyte with an undivided cell (entry 1). Notably, only C2-substituted quinoline product **3a** was isolated, without the detection of a C4-substituted isomer. When a sacrificial zinc anode was used, no desired reaction was observed, highlighting the essential role of the paired electrolysis (entry 2). Other cathodes with a lower overpotential than stannum, for example, aluminum, were less suitable, indicating that a Sn cathode was necessary to avoid the competing proton reduction (entry 3).[24] Further evaluation of various solvents revealed that the use of DMF/MeCN (7 : 1) was crucial for the efficient conversion of this coupling reaction. Reactions using other solvents, such as, DMF, MeCN, and DMSO, exhibited a dramatic decrease in reaction efficiency (entries 4–6). The choice of electrolyte also proved important to the success of the coupling, with $n$$Bu_4NBr$ being optimal, while electrolytes with other counteranions, for example, $n$$Bu_4NOAc$, $n$$Bu_4NI$, and $n$$Bu_4NCl$, were less effective (entries 7–9). Replacing TFA with other acids, such as HCl and H_2SO_4, led to no formation of CF_3-substituted tertiary alcohol **3a** (entry 10). In

Table 1 Optimization of the reaction conditions[a]



Entry	Variation from standard conditions	Yield[b]
1	None	76%
2	Zn(+)/Sn(−) instead of C(+)/Sn(−)	0%
3	C(+)/Al(−) instead of C(+)/Sn(−)	34%
4	DMF as the solvent	65%
5	MeCN as the solvent	30%
6	DMSO as the solvent	21%
7	$n$$Bu_4NOAc$ instead of $n$$Bu_4NBr$	19%
8	$n$$Bu_4NI$ instead of $n$$Bu_4NBr$	40%
9	$n$$Bu_4NCl$ instead of $n$$Bu_4NBr$	61%
10	Conc. HCl or H_2SO_4 instead of TFA	0%
11	SmI_2 instead of $CoCl_2·6H_2O$	54%
12	$CoBr_2$ instead of $CoCl_2·6H_2O$	66%
13	$Co(OAc)_3$ instead of $CoCl_2·6H_2O$	52%
14	10 mA, 36 h instead of 20 mA, 8 h	70%
15	rt	49%
16	Without current	0%

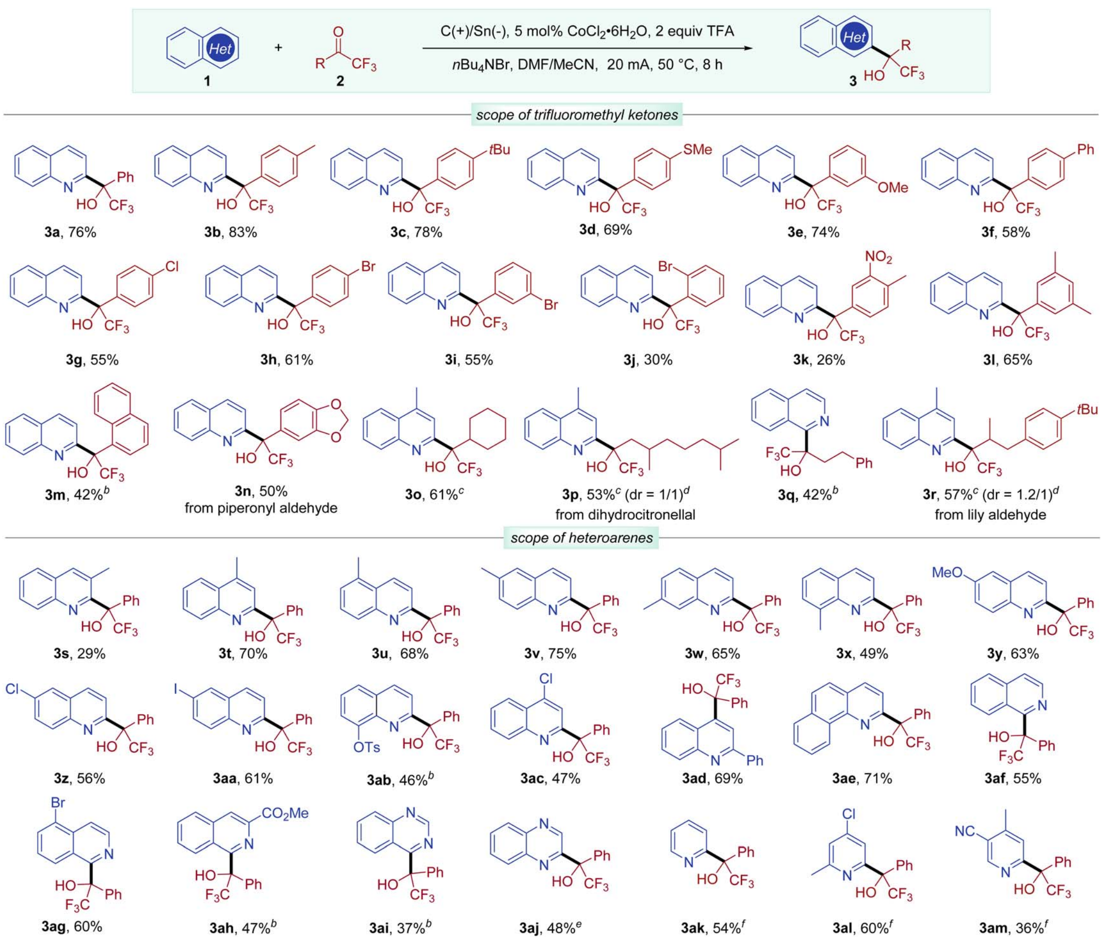
[a] Conditions: **1a** (0.3 mmol), **2a** (2 equiv.), $CoCl_2·6H_2O$ (5 mol%), TFA (2 equiv.), $n$$Bu_4NBr$ (2 equiv.), DMF (3.5 mL), MeCN (0.5 mL), graphite anode (1 cm × 1 cm × 0.2 cm), Sn cathode (1 cm × 1 cm × 0.1 cm), constant current (20 mA), undivided cell, 50 °C, 8 h. [b] Isolated yield.

addition, switching $CoCl_2{\cdot}6H_2O$ to SmI_2, $CoBr_2$, or $Co(OAc)_3$ gave inferior yields (entries 11–13). Notably, the coupling reaction worked equally well at a lower current (10 mA), albeit with a longer reaction time (entry 14). When the electrolysis was conducted at room temperature, the isolated yield of **3a** was modest (49%, entry 15). As expected, no conversion was observed without current (entry 16).

With these optimized conditions in hand, we then sought to evaluate the substrate scope with respect to trifluoromethyl ketones (Scheme 2). Trifluoromethyl aryl ketones bearing different substituents on the phenyl ring were well tolerated (**3a–3k**), including electron-donating groups (Me, *t*Bu, MeS or MeO), phenyl, and electron-withdrawing groups (Cl, Br, or NO_2). Aryl ketones with *meta* or *para* bromo-substituents exhibited good reactivity (**3h** and **3i**), while *ortho* bromo-substituted aryl ketones delivered the desired product **3j** in a lower yield, probably due to steric hindrance. 3,5-Dimethylphenyl and naphthyl alcohol products **3l** and **3m** were also obtained in synthetically useful yields. The heterocyclic substrate derived from piperonyl aldehyde was also effective, leading to tertiary alcohol **3n** in 50% yield. Unfortunately, methyl 4-(2,2,2-trifluoroacetyl)benzoate with an ester group gave a complex mixture and 2,2,3,3,3-pentafluoro-1-phenylpropan-1-one with a longer perfluoroalkyl group was unreactive (see Scheme S1, in the ESI†).

Besides aryl ketones, aliphatic trifluoromethyl ketones were also examined in this transformation. A cycloalkyl trifluoromethyl ketone was converted to the corresponding alcohol product **3o** in 61% yield. Trifluoromethyl ketones with linear alkyl substituents also underwent efficient Minisci-type reactions to afford alcohols (**3p–3r**). Specifically, trifluoromethyl ketones derived from natural products, including dihydrocitronellal and lily aldehyde, were well transformed into the desired alcohols **3p** and **3r**.

We next investigated the scope of the heteroarene component using 2,2,2-trifluoroacetophenone (**2a**). An initial evaluation of the substituent effect at different positions of quinolines demonstrated that the reactivity was mainly determined by steric effects, with 3-methylquinoline delivering **3s** in 29% yield. Quinolines bearing a methyl group at other positions afforded alcohol products **3t–3x** in good yields. Simple quinolines bearing MeO, Cl, and I were suitable substrates, regioselectively providing C2-substituted products **3y–3aa** in good yields. Interestingly, an 8-hydroxyquinoline derivative could be

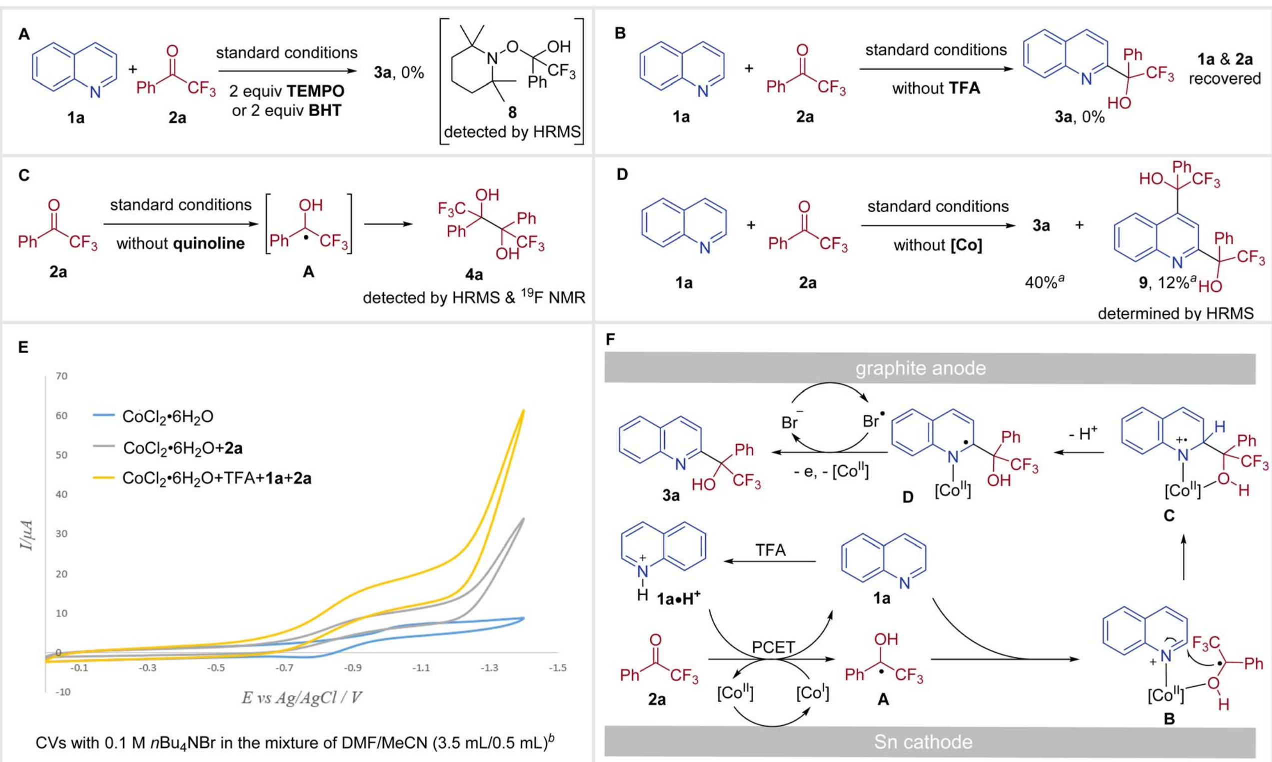


Scheme 2 Substrate scope [a]reaction conditions: undivided cell, graphite anode (1 cm × 1 cm × 0.2 cm), Sn cathode (1 cm × 1 cm × 0.1 cm), constant current (20 mA), 1 (0.3 mmol), 2 (2 equiv.), $CoCl_2{\cdot}6H_2O$ (5 mol%), TFA (2 equiv.), Bu_4NBr (2 equiv.), DMF (3.5 mL), MeCN (0.5 mL), 50 °C, 8 h. Isolated yield. [b]12 h. [c]ketones (3 equiv.). [d]Determined by ^1H NMR. [e]TFA (3 equiv.). [f]6,6′-dimethyl-2,2′-bipyridine (10 mol%) was used.

functionalized to provide **3ab** without incident, showing potential for pharmacological applications.[4b] 4-Chloroquinoline underwent coupling with **2a** exclusively at the C2-position (**3ac**), while 2-phenylquinoline was selectively hydroxyalkylated at the C4-position (**3ad**). Benzo[*h*]quinoline was also an effective coupling partner leading to **3ae** in 71% yield. Moreover, simple isoquinoline and isoquinolines bearing a Br or ester group reacted well in this coupling reaction at the C1 site (**3af**–**3ah**). It is important to note that quinazoline and quinoxaline readily participated in this electrocatalytic protocol, affording **3ai** and **3aj**, respectively. Notably, simple pyridine and pyridines bearing methyl, chloro, or cyano substituents were also found to be amenable to this coupling reaction, providing **3ak**–**3am** in 36–60% yields, when 6,6′-dimethyl-2,2′-bipyridine was employed as a ligand. Moreover, selective mono-alkylation could be achieved with 2,6-unsubstituted pyridine substrates.

To gain further insight into the mechanism of this redox-neutral coupling of *N*-heteroarenes with trifluoromethyl ketones, we conducted several control experiments (Scheme 3). A ketyl radical pathway was indicated by the radical-trapping experiment, as no desired reaction was observed in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT) and TEMPO-adduct **8** could be detected by HRMS (Scheme 3A). In the absence of TFA, no reactivity was obtained with only the recovery of starting materials **1a** and **2a** (Scheme 3B), suggesting that a PCET process might be involved. Evidence that electrolysis of ketone **2a** delivers the ketyl radical **A** is supported by the formation of pinacol product **4a** from the reaction carried out in the absence of a *N*-heteroarene under standard conditions (Scheme 3C). Without using a cobalt catalyst, the reaction of quinoline **1a** with **2a** underwent inefficiently to provide C2-substituted product **3a** in 40% yield, along with 12% of C2 and C4 disubstituted product **9** (Scheme 3D), highlighting the importance of the cobalt catalyst for both reactivity and regioselectivity. During the solvent screening, we did not observe any significant influence of solvents on C2/C4 regioselectivity. Therefore, the coordination of Co with substrates was proposed to explain regioselectivity.[13c,21]

In order to reveal the essential role of $CoCl_2 \cdot 6H_2O$, we next performed the cyclic voltammetry (CV) experiments. Examination of $CoCl_2 \cdot 6H_2O$ showed a reversible reduction peak at $E = -1.02$ V *vs.* Ag/AgCl, which was assigned to the reduction of Co(II) to Co(I).[25] Addition of **2a** to the CV solution of $CoCl_2 \cdot 6H_2O$ resulted in increased reductive current and loss of reversibility (Scheme 3E, gray trace).[26] When **1a**, TFA, and **2a** were added to the CV solution of $CoCl_2 \cdot 6H_2O$, a more significant increase in catalytic current was observed (Scheme 3E, yellow trace). Moreover, the catalytic current increased as a function of the ketone concentration (see Fig. S7 in the ESI†). Taken together, these results suggest that a PCET process takes place between Co(I) and **2a** forming a ketyl radical and the resulting Co(II) is reduced to Co(I) at the cathode.



Scheme 3 Mechanistic experiments and proposal [a]yields were determined by ^{19}F NMR analysis using (trifluoromethyl)benzene as an internal standard. [b]CVs of a 0.01 M solution of $CoCl_2 \cdot 6H_2O$ (blue trace), the mixture of 0.01 M $CoCl_2 \cdot 6H_2O$ and 0.1 M **2a** (gray trace), the mixture of 0.01 M $CoCl_2 \cdot 6H_2O$, 0.1 M **2a**, 0.1 M TFA and 0.1 M **1a** (yellow trace) with 0.1 M TBAB at 100 mV s^{-1} in the mixture of DMF/MeCN (3.5 mL/0.5 mL).

On the basis of these mechanistic experiments, a plausible reaction pathway for our redox-neutral coupling of *N*-heteroarenes with trifluoromethyl ketones is outlined in Scheme 3F. Initially, reduction of Co(II) at the cathode forms the Co(I) catalyst, which facilitates a homogeneous PCET with **2a** to give ketyl radical **A**. At this stage, the ketyl radical **A** and **1a** could be coordinated onto the Co(II) catalyst, forming the intermediate **B**. Subsequently, intramolecular radical addition delivers **C**, which then loses a proton to afford **D**. Meanwhile, $n\mathrm{Bu_4NBr}$ performs a dual role as supporting electrolyte and a redox mediator. Thus, bromine radicals ($\mathrm{Br^{\bullet}}$) could be generated from the oxidation of bromide ions ($\mathrm{Br^-}$) at the anode ($E = +0.84$ V *vs.* Ag/AgCl, see Fig. S8 in the ESI†).[27] In the final step, $\mathrm{Br^{\bullet}}$ accomplishes a single electron oxidation of intermediate **D**,[28] and the subsequent dissociation of Co(II) delivers the desired tertiary alcohol product **3a**.

Conclusions

In summary, we have established the cobalt-electrocatalytic C–H hydroxyalkylation of *N*-heteroarenes with trifluoromethyl ketones, featuring broad substrate scope, ideal atom economy, and excellent regioselectivity. This redox-neutral method involves carbonyl umpolung *via* electrocatalytic proton-coupled electron transfer, radical addition to heteroarenes, and rearomatization. By merging paired electrolysis and cobalt catalysis, this regioselective C–H hydroxyalkylation avoids the known competing spin-center shift process and offers an efficient access to high-value pharmacophores, *N*-heteroaryl trifluoromethyl carbinols.

Data availability

The ESI† contains method description, product characterization data, and NMR spectra.

Author contributions

T. H. and C. L. performed the experiments, obtained all data, and analyzed the results. S. H. designed the project, directed the study, and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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