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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01235 • Publication Date (Web): 07 Jul 2017

NHC-Cu(I)-catalyzed Friedländer-type annulation of fluorinated o-aminophenones with alkynes on Water. Competitive base-catalyzed dibenzo[*b*,*f*][1,5]diazocine formation

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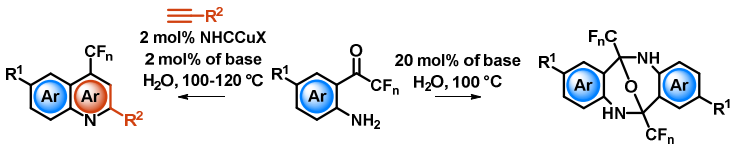
Graphical abstract



Abstract: An efficient, easily scalable synthesis of 4-trifluoromethylquinolines and naphthydrines (as well as their difluoro- and perfluoro-analogues) as a result of tandem direct catalytic alkynylation/dehydrative condensation of o-aminofluoromethylketones (o-FMKs), for the first time catalyzed by NHC-copper(I) complexes on water, is reported. A wide range of terminal alkynes is tolerated under the reaction conditions, including β-lactam-, steroid-, and sugar-derived ones, leading to desired quinolines and naphthydrines with good yields. Further investigations proved that o-FMKs could be

efficiently transformed into a rare class of heterocyclic compounds – dibenzo[*b*,*f*][1,5]diazocines – by a base-catalyzed condensation, also on water. The developed method was applied for gram-scale synthesis of a fluorinated analogue of G protein-coupled receptor antagonist (GPR91).

Keywords: o-aminofluorophenone, Friedländer reaction, copper, *N*-heterocyclic carbene, quinoline, naphthydrine, on water

Introduction

Fluorine-containing organic molecules, in particular fluorinated heterocycles, constitute a privileged structural motif in many areas of modern society, including material science, pharmaceutical industry, agrochemicals, fine chemicals,[1] and most of all medicinal chemistry.[2] More than 30% of all compounds present on the worldwide agrochemical and pharmaceutical market contain fluorine or fluorinated groups.[1b,3] The incorporation of fluorine into organic compounds strongly affects their biological properties, simultaneously allowing for structural elaboration, and hence has become crucial for modern drug development. It is well-established that the presence of fluorine improves bioavailability and increases lipophilicity and metabolic stability.[2,3b,4] Iconic examples of the beneficial properties bestowed upon fluorinated compounds are Ezetimibe[5] (inhibitor of cholesterol adsorption) and Efavirenz[6] (non-nucleoside inhibitor of reverse transcriptase of HIV), which have been commercialized in the last decade.

Among a plethora of fluorinated heterocycles, quinolines and quinolones have retained long-standing interest of the synthetic community. Tremendous advances in

the field of fluorination[7] have naturally led to the discovery of fluorinated quinolines or quinolones exhibiting remarkable biological properties, and some of them have been introduced to the pharmaceutical market. Representative examples include fluoroquine and mefloquine (antimalarial drugs), brequinar® (used in transplantation and for the treatment of psoriasis and rheumatic arthritis), flosequinan (used for the treatment of heart disease) and many derivatives of fluoroquinolones with a broad spectrum of antibacterial activity (Figure 1).[8]

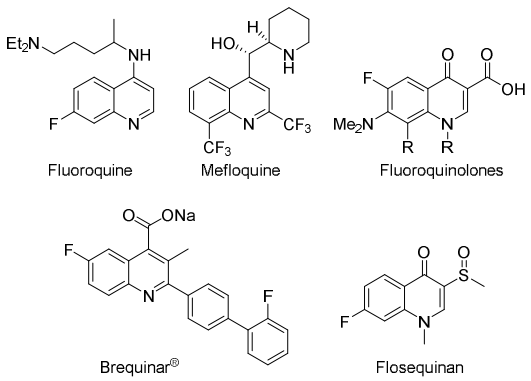
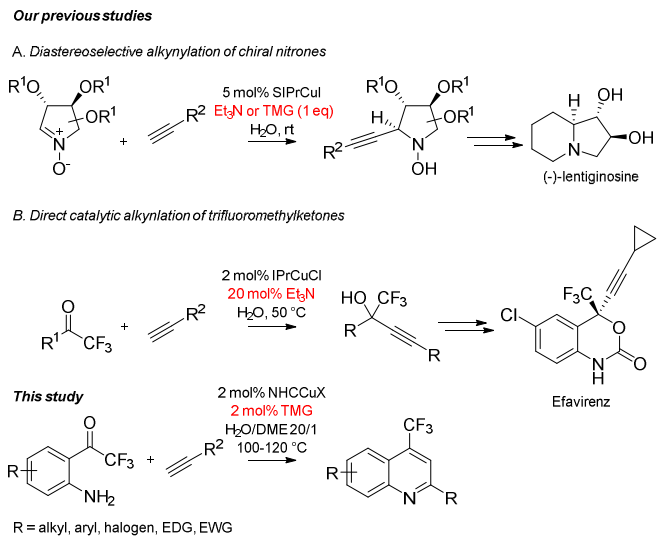


Figure 1. Representative structures of biologically active fluorine-containing quinolines and quinolones.

Due to the importance of quinolines in natural product synthesis and medicinal chemistry, many useful methods for their preparation have been developed to date. Among classical methods leading to this heterocyclic scaffold, including the Skraup reaction,[9] the Doebner-von Miller reaction,[10] the Gould-Jacobs reaction,[11] the Condrad-Limpach reaction,[12] the Combes synthesis,[13] the Knorr synthesis,[14] and the Niementowski synthesis,[15] the Friedländer reaction[16] constitutes an obvious choice due to its simplicity. Generally, the classical protocol for the latter involves an acid- or a base-catalyzed reaction between a 2-aminocarbonyl compound with an α-methylene

ketone. However, in most cases high temperature is required.[16b] To avoid harsh conditions and expand the scope of substrates in terms of functional group compatibility, an alternative route based on tandem addition of terminal alkynes to 2-aminobenzaldehydes and spontaneous cyclization has been developed and serves as an excellent alternative. Gold(I) complexes[17] have most often been used as catalysts, in addition to sparse reports devoted to silver(I),[18] iron(III),[19] and copper salts (which necessitate the preactivation of the carbonyl group via an iminium ion).[20] In this respect, the application of o-aminotrifluoromethylketones (o-TFMKs) for the synthesis of fluorinated quinolines is largely unexplored. To date, the application of a stoichiometric amount of $Zn(OTf)_2$[21] and catalytic pyrophoric Ag/PCy_3[22] have been reported with an extremely narrow scope of substrates.

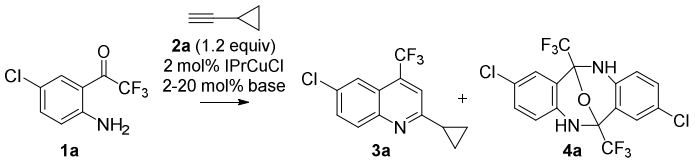


Scheme 1. Direct catalytic alkynylation of different electrophiles on water catalyzed by NHCCuX complexes

Herein, we present the first application of *N*-heterocyclic carbene copper(I) complexes (NHCCuX) as efficient catalysts (2 mol%) for the synthesis of fluorine-containing

quinolines (CF_3, CF_2H, CnF_{2n+1}) and naphthydrines via direct catalytic alkynylation/dehydrative cyclization sequence on water (Friedländer-type reaction). Recently, we have proved the effectiveness of *N*-heterocyclic carbene copper(I) complexes in direct catalytic alkynylation of chiral nitrones[23] and trifluoromethylketones[24] (TFMKs) on water (Scheme 1). The key rationale for a successful transformation was based on the observation that NHC-copper(I) complexes can form stable, monomeric (as confirmed by X-ray crystallography[25]), stable, highly reactive (e.g in triazole formation[26]) and moisture-insensitive acetylides, in contrast to polymeric ones, generated from copper(I) salts themselves.[27] Moreover, strong σ-donor properties of the NHC ligands enhance the nucleophilicity of the C_{sp} carbon atom of the acetylide, facilitating the addition to the electrophile.[28] Bearing in mind the successful application of NHCCuX complexes for the alkynylation of nitrones and TFMKs, we anticipated that the same catalytic system, namely NHCCuX/water, should deliver a practical route to fluorinated quinolines as a result of direct catalytic alkynylation/dehydrative cyclization sequence.

Results and discussion



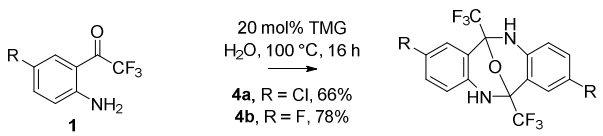
Scheme 2. Model reaction.

Table 1. Initial optimization of the reaction conditions[a]

Entry	Base (mol %)	Solvent	Temperature (°C)	Reaction time (h)	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	Et_3N (20)	DME, DCE, toluene, DMF, DMSO, pyridine	50	48	-	-
2	Et_3N (20)	EtOH	50	48	10	n.d.
3	Et_3N (20)	H_2O/DME (20/1)	50	48	23	22
4	Et_3N (20)	H_2O/DME (20/1)	100	16	42	43
5	TMG (20)	H_2O/DME (20/1)	100	16	53	15
6	TMG (2)	H_2O/DME (20/1)	100	16	55	26
7	TMG (2)	H_2O/DME (20/1)	100	16	61	21

[a] Reactions conditions: ketone **1a** (1.0 mmol), alkyne **2a** (1.2 mmol), NHCCuX (0.02 mmol), tetradecane (10 μL), DME (0.1 mL), H_2O (2 mL) and appropriate amount of base; conversion was based on GC with tetradecane as internal standard; [b] isolated yield after chromatography; n.d. – not determined, TMG – 1,1,3,3-Tetramethylguanidine.

At the outset of our study, we selected the reaction of cyclopropylacetylene (**2a**) with o-TFMK **1a** (Scheme 2). First, we examined the effect of solvent on the model reaction. When substrates were mixed together in common organic solvents (Table 1, entry 1) in the presence of 2 mol% IPrCuCl and 20 mol% of Et_3N, only unreacted starting materials were detected, even after 48 h at 50 °C. However, when EtOH was used, the expected quinoline **3a** was isolated with poor 10% yield after chromatography (Table 1, entry 2). The best 42% yield was obtained when the reaction was conducted in a mixture of water and DME (v/v 20:1)[29] at a higher temperature, which is consistent with our previous findings.[23-24] Surprisingly, dibenzo[*b*,*f*][1,5]diazocine **4a** was also isolated as a by-product with 43% yield. In order to improve the yield of quinoline **3a**, we screened carefully the influence of the type and the amount of base. After some experimentation, it was found that the yield of quinoline **3a** could be improved to 61% when 2 mol% of 1,1,3,3-tetramethylguanidine (TMG) were used. Dibenzo [*b*,*f*][1,5]diazocine **4a** was isolated with 21% yield in this case. These results clearly suggested that the formation of dibenzo[*b*,*f*][1,5]diazocine **4a** is a base-catalyzed process and its formation can be suppressed by lowering the loading of TMG to an equimolar amount relative to the NHCCuX complex used.



Scheme 3. TMG-catalyzed formation of dibenzo[*b*,*f*][1,5]diazocine **4**.

To the best of our knowledge, this is the first example of a base-catalyzed synthesis of a dibenzo[*b*,*f*][1,5]diazocine on water. Similar compounds have been reported as by-products by Wang[30] during the synthesis of quinolines via the Friedländer reaction and by Warm[31] in an attempt towards the large-scale preparation of efavirenz. To confirm the base-catalyzed mechanism, ketones **1** were treated with 20 mol% of TMG on water, furnishing heterocycles **4a** and **4b** cleanly in 66% and 58% yield, respectively (Scheme 3). Inquiries into the scope of formation of dibenzo[*b*,*f*][1,5]diazocines of type **4** are underway with promising results.

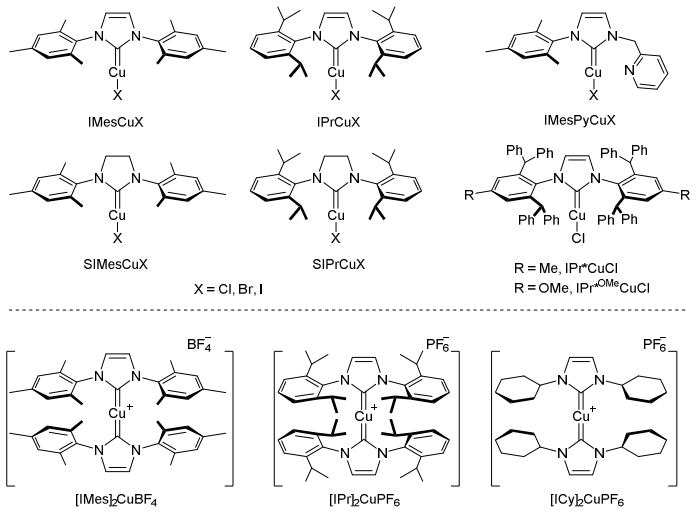


Figure 2. NHC metal complexes used for quinoline **3a** formation.

Table 2. The influence of the NHC carbene ligand and the counterion on the alkynylation/cyclization sequence leading to quinoline **3a** and diazocine **4a**.

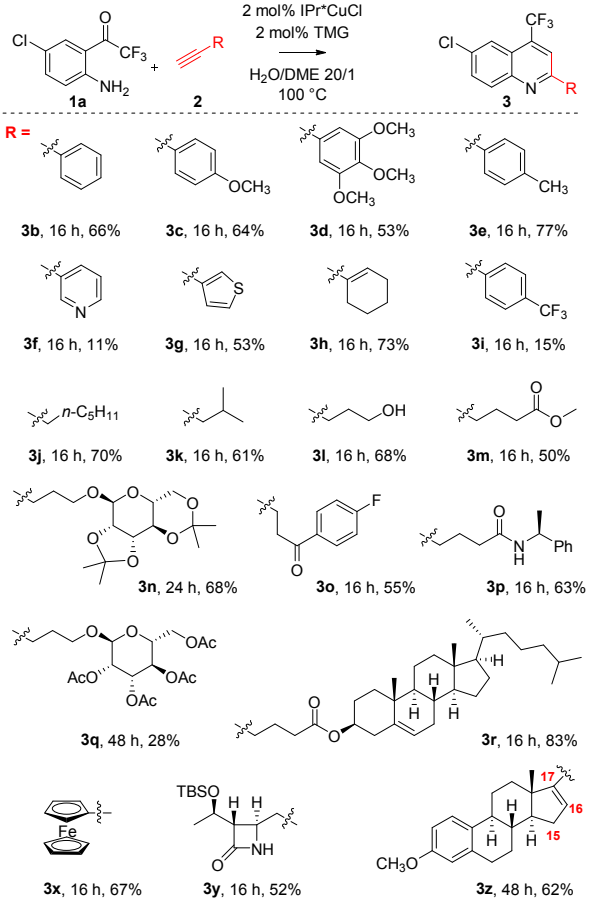
Entry	NHCCuX (2 mol%)	Conversion (%)[a]	Quinoline **3a** (%)[b,c]	Diazocine **4a** (%)[b,c]
1	IMesCuCl	94	42 (48)	39 (40)
2	IMesCuBr	91	51 (57)	28 (28)
3	SIMesCuCl	95	35 (45)	40 (40)
4	SIMesCuBr	91	33 (44)	35 (41)
5	IPrCuCl	91	44 (50)	16 (22)
6	IPrCuBr	92	46 (53)	31 (34)
7	IPrCuI	90	37 (45)	32 (33)
8	SIPrCuCl	87	32 (49)	22 (27)
9	SIPrCuBr	95	53 (54)	30 (33)
10	SIPrCuI	94	48 (52)	31 (33)
11	$[IMes]_2CuBF_4$	91	26 (28)	61 (63)
12	$[ICy]_2PF_6$	94	44 (47)	35 (36)
13	$[IPr]_2PF_6$	90	37 (41)	47 (48)
14	PyIMesCuCl	96	49 (53)	33 (34)
15	IPr*CuCl	94	71 (78)	7 (8)

16	IPr*CuCl	n.d.	76[d]	11[d]

[a] Reactions conditions: ketone **1a** (1.0 mmol), alkyne **2a** (1.2 mmol), NHCCuX (0.02 mmol), TMG (0.02 mmol), tetradecane (10 µL), DME (0.1 mL), H_2O (2 mL), 16h, 100 °C; conversion was based on GC with tetradecane as internal standard; [b] isolated yield after chromatography; [c] estimated yield based on GC from calibration curve is given in parentheses (see ESI); [d] reaction conducted on 5.0 mmol scale of **1a**; n.d. – not determined.

This unprecedented product distribution led us to examine the influence of the electronic and steric nature of the NHC carbene-copper(I) complex in more detail (for the structures of NHC complexes used, see Figure 2). Initially, we were pleased to find that copper(I) complexes bearing IMes or SIMes carbene ligands also catalyze the formation of quinoline **3a**. However, no clear conclusion could be given regarding the role of counterion in the copper complex (Table 2, entries 1-4). Quinoline **3a** was isolated with moderate 33–51% yield. In a series of more hindered unsaturated IPr or SIPr complexes, the yield of the reaction could be slightly improved by changing the counterion from iodide or chloride to bromide (Table 2, entry 6 and 9). Unfortunately, in all cases dibenzo[*b*,*f*][1,5]diazocine **4a** was also formed in significant quantities, up to 32%. Unexpectedly, dibenzo[*b*,*f*][1,5]diazocine **4a** was isolated in higher yield when the reaction was catalyzed by homoleptic ionic $[ICy]_2CuBF_4$. Other ionic complexes were less effective. The best results in terms of conversion and yield were obtained when sterically hindered complex IPr*CuCl was applied. Quinoline **3a** was isolated in 71% yield while dibenzo[*b*,*f*][1,5]diazocine was formed in low 7% yield (Table 2, Entry 15).

Pleasingly, the same reaction conducted on 5.0 mmol scale furnished cleanly product in 76% after chromatography (more than 1 g of **3a** was isolated, Table 2, entry 16).



Scheme 4. The scope of alkynes.

With the optimized conditions (2 mol% of IPr*CuCl and 2 mol% of TMG on water) in hand, we explored the scope of alkynes. It was found that phenylacetylene and its derivatives afforded products **3b**-**e** with good yields when electron-donating substituents were present, while electron-withdrawing groups such as CF_3 gave poor yields (Scheme 4, **3i**). Further investigations revealed that heterocyclic substituents were tolerated under the reaction conditions. 3-Ethynylthiophene furnished product **3g** cleanly in 53% yield, while 3-ethynylpyridine in only 11% yield. Next, we turned our attention to alkyl-

substituted alkynes. In those cases, quinolines **3j-p** were formed in good yields in the presence of alkene, ketone, ester, amide or free hydroxyl functional groups. To illustrate the broad scope of substrates for the synthesis of trifluorometylquinolines further, ferrocene-, β-lactam-, sugar-, and steroid-derived alkynes were selected. Pleasingly, the Friedländer-type reaction furnished the respective heterocycles **3n**, **q**-**y** in excellent. Only glucose tetraacetate afforded product **3q** in low 28% yield. It should be stressed that the reported yield of quinoline formation in the range of 60-70% is still satisfactory, bearing in mind the competitive self-condensation of o-TFMK leading to dibenzo[*b*,*f*][1,5]diazocine **4a**, observed in all cases.

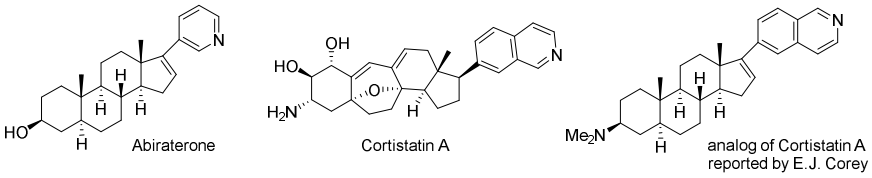
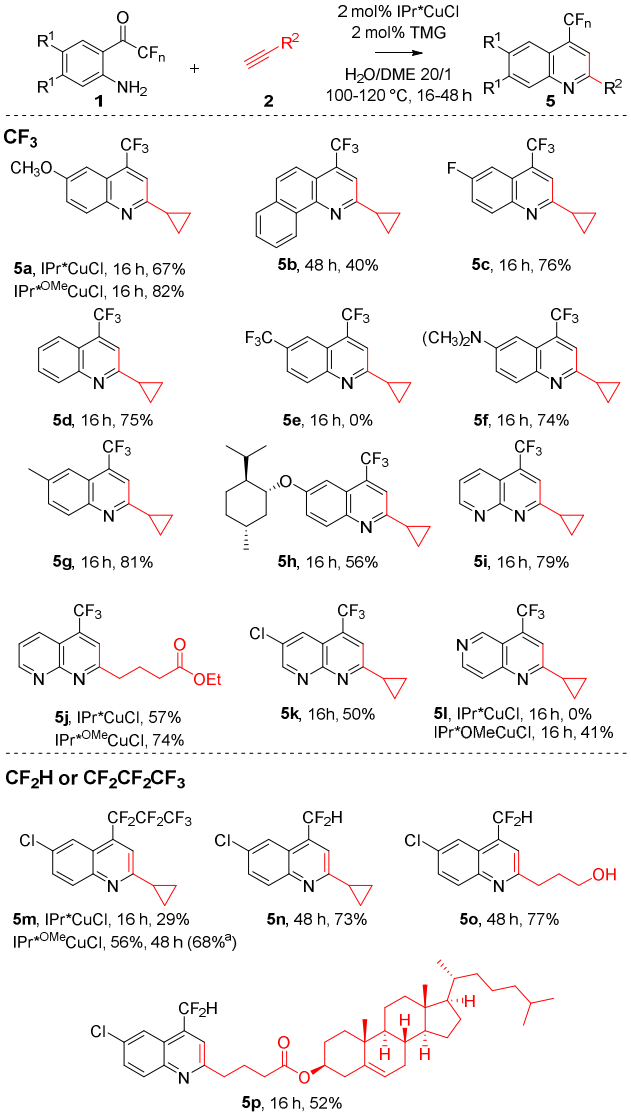


Figure 3. Representative examples of biologically active steroids bearing heterocyclic substituent.

Finally, the developed methodology was applied for the synthesis of structurally complex and pharmaceutically relevant estrone derivative **3z** which is of high importance from the perspective of medicinal applications. The class of compounds consisting of a heterocyclic subunit (usually quinolone, isoquinoline or pyridine) attached to the steroid core in position C17 (for numbering, see Scheme 4, structure **3z**) exhibit a broad spectrum of biological activities including antiangiogenic (e.g. natural products of the cortistatin family[32]) or proven anticancer ones (e.g. semisynthetic analogue of cardenolides – abiraterone,[33] Figure 3). Recently, Corey has simplified the structure of naturally occurring cortistatins bearing an unusual steroid scaffold to a

simple androstane derivative and confirmed its prominent antiangiogenic activity.[34] Regarding the synthetic efforts towards cortistatin and its analogues,[34-35] the key transformation involved a palladium-catalyzed (10–50 mol% of Pd) Stille coupling of a sterically congested steroid vinyl iodide or enol triflate located in a neopentyl position. The application of palladium and tin compounds to the synthesis of biologically active molecules can affect biological evaluation due to toxic heavy metal contamination. The developed method offers an attractive alternative for the construction of heterocycle-steroid hybrids via a palladium-free protocol. The respective estrone derivative **3z** was isolated in 62% yield using only 2 mol% of the IPr*CuCl complex.

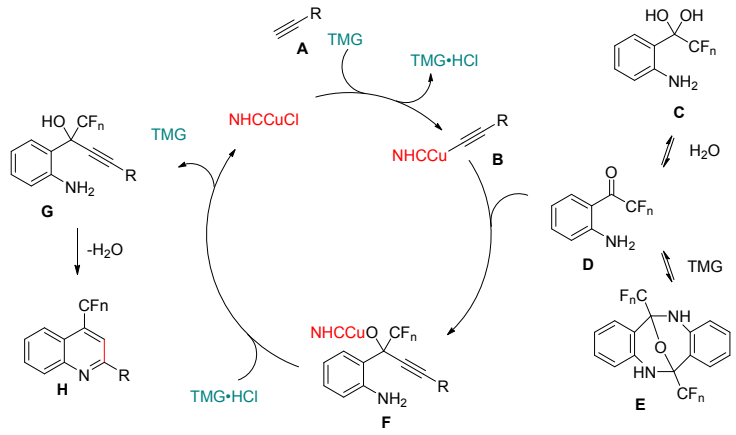


Scheme 5. The scope of fluoroketones. [a] 5 mol% of IPr*OMeCuCl was used.

Next, we explored variously substituted o-TFMKs for the synthesis of quinolines. Ketones bearing strongly and weakly electron-donating groups, such as NMe_2, OMe, Me, F, H as well as a naphthyl moiety furnished the corresponding quinolines **5a**,**c**,**d**,**f**-**h** and benzo[*h*]quinoline **5b** in moderate to good yields (Scheme 5). Further improvement of the formation of **5a** was accomplished by fine tuning the electronic properties of NHC ligand. Application of IPr*^{OMe}CuCl complex, introduced by Kobayashi,[36] in place of

IPr*CuCl resulted in increases in yield, up to 82%. Presumably, this can be attributed to the electron-donating properties of the methoxy group attached to the NHC ligand which enhance the nucleophilicity of the copper acetylide. Similarly, IPr*^{OMe}CuCl appeared to be the complex of choice for the synthesis of fluorinated 1,6- and 1,8-naphythyridines **5i-k** and **5l**, accessible by other methods only with difficulty.

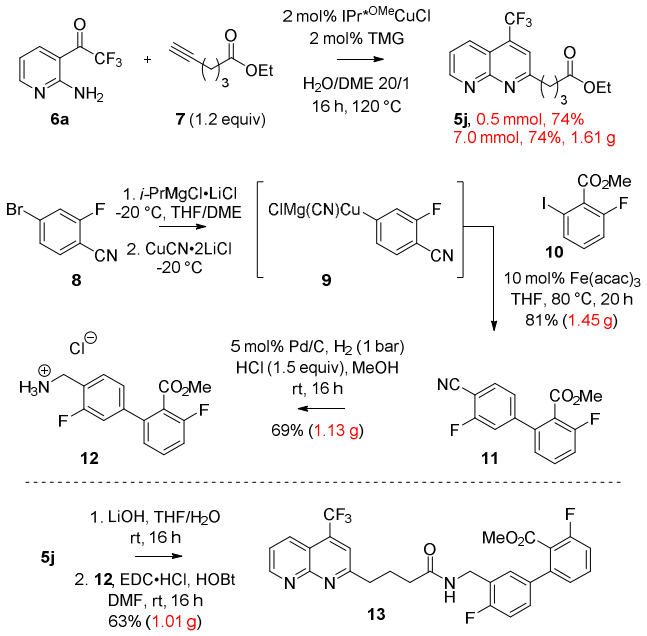
Further investigations were directed at the synthesis of difluoromethyl-containing quinolines. It is well-established that CF_2H can act as a bioisostere of hydroxyl, *N*-hydroxamic acid and thiol groups,[37] which offers new routes for drug design. CF_2H constitutes a good platform for lipophilic interactions as a hydrogen bond donor[37-38] and may enhance membrane permeability, binding affinity and bioavailability. Although direct introduction of CF_2H onto arenes has become the subject of intensive research in recent years (including Pd,[39] Ni,[40] Cu[41] or Zn[42] catalyzed transformations), the developed methods usually need harsh conditions and are incompatible with many functional groups. Furthermore, the complexity of reagent mixtures used or catalytic systems makes these approaches far from practical, especially on a large scale. Bearing in mind the practical aspects, the developed protocol has revealed a simple procedure of difluoromethylquinoline synthesis. Indeed, heating a mixture of difluorometylketone and a terminal alkyne on water in the presence of 2 mol% IPr*CuCl and 2 mol% of TMG afforded the respective quinolones **5n-o** in good yields (52–77%), also in the case of cholesterol derivative **5p**. The same conditions appeared compatible with the synthesis of perfluoroalkyl-quinoline **5m.** However, IPr*^{OMe}CuCl had to be used to maintain a reasonable 56% isolated yield.



Scheme 6. A plausible catalytic cycle; NHC – N-heterocyclic carbene, TMG – 1,1,3,3-Tetramethylguanidine

Based on our experiments and literature data,[22] a plausible catalytic cycle of the NHCCuX-catalyzed Friedländer reaction leading to quinolines was proposed (Scheme 6). The NHCCuX complex interacts with terminal alkyne **A** (via universally accepted π-activation mode) forming the mononuclear copper acetylide **B** and releasing an amine hydrochloride simultaneously (if copper chloride complex is used). The structure of the NHC-copper acetylide was confirmed independently by NMR spectroscopy and X-ray crystallography (by Nolan[26b] and Jones,[25] respectively). Next, the monomeric acetylide **B** undergoes an addition to the fluorinated ketone **D**, affording copper alkoxide **F** which is protonated by the strongest Brönsted acid present in the system – amine hydrochloride. The protonation step regenerates the NHCCuCl complex and the amine needed for the activation of terminal alkyne **A**, closing the catalytic cycle. The spontaneous dehydrative cyclization of the propargyl alcohol **G**, which may be enhanced by the NHCCuX complex via π-activation or by the Brönsted acid,[22] affording quinoline **H**. It should be stressed that other side reactions, such as self-condensation or hydratation could decrease the yield of quinoline **H**. For those reasons, an equivalent

loading of the base and the NHCCuX complex has to be used to prevent the formation of dibenzo[*b*,*f*][1,5]diazocine **E** (see, Table 1).



Scheme 7. The application of the Friedländer-type reaction to a gram-scale synthesis of a fluorinated analogue of a G protein-coupled receptor antagonist (GPR91); TMG – 1,1,3,3-tetramethylguanidine, HOBt – 1-hydroxybenzotriazole, EDC•HCl – 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

The utility of the developed method is further illustrated through a scalable synthesis of a fluorinated analogue **13** of G protein-coupled receptor antagonist (known as GPR91, Scheme 7). GPR91 belongs to a class of membrane proteins able to bind an extracellular succinate – an intermediate in the Krebs cycle.[43] The binding of succinate to GPR91 can affect a wide array of physiological and pathological processes such as inhibition of lipolysis, regulation of blood pressure, cardiac hypertrophy, angiogenesis in retinal tissues, etc.[44] Among non-peptide small organic molecules which serve as

ligands for GPR91, naphthydrines coupled with biphenyl-derived benzylamine, originally synthesized and evaluated by Merck as inhibitors of Bradykinin B1 receptor[45] (BK_1R), have witnessed a growing interest.[46] However, their fluorinated analogues have not been investigated to date. Herein, we present a scalable convergent route to this class of compounds. First, we synthesized fluorinated naphthydrine **5j** applying the developed method on a 0.5 mmol scale which afforded the product in 74% yield. Pleasingly, we found that a 14-fold increase in scale furnished the product cleanly with equally excellent yield, further underlining the practical aspect of the developed method.

The intermediate benzylamine derivative **12** was synthesized by a two-step sequence. The key biphenyl **11** was synthesized via Fe-catalyzed aryl-aryl cross-coupling under conditions developed by Knochel.[47] Arylcopper reagent **9**, generated from the respective nitrile **8**, was coupled with iodoester **10** to afford biaryl **11** in 81% yield on large scale (1.45 g). It should be noted that homocoupling product was observed when the arylcopper species was generated from iodoester **10**. Subsequent chemoselective reduction of nitrile group to amine appeared to be challenging. BH_3 and common metal hydrides ($NaBH_4$ in combination with $CoCl_2$, CuCl) appeared to be unsuccessful, whereas the reduction in the presence of Raney nickel furnished secondary amine[48] (for details, see ESI). Gratifyingly, Pd-catalyzed reduction in the presence of HCl in MeOH cleanly afforded the respective amine hydrochloride **12** without chromatography on gram scale. The obtained amine **12** was coupled with ester **5j** (after hydrolysis of the latter), mediated by the mixture of EDC•HCl/HOBt to give amide **13** with 63% yield after two steps. The evaluation of biological activity of naphthydrine **13** and its analogues are in progress.

Conclusion

In summary, we developed an efficient synthesis of trifluoromethylquinolines (and their difluoromethyl- and perfluoroalkyl- analogues) and naphthydrines via tandem direct catalytic alkynylation of o-aminofluoromethylketones/condensation sequence, for the first time on water in the presence of a catalytic amount of NHC-copper(I) complexes. The established method allows to obtain a series of fluorinated quinolines with good to moderate yields. During the optimization of the reaction conditions, it was found that *o*-aminotrifluoromethylketones undergo base-catalyzed self-condensation leading to a rare example of dibenzo[*b*,*f*][1,5]diazocine synthesis. Further experiments confirmed that the formation of dibenzo[*b*,*f*][1,5]diazocines is catalyzed by a weak base on water. The studies on the scope of the formation of dibenzo[*b*,*f*][1,5]diazocines are underway with promising results.

Experimental section

General remarks

NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions (unless indicated otherwise); chemical shifts are quoted on the δ scale, ppm, with the solvent signal as the internal standard ($CHCl_3$, ^{1}H NMR 7.26 ppm; $CDCl_3$, ^{13}C NMR 77.00 ppm, DMSO-d_6 2.50 ppm, ^{13}C NMR 39.40 ppm). High resolution mass spectra (HRMS) were taken using EI technique or electrospray ionization (ESI). Column chromatography was performed on Merck silica gel 60, 230-400 mesh. TLC was performed on aluminum sheets, Merck 60F 254. Anhydrous solvents were obtained by distillation over $CaCl_2$

(CH_2Cl_2) or Na/benzophenone (THF, hexane, MTBE). Air-sensitive reactions were performed in flame-dried glassware under atmosphere of argon. Organic extracts were dried and solvents were evaporated in a rotary evaporator. Reagents were used as they were purchased unless otherwise indicated (which is specified at beginning of each section). The name of compounds were generated using ACD Lab Name 12.0 software.

Synthesis of N-heterocyclic carbene copper(I) complexes

$[IMes]_2CuPF_6$, SIPrAgCl and IPrAuCl were commercially available from Aldrich and used as received. SIMesCuCl,[49] SIMesCuBr,[26a] IMesCuCl,[49] IMesCuBr,[50] SIPrCuCl,[49] SIPrCuBr,[51] SIPrCuI,[51] SIPrCuOTf,[52] SIPrOAc,[53] IPrCuCl,[49] IPrCuBr,[51] IPrCuI,[51] IPr*CuCl,[49] $[ICy]_2CuPF_6$,[26b] and $[IPr]_2CuPF_6$[54] were prepared followed by literature procedure.

{1,3-bis[2,6-bis(Diphenylmethyl)-4-methoxyphenyl]-1,3-dihydro-2*H*-imidazol-2-ylidene}(chloro)copper $IPr^{*OMe}CuCl$ was prepared applying literature procedure developed by Cazin *et*. *al*.[49] In a glove box, a 20-mL screw-cap vial was charged with K_2CO_3 (281.9 mg, 2.04 mmol, 2.0 equiv), $IPr^{*OMe}Cl$ (1.0 g, 1.02 mmol), CuCl (100.8 mg, 1.02 mmol, 1.0 equiv) and anhydrous acetone (10 mL). Next the vial was capped, removed from the glove box and the resulting suspension was vigorously stirred for 20h at 60 °C (temp. of oil bath). Then solvent was evaporated, DCM (20 mL) was added and the resulting mixture was filtered through a pad of Celite (washing with DCM). The crude copper(I) complex was dissolved in minimum volume of DCM (6 mL) and crashed with *n*-pentane (28 mL). The obtained solid was filtered, washed with *n*-pentane (3 x 10 mL), and dried in vacuo to give $IPr^{*OMe}CuCl$ as a white solid (933.3 mg, 88%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.28–7.18 (m, 24H), 7.13–7.08 (m, 8H), 6.98–6.91 (m, 8H), 6.62

(s, 4H), 5.86 (s, 2H), 5.25 (s, 4H), 3.62 (s, 6H). ^{1}H NMR data are in agreement with those reported.[36]

Synthesis of alkynes

Cyclopropylethyne (**2a**), ethynylbenzene (**2b**), 1-ethynyl-4-methoxybenzene (**2c**), 5-ethynyl-1,2,3-trimethoxybenzene (**2d**), 1-ethynyl-4-methylbenzene (**2e**), 3-ethynylpyridine (**2f**), 3-ethynylthiophene (**2g**), 1-ethynylcyclohexene (**2h**), 1-ethynyl-4-trifluoromethylbenzene (**2i**), octy-1-yne (**2j**), 4-methylpent-1-yne (**2k**), pent-4-yne-1-ol (**2l**), methyl hex-5-ynoate (**2m**) and ethynylferrocene (**2x**) are commercially available and used as received without further purification. 1-(4-Fluorophenyl)pent-4-yl-1-one (**2o**),[24] ethyl hex-5-ynoate (**7**),[55] (3β)-cholest-4-en-3yl hex-5-ynoate (**2r**),[56] 17-ethynyl-3-methoxyestra-1(10),2,4,16-tetraene (**2z**)[57] and (3*S*,4*R*)-3-{(1*R*)-{[*tert*-butyl(dimethyl)silyl]oxo}ethyl-4-prop-2-yn-1yl)azetidine-2-one (**2y**)[58] were prepared followed by literature procedure.

Pent-4-yn-1-yl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**2q**) To a solution of 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose (4.37 g, 11.2 mmol), MS 3Å (4 g) in anhydrous DCM (80 mL) and 4-pentyn-1-ol (**2l**) (2.08 mL, 22.4 mmol, 2.0 equiv), cooled to -10 °C, $BF_3{\cdot}Et_2O$ (11.2 mL, 89.6 mmol, 8.0 equiv) was added dropwise. The resulting mixture was slowly allowed to reach rt and stirred for 16 h. The reaction mixture was then quenched by addition of solid $NaHCO_3$ (10 g) and stirred at rt. After 30 min. the reaction mixture was washed with sat. aqueous $NaHCO_3$ (3 x 50 mL), dried over $MgSO_4$, and solvent was evaporated. The residue was chromatographed on silica FCC (15-30% EtOAc/hexanes) to give a light yellow oil (1.55 g, 33%, CAS: 1327252-78-7, no spectral data available for comparison were reported). $[a]_D^{23}$ = 46.4 (c = 1.1, $CHCl_3$); IR

(film) 3283, 2958, 2939, 2117, 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (dd, *J* = 10.0, 3.2 Hz, 1H), 5,29 (t, *J* = 9.6 Hz, 1H), 5.22 (dd, *J* = 3.2, 1.6 Hz, 1H), 4.80 (d, *J* = 1.6 Hz, 1H), 4.27 (dd, *J* = 12.2, 5.2 Hz, 1H), 4.10 (dd, *J* = 12.3, 2.4 Hz, 1H), 4.00 (ddd, *J* = 9.6, 5.2, 2.4 Hz, 1H), 3.83 (ddd, *J* = 9.6, 7.2, 5.6 Hz, 1H), 3.55 (ddd, *J* = 9.6, 5.6, 5.6 Hz, 1H), 2.35–2.27 (m, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.89–1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.0, 169.8, 169.7, 97.6, 83.2, 69.6, 69.1, 69.0, 68.5, 66.5, 66.2, 62.4, 27.9, 20.8, 20.7, 20.6, 20.6, 15.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{26}O_{10}Na$ 437.1424; Found:437.1416.

Pent-4-yn-1-yl α-D-mannopyranoside (**14**) To a stirred solution of pent-4-yn-1-yl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**2q**) (875.0 mg, 2.24 mmol) in dry MeOH (20 mL), KOMe (15.7 mg, 0.224 mmol, 0.1 equiv) was added at rt and stirred for 3h. Then solvent was evaporated and residue was passed through pad of silica (10% MeOH/DCM) to give a colourless oil (474.4 mg, 86%). The obtained pent-4-yn-1-yl α-D-mannopyranoside (**14**) was used without further purification in the next step. $[a]_D^{23}$ = -70.7 (c = 1.9, MeOH); ^{13}C NMR (100 MHz, CD_3OD) δ 101.6, 84.3, 74.5, 72.7, 72.2, 69.9, 68.5, 66.9, 62.8, 29.6, 15.9; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{18}O_6Na$ 269.1001; Found: 269.0991.

(3a*S*,4*S*,5a*R*,9a*R*,9b*S*)-2,2,8,8-Tetramethyl-4-(pent-4-yn-1-yloxy)hexahydro[1,3]dioxolo[4,5]pyrano [3,2-*d*][1,3]dioxine (**2n**) To a stirred rt solution of the tetraol **14** (0.397 g, 1.71 mmol) in dry DMF (13 mL) under atmosphere of argon, $Me_2C(OMe)_2$ (1.32 mL, 10.9 mmol, 10.0 equiv) and *p*-TsOH (20.9 mg, 0.11 mmol, 0.1 equiv) were added at rt. The reaction mixture was stirred for 3 h before

acetone (2.7 mL) was introduced. After 24 h the reaction was diluted with Et_2O (20 mL) and washed with sat. $NaHCO_3$ solution (2 x 20 mL). The organic layer was separated, washed with H_2O (3 x 20 mL), brine (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by chromatography on silica (5% EtOAc/hexanes) to give diacetal **2n** as a colourless oil (441.0 mg, 79%). α = -70.7 (c = 1.9, MeOH); IR (film) 3278, 2990, 2939, 2915, 2876, 2117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.00 (s, 1H), 4.18–4.09 (m, 2H), 3.87 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.84–3.69 (m, 3H), 3.63–3.44 (m, 2H), 2.30 (dt, *J* = 7.2, 2.8 Hz, 2H), 1.95 (t, *J* = 2.8 Hz, 1H), 1.86–1.74 (m, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 99.7, 97.8, 83.3, 76.1, 74.9, 72.7, 68.8, 65.9, 62.1, 61.4, 29.0, 28.2, 28.1, 26.1, 18.8, 15.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{26}O_6Na$ 349.1627; Found: 349.1629.

***N*-[(1*S*)-1-Phenylethyl]hex-5-ynamide (2p)** To a solution of 5-hexynoic acid (1 g, 8.91 mmol) in DCM (20 mL), cooled to 0 °C, EDC (2.05 g, 10.7 mmol, 1.2 equiv) and (*S*)-methylbenzylamine (1 g, 8.91 mmol, 1.2 equiv) were added, and stirred for 3h at rt. Then reaction mixture was diluted with water (40 mL) and organic phase was separated, washed with 5% HCl_{aq} (2 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was passed through a pad of silica (eluted with 40% EtOAc/hexanes) to give a waxy solid (1.83 g, 95%). $[\alpha]_D^{23}$ = -92.7 (c = 0.94, $CHCl_3$); IR (film) 3292, 3063, 2972, 2934, 2116, 1614, 1545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 5H), 5.83 (br s, *J* = 6.3 Hz, 1H), 5.19–5.06 (m, 1H), 2.37–2.19 (m, 4H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.91–1.80 (m, 2H), 1.48 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 143.2,

128.6, 127.3, 126.1, 83.5, 69.2, 48.7, 35.1, 24.1, 21.7, 17.8; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{17}NONa$ 238.1208; Found: 238.1204.

Synthesis of ortho-aminotrifluoromethylketones (o-TFMK's) and their derivatives containing difluoromethyl group and perfluoroalkyl chain

1-(2-Amino-5-chlorophenyl)-2,2,2-trifluoroethanone (**1a**),[6a] 2,2-difluoro-1-(morpholin-4-yl)ethanone[59] were prepared according to literature procedure. 1-(2-Amino-5-chloropyridin-3-yl)-2,2-difluoroethanone is commercially available and was used as received.

General procedure To a solution of amide (x mmol) and TMEDA (1.0 equiv), cooled to -20 °C (or lower temp.) in MTBE (or THF), a solution of *n*-BuLi (2.2 equiv) was added dropwise by means of syringe pump within 30 min. - 2h while the temperature was kept below -10 °C (or lower as indicated). The mixture was aged at -5 – 5 °C for 2-4 h, cooled below -30 °C (or -65 °) and CF_3CO_2Et (1.4 equiv) or other source of fluorinated group was added. Then reaction mixture was stirred for 0.5 - 1h at rt, quenched with 5% HCl (or 10% citric acid). Then solvents were evaporated. In some cases product was separated by chromatography or crystallization from unreacted substrate. Then residue was treated with 36% aqueous HCl or its solution in dioxane (4M in dioxane), and stirred for 2-16h at 70-90 °C (temp. of oil bath). Then reaction mixture was neutralized with sat. solution of K_2CO_3 (or $NaHCO_3$) and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica and further purified by crystallization (usually from *n*-heptane) to give a pure *ortho*-aminofluorophenones and its derivatives.

1-(2-Amino-5-methoxyphenyl)-2,2,2-trifluoroethanone (**1b**) To a solution of amide *N*-(4-methoxyphenyl)-2,2-dimethylpropanamide (11.41 g, 55.1 mmol) in Et_2O (60 mL) and TMEDA (8.5 mL, 55.1 mmol, 1.0 equiv), cooled to -20 °C, a solution of *n*-BuLi (48.5 mL, 121.2 mmol, 2.2 equiv, *n*-BuLi 2.5 M in hexanes) was added dropwise while the temperature was kept below 0 °C. The mixture was aged at 0-5 °C for 4 h and cooled below -20 °C, and CF_3CO_2Et (8.0 mL, 67.2 mmol, 1.4 equiv) was added rapidly (internal temp. reached 10 °C). Then reaction mixture was stirred for 1h at rt, quenched with 5% HCl (40 mL). The aqueous phase was separated and extracted with MTBE (3 x 50 mL). The residue was treated with 36% HCl (20 mL), and stirred for 16h at 90 °C (temp. of oil bath). Then reaction mixture was cooled to 0 °C and washed with EtOAc to give a white solid. The obtained solid was suspended in MTBE (40 mL) and treated with aq sat. solution of NaOAc (80 mL). After 30 min. of vigorous stirring, organic phase was separated, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica (5-15% EtOAc/hexanes) to give an orange solid (1.64 g, 14%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.13 (m, 1H), 7.09 (dd, J = 9.1, 2.8 Hz, 1H), 6.69 (d, J = 9.1 Hz, 1H), 6.23 (br s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 (q, J_{CF} = 33.0 Hz), 150.0, 148.7, 127.4, 118.9, 117.1 (q, J_{CF} = 289.8 Hz), 111.4 (q, J_{CF} = 4.3 Hz), 110.4, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.9. ^{1}H NMR data are in agreement with those reported.[60] ^{13}C NMR spectra is described by authors without C-F coupling constants and the accurate description and the copy of spectra are included in this experimental section.

1-(1-Aminonaphtalene-2yl)-2,2,2-trifluoroethanone (**1c**) To a solution of 2,2-dimethyl-*N*-(naphthalen-1-yl)propanamide (10.0 g, 44.0 mmol) in MTBE (80 mL) and TMEDA (6.8

mL, 44.0 mmol, 1.0 equiv), cooled to -20 °C, a solution of *n*-BuLi (38.7 mL, 96.8 mmol, 2.2 equiv, BuLi 2.5 M in hexane) was added dropwise by means of syringe pump within 2h while the temperature was kept below -10 °C. The mixture was aged at -5 - 0 °C for 2 h and cooled below -30 °C, and CF_3CO_2Et (7.35 mL, 61.8 mmol, 1.4 equiv) was added rapidly (internal temp. reached 20 °C). Then reaction mixture was stirred for 1h at rt, quenched with 5% HCl (40 mL) and solvents were evaporated. The residue was treated with 36% HCl (20 mL), and stirred for 5h at 70 °C (temp. of oil bath). Then reaction mixture was neutralized with sat. solution of K_2CO_3 and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica (toluene) and further purified by crystallization (*n*-heptane) to give a bright-yellow solid (3.03 g, 29%). M.p. 137.5–138.6 °C (*n*-heptane); IR (KBr) 3461, 3313, 1647, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.70 (br s, 2H) overlapping 7.94-7.90 (pseudo dd, 1H) and 7.75–7.71 (m, 1H), 7.69–7.71 (m, 2H), 7.55–7.48 (m, 1H), 7.05 (d, J = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9 (J_{CF} = 32.9 Hz), 153.3, 136.8, 130.6, 128.7, 126.1, 125.1 (J_{CF} = 4.3 Hz), 122.6, 121.9, 117.5 (J_{CF} = 289.4 Hz), 116.4, 105.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_9F_3NO$ 240.0636; Found: 240.0632.

1-(2-Amino-5-fluorophenyl)-2,2,2-trifluoroethanone (**1d**) To a solution of *N*-(4-fluorophenyl)-2,2-dimethylpropanamide (9.37 g, 48.0 mmol) in MTBE (150 mL) and TMEDA (7.4 mL, 48.0 mmol, 1.0 equiv), cooled to -20 °C, a solution of *n*-BuLi (45.8 mL, 109.0 mmol, 2.27 equiv, BuLi 2.38 M in hexanes) was added dropwise while the temperature was kept below 0 °C. The mixture was aged at 0-5 °C for 2 h and cooled

below -20 °C, and CF_3CO_2Et (8.0 mL, 67.2 mmol, 1.4 equiv) was added rapidly (internal temp. reached 10 °C). Then reaction mixture was stirred for 1h at rt, quenched with 5% HCl (40 mL) and solvents were evaporated. The residue was treated with 36% HCl (20 mL), and stirred for 3h at 70 °C (temp. of oil bath). Then reaction mixture was cooled to 0 °C and washed with EtOAc to give a white solid. The obtained solid was suspended in MTBE (40 mL) and treated with aq sat. solution of NaOAc (80 mL). After 30 min. of vigorous stirring, organic phase was separated, dried over $MgSO_4$, and evaporated. The residue was crystallized from *n*-heptane to give a bright-yellow solid (7.65 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–739 (m, 1H), 7.21–714 (m, 1H), 6.70 (dd, J = 9.2, 4.5 Hz, 1H), 6.36 (br s, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7 (dq, J_{CF} = 34.0, 3.3 Hz, C=O), 153.2 (d, J_{CF} = 238.4 Hz), 150.0, 125.7 (d, J_{CF} = 24.3 Hz), 118.9 (d, J_{CF} = 7.1 Hz), 116.8 (q, J_{CF} = 289.5 Hz), 115.3 (dq, J_{CF} = 23.4, 4.3 Hz), 110.0 (d, J_{CF} = 6.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.1, -127.1. CAS registry number - 214288-07-0, no spectroscopic data are available for comparison.

1-(2-Aminophenyl)-2,2,2-trifluoroethanone (**1e**) To a solution of 2,2-dimethyl-*N*-phenylpropanamide (7.80 g, 44.0 mmol) in MTBE (100 mL) and TMEDA (6.8 mL, 44.0 mmol, 1.0 equiv), cooled to -20 °C, a solution of *n*-BuLi (38.7 mL, 96.8 mmol, 2.2 equiv, *n*-BuLi 2.5 M in hexane) was added dropwise by means of syringe pump within 2h while the temperature was kept below -10 °C. The mixture was aged at 25 °C for 3 h (yellow solid has formed), cooled below -25 °C, and CF_3CO_2Et (7.35 mL, 61.8 mmol, 1.4 equiv) was added rapidly (internal temp. reached 0 °C). Then reaction mixture was stirred for 16h at rt and quenched with 5% HCl (100 mL). The organic phase was separated and solvents were evaporated. The residue was chromatographed on silica (5-10%

EtOAc/hexanes) to give a yellow oil (5.1 g) and unreacted substrate (1.6 g). The crude TFMK was treated with 36% HCl (20 mL) at rt (white solid was formed immediately) and stirred for 3h at 90 °C (temp. of oil bath, yellow solution has been formed at 70 °C). Then reaction mixture was neutralized with sat. solution of Na_2CO_3 and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over $MgSO_4$, and evaporated. The residue was purified by crystallization (*n*-heptane, 8 mL, -40 °C, 2h) to give a bright yellow solid (2.66 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.73 (m, 1H), 7.43–7.36 (m, 1H), 6.77–6.68 (m, 2H), 6.45 (br s, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8 (q, J_{CF} = 33.1 Hz), 151.1, 136.6, 131.3 (q, J_{CF} = 4.1 Hz), 117.4, 117.1 (q, J_{CF} = 289.7 Hz), 116.4, 111.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.6. ^{1}H NMR data are in agreement with those reported.[60] ^{13}C NMR spectra is described by authors without C-F coupling constants and the accurate description and the copy of spectra are included in this experimental section.

1-[2-Amino-5-(trifluoromethyl)phenyl]-2,2,2-trifluoroethanone (**1f**) To a solution of 2,2-dimethyl-*N*-[4-(trifluoromethyl)phenyl]propanamide (10.8 g, 44.0 mmol) in MTBE (130 mL) and TMEDA (6.8 mL, 44.0 mmol, 1.0 equiv), cooled to -20 °C, a solution of *n*-BuLi (38.7 mL, 96.8 mmol, 2.2 equiv, *n*-BuLi 2.5 M in hexane) was added dropwise by means of syringe pump within 1h while the temperature was kept below -20 °C. The mixture was aged at 0 - 5 °C for 2 h (a brown-black solid has been formed), cooled below -25 °C, and CF_3CO_2Et (7.35 mL, 61.8 mmol, 1.4 equiv) was added rapidly (internal temp. reached 0 °C). Then reaction mixture was stirred for 1h at rt, quenched with 5% HCl (100 mL) and organic phase was separated and solvents were evaporated. The yellow-green residue was treated with 36% HCl (100 mL), and stirred for 16h at 90

°C (temp. of oil bath). Then reaction mixture was neutralized with solid Na_2CO_3 and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica (10% EtOAc/hexanes) to give a bright yellow solid (4.44 g, pure fraction). Additional 1.89 g of product was obtained by crystallization (*n*-heptane) of mixed fraction after chromatography. (4.44 g + 1.89 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.58 (dd J = 8.9, 1.8 Hz, 1H), 6.83 (d, J = 2.2 Hz, 1H), 6.75 (br s, NH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7 (q, J_{CF} = 34.0 Hz), 154.7, 132.6 (q, J_{CF} = 3.0 Hz), 129.3 – 129.0 (m), 123.8 (q, J_{CF} = 269.3 Hz), 118.6 (q, J_{CF} = 33.4 Hz), 118.1, 116.7 (q, J_{CF} = 289.4 Hz), 109.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3, -69.8. ^{1}H NMR data are in agreement with those reported.[60] ^{13}C NMR spectra is described by authors without C-F coupling constants and the accurate description and the copy of spectra are included in this experimental section.

1-[2-Amino-5-(dimethylamino)phenyl]-2,2,2-trifluoroethanone (**1g**) To a solution of *N*-[4-(dimethylamino)phenyl]-2,2-dimethylpropanamide (4.99 g, 22.66 mmol) and TMEDA (45.34 mmol, 6.95 mL, 2.0 eq) in THF, cooled to -60 °C, *n*-BuLi (19.9 mL, 45.34 mmol, 2.2 equiv, 2.28 M in hexane) was added dropwise by means of syringe pump within 30 min. (temp. has increased to -50 °C), and the reaction was stirred for 4h at 0 – -5 °C degree (internal temperature; reaction mixture was stirred by means of mechanical stirrer due to lithium dianion precipitation). Then reaction mixture was cooled to -65 °C and CF_3CO_2Et (3.77 mL, 31.73 mmol, 1.4 equiv) was added within 5 min. (the internal temp. has risen to -35 °C). Then cooling bath was removed, and the reaction mixture was allowed to warm up to 0 °C and stirred for additional 1h at this

temp. and quenched with 10% citric acid (100 mL). Then mixture was diluted with EtOAc (100 mL), and aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (2 x 100 mL), dried over $MgSO_4$, evaporated and dried in vacuo to give an orange foam. The residue was chromatographed on silica (20% EtOAc/hexanes) to give a brown oil contains some impurities. Protected aminofluoroketone was used in the next step without further purification.

The crude aminofluoroketone derivative was treated with HCl in dioxane (20 mL, 4M in dioxane) and water (2 mL) and resulting mixture was heated at 90 °C for 16h. Then reaction mixture was neutralized with sat. solution of Na_2CO_3 (100 mL), and aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (2 x 100 mL), dried over $MgSO_4$, and evaporated. The residue purified by chromatography (25% EtOAc/hexanes) to give a brown-black oil which solidified upon solid in the fridge (720.2 mg, 14%). M.p. 72.2–73.0 °C (*n*-heptane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 8.9, 2.8 Hz, 1H), 7.08–7.03 (m, 1H), 6.69 (d, J = 9.1 Hz, 1H), 6.08 (br s, NH, 2H), 2.84 (s, CH_3, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4 (q, J_{CF} = 32.7 Hz), 146.9, 142.3, 127.2, 118.5, 117.2 (q, J_{CF} = 289.9 Hz), 113.3 (q, J_{CF} = 4.3 Hz), 111.3, 41.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.8. The structure of ketone **1g** has reported by Patel,[61] however no spectroscopic data are available for comparison (no CAS registry number). Copy of spectra are included in this experimental section.

1-(2-Amino-5-methylphenyl)-2,2,2-trifluoroethanone (**1h**) To a solution of 2,2-dimethyl-*N*-(4-methylphenyl)propanamide (8.42 g, 44.0 mmol) in MTBE (100 mL) and TMEDA (6.8 mL, 44.0 mmol, 1.0 equiv), cooled to -20 °C, a solution of *n*-BuLi (38.7 mL,

96.8 mmol, 2.2 equiv, *n*-BuLi 2.5 M in hexane) was added dropwise by means of syringe pump within 1h while the temperature was kept below -10 °C. The mixture was aged at 10-15 °C for 5 h (a light-yellow solid has been formed), cooled below -25 °C, and CF_3CO_2Et (7.35 mL, 61.8 mmol, 1.4 equiv) was added rapidly (internal temp. reached 0 °C). Then reaction mixture was stirred for 16h at rt and quenched with 5% HCl (100 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). Then combined organic phases were washed with brine (1 x 100 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (5% EtOAc/hexanes) to give a yellow oil (8.31 g) and unreacted substrate (**S45**). The crude TFMK was treated with 36% HCl (30 mL) at rt (white solid was formed immediately) and stirred for 16h at 90 °C (temp. of oil bath, grey solid has been formed). Then reaction mixture was cooled to rt, neutralized with sat. solution of Na_2CO_3 (pH = 9) and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over $MgSO_4$, and evaporated. The residue was purified by crystallization (*n*-heptane, 12 mL, -45 °C, 2h) to give an orange solid (4.59 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (br s, 1H), 7.21 (dd, J = 8.6, 2.0 Hz, 1H), 6.65 (d, J = 8.6 Hz, 1H), 6.30 (br s, 2H), 2.26 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6 (q, J_{CF} = 33.1 Hz), 151.3, 138.2, 130.3 (q, J_{CF} = 4.0 Hz), 125.4, 117.5, 117.1 (q, J_{CF} = 289.8 Hz), 111.0, 20.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.5. CAS registry number - 205756-35-0; no spectroscopic data are available for comparison. Copy of spectra are included in this experimental section.

(1*R*,2*S*,5*R*)-5-Methyl-2-(propan-2-yl)cyclohexyl 4-nitrophenyl ether (**15**) was prepared by literature procedure,[62] however 75% isolated reported in the literature has

not been achieved. To a solution of *p*-chloronitrobenzene (11.03 g, 70 mmol) and (-)-mentol (10.93 g, 70 mmol) in dry DMSO (120 mL), a suspension of NaH (3.1 g, 77.0 mmol, 1.1 equiv) was added in portions at rt (evolution of hydrogen has not been observed). The reaction mixture was heated at 70-75 °C (bath temp.; **strong evolution of hydrogen !!!**) and the reaction mixture was kept at this temp. for 16 h. Then reaction mixture cooled to rt, diluted with 5% HCl (300 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed brine (3 x 100 mL), dried over $MgSO_4$ and evaporated. The obtained black oil was adsorbed on silica (50 g) and was washed with a mixture of EtOAc and hexanes (5% EtOAc/hexanes) to give an orange oil which was further purified by crystallisation from MeOH (70 mL) to give an light-orange solid (6.21 g, 32%). CAS registry number - 85002-82-0, 94730-54-8, no spectroscopic data are available for comparison. IR (KBr) 3298, 2956, 2921, 2871, 1647, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21–8.14 (m, 2H, =C-H), 6.96–6.90 (m, 2H, =C-H), 4.16 (ddd, *J* = 10.6, 10.6, 4.2 Hz, 1H, CHOAr), 2.16–2.05 (m, 2H), 1.79–1.70 (m, 2H), 1.61–1.45 (m, 2H), 1.18–0.96 (m, 3H), 0.94 (d, *J* = 7.7 Hz, 3H), 0.92 (d, *J* = 8.1 Hz, 3H), 0.75 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.70, 141.0, 126.0, 115.00, 78.4, 47.8, 39.9, 34.3, 31.4, 26.3, 23.8, 22.0, 20.6, 16.6.

4-{[(1*R*,2*S*,5*R*)-5-Methyl-2-(propan-2-yl)cyclohexyl]oxy}aniline (**16**) To a solution of nitrocompound **15** (6.21 g, 22.4 mmol) in reagent-grade EtOAc (100 mL), 10% Pd/C (238.3 mg, 0.22 mmol, 1 mol%) was added and the resulting mixture was shaken in Parr apparat for 4h at rt (H_2 pressure - 4 bar; in some cases reduction of nitro group has appeared strongly exothermic and the respective caution should be maintained; temp. of the reaction mixture has increased from 17°C to 24 °C within 30 min.). Then argon

was bubbled trough the reaction mixture for 5 min. and palladium catalyst was filtered through a pad of Celite (washed with EtOAc), and solvent was evaporated to give a light-yellow oil (5.5 g). The crude amine **S35** product was used in the next step without further purification. CAS registry number - 94730-56-0, 94661-07-1.

2,2-dimethyl-*N*-(4-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}phenyl)propanamide (**17**) To a solution of aniline **16** (5.50 g, 22.4 mmol) and Et_3N (4.7 mL, 33.6 mmol) in DCM, cooled to 0 °C, PivCl (3.5 mL, 29.1 mmol, 1.3 equiv) was added dropwise. After 10 min. cooling bath was removed and reaction mixture was stirred for 16h at rt. Then reaction mixture was diluted with 5% HCl (100 mL), organic phase was separated, dried over $MgSO_4$, and evaporated. The residue was purified by crystallisation (*n*-heptane, 90 mL) to give a white crystalline amide **17** (6.68 g, 90%). M.p. 168.6–169.2 °C (*n*-heptane); $[\alpha]_D^{23}$ = -45.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.35 (m, 2H), 7.21 (br, 1H, NH) 6.88–6.82 (m, 2H), 3.95 (ddd, *J* = 10.6, 10.6, 4.1 Hz, 1H, CHO), 2.35–2.16 (m, 1H), 2.15–2.07 (m, 1H), 1.76–1.65 (m, 2H), 1.54–1.36 (m, 2H), 1.30 [s, 9H, NHC($C\underline{H}_3$)$_3$], 1.17–0.86 (m, 4H) overlapping 0.92 (d, *J* = 7.0 Hz, 3H) and 0.91 (d, *J* = 6.5 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3 (C=O), 163.7, 141.0, 126.0, 115.0, 78.4, 47.8, 39.9, 34.3, 31.4, 26.4, 23.8, 22.0, 20.6, 16.6; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{33}NO_2Na$ 354.2409; Found: 354.2409.

2,2-Dimethyl-*N*-[4-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-(trifluoroacetyl)phenyl]propanamide (**18**) To a solution of amide **17** (6.50 g, 19.6 mmol) and TMEDA (3.02 mL, 19.6 mmol, 1.0 equiv) in anhydrous MTBE (50 mL), cooled to -20 °C, *n*-BuLi (18.7 mL, 43.1 mmol, 2.2 equiv, *n*-BuLi 2.31 M in hexane) was

added dropwise by means of syringe pump within 40 min. (the internal temp. has increased to -8 °C). Then cooling bath was removed and the resulting reaction mixture was stirred for 4h at 20 °C (bright-yellow precipitate has formed). Then reaction mixture was cooled to -25 °C, and CF_3CO_2Et (3.3 mL, 27.4 mmol, 1.4 equiv) was added rapidly (internal temp. has increased to 10 °C) and reaction mixture was stirred at rt for 1.5h. The resulting reaction mixture was quenched with 5% HCl (200 mL), and aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica (5% EtOAc/hexanes) to give a bright orange oil (4.68 g, 56%). The resulting amide **18** was used in the next step without further purification.

1-(2-Amino-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}phenyl)-2,2,2-trifluoroethanone (**1i**) To round-bottom flask containing amide **18** (4.2 g, 9.82 mmol), HCl in dioxane (35 mL, 4M in dioxane) and water (5 mL) were added and stirred for 2h at 90 °C (TLC analysis indicated absence of substrate, 5% EtOAc/hexanes). Then reaction mixture was cooled to rt, diluted with DCM (50 mL), neutralized with solid $NaHCO_3$ (ca. 12 g) and stirred for additional 15 min. Then solid was filtered, washed with DCM (5 times), and solvents were evaporated. The residue was chromatographed on silica (5% EtOAc/hexanes) to give an deep-orange oil (2.98 g, 88%). α = -113.6 (c = 0.69, $CHCl_3$); IR (film) 3483, 3367, 2957, 2927, 2871, 1668, 1592, 1547, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.21 (m, 1H), 7.09 (dd, *J* = 9.1, 2.8 Hz, 1H), 6.67 (d, *J* = 9.1 Hz, 1H), 6.19 (br s, 2H), 3.08 (ddd, *J* = 10.5, 10.5, 4.2 Hz, 1H), 2.32–2.20 (m, 1H), 2.12–2.02 (m, 1H), 1.76–1.63 (m, 2H), 1.52–1.34 (m, 2H), 1.14–0.86 (m, 3H) overlapping 0.94 (d, *J* = 6.8 Hz, 3H) and 0.91 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2 (q, J_{CF} = 33.0 Hz), 148.6, 148.5, 129.4, 118.7, 117.1 (q, J_{CF} = 289.8 Hz), 116.5 (q, J_{CF} = 4.2 Hz), 110.8, 79.8, 48.1, 40.4, 34.5, 31.4, 25.9, 23.5, 22.1, 20.8, 16.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}F_3NO_2$ 344.1837; Found: 344.1830.

1-(2-Amino-5-chlorophenyl)-2,2,3,3,4,4,4-heptafluorobutan-1-on (1j) To a solution of *N*-(4-chlorophenyl)-2,2-dimethylpropanamide (5 g, 23.62 mmol) and TMEDA (23.62 mmol, 3.6 mL) in anhydrous THF (50 mL), cooled to -20 °C, *n*-BuLi (22.8 mL, 51.96 mmol, 2.2 equiv, 2.28 M) was added dropwise by means of syringe pump within 30 min. (the internal temp. has increased to -8 °C; a white precipitated which was formed has been dissolved to give an orange solution). The resulting reaction mixture was stirred for 4h at 0 °C (bright-yellow precipitate has formed). Then reaction mixture was cooled to -30 °C, and ethyl heptafluorobutanoate (5.7 mL, 33.1 mmol, 1.4 equiv) was added rapidly (internal temp. has increased to 10 °C), cooling bath was removed, stirring was continued for 1h and the reaction mixture was quenched with water (100 mL). The aqueous phase was separated and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica (200 g, 10% EtOAc/hexanes) to give a yellow oil (2.11 g) which was used in the next step without further purification.
The obtained partially purified ketone was treated with solution of HCl in dioxane (10 mL, 4M) and water (1 mL), and reaction mixture was heated at 90 °C for 2h (TLC indicated absence of substrate). Then solvent was evaporated and crude amine hydrochloride (*attempts to separate of free aminoketone from by-products has failed*) was purified by chromatography on silica (5-25% EtOAc/hexanes) to give a bright-

yellow oil. The resulting hydrochloride was dissolved in $CHCl_3$ (10 mL) and sat. aq. solution of $NaHCO_3$ (10 mL) was added. The biphasic mixture was vigorously stirred for 30 min. Then organic phase was separated, dried over $MgSO_4$, and evaporated to give a bright-orange solid (951.6 mg, 10%). M.p. 57.8–59.1 °C (*n*-heptane); IR (film) 3494, 3370, 1664, 1622, 1587, 1539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.32 (dd, J = 9.0, 2.4 Hz, 1H), 6.69 (d, J = 9.0 Hz, 1H), 6.50 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2 (t, J_{CF} = 24.2 Hz), 151.8, 136.9, 130.2–129.8 (m), 120.9, 119.2, signals in the region of 120-102 ppm has been omitted in description of spectra for clarity due to complicated multiplicity; ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.8 (t, J = 9.5 Hz), -110.9 – - 111.1 (m), -125.0 – - 125.2 (m); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_6F_7ClNO$ 324.0026; Found: 324.0019.

1-(2-Amino-5-chlorophenyl)-2,2-difluoroethanone (**1k**) To a solution of *N*-(4-chlorophenyl)-2,2-dimethylpropanamide (10.0 g, 44.7 mmol) and TMEDA (44.7 mmol, 6.8 mL, 2.0 equiv) in THF (100 mL), cooled to -40 °C, *n*-BuLi (39.3 mL, 98.3 mmol, 2.2 equiv, 2.5 M in hexane) was added dropwise by means of syringe pump within 30 min. (temp. has increased to -25 °C), and the reaction was stirred for 2h at 0 - -5 °C degree (internal temperature; reaction mixture was stirred by means of mechanical stirrer due to lithium dianion precipitation). Then reaction mixture was cooled to -40 °C and 2,2-difluoro-1-(morpholin-4-yl)ethanone (10.3 g, 62.6 mmol, 1.4 equiv) was added (the internal temp. has risen to -15 °C). Then reaction mixture was allowed to stir below 0 °C for additional 1h and quenched with 10% citric acid (100 mL). Then mixture was diluted with EtOAc (100 mL), and aqueous phase was separated and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (2 x 100 mL), dried over

$MgSO_4$, evaporated. The residue was chromatographed on silica (5% EtOAc/hexanes) to give amide containing some impurities which was used in the next step without further purification.

The obtained o-TFMK derivative was treated with 36% HCl (40 mL) and the resulting mixture was heated at 90 °C for 16h. Then reaction mixture was quenched with sat. solution of Na_2CO_3 (100 mL), and aqueous phase was extracted with MTBE (3 x 30 mL). The combined organic phases were washed with brine (2 x 100 mL), dried over $MgSO_4$, and evaporated. The residue crystalized from *n*-heptane (15 mL) to give an orange solid (3.13 g). The mother liquid was evaporated and the resulting solid was recrystallized from *n*-heptane to give additional portion of ketone **1k** (567.7 mg, summary yield 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.40 (m, 1H), 7.29 (dd, J_{CF} = 9.0, 2.4 Hz, 1H), 6.57 (d, J_{CF} = 9.0 Hz , 1H), 6.39 (br s, 2H, NH) overlapping 6.28 (t, J_{CF} = 53.6 Hz, 1H, CF_2H). Spectral data are in agreement with those reported.[59]

1-(2-Aminopyridin-3-yl)-2,2,2-trifluoroethanone (**6a**) To a solution of 2,2-dimethyl-*N*-(pyridin-2-yl)propanamide amide (5 g, 28.05 mmol) and TMEDA (56.11 mmol, 8.6 mL, 2.0 equiv) in THF (50 mL), cooled to -60 °C, *n*-BuLi (24.6 mL, 56.11 mmol, 2.2 equiv, 2.28 M in hexane) was added dropwise by means of syringe pump within 30 min. (temp. has increased to -50 °C), and the reaction was stirred for 4h at 0 - -5 °C degree (internal temperature; reaction mixture was stirred by means of mechanical stirrer due to lithium dianion precipitation). Then reaction mixture was cooled to -65 °C and CF_3CO_2Et (4.67 mL, 39.27 mmol, 1.4 equiv) was added (the internal temp. has risen to -45 °C). Then cooling bath was removed, and the reaction mixture was allowed to warm up to -20 °C

(exothermic reaction begins at -35 °C) and stirred for additional 30 min. and quenched with sat. NH_4Cl (100 mL). Then mixture was diluted with EtOAc (150 mL), and organic phase was separated, washed with citric acid (1 x 100 mL), brine (2 x 100 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (25-60% EtOAc/hexanes) to give yellow solid (4.68 g). ^{1}H NMR indicated some impurities and thus obtained pyridine derivative was used in the next step without further purification.

The crude pyridine derivative was treated with HCl in dioxane (20 mL, 4M in dioxane) and water (2 mL) and the resulting mixture was heated at 90 °C for 16h. Then reaction mixture was quenched with sat. solution of $NaHCO_3$ (100 mL), and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (2 x 100 mL), dried over $MgSO_4$, and evaporated. The residue was crystallized (*n*-heptane, to remove partially contaminations) and then was passed through pad of silica (10% MeOH/DCM) to give a yellow solid (2.45 g, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 4.6, 1.8 Hz, 1H), 8.10–8.04 (m, 1H), 7.17 (br s, 2H), 6.70 (dd, J = 20.2, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 (q, J_{CF} = 33.8 Hz), 160.4, 156.8, 140.5 (q, J_{CF} = 4.0 Hz), 114.8 (q, J_{CF} = 289.5 Hz), 112.8, 106.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.2. CAS registry number - 1060801-31-1; no spectroscopic data are available for comparison. Copy of spectra are included in this experimental section.

1-(4-Aminopyridin-3-yl)-2,2,2-trifluoroethanone (**6b**) To a solution 2,2-dimethyl-*N*-(pyridin-4-yl)propanamide (4.04 g, 22.66 mmol) TMEDA (45.34 mmol, 6.95 mL) amide in THF (40), cooled to -60 °C, *n*-BuLi (19.9 mL, 45.34 mmol, 2.2 equiv, 2.28 M in hexane) was added dropwise by means of syringe pump within 30 min. (temp. has increased to -50 °C), and the reaction was stirred for 4h at 0 - -5 °C degree (internal

temperature; reaction mixture was stirred by means of mechanical stirrer due to lithium dianion precipitation). Then reaction mixture was cooled to -65 °C and CF_3CO_2Et (3.77 mL, 31.73 mmol, 1.4 equiv) was added (the internal temp. has risen to -35 °C). Then cooling bath was removed, and the reaction mixture was allowed to warm up to -10 °C and stirred for additional 1h and quenched with 10% citric acid (100 mL). Then mixture was diluted with EtOAc (100 mL), and aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (2 x 100 mL), dried over $MgSO_4$, evaporated and dried in vacuo to give a yellow foam (6.1 g) which was used in the next step without further purification.

The crude pyridine derivative was treated with HCl in dioxane (20 mL, 4M in dioxane) and water (2 mL) and the resulting mixture was heated at 90 °C for 16h. Then reaction mixture was quenched with sat. solution of Na_2CO_3 (100 mL), and aqueous phase was extracted with EtOAc (3 x 50 mL), The combined organic phases were washed with brine (2 x 100 mL), dried over MgSO4, and evaporated. The residue purified by chromatography (5-10% MeOH/DCM) and further crystallized (toluene/*n*-heptane = 50:50) to give a brown-orange solid (2.99 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93–8.86 (m, 1H), 8.25 (d, J = 6.0 Hz, 1H), 6.61 (d, J = 6.0 Hz, 1H), (NH_2 group was exchange with deuterium); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3 (q, J_{CF} = 35.2 Hz), 156.4, 154.1 (q, J_{CF} = 5.2 Hz), 153.0, 116.5 (q, J_{CF} = 289.0 Hz), 111.5, 109.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.1 CAS registry number: 1343447-95-9; no spectra available for comparison. Copy of spectra are included in this experimental section.

1-(2-Amino-5-chloropyridin-3-yl)-2,2,2-trifluoroethanone (**6c**) To a solution of *N*-(5-chloropyridin-2-yl)-2,2-dimethylpropanamide (5.0 g, 23.51 mmol) in MTBE (50 mL) and

TMEDA (3.6 mL, 23.51 mmol, 1.0 equiv), cooled to -35 °C, a solution of *n*-BuLi (20.7 mL, 51.72 mmol, 2.2 equiv, 2.5 M in hexanes) was added dropwise by means of syringe pump within 1h while the temperature was kept below -20 °C. The mixture was aged at 0-5 °C for 2 h (a light-orange solid has been formed), cooled to -45 °C, and CF_3CO_2Et (3.92 mL, 32.91 mmol, 1.4 equiv) was added rapidly (internal temp. reached -10 °C). Then reaction mixture was stirred for 16h at rt and quenched with 5% HCl (100 mL). Then reaction mixture was stirred for 16h at rt and quenched with 5% HCl (50 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). Then combined organic phases were washed with brine (1 x 100 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (25% EtOAc/hexanes - EtOAc) to give an orange solid (3.96 g). ^{1}H NMR indicated some impurities and thus obtained aminofluoroketone was used in the next step without further purification.

The crude aminopyridine was treated with 36% HCl (30 mL) at rt and stirred for 16h at 90 °C (temp. of oil bath, a white solid has been formed). Then reaction mixture was cooled to rt, neutralized with sat. solution of Na_2CO_3 (pH = 9) and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica to give a yellow solid (1.15 g, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 2.5 Hz, 1H), 8.02–7.99 (m, 1H), 7.09 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5 (q, J_{CF} = 34.8 Hz), 158.5, 155.7, 137.9 (q, J_{CF} = 4.2 Hz), 119.2, 116.6 (q, J_{CF} = 289.3 Hz), 106.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.1. Spectral data are in agreement with those reported.[63]

General procedure for synthesis of quinoline and naphthydrine derivatives: To a screw-cap vial, trifluoromethylketone (TFMK), alkyne (1.2 equiv), copper catalyst (2 mol%) and DME (100 µL) were added. The obtained mixture was stirred at rt (2-3 min.) until complete dissolution of the substrates. Then, a solution of TMG (*N*,*N*,*N*',*N*'-tetramethylguanidine, 0.01 mmol, 2 mol%) in degassed water (2 mL) was added. The biphasic mixture was stirred for the indicated time at 100-120 °C (oil bath temp.) with vigorous stirring. Next, the reaction mixture was diluted with EtOAc (2-3 mL), and the aqueous phase was separated and extracted with two additional portions of EtOAc. The combined extracts were washed with brine (1 x 10 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (silica : crude reaction mixture = 30 : 1 w/w) using an appropriate eluting system to afford the product.

6-Chloro-2-cyclopropyl-4-(trifluoromethyl)quinoline (**3a**) was obtained according to the general procedure from ketone **1a** (223.6 mg, 1.0 mmol), TMG (2.5 µL, 0.02 mmol, 2 mol%), ethynylcyclopropane (**2a**) (134.0 µL, 1.2 mmol, 1.2 eq.), IPr*CuCl (20.2 mg, 0.02 mmol, 2 mol%), water (2 mL) and DME (0.1 mL). The crude product was chromatographed on silica (2% EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (96.4 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.99 (m , 1H), 7.94 (dd, *J* = 9.0, 0.3 Hz, 1H), 7.65 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.54 (s, 1H), 2.29–2.21 (m, 1H), 1.27–1.21 (m, 2H), 1.18–1.11 (m, 2H). ^{1}H NMR data are in agreement with those reported.[64]

Gram –scale preparation of **3a** was conducted according to the general procedure with ketone **1a** (1.12 g, 5.0 mmol), TMG (12.5 µL, 0.1 mmol, 2 mol%), ethynylcyclopropane (**2a**) (0.5 mL, 6.0 mmol, 1.2 equiv), IPr*CuCl (101.2 mg, 0.1 mmol,

2 mol%), water (10 mL) and DME (0.5 mL). The crude product was chromatographed on silica (2% EtOAc/hexanes) to give quinolone 3a (1.032 g, 76%) and diazocine **4a** (75.1 mg, 7%)

6-Chloro-2-phenyl-4-(trifluoromethyl)quinoline (**3b**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), ethynylbenzene (**2b**) (67.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (2% EtOAc/hexanes) to give a colourless oil (66.6 mg, 43%). IR (KBr) 3094. 3063, 3038, 1610, 1550, 1152, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.15 (m, 4H), 8.13–8.09 (m, 1H), 7.75 (dd, J = 9.0, 2.2 Hz, 1H), 7.60–7.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 147.5, 137.9, 134.3 (q, J_{CF} = 31.7 Hz), 134.0, 132.1, 131.4, 130.3, 129.1, 127.4, 123.3 (q, J_{CF} = 273.1 Hz), 122.9 (q, J_{CF} = 2.3 Hz), 122.4, 116.7 (q, J_{CF} = 5.2 Hz); ^{19}F NMR (376 MHz) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{10}ClF_3N$ 308.0454; Found 308.0455.

6-Chloro-2-(4-methoxyphenyl)-4-(trifluoromethyl)quinoline (**3c**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 1-ethynyl-4-methoxybenzene (**2c**) (78.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (2% EtOAc/hexanes) to give a colourless oil (107.6 mg, 64%). IR (KBr) 3070, 2967, 2938, 2917, 2840, 1610, 1546, 1148, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.10 (m, 4H), 8.09–8.04 (m, 1H), 7.71 (dd, J = 9.0, 2.2 Hz,

1H), 7.09–7.02 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 156.3, 147.5, 134.1 (q, J_{CF} = 31.6 Hz), 133.4, 131.8, 131.3, 130.5, 128.9, 123.3 (q, J_{CF} = 273.2 Hz), 122.9 (q, J_{CF} = 2.2 Hz), 122.0, 116.2 (q, J_{CF} = 5.3 Hz), 114.5, 55.4; ^{19}F NMR (376 MHz) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{12}ClF_3NO$ 338.0560; Found: 338.0561.

6-Chloro-4-(trifluoromethyl)-2-(3,4,5-trimethoxyphenyl)quinoline (**3d**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 1-ethynyl-3,4,5-trimethoxybenzene (**2d**) (115.0 mg, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (5% EtOAc/toluene) to give a colourless oil which spontaneously solidified upon standing in the fridge (106.0 mg, 53%). M.p. 134.5–136.5 °C; IR (KBr) 3097, 2937, 2842, 1581, 1167, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 1H), 8.13–8.05 (m, 2H), (dd, *J* = 9.0, 2.2 Hz, 1H), 7.40 (br s, 2H), 4.02 (s, 6H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 153.8, 147.4, 140.5, 134.4 (q, J_{CF} = 31.7 Hz), 133.9, 133.4, 132.0, 131.5, 123.3 (q, J_{CF} = 273.1 Hz), 122.9 (q, J_{CF} = 2.4 Hz), 122.3 (q, J_{CF} = 1.1 Hz), 116.7 (q, J_{CF} = 5.2 Hz), 104.9, 61.0, 56.4; ^{19}F NMR (376 MHz) δ -61.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{16}ClF_3NO_3$ 398.0771; Found: 398.0769.

6-Chloro-2-(4-methylphenyl)-4-(trifluoromethyl)quinoline (**3e**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 1-ethynyl-4-methylbenzene (**2e**) (76.1 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The

reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (2.5 % EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (109.8 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.15 (m, 2H), 8.11–8.06 (m, 3H), 7.74 (dd, J = 9.0, 2.2 Hz, 1H), 7.38–7.33 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 147.5, 140.6, 135.1, 134.1 (q, J_{CF} = 31.6 Hz), 133.7, 132.0, 131.2, 129.8, 127.3, 123.3 (q, J_{CF} = 273.1 Hz), 129.9 (q, J_{CF} = 2.3 Hz), 122.2, 116.5 (q, J_{CF} = 5.2 Hz), 21.4; ^{19}F NMR (376 MHz) δ -61.7. ^{1}H NMR data are in agreement with those reported.[22] ^{13}C NMR spectra are described by the authors without C-F coupling constants and the accurate description is provided above. A copy of the spectra is included in the ESI.

6-Chloro-2-(pyridin-3-yl)-4-(trifluoromethyl)quinoline (**3f**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 3-ethynylpyridine (**2f**) (62.0 mg, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (25% EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (17.8 mg, 11%). M.p. 157.2–157.5 °C; IR (film) 3059, 1613, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (br s, 1H), 8.78 (br s, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.24–8.16 (m, 2H), 8.15–8.10 (m, 1H), 7.78 (dd, J = 9.2, 2.0 Hz, 1H), 7.55–7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 151.1, 148.7, 147.6, 134.8 (q, J_{CF} = 31.9 Hz), 134.7, 134.7, 132.2, 131.8, 123.9 (m), 123.1 (q, J_{CF} = 273.2 Hz), 123.0 (q, J_{CF} = 2.3 Hz), 122.6, 116.2 (q, J_{CF} = 5.2 Hz); ^{19}F NMR (376 MHz) δ -61.7; HRMS (EI) *m/z*: [M$^{\cdot+}$] Calcd for $C_{15}H_8ClF_3N_2$ 308.0328; Found: 308.0321.

6-Chloro-2-(thiophen-3-yl)-4-(trifluoromethyl)quinoline (**3g**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 3-ethynylthiopene (**2g**) (59.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (3% EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (84.1 mg, 53%). M.p. 145.0–146.0 °C; IR (KBr) 3095, 1641, 1554, 1148, 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.00 (m, 4H), 7.86 (dd, J = 5.1, 1.2 Hz, 1H), 7.71 (dd, J = 9.0, 2.2 Hz, 1H), 7.47 (q, J = 5.1, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 147.5, 141.2, 134,2 (q, J_{CF} = 31.7 Hz), 133.7, 131.8, 131.4, 127.0, 126.5, 125.8, 123.2 (q, J_{CF} = 273.2 Hz), 123.0 (q, J_{CF} = 2.2 Hz), 122.2, 116.9 (q, J_{CF} = 5.3 Hz); ^{19}F NMR (376 MHz) δ -61.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_8ClF_3SNa$ 314.0018; Found: 314.0017.

6-Chloro-2-(cyclohex-1-en-1-yl)-4-(trifluoromethyl)quinoline (**3h**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 1-ethynylcyclohexene (**2h**) (70.5 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (3% EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (114.1 mg, 73%). M.p. 101.8–105.2 °C; IR (KBr) 3048, 2942, 2910, 2832, 1632, 1612, 1550, 1153, 1125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.00 (m, 2H), 7.90 (br s, 1H), 7.70–7.64 (m, 1H), 6.88–6.83 (m, 1H), 2.73–2.65 (m, 2H), 2.39–2.31 (m, 2H), 1.89–1.80 (m, 2H), 1.78–1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

158.4, 147.0, 137.0, 133.4 (q, J_{CF} = 31.4 Hz), 133.2, 132.4, 131.8, 130.9, 123.4 (q, J_{CF} = 272.2 Hz), 122.8 (q, J_{CF} = 2.3 Hz), 122.0, 115.8 (q, J_{CF} = 5.3 Hz), 26.3, 25.6, 22.6, 22.0; ^{19}F NMR (376 MHz) δ -61.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}ClF_3N$ 312.0767; Found: 312.0768.

6-Chloro-4-(trifluoromethyl)-2-[4-(trifluoromethyl)phenyl] (**3i**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 1-ethynyl-4-trifluoromethylbenzene (**2i**) (98.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (2% EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (29.0 mg, 15%). M.p. 165.5–166.8 °C; IR (KBr) 3070, 2967, 2938, 2916, 2840, 1610, 1546, 1149, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br d, *J* = 8.2 Hz, 2H), 8.24–8.16 (m, 2H), 8.15–8.11 (m, 1H), 7.84–7.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 147.5, 141.1, 134.8, 134.7 (q, J_{CF} = 31.9 Hz), 132.5, 132.1 (q, J_{CF} = 32.4 Hz), 131.8, 127.8, 126.0 (q, J_{CF} = 3.8 Hz), 124.0 (q, J_{CF} = 270.1 Hz), 123.2 (q, J_{CF} = 273.1 Hz), 123.0 (q, J_{CF} = 2.4 Hz), 122.7, 116.5 (q, J_{CF} = 5.3 Hz); ^{19}F NMR (376 MHz) δ -61.7, -62.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_8ClF_6N$ 376.0328; Found: 376.0323.

6-Chloro-2-hexyl-4-(trifluoromethyl)quinoline (**3j**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 1-octyne (**2j**) (88.5 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (2% EtOAc/hexanes) to give a

colourless oil (110.6 mg, 70%). IR (film) 2957, 2929, 2858, 1613, 1164, 1137 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09–8.03 (m, 2H), 7.70 (dd, J = 9.0, 2.4 Hz, 1H), 7.59 (br s, 1H), 3.01 (t, J = 7.6 Hz, 2H), 1.91–1.74 (m, 2H), 1.52–1.21 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 147.2, 133.6 (q, J_{CF} = 31.7 Hz), 133.4, 131.3, 131.0, 123.3 (q, J_{CF} = 273.0 Hz), 122.9 (q, J_{CF} = 2.3 Hz), 122.0, 119.2 (q, J_{CF} = 5.1 Hz), 39.2, 31.6, 29.5, 29.1, 22.5, 14.0; ^{19}F NMR (376 MHz) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}ClF_3N$ 316.1080; Found: 316.1080.

6-Chloro-2-(2-methylpropyl)-4-(trifluoromethyl)quinoline (**3k**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 4-methylpent-1-yne (**2k**) (70.5 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (5% EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (87.4 mg, 61%). M.p. 56.0–58.0 °C; IR (KBr) 3107, 3071, 2958, 2872, 1608,1154, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.02 (m, 2H), 7.70 (dd, J = 9.0, 2.2 Hz, 1H), 7.56 (s, 1H), 2.89 (d, J = 7.6 Hz, 2H), 2.24 (hept, J = 6.8 Hz, 1H), 0.99 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 147.2, 133.4 (q, J_{CF} = 31.7 Hz), 134.4, 131.4, 131.0, 123.2 (q, J_{CF} = 273.0 Hz), 122.9 (q, J_{CF} = 2.3 Hz), 122.0, 119.6 (q, J_{CF} = 5.1 Hz), 48.1, 29.2, 22.5; ^{19}F NMR (376 MHz) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{14}ClF_3N$ 288.0767; Found: 288.0768.

3-[6-Chloro-4-(trifluoromethyl)quinolin-2-yl]propan-1-ol (**3l**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), pent-4-yne-1-ol (**2l**) (50.4 mg, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg,

0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (40–50% EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (104.9 mg, 68%). M.p. 94.0–95.0 °C; IR (KBr) 3374, 3296, 3097, 3067, 3039, 2964, 2893, 1617, 1557, 1152, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.01 (m, 2H), 7.71 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.63 (br s, 1H), 3.77 (t, *J* = 6.0 Hz, 2H), 3.19 (t, *J* = 7.1 Hz, 2H), 2.18–2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 146.7, 134.0 (q, J_{CF} = 31.8 Hz), 133.7, 131.3, 131.0, 123.1 (q, J_{CF} = 273.4 Hz), 122.9 (q, J_{CF} = 2.3 Hz), 122.0, 119.5 (q, J_{CF} = 5.0 Hz), 62.0, 35.8, 31.1; ^{19}F NMR (376 MHz) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{12}ClF_3NO$ 290.0560; Found: 290.0555.

Methyl 4-[6-chloro-4-(trifluoromethyl)quinolin-2-yl]butanoate (**3m**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), methyl hex-5-ynoate (**2m**) (74.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (5% EtOAc/toluene) to give a colourless oil which spontaneously solidified upon standing in the fridge (82.7 mg, 50%). M.p. 54.0–56.0 °C; IR (KBr) 3077, 2973, 2954, 2921, 2898, 2852, 1732, 1620, 1560, 1146, 1125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.02 (m, 2H), 7.71 (dd, *J* = 9.0, 2.2 Hz, 1H); 7.60 (s, 1H), 3.67 (s, 3H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.26–2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 161.4, 147.1, 133.8 (q, J_{CF} = 31.8 Hz), 133.6, 131.4, 131.2, 123.2 (q, J_{CF} = 273.1 Hz), 122.9 (q, J_{CF} = 2.4 Hz), 122.1 (q, J_{CF} = 1.2Hz), 119.2 (q, J_{CF} = 5.1 Hz), 51.6, 38.0,

33.3, 24.1; ^{19}F NMR (376 MHz) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{14}ClF_3NO_2$ 332.0665; Found: 332.0666.

6-Chloro-2-(3-{[(3a*S*,4*S*,5a*R*,9a*R*,9b*S*)-2,2,8,8-tetramethylhexahydro[1,3]dioxolo[4,5]pyrano[3,2-*d*][1,3]dioxin-4-yl]oxy}propyl)-4-(trifluoromethyl)quinoline (**3n**) was prepared according to the general procedure from *o*-TFMK **1a** (111.8 mg, 0.5 mmol), (3a*S*,4*S*,5a*R*,9a*R*,9b*S*)-2,2,8,8-Tetramethyl-4-(pent-4-yn-1-yloxy)hexahydro[1,3]dioxolo[4,5]pyrano [3,2-*d*][1,3]dioxine (**2n**) (163.1 mg, 0.5 mmol), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 100 °C for 24 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (20–30% MTBE/hexanes) to give a light-yellow oil (181.4 mg, 68%). Purity based on HPLC: 99% (major peak 8.4 min., LiChrospher® Si60 column, 250 mm x 4.6 mm, 5 µm, DAD detector 209 nm, MTBE/hexane = 40:60; 1.0 mL/min); M.p. 95.5–96.4 °C; $[a]_D^{23}$ = 5.8 (c = 1.1, $CHCl_3$); IR (film) 2991, 2938, 1613, 1496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.03 (m, 2H), 7.71 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.61 (s, 1H), 5.0 (s, 1H), 4.11–4.05 (m, 2H), 3.86–3.77 (m, 2H), 3.77–3.68 (m, 2H), 3.61–3.48 (m, 2H), 3.12 (t, *J* = 7.6 Hz, 2H), 2.25–2.08 (m, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 147.2, 133.8 (q, J_{CF} = 31.7 Hz), 133.6, 131.4, 131.2, 123.2 (q, J_{CF} = 273.1 Hz), 122.9 (q, J_{CF} = 2.3 Hz), 122.0, 119.2 (q, J_{CF} = 5.1 Hz), 109.4, 99.7, 97.9, 76.1, 74.9, 72.7, 66.9, 35.6, 29.0, 28.7, 28.2, 26.1, 18.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{30}ClF_3NO_6$ 532.1714; Found: 532.1703.

3-[6-Chloro-4-(trifluoromethyl)quinolin-2-yl]-1-(4-fluorophenyl)propan-1-one (**3o**) was obtained according to the general procedure from ketone **1a** (111.8 mg, 0.5 mmol), TMG (1.25 µL, 0.01 mmol, 2 mol%), 1-(4-Fluorophenyl)pent-4-yl-1-one (**2o**) (105.7 mg, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. The crude product was chromatographed on silica (5% EtOAc/hexanes) to give a colourless oil which spontaneously solidified upon standing in the fridge (105.0 mg, 55%). M.p. 141.5–142.5 °C; IR (film) 3357, 3038, 3058, 2926, 1688, 1616, 1600, 1561 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.01 (m, 3H), 7.93 (br d, J = 9.2 Hz, 1H), 7.71 (br s, 1H), 7.67 (dd, J = 9.0, 2.0 Hz, 1H), 7.19–7.10 (m, 2H), 3.63 (t, J = 6.6 Hz, 2H), 3.49 (t, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 165.8 (d, J_{CF} = 253.1 Hz), 160.7, 147.0, 133.6 (q, J_{CF} = 31.8 Hz), 133.5, 133.4 (d, J_{CF} = 3.0 Hz), 131.1 (d, J_{CF} = 20.7 Hz), 130.7 (d, J_{CF} = 9.2 Hz), 123.2 (q, J_{CF} = 273.1 Hz), 123.0 (q, J_{CF} = 2.4 Hz), 122.2, 119.9 (q, J_{CF} = 5.2 Hz), 115.7 (d, J_{CF} = 21.7 Hz), 36.2, 32.4; ^{19}F NMR (376 MHz) δ -61.7, -105.2; HR MS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{13}ClF_4NO$ 382.0619; Found: 382.0622.

4-[6-Chloro-4-(trifluoromethyl)quinolin-2-yl]-*N*-[(1*S*)-1-phenylethyl]butanamide (3p) was prepared according to the general procedure from *o*-TFMK **1a** (111.8 mg, 0.5 mmol), *N*-[(1*S*)-1-phenylethyl]hex-5-ynamide (**2p**) (129.2 mg, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (30–50% EtOAc/hexanes) to give a white solid

(132.4 mg, 63%). M.p. 161.7–162.8 °C (*n*-heptane); $[\alpha]_D^{23}$ = -26.2 (c = 0.22, $CHCl_3$); IR (KBr) 3282, 3062, 2971, 2925, 2872, 1636, 1543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07–8.03 (m, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.68 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.59 (s, 1H), 7.37–7.22 (m, 5H), 6.25 (br d, *J* = 7.4 Hz, 1H), 5.20–5.10 (m, 1H), 3.05 (t, *J* = 7.3 Hz, 2H), 2.29–2.11 (m, 4H), 1.51 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 161.6, 146.9, 143.3, 134.0 (q, J_{CF} = 31.8 Hz), 133.5, 131.2, 131.1, 128.6, 127.3, 126.2, 123.1 (q, J_{CF} = 273.2 Hz), 122.9 (q, J_{CF} = 2.4 Hz), 122.1, 119.4 (q, J_{CF} = 5.1 Hz), 48.8, 37.5, 35.4, 25.0, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{20}ClF_3N_2ONa$ 443.1114; Found: 443.1108.

3-[6-Chloro-4-(trifluoromethyl)quinolin-2-yl]propyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3q**) was prepared according to the general procedure from *o*-TFMK **1a** (111.8 mg, 0.5 mmol), pent-4-yn-1-yl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**2q**) (207.1 mg, 0.5 mmol), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 100 °C for 48 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (40% MTBE/hexanes) to give a yellow oil (85.5 mg, 28%). Purity based on HPLC: 95% (major peak 6.8 min., LiChrospher® Si60 column, 250 mm x 4.6 mm, 5 µm, DAD detector 254 nm, MTBE/hexane = 20:80; 1.0 mL/min); $[a]_D^{23}$ = 32.7 (c = 1.2, $CHCl_3$); IR (film) 2957, 2937, 1751, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08–8.02 (m, 2H), 7.71 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.63 (br s, 1H), 5.34 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.29 (dd, *J* =11.6, 9.6 Hz, 1H), 5.25 (dd, *J* = 3.2, 1.6 Hz, 1H), 4.82 (d, *J* = 1.6 Hz, 1H), 4.25 (dd, *J*

= 12.0, 5.2 Hz, 1H), 4.06 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.97 (ddd, *J* = 9.6, 5.2, 2.4 Hz, 1H), 3.81 (dt, *J* = 9.8, 6.4 Hz, 1H), 3.57 (dt, *J* = 9.8, 6.4 Hz, 1H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.27–2.16 (m, 2H), 2.15 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 169.8, 169.7, 161.3, 147.1, 133.8 (q, J_{CF} = 31.8 Hz), 133.6, 131.3, 131.2, 123.1 (q, J_{CF} = 273.2 Hz), 122.9 (q, *J* = 2.3 Hz), 122.1, 119.3 (q, *J* = 5.1 Hz), 97.7, 69.6, 69.1, 68.6, 67.5, 66.2, 62.5, 35.2, 28.4, 20.8, 20.6, 20.6, 20.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{29}ClF_3NO_{10}Na$ 642.1330; Found: 642.1315.

(3β)-Cholest-5-en-3-yl 4-[6-chloro-4-(trifluoromethyl)quinolin-2-yl]butanoate (**3r**) was prepared according to the general procedure from *o*-TFMK **1a** (111.8 mg, 0.5 mmol), (3β)-cholest-5-en-3-yl hex-5-ynoate (**2r**) (240.4 mg, 0.5 mmol), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (10% MTBE/hexanes) to give a yellow oil (286.3 mg, 83%). $[a]_D^{23}$ = -15.9 (c = 1.5, $CHCl_3$); Purity based on HPLC: 98% (major peak 8.6 min., LiChrospher® Si60 column, 250 mm x 4.6 mm, 5 µm, DAD detector 208 nm, MTBE/hexane = 5:95; 1.0 mL/min); IR (film) 2948, 2868, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.05 (m, 2H), 7.71 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.61 (s, 1H), 5.39–5.33 (m, 1H), 4.70–4.56 (m, 1H), 3.11–3.02 (m, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 2.35–2.27 (m, 2H), 2.24–2.12 (m, 2H), 2.06–1.76 (m, 5H), 1.65–1.08 (m, 21H) overlapping 1.01 (s, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 1.7 Hz, 3H), 0.87 (d, *J* = 1.7 Hz, 3H), 0.68 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 161.5, 147.2, 139.6, 133.8 (q, J_{CF} = 31.7 Hz), 133.6, 131.4, 131.2, 123.2 (q, J_{CF} = 273.1 Hz), 122.9 (q, J_{CF} = 2.3 Hz), 122.7, 122.1, 119.3 (q, J_{CF} = 5.1 Hz), 74.1, 56.7, 56.2, 50.0, 42.3, 39.7, 39.5, 38.2, 38.0, 37.0, 36.6, 36.2, 35.8, 33.9, 31.9, 31.9, 28.2, 28.0, 27.8, 24.3, 24.3, 23.8, 22.8, 22.6, 21.0, 19.3, 18.7, 11.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{41}H_{56}ClF_3NO_2$ 686.3952; Found: 686.3958.

6-Chloro-2-ferrocenyl-4-(trifluoromethyl)quinoline (**3x**) was prepared according to the general procedure from *o*-TFMK **1a** (111.8 mg, 0.5 mmol), ethynylferocene (**2x**) (126.0 mg, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Th reaction mixture was heated at 100 °C for 16h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (5% Et_2O/hexanes) to give a red solid (138.2 mg, 67%). M.p. 183.2–184.6 ($CHCl_3$, by slow evaporation); IR (KBr) 3103, 3068, 1908, 1792, 1612, 1550, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.0 Hz, 1H), 8.03–8.01 (m, 1H), 7.78 (s, 1H), 7.68 (dd, *J* = 9.0, 2.2 Hz, 1H), 5.08 (t, *J* = 2.0 Hz, 2H), 4.55 (t, *J* = 2.0 Hz, 2H), 4.09 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 147.6, 133.0 (q, J_{CF} = 32.0 Hz), 132.7, 131.3, 131.1., 123.3 (q, J_{CF} = 273.0 Hz), 123.1 (q, J_{CF} = 2.3 Hz), 121.7, 117.0 (q, J_{CF} = 5.3 Hz), 82.3, 71.2, 69.8, 68.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{14}ClF_3NFe$ 416.0116; Found: 416.0100.

(3*S*,4*R*)-3-[(1*R*)-1-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl]-4-{[6-chloro-4-(trifluoromethyl)quinolin-2-yl]methyl}azetidin-2-one (3y) was prepared according to

the general procedure from *o*-TFMK **1a** (111.8 mg, 0.5 mmol), (3*S*,4*R*)-3-{(1*R*)-{[tert-butyl(dimethyl)silyl]oxo}ethyl-4-prop-2-yn-1yl)azetidine-2-one (**2y**) (160.5 mg, 0.6 mmol, 1.1 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). The reaction mixture was heated at 100 °C for 16h. Then reaction mixture was extracted with EtOAc (3 x 3 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (20% EtOAc/toluene) to give a white solid (123.1 mg, 52%). M.p. 129.4–130.3 °C (*n*-heptane); $[a]_D^{23}$ = 41.3 (c = 1.01, $CHCl_3$); IR (film) 3244, 2954, 2930, 2857, 1756, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.04 (m, 1H) overlapping 8.06 (d, *J* = 9.0 Hz, 1H), 7.75 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.58 (s, 1H), 6.17 (br s, 1H), 4.27–4.18 (m, 2H), 3.41 (dd, *J* = 15.1, 4.4 Hz, 1H), 3.29 (dd, *J* = 15.1, 9.0 Hz, 1H), 3.03–2.97 (m, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 158.7, 147.2, 134.2 (q, J_{CF} = 31.9 Hz), 134.1, 131.5, 123.0 (q, J_{CF} = 273.2 Hz), 123.0 (q, J_{CF} = 2.3 Hz), 122.2, 119.4 (q, J_{CF} = 5.1 Hz), 65.6, 64.4, 49.6, 43.5, 25.7, 22.5, 17.9, -4.3, -5.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{29}ClF_3N_2O_2Si$ 473.1639; Found: 473.1638.

17-[6-Chloro-4-(trifluoromethyl)quinolin-2-yl]-3-methoxyestra-1(10),2,4,16-tetraene (**3z**) was prepared according to the general procedure from *o*-TFMK **1a** (72.1 mg, 0.322 mmol, 1.2 eqiuv), 17-ethynyl-3-methoxyestra-1(10),2,4,16-tetraene (**2z**) (78.6 mg, 0.269 mmol), IPr*CuCl (5.4 mg, 5.38 10^{-6} mmol, 2 mol%), TMG (0.67 µL, 0.619 mg, 5.38 10^{-6} mmol, 2 mol%), DME (100 µL) and water (1.1 mL). The reaction mixture was heated at 100 °C for 48 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and

evaporated. The residue was chromatographed on silica (5% MTBE/hexanes, the unreacted *o*-TFMK was separated) to give a mixture of starting alkyne and quinoline derivative **3z**. This mixture of was further separated by reversed-phase column chromatography (MeOH) to give **3z** as a white solid (86.9 mg, 62%). M.p. 96.6–97.7 (crystals were obtained by slow evaporation of DCM solution); $[a]_D^{23}$ = 49.9 (c = 0.72, $CHCl_3$); Purity based on HPLC: 99% (major peak 21.0 min., YMC-Pack Pro C18 column, 250 mm x 4.6 mm, 5 µm, UV detector 254 nm, MeOH; 1.0 mL/min); IR (KBr) 2923, 2851, 1610, 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 1H), 8.05–8.02 (m, 1H), 7.91 (s, 1H), 7.69 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.69–6.64 (m, 2H), 3.80 (s, 3H), 3.04–2.86 (m, 3H), 2.47 (ddd, *J* = 16.4, 6.3, 3.4 Hz, 1H), 2.45–2.29 (m, 2H), 2.25 (ddd, *J* = 16.4, 11.5, 1.2 Hz, 1H), 2.04–1.95 (m, 1H), 1.91–1.40 (m, 5H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 155.1, 154.2, 147.1, 137.9, 135.3, 133.3, 133.0 (q, J_{CF} = 31.5 Hz), 132.9, 132.0, 130.9, 126.1, 123.3 (q, J_{CF} = 273.0 Hz), 122.9 (q, J_{CF} = 2.3 Hz), 121.8, 117.5 (q, J_{CF} = 5.2 Hz), 113.9, 111.5, 56.4, 55.2, 47.9, 44.3, 37.2, 35.4, 32.0, 29.7, 27.8, 26.7, 16.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{28}ClF_3NO$ 498.1812; Found: 498.1816.

2-Cyclopropyl-6-methoxy-4-(trifluoromethyl)quinoline (**5a**) was prepared according to the general procedure from 1-(2-amino-5-methoxyphenyl)-2,2,2-trifluoroethanone (**1b**) (109.6 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 120 °C for 16h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic

phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (2% EtOAc/hexanes) to give a light-yellow oil (89.8 mg, 67%). The reaction conducted on 0.5 mmol scale with IPr*^{OMe}CuCl (10.4 mg, 0.00005 mmol, 2 mol%) afforded product in 82% yield (109.4 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.2 Hz, 1H), 7.47 (s, 1H), 7.37 (dd, J = 9.2, 2.7 Hz, 1H), 7.32–7.27 (m, 1H), 3.93 (s, 3H), 2.27–2.18 (m, 1H), 1.22–1.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 157.8, 145.1, 132.6 (q, J_{CF} = 30.9 Hz), 131.0, 127.2 (q, J_{CF} = 277.1 Hz), 122.5, 117.2 (q, J_{CF} = 5.3 Hz), 102.0 (q, J_{CF} = 2.3 Hz), 55.5, 17.8, 10.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3. ^{1}H NMR spectral data are in agreement with those reported.[64] ^{13}C NMR spectra are described by the authors without C-F coupling constants and the accurate description is provided above. A copy of the spectra is included in the ESI.

2-Cyclopropyl-4-(trifluoromethyl)benzo[*h*]quinoline (**5b**) was prepared according to the general procedure from 1-(1-aminonaphtalene-2yl)-2,2,2-trifluoroethanone (**1c**) (119.6 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 eqiuv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%) and water (2 mL). Reaction mixture was heated at 120 °C for 48 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (5% EtOAc/hexanes) to give a colourless oil (58.1 mg, 40%). IR (KBr) 3092, 3000, 1603, 1560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30–9.23 (m, 1H), 7.98–7.78 (m, 3H), 7.76–7.66 (m, 3H), 2.37–2.28 (m, 1H), 1.43–1.36 (m, 2H), 1.23–1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 147.2, 133.8 (q, J_{CF} = 31.0 Hz), 133.4,

131.1, 128.6, 127.9, 127.6, 127.1, 124.9, 123.8 (q, J_{CF} = 273.1 Hz), 120.8 (q, J_{CF} = 2.5 Hz), 119.5 (q, J_{CF} = 1.4 Hz), 117.3 (q, J_{CF} = 5.4 Hz), 18.1, 11.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{13}F_3N$ 288.1000; Found: 288.0992.

2-Cyclopropyl-6-fluoro-4-(trifluoromethyl)quinoline (**5c**) was prepared according to the general procedure from 1-(2-amino-5-fluorophenyl)-2,2,2-trifluoroethanone (**1d**) (103.4 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (2% EtOAc/hexanes) to give a colourless oil (97.5 mg, 76%). IR (KBr) 3094, 3013, 1931, 1627, 1566, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.71–7.62 (m, 1H), 7.54 (br s, 1H), 7.52–7.44 (m, 1H), 2.30–2.19 (m, 1H), 1.28–1.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J_{CF} = 2.8 Hz), 160.4 (d, J_{CF} = 247.0 Hz), 146.1, 133.6 (dq, J_{CF} = 31.5, 5.6 Hz), 132.0 (d, J_{CF} = 9.2 Hz), 123.4 (q, J_{CF} = 272.8 Hz), 121.9 (d, J_{CF} = 9.4 Hz), 120.1 (d, J_{CF} = 25.4 Hz), 118.0 (q, J_{CF} = 5.2 Hz), 107.9 (dq, J_{CF} = 24.3, 2.2 Hz), 18.0, 10.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.2, -111.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{10}F_4N$ 256.0749; Found: 256.0750.

2-Cyclopropyl-4-(trifluoromethyl)quinoline (**5d**) was prepared according to the general procedure from 1-(2-Aminophenyl)-2,2,2-trifluoroethanone (**1e**) (94.6 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg,

0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 120 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (2% EtOAc/hexanes) to give a colourless oil (89.0 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.01 (m, 2H), 7.75–7.68 (m, 1H), 7.57–7.50 (m, 2H), 2.32–2.25 (m, 1H), 1.28–1.10 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.6. Spectral data are in agreement with those reported.[21]

2-Cyclopropyl-*N*,*N*-dimethyl-4-(trifluoromethyl)quinolin-6-amine (**5f**) was prepared according to the general procedure from 1-[2-Amino-5-(dimethylamino)phenyl]-2,2,2-trifluoroethanone (**1g**) (116.1 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (4 x 2 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica (10–30% EtOAc/hexanes) to give a yellow solid (103.6 mg, 74%). M.p. 75.0–75.4 (*n*-pentane); IR (KBr) 2923, 2852, 1620, 1609, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 9.4 Hz, 1H), 7.37 (s, 1H), 7.39-7.32 (dd, J = 9.4, 2.8 Hz, 1H), 7.02–6.97 (m, 1H), 3.08 (s, 6H), 2.25–2.15 (m, 1H), 1.17–1.09 (m, 2H), 1.09–1.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 148.5, 143.0, 131.5 (q, J_{CF} = 30.5 Hz), 130.1, 124.1 (q, J_{CF} = 272.5 Hz), 123.0, 119.5, 116.9 (q, J_{CF} = 5.4 Hz), 101.2 (q, J_{CF} = 2.2 Hz), 40.5, 17.7, 9.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}F_3N_2$ 281.1266; Found: 281.1268.

2-Cyclopropyl-6-methyl-4-(trifluoromethyl)quinolone (5g) was prepared according to the general procedure from 1-(2-amino-5-methylphenyl)-2,2,2-trifluoroethanone (**1h**) (101.6 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 120 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (2% EtOAc/hexanes) to give a colourless oil which solidified upon standing (102.3 mg, 81%). M.p. 64.3–64.8 (*n*-heptane, -78 °C); IR (KBr) 3092, 3006, 2922, 2867, 1611, 1561, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (br d, J = 8.6 Hz, 1H), 7.81 (br s, 1H), 7.55 (dd, J = 8.6, 1.6 Hz, 1H), 7.47 (s, 1H), 2.55 (s, 3H), 2.30–2.20 (m, 1H), 1.26–1.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 147.5, 136.7, 133.3 (q, J_{CF} = 31.1 Hz), 132.1, 129.3, 123.7 (q, J_{CF} = 272.9 Hz), 122.7 (q, J_{CF} = 2.1 Hz), 121.4, 116.9 (q, J_{CF} = 5.3 Hz), 21.9, 18.0, 10.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{13}F_3N$ 252.1000; Found: 252.1001.

2-Cyclopropyl-6-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-4-(trifluoromethyl)quinoline (**5h**) was prepared according to the general procedure from 1-(2-amino-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}phenyl)-2,2,2-trifluoroethanone (**1i**) (171.7 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (4 x 2 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over Na_2SO_4 and

evaporated. The residue was chromatographed on silica (30–50% EtOAc/hexanes) to give a yellow oil (109.8 mg, 56%). IR (KBr) 2956, 2927, 2871, 1620, 1502cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.1 Hz, 1H), 7.45 (s, 1H), 7.40–7.32 (m, 2H), 4.18 (dd, J = 10.5, 10.5, 4.1 Hz, 1H), 2.28–2.15 (m, 3H), 1.81–1.69 (m, 2H), 1.65–1.46 (m, 2H), 1.19–1.13 (m, 3H), 1.13–1.05 (m, 3H), 1.00–0.97 (m, 1H), 0.95 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H) 0.79 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 156.6, 144.9, 132.5 (q, J_{CF} = 30.8 Hz), 131.0, 123.8 (q, J_{CF} = 272.9 Hz), 123.1, 122.6, 117.1 (q, J_{CF} = 5.3 Hz), 104.8 (q, J_{CF} = 2.2 Hz), 78.2, 48.1, 40.1, 34.5, 31.4, 26.2, 23.7, 22.1, 20.7, 17.8, 16.6, 10.2, 10.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{23}H_{29}F_3NO$ 392.2201; Found: 392.2198.

2-Cyclopropyl-4-(trifluoromethyl)-1,8-naphthyridine (**5i**) was prepared according to the general procedure 1-(2-aminopyridin-3-yl)-2,2,2-trifluoroethanone (**6a**) (95.0 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*^{OMe}CuCl (10.4 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100 µL) and water (2 mL). Reaction mixture was heated at 120 °C for 16 h. Then reaction mixture was extracted with EtOAc (4 x 2 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica (30% EtOAc/hexanes) to give an orange solid (93.7 mg; 79%). M.p. 71.3–71.8 °C (*n*-pentane); IR (KBr) 3078, 3004, 1622, 1599, 1507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (dd, J = 2.4 Hz, J = 1.7 Hz, 1H), 8.45–8.38 (m, 1H), 7.68 (s, 1H), 7.49 (dd, J = 8.4, 4.2 Hz, 1H), 2.34–2.25 (m, 1H), 1.48–1.42 (m, 2H), 1.24–1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 156.5, 153.9, 134.9 (q, J_{CF} = 31.8 Hz), 133.3 (q, J_{CF} = 2.0 Hz), 123.0 (q, J_{CF} = 273.4 Hz), 121.9, 119.0 (q, J_{CF} = 5.0 Hz), 116.2,

18.6, 12.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.0; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_9F_3N_2Na$ 261.0616; Found: 261.0614.

6-Chloro-2-Cyclopropyl-4-(trifluoromethyl)-1,8-naphthydrine (**5k**) was prepared according to the general procedure from 1-(2-amino-5-chloropyridin-3-yl)-2,2,2-trifluoroethanone (**6c**) (101.5 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%) and water (2 mL). Reaction mixture was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (10% Et_2O/*n*-pentane) to give a colourless oil which solidified upon standing in the fridge (68.2 mg, 50%). M.p. 93.0–94.4 °C (crystals were obtained by slow evaporation of DCM solution; attempts to crystalize quinoline **5k** from *n*-heptane, *n*-pentane, or its mixture with EtOH, Et_2O has failed); IR (film) 3088, 3069, 3011, 1611, 1478 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 2.5 Hz, 1H), 8.37–8.32 (m, 1H), 7.70 (s, 1H), 2.34–2.23 (m, 1H), 1.48–1.38 (m, 2H), 1.27–1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 154.5, 153.2, 134.2 (q, J_{CF} = 32.1 Hz), 131.6 (q, J_{CF} = 2.2 Hz), 129.5, 122.7 (q, J_{CF} = 273.2 Hz), 119.8 (q, J_{CF} = 5.0 Hz), 116.4, 18.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9F_3N_2Cl$ 273.0406; Found: 273.0407.

2-Cyclopropyl-4-(trifluoromethyl)-1,6-naphthyridine (**5l**) was prepared according to the general procedure from 1-(4-aminopyridin-3-yl)-2,2,2-trifluoroethanone (**6b**) (95.0 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*^{OMe}CuCl (10.4 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), DME (100

μL) and water (2 mL). Reaction mixture was heated at 120 °C for 16 h. Then reaction mixture was extracted with EtOAc (4 x 2 mL), and the combined organic phases were washed with brine (1 x 20 mL), dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica (1.5–3% acetone/DCM) to give an orange solid (49.2 mg, 41%). M.p. 118.2–118.9 °C (*n*-pentane); IR (KBr) 3015, 1613, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.78 (d, *J* = 5.8 Hz, 1H), 7.83 (d, *J* = 5.8 Hz, 1H), 7.62 (s, 1H), 2.33–2.26 (m, 1H), 1.41–1.29 (m, 2H), 1.29–1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 151.2, 148.9 (q, J_{CF} = 3.0 Hz), 147.6, 134.2 (q, J_{CF} = 32.9 Hz), 122.9 (q, J_{CF} = 273.3 Hz), 122.0, 118.8 (q, J_{CF} = 5.2 Hz), 117.0, 18.8, 12.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 ; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{10}F_3N_2$ 239.0796; Found: 239.0794.

6-Chloro-2-cyclopropyl-4-(heptafluoropropyl)quinolone (**5m**) was obtained according to the general procedure from ketone 1-(2-amino-5-chlorophenyl)-2,2,3,3,4,4,4-heptafluorobutan-1-on (**1j**) (161.8 mg, 0.5 mmol), TMG (1.25 μL, 0.01 mmol, 2 mol%), cyclopropylacetylene **2a** (55.0 μL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.2 mg, 0.01 mmol, 2 mol%), water (2 mL) and DME (0.1 mL). The reaction mixture was heated at 120 °C for 16h. The crude product was chromatographed on silica (5% Et_2O/*n*-pentane) to give quinoline **5m** as a colourless oil (54.3 mg, 29%, 92% based on recovered starting ketone) and unreacted substrate (72.3 mg). Additional experiments were conducted with 2 mol% of IPr*^{OMe}CuCl to afford product **5m** with 51% (94.6 mg, after 16h at 120 °C) and 56% (103.6 mg, after 48h at 120 °C) and 5 mol% of IPr*^{OMe}CuCl (126.3 mg of **5m**, 68%). IR (film) 3011, 1604, 1557, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07–8.01 (m, 1H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.65 (dd, *J* = 9.0, 2.2

Hz, 1H), 7.50 (s, 1H), 2.30–2.20 (m, 1H), 1.28–1.11 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 147.6, 132.8, 132.0 (t, J_{CF} = 22.8 Hz), 131.4, 130.8, 123.3–123.6 (m), 123.0, 121.0 (t, J_{CF} = 8.6 Hz), 18.0, 11.2. Signals in the region of 120–102 ppm has been omitted in description of spectra for clarity due to complicated multiplicity; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.8 (t, J = 10.2 Hz), -107.8 — -108.0 (m), -124.7 – -124.8 (m); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{10}ClF_7N$ 372.0390; Found: 372.0380.

6-Chloro-2-cyclopropyl-4-(difluoromethyl)quinolone (**5n**) was prepared according to the general procedure from 1-(2-amino-5-chlorophenyl)-2,2-difluoroethanone (**1k**) (102.8 mg, 0.5 mmol), cyclopropylacetylene (**2a**) (51.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), water (2 mL) and DME (0.1 mL). Reaction mixture was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (5% EtOAc/hexanes) to give a colourless oil (68.7 mg, 54%). Additional experiment was conducted on the same scale at 100 °C for 48 h to give a quinoline **5n** with 73% (92.6 mg). M.p. 63.7–64.1; IR (film) 3090, 3013, 2972, 1743, 1613 1557 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.91 (m, 2H), 7.63 (dd, J = 9.0, 2.2 Hz, 1H), 7.39 (br s, 1H), 7.02 (t, J_{HF} = 54.5 Hz, 1H), 2.29–2.19 (m, 1H), 1.27–1.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 147.0, 136.7 (t, J_{CF} = 21.6 Hz), 132.1, 131.1, 130.6, 123.1 (t, J_{CF} = 2.8 Hz), 122.3, 117.9 (t, J_{CF} = 7.7 Hz), 113.4 (t, J_{CF} = 239.2 Hz), 18.1, 10.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9; HRMS (EI) *m/z*: $[M^{\bullet+}]$ Calcd for $C_{13}H_{10}F_2NCl$ 253.0470; Found: 253.0491.

3-[6-Chloro-4-(difluoromethyl)quinolin-2-yl]propan-1-ol (**5o**) was prepared according to the general procedure from 1-(2-Amino-5-chlorophenyl)-2,2-difluoroethanone (**1k**) (102.8 mg, 0.5 mmol), pent-4-yn-1-ol (**2l**) (56.0 µL, 0.6 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), water (2 mL) and DME (0.1 mL). Reaction mixture was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (50–75% EtOAc/hexanes) to give a light-yellow oil which solidified upon standing (96.4 mg, 71%). The experiment was conducted on the same scale at 100 °C for 48 h, affording product **5o** with 77% (104.1 mg) yield. M.p. 75.5–76.8 (*n*-pentane); IR (KBr) 3252, 2950, 2925, 2858, 1620, 1567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06–7.99 (m, 2H), 7.70 (dd, J = 9.0 , 2.3 Hz, 1H), 7.52 (br s, 1H), 7.05 (t, J_{HF} = 54.4 Hz, 1H), 3.77 (t, J = 7.7 Hz, 2H), 3.23 (br s, 1H, OH) overlapping 3.19 (t, J = 7.0 Hz, 2H), 2.18–2.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 146.4, 137.6 (t, J_{CF} = 21.8 Hz), 133.2, 131.0, 131.0, 123.2 (t, J_{CF} = 2.7 Hz), 122.4 (t, J_{CF} = 1.4 Hz), 119.6 (t, J_{CF} = 7.6 Hz), 113.2 (t, J_{CF} = 239.5 Hz), 62.3, 36.0, 31.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}F_2NOCl$ 272.0654; Found: 272.0646.

3(β)-Cholest-5-en-3-yl [4-(6-Chloro-4-(difluoromethyl)quinolin-2-yl]butanoate (**5p**) was prepared according to the general procedure from 1-(2-amino-5-chlorophenyl)-2,2-difluoroethanone (**1k**) (102.8 mg, 0.5 mmol), (3β)-cholest-4-en-3yl hex-5-ynoate (**2r**) (280.1 mg, 0.58 mmol, 1.2 equiv), IPr*CuCl (10.1 mg, 0.00005 mmol, 2 mol%), TMG (1.25 µL, 0.00005 mmol, 2 mol%), water (2 mL) and DME (0.1 mL). Reaction mixture

was heated at 100 °C for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL), and combined organic phases were washed with brine (1 x 20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (10% MTBE/hexanes). Thus obtained mixture of steroidal alkyne and product **5p** was subjected to chromatography on RP-18 silica (MeOH) to give a white solid (173.9 mg, 52%). $[a]_D^{23}$ = -13.1 (c = 1.32, MeOH/$CHCl_3$ 1/1); M.p. 110.5–111.7 (attempts to crystalize quinoline **5p** failed; compound does not dissolved in common organic solvents – DCM, EtOH, MeOH, DMSO, DMF, hexanes, MeCN, MTBE, Et_2O; slightly soluble in $CHCl_3$ – ca. 2 mg/5 mL); IR (film) 3439, 2947, 2868, 1729, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.1 Hz, 1H), 8.04–8.01 (m, 1H), 7.69 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.49 (s, 1H), 7.05 (t, *J* = 54.4 Hz, 1H), 5.39–5.34 (m, 1H), 4.69–4.55 (m, 1H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 2.34–2.26 (m, 2H), 2.23–2.13 (m, 2H), 2.05–1.92 (m, 5H), 1.90–1.77 (m, 5H), 1.62–0.86 (m, 16H) overlapping 1.01 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 161.8, 146.9, 139.6, 137.3 (t, J_{CF} = 22.0 Hz), 131.4, 130.8, 123.3 (t, J_{CF} = 2.5 Hz), 122.7, 122.4, 119.4 (t, J_{CF} = 7.6 Hz), 113.3 (t, J_{CF} = 239.4 Hz), 74.1, 56.7, 56.2, 50.1, 42.3, 39.8, 39.5, 38.2, 38.1, 37.0, 36.6, 36.2, 35.8, 34.0, 31.9, 31.9, 29.7, 28.2, 28.0, 27.8, 24.5, 24.3, 23.8, 22.8, 22.6, 21.0, 19.3, 18.7, 11.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{41}H_{57}F_2NO_2Cl$ 668.4046; Found: 668.4043.

Synthesis of dibenzo[b,f][1,5]diazocines

2,8-Dichloro-6,12-bis(trifluoromethyl)-5,6,11,12-tetrahydro-6,12-epoxydibenzo[*b,f*][1,5]diazocine (**4a**) 1-(2-Amino-5-chlorophenyl)-2,2,2-

trifluoroethanone (**1a**) (223.6 mg, 1.0 mmol), TMG (25.1 µL, 0.2 mmol, 20 mol%) and water (2 mL) were placed in a screw-cap 4 mL vial and heated at 100 °C (temp. of oil bath) for 16 h. Then reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica (5% EtOAc/hexanes). Compound **4a** was isolated as a yellow oil (141.2 mg, 66%) which spontaneously solidified upon standing in the fridge. M.p. 217–220 °C (EtOAc; by slow evaporation); IR (film) 3379, 3350, 1610 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (s, 2H), 7.22 (dd, J = 8.6, 2.3 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.90 (br s, NH, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 130.9, 127.6, 125.6 (q, $J_{C\text{-}F}$ = 32.0 Hz), 122.4 (q, $J_{C\text{-}F}$ = 282.5 Hz), 121.4, 120.8, 82.9 (q, J = 32.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -79.1. HRMS (ESI-TOF) *m/z*: $[M\text{-}H]^-$ Calcd for $C_{16}H_7Cl_2F_6N_2O$ 426.9840; Found: 426.9845. Spectral data are in agreement with those reported.[31]

2,8-Fluoro-6,12-bis(trifluoromethyl)-5,6,11,12-tetrahydro-6,12-epoxydibenzo[*b*,*f*][1,5]diazocine (**4b**) 1-(2-Amino-5-fluorophenyl)-2,2,2-trifluoroethanone (**1d**) (207.1 mg, 1.0 mmol), Et_3N (28 µl, 0,2 mmol), TMG (25.1 µL, 0.2 mmol, 20 mol%) and water (2 mL) were placed in a screw-cap 4 mL vial and heated at 100 °C (temp. of oil bath) for 16 h. Then reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica (5% EtOAc/hexanes). Compound **4b** was isolated as a yellow oil (154.7 mg, 78%) which spontaneously solidified upon standing in the fridge. M.p. 169.1–169.5 °C (DCM; by slow evaporation); IR (film) 3426, 3370, 3328, 1891, 1725, 1499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.17 (m, 2H), (ddd, J = 8.9, 7.9, 2.8 Hz, 2H), 6.86 (dd, J = 8.9, 4.9

Hz, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (d, J_{CF} = 241.1 Hz), 135.9 (d, J_{CF} = 2.4 Hz), 122.5 (q, J_{CF} = 282.3 Hz), 121.7 (d, J_{CF} = 7.8 Hz), 121.6 (d, J_{CF} = 7.2 Hz), 118.2 (d, J_{CF} = 23.0 Hz), 112.6 (dq, J_{CF} = 24.5, 3.2 Hz), 83.4 (dq, J_{CF} = 32.0, 2.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.3, -118.8; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{16}H_7F_8N_2O$ 395.0431; Found: 395.0439.

Synthesis of fluorinated analogue of G protein-coupled receptor antagonist (GPR91)

Ethyl 4-[4-(trifluoromethyl)-1,8-naphthyridin-2-yl]butanoate (**5j**) was prepared according to the general procedure 1-(2-aminopyridin-3-yl)-2,2,2-trifluoroethanone (**6a**) (1.33 g, 7.0 mmmol), ethyl hex-5-ynoate (**7**) (1.18 g, 8.4 mmol, 1.2 equiv), IPr*^{OM}CuCl (145.6 mg, 0.14 mmol, 2 mol%), TMG (17.5 µL, 0.14 mmol, 2 mol%), water (28 mL) and DME (1.4 mL). Reaction mixture was heated at 120 °C for 20 h. Then reaction mixture was extracted with EtOAc (4 x 20 mL), and combined organic phases were washed with brine (1 x 20 mL), dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica (30–50% EtOAc/hexanes) to give an orange oil (1.61 g, 74%). IR (film) 2981, 2938, 1732, 1621, 1601 1555, 1504 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20–9.10 (m, 1H), 8.44 (d, *J* = 8.3 Hz, 1H), 7.66 (s, 1H), 7.58-7.52 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.14 (t, *J* = 7.4 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.31–2.19 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 165.2, 156.2, 154.1, 135.6 (q, J_{CF} = 31.9 Hz), 133.2 (q, J_{CF} = 2.0 Hz), 122.9 (q, J_{CF} = 273.3 Hz), 122.6, 119.5 (q, J_{CF} = 4.9 Hz), 116.4, 60.3, 38.2, 33.5, 23.9, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.9; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{15}F_3N_2O_2Na$ 335.0983; Found: 335.0976.

Methyl 4'-cyano-3,3'-difluorobiphenyl-2-carboxylate (11) To a solution of nitrile **8** (4.0 g, 20.0 mmol) in anhydrous DME (25 mL), cooled to -20 °C, commercially available solution of *i*-PrMgCl•LiCl (14.6 mL, 19.0 mmol, 1.3M in THF) was added (the colour of the reaction mixture changed from light-yellow to deep orange). After 15 min, a freshly prepared solution of CuCN•2LiCl in THF (by mixing of CuCN - 1.62 g, 18.0 mmol and LiCl - 1.53 g, 36 mmol in THF – 25 mL) was added dropwise (the colour of the reaction mixture changed from deep orange to green) and stirred for additional 15 min at -20 °C. In a separate Schlenk tube, a solution of iodoester **10** (1.82 g, 6.5 mmol) and $Fe(acac)_3$ (230.0 mg, 0.65 mmol, 10 mol%) in anhydrous DME (15 mL) was prepared and slowly added to the organocopper compound **9**. The resulting mixture was stirred at 80 °C (temp. of oil bath) for 20 h. Then reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine (1 x 100 mL), dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica (15–30% MTBE/hexanes) giving a yellow solid (1.45 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 1H), 7.58–7.50 (m, 1H), 7.30–7.14 (m, 4H), 3.76 (s, 3H); CAS registry number 1026635-99-3; no spectroscopic data are available for comparison.

[3,3'-Difluoro-2'-(methoxycarbonyl)biphenyl-4-yl]methanaminium chloride (12) To a solution of nitrile **11** (1.43 g, 5.23 mmol) in anhydrous MeOH (100 mL), a solution of HCl in MeOH (6.25 mL, 1.5 equiv, 1.25 M in MeOH) and 10% Pd/C (278 mg, 0.26 mmol, 5 mol%) were added. The flask was evacuated (water aspirator) and back-filled with hydrogen (3 times) and the reaction mixture was vigorously stirred at rt under atmosphere of hydrogen (balloon). After 16h, argon was purged through the reaction

mixture for 10 min. and then it was filtered through a pad of celite (washing with MeOH). Then, the solvent was evaporated and the residue was treated with MTBE (50 mL), heated to reflux for 15 min. and filtered while hot. The obtained solid was washed with MTBE (2 x 10 mL) and dried in vacuo to afford hydrochloride **12** as an off-white solid (1.13 g, 69%). M.p. 210.1–210.5 °C; IR (KBr) 2970, 2951, 2909, 2875, 2707, 2627, 2021, 1741, 1627, 1609, 1568, 1508 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (br s, 3H), 7.79–7.58 (m, 2H), 7.48–7.16 (m, 4H), 4.09 (br s, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 160.0 (d, J_{CF} = 246.3 Hz), 158.8 (d, J_{CF} = 247.1 Hz), 141.0 (dd, J_{CF} = 8.0, 2.0 Hz), 139.6, 132.4 (d, J_{CF} = 9.1 Hz), 131.6 (d, J_{CF} = 3.7 Hz), 125.9 (d, J_{CF} = 2.8 Hz), 124.1 (d, J_{CF} = 3.0 Hz), 121.0 (d, J_{CF} = 32.5 Hz), 120.8 (d, J_{CF} = 35.1 Hz), 115.5 (d, J_{CF} = 21.2 Hz), 114.9 (d, J_{CF} = 22.7 Hz), 52.7, 35.3 (d, J_{CF} = 4.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ -115.7, -116.3; Anal. Calcd for $C_{15}H_{14}ClF_2NO_2 \cdot 1/2H_2O$: C, 55.82; H, 4.68; N, 4.34 Found: C, 55.84; H, 4.74; N, 4.67; HRMS (ESI-TOF) *m/z*: $[M\text{-}Cl]^+$ Calcd for $C_{15}H_{14}F_2NO_2$: 278.0993; Found: 278.0984.

Lithium 4-[4-(trifluoromethyl)-1,8-naphthyridin-2-yl]butanoate To a solution of ester **5j** (1.0 g, 3.2 mmol) in a mixture of THF (50 mL) and water (2 mL), $LiOH \cdot H_2O$ (268.5 mg, 6.4 mmol, 2.0 equiv) was added at rt and stirred for 16 h. Then, the solvent was evaporated and the residue was dried in vacuo for 16 h to give a yellow solid (928.5 mg). The resulting lithium salt was used in the next step without further purification and can be stored for a long time without decomposition under argon atmosphere.

Methyl 3,3'-difluoro-4'-[({4-[4-(trifluoromethyl)-1,8-naphthyridin-2-yl]butanoyl}amino)methyl]biphenyl-2-carboxylate (13) To a solution of lithium 4-[4-(trifluoromethyl)-1,8-naphthyridin-2-yl]butanoate (863.0 mg, 2.97 mmol) in anhydrous

DMF (60 mL), HOBt (683.3 mg, 4.46 mmol, 1.5 equiv) was added and stirred for 15 min. (until all of the solid has dissolved). Then, amine hydrochloride **12** (977.4 mg, 3.12 mmol, 1.05 eq) was added and stirred at rt. After 15 min., the reaction mixture was cooled to 0 °C and EDC•HCl (854.0 mg, 4.46 mmol, 1.5 equiv) was added in one portions (colour of the reaction mixture changed from yellow to light-green). After additional 15 min. DIPEA (1.54 mL, 8.91 mmol, 3.0 equiv) was added, the cooling bath was removed and the resulting reaction mixture was stirred at rt for 16 h. The reaction mixture was cooled to 0 °C and water was slowly added (50 mL). The resulting mixture was diluted with EtOAc (30 mL), and the organic phase was separated, washed with water (2 x 75 mL), brine (7 x 50 mL), dried over Na_2SO_4 and the solvents were evaporated. The residue was chromatographed on silica (1–3% MeOH/DCM) to give an off-white gummy solid (1.013 g, 63%, after 2 steps). IR (film) 3291, 3060, 2952, 1736, 1657, 1555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (br d, J = 2.6 Hz, 1H), 8.42 (d, J = 8.3 Hz, 1H), 7.68 (s, 1H), 7.53 (dd, J = 8.4, 4.2 Hz, 1H), 7.43–7.32 (m, 2H), 7.12–7.96 (m, 4H), 6.89–6.82 (m, 1H), 4.50 (d, J = 5.7 Hz, 2H), 3.66 (s, 3H), 3.14 (t, J = 7.3 Hz, 2H), 2.42 (t, J = 7.1 Hz, 2H), 2.32–2.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 165.8, 165.4, 160.5 (d, J_{CF} = 245.8 Hz), 159.6 (d, J_{CF} = 250.0 Hz), 155.9, 153.9, 140.7 (dd, J_{CF} = 2.0, 2.0 Hz), 140.3 (dd, J_{CF} =8.1, 2.2 Hz), 135.6 (q, J_{CF} = 31.2 Hz), 133.3, 131.3 (d, J_{CF} = 8.9 Hz), 130.1 (d, J_{CF} = 4.8 Hz), 126.3 (d, J_{CF} = 1.3 Hz), 125.2 (d, J_{CF} = 10.3 Hz), 124.0 (d, J_{CF} = 3.2 Hz), 122.6, 122.8 (q, J_{CF} = 273.5 Hz), 121.3 (d, J_{CF} = 17.0 Hz), 119.7 (q, J_{CF} = 4.9 Hz), 116.4, 115.2 (d, J_{CF} = 4.7 Hz), 114.9 (dd, J_{CF} = 3.5 Hz), 52.4, 38.0, 37.0 (d, J_{CF} = 3.7 Hz), 35.3, 24.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.9, -

114.8, -118.5; HRMS (EI) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{22}F_5N_3O_3Na$ 566.1479, Found: 566.1477.

Dimethyl 4',4''-(iminodimethanediyl)bis(3,3'-difluorobiphenyl-2-carboxylate) (19) To a solution of nitryle **11** (1.25 g, 4.57 mmol) in MeOH (15 mL), ammonia (5.5 mL) and freshly prepared Raney Nickel (2.5 g) were added and vigorously stirred for 16h at rt. Then reaction mixture was filtered through pad of celite (washing with MeOH), solvent was evaporated and the residue was chromatographed on silica (40-50% EtOAc/hexanes) to give a colourless oil (432.8 mg, 35 %). IR (film) 3348, 3003, 2952, 2845, 1736, 1612, 1567, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.40 (m, 4H), 7.20–7.04 (m, 8H), 3.92 (s, 4H), 3.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 160.9 (d, J_{CF} = 245.2 Hz), 159.6 (d, J_{CF} = 250.0 Hz), 140.9 (dd, J_{CF} = 2.3, 2.3 Hz), 140.0 (d, J_{CF} = 8.2, 2.3 Hz), 131.3 (d, J_{CF} = 8.9 Hz), 130.3 (d, J_{CF} = 5.3 Hz), 126.6 (d, J_{CF} = 14.9 Hz), 125.3 (d, J_{CF} = 3.1 Hz), 123.9 (d, J_{CF} = 31.8 Hz), 115.1 (d, J_{CF} = 23.0 Hz), 114.9 (d, J_{CF} = 9.1 Hz), 52.4, 46.3 (d, J_{CF} = 2.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8, -118.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{24}NO_4F_4$ 538.1641; Found: 538.1636.

Associated content

Supporting Information Available

Detailed experimental procedures for the synthesis of substrates, copies of ^1H, ^{13}C and ^{19}F NMR spectra for all compounds and HPLC data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The author declare no competing financial interest.

Acknowledgment

This research was supported by Polish Ministry of Science and Higher Education (grant Iuventus Plus IP2012 064172). We are grateful to Dr. Wioletta Kośnik for a helpful and critical discussion during the preparation of the manuscript.

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