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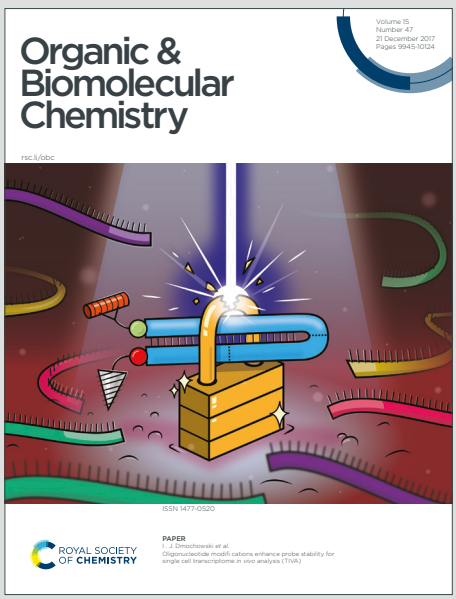

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ARTICLE

Copper-Catalyzed and Additive Free Decarboxylative Trifluoromethylation of Aromatic and Heteroaromatic Iodides

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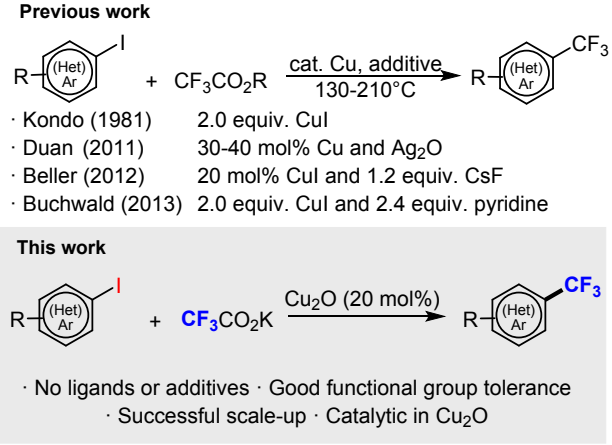
Martin B. Johansen*[a] and Anders T. Lindhardt*[b]

A copper-catalyzed decarboxylative trifluoromethylation of (hetero)aromatic iodides has been developed. Importantly, this new copper-catalyzed reaction operates in the absence of any ligands and metal additives. The protocol shows good functional group tolerance and is compatible with heteroaromatic systems. The reaction proved scalable to a 15 mmol scale with increased yield. Finally, late-stage installation of the trifluoromethyl functionality afforded the *N*-trifluoroacetamide variant of the antidepressant agent, Prozac, demonstrating the applicability of the developed method.

Introduction

The development of cost-effective methods to install the trifluoromethyl (CF_3) group in (hetero)aromatic compounds is of special interest as this motif can be strategically positioned to fine-tune metabolic and chemical properties of pharmaceuticals and agrochemicals.[1] As an example the CF_3 group is known to block potential oxidation sites compared to its non-fluorinated (CH_3) counterpart. The general lack of fluorine in natures pool of carbon based compounds has resulted in a plethora of synthetic methods towards its installation.[2,3] The industrial Swarts process, that utilizes antimony trifluoride and chlorine gas to afford benzylic fluorination, has a low functional group tolerance and is unsuitable for late stage funtionalization.[4] C-H activation of aromatic compounds, employing trifluoromethyl radicals, derived from precursors such as Langlois reagent, allows installation of CF_3 under mild reaction conditions. However, the addition step of the trifluoromethyl radical in these reactions often lack regioselectivity.[5] Alternatively, nucleophilic trifluoromethylation protocols aided by the presence of a transition metal ensures that CF_3 installation occurs with excellent regioselectivity, an example being the Trifluoromethylator.[6] Catalytic protocols applying copper or palladium normally rely on expensive TMS-CF_3 or TES-CF_3 as the source of anionic CF_3.[7] This in combination with the need of additional metal mediators and additives, leads to costly setups unsuited for scale-up.[8-10] Among the most cost effective CF_3-anion precursors are the metal trifluoroacetates.[8,11] The low cost of these CF_3 building blocks counterbalances the higher cost of aromatic iodides and therefore justifies their application in the copper mediated trifluoromethylation, even on kilogram scale.[11b] Surprisingly, only few alternative protocols have been reported since the first decarboxylative trifluoromethylation method using sodium trifluoroacetate (NaTFA) described by the group of Kondo in 1981 (Scheme 1).[12a]

The group of Buchwald recently reported on the trifluoromethylation of heteroaromatic iodides with potassium trifluoroacetate (KTFA) performed in just 16 minutes with temperatures reaching 210°C utilizing a continuous flow process.[12b] Trifluoromethylations relying on a catalytic loading of copper have been reported by both Duan and Beller.[12c-d] However, the addition of silver(I) oxide or excess cesium fluoride to promote decarboxylation of NaTFA and methyl trifluoroaceate (MTFA), respectively, to release the CF_3 anion proved necessary. Despite the low cost of the CF_3 precursors, the application of (super)stoichiometric ligated copper complexes combined with specialized additives prevents cost effective scaling of such trifluoromethylation protocols.



Scheme 1. Previous strategies for copper mediated or catalysed decarboxylative aromatic trifluoromethylation[12a-d].

The plausible mechanism for decarboxylative trifluoromethylations of aromatic iodides is depicted in scheme

[a] *Department of Engineering, Carbon Dioxide Activation Center (CADIAC), Interdisciplinary Nanoscience Center (iNANO), Aarhus University, Gustav Wieds Vej 14, DK-8000 Aarhus C. E-mail: bundgaard@eng.au.dk.*

[b] *Present address: Danish Technological Institute, Life Science Division, Kongsvang Allé 29, DK-8000 Aarhus C. E-mail: andl@dti.dk.*

† Electronic Supplementary Information (ESI) available: Optimization tables, synthesis of starting materials, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra of all reported compounds. See DOI: 10.1039/x0xx00000x

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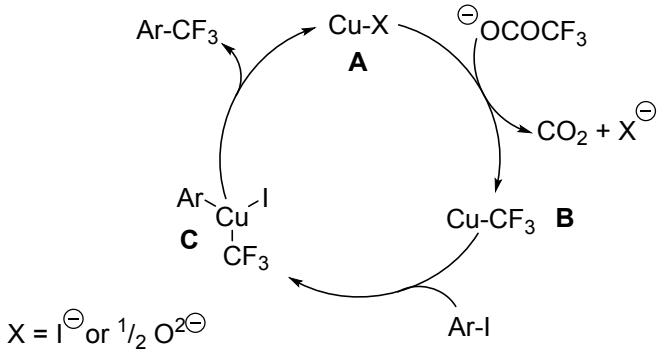
2.[10,12b,12d] Cu(I)X (**A**) undergoes transmetalation with a CF_3-anion formed by decarboxylation of trifluoroacetate to form Cu(I)CF_3 (**B**) under the liberation of anion X. Oxidative addition into the aryl iodide affords the Cu(III) oxidative complex (**C**). Finally, reductive elimination yields the trifluoromehylated product with regeneration of CuX (**A**).



Scheme 2. Suggested reaction mechanism of the copper-catalyzed decarboxylative trifluoromethylation. .

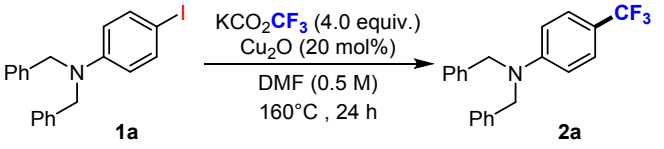
Herein, we wish to report on the copper-catalyzed decarboxylative trifluormethylation of aryl iodides. The protocol takes advantage of simple copper(I) oxide, in the presence of cost-effective KTFA and *operates without the need of added ligands or expensive metal additives*.[13,14] The protocol effectively installed the CF_3 functionality with good functional group compatibility. When the reaction scale was increased from 0.5 mmol to 15 mmol, based on the aryl iodide as the limiting reagent, an increase in isolated yield was observed. Finally, the protocol was applied towards late-stage installation of the CF_3 moiety into Prozac, an antidepressant drug. An inhibitory effect of iodide onto the catalytic efficiency was observed during this work, which positions copper(I) oxide as a superior catalyst when compared to classically utilized copper(I) iodide. It is, to the best of our knowledge, the first copper catalyzed decarboxylative trifluoromethylation method operating in the absence of ligands and other metal additives.

Results and discussion

Optimization was performed using *N,N*-Dibenzylated 4-iodoaniline (**1a**) as the model substrate (Table 1). An initial lead was identified upon reacting four equivalents of KTFA in the presence of copper(I) oxide (Cu_2O, 10 mol%). This reaction resulted in a good yield of 62% determined by ^{1}H NMR analysis of the reaction mixture (entry 1). The cation of the trifluoroacetate salt proved imperative to the reaction outcome, resulting in low 30% or 37% yield when applying sodium or cesium trifluoroacetate salts, respectively (entry 2-3).

Another important observation was that sodium trifluoroacetate was fully consumed during the course of the reaction whereas only 16% of KTFA was converted (Table SI-1).[15] Increasing the loading of KTFA to six equivalents had little effect whereas two equivalents resulted in a decreased yield (entry 4-5). Attempts to lower the temperature to 150°C or increasing it to 170°C resulted in a decreased yield in both situations (entry 6-7). No turnover occurred when an experiment was performed in the absence of Cu_2O (entry 8). A search through the literature reveals copper iodide (CuI) to be the most utilized catalyst in decarboxylative trifluoromethylations.

Table 1 Optimization of the reaction conditions.



entry	deviation from standard conditions	yield[a] [%]
1	10 mol% Cu_2O	62
2	10 mol% Cu_2O and NaTFA	30
3	10 mol% Cu_2O and CsTFA	37
4	10 mol% Cu_2O and 2.0 equiv. KTFA	54
5	10 mol% Cu_2O and 6.0 equiv. KTFA	62
6	10 mol% Cu_2O and 150°C	49
7	10 mol% Cu_2O and 170°C	53
8	no copper(I) catalyst	0
9	20 mol% CuI	54
10	40 mol% CuI	72
11	**none**	**86**
12	40 mol% 1,10-phenanthroline added	91
13	NMP	85
14	DMSO, DMPU, butyronitrile, diglyme or DMAc[b]	0 - 65
15	1-16 h[c]	23 - 78
16	≈1 atm pressure[d]	87
17	Argon atmosphere replaced with air[d]	30
18	2.0 equiv. KTFA	68
19	3.0 equiv. KTFA	81

[a]Yield was obtained by ^{1}H NMR analysis of the crude reaction mixture, using α,α,α-trifluorotoluene as an internal standard. [b]See ESI Table SI-5 for detailed information. [c]See ESI Table SI-6 for detailed information. [d]Yield was obtained by ^{1}H NMR analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard.

However, in our hands CuI turned out less active when compared to similar loadings, compared based on copper equivalents, of Cu_2O (entry 9).[16] Increasing the catalyst loading to 40 mol% copper(I) of both CuI and Cu_2O afforded a ^{1}H NMR yield of 72% and 86%, respectively (entry 10-11). Interestingly, only a small increase in yield from 86% to 91% was observed upon addition of the classic copper ligand 1,10-phenanthroline (40 mol% - entry 12). Given this minor effect of added ligand, it was decided to omit this from further studies. NMP proved to be an equally suitable solvent (entry 13).[17] Other high boiling solvents such as DMSO, DMPU, butyronitrile, diglyme and DMAc all lead to significant decreases in yield (entry 14). Reaction times below 24 hours led to deterioration of the reaction yield (entry 15 – see ESI for reaction details). By installing a balloon to equilibrate the pressure, the reaction was performed at atmospheric pressure which had no effect on the reaction outcome (entry 16). However, a significant drop in yield is observed when the reaction is performed under ambient air (entry 17). The loading of KTFA was reinvestigated and resulted in a NMR yield of 68% and 81% for 2 and 3 equivalents, respectively (entries 18-19). Due to the higher yield of 86% of

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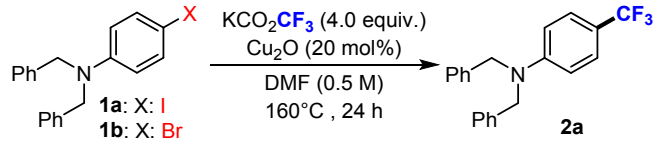
2a seen in entry 11, it was decided to proceed with reaction conditions using 4 equivalents of KTFA.

During optimization, an interesting halide effect was observed (Table 2). Upon addition of KI (1.0 equivalent) to the optimized reaction conditions, the ^{1}H NMR yield of **2a** dropped to 37% (entry 2). Next, substitution of **1a** with the corresponding aryl bromide **1b**, thereby eliminating the presence of iodide in the reaction medium, only afforded a mere 21% yield of **2a** (entry 3). This result was explained by the reluctant oxidative addition of copper(I) into the Ar-Br bond.[18]

Table 2 Iodide effect.



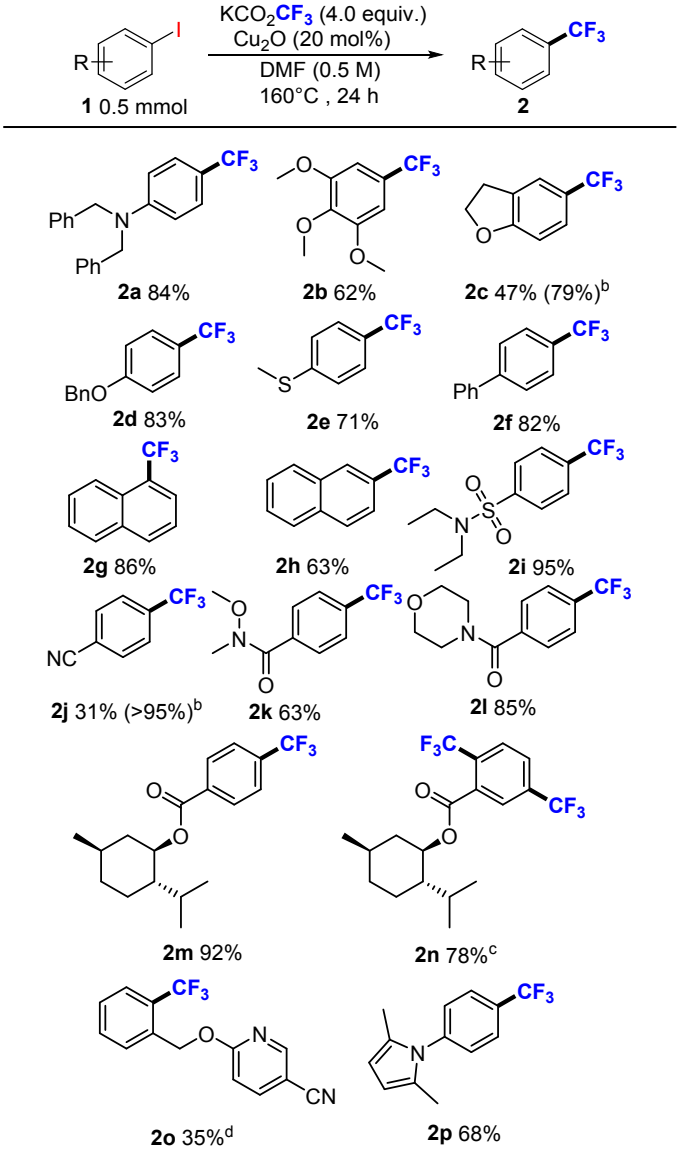
entry	deviation from standard conditions	yield[a] [%]
1	X = I	86
2	X = I and 1.0 equiv. KI	37
3	X = Br	21
4	X = Br and 20 mol%. KI	43[b]
5	X = Br and 1.0 equiv. KI	14[b]

[a] Yield was obtained by ^{1}H NMR analysis of the crude reaction mixture, using α,α,α-trifluorotoluene as an internal standard. [b] The corresponding aryl iodide (**1a**) was identified as side product by ^{1}H NMR analysis.

Repeating the reaction in entry 3 with the addition of 20 mol% KI increased the yield to 43% (entry 4). Notably, addition of KI resulted in the detection of **1,** by ^{1}H-NMR analysis of the reaction mixture, suggesting competing copper(I) catalyzed Finkelstein reaction.[19] Addition of one equivalent of KI in combination with **1b** once again had an inhibitory effect on the reaction outcome and only 14% of **2a** was formed (entry 5). In conclusion, a low concentration of iodide seems to improve the catalytic efficiency, whereas high concentration, as would be the case towards the end of the reaction, appeared to inhibit catalytic turnover. These findings suggests that copper catalyzed decarboxylative trifluoromethylations of aryl iodides is subject to catalyst poisoning by the iodide formed during reaction progression.[20] This effect might also explain why Cu_2O is a superior copper(I) source in this transformation, as CuI initially brings in stoichiometric loading of iodide with itself. Attempts to remove iodide *in situ* proved unsuccessful in our hands (See ESI Table SI-9).

With optimized conditions in hand, the scope of the transformation was investigated (Scheme 3). Aryl iodides carrying electron donating functionalities (compounds **2a**-**e**) were isolated in yields ranging from 47% to 84%. **2c** proved difficult to isolated and only afforded an isolated yield of 47%, however, ^{1}H-NMR analysis revealed a yield of 79% based on the presence of an internal standard. 1- and 2-iodonaphthalene and 4-phenyl-iodobenzene afforded the target compounds in 86%, 71% and 82%, respectively (compounds **2f-h**). **2i**, carrying a *N,N*-Diethyl sulfonamide, afforded a near quantitative isolated yield of 95%. Similar to compound **2c**, isolation of **2j** proved troublesome and only a mere 31% could be secured upon column chromatography.

Scheme 3 Trifluoromethylation of aromatic iodides.[a]



[a] Information of standard reaction conditions can be found in the experimental section. Isolated yields are reported. [b] ^{1}H NMR yield using α,α,α-trifluorotoluene as an internal standard. [c] 0.4 equiv. Cu_2O used and reaction scale was 0.25 mmol, otherwise standard reaction conditions. [d] NaTFA was used instead of KTFA and 140˚C was used instead of 160˚C.

Besides sulfonamides, two *para*-functionalized amides, compounds **2k** and **2l**, were prepared in a 63% and 85% yield, respectively. The (L)-menthol ester derivative **2m** was isolated in an excellent 92% yield. Menthyl 2,5-diiodebenzoate underwent double trifluoromethylation to afford **2n** in an excellent 78% yield, using 40 mol% Cu_2O. The yield of **2o** initially turned out very low and it was speculated that the low yield of **2o** was due to competing decomposition of either its starting material or product itself at 160°C. However, lowering the temperature to 140°C combined with the faster decarboxylating sodium trifluoroacetate CF_3-precursor allowed

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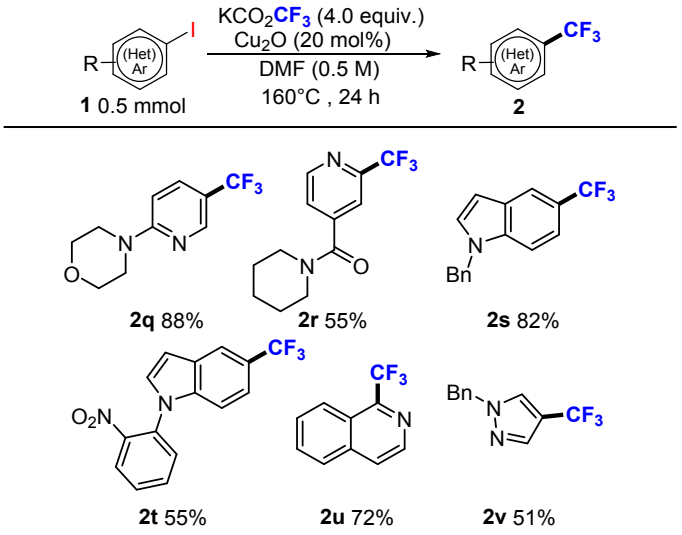
2o to be secured in 35% isolated yield after column chromatography. The trifluoromethylation product of pyrrole substituted aryl iodide (**2p**) was isolated in a 68% yield.

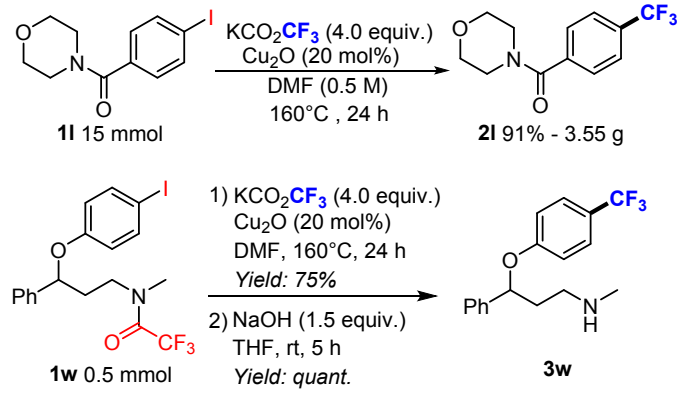
Scheme 4 Trifluoromethylation of heteroaromatic iodides.[a]



[a] Information of standard reaction conditions can be found in the experimental section. Isolated yields are reported.

Our attention was turned towards testing nitrogen-based heteroaromatic substrates under the developed conditions (Scheme 4). Trifluoromethylation of 2-(4-morpholyl)-5-iodopyridine afforded the target compound **2q** in a high isolated yield of 88%. The isonicotinic piperidyl amide also proved reactive and afforded **2r** in a good isolated yield of 55%. *N*-Benzyl- and *N*-(2-nitrobenzene) functionalized indole (compounds **2s** and **2t**) were isolated in 82% and 55% yield, respectively. 1-Iodoisoquinoline (**2u**) proved reactive and afforded good isolated yields of 72%. Finally, the target trifluoromethylated product of 1-benzyl-4-iodo-1*H*-pyrazole (**2v**) was isolated in a reasonable 51% yield.

Scheme 5 Scale-up synthesis of **2l** (top) and synthesis of Prozac (**3w**) (bottom).[a]



[a] Information of reaction conditions can be found in the experimental section. Isolated yields are reported.

Next, the developed conditions were tested on a 15 mmol reaction scale resulting in the isolation of **2l** in an excellent 91% yield (3.55 g) after column chromatography (Scheme 5, top). The increased yield and improved performance when scaled to 15 mmol scale clearly indicate the robustness of the method.

Finally, the synthesis of the antidepressant drug, Prozac, was attempted using the protocol for late stage trifluoromethyl group installation (Scheme 3, bottom).

Copper-catalyzed decarboxylative trifluoromethylation of **1w** afforded **2w** in 75% isolated yield. Simple alkaline hydrolysis of the trifluoroacetamide protection group afforded Prozac (**3w**) in a quantitative yield.

Conclusions

In conclusion, a ligand and additive free copper-catalyzed decarboxylative trifluoromethylation protocol has been developed. The Cu_2O catalyst precursor turned out to be superior to the similar and commonly utilized CuI-catalyst, which was argued to be related to an inhibitory effect of iodide at elevated concentrations.

The protocol proved useful in the presence of a good range of functionalized (hetero)aromatic iodides. An increase in yield was observed, when the protocol was tested on a 15 mmol scale, resulting in the isolation of 3.55 g (91% yield) of **2l**. Finally, late stage functionalization, under the developed conditions, was applied in the synthesis of antidepressant drug, Prozac.

Experimental section

General Considerations

Trifluoroacetate salts were dried under reduced vacuum at 100˚C overnight before use. All other purchased chemicals (including the commercially available aryl iodides: 1c, 1e, 1f, 1g, 1h, 1j, and 1u) were used as received without further purification. Solvents used in trifluoromethylation experiments were degassed with argon and kept over 3 Å molecular sieves in a glovebox. Flash column chromatography was carried out on silica gel 60 (230-400 mesh). The chemical shifts in ^{1}H NMR and ^{13}C NMR are reported in ppm relative to the solvent residual peak.[21] All ^{19}F chemicals shifts are unlocked. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 101 MHz and ^{19}F NMR spectra were recorded at 376 MHz, all at room temperature on a Bruker Ascend™ 400 spectrometer. HRMS spectra were recorded on an LC TOF (ES) apparatus. Melting points (mp) were obtained on a capillary melting point apparatus and are uncorrected.

Handling of pressurized reaction chambers

COtubes, the reaction chambers used in this study, and aluminum heat-blocks were obtained from SyTracks.com. The tubes are pressure tested up to 5 bar. The maximum pressure in the COtubes was measured to 4.4 bar during trifluoromethylations under the developed conditions (see ESI). However, it is highly recommended that the heating block is enclosed by a protecting shield or similar safety precaution. The COtubes were allowed to cool after the reaction and were opened **carefully** to avoid excessive bubble evolvement during pressure relief.

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General procedure for trifluoromethylation of aryl iodides

In an argon filled glovebox aryl iodide (0.50 mmol, 1 equiv.), cuprous oxide (14.3 mg, 0.20 equiv.), and potassium trifluoroacetate (304 mg, 4 equiv.) were mixed with 1 mL DMF in a 10 mL CO-tube equipped with an egg-shaped stir bar. The CO-tube was sealed with a Teflon seal, taken outside the glovebox, and left to stir continuously for 24 h in a preheated aluminum-block at 160°C. The CO-tube was cooled to room temperature, taken back into the glovebox and carefully depressurized (WARNING: pressure build-up). A 5 µL aliquot of the reaction mixture was taken out for ^{1}H and ^{19}F NMR analyses. If full conversion was observed, workup and purification was performed. Otherwise, the remaining aryl iodide was coupled with an alkyne in an unoptimized Sonogashira reaction[9c] as the trifluoromethylated product in most cases co-eluted with the corresponding aryl iodide.

In the glovebox was CuI (5 mg, 0.05 equiv.), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.05 equiv.), triethylamine (0.50 mL), and 2-methyl-3-butyn-2-ol (97 µl, 2.0 equiv.) added to the reaction mixture. The CO-tube was resealed with a Teflon seal, taken outside the glovebox, and left to stir in a preheated aluminum-block at 60°C for 4 hours. The reaction mixture was cooled and purified.

General workup procedure A The reaction mixture was diluted with EtOAc (30 mL) and washed with ammonium hydroxide solution and brine (V/V = 1:1, 2 x 10 mL). The aqueous phase was separated and extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL), dried above Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography. If the crude product was a solid, it was dissolved in CH_2Cl_2 and concentrated onto silica before purification.

General workup procedure B The reaction mixture was diluted with Et_2O (30 mL) and washed with ammonium hydroxide solution and brine (V/V = 1:1, 2 x 10 mL). The aqueous phase was separated and extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL), dried above Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography. If the crude product was a solid, it was dissolved in CH_2Cl_2 and concentrated onto silica before purification.

***N*,*N*-Dibenzyl-4-(trifluoromethyl)aniline (2a).** Prepared from *N,N*-dibenzyl-4-iodoaniline and isolated using Sonogashira reaction with 0.05 equiv. $PdCl_2$ and 0.05 equiv. 1,3-bis(diphenylphosphino)propane instead of 0.05 equiv. $Pd(PPh_3)_2Cl_2$, and then General workup procedure A. The crude product was purified by flash column chromatography using pentane/Et_2O/CH_2Cl_2 (150:1:1) as eluent to afford the title product (142 mg, 84%) as a white solid. R*f*: 0.25 (in pentane/Et_2O/CH_2Cl_2 150:1:1); mp 111-112°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.18 (m, 12H), 6.74 (d, *J* = 8.6 Hz, 2H), 4.71 (s, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 137.6, 129.0, 127.4, 126.7 (q, *J* = 3.8 Hz), 126.6, 125.2 (q, *J* = 271.2 Hz), 118.4 (q, *J* = 32.6 Hz), 111.7, 54.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.9 ppm; HRMS *m/z* calculated for $C_{21}H_{19}F_3N$ $[M + H]^+$ 342.1464, found 342.1475. The NMR data are in agreement with literature.[9c]

1,2,3-Trimethoxy-5-(trifluoromethyl)benzene (2b). Prepared from 1,2,3-trimethoxy-5-iodobenzene and isolated using Sonogashira reaction and General workup procedure A. The crude product was purified by flash column chromatography using pentane/Et_2O (15:1) as eluent to afford the title product (73 mg, 62 %) as a white solid. R*f*: 0.23 (in pentane/Et_2O 15:1); mp 67-68°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H), 3.90 (s, 6H), 3.88 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 140.8, 125.8 (q, *J* = 32.7 Hz), 124.2 (q, *J* = 272.0 Hz), 102.7 (q, *J* = 3.9 Hz), 61.0, 56.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.1 ppm; HRMS *m/z* calculated for $C_{10}H_{12}F_3O_3$ $[M + H]^+$ 237.0733, found 237.0732. The NMR data are in agreement with literature.[12b]

5-(Trifluoromethyl)-2,3-dihydro-1-benzofuran (2c). Prepared from 5-iodo-2,3-dihydro-1-benzofuran and isolated using Sonogashira reaction and General workup procedure A. The crude product was purified by flash column chromatography using pentane as eluent to afford the title product (44 mg, 47 %) as a corlorless oil. R*f*: 0.25 (in pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 4.65 (t, *J* = 8.8 Hz, 2H), 3.25 (t, *J* = 8.8 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 127.9, 126.1 (q, *J* = 4.0 Hz), 124.8 (q, *J* = 270.0 Hz), 122.9 (q, *J* = 32.2 Hz), 122.4 (q, *J* = 3.7 Hz), 109.4, 72.0, 29.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.0 ppm; HRMS *m/z* calculated for $C_9H_8F_3O$ $[M + H]^+$ 189.0522, found 189.0542.

1-(Benzyloxy)-4-(trifluoromethyl)benzene (2d). Prepared from 1-(benzyloxy)-4-iodoobenzene and isolated using Sonogashira reaction and General workup procedure A**.** The crude product purified by flash column chromatography using pentane as eluent to afford the title product (104 mg, 83 %) as a white solid. R*f*: 0.24 (in pentane); mp 83-84°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 2H), 7.48 – 7.31 (m, 5H), 7.04 (d, *J* = 8.6 Hz, 2H), 5.12 (s, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 136.4, 128.9, 128.4, 127.6, 127.1 (q, *J* = 3.8 Hz), 123.3 (q, *J* = 32.8 Hz), 115.0, 70.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.5 ppm; HRMS *m/z* calculated for $C_{14}H_{12}F_3O$ $[M + H]^+$ 253.0835, found 253.0849. The NMR data are in agreement with literature.[22]

Methyl(4-(trifluoromethyl)phenyl)sulfane (2e). Prepared from 4-iodothioanisole and isolated using Sonogashira reaction and General workup procedure B. The crude product was purified by flash column chromatography using pentane as eluent to afford the title product (70 mg, 71 %) as a white solid. R*f*: 0.40 (in pentane); mp 35-36°C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.52 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 2.51 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 126.8 (q, *J* = 32.7 Hz), 125.6, 125.51 (q, *J* = 3.8 Hz), 121.5 (q, *J* = 271.5 Hz), 15.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3 ppm; HRMS *m/z* calculated for $C_8H_8F_3S$ $[M + H]^+$ 193.0293, found 193.0296. The NMR data are in agreement with literature.[22]

4-(Trifluoromethyl)-1,1'-biphenyl (2f). Prepared from 4-iodo-1-1'-biphenyl and isolated using Sonogashira reaction and General workup procedure A. The crude product was purified by flash column chromatography using pentane as eluent to afford the title product (90 mg, 82 %) as a white solid. R*f*: 0.55

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(in pentane); mp 63-64°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 4H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.46 – 7.39 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (d, *J* = 1.5 Hz), 139.9, 129.5 (q, *J* = 32.5 Hz), 129.1, 128.3, 127.6, 127.4, 125.9 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4 ppm; HRMS *m/z* calculated for $C_{13}H_9F_3$ $[M]^{\cdot}$ 222.0656, found 222.0628. The NMR data are in agreement with literature.[22]

1-(Trifluoromethyl)naphthalene (2g). Prepared from 1-iodonaphtalene and isolated using General workup procedure B. The crude product was purified by flash column chromatography using pentane as eluent to afford the title product (83 mg, 86 % (corrected for residual aryl iodide)) as a colorless oil. R*f*: 0.78 (in pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.51 (t, *J* = 7.8 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.0, 132.9, 129.1, 128.9, 127.8, 126.7, 126.3 (q, *J* = 29.8 Hz), 124.9 (q, *J* = 272.0 Hz), 124.8 (q, *J* = 6.0 Hz), 124.4 (q, *J* = 2.4 Hz), 124.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.7 ppm; HRMS *m/z* calculated for $C_{11}H_8F_3$ $[M + H]^+$ 197.0573, found 197.0578. The NMR data are in agreement with literature.[12b]

2-(Trifluoromethyl)naphthalene (2h). Prepared from 2-iodonaphtalene and isolated using Sonogashira reaction and General workup procedure A. The crude product was purified by flash column chromatography using pentane as eluent to afford the title product (66 mg, 63%) as a white solid. R*f*: 0.62 (in pentane); mp 65-66°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.98 – 7.89 (m, 3H), 7.68 – 7.56 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 132.3, 129.1, 129.0, 128.2, 128.0, 127.7, 127.3, 125.8 (q, *J* = 4.6 Hz), 125.6 (q, *J* = 270.3 Hz), 121.6 (q, *J* = 3.1 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3 ppm; HRMS *m/z* calculated for $C_{11}H_8F_3$ $[M + H]^+$ 197.0573, found 197.0562. The NMR data are in agreement with literature.[23]

***N*,*N*-Diethyl-4-(trifluoromethyl)benzenesulfonamide (2i).** Prepared from *N,N*-diethyl-4-iodobenzenesulfonamide and isolated using Sonogashira reaction and General workup procedure A**.** The crude product purified by flash column chromatography using pentane/Et_2O (15:1) as eluent to afford the title product (133 mg, 95 %) as a light yellow oil. R*f*: 0.20 (in pentane/Et_2O 15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 3.27 (q, *J* = 7.2 Hz, 4H), 1.14 (t, *J* = 7.2 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 134.1 (q, *J* = 33.0 Hz), 127.6, 126.3 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 272.8 Hz), 42.3, 14.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 ppm; HRMS *m/z* calculated for $C_{11}H_{15}F_3NO_2S$ $[M + H]^+$ 282.0770, found 282.0768. The NMR data are in agreement with literature.[12b]

4-(Trifluoromethyl)benzonitrile (2j). Prepared from 4-iodobenzonitrile and isolated using General workup procedure A. The crude product was purified by flash column chromatography using pentane/Et_2O (40:1) as eluent to afford the title product (26 mg, 31 %) as a white solid. R*f*: 0.23 (in pentane/Et_2O 40:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7 (q, *J* = 33.4 Hz), 132.8, 126.3 (q, *J* = 3.7 Hz), 123.2 (q, *J* = 273.0 Hz), 117.6, 116.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.5 ppm; HRMS *m/z* calculated for $C_8H_4F_3N$ $[M]^{\cdot+}$ 171.0296, found 171.0266. The NMR data are in agreement with literature.

***N*-Methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (2k).** Prepared from *N*-methoxy-*N*-methyl-4-iodobenzamide and isolated using Sonogashira reaction and General workup procedure A. The crude product was purified by flash column chromatography using pentane/Et_2O (1:1) as eluent to afford the title product (75 mg, 63 %) as a red oil. R*f*: 0.34 (in pentane/Et_2O 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 3.52 (s, 3H), 3.36 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 137.7, 132.4 (q, *J* = 32.7 Hz), 128.7, 125.1 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.4 Hz), 61.3, 33.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 ppm; HRMS *m/z* calculated for $C_{10}H_{11}F_3NO_2$ $[M + H]^+$ 234.0736, found 234.0742. The NMR data are in agreement with literature.[25]

Morpholino(4-(trifluoromethyl)phenyl)methanone (2l). Prepared from morpholino(4-iodophenyl)methanone and isolated using Sonogashira reaction and General workup procedure A. The crude product was purified by flash column chromatography using pentane/Et_2O (1:4) and CH_2Cl_2/EtOAc (15:1) as eluent to afford the title product (110 mg, 85 %) as a yellow solid. R*f*: 0.25 (in CH_2Cl_2/EtOAc 15:1); mp 53-54°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 3.86 – 3.36 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 139.0, 132.0 (q, *J* = 32.5 Hz), 127.6, 125.8 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.5 Hz), 66.9, 48.2, 42.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 ppm; HRMS *m/z* calculated for $C_{12}H_{13}F_3NO_2$ $[M + H]^+$ 260.0893, found 260.0895. The NMR data are in agreement with literature.[26]

Scale-up experiment Prepared from 15 mmol morpholino(4-iodophenyl)methanone and General workup procedure A. The crude product was purified by flash column chromatography using CH_2Cl_2/EtOAc (10:1) as eluent to afford an inseparable mixture of the title product (3.55 g, 91%) and corresponding iodide (0.25 g, 5%) as a yellow solid. mp 48-49°C. morpholino(4-(trifluoromethyl)phenyl)methanone: ^{1}H NMR (400 MHz, $CDCl_3$) δ *inter alia* 7.69 (d, *J* = 7.9 Hz, 2H), 7.53 (d, *J* = 7.9 Hz, 2H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 ppm. morpholino(4-iodophenyl)methanone: ^{1}H NMR (400 MHz, $CDCl_3$) δ *inter alia* 7.77 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H) ppm.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-(trifluoromethyl)benzoate (2m). Prepared from (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-iodobenzoate and isolated using Sonogashira reaction with 0.005 equiv. $Pd(PPh_3)_2Cl_2$ and 0.005 equiv. CuI and General workup procedure A. The crude product was purified by flash column chromatography using pentane/Et_2O/CH_2Cl_2 (100:1:1) as eluent to afford the title product (150 mg, 92%) as a colorless oil. R*f*: 0.27 (in pentane/Et_2O/CH_2Cl_2 100:1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 4.96 (td, *J* = 10.9, 4.4 Hz, 1H), 2.13 (m, 1H), 1.98 – 1.87 (m, 1H), 1.79 – 1.70 (m, 2H), 1.57 (m, 2H), 1.13 (m, 2H), 0.97 – 0.89 (m, 7H), 0.80 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 134.4 (q, *J* = 32.6 Hz), 134.2, 130.1, 125.5 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.7 Hz), 75.8, 47.4, 41.0, 34.4, 31.6, 26.7, 23.8, 22.2, 20.9, 16.7 ppm;

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^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 ppm; HRMS *m/z* calculated for $C_{18}H_{23}F_3NaO_2$ $[M + H]^+$ 351.1542, found 351.1544.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2,5-bis(trifluoromethyl)benzoate (2n). Prepared from 0.25 mmol (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2,5-diiodobenzoate with 0.40 equiv. Cu_2O, 4.0 equiv. KTFA in 0.50 mL DMF**.** The crude product isolated using Sonogashira reaction with 0.005 equiv. $Pd(PPh_3)_2Cl_2$ and 0.005 equiv. CuI and General workup procedure A and was purified by flash column chromatography using pentane/Et_2O/CH_2Cl_2 (100:1:1) as eluent to afford the title product (77 mg, 78%) as a white solid. mp 52-53˚C R*f*: 0.34 (in pentane/Et_2O/CH_2Cl_2 100:1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 4.99 (td, *J* = 11.0, 4.4 Hz, 1H), 2.21 – 2.13 (m, 1H), 1.91 (pd, *J* = 7.0, 2.7 Hz, 1H), 1.79 – 1.69 (m, 2H), 1.63 – 1.47 (m, 2H), 1.22 – 1.06 (m, 2H), 0.99 – 0.87 (m, 7H), 0.82 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 134.2 (q, *J* = 33.7 Hz), 133.3 (q, *J* = 2.1 Hz), 132.0 (q, *J* = 32.9 Hz), 127.8 (q, *J* = 4.0 Hz), 127.7 (q, *J* = 5.4 Hz), 127.2 (q, *J* = 3.8 Hz), 123.0 (q, *J* = 271.3 Hz), 122.8 (q, *J* = 272.5 Hz), 77.3, 47.1, 40.4, 34.3, 31.7, 26.3, 23.5, 22.2, 20.9, 16.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.6, -63.3 ppm; HRMS *m/z* calculated for $C_{19}H_{22}F_6NaO_2$ $[M + Na]^+$ 419.1416, found 419.1415.

6-((2-(Trifluoromethyl)benzyl)oxy)nicotinonitrile (2o). Prepared from 6-((2-iodobenzyl)oxy)nicotinonitrile with 4.0 equiv. $NaCO_2CF_3$ instead of KCO_2CF_3 and reacted for 8 hours at 140˚C instead of 24 hours at 160˚C**.** The crude product isolated using Sonogashira reaction and General workup procedure A and was purified by flash column chromatography using pentane/Et_2O (15:1) as eluent to afford the title product (48 mg, 35%) as a brown solid. R*f*: 0.18 (in pentane/Et_2O 5:1); mp 79-80°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.2 Hz, 1H), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 5.63 (s, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 152.1, 141.4, 134.7 (d, *J* = 1.6 Hz), 132.2, 129.9, 128.4 (q, *J* = 20.8 Hz), 128.4, 126.3 (q, *J* = 5.6 Hz), 124.3 (q, *J* = 273.8 Hz), 117.2, 112.1, 103.2, 65.2 (q, *J* = 2.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.1 ppm; HRMS *m/z* calculated for $C_{14}H_{10}F_3N_2O$ $[M + H]^+$ 279.0740, found 279.0742.

2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole (2p). Prepared from 2,5-dimethyl-1-(4-iodophenyl)-1*H*-pyrrole and isolated using Sonogashira reaction and General workup procedure A**.** The crude product purified by flash column chromatography using pentane as eluent to afford the title product (80 mg, 68 %) as an off-white solid. R*f*: 0.22 (in pentane); mp 68-69°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 5.95 (s, 2H), 2.06 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 130.2 (q, *J* = 32.9 Hz), 129.1, 129.0, 126.7 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 272.1 Hz), 107.0, 13.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5 ppm; HRMS *m/z* calculated for $C_{13}H_{13}F_3N$ $[M + H]^+$ 240.0995, found 240.0987. The NMR data are in agreement with literature.[27]

4-(5-(Trifluoromethyl)pyridin-2-yl)morpholine (2q). Prepared from 4-(5-iodopyridin-2-yl)morpholine and isolated using Sonogashira reaction and General workup procedure A**.** The crude product purified by flash column chromatography using pentane/EtOAc (10:1) as eluent to afford the title product (102 mg, 88%) as an orange solid. R*f*: 0.27 (in pentane/EtOAc 10:1); mp 48-59°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.5 Hz, 1H), 7.65 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.63 (d, *J* = 9.0 Hz, 1H), 3.88 – 3.76 (m, 4H), 3.67 – 3.54 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 145.9 (q, *J* = 4.4 Hz), 134.7 (q, *J* = 3.3 Hz), 124.7 (q, *J* = 270.4 Hz), 115.9 (q, *J* = 33.1 Hz), 105.6, 66.7, 45.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.2 ppm; HRMS *m/z* calculated for $C_{10}H_{12}F_3N_2O$ $[M + H]^+$ 233.0896, found 233.0908. The NMR data are in agreement with literature.[28]

Piperidin-1-yl(2-(trifluoromethyl)pyridin-4-yl)methanone (2r). Prepared from (2-iodopyridin-4-yl)(piperidin-1-yl)methanone and isolated using Sonogashira reaction and General workup procedure A**.** The crude product purified by flash column chromatography using CH_2Cl_2/EtOAc (15:1) as eluent to afford the title product (70 mg, 55%) as a brown solid. R*f*: 0.27 (in CH_2Cl_2/EtOAc 15:1); mp 65-66°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.9 Hz, 1H), 7.67 (s, 1H), 7.46 (d, *J* = 4.9 Hz, 1H), 3.79 – 3.66 (m, 2H), 3.27 (t, *J* = 5.5 Hz, 2H), 1.76 – 1.65 (m, 4H), 1.58 – 1.49 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 150.6, 149.0 (q, *J* = 34.9 Hz), 146.0, 123.82, 121.3 (q, *J* = 274.5 Hz), 118.3 (q, *J* = 2.9 Hz), 48.7, 43.3, 26.6, 25.5, 24.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.2 ppm; HRMS *m/z* calculated for $C_{12}H_{14}F_3N_2O$ $[M + H]^+$ 259.1053, found 259.1059.

1-Benzyl-5-(trifluoromethyl)-1*H*-indole (2s). Prepared from 1-benzyl-5-iodo-1*H*-indole and isolated using Sonogashira reaction and General workup procedure A. The crude product was purified by flash column chromatography using pentane/Et_2O (40:1) as eluent to afford the title product (112 mg, 82 %) as an off-white solid. R*f*: 0.38 (in pentane/Et_2O 40:1); mp 58-59°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.41 – 7.17 (m, 5H), 7.08 – 7.05 (m, 2H), 6.61 (d, *J* = 3.1 Hz, 1H), 5.31 (s, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 137.0, 130.2, 129.0, 128.2, 128.0, 126.9 (q, *J* = 272.0 Hz), 126.9, 122.13 (q, *J* = 31.7 Hz), 118.9 (q, *J* = 4.3 Hz), 118.6 (q, *J* = 3.5 Hz), 110.1, 102.91, 50.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.2 (d, *J* = 6.2 Hz) ppm; HRMS *m/z* calculated for $C_{16}H_{13}F_3N$ $[M + H]^+$ 276.0995, found 276.0993. The NMR data are in agreement with literature.[9c]

1-(2-Nitrophenyl)-5-(trifluoromethyl)-1*H*-indole (2t). Prepared from 1-(2-nitrophenyl)-5-iodo-1*H*-indole and isolated using Sonogashira reaction and General workup procedure A. The crude product was purified by flash column chromatography using pentane/Et_2O (4:1) as eluent to afford the title product (85 mg, 55 %) as a yellow solid. R*f*: 0.23 (in pentane/Et_2O 4:1); mp 120-121°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.01 (s, 1H), 7.82 (td, *J* = 7.7, 1.5 Hz, 1H), 7.68 (td, *J* = 7.9, 1.4 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.32 – 7.26 (m, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 3.3 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 138.1, 133.9, 132.2, 129.9, 129.8, 129.2, 128.3, 125.7, 125.2 (q, *J* = 270.0 Hz), 123.4 (q, *J* = 31.9 Hz), 119.9 – 119.7 (m), 119.1 (t, *J* = 4.3 Hz), 109.8, 105.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.6 ppm; HRMS *m/z* calculated for $C_{15}H_{10}F_3N_2O_2$ $[M + H]^+$ 307.0689, found 307.0687. The NMR data are in agreement with literature.[12b]

1-(Trifluoromethyl)isoquinoline (2u). Prepared from 1-iodoisoquinoline and isolated using Sonogashira reaction and General workup procedure B. The crude product was purified

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by flash column chromatography using pentane/Et_2O 20:1 as eluent to afford the title product (73 mg, 72 % (corrected for residual aryl iodide)) as a yellow oil. R*f*: 0.24 (in pentane/Et_2O 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 5.6 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 5.6 Hz, 1H), 7.82 – 7.69 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6 (q, *J* = 33.2 Hz), 140.9, 137.3, 131.0, 129.0, 127.7, 124.89 – 124.72 (m, 2C), 124.7, 122.4 (q, *J* = 276.3 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 ppm; HRMS *m/z* calculated for $C_{10}H_7F_3N$ $[M + H]^+$ 198.0525, found 198.0526. The NMR data are in agreement with literature.[12b]

1-Benzyl-4-(trifluoromethyl)-1*H*-pyrazole (2v). Prepared 1-benzyl-4-iodo-1*H*-pyrazole and isolated using Sonogashira reaction and General workup procedure A**.** The crude product purified by flash column chromatography using pentane/EtOAc (15:1) as eluent to afford the title product (59 mg, 51%) as an yellow oil. R*f*: 0.31 (in pentane/EtOAc 15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.63 (s, 1H), 7.45 – 7.33 (m, 3H), 7.29 – 7.22 (m, 2H), 5.32 (s, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 135.2, 129.2, 128.75, 128.7 – 128.6 (m), 128.1, 122.7 (q, *J* = 266.0 Hz), 114.1 (q, *J* = 39.5 Hz), 56.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.3 ppm; HRMS *m/z* calculated for $C_{11}H_{10}F_3N_2$ $[M + H]^+$ 227.0791, found 227.0794. The NMR data are in agreement with literature.[12b]

2,2,2-Trifluoro-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)acetamide (2w). Prepared from 2,2,2-trifluoro-N-(3-(4-iodophenoxy)-3-phenylpropyl)-*N*-methylacetamide and isolated using Sonogashira reaction and General workup procedure A**.** The crude product purified by flash column chromatography using pentane/CH_2Cl_2 (1:1) as eluent to afford the title product (150 mg, 75%) as a yellow oil. R*f*: 0.33 (in pentane/ CH_2Cl_2 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ *Mixture of rotamers (major/minor 1.88:1)* 7.48 – 7.40 (m, 2H), 7.40 – 7.24 (m, 5H), 6.92 – 6.84 (m, 2H), 5.26 – 5.15 (m, 1H), 3.65 (t, *J* = 7.4 Hz, 2H), 3.14 (s, 3H), 3.04 (s, 3H), 2.38 – 2.23 (m, 1H), 2.21 – 2.10 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ *Mixture of rotamers* 160.2, 160.1, 157.1 (q, *J* = 35.8 Hz), 157.1 (q, *J* = 35.8 Hz), 140.2, 139.8, 129.2, 129.1, 128.5, 128.3, 127.1 – 126.9 (m), 125.8, 125.6, 123.9 – 122.7 (m), 116.6 (q, *J* = 288.3 Hz), 116.5 (q, *J* = 288.9 Hz), 115.8 (d, *J* = 5.4 Hz), 78.2, 77.8, 47.1, 46.7 – 46.4 (m), 37.5, 35.6, 35.5 (q, *J* = 3.5 Hz), 34.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ *Mixture of rotamers* -61.6, -61.6, -68.9, -69.9 ppm; HRMS *m/z* calculated for $C_{19}H_{17}F_6NNaO_2$ $[M + Na]^+$ 428.1056, found 428.1056.

***N*-Methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine (Prozac) (3w).** 2,2,2-trifluoro-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)acetamide (150 mg, 0.37 mmol, 1.0 equiv.) and 2M NaOH (aq) (0.28 mL, 1.5 equiv.) were dissolved in THF (2 mL) and stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, redissolved in Et2O (30 mL) and washed with water (2×15 mL), sat. K_2CO_3 (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound as a yellow oil (115 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.30 – 7.26 (m, 4H), 7.23 – 7.18 (m, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.25 (dd, *J* = 8.2, 4.7 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.37 (s, 3H), 2.21 – 2.08 (m, 1H), 2.01 – 1.89 (m, 1H), 1.24 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 141.2, 128.9, 127.9, 126.9 (q, *J* = 3.7 Hz), 125.9, 124.5 (q, *J* = 272.0 Hz), 122.9 (q, *J* = 32.7 Hz), 115.9, 78.8, 48.4, 38.9, 36.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.5 ppm; HRMS *m/z* calculated for $C_{17}H_{19}F_3NO$ $[M + H]^+$ 310.1413, found 310.1423. The NMR data are in agreement with literature.[29]

Conflicts of interest

The authors declare the following competing financial interests: Anders T. Lindhardt is co-owner of SyTracks A/S, which commercializes the COtube technology.

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