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Electrochemically driven, cobalt–carbon bond-mediated direct intramolecular cyclic and acyclic perfluoroalkylation of (hetero)arenes using $X(CF_2)_4X$†

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A proof-of-concept for the one-step, synthetically challenging cyclic and acyclic perfluoroalkylation of (hetero)arenes driven by the valence change of a vitamin B_{12} derivative as a cobalt catalyst in the presence of fluoroalkylating reagents ($X(CF_2)_4X$) is presented. The consecutive formation of cobalt–carbon bonds and generation of fluoroalkyl radicals by homolysis are the key steps for the reaction to proceed.

The cobalt–carbon (Co–C) bond is recognized as a crucial catalytic intermediate, and has been extensively studied for radical-mediated reactions in the fields of bioinorganic and organometallic chemistry.[1–7] In particular, fluorine substitution of aromatic compounds is an interesting research topic due to the dramatic impact of this reaction on the physical, chemical, and biological properties of the substrates.[8–11] In this context, methods for the stoichiometric or catalytic mono-, di-, and trifluoromethylation, and other perfluoroalkylations of (hetero)arenes have been extensively studied.[12–20] Nonetheless, catalytic radical fluoroalkylation mediated by Co–C intermediates is still less explored. Recently, our group has investigated electrochemically driven, radical fluoroalkylation reactions using the vitamin B_{12} derivative, heptamethyl cobyrinate perchlorate [Cob(II)7C_1ester]ClO_4 (**C1**), as a cobalt catalyst and fluoroalkylating reagents such as $BrCF_2COOEt$, CF_3I, and R_fI (Scheme 1(a and b)).[21,22] These reactions proceed as follows: first, the Co(I) species is generated from **C1** by controlled-potential electrolysis at −0.8 V *vs.* Ag/AgCl, and it quickly reacts with the fluoroalkylating reagent, *e.g.*, R_fI, to form a Co(III)–R_f complex. The Co(III)–R_f complex releases a R_f radical under visible-light irradiation (≥420 nm). Finally, the generated R_f radical reacts with nonactivated (hetero)arenes to afford the fluoroalkylated product. Despite these advances, the radical fluoroalkylation *via* homolysis of a Co–C bond cannot be clearly distinguished from the reaction obtained by directly reducing fluoroalkylating agents with conventional photoredox catalysts. This situation motivated us to explore in more detail the radical-generating ability from the homolysis of a Co–C bond. Herein, we investigated the intramolecular fluoroalkylating cyclization of (hetero)arenes promoted by formation of a Co–C bond and subsequent generation of fluoroalkyl radicals by homolysis in the presence of the dihalogenated fluoroalkylating reagents $X(CF_2)_4X$ (Scheme 1(c)).

We selected $X(CF_2)_nX$ as alkylating reagents because, although the $-(CF_2)_n-$ moiety is becoming increasingly important for a diverse array of functional compounds,[23–27] methods for the construction of fluoroalkyl-containing rings on aromatic compounds are still scarce. Although a number of studies have been reported in this regard, stoichiometric or harsh conditions are normally required.[23,25,28,29] To the best of our knowledge, Co–C bond mediated one-step catalytic C–H intramolecular fluoroalkylating cyclization of unactivated (hetero)arenes through an electrocatalytic method under mild conditions has not been explored yet.

In this study, we demonstrate an electrolysis-driven, intramolecular fluoroalkylating cyclization of (hetero)arenes using dihalogenated fluoroalkylating reagents ($X(CF_2)_4X$; X = I, Br) and the vitamin B_{12} derivative (**C1**) as cobalt catalyst under mild conditions. We also present that $X(CF_2)_nX$ ($n = 4, 6$) can serve as a $-(CF_2)_nH$ source especially in the presence of methanol (CH_3OH) solvent, leading to an acyclic perfluoroalkylated compound containing the $-(CF_2)_nH$ functional group (Scheme 1(c)). This is the first report on catalytic Co–C bond-mediated intramolecular cyclic and acyclic perfluoroalkylation of (hetero)arenes through an electrochemical method, which provides a new method for the preparation of a large number of synthetically important functional compounds. Although the

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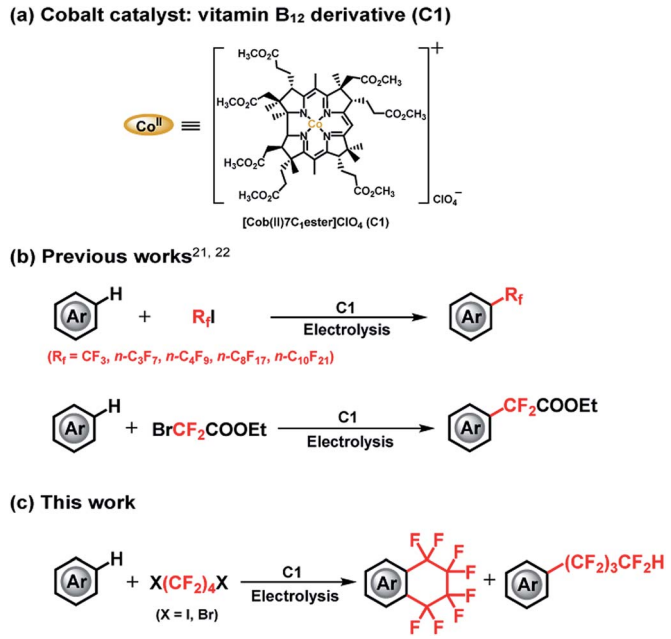


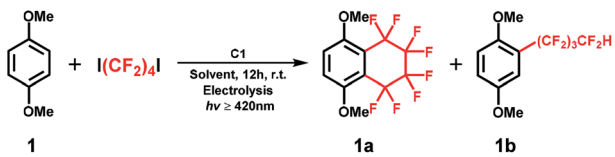
Scheme 1 (a) Molecular structure of **C1**. (b) Trifluoromethylation, perfluoroalkylation and difluoroacylation of (hetero)arenes catalyzed by **C1**. (c) This work.

electrochemically enabled fluoroalkylation strategies[30–35] have increasingly emerged in recent years, this work should provide a new insight into various fields.

To investigate the abovementioned fluoroalkylation reactions, we firstly focused on the redox behaviour of **C1** as catalyst in the presence or absence of octafluoro-1,4-diiodobutane (1,4-$C_4F_8I_2$) in CH_3OH by cyclic voltammetry (CV) at a scan rate of 100 mV s^{-1} under nitrogen (Fig. S1†). We observed a reversible Co(II)/Co(I) redox couple of **C1** at −0.63 V *vs.* Ag/AgCl. After adding 2 eq. 1,4-$C_4F_8I_2$ to **C1**, the voltammetric pattern was changed, and a new irreversible reduction wave at *ca.* −0.76 V *vs.* Ag/AgCl appeared. This can be ascribed to the reduction of the fluoroalkylated derivative of **C1**, which suggested the suitability of **C1** for this molecular transformation. Subsequently, we conducted the fluoroalkylation of (hetero)arenes using 1,4-dimethoxybenzene (**1**) as the model substrate and 1,4-$C_4F_8I_2$ as a perfluoroalkylating source in the presence of **C1** (1 mol%) catalyst at room temperature employing an electrochemical approach (Fig. S2†). The CV results indicated that the electrolysis potential at −0.8 V *vs.* Ag/AgCl is suitable for this fluoroalkylation reaction, which was in associating with our previous work.[21]

The optimized results of the reaction are summarized in Table 1. Firstly, an extensive screening involving the solvent, flow rate and amounts of fluoroalkylating reagent, cathode, other vitamin B_{12} model complex (**C2**), and visible-light irradiation afforded the optimal conditions (see the ESI in Table S1, Fig. S3 and S4†). The results initially provided us with some optimal reaction conditions, such as carbon felt as the cathode, **C1** as the cobalt catalyst and visible-light irradiation. Subsequently, we firstly continued to perform the reaction with the flow rate of 1,4-$C_4F_8I_2$ (0.5 eq. of substrate per 1 h, 6 eq. in total) for 12 h, yielding the desired products **1a** (13%) and **1b** (22%) (Table 1, entry 1). Furthermore, we found that visible-light irradiation condition promoted the better transformation of **1**, giving rise to a relatively higher yield of **1a** (24%) and **1b** (41%) (Table 1, entry 2; Fig. S3†). Using other alcohol solvents and DMSO all led to incomplete conversions and lower yields (Table 1, entries 3–5). To accelerate the catalytic reaction, −1.2 V *vs.* Ag/AgCl was chosen as the electrolysis potential, which afforded similar yields for both desired products (Table 1, entry 6)

Table 1 Optimization of the reaction conditions for the fluoroalkylation of **1** with 1,4-$C_4F_8I_2$[a]



Entry	Potential (V) *vs.* Ag/AgCl	Solvent[b]	Conversion[c] (%)	**1a**, Yield[c] (%)	**1b**, Yield[c] (%)	Total yield[c] (%)
1[d]	−0.8 V	CH_3OH	86	13	22	35
2	−0.8 V	CH_3OH	>99	24	41	65
3	−0.8 V	Ethanol	38	3	9	12
4	−0.8 V	1-Propanol	53	4	12	16
5	−0.8 V	DMSO	77	3	4	7
6	−1.2 V	CH_3OH	>99	24	38	62
7[e]	−1.2 V	CH_3OH	75	2	9	11

[a] Reaction conditions: [**C1**] = 5.0 × 10^{-4} M; [1,4-dimethoxybenzene (**1**)] = 5.0 × 10^{-2} M; [1,4-$C_4F_8I_2$] = 0.5 eq. of substrate per 1 h, 6 eq. in total; reaction time: 12 h; [*n*-Bu_4NClO_4] = 0.1 M; with visible light (≥420 nm); decafluorobiphenyl ($C_{12}F_{10}$) as the internal standard. Working electrode (WE): carbon felt; counter electrode (CE): Zn plate; reference electrode (RE): Ag/AgCl (3.0 M NaCl aq.). [b] Abbreviations: CH_3OH, methanol; DMSO, dimethyl sulfoxide. [c] The conversions and yields are based on the initial concentration of 1,4-dimethoxybenzene (**1**) and were determined by gas chromatography-mass spectrometry (GC-MS). [d] In the absence of visible-light irradiation. [e] In the dark.

compared with the reaction performed under a potential of −0.8 V *vs.* Ag/AgCl (Table 1, entry 2). Additionally, the dark condition was optimized at −1.2 V *vs.* Ag/AgCl and resulted in **1a** of 2% yield and **1b** of 9% yield, which confirms the efficiency of visible-light irradiation for the fluoroalkylation (Table 1, entry 7). Notably, the reaction was inhibited in the presence of the radical scavenging reagents 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and *N*-*tert*-butyl-α-phenylnitrone (PBN), and no formation of the desired products **1a** and **1b** was observed. Indeed, a signal attributable to the PBN spin adduct was detected by electron spin resonance experiment (Fig. S5†). These results indicate that some radical intermediates were formed during the reaction process. On the basis of these results, the optimized condition for the controlled-potential electrolysis was established at −0.8 V *vs.* Ag/AgCl in CH_3OH with 6 eq. 1,4-$C_4F_8I_2$ reagent of aromatic substrate in the presence of **C1** catalyst (1 mol%) for 12 h at room temperature (Table 1, entry 2).

With the optimized reaction conditions in hand, we evaluated the scope of the **C1**-mediated direct fluoroalkylation of (hetero)arenes (Fig. 1 and Table 2). As shown in Fig. 1, other two fluoroalkylating reagents, 1,4-dibromooctafluorobutane (1,4-$C_4F_8Br_2$) and dodecafluoro-1,6-diiodohexane (1,6-$C_6F_{12}I_2$), were examined for these attractive fluoroalkylations. The two desired fluoroalkylated products **1a** and **1b** were obtained in lower yields using 1,4-$C_4F_8Br_2$ (5% and 16%, respectively), indicating that the latter exhibited lower reactivity than 1,4-$C_4F_8I_2$. Moreover, after examining the reactivity of long-chain fluoroalkylating reagent (1,6-$C_6F_{12}I_2$), a moderate yield of 51% was obtained for the selective formation of acyclic perfluoroalkylated arene **1c**, whereas the product of the intramolecular fluoroalkylating cyclization of **1** was not detected. This suggests that the intramolecular cyclization depends on the number of –CF_2– units of the $(CF_2)_n$ group. These results indicated that 1,4-$C_4F_8I_2$ was the best fluoroalkylating reagent, and it was used for further expanding the substrate scope of the reaction.

Thus, several (hetero)arenes (**2**–**7**) were evaluated for these transformations under the standard conditions (Table 2). The substrate 1,2,4-trimethoxybenzene (**2**) underwent this transformation, affording **2a** and **2b** in 11% and 29% yield, respectively. Other aromatic compounds, such as 1,4-diethoxybenzene (**3**) and 2,2-dimethyl-1,3-benzodioxole (**4**) also showed good

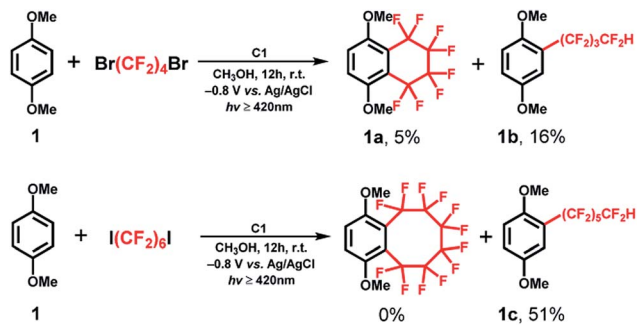
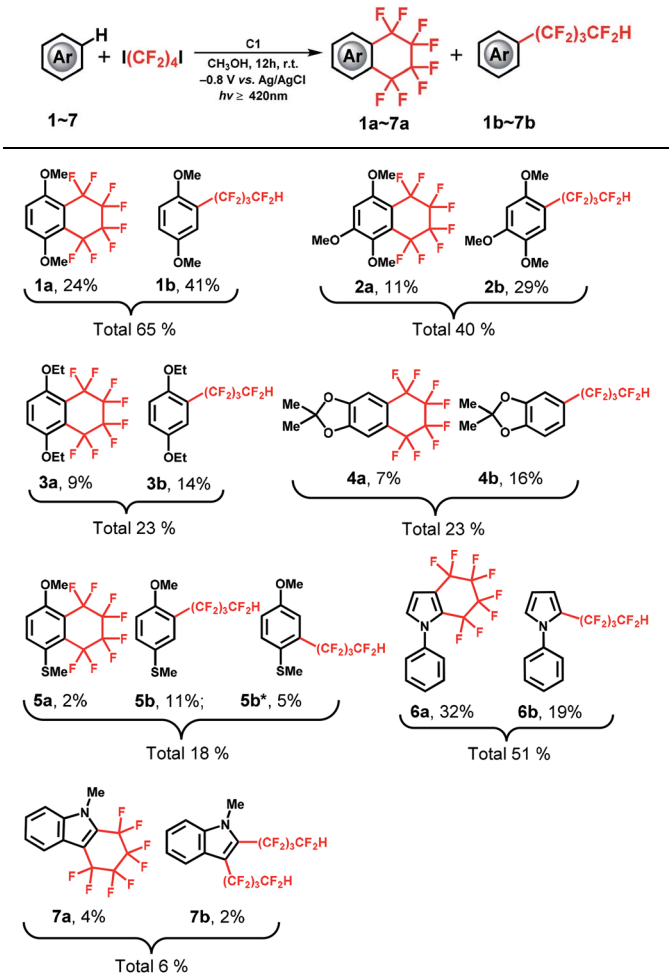


Fig. 1 Optimization of the reaction conditions with other fluoroalkylating reagents such as 1,4-$C_4F_8Br_2$ and 1,6-$C_6F_{12}I_2$.

Table 2 Substrate scope of electrochemical fluoroalkylation of (hetero)arenes[a]



[a] Reaction conditions: [**C1**] = 5.0 × 10^{-4} M; [substrate (**1**–**7**)] = 5.0 × 10^{-2} M; [1,4-$C_4F_8I_2$] = 0.5 eq. of substrate per 1 h, 6 eq. in total; reaction time: 12 h; [*n*-Bu_4NClO_4] = 0.1 M; decafluorobiphenyl ($C_{12}F_{10}$) as the internal standard. WE: carbon felt; CE: Zn plate; RE: Ag/AgCl (3.0 M NaCl aq.). The yields are based on the initial concentration of aromatic substrate and were determined by gas chromatography-mass spectrometry (GC-MS).

tolerance to the reaction conditions, yielding the desired products **3a** and **3b** in 9% and 14% yield and **4a** and **4b** in 7% and 16% yield, respectively. In addition, 4-methoxythioanisole (**5**) was examined, and the cyclic perfluoroalkylating product **5a** was obtained in 2% yield, along with acyclic products **5b** and **5b*** in 11% and 5% yield, respectively. Fortunately, the substrate 1-phenylpyrrole (**6**) reacted completely with 1,4-$C_4F_8I_2$ under the standard conditions, providing fluoroalkylated products **6a** in 32% yield and **6b** in 19% yield. Moreover, this C–H fluoroalkylation could be extended to 1-methylindole (**7**), yielding the cyclic fluoroalkylated product **7a** in 4% yield. Interestingly, the –$(CF_2)_4H$ group could be introduced at two positions of the indole ring, yielding the **7b** product in 2% yield. Although moderate to low yields and selectivity are obtained

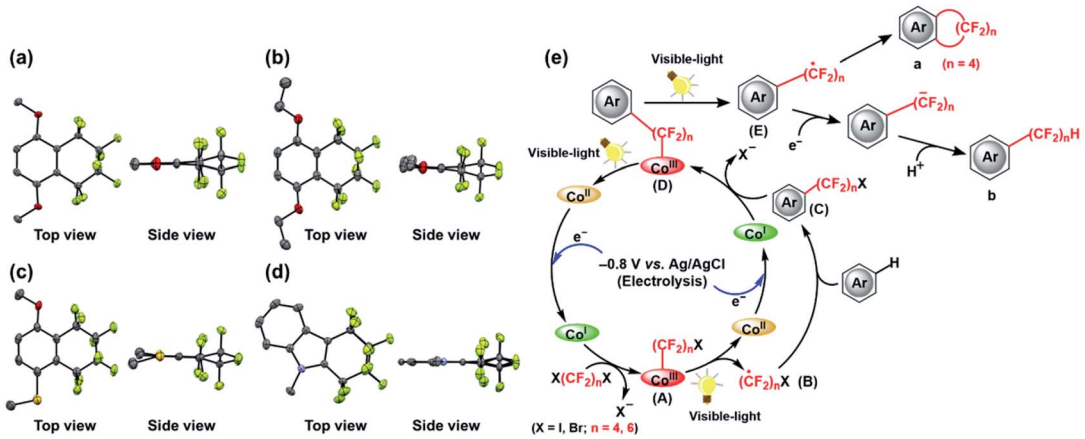


Fig. 2 Crystal structures of (a) **1a**, (b) **3a**, (c) **5a**, and (d) **7a**, showing displacement ellipsoids at the 50% probability level. Hydrogen atoms have been omitted for clarity. Color code: C, gray; N, light blue; O, red; F, light green; S, yellow. (e) Mechanistic study of radical fluoroalkylation mediated by **C1**.

mainly due to other by-products formation, these results demonstrate that this method for the electrochemically-driven **C1**-catalyzed intramolecular cyclic and acyclic perfluoroalkylation of aromatic compounds containing the $-(CF_2)_n-$ group provides a useful tool for the modification of multifunctionalized molecules. The crystal structures of cyclic perfluoroalkylated compounds (**1a**, **3a**, **5a** and **7a**) are shown in Fig. 2(a)–(d). On the basis of the above experimental results and the previously reported studies,[21,22] we propose the preliminary reaction mechanism illustrated in Fig. 2(e).

Firstly, the potential at −0.8 V *vs.* Ag/AgCl gives rise to a supernucleophilic Co(I) species as the key intermediate during the whole catalytic process. Subsequently, the Co(I) species reacts with $X(CF_2)_nX$ (X = I, Br; $n = 4, 6$), yielding the intermediate Co(III)–$(CF_2)_nX$ complex (**A**) with the concomitant release of a halogen ion X^-.[36] Formation of the key perfluoroalkylated radical intermediate $\cdot(CF_2)_nX$ (**B**) is then accomplished *via* photodynamically driven homolytic Co(III)–$(CF_2)_nX$ (**A**) cleavage, and (**B**) then reacts with the nonactivated (hetero)arenes to afford another crucial intermediate (hetero)arene–$(CF_2)_nX$ (**C**). Similarly, this complex reacts with the Co(I) species to form the Co(III)–$(CF_2)_n$–(hetero)arene (**D**), along with the release of another X^-. The homolysis of this Co(III)–C bond provides a radical adduct $\cdot(CF_2)_n$–(hetero)arene (**E**) that undergoes intramolecular addition to the aromatic substrate to furnish the cyclic fluoalkylated product **a**. This intramolecular cyclization proceeds in the case of $n = 4$. At the same time, a single-electron transfer to $\cdot(CF_2)_n$–(hetero)arene (**E**) proceeds to give the corresponding radical anion, which is then protonated to form the final acyclic perfluoroalkylated product **b**. Overall, the reactions are driven by the consecutive formation of Co–C bonds and the formation of a fluoroalkyl radical species by homolysis, which is a very rare example up to date. A relatively high turnover number (TON) of 130 was observed due to the inherent high stability of the vitamin B_{12} framework, indicating the significant factor of Co–C bond for these molecular transformations. At this stage, isolation of the Co(III)–R_f species (**A**), (**D**) and (**C**) intermediate under the described conditions was not attempted.

In conclusion, we have developed an electrochemically driven, cobalt(III)–carbon bond-mediated direct C–H radical intramolecular fluoroalkylating cyclization and acyclic perfluoroalkylation of (hetero)arenes using $X(CF_2)_4X$ as fluoroalkylating reagent and a vitamin B_{12} derivative as a cobalt catalyst. This protocol provides a new direction for one-step synthesis of cyclic perfluoroalkylated (hetero)arenes with a C_4F_8-containing six-membered ring and acyclic perfluoroalkylated compounds containing $-C_4F_8H$ group, which cannot be obtained by the stoichiometric reactions. Although yields and selectivity still have room for improvement, and electron-rich compounds are required as substrates, these new reactions proceeding under mild conditions are valuable as a proof-of-concept from the viewpoint of bioinorganic and organometallic chemistry. Mechanistic studies, substrate variations, and improvement of selectivity for these perfluoroalkylated compounds are still underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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