Cobalt(III) Halide Metal-Organic Frameworks Drive Catalytic Halogen Exchange

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ABSTRACT: The selective halogenation of complex (hetero)aromatic systems is a critical yet challenging transformation relevant to medicinal chemistry, agriculture, and biomedical imaging. However, current methods are limited by toxic reagents, expensive homogeneous second- and third-row transition metal catalysts, and/or poor substrate tolerance. Herein, we demonstrate that porous metal–organic frameworks (MOFs) containing terminal Co(III) halide sites represent a rare and general class of heterogeneous catalysts for the controlled installation of chlorine and fluorine centers into electron-deficient (hetero)aryl bromides using simple metal halide salts. Mechanistic studies support that these halogen exchange (halex) reactions proceed via redox-neutral nucleophilic aromatic substitution (S_NAr) at the Co(III) sites. The MOF-based halex catalysts are recyclable, enable scalable halogenation with minimal waste generation, and facilitate halex in continuous flow. Our findings represent the first example of S_NAr catalysis using MOFs, expanding the lexicon of synthetic transformations enabled by these materials.

INTRODUCTION

Halogenated molecules are abundant in medicinal and agricultural chemistry, with fluorinated and chlorinated molecules representing > 25% of active pharmaceuticals and > 30% of agrochemicals.[1-4] The replacement of hydrogen atoms in bioactive molecules with fluorine or chlorine generally leads to improved physiological effectiveness and bioavailability, termed the "magic fluorine" and "magic chlorine" effects, respectively.[5-7] Among halogenated molecules, 2-haloheteroarenes are particularly common,[8-12] exemplified by radiotracers for ^{18}F positron emission tomography (PET),[8,9] natural products,[10] anticancer drugs,[13,14] and painkillers (Figure 1a).[10,15] Despite the ubiquity of halogens in bioactive molecules, their selective, late-stage installation, especially with inexpensive metal halide salts, remains a major challenge.

Selective halogenation is inherently difficult due to the extreme reactivity of halogenating agents such as F_2 and Cl_2, both of which are impractically hazardous for common laboratory use.[16-18] As an alternative, the Balz-Schiemann reaction—which involves the thermolysis of potentially explosive tetrafluoroborate diazonium salts—requires harsh conditions and displays modest heterocycle compatibility.[19,20] The most common method for incorporating halogens into heteroarenes is via nucleophilic halogen exchange (halex), a nucleophilic aromatic substitution (S_NAr) reaction in which an existing halogen (e.g., Br) is replaced with the desired halogen (e.g., Cl, F).[21,22] Traditionally, this process requires the use of high reaction temperatures (> 200 °C) and/or complex phase-transfer catalysts due to the poor solubility of simple metal halide salts such as KF.[23,24] More complex halex reagents consist of soluble tetraalkylammonium[25-28] or acyl imidazolium salts,[29] stoichiometric reagents that generate soluble and/or toxic organic byproducts that can be challenging to separate from the desired product

(Figure 1b).[28-30] Catalytic halex has been achieved using a number of second- and third-row transition metal reagents;[31-35] however, examples of halex mediated by more abundant first-row transition metal catalysts remain rare.[36-39] This is likely because all examples of transition-metal catalyzed halex reported to date proceed through a cross-coupling mechanism, with a halide exchange step (rather than transmetalation) prior to sluggish reductive elimination to form the aryl halide product.[33,40] This is in contrast to the outer-sphere halide transfer mechanism through which simple metal halide salts (e.g., KF, CsF) mediate halex.[24,41] Notably, examples of heterogeneous and recyclable catalysts for halex remain limited to ill-defined materials such as Ni metal and Pd/C.[36,42]

Highly nucleophilic halide sites are critical to halex. Terminal metal halide (M–X) species potentially offer the nucleophilicity necessary to facilitate catalytic halogen exchange, but they require bulky ligand systems to prevent μ-dimerization in solution.[33,40,43] While this dimerization is difficult to combat in molecular systems, a solid-state platform bearing discrete terminal M–X sites at structurally integral points would prevent dimerization entirely. Indeed, metal–organic frameworks (MOFs), crystalline materials constructed from organic linkers and inorganic nodes, can possess terminal M–X centers.[44-47] For example, the framework Co_2Cl_2(btdd) (btdd^{2-} = bis(1H-1,2,3-triazolo[4,5-b],[4′,5′-i])dibenzo[1,4]dioxin)[48] can be oxidized by the elemental halogens Cl_2 and Br_2 to afford the frameworks Co_2Cl_4(btdd) and $Co_2Br_2Cl_2$(btdd), respectively, which bear terminal Co(III)–X centers pointing into their pores (X_T, Figure 2a).[47] Moreover, MOFs offer inherent recyclability and scalability over homogeneous catalysts and compatibility with application in continuous flow.[49]

Herein, we demonstrate that $Co_2X_2Cl_2$(btdd) (X = F, Cl, Br, I) MOFs containing terminal M–X sites catalyze the
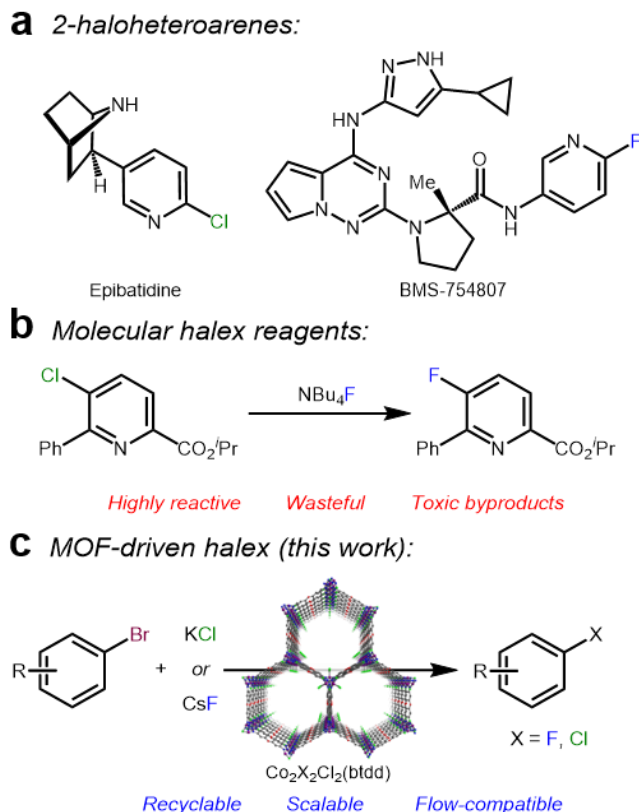
Figure 1. a) Examples of 2-halopyridines present in a natural product (Epibatidine)[10] and a pharmaceutical (BMS-754807).[13] b) Representative example of halex by soluble fluoride reagents.[25, 28] c) Halex driven by $Co_2X_2Cl_2(btdd)$. Purple, gray, blue, red, and green spheres correspond to cobalt, carbon, nitrogen, oxygen, and chlorine, respectively.

chlorination and fluorination of a range of electron deficient (hetero)arenes using simple metal halide salts (Figure 1c). These frameworks are among the first heterogeneous and recyclable catalysts for halex[50] and the first MOF-based catalysts for S_NAr reactions. The catalytic transformations can be readily scaled in batch or continuous flow, providing a green alternative to current approaches. Overall, this work establishes a transformation previously unexplored using MOF catalysts and facilitates the development of a range of nucleophilic reactions, including those prohibited using molecular catalysts.

RESULTS AND DISCUSSION

MOF Synthesis

Assessment of the suitability of $Co_2X_2Cl_2(btdd)$ frameworks as halex catalysts requires a method to prepare these frameworks reliably on gram-scale. By merging previously reported high-concentration and ionothermal methods,[46,51] we achieved the first high-concentration solvothermal synthesis of $Co_2Cl_2(btdd)$, enabling its rapid synthesis on gram-scale (SI Section 3). Simply combining the H_2btdd linker, $CoCl_2•6H_2O$, N,N-dimethylformamide (DMF), and concentrated HCl together at a linker concentration of 1.0 M in a Teflon autoclave at 160 °C for 16 h affords $Co_2Cl_2(btdd)$ in 60% yield. The powder X-ray diffraction (PXRD) pattern of

$Co_2Cl_2(btdd)$ prepared under high-concentration conditions is in good agreement with the simulated pattern based on the expected structure (SI Figure S2).[48] The prepared MOF possesses a record-high 77 K N_2 Brunauer-Emmett-Teller (BET) surface area (2532 ± 119 m²/g) after soaking in organic solvents to remove soluble impurities and activation under vacuum (SI Figure S3). Scanning electron microscopy (SEM), combustion elemental analysis, and thermogravimetric analysis (TGA) further support the successful synthesis of high-quality $Co_2Cl_2(btdd)$ under these conditions (SI Figures S6–7, SI Table S1).[46]

Activated $Co_2Cl_2(btdd)$ was employed to prepare the halogenated Co(III) analogs via one-electron oxidation with electrophilic halogen sources (Figure 2). Following methods reported in the literature,[47] the chlorinated framework $Co_2Cl_4(btdd)$ was prepared via oxidative halogenation using Cl_2 or $PhICl_2$ (Figure 2a). The brominated framework was similarly synthesized using a modified vapor diffusion method with Br_2, affording $Co_2Br_2Cl_2(btdd)$ (Figure 2a). The prepared samples of $Co_2Cl_4(btdd)$ and $Co_2Br_2Cl_2(btdd)$ demonstrate comparable crystallinities and BET surface areas to those reported in the literature (Figure 2c–d, SI Figures S10–11).[47] Inspired by these results, we sought to access the entire halogenated series of $Co_2X_2Cl_2(btdd)$ MOFs by preparing the novel fluorinated and iodinated frameworks. An analogous hypervalent iodine oxidant to $PhICl_2$, $PhIF_2$,[52] was employed to access $Co_2F_2Cl_2(btdd)$ for the first time (Figure 2a). Previous attempts to prepare the Co(III)–I material with solution-state iodination were unsuccessful;[47] however, heating solid I_2 at 60 °C was found to yield $Co_2I_2Cl_2(btdd)$ via vapor diffusion.

All halogenated Co(III) frameworks retain their crystallinity by PXRD (Figure 2c) and demonstrate reasonably attenuated surface areas compared to $Co_2Cl_2(btdd)$ (Figure 2d, SI Figures S10–11). Characterization by combustion elemental analysis, X-ray photoelectron spectroscopy (XPS), and energy-dispersive X-ray spectroscopy (EDS) further supports the successful oxidative halogenation of all four MOFs (see SI Section 4 for details). In particular, EDS images confirm the uniform distribution of the appropriate halogens throughout the MOF crystallites (SI Figures S15, S17–19, SI Tables S2, S4–6). Among these techniques, combustion elemental analysis was found to yield the most reliable data for quantifying the halogen content of MOFs (SI Tables S1, S11–14). With the exception of $Co_2F_2Cl_2(btdd)$, which contains F atoms that are difficult to detect via combustion analysis,[53] the halogen contents of all Co(III) MOFs were found to be within ~4% of the theoretical values. Notably, all four MOFs were also found to retain significant amounts of Cl due to the preservation of the bridging μ-Cl sites in the framework (Cl_B, Figure 2a, see below for further discussion).

Superconducting quantum interference device (SQUID) magnetometry was used to quantify the extent of Co(III) incorporation in the oxidized MOFs (Figure 2b). Isothermal moment vs. field (MvH) measurements were performed at 5 K, sweeping from –9 T to 9 T and back. The parent activated Co(II) framework exhibits a linear response to the changing magnetic field, as expected for a d^7 metal in a square pyramidal ligand field (S = 1/2), with a maximum magnetization value of 2.28 μ_B per formula unit. This value
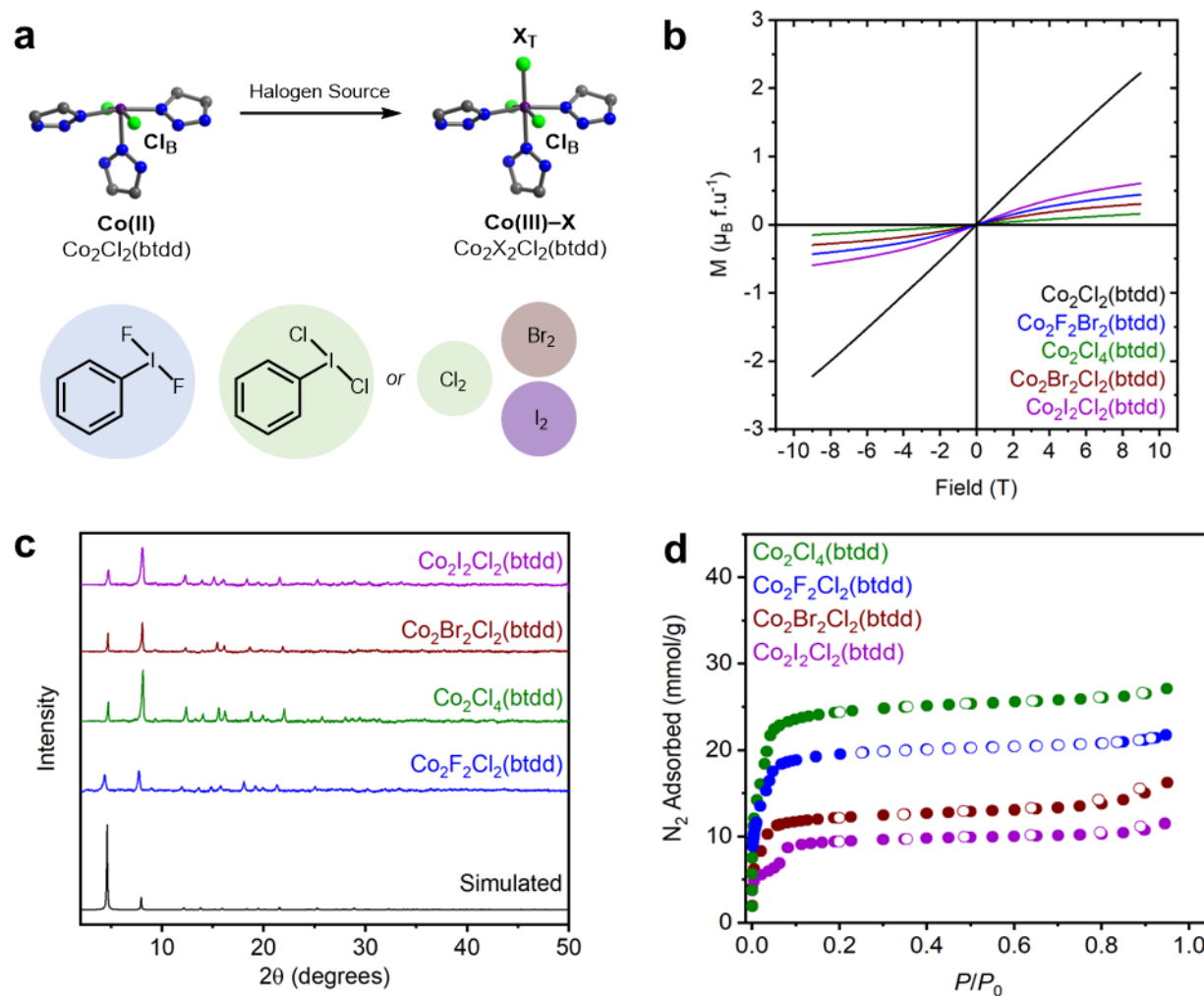
Figure 2. a) Oxidation of $Co_2Cl_2(btdd)$ to $Co_2Cl_2X_2(btdd)$ (X = F, Cl, Br, I) with the corresponding halogen sources. Cl_B represents the bridging chlorides of the secondary building unit, while X_T represents terminal halogens appended to the metal site, pointing into the pore. b) SQUID magnetometry moment vs field (MvH) measurements of $Co_2Cl_2(btdd)$ (black), $Co_2F_2Cl_2(btdd)$ (blue), $Co_2Cl_4(btdd)$ (green), $Co_2Br_2Cl_2(btdd)$ (brown), and $Co_2I_2Cl_2(btdd)$ (purple). c) PXRD patterns of $Co_2F_2Cl_2(btdd)$ (blue), $Co_2Cl_4(btdd)$ (green), $Co_2Br_2Cl_2(btdd)$ (brown), and $Co_2I_2Cl_2(btdd)$ (purple). The simulated pattern based on the SCXRD structure of $Mn_2Cl_2(btdd)$ is included for reference. d) N_2 adsorption (filled circles) and desorption (open circles) isotherms of activated $Co_2F_2Cl_2(btdd)$ (blue), $Co_2Cl_4(btdd)$ (green), $Co_2Br_2Cl_2(btdd)$ (brown), and $Co_2I_2Cl_2(btdd)$ (purple).

was used as the reference point for a 100% Co(II) material when calculating the percentage of residual Co(II) centers in the oxidized samples.[47] All samples of MOF collected after oxidation exhibit attenuated maximum magnetization values and S-curve-shaped profiles compared to the parent $Co_2Cl_2(btdd)$, indicative of a predominantly low-spin octahedral Co(III) d^6 material (S = 0) diluted with some percentage of residual, paramagnetic Co(II) sites. In all cases, the halogenated MOFs exhibit >80% conversion of the Co(II) sites to Co(III)–X centers (Figure 2b, SI Figure S44).

The bridging μ-Cl ligands of $M_2Cl_2(btdd)$ (M = Co, Ni) frameworks have been shown to be labile towards halogen exchange without framework decomposition.[54–56] This attribute is required for the terminal M–X sites as well to facilitate halex catalysis. In order to assess whether these terminal M–X sites can be exchanged, $Co_2Br_2Cl_2(btdd)$ was soaked in a 0.1 M solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF). This procedure affords a sample of $Co_2F_2Cl_2(btdd)$ with a comparable PXRD pattern and BET

surface area to the material synthesized from $Co_2Cl_2(btdd)$ using $PhIF_2$ (SI Figures S10–11). Notably, this anion-exchanged framework does not contain residual tetraalkylammonium cations, as determined via a lack of alkyl stretches in its infrared (IR) spectrum (SI Figure S14). Further, EDS confirms the full exchange of terminal Br ions for F ions while also retaining some of the bridging μ-Cl ligands, although quantifying the degree of exchange between the bridging anions remains difficult (SI Figure S16, Table S3). This measurement confirms that the terminal M–X sites in $Co_2X_2Cl_2(btdd)$ readily undergo halogen exchange.
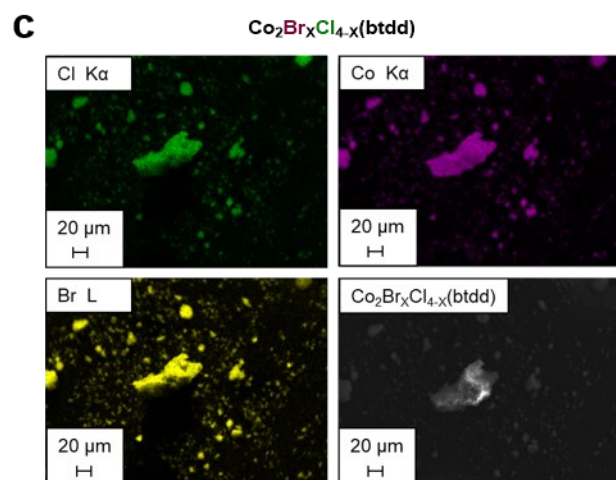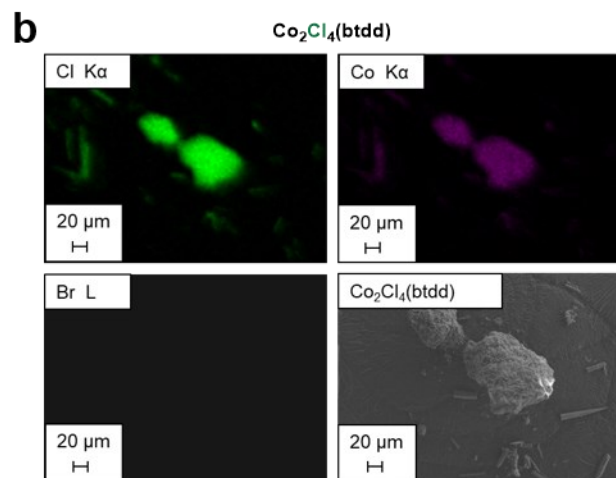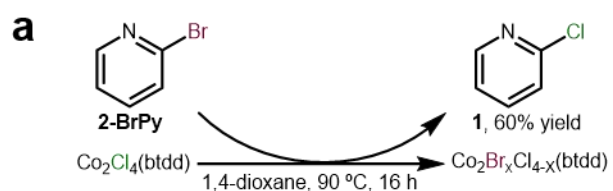
Figure 3. a) Stoichiometric halex of 2-bromopyridine with Co_2Cl_4(btdd). b) EDS elemental maps (top, bottom left) and SEM image (bottom right) of Co_2Cl_4(btdd). c) EDS elemental maps (top, bottom left) and SEM image (bottom right) of $Co_2Br_xCl_{4-x}$(btdd) recovered from the stoichiometric reaction in Figure 3a.

Reaction Development

We hypothesized that the terminal Co(III)–X sites in the $Co_2X_2Cl_2$(btdd) MOFs should function as reactive nucleophilic sites capable of undergoing halex with suitable electrophiles (Figure 3). Indeed, treatment of 2-bromopyridine (**2-BrPy**) with a stoichiometric amount of Co_2Cl_4(btdd) in 1,4-dioxane at 90 °C results in halogen exchange: 2-chloropyridine (**1**) was detected in 60% yield (Figure 3a), and Br was incorporated into the framework to produce $Co_2Br_xCl_{4-x}$(btdd), as confirmed by EDS before and after the stoichiometric halex reaction (Figure 3b–c). Notably, the resulting brominated framework was washed thoroughly with organic solvents to ensure that residual organics were removed from the MOF; thus, only Br covalently appended
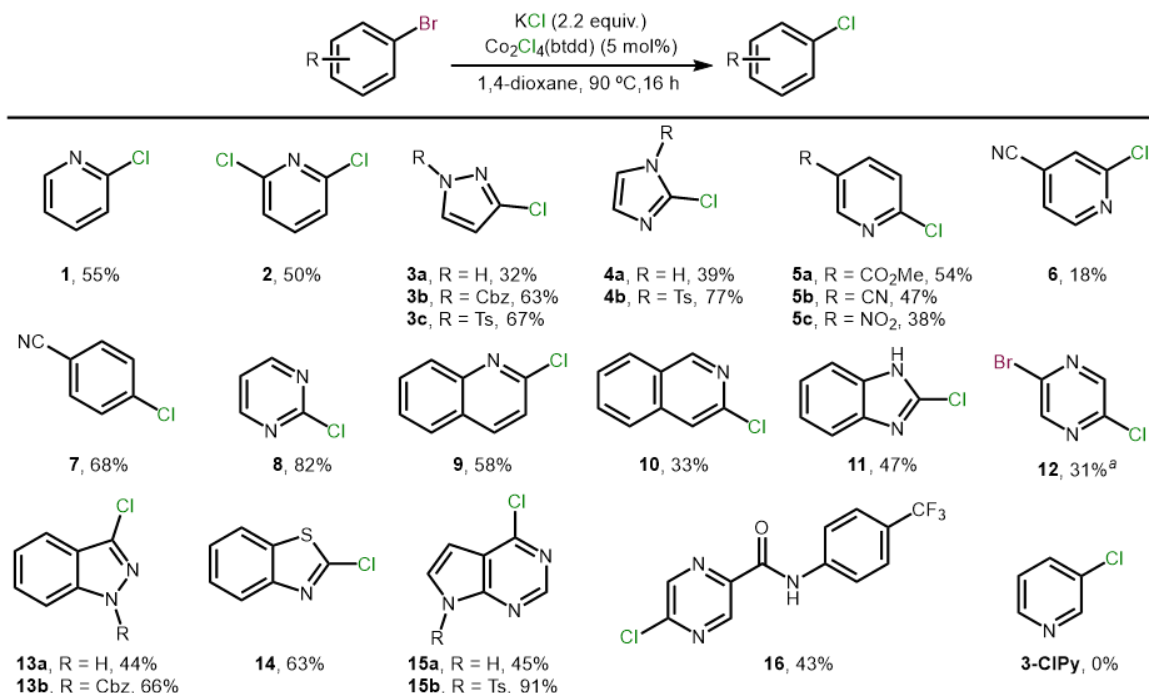
Table 1. Optimization of catalytic chlorination.

Entry	Deviation from Std.	GC Yield
1	None	50%
2	25 ºC	10%
3	No KCl	3%
4	No MOF	0%
5	Co_2Cl_2(btdd) instead of Co_2Cl_4(btdd)	0%
6	$CoCl_2 \cdot 6H_2O$ instead of Co_2Cl_4(btdd)	0%
7	$[Co(NH_3)_5Cl]Cl_2$ instead of Co_2Cl_4(btdd)	0%
8	$[Co(NH_3)_6]Cl_3$ instead of Co_2Cl_4(btdd)	0%
9	Filter reaction mixture after 30 min	3%
10	$Co_2Br_2Cl_2$(btdd) instead of Co_2Cl_4(btdd)	50%

to the metal center of the framework should be detected with this technique. The partially halogen-exchanged MOF $Co_2Br_xCl_{4-x}$(btdd) collected from this stoichiometric reaction retains its crystallinity, as confirmed by PXRD (SI Figure S47). Additionally, the halex process is redox-neutral, indicated by the framework demonstrating nearly identical MvH field responses before and after the reaction (SI Figure S48). Lastly, graphite-furnace atomic adsorption spectroscopy (GFAAS) of the filtrate confirmed that metal leaching does not occur during this stoichiometric reaction, supporting that the reaction is not mediated by soluble Co salts (SI Table S16). Overall, this stoichiometric reaction supports that the terminal Co(III)–Cl sites in Co_2Cl_4(btdd) are nucleophilic enough to undergo halex with activated (hetero)aryl bromides. This is the first time that a nucleophilic exchange has been demonstrated using isolated M–X sites in MOFs.

Inspired by this finding, we set out to render this reaction catalytic using KCl as an inexpensive halide source (Table 1, see SI Table 16 for optimization details). By dropping the loading of Co_2Cl_4(btdd) to 5 mol% and employing a slight excess of KCl (2.2. equiv.), **1** was obtained in comparable yield (50%) to the stoichiometric reaction (entry 1, Table 1). The modest yield of this reaction is likely because it is reversible, as the bromination of 2-chloropyridine using KBr could be driven using the corresponding brominated MOF (SI Section 5). Control experiments confirm that heat, exogenous chloride, and chlorinated MOF are all necessary for the reaction to proceed in good yield (entries 2–4, Table 1). Critically, attempts to drive the reaction using the Co(II) MOF Co_2Cl_2(btdd) were unsuccessful (entry 5, Table 1), which serves as evidence that the terminal Co(III)–Cl sites in Co_2Cl_4(btdd)—and not the presumably less-labile bridging Cl sites—are vital to halex. Similarly, $CoCl_2 \cdot 6H_2O$ and the simple Co(III) salts $[Co(NH_3)_3Cl]Cl_2$ and $[Co(NH_3)_3Cl]Cl$ are ineffective catalysts (entries 6–8, Table 1). A heterogeneous control test, in which the reaction was allowed to proceed for 30 min before filtering to remove the MOF, resulted in minimal product (3% yield). These control experiments

Table 2. Scope of Co$_2$Cl$_4$(btdd)-catalyzed chlorination. Isolated yield unless otherwise noted.

1, 55%

2, 50%

3a, R = H, 32%
3b, R = Cbz, 63%
3c, R = Ts, 67%

4a, R = H, 39%
4b, R = Ts, 77%

5a, R = CO$_2$Me, 54%
5b, R = CN, 47%
5c, R = NO$_2$, 38%

6, 18%

7, 68%

8, 82%

9, 58%

10, 33%

11, 47%

12, 31%[a]

13a, R = H, 44%
13b, R = Cbz, 66%

14, 63%

15a, R = H, 45%
15b, R = Ts, 91%

16, 43%

3-ClPy, 0%

[a]GC yield relative to an internal standard of dodecane; product is contaminated with the dichlorinated product 2,5-dichloro-pyrazine.
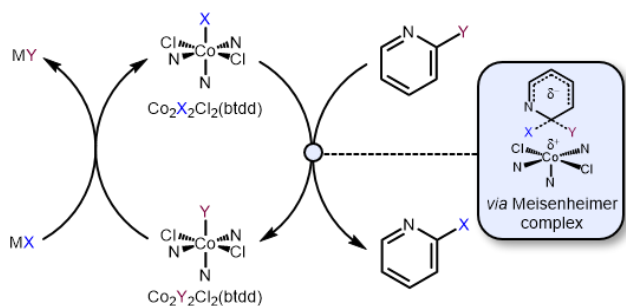

Figure 4. Proposed mechanism of MOF-driven halex catalysis.

support that the unique coordination environment of the Co(III)–Cl sites within Co$_2$Cl$_4$(btdd) is key for effective catalysis, producing Co$_2$Br$_x$Cl$_{4-x}$(btdd) that can be turned over by the exogenous KCl in solution (Figure 4).

With optimized conditions in hand, we explored the scope of the Co$_2$Cl$_4$(btdd)-catalyzed chlorination of electron-deficient (hetero)aryl bromides (Table 3). A range of (hetero)aryl bromides, including 5- and 6-membered heteroarenes, react smoothly to afford the corresponding (hetero)aryl chlorides. Notably, reports of halex reactions with 5-membered heterocycles are limited, supporting that the enhanced nucleophilicity of the halide sites within the MOF enables otherwise difficult transformations under mild conditions.[57–59] In most cases, the free N–H 5-membered heteroaryl bromides can be used directly to produce the desired products in modest yields (3a, 4a, 11, 13a, 15a), although the use of N-protecting groups generally leads to higher yields. The reaction tolerates a range of electrophilic

functional groups commonly found in drug-like molecules, including esters (5a), nitriles (5b, 7), nitroaromatics (5c), and amides (16). Notably, electron-deficient aryl bromides are also suitable substrates (7), further supporting that these reactions likely proceed via an S$_N$Ar mechanism. Background reactions in the absence of Co$_2$Cl$_4$(btdd) were conducted with five substrates; the expected products were observed in ≤ 1% yield in all cases (SI Table S19).

We next evaluated whether Co(III)–X MOFs can catalyze other halex reactions, specifically the fluorination of (hetero)aryl bromides with simple metal fluoride salts (see SI Table S18 for optimization details). Initial studies using Co$_2$F$_2$Cl$_2$(btdd) resulted in poor yields and framework decomposition (entry 17, SI Table S18). This is likely due to the fragility of the isolated Co(III)–F framework, which demonstrates lower crystallinity compared to the other halogenated frameworks prepared herein (Figure 2c). However, with the knowledge that Co$_2$F$_2$Cl$_2$(btdd) can be prepared via anion exchange (see discussion above), this decomposition issue could be circumvented by generating Co(III)–F sites *in situ* from Co$_2$Br$_2$Cl$_2$(btdd) (see SI Table S18 for optimization details). Further modifications had to be made in order to accommodate the insolubility of metal fluoride salts, including the switch to the high-boiling solvent sulfolane and the addition of *tert*-amyl alcohol (*t*-AmOH) and 18-crown-6, both of which are reported to improve the solubility of metal fluoride salts (SI Table S18).[60] Notably, Co$_2$Cl$_2$(btdd) does not catalyze this transformation (SI Table S18), further supporting the importance of the terminal M–X sites for halex catalysis.

Table 3. Scope of $Co_2Br_2Cl_2$(btdd)-catalyzed fluorination. Isolated yield unless otherwise noted.
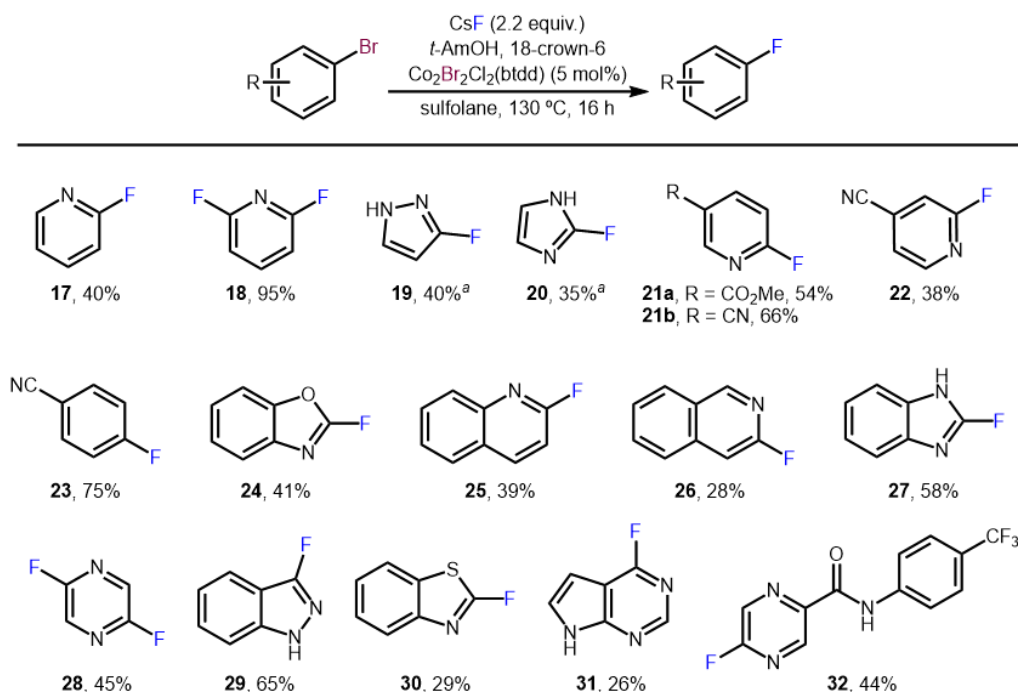
[a] ^{19}F NMR yield relative to an internal standard of fluorobenzene.

Using these optimized conditions, we explored the scope of the MOF-catalyzed fluorination of electron-deficient (hetero)aryl bromides (Table 3). Despite the independent importance of 5-membered heteroarenes and fluoroarenes in the pharmaceutical industry, 5-membered heteroaryl fluorides remain understudied due to a lack of methods available for their synthesis.[61] Fluorination of the free N–H 5-membered heteroaryl bromides **19** and **20** proceed in comparable yields to the corresponding chlorination reactions. The reaction also tolerates a range of pharmaceutically relevant functional groups, including esters (**21a**), nitriles (**21b**), and amides (**32**). The relatively mild conditions combined with the enhanced nucleophilicity of the halide sites in the MOF afford access to a number of heteroaryl fluorides that have not previously been prepared via halex (**27**, **29**, **30**, **31**).[62–65] Background reactions in the absence of $Co_2Br_2Cl_2$(btdd) were run on five substrates (SI Table S20), all of which proceeded in ≤ 3% yield. These findings are the first report of a Co species, regardless of oxidation state or solubility, mediating fluorination via halex.
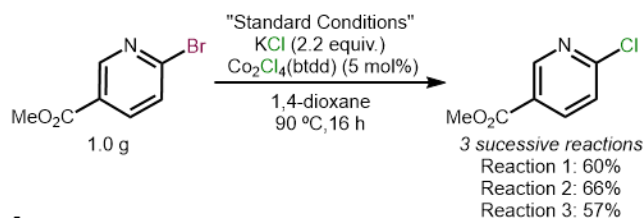
Further mechanistic investigations were conducted to validate the proposed catalytic cycle (Figure 4). Halex reactions—and S_NAr reactions in general—typically proceed through a reactive intermediate known as a Meisenheimer or σ- complex (Figure 4).[66] To probe the mechanism of MOF-catalyzed halex, 3-bromopyiridine, a classically S_NAr-inactive substrate,[26] was subjected to the optimized chlorination conditions. Gratifyingly, no chlorinated product (**3-ClPy**) was observed (Table 2). Because the $Co_2Br_XCl_{4-X}$(btdd) MOF generated from the catalytic chlorination reaction contains Co(III)–Br centers that should be regenerated to Co(III)–Cl centers by exogenous KCl, $Co_2Br_2Cl_2$(btdd) should be able to drive catalytic chlorination reactions similarly to its fully chlorinated counterpart.

Indeed, the chlorination of **2-BrPy** to **1** with $Co_2Br_2Cl_2$(btdd) proceeded with comparable yield (50%, entry 10, Table 1) to that carried out with Co_2Cl_4(btdd) (50%), indicating that the reaction is agnostic to the halogen starting on the Co(III)–X centers. Similarly, as mentioned above, KBr could be used to convert **1** to **2-BrPy** (44% yield), further supporting that halex reactions can be driven to produce different heteroaryl halides based on the exogeneous metal halide salt employed (SI Section 5.1). Finally, a gas release study was conducted to rule out Cl_2 release during the reaction,[47] despite the Co(III) oxidation state being retained (SI Figure S49). When Co_2Cl_4(btdd) was heated to 90 °C in 1,4-dioxane for 16 h, the resulting solution did not contain dissolved Cl_2 and the MOF did not undergo a color change, ruling out the involvement of generated Cl_2 during the reaction (SI Figure S49). Taken together, these results strongly point to the reaction proceeding through a S_NAr mechanism. At this time, we cannot rule out that the reaction proceeds through a concerted S_NAr pathway instead of through a discrete Meisenheimer intermediate.[67]

Due to their insolubility, MOFs offer an inherent advantage compared to molecular catalysts—recyclability. As such, reactions performed on large scale are less wasteful because the catalyst can be recovered, regenerated, and reused in subsequent reactions.[68,69] To exemplify this, a gram-scale chlorination was performed (Figure 5a), affording **5a** in comparable yield (60%) to the small-scale reaction (54%). The MOF used in this reaction was collected, washed with water and MeOH to remove residual reactants, and reactivated under vacuum before being reused in subsequent gram-scale chlorination reactions. Three consecutive reactions with the same batch of MOF exhibit comparable yields (60%, 66%, 57%, respectively) to the small-scale reaction

(Figure 5a). After the final reaction, the collected MOF was found to be crystalline via PXRD but contaminated with residual KCl and KBr (SI Figure S56). The contaminants were removed by washing with water and MeOH, and the resulting crystalline sample of MOF demonstrates a BET surface area comparable to Co_2Br_2(btdd) (1059 ± 35 m^2/g) (SI Figure S56–57). These Co(III)–X MOFs represent the first recyclable catalysts for halex reactions.
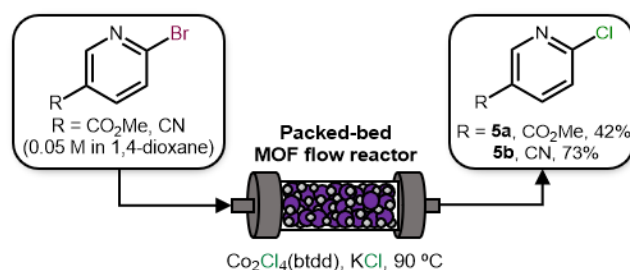

Figure 5. a) Gram-scale, recyclable chlorination using Co_2Cl_4(btdd). b) Chlorination in flow using a packed-bed inspired MOF flow reactor packed with Co_2Cl_4(btdd) and KCl.

As heterogeneous catalysts, MOFs are also prime candidates for reactions performed in continuous flow.[49] Heterogeneous catalysis in flow can result in increased yields and decreased reaction times due to the increased interfacial area and mass transfer compared to batch conditions, while also improving catalyst lifetimes and enabling catalyst recovery by combining reagent / catalyst separation with the reaction step.[49] By using a simple packed-bed flow reactor loaded with MOF and KCl (SI Figure S55), **5a** and **5b** can both be prepared from their corresponding heteroaryl bromides in comparable yields (42%, 73%, respectively) on a similar timescale to batch reactions (Figure 5b).

CONCLUSION

In summary, we have demonstrated the first example of MOF-catalyzed halex, a scalable reaction that can be adapted to function in continuous flow. A novel MOF synthesis, used to prepared gram-scale batches of MOFs, was developed to streamline reaction development. Both halogenation reactions reported herein are milder than reported halex reactions using simple metal halide salts, and both show high tolerance for a range of pharmaceutically relevant heterocyclic systems and functional groups. As a result, this transformation represents a significant advance in the use of MOFs to catalyze reactions relevant to medicinal chemistry, an emerging application for these powerful materials.[70,71] Although herein we focus on the fluorination and chlorination of hetero(aryl) bromides, this MOF platform can theoretically be used to drive other pharmaceutically relevant nucleophilic transformations, which we will explore in future work.

ASSOCIATED CONTENT

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Author Contributions

T.J.A. and P.J.M. conceived the project. T.J.A. synthesized and characterized all samples and conducted all measurements. T.J.A and P.J.M prepared and approve of the final version of this manuscript.

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Notes

P.J.M. is listed as a co-inventor on several patents related to MOFs.

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