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Towards a Practical Perfluoroalkylation of (Hetero)Arenes with Perfluoroalkyl Bromides using Cobalt Nanocatalysts

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A convenient methodology for perfluoralkylation including trifluoromethylation of (hetero)arenes with perfluoroalkyl bromides was devloped. Key for the success is the use of a specific cobalt-based nanocatalyst, which can be recycled at least up to 4 times. The scope of this first cobalt-catalyzed perfluoroalkylation is presented and detailed catalyst characterization (e.g. analytical STEM, XPS, and XRD) has been carried out.

Introduction

In recent years there is an increasing interest in the synthesis of bio-active compounds containing carbon-fluorine bonds.[1] Apart from aromatic fluorinations, also perfluoroalkylation reactions came into the focus of both academia and industrial research.[2] In particular, the introduction of trifluoromethyl,[3] difluoromethyl[4] and trifluoroethyl[5] groups into aromatic scaffolds is of current interest.

In general, perfluoroalkylations of arenes or olefins have been achieved from the corresponding iodides either in the presence of metal catalysts (e.g. dppfNi(*o*-tol)Cl, Pt/C, Pd(xantphos)$_2$, Pd(BINAP)$_2$, Ru(bpy)$_3$Cl$_2$) or radical initiators[6], e.g. Fenton-type radicals from H_2O_2, ACCN, eosin Y with white light or $Na_2S_2O_4$. The mechanism of these transformations is believed to proceed via radical intermediates. In comparison, perfluoroalkyl bromides[7] and chlorides[8] are less used because of their lower reactivity, despite advantages with respect to price and waste generation. Hence, there is a growing interest in the activation of perfluoroalkyl bromides. For example, we developed the perfluoroalkylation of arenes and heteroarenes with commercial platinum on charcoal as the catalyst.[9] Unfortunately, in this case using long chain perfluoroalkyl bromides, the scope was limited and the reactions proceeded often sluggishly.

Regarding trifluoromethylation, today´s state-of-the-art reagents for laboratory scale synthesis constitute Umemoto´s,[10] Togni´s,[11] Langlois´,[12] and the Ruppert-Prakash´s reagent[13] as well as $CuCF_3$ developed by Grushin.[14] However, due to their price and availability, larger applications are difficult to be realized with these reagents. In contrast, trifluoromethyl iodide[15] was used efficiently for such transformations even on a kg-scale.[16]

To overcome the aforementioned problems and to develop a more practical procedure, we envisioned the use of perfluoroalkyl bromides including CF_3Br as building blocks. Although this latter substrate is also ozone-depleting, it is available on kg-scale for reasonable price. Previous studies proved that C-H fuctionalizations of arenes and heteroarenes to the trifluoromethylated derivatives are possible, but required high loadings of precious metals.[9, 17] Following our general interest to replace such materials by abundant base metal catalysts, herein, we describe a convenient methodology using supported cobalt nanoparticles.

Results and Discussion

Development of the catalyst and optimal reaction system

As a model system, the reaction of neat 4-methylpyridine with perfluorohexyl bromide was studied in the presence of several catalysts at 130°C (Figure 1). It should be noted that such perfluoroalkylation of electron-deficient heteroarenes is challenging compared to the reaction of electron-rich substrates. In general, base was added to the benchmark reaction to trap the resulting HBr. Initially, around 100 potential catalysts were explored for their activity and selectivity. In these preliminary tests, we found that cobalt nanoparticles on nitrogen-doped carbon (Co@N/C), which was previously developed in our group for nitro hydrogenations,[18] and further applied for alcohol oxidations,[19] epoxidations,[20] aerobic dehydrogenations,[21] and reductive aminations,[22] is surprisingly able to activate perfluorohexyl bromide giving up to 49% of the product, which is even better than the previous platinum on carbon catalyst. Hence, special emphasis was put

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on the testing of such materials. A control experiment without any catalyst resulted in no formation of the desired product. For the preparation of the active catalysts, typically a pyrolysis step of the cobalt-supported pre-catalyst is necessary.[18c] However, here the pyrolysis temperature has no obvious influence on the activity of the catalyst for this transformation (**Cat1 – 3**). In contrast, the anion of the cobalt precursor and the weight percent (wt%) of the metal have significant effect on the yield of **3a** (**Cat4 – 6**, see also SI, Table S1). Changing the support and the metal centre resulted in only 20% or lower yield of **3a** (**Cat7 – 13**, see also SI, Table S2).

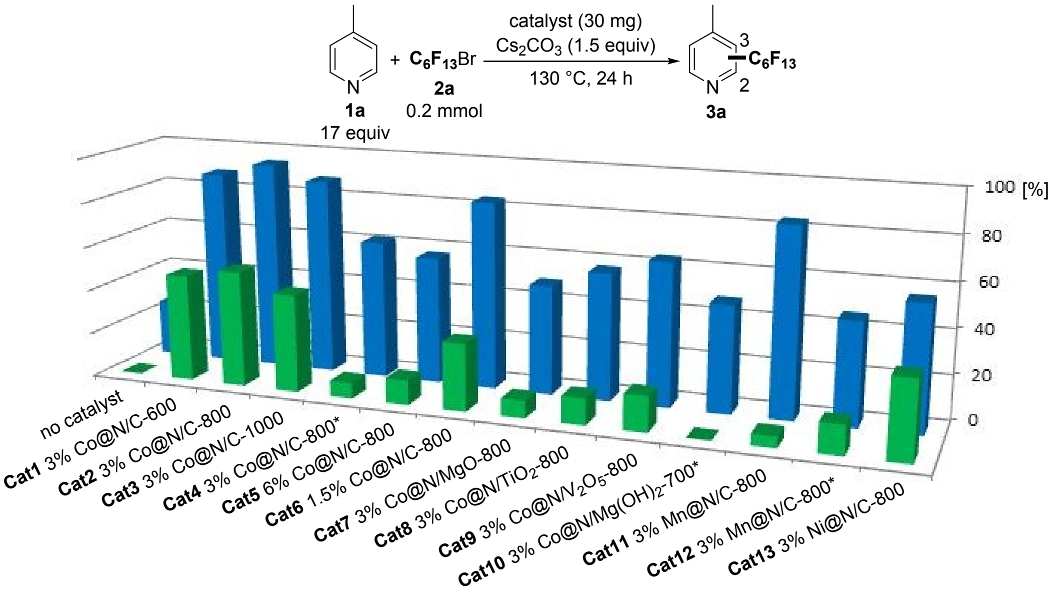
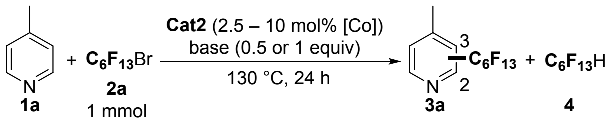


Figure 1. Selected results of the catalyst screening for the perfluorohexylation of 4-picoline with perfluorohexyl bromide in the presence of heterogeneous nanoparticles and Cs_2CO_3. Green bars display the selectivity; blue bars refer to the conversion of the perfluorohexyl bromide. Data received by ^{19}F NMR spectroscopy. If not stated otherwise the catalyst is prepared by wet impregnation of the support with an alcoholic $Co(OAc)_2Phen_2$-solution and subsequent pyrolysis in a crucible at 800 °C under argon atmosphere. **Cat4**: cobalt nitrate was used instead of cobalt acetate; **Cat10**: the material was washed with 1M HNO_3; **Cat12**: Mn(III) acetate was used as the precursor; **Cat13**: Ni(II) acetate was used as the precursor.

Table 1. Perfluorohexylation of 4-picoline: Different reaction conditions.



entry	[Co] / mol%	base (equiv)	solvent	conv. of **2a** / %	yield / %	
					3a	**4**
1	10	Cs_2CO_3 (1)	$CHCl_3$	13	0	0
2	10	Cs_2CO_3 (1)	MeCN	73	11	30
3	10	Cs_2CO_3 (1)	THF	100	0	72
4	10	Cs_2CO_3 (1)	--	100	63	7
5	5	Cs_2CO_3 (1)	--	98	54	7
6	2.5	Cs_2CO_3 (1)	--	84	42	6
7	10	Cs_2CO_3 (0.5)	--	85	51	6
8[a]	10	Cs_2CO_3 (1)	--	42	2	3
9	10	K_2CO_3 (1)	--	87	55	8

Reaction conditions: In case of using solvent: 5 equiv **1a**, 1 mL solvent. In the case of no solvent: 1 mL **1a**. Conversions and yields were determined by ^{19}F NMR with 1,2-difluorobenzene as the standard. [a] Reaction was performed at 110 °C.

To get a more efficient catalytic system, some of the prepared catalysts were washed with acid using 0.5 M H_2SO_4 to remove the larger inactive nanoparticles (see SI, Table S3). We also synthesized highly dispersed cobalt nanoparticles with $Mg(OH)_2$ as the support, which unfortunately gave no formation of **3a**.[23]

With the most suitable catalyst (3% Co@N/C-800, **Cat2**) in hand, we tested the influence of some reaction parameters. As shown in Table 1, using different solvents, e.g. $CHCl_3$, MeCN and THF, gave significant lower yield of **3a** compared to the neat experiment. In all cases, a drastic increase in the formation of the reductive product $C_6F_{13}H$ was observed (Table 1, entries 1 – 4; for more examples, see SI, Table S4). Reducing the amount of **Cat2** or Cs_2CO_3 both only slightly decreased the desired product yield (Table 1, entries 5 – 7; for more examples, see SI, Table S5). Attempts to decrease the reaction temperature failed and at lower temperature (110 °C) product formation was almost inhibited (Table 1, entry 8, see also SI, Table S6). Variation of bases showed that Cs_2CO_3 gave optimal results, while K_2CO_3 and K_2PO_4 decreased the reaction rate but gave comparable selectivities of **3a**, most likely due to the lower solubility of them. Liquid organic bases resulted in an increase of the reductive product (Table 1, entry 9, see also SI, Table S7).

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Next, catalyst recycling was investigated. As shown in Figure 2, reuse of the catalyst is possible up to 4 times without deactivation. After that a decrease in conversion and product yield is observed.

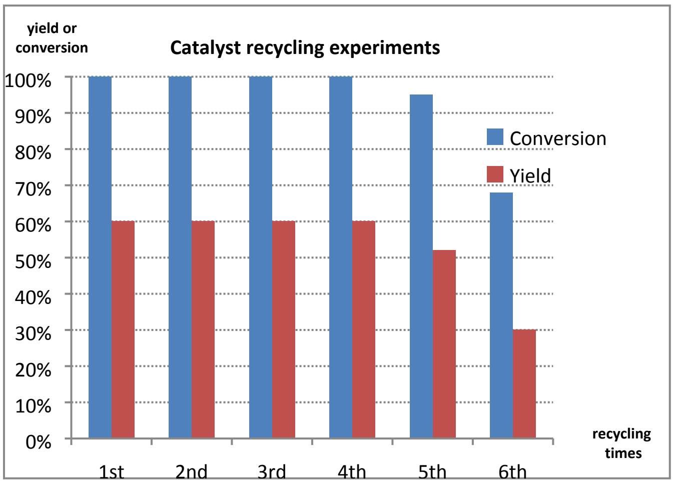
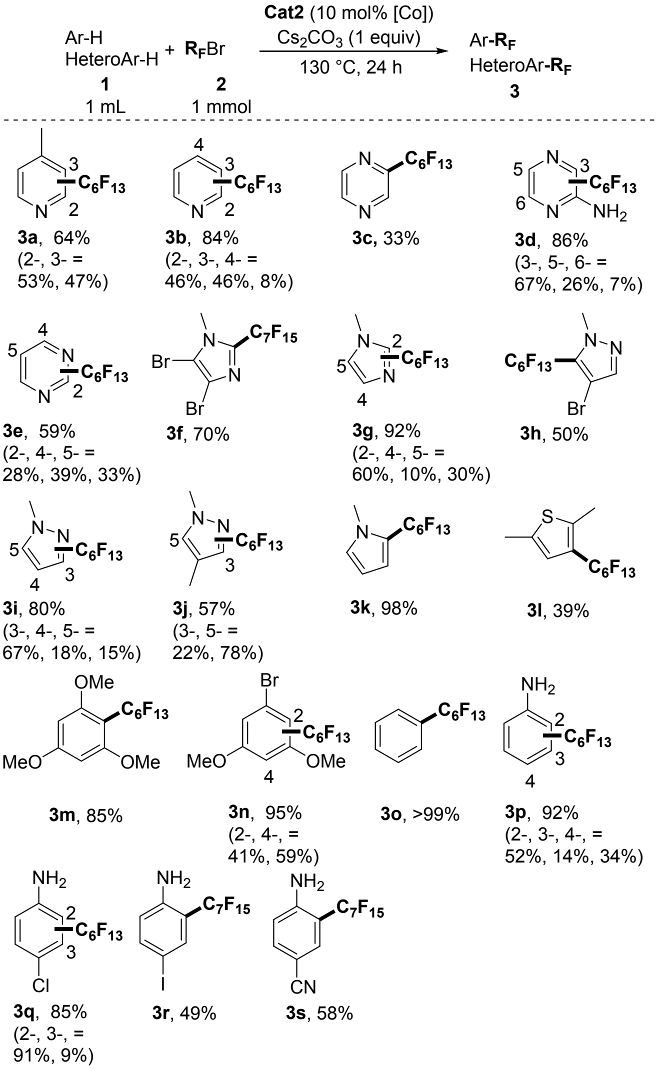


Figure 2. Catalyst recycling experiments for the cobalt-catalyzed perfluorohexylation of 4-picoline. Reactions conditions: **2a** (1 mmol), **1a** (1 mL), **Cat2** (10 mol% [Co]), Cs_2CO_3 (1 equiv), 130 °C, 24 h. Conversion and yields were determined by ^{19}F NMR with 1,2-difluorobenzene as the standard.

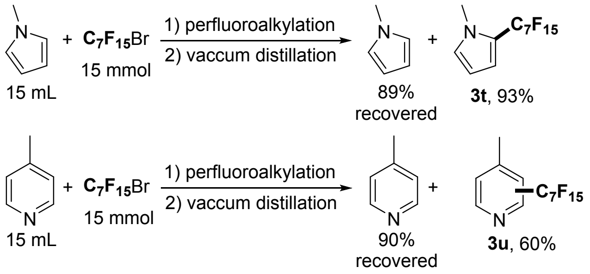
Synthesis of perfluoroalkylated (hetero)arenes

Under the optimized conditions, we explored the scope of this novel perfluoroalkylation process using 18 different (hetero)arenes (Scheme 1). Most of these perfluoroalkylated compounds were successfully isolated in moderate to good yields by combi-flash chromatography or micro-destillation. In agreement with our previous publication, regioselectivity-wise perfluoroalkylation occurred in general at the most electron-rich position.[6d] Apart from 4-picoline, other demanding six-membered heterocycles such as derivatives of pyridine, pyrazine, and pyrimidine were functionalized and the desired products **3b** – **3e** were obtained in decent to good yields (33-86%). Similarly, *N*-methylimidazoles **3f** and **3g** and *N*-methylpyrazoles **3h** – **3j** were also smoothly perfluoroalkylated in excellent yields (up to >99%). *N*-Methylpyrrole proved to be the most active substrate and gave selectively the product perfluoroalkylated in 2-position in 98% yield. Apart from heterocycles, various arenes could be successfully perfluoralkylated, too. For example, perfluorohexylbenzene **3o** was obtained in quantitative yield (>99%) with benzene as the parent molecule. In general, transformations of electron-rich benzenes proceeded faster and gave increased yields of the desired products compared to electron-deficient substrates. For example, aniline provided the desired product **3p** in 92% yield (as a mixture of three isomers in a ratio of 52:34:14), while 4-cyanoaniline gave only 58% of the corresponding product **3s**. Notably, for all substituted anilines, perfluoroalkylation occurred highly selectively (>90%) at the 2-position and *N*-perfluoroalkylation was not observed in all cases.

A notable feature of this protocol is the practicability and the reactions can be easily performed on multi-g scale. To demonstrate this feature, reactions of *N*-methylpyrrole and less reactive 4-methylpyridine with perfluoroheptyl bromide were performed in a 25 mL autoclave on 15 mmol scale (Scheme 2).



Scheme 1. Perfluoroalkylation of (hetero)arenes with perfluoroalkyl bromides using cobalt nanocatalysts. Isolated yields. Selectivities were determined by ^{19}F NMR.



Scheme 2. Scale up reactions for the perfluoroalkylation of *N*-methylpyrrole and 4-picoline. Reaction conditions of 1): **Cat2** (10 mol% [Co]), Cs_2CO_3 (1 equiv), 130 °C, 20h. Isolated yields by distillation.

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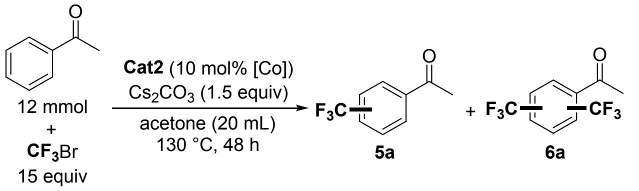
Separation of the starting material and the products was readily achieved by vacuum distillation. Further separation of the isomers can be done by column chromatography. Analysis of the gas phase (after trapping it in a cooling trap) by GC-MS revealed unreacted starting material, reductive dehalogention product and two molecules corresponding to a smaller perfluoroalkyls, which exact structure could not be assigned due to fast fragmentation.

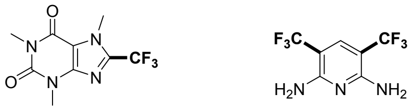
Next, catalytic trifluoromethylations using CF_3Br were explored (Table 2). Here, acetophenone was used as an electronically deactivated substrate, which has been only trifluoromethylated before with stoichiometric amounts of $CuCF_3$ with the corresponding aryl iodides[24] or the diazonium salt.[25] Obviously due to its gaseous nature under ambient conditions, it is impossible to perform the reaction of CF_3Br under neat conditions. Nevertheless, using acetone as solvent,[17] the desired reaction took place and apart from the major isomer (43% 2-trifluoromethylacetophenone), the corresponding 3- and 4-isomer were observed in 23 and 34% yield, respectively. Moreover, also small amount (3-7%) of bis-trifluoromethylated product was detected. Notably, for this transformation the catalyst was recycled up to 6 times without loss of activity.

Table 2. Cobalt-catalyzed trifluoromethylation of acetophenone with CF_3Br.



entry	conversion of acetophenone/ %	yield of **5a** / %	yield of **6a** / %
1	74	37	6
2[a]	74	44	7
3[a]	78	34	4
4[a]	65	42	5
5[a]	--	47	4
6[a, b]	57	42	3

Reaction conditions: Conversions were determined by GC with hexadecane as the standard. Yields were determined by ^{19}F NMR with 1,2-difluorobenzene as the standard. [a] The catalyst was recycled from the previous entry. [b] Reaction time 312 h.



5b, 74% **6c**,[a] 29%

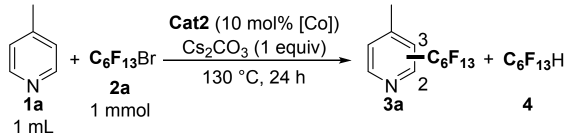
Scheme 3. Two examples for trifluoromethylation of heteroarenes. Reaction conditions: heteroarene (2 mmol), CF_3Br (12 bar), **Cat2** (10 mol% [Co]), Cs_2CO_3 (1.5 equiv), acetone (4 mL), 130°C, 48h. [a] Reaction was performed at 150 °C for 24 h.

In addition to acetophenone, trifluoromethylation of theophylline and 2,6-diaminopyridine were investigated, too. As shown in Scheme 3, trifluoromethylated product **5b** was obtained in 74% yield using theophylline as substrate. Using 2,6-diaminopyridine, bis-trifluoromethylation occurred to give **6c** in 29% isolated yield.

Mechanistic investigations and catalyst characterization

To understand the mechanism of this novel catalytic system, several control experiments were performed and the structure of the catalyst was investigated in detail. Obviously, it was not possible to investigate the reaction *in situ* by NMR spectroscopy due to the heterogeneous nature of the catalyst. Unfortunately, EPR studies did not show any organic radicals for the reaction of perfluorhexyl bromide with 4-picoline, or the most reactive substrate *N*-methyl pyrrol at 120 °C. To indirectly measure highly active, short living radicals, the commonly used spin trapping reagent DMPO was added, but again no radical formation was observed.[26] Even after additional heating then fast freezing of this solution no signals were detected.

Table 3. The effect of radical scavengers on this cobalt-catalyzed perfluorohexylation of 4-picoline.



entry	scavenger (mol%)	conversion of **2a**/ %	yield of **3a** / %	yield of **4** / %
1	--	100	59	8
2[a]	--	87	40	6
3	TEMPO (20)	100	38	28
4	TEMPO (100)	100	3	51
5	dinitrotoluene (20)	100	56	17
6	dinitrotoluene (100)	96	45	23
7	hydroquinone (20)	100	48	13
8	hydroquinone (100)	100	29	11
9[b]	*t*-butylhydroperoxide (20)	100	55	17
10[b,c]	*t*-butylhydroperoxide (100)	100	51	19

Reaction conditions: Conversions and yields were determined by ^{19}F NMR with 1,2-difluorobenzene as the standard. [a] cooled down after 6 hours to 70°C and filtrated at this temperature. [b] *t*-butyl hydroperoxide is 70 wt.% solution in water.

Next, the effect of the addition of radical scavengers was studied. In case of other catalysts for such transformations, e.g. dppfNi(*o*-tol)Cl or Pt/C, the corresponding radicals were quenched in the presence of 1 equiv TEMPO.[6d, 9] Surprisingly, in this protocol, TEMPO did not stop the reaction, but only

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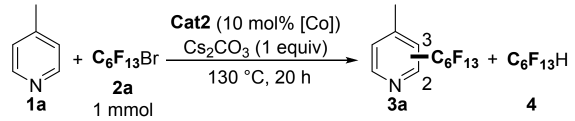
increased the formation of the side product $C_6F_{13}H$ (Table 3, entries 3 and 4). Also, the perfluoroalkylated TEMPO molecule could not be identified by HRMS. Addition of other scavengers like *p*-dinitrobenzene, hydroquinone and *t*-butylhydroperoxide resulted in slight decrease of the desired product and increase of $C_6F_{13}H$ (Table 3, entries 5 – 10). However, in general the effects of these quenching reagents are very small. Apparently in contrast to other previously reported radical perfluoroalklyations, which are highly influenced by catalytic amounts of scavengers,[8, 27] the presented methodology is much more tolerant to these additives (see also in SI, Table S8).

During the optimization process, we realized that major side reactions are the hydrodehalogenation of the perfluoroalkyl halide and additional decomposition side reactions, observable in the crude ^{19}F NMR spectra. For example, the reaction of 4-methylpyridine with perfluorohexyl bromide gave full conversion; however, only 60% of the desired product was formed. Additionally, around 10% of the reductive product, *vide supra*, is produced.[6a, 8, 28] To exclude the formation of this reductive product by traces of water, several control experiments were performed (Table 4). Unexpectedly, the reaction proceeded even when using water as the solvent demonstrating the robustness of the protocol.

Table 4. Influence of water on the perfluorohexylation of 4-picoline.



entry	amount of H_2O	amount of **1a**	conversion of **2a**	yield of **3a** / %	yield of **4** / %
1	--	20 equiv	98	52	8
2	1 equiv	20 equiv	98	48	9
3	10 equiv	20 equiv	98	50	7
4	1800 equiv	5 equiv	93	33	9
5	1800 equiv	1.1 equiv	93	8	11
6	1800 equiv	0.5 equiv	65	4	11

Conversions and yields were determined by ^{19}F NMR with 1,2-difluorobenzene as the standard.

In contrast, proton scavenging from organic solvents occurred more easily and was identified as the major reaction during the solvent screening process. Here, an increase of the reductive side product was observed with an increasing amount of alkyl groups at the arenes (for benzene, toluene, and mesitylene: $C_6F_{13}H$ = 0%; 9%; 45%, respectively under neat reaction conditions).

As shown in Scheme 1, the reaction of pyrazine with perfluorhexyl bromide gave only 33% of the desired product and a major degradation process of the fluorinated substrate was observed in this case.[29] To identify the fate of the perfluoroalkyl halide we had a closer look at the filtrated and washed catalyst. Indeed, we observed the formation of insoluble fluorinated materials during the reaction leading to an increased mass of the recycled catalyst material (Table 5). As a consequence the elemental analysis for the catalyst after 6th recycling revealed the emergence of more than 14% fluorine atoms both for perfluoroalkylation and trifluoromethylation reactions (Table 5, entries 4 and 5).

Analysis of the recycled catalysts by X-ray powder diffraction revealed the formation of CsBr and Cs_2SiF_6 in the catalyst material during the recycling procedure. Whereas the formation of CsBr is not surprising, the presence of Cs_2SiF_6 is unexpected. The formation might be caused by free HF in the starting materials, the presence of Si in the used carbon support and/or the usage of glass and Si containing steel made compounds during the catalytic testing. However, small amounts of metallic cobalt could be identified in the recycled samples (see SI, Figure S3).[30]

Table 5. Elementary analysis of **Cat2** before and after different reactions.

entry	C / %	H / %	N / %	Co / %	F / %	mass / mg
1	82.9	0.3	2.3	3.1	0	200
2	56.0	0.3	3.5	1.4	15.2	400
3	55.2	0.3	3.5	1.1	26.0	400
4	59.6	0.7	3.0	0.9	14.1	--
5	60.1	1.9	0.9	0.5	15.1	--

Reaction conditions: entry 1, fresh catalyst; entry 2, catalyst recycled after the perfluoroalkylation pyrazine with $C_6F_{13}Br$ using the reaction conditions in Scheme 1; entry 3, catalyst recycled after the perfluoroalkylation of pyrazine with $C_6F_{13}I$ using the reaction conditions in Scheme 1; entry 4, catalyst after 6th recycling as shown in Figure 2; entry 5, catalyst after 6th recycling as shown in Table 2.

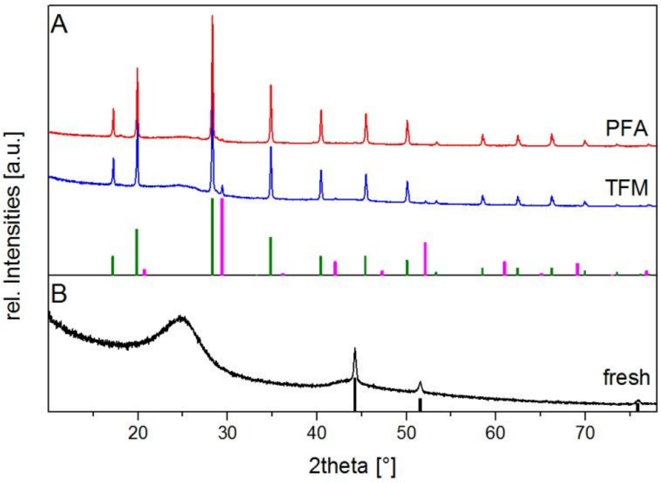


Figure 3. A) Powder diffraction pattern of recycled catalyst after the 6th cycle of trifluoromethylation (TFM) and perfluoroalkylation (PFA). Coloured bars represent peak position and relative intensities of identified main phases: green (pdf 00-007-006, Cs_2SiF_6); mangenta (pdf 00-005-0588, CsBr) respectively. B) Powder diffraction pattern of the fresh catalyst as well as peak position and relative intensities of metallic cobalt reference dataset (pdf 00-015-0806).

XPS (X-ray photoelectron spectroscopy) analysis confirms the presence of caesium and fluoride species on the catalyst

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surface after recycling. In contrast the surface of the fresh catalyst is composed of C, N, O and Co only, see SI, Figure S4 for survey spectra of the fresh and recycled catalysts. High resolution spectra of the C 1s, N 1s, F 1s and Co 2p region are shown in SI, Figure S5 A to D, respectively. Whereas for the fresh catalyst mainly C-C and C-C/C-H bonds (248.0 eV and 284.8 eV) can be observed both recycled catalysts show the formation of C-O/C-OH functionalities (286 eV – 292 eV) as well as a rather broad feature at about 292 eV indicating the formation of CF_2. Only minor changes can be observed in the N 1s spectra so that the two observed signals for pyridinic and pyrrolic nitrogen seem to be rather stable.[31] The F 1s spectra is composed of one main feature characteristic for organic fluorine bonds at 688 eV. In the fresh catalyst no F can be detected. The Co 2p spectra in Figure SZD reveals the presence of cobalt in an oxidic state, probably Co_3O_4 as main component but CoO cannot be excluded completely.[32] Interestingly on catalyst–PFA no Co can be detected, indicating a coverage of the Co structures e.g. by graphitic layers as observed by TEM.

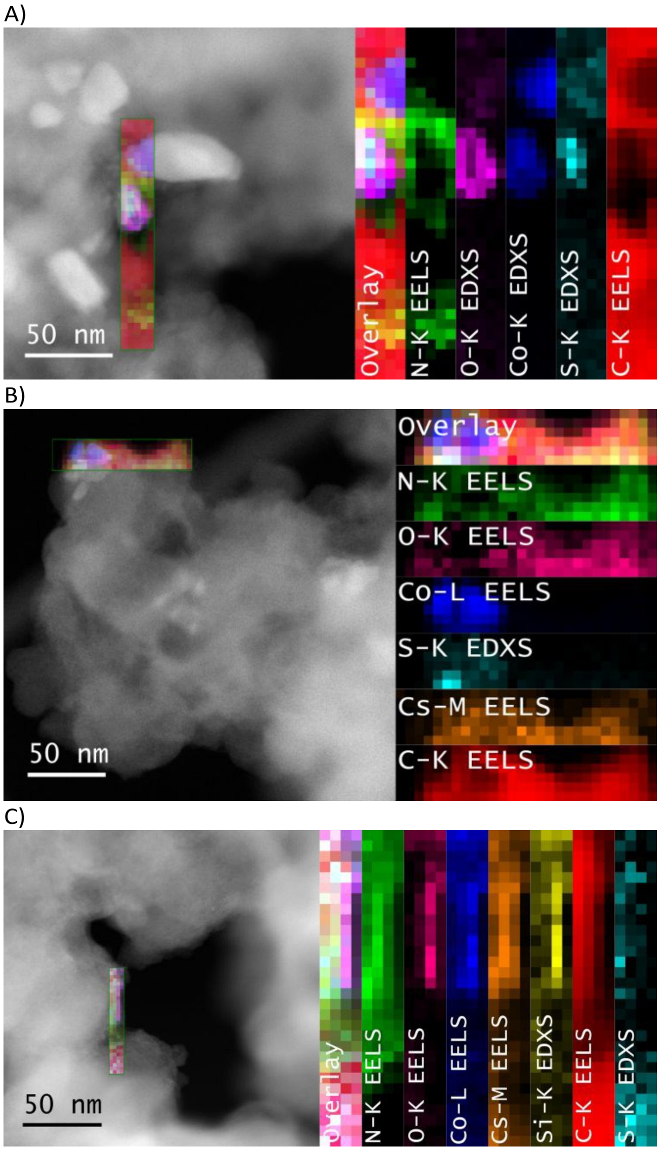

Figure 5 Annular dark field (ADF) – STEM images with EELS and EDXS elemental maps of the marked regions. A) Fresh catalyst, B) catalyst-TFM after 6th recycling, C) catalyst-PFA after 6th recycling.

Next, scanning transmission electron microscopy (STEM) analysis including high angle annular dark field (HAADF), annular dark field (ADF) and annular bright field (ABF) imaging, energy dispersive x-ray (EDX) and electron energy loss spectroscopy (EELS) was applied to the original catalyst. This material revealed metallic cobalt particles, as well as metallic cobalt particles partially covered by cobalt oxide shells and highly dispersed cobalt in unknown oxidation state (Figure 5A, see also SI, Figure S6). The metallic Co surfaces are typically covered with graphite layers when not covered by an oxide shell (SI, Figure S7). Additionally, there is a mixed C, N, Co containing phase formed from the pyrolysis of 1,10-phenanthroline, as well as sulfur impurities probably from the vulcan support.

A distinct enrichment of Cs could be observed in the recycled material (Figure 5B and 5C). Especially two crystals containing of F, O, Cr, Fe, Cs and F, O, Si, Cs respectively could be found (SI, Figure S10 and S13) as well as highly dispersed Cs containing particles on the shells of the graphite layers, which provide more contrast compared to cobalt, although the catalyst material was washed with water intensively. Overall, the presence of Co particles decreased although a dispersed Co and N phase remains on the surface of the support (SI, Figure S8 and S11). The sulfur impurities partly migrated during the changing process to the surface of the layers to cobalt-rich areas, indicated by EELS analysis (Figure 5B and 5C). The probed material is less uniform than the primal catalyst. In terms of impurities, it is necessary to say that in case of trifluoromethylation reaction, the reaction was performed in a stainless steel autoclave, while the perfluoroalkylation was performed in a screw cap glass vial. Under the reaction conditions these materials seem to be attacked in a minor extent, leading to Fe and Cr impurities (SI, Figure S8) in the Cat-TFM sample and Si impurities (Figure 5C, see also SI, Figure S11) in the Cat-PFA sample. The catalytic influence of these impurities remains unclear, but a deactivating effect cannot be excluded.

Conclusions

Here, we present a useful methodology for perfluoralkylations including trifluoromethylations of (hetero)arenes using perfluoroalkyl bromides. Crucial for this transformation is the usage of a specific heterogeneous catalyst with supported cobalt nanoparticles, which can be also recycled. This novel procedure does not need additional activators or precious metals or ligands. Regarding substrates it should be noted that ketone, amino, cyano, and methoxy groups, as well as different halides are well-tolerated. The resulting products, especially the bromide- and amino-substituted derivatives constitute interesting building blocks, which can be easily further processed.

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Conflicts of interest

There are no conflicts to declare.

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Notes and references

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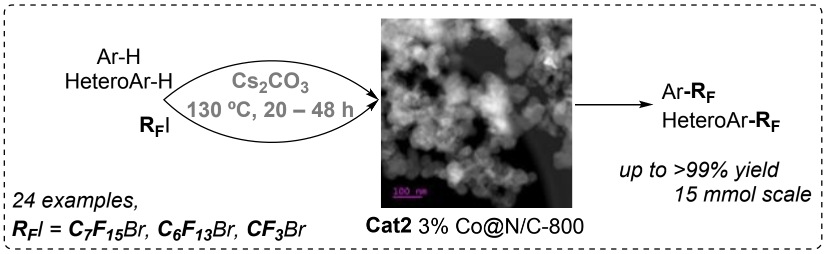

A convenient methodology for perfluoroalkylation including trifluoromethylation of (hetero)arenes with perfluoroalkyl bromides was developed. Key for the success is the use of a specific cobalt-based nanocatalyst, which can be recycled at least up to 4 times. The scope of this novel cobalt-catalyzed perfluoroalkylation is presented and detailed catalyst characterization (e.g. EDX- and EELS-assisted TEM, XPS, and XRD) has been carried out.