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Electrophilic trifluoromethylation of arenes and N-heteroarenes using hypervalent iodine reagents

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ABSTRACT

The reaction of hypervalent iodine trifluoromethylating reagents with a variety of arenes and N-heteroarenes gives access to the corresponding trifluoromethylated compounds. In comparative studies, 1-trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (**2**) proved to be the superior to 1-trifluoromethyl-1,2-benziodoxol-3-(^{1}H)-one (**1**) for the direct aromatic trifluoromethylation. Depending on the individual substrates, additives such as zinc bis(trifluoromethylsulfonyl)imide or tris(trimethylsilyl)silyl chloride proved helpful in promoting the reactions. In the case of nitrogen heterocycles a pronounced tendency for the incorporation of the trifluoromethyl group at the position adjacent to nitrogen was observed.

1. Introduction

Organofluorine compounds are of great interest in material sciences and play an important role as active pharmaceutical ingredients and crop protecting agents. Fluorinated drugs nowadays make up ca. 20% of all newly marketed pharmaceuticals and at least 30% of all agrochemicals [1]. Apart from single fluorine atoms, trifluoromethyl groups especially at aromatic positions are the most important fluorine-containing units used in the design of new potential drugs and crop protection agents. Popular examples of bioactive aromatics and heteroaromatics bearing CF_3 substituents are the antidepressant Fluoxetine (Prozac®), the malaria agent Mefloquine (Lariam®) and the insecticide Chlorfenapyr (Fig. 1). Therefore, development of new methods for trifluoromethylation of aromatic and heteroaromatic compounds is an important task.

Main strategies for the direct introduction of CF_3 groups are based on the use of nucleophilic transfer reagents such as (trifluoromethyl)trimethylsilane ($TMSCF_3$, Ruppert-Prakash reagent) [2]. In contrast, trifluoromethylation requiring an electrophilic approach [3] has proven to be very challenging, though advances have been achieved recently. So far two principal classes of reagents showed their potential for electrophilic CF_3 transfer: trifluoromethyl chalcogenium salts [4] initially introduced by Yagupolskii and extensively explored by Umemoto and hypervalent iodine derivatives developed by our group [5]. The latter reagents can be easily prepared from 2-iodobenzoic acid and can be used for the trifluoromethylation of a variety of nucleophiles (Scheme 1). The results of our previous studies on the trifluoromethylation of various substrates reveal a general trend in the activity of both reagents suggesting that benziodoxolone **1** is usually more suitable in reactions with harder reactants such as alcohols and sulfonic acids, while dimethyl benziodoxole **2** shows higher activity with softer sulfur, phosphorous and carbon nucleophiles [6].

In general, the introduction of CF_3 units into aromatic systems is not trivial. The trifluoromethylation of electron-rich aromatic compounds such as phenol or aniline has been achieved upon reaction with trifluoromethanesulfinate salts [7], or under radical reaction conditions using CF_3Br [8]. Most aromatic CF_3 building blocks are synthesized by treatment of corresponding benzoic acid derivatives with sulfur tetrafluoride [9], or with the newly developed phenylsulfur trifluoride [10] or by halogen exchange reactions of trichloromethyl arenes using Lewis acids and HF as fluoride source [11]. However, such reaction conditions are not compatible with a large number of functional groups, thus amply justifying the search for mild and reliable methods for a direct trifluoromethylation, i.e. involving the transfer of an intact CF_3 group from a suited source. Benziodoxole **2** has been used very recently by MacMillan and co-worker in the organocatalytic trifluoromethylation of aldehydes [12] and by Yu and co-workers in the Pd-catalyzed ortho-trifluoromethylation of arenes [13].

In the course of a systematic study of the reactivity of our new reagents **1** and **2** toward a variety of potential nucleophilic CF_3 acceptors we investigated a series of representative arenes and heterocyclic compounds as substrates. While we have found that

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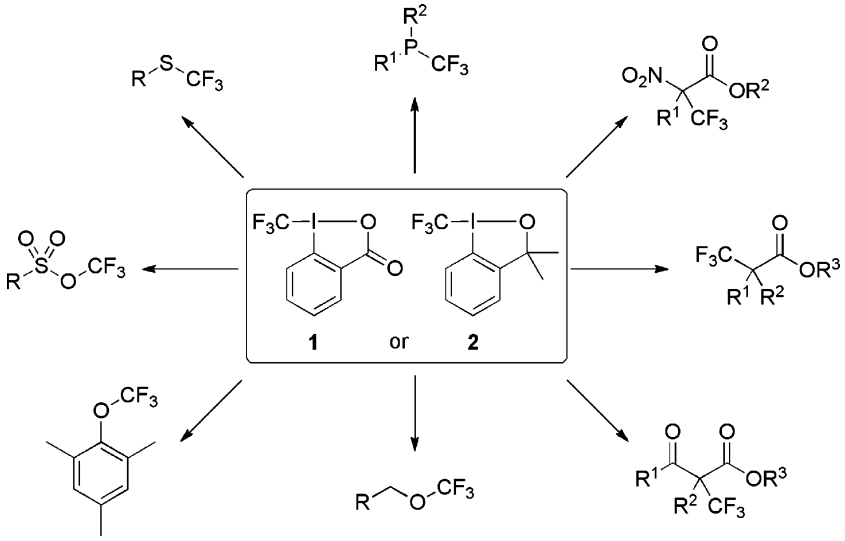


Scheme 1. Application of hypervalent iodine trifluoromethylation reagents **1** and **2**.

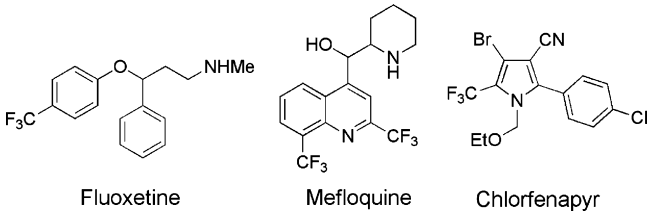


Fig. 1. Examples of aromatic and heteroaromatic trifluoromethylated drugs.

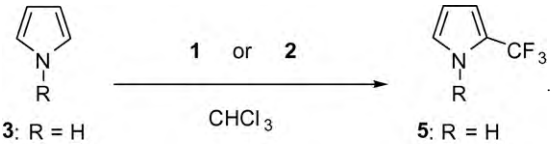
the reactivity is quite broad and trifluoromethylation indeed occurs, the use of this reaction as a method for the efficient and high-yield synthesis of specific target compounds is less general.

2. Results and discussion

In a first screening, we compared the reactivity of both reagents in the reaction with the electron-rich substrates pyrrole and N-phenylpyrrole [14] (Table 1). Chloroform was chosen as the solvent ensuring good solubility of both reagent and substrates. While the transformation of pyrrole (**3**) gave trifluoromethylated compound **5** in very good yield within 5 h in both cases (with a slightly better result using **2**, entries 1, 2), the reaction with N-phenyl pyrrole (**4**) revealed a clear difference between the reactivities of the two reagents. Using benziodoxolone **1**, no CF_3 transfer was observed. Longer reaction times or higher temperature led mainly to decomposition of the reagent (entries 3–5). In contrast, trifluoromethylation was successful when dimethyl benziodoxole **2** was used. The best result was achieved using a slight excess of the reagent (1.5 equiv.) at 60 °C giving 1-phenyl-2-(trifluoromethyl)-pyrrole (**6**) in 76% yield (entry 9). These results indicate that the softer reagent **2** is more prone to react with soft nucleophiles, such as aromatic systems, than the harder benziodoxolone **1**, this going along with our previous observations on the comparative reactivity of both reagents. Moreover, after the initial screening it became clear that only electron-rich aromatic compounds such as pyrrole may be trifluoromethylated at room temperature, whereas less reactive systems require additional activation for the reaction to take place. Elevated temperature is a possible solution, however, it also favors decomposition of the reagent, at least to some extent. It has previously been shown in our group that zinc salts can significantly improve the yields in trifluoromethylation reactions of aliphatic alcohols [6d]. Therefore, we decided to carry out an additional screening involving selected zinc Lewis acids as additives promoting the reaction of N-phenylpyrrole (**4**) as the model substrate (Table 2).

In line with the results obtained for the trifluoromethylation of alcohols, good to excellent yields were achieved when excess of the pyrrole derivative was used with either one of the zinc additives (entries 1–3). However, in terms of adjusting the procedure for potential applications it is preferable to avoid using excess of the starting material. Thus, when the substrate was used in equimolar or substoichiomeric amounts, the yields dropped significantly in the case of the additive $Zn(NTf_2)_2$. At the same time, formation of a stable intermediate was observed by ^{19}F NMR spectroscopy in form of a broad signal, probably originating from a complex formed by $Zn(NTf_2)_2$ and the reagent [6d]. The intermediate slowly decomposed to give mainly volatile HCF_3, which was detected by ^{19}F NMR spectroscopy, and the fluorinated target compound in moderate yields (entries 4 + 5). A similar intermediate complex was observed with $ZnBr_2$ after 24 h, however, this complex further reacted to give 1-phenyl-2-(trifluoromethyl)pyrrole (**6**) in almost quantitative yield after 48 h.

Table 1
Comparison of reagents **1** and **2** in the trifluoromethylation of pyrrole (**3**) and N-phenylpyrrole (**4**).



Entry	Substrate	Reagent (equiv.)	T [°C]	t [h]	Yield [%][a]
1	**3**	**1** (1.0)	20	5	89
2	**3**	**2** (1.0)	20	5	92 (87)
3	**4**	**1** (1.0)	20	24	0[b]
4	**4**	**1** (1.0)	20	120	0[c]
5	**4**	**1** (1.0)	60	24	7[c]
6	**4**	**2** (1.0)	20	24	5[b]
7	**4**	**2** (1.0)	20	120	25
8	**4**	**2** (1.0)	60	24	58
9	**4**	**2** (1.5)	60	24	76 (38)

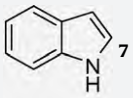
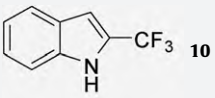
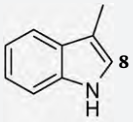
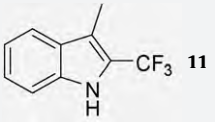
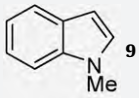
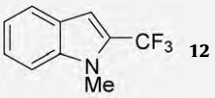
[a] Yields were determined by ^{19}F NMR using $C_6H_5CF_3$ as internal standard. Numbers in brackets are isolated yields.
[b] Reaction not complete, >90% of the reagent not consumed.
[c] Decomposition of the reagent.

Table 2
Zinc-mediated trifluoromethylation of N-phenylpyrrole (**4**).

Entry	Ratio s/r[a]	Additive (equiv.)	T [°C]	t [h]	Yield [%][b]
1	10:1	$Zn(NTf_2)_2$ (1.0)	20	24	>99
2	3:1	$Zn(NTf_2)_2$ (1.0)	20	24	>99
3	3:1	$ZnBr_2$ (1.0)	20	24	79
4	1:1	$Zn(NTf_2)_2$ (1.0)	20	24	23[c]
5	1:2	$Zn(NTf_2)_2$ (0.5)	20	48	25[c]
6	1:2	$ZnBr_2$ (0.5)	20	48	96 (89)

[a] Molar ratio substrate **4**/reagent **2**.
[b] Yields – based on the limiting component – were determined by ^{19}F NMR using $C_6H_5CF_3$ as internal standard. Numbers in brackets are isolated yields.
[c] Formation of a stable intermediate, see text.

Table 3
Trifluoromethylation of different indoles **7**–**9**.

Entry	Substrate	Reagent [equiv.]	Additive [equiv.]	T [°C]	t [h]	Product	Yield [%][a]
1	 **7**	1.5	–	80	24	 **10**	30 (30)
2		2.0	$Zn(NTf_2)_2$ (0.5)	20	48		25
3		2.0	$Zn(NTf_2)_2$ (0.5)	60	24		27
4		2.0	$ZnBr_2$ (0.5)	60	24		22
5	 **8**	1.5	–	80	48	 **11**	71 (53)
6		2.0	$ZnBr_2$ (0.5)	20	24		64
7		2.0	$ZnBr_2$ (0.5)	80	24		94
8		2.0	$Zn(NTf_2)_2$ (0.5)	20	48		92
9		2.0	$Zn(NTf_2)_2$ (0.5)	80	24		98
10	 **9**	1.5	–	80	24	 **12**	17
11		2.0	–	60	48		65 (52)
12		2.0	$Zn(NTf_2)_2$ (0.5)	80	24		27

[a] Yields – based on substrate – were determined by ^{19}F NMR using $C_6H_5CF_3$ as internal standard. Numbers in brackets are isolated yields.

Having demonstrated that zinc salts successfully promote aromatic trifluoromethylation of N-phenylpyrrole, we subsequently applied these additives for the corresponding transformation of different indole derivatives (Table 3). However, the results of our extensive studies led us to the conclusion that the use of zinc additives is not the universal solution for trifluoromethylation of heteroaromatic compounds. Thus, while both zinc salts promoted the reaction with 3-methylindole (**8**) to give the corresponding trifluoromethylated derivative **11** in excellent yields (entries 5–9), they did not significantly affect the CF_3 transfer to 1-H-indole (**7**) (entries 2–4). In the contrary, the use of $Zn(NTf_2)_2$ led to a decreased yield of the trifluoromethylation of N-methylindole (**9**) (entry 12). The reactions were complete after 24 h at 80 °C, lower temperatures required longer reaction times of 48 h in order to obtain almost quantitative transformations.

These results point out the delicate balance between necessary activation and facilitated decomposition of the reagent. The outcome of the reaction seems to be strongly dependent on the electronic structure of the respective substrates. Nevertheless, compared to the only two radical processes reported in the literature [15] our yields represent the best results in terms of direct trifluoromethylation of indoles. Interestingly, and in

Table 4
Trifluoromethylation of various N-heteroarenes[a].

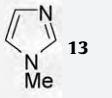
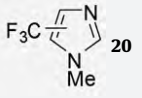
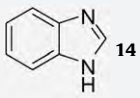
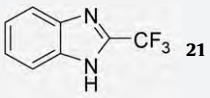
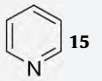
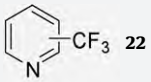
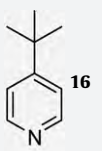
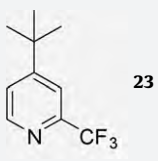
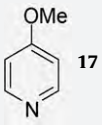
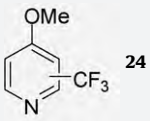
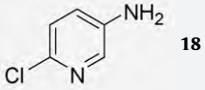
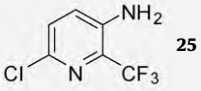
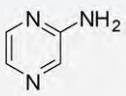
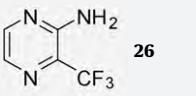
Entry	Substrate	Additive [equiv.]	t [h]	Product(s)	Yield [%][b]
1	 **13**	–	96	 **20**	5-CF_3: 37[c] 2-CF_3: 25
2		TTMSSCl (0.3)	24		5-CF_3: 29 2-CF_3: 20
3	 **14**	–	48	 **21**	18[d]
4		TTMSSCl (0.3)	48		42
5	 **15**	–	96	 **22**	2-CF_3: 17[e] 3-CF_3: 16 4-CF_3: 3
6	 **16**	–	96	 **23**	32[f]
7		TTMSSCl (0.3)	24		16

Table 4 (*Continued*)

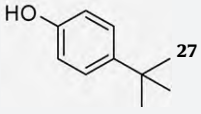
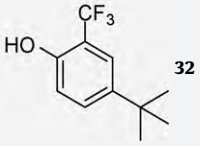
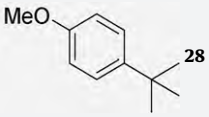
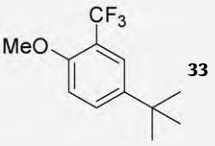
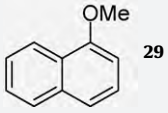
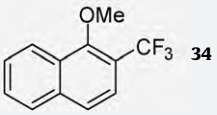
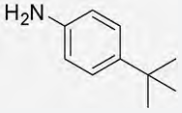
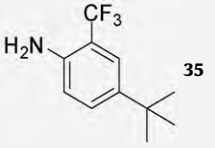
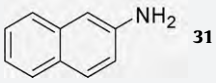
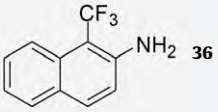
Entry	Substrate	Additive [equiv.]	*t* [h]	Product(s)	Yield [%][b]
8	 **17**	–	48	 **24**	2-CF_3: 20[f] 3-CF_3: 9
9	 **18**	–	24	 **25**	10
10		TTMSSCl (0.3)	24		49
11		TTMSSCl (1.0)	24		52 (47)
12	 **19**	–	48	 **26**	5
13		TTMSSCl (0.3)	24		41
14		TTMSSCl (1.0)	24		58 (6)

[a] 2.0 equiv. of **2**, 80 °C, CH_3CN as solvent.
[b] Yields – based on substrate – were determined by ^{19}F NMR using $C_6H_5CF_3$ as internal standard. Numbers in brackets are isolated yields. Not isolated compounds were identified by comparing the characteristic shifts of the respective ^{19}F NMR signal with the literature data.
[c] δ ^{19}F = 59.7 ppm (5-CF_3) and 62.0 ppm (2-CF_3) [18].
[d] δ ^{19}F = 61.2 ppm [19].
[e] δ ^{19}F = 68.0 ppm (2-CF_3), -62.5 ppm (3-CF_3) and -64.9 ppm (4-CF_3) [20].
[f] Chemical shift compared to that of trifluoromethylated pyridine **22**.

contrast to usual electrophilic substitutions on indoles, the transfer of the CF_3 unit occurs exclusively to the 2-position for all substrates **7**–**9**, likely indicating a directing effect by the N-atom of the indole ring.

In general, trifluoromethylation of more electron deficient N-heteroarenes required higher reaction temperatures of 80 °C, while longer reaction times at lower temperatures mainly resulted in slow decomposition of the reagent (Table 4). Surprisingly, the use of zinc additives led exclusively to decomposition of the reagent. Thermal activation gave corresponding trifluoromethylated N-heteroarenes in moderate yields. In the case of N-methylimidazole (**13**), pyridine (**15**) and 4-methoxypyridine (**17**) (entries 1 + 2, 5 + 8) the reaction afforded regioisomeric mixtures that could not be isolated. However, they were identified by comparing the

Table 5
Trifluoromethylation of activated arenes.

Entry	Substrate	Reagent [equiv.]	Additive [equiv.]	*t* [h]	Product	Yield [%][a]
1	 **27**	2.0	–	24	 **32**	22[b]
2		2.0	TTMSSCl (1.0)	24		43
3	 **28**	2.0	–	72	 **33**	0
4		2.0	TTMSSCl (1.5)	24		58 (58)
5	 **29**	2.0	TTMSSCl (1.0)	24	 **34**	27
6	 **30**	2.0	–	24	 **35**	29
7		2.0	TTMSSCl (0.3)	24		57[c]
8		2.0	TTMSSCl (1.0)	24		66 (61)
9	 **31**	1.5	–	24	 **36**	85
10		1.5	TTMSSCl (0.3)	24		94 (87)

[a] Yields – based on substrate – were determined by ^{19}F NMR using $C_6H_5CF_3$ as internal standard. Numbers in brackets are isolated yields. Not isolated compounds were identified by comparing the characteristic shifts of the respective ^{19}F NMR signal with the literature data.
[b] δ = 62.0 ppm [21].
[c] The use of 4 equiv. of CF_3 reagent **2** under the same conditions gave 43% of 2,6-CF_3-4-*t*Bu-aniline.

characteristic shifts of the respective ^{19}F NMR signals with the literature data. In the case of pyridines, electrophilic substitution also occurred mainly at the 2-position indicating again the directing effect of the heteroatom via a possible interaction with the iodine atom of the reagent.

During previous attempts to investigate the mechanism of aromatic trifluoromethylations, we had successfully used tris(trimethylsilyl)silane (TTMSS) as an additive, often otherwise used in radical transformations as substitute for toxic tin reagents due to the similar Si–H and Sn–H bond dissociation energies [16,17]. However, tris(trimethylsilyl)silyl chloride (TMSSCl) showed exactly the same positive effect as the silane in a comparative study in promoting the reaction. Thus, we clearly established the obvious potential of these hypersilyl additives in supporting the trifluoromethylation reaction. While TTMSSCl did not improve the transformations of N-methylimidazole (**13**) and tert-butylpyridine (**16**) (entries 1 + 2, 6 + 7), it had a remarkable effect in the trifluoromethylations of benzimidazole (**14**), 3-amino-6-chloropyridine (**18**) and 3-aminopyrazine (**19**) leading to moderate yields of 42–58% (entries 3 + 4, 9–14). Notably, only the hypersilyl derivative was a suitable promotor of the reaction. Other silyl additives such as trimethylsilyl triflate or the corresponding chloride exclusively led to a rapid decomposition of the reagent. The exact role of this additive remains obscure. An activation through coordination by the oxygen atom of the reagent similar to the activation by zinc additives can be postulated. The fact that especially the yields of the substrates bearing free amino functionalities is significantly increased using TTMSSCl may indicate a template effect of the additive in combination with these substituents.

The successful conditions using hypersilyl chloride as the additive were also applied to the trifluoromethylation of different homoaromatic compounds (**27**–**31**) bearing activating substituents such as hydroxy, methoxy or amino groups (Table 5). Compared to the reactions carried out using only thermal activation, the transformations using hypersilyl agent TMSSCl gave significantly higher yields with all substrates.

3. Conclusion

In summary, we have shown the high potential of benziodoxole **2** as a reagent for the direct trifluoromethylation of aromatic systems. To our knowledge, this is the most detailed study in direct electrophilic aromatic trifluoromethylation with the broadest substrate scope so far. Due to the straightforward synthesis of the reagent and the simple reaction procedures, this method represents a viable access to various trifluoromethylated arenes and N-heteroarenes of otherwise difficult synthesis.

4. Experimental

4.1. General considerations

All reactions were carried out in Schlenk flasks under an Ar atmosphere. The reactions were monitored by TLC or ^{19}F NMR spectroscopy. After no more reagent **2** was detectable, a defined amount of benzotrifluoride (BTF) as internal standard and C_6D_6 or CD_3CN, respectively, were added. The yields were calculated from the ^{19}F NMR integrals.

The products were isolated after removal of the solvent under reduced pressure and purification by distillation, flash column chromatography or preparative HPLC.

4.2. 2-(Trifluoromethyl)pyrrole (5)

1-Trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (**2**, 165 mg, 0.500 mmol) was dissolved in dry $CHCl_3$ (2 mL). Pyrrole (**3**, 34.0 mg, 0.500 mmol) was added and the mixture was stirred in the dark for 5 h at room temperature. After removal of the solvent under reduced pressure, the brownish crude product was purified by bulb to bulb destillation (60 mbar, 60 °C) to give 59.0 mg (0.437 mmol, 87%) of a colorless oil. ^1H NMR (250 MHz, acetone-D_6): δ = 6.29 (m, 1H, H_{Ar}), 6.64 (m, 1H, H_{Ar}), 6.92 (q, $^4J_{HF}$ = 1.8 Hz, 1H, H_{Ar}), 8.72 (br s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.7 (C_{Ar}), 110.4 (q, $^3J_{CF}$ = 2.9 Hz, $C_{Ar}C_{Ar}CF_3$), 120.9 (C_{Ar}), 121.7 (q, $^1J_{CF}$ = 265.8 Hz, CF_3), 128.6 ($C_{Ar}CF_3$) ppm. ^{19}F NMR (188 MHz, acetone-D_6) δ = −59.2 ppm.

4.3. 1-Phenyl-2-(trifluoromethyl)pyrrole (6)

Reagent **2** (200 mg, 0.600 mmol) and zinc dibromide (34.0 mg, 0.150 mmol) were suspended in dry $CHCl_3$ (2 mL). N-phenylpyrrole (**4**, 42.0 mg, 0.300 mmol) was added and the mixture was stirred for 2 d at room temperature. The solvent was removed under reduced pressure. Purification by column chromatography (hexane/dichloromethane 30:1, R_f = 0.60) gave 56.0 mg (0.265 mmol, 89%) of a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.30 (m, 1H, H_{Ar}), 6.76 (m, 1H, H_{Ar}), 6.91 (m, 1H, H_{Ar}), 7.40–7.43 (m, 2 H, H_{Ar}), 7.46–7.49 (m, 3 H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.6 (C_{Ar}), 113.1 (q, $^3J_{CF}$ = 3.4 Hz, $C_{Ar}C_{Ar}CF_3$), 121.6 (q, $^1J_{CF}$ = 268.7 Hz, CF_3), 122.7 (q, $^2J_{CF}$ = 38.6 Hz, $C_{Ar}CF_3$), 126.9 (q, $^4J_{CF}$ = 1.0 Hz, $C_{Ar}NC_{Ar}CF_3$), 127.6 (q, $^4J_{CF}$ = 1.9 Hz, $C_{Ar}C_{Ar}C_{Ar}CF_3$), 128.9 (C_{Ar}), 129.4 (C_{Ar}), 139.6 (C_{Ar}) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −55.9 ppm. IR (KBr): $\tilde{V}$ = 2922 (w), 2852 (vw), 1463 (w), 1259 (w, ν(CF)), 1120 (w) cm^{-1}. MS (EI): *m/z* (%): 211 (25) [M^+], 191 (28) [M^+–HF], 164 (29), 77 (82) [$C_6H_5^+$]. HRMS ($C_{11}H_8F_3N$): calcd. 211.0604; found 211.0604.

4.4. 2-(Trifluoromethyl)indole (10)

Reagent **2** (247 mg, 0.750 mmol) was dissolved in dry CH_3CN (2 mL). Indole (**7**, 59.0 mg, 0.500 mmol) was added and the mixture was stirred for 24 h at 80 °C. The solvent was removed under reduced pressure. Purification by column chromatography (hexane/dichloromethane 3:2, R_f = 0.40) gave 28.0 mg (0.151 mmol, 30%) of a colorless solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.97 (s, 1H, H_{Ar}), 7.24 (t, ^3J = 7.4 Hz, 1H, H_{Ar}), 7.37 (t, ^3J = 7.5 Hz, 1H, H_{Ar}), 7.46 (d, ^3J = 8.1 Hz, 1H, H_{Ar}), 7.73 (d, ^3J = 8.2 Hz, 1H, H_{Ar}), 8.40 (br s, 1H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 104.7 (q, $^3J_{CF}$ = 3.5 Hz, $C_{Ar}C_{Ar}CF_3$), 112.1 (C_{Ar}), 121.6 (C_{Ar}), 121.7 (q, $^1J_{CF}$ = 268.4 Hz, CF_3), 122.5 (C_{Ar}), 125.2 (C_{Ar}), 126.2 (q, $^2J_{CF}$ = 38.0 Hz, $C_{Ar}CF_3$), 127.0 (C_{Ar}), 136.6 (C_{Ar}) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −60.5 ppm. IR (KBr): $\tilde{V}$ = 3384 (w), 2924 (w), 2359 (w), 1705 (w), 1590 (w), 1557 (vw), 1455 (w), 1371 (w), 1305 (w), 1250 (w, ν(CF)), 1231 (w), 1162 (m), 1113 (s), 1083 (m), 1031 (w), 1006 (w), 942 (w), 808 (w), 741 (m), 725 (w), 641 (vw) cm^{-1}. MS (EI): *m/z* (%): 185 (100) [M^+], 165 (72) [M^+–HF]. HRMS ($C_9H_6F_3N$): calcd. 185.0447; found 185.0447.

4.5. 1-Methyl-2-(trifluoromethyl)indole (11)

Reagent **2** (330 mg (1.00 mmol) was dissolved in dry CH_3CN (2 mL). N-methylindole (**8**, 65.0 mg, 0.500 mmol) was added and the mixture was stirred for 24 h at 80 °C. The solvent was removed under reduced pressure. Purification by column chromatography (hexane/dichloromethane 10:1, R_f = 0.70) gave 52.0 mg (0.261 mmol, 52%) of a colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, NCH_3), 6.98 (m, 1H, H_{Ar}), 7.22–7.26 (m, 1H, H_{Ar}), 7.40–7.42 (m, 2 H, H_{Ar}), 7.72 (d, ^3J = 8.2 Hz, 1H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.1 (NCH_3), 104.7 (q, $^3J_{CF}$ = 3.9 Hz, C_{Ar}-$C_{Ar}CF_3$), 110.2 (C_{Ar}), 121.1 (C_{Ar}), 121.9 (q, $^1J_{CF}$ = 269.0 Hz, CF_3), 122.6 (C_{Ar}), 124.8 (C_{Ar}), 126.1 (C_{Ar}), 127.6 (q, $^2J_{CF}$ = 36.8 Hz, $C_{Ar}CF_3$), 138.9 (C_{Ar}) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −59.5 ppm. IR (KBr):

$\tilde{V}$ = 2918 (m), 2641 (m), 1669 (s), 1579 (m), 1560 (m), 1464 (m), 1428 (m), 1402 (m), 1293 (m), 1264 (m, ν(CF)), 1164 (m), 1147 (m), 1109 (m), 1044 (w), 1013 (m), 989 (m), 955 (w), 890 (m), 806 (m), 794 (m), 733 (m), 677 (m), 633 (m) cm^{-1}. MS (EI): *m/z* (%): 199 (100) [M^+], 130 (61) [M^+–CF_3]. HRMS ($C_{10}H_8F_3N$): calcd. 199.0604; found 199.0605.

4.6. 3-Methyl-2-(trifluoromethyl)indole (12)

Reagent **2** (247 mg, 0.750 mmol) was dissolved in dry CH_3CN (2 mL). 3-Methylindole (**9**, 65.0 mg, 0.500 mmol) was added and the mixture was stirred for 48 h at 80 °C. The solvent was removed under reduced pressure. Purification by column chromatography (hexane/dichloromethane 3:1, R_f = 0.35) gave 53.0 mg (0.266 mmol, 53%) of a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.49 (q, $^5J_{HF}$ = 1.8 Hz, 3 H, CH_3), 7.23 (m, 1H, H_{Ar}), 7.34–7.37 (m, 2 H, H_{Ar}), 7.69 (d, ^3J = 8.2 Hz, 1H, H_{Ar}), 8.17 (br s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.7 (CH_3), 112.0 (C_{Ar}), 114.5 (q, $^3J_{CF}$ = 3.1 Hz, $C_{Ar}C_{Ar}CF_3$), 120.5 (C_{Ar}), 120.8 (C_{Ar}), 121.8 (q, $^2J_{CF}$ = 36.4 Hz, $C_{Ar}CF_3$), 122.6 (q, $^1J_{CF}$ = 268.3 Hz, CF_3), 125.2 (C_{Ar}), 128.5 (C_{Ar}), 135.6 (C_{Ar}) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −58.6 ppm. IR (KBr): $\tilde{V}$ = 3383 (m), 2927 (w), 1693 (vw), 1592 (w), 1569 (w), 1452 (m), 1373 (m), 1316 (m), 1256 (m, ν(CF)), 1196 (m), 1150 (s), 1106 (s), 1077 (m), 1030 (m), 1002 (m), 888 (w), 798 (w), 755 (m), 734 (w), 716 (w), 692 (w) cm^{-1}. MS (EI): *m/z* (%): 199 (100) [M^+], 130 (61) [M^+–CF_3]. HRMS ($C_{10}H_8F_3N$): calcd. 199.0604; found 199.0601.

4.7. 3-Amino-6-chloro-2-(trifluoromethyl)pyridine (25)

Reagent **2** (200 mg, 0.600 mmol), tris(trimethylsilyl)silyl chloride (80.0 mg, 0.300 mmol) and 3-amino-6-chloropyridine (**18**, 39.0 mg, 0.300 mmol) were dissolved in dry CH_3CN (2 mL) and the mixture was stirred for 24 h at 80 °C. The solvent was removed under reduced pressure. Purification by column chromatography (hexane/dichloromethane 3:2, R_f = 0.40) gave 28.0 mg (0.141 mmol, 47%) of a beige solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.31 (br s, 2 H, NH_2), 7.12 (d, ^3J = 8.6 Hz, 1H, H_{Ar}), 7.27 (d, ^3J = 8.6 Hz, 1H, H_{Ar}) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 122.5 (q, $^1J_{CF}$ = 274.2 Hz, CF_3), 128.5 (q, ^3J = 1.0 Hz, $C_{Ar}NH_2$), 128.8 (C_{Ar}), 130.1 (q, ^2J = 34.4 Hz, $C_{Ar}CF_3$), 139.1 (C_{Ar}), 140.4 (C_{Ar}) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −66.0 ppm. IR (KBr): $\tilde{V}$ = 3523 (m), 3360 (m), 3252 (w), 3236 (w), 2922 (vw), 1640 (m), 1596 (m), 1462 (s), 1418 (s), 1344 (m), 1307 (m), 1252 (m, ν(CF)), 1174 (m), 1157 (m), 1120 (s), 1090 (s), 1052 (s), 871 (s), 826 (s), 755 (m), 682 (s), 644 (s), 539 (w) cm^{-1}. MS (EI): *m/z* (%): 198/196 (34/100) [M^+], 176 (48) [M^+–HF], 149 (48), 141 (38). HRMS ($C_6H_4ClF_3N_2$): calcd. 196.0010; found 196.0009.

4.8. 2-Amino-3-(trifluoromethyl)pyrazine (26)

Reagent **2** (200 mg, 0.600 mmol), tris(trimethylsilyl)silyl chloride (80.0 mg, 0.300 mmol) and 2-amino-pyrazine (**19**, 29.0 mg, 0.300 mmol) were dissolved in dry CH_3CN (2 mL) and the mixture was stirred for 24 h at 80 °C. The solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (hexane/isopropanol 95:5, OD-H column) to give 3.0 mg (0.018 mmol, 6%) of a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (br s, 2 H, NH_2), 8.01 (d, ^3J = 2.4 Hz, 1H, H_{Ar}), 8.21 (d, ^3J = 2.0 Hz, 1H, H_{Ar}) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = –67.5 ppm.

4.9. 4-tert-Butyl-1-methoxy-2-(trifluoromethyl)benzene (33)

Reagent **2** (200 mg, 0.600 mmol) and tris(trimethylsilyl)silyl chloride (125 mg, 0.450 mmol, 1.50 equiv.) were dissolved in dry CH_3CN (2 mL). After addition of 4-tert-butylanisole (**28**, 49.0 mg, 0.300 mmol,), the mixture was stirred for 24 h at 80 °C. The solvent was removed under reduced pressure. Purification by column chromatography (hexane/dichloromethane 4:1, R_f = 0.40) gave 40.0 mg (0.173 mmol, 58%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, C(CH_3)$_3$), 3.92 (s, 3 H, OCH_3), 6.98 (d, ^3J = 8.4 Hz, 1H, H_{Ar}), 7.54 (dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz, 1H, H_{Ar}), 7.61 (d, ^4J = 2.0 Hz, 1H, H_{Ar}) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 31.7 (C(CH_3)$_3$), 34.6 (C(CH_3)$_3$), 56.4 (OCH_3), 112.1 (C_{Ar}), 118.4 (q, $^2J_{CF}$ = 30.7 Hz, $C_{Ar}CF_3$), 124.3 (q, $^3J_{CF}$ = 5.3 Hz, $C_{Ar}C_{Ar}CF_3$), 124.4 (q, $^1J_{CF}$ = 272.5 Hz, CF_3), 130.3 (C_{Ar}), 143.4 (C_{Ar}C(CH_3)$_3$), 155.7 (q, $^3J_{CF}$ = 5.3 Hz, $C_{Ar}O$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = –62.1 ppm. IR (KBr): $\tilde{V}$ = 2962 (w), 1619 (w), 1587 (vw), 1508 (m), 1463 (w), 1419 (vw), 1365 (w), 1324 (m), 1279 (m), 1252 (s, ν(CF)), 1182 (w), 1118 (s), 1056 (s), 1026 (m), 901 (w), 879 (w), 819 (m), 760 (w), 685 (m), 651 (w), 612 (w) cm^{-1}. MS (EI): *m/z* (%): 232 (13) [M^+], 217 (100) [M^+–CH_3], 189 (17). HRMS ($C_{12}H_{15}F_3O$): calcd. 232.1070; found 232.1069.

4.10. 4-tert-Butyl-2-(trifluoromethyl)aniline (35)

Reagent **2** (200 mg, 0.600 mmol) and tris(trimethylsilyl)silyl chloride (24.0 mg, 90.0 μmol) were dissolved in dry CH_3CN (2 mL). After addition of 4-tert-butylaniline (**30**, 45.0 mg, 0.300 mmol), the mixture was stirred for 24 h at 80 °C. The solvent was removed under reduced pressure. Purification by column chromatography (hexane/dichloromethane 3:2, R_f = 0.40) gave 40.0 mg (0.183 mmol, 61%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (s, 9 H, C(CH_3)$_3$), 4.08 (br s, 2 H, NH_2), 6.73 (d, ^3J = 8.4 Hz, 1H, H_{Ar}), 7.37 (dd, ^3J = 8.4 Hz, ^4J = 1.9 Hz, 1H, H_{Ar}), 7.45 (d, ^4J = 1.9 Hz, 1H, H_{Ar}) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 31.7 (C(CH_3)$_3$), 34.4 (C(CH_3)$_3$), 113.8 (q, $^2J_{CF}$ = 29.4 Hz, $C_{Ar}CF_3$), 117.6 (C_{Ar}), 123.3 (q, $^3J_{CF}$ = 5.3 Hz, $C_{Ar}C_{Ar}CF_3$), 125.6 (q, $^1J_{CF}$ = 272.8 Hz, CF_3), 130.4 (q, $^4J_{CF}$ = 1.2 Hz, C_{Ar}), 141.1 (C_{Ar}C(CH_3)$_3$), 142.4 (q, $^3J_{CF}$ = 1.7 Hz, $C_{Ar}N$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −62.3 ppm. IR (KBr): $\tilde{V}$ = 2961 (w), 1632 (m), 1582 (vw), 1508 (m), 1465 (vw), 1428 (w), 1365 (w), 1330 (w), 1314 (w), 1296 (m), 1254 (s, ν(CF)), 1140 (m), 1100 (s), 1050 (m), 897 (w), 886 (w), 824 (m), 760 (w), 694 (w), 662 (w), 648 (w) cm^{-1}. MS (EI): *m/z* (%): 217 (19) [M^+], 202 (100) [M^+–CH_3]. HRMS ($C_{11}H_{14}F_3N$): calcd. 217.1073; found. 217.1073.

4.11. 2-(Trifluoromethyl)naphthtyl-1-amine (36)

Reagent **2** (150 mg, 0.450 mmol) and tris(trimethylsilyl)silyl chloride (25.0 mg, 90.0 μmol) were dissolved in dry CH_3CN (2 mL). After the addition of 2-naphthylamine (**31**, 43.0 mg, 0.300 mmol), the mixture was stirred for 24 h at 80 °C. The solvent was removed under reduced pressure. Purification by column chromatography (hexane/dichloromethane 3:2, R_f = 0.35) gave 55.0 mg (0.261 mmol, 87%) of a reddish solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.65 (br s, 2 H, NH), 6.82 (d, ^3J = 8.8 Hz, 1H, H_{Ar}), 7.33 (t, ^3J = 7.3 Hz, 1H, H_{Ar}), 7.54 (m, 1H, H_{Ar}), 7.70–7.74 (m, 2 H, H_{Ar}), 8.02–8.06 (m, 1H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 103.0 (q, $^2J_{CF}$ = 32.4 Hz, $C_{Ar}CF_3$), 120.3 (C_{Ar}), 123.4 (C_{Ar}), 123.5 (q, $^3J_{CF}$ = 4.3 Hz, $C_{Ar}C_{Ar}CF_3$), 127.5 (q, $^1J_{CF}$ = 268.7 Hz, CF_3), 128.3 (C_{Ar}), 128.4 (C_{Ar}), 128.9 (C_{Ar}), 131.9 (q, $^4J_{CF}$ = 1.9 Hz, $C_{Ar}C_{Ar}C_{Ar}CF_3$), 133.8 (C_{Ar}), 144.2 (q, $^3J_{CF}$ = 2.3 Hz, $C_{Ar}NH_2$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −51.9 ppm. IR (KBr): $\tilde{V}$ = 3424 (w), 3057 (vw), 1630 (m), 1577 (w), 1512 (w), 1479 (m), 1434 (m), 1415 (w), 1378 (m), 1353 (w), 1309 (m), 1263 (m), 1243 (m, ν(CF)), 1178 (w), 1142 (m), 1129 (m), 1077 (s), 986 (m), 941 (m), 860 (vw), 834 (vw), 813 (m), 780 (vw), 745 (m), 724 (w), 696 (vw), 678 (w), 642 (w) cm^{-1}. MS (EI): *m/z* (%): 211 (100) [M^+], 191 (52) [M^+–HF], 164 (69). HRMS ($C_{11}H_8F_3N$): calcd. 211.0604; found 211.0605.

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