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Pyrazole-3/5-carboxylic acids from 3/5-trifluoromethyl *NH*-pyrazoles

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ABSTRACT

We report here the transformation of 3/5-trifluoromethylpyrazoles derivative into the corresponding *NH*-pyrazole-3/5-carboxylic acids. Moreover, from 4- or 5-iodinated-3/5-trifluoromethylpyrazoles building blocks and the use of Suzuki–Miyaura or Negishi reactions followed by the trifluoromethyl hydrolysis, we illustrate short and original accesses to many series of *NH*-pyrazole-3/5-carboxylic acids otherwise difficult to prepare.

1. Introduction

Over the last 150 years, pyrazole-bearing derivatives have remained the focus of research as biological effect of interest in medecine[1] or cropscience[2] kept on being discovered, thus leading to further work on the chemistry of this heterocycle.[3–7] In the course of our work on the synthesis of new chemical entities in the alkoxypyrazoles series,[8–15] we observed the transformation of the 5-trifluoromethylpyrazole **1** into the pyrazole-3-carboxylic acid **3**. A thorough literature search pointed out that such transformation has been mentioned for 3-trifluoromethylpyrazole hydrolysis/ethanolysis although no actual example is provided in the patent.[16] However, a very recent publication reports the ammonolysis of various trifluoromethylpyrazoles, which certainly take place by the same mechanism as their hydrolysis.[17]

2. Results/discussion

As depicted in Table 1, the optimization of this reaction led to use a microwave oven and compound **3** was thus obtained in 94% yield. The mechanism of this hydrolysis is likely to proceed as described for other trifluoromethyl-bearing substrates prone to anion-assisted fluorine departure.[18–26] Our recent review[27] of the synthetic accesses to 3/5-pyrazole carboxylic acids pointed out some of the difficulties that can be encountered in the synthesis of 3/5-carboxypyrazoles. Namely if 5-substituted-3-carboxypyrazoles are relatively easy to prepare by condensation reaction between hydrazine and β-diketones, it is not the case for 4-substitued 3-carboxypyrazoles as longer low-yielding routes and/or hazardous chemical have to be used. To a lesser degree, these statements are also true for the synthesis of 3/5-trifluoromethylpyrazoles.[28–32] With in mind the design of modular accesses to a vast array of 3/5-trifluoromethylpyrazoles and consequently pyrazole-3/5-carboxylic acids, we first verified the generality of this hydrolysis.

From the 3-trifluoromethyl-bearing pyrazoles **5a**–**g** (three of them readily available, the other one made by optimized condensation reaction), the pyrazole acids **6b**–**f** could be obtained in good yields, although **6a** and **6g** required a recrystallization from acetic acid, which lowered the yields of these quite water-soluble products.

From the 4-iodinated trifluoromethylpyrazoles **7** and **8**, we previously reported,[15] we set to undertake Pd-catalyzed cross-coupling reactions with boronic acids. It quickly became evident that a temporary NH protection of pyrazole **7** was necessary for Suzuki–Miyaura reactions to proceed in good yield. A convenient protection, using vinyl ethyl ether in the presence of catalytic amount of pyridinium *para*-toluenesulfonate (PPTS), led to the mixture of 1-ethoxyethyl isomers **9a**–**p** ((Table 2; one arbitrary isomer is depicted). Upon concentration to dryness, the resulting crude reaction products were arylated under optimized Suzuki–Miyaura conditions using a pre-milled 1:2 mixture of palladium acetate and XPhos ligand as a precatalyst. This was followed by an in situ acid hydrolysis of the 1-ethoxyethyl protecting group

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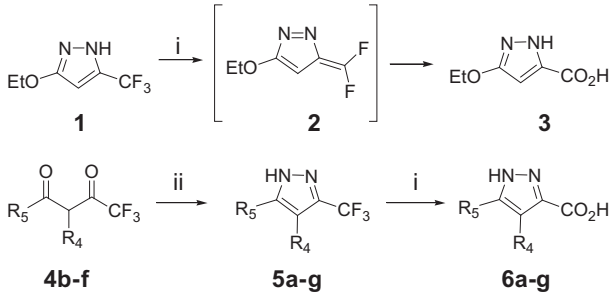
Table 1
Preparation and hydrolysis of 3-trifluoromethylpyrazoles **5a**–**g**

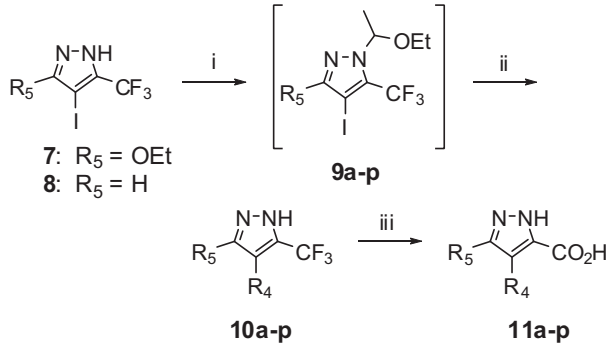


	R_4	R_5	% **5**	% **6**
a	H	H	—	7[a]
b	H	Ph	86	97
c	H	Furan-2-yl	78	73
d	H	Thiophen-2-yl	81	82
e	H	CH_3	—	61
f	$-(CH_2)_4-$		66	51
g	Cl	H	—	23[a]

(i): NaOH (5 equiv), EtOH/H_2O, MW, 120 °C; (ii): (a) NH_2NH_2, EtOH/H_2O, reflux; (b) 2 N HCl, reflux.
[a] After a recrystallization.

to afford compounds **10a**–**h** in high yields. The overall sequence was thus performed in one pot using parallel experimentation techniques and can be easily adapted to existing robotic reaction equipment. Hydrolysis of compounds **10a**–**h** was then easily achieved, under basic conditions in 1 h at 120 °C using a microwave oven, providing acids **11a**–**h** in yields between 78 and 89% (Table 2).

Table 2
Preparation and hydrolysis of 3-trifluoromethylpyrazoles **10a**–**p**

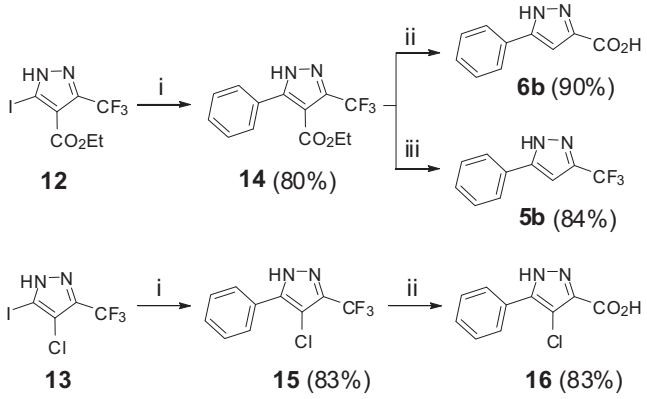


	R_4	R_5	% **10**	% **11**
a	C_6H_5	OEt	82	78
b	2-ClC_6H_4	OEt	63	85
c	3-ClC_6H_4	OEt	96	87
d	4-ClC_6H_4	OEt	84	81
e	2-$MeOC_6H_4$	OEt	88	89
f	3-$MeOC_6H_4$	OEt	92	80
g	4-$MeOC_6H_4$	OEt	96	88
h	4-$CF_3C_6H_4$	OEt	91	86
i	C_6H_5	H	91	40
j	2-ClC_6H_4	H	90	73
k	3-ClC_6H_4	H	92	78
l	4-ClC_6H_4	H	50	64
m	2-$MeOC_6H_4$	H	93	60
n	3-$MeOC_6H_4$	H	76	58
o	4-$MeOC_6H_4$	H	92	36
p	4-$CF_3C_6H_4$	H	82	71

(i): Ethylvinylether, PPTS, CH_2Cl_2; (ii): (a) $ArB(OH)_2$, K_2CO_3, $Pd(OAc)_2$/XPhos (1:2), dioxane/H_2O 80 °C; (b) 6 M HCl, 80 °C; (iii): NaOH, EtOH/H_2O, MW, 120 or 150 °C.

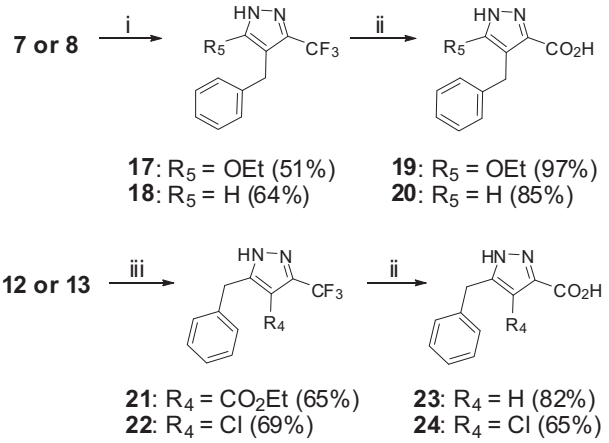
The same sequence was applied to the pyrazole **8** and afforded the 4-aryl derivatives **10i**–**p**. Hydrolysis of the trifluoromethyl group of these compounds turned out to be slower at 120 °C, hence the 40% yield in the case of **11i**. However, a temperature increase to 150 °C led to the corresponding *NH*-pyrazole-3/5-carboxylic acids **11j**–**p** in acceptable yield for the same reaction time.

As depicted in Scheme 1, in a more limited series of coupling experiments with 5-iodopyrazoles,[15] no protection was found necessary for the Suzuki–Miyaura cross-coupling of **12** or **13** with phenylboronic acid using $PdCl_2$(dppf) as a catalyst. The corresponding 5-phenyl derivatives **14** and **15** were obtained in 80 and 83% yields, respectively. Upon an increase of reaction time as well as sodium hydroxide concentration, the hydrolysis of compound **14** took place along with a decarboxylation and provided acid **6b** in 90% yield. Alternatively, a selective decarboxylation of **14** without affecting its trifluoromethyl group could be performed, using hot 66% sulfuric acid, to give compound **5b** in 84% yield. The trifluoromethyl hydrolysis of 4-chloro derivative **15** gave the corresponding acid **16** in 83% yield.



Scheme 1. (i): $PhB(OH)_2$, Cs_2CO_3, $PdCl_2$(dppf), *n*-PrOH/H_2O, MW, 110 °C; (ii): NaOH, EtOH/H_2O, MW, 150 °C; (iii): H_2SO_4 66%, 130 °C.

As depicted in Scheme 2, benzylation of the readily available building blocks[15] **7**, **8**, **12**, and **13**, using the Negishi palladium-catalyzed reaction with benzylzinc bromide, was also studied. Interestingly, a nitrogen protecting group could be avoided in these four cases.



Scheme 2. (i): $PhCH_2ZnBr$, $Pd(OAc)_2$/XPhos (1:2), 85 °C; (ii): NaOH, EtOH/H_2O, MW, 150 °C; (iii): $PhCH_2ZnBr$, $PdCl_2$(dppf), 120 °C.

Once again, from compound **7** or **8**, an intimate 1:2 mixture of palladium acetate and XPhos was found to be an efficient

precatalyst, and led to compounds **17** and **18** in 51 and 64% yields, respectively. It should be mentioned that, although we do not have a clear explanation, the use of a microwave oven was repeatedly detrimental to the reaction yield in these cases. The trifluoromethyl-bearing compounds **17** and **18** were then subjected to hydrolysis to give compounds **19** and **20** in 97 and 85% yields, respectively. From the 5-iodinated building blocks **12** and **13**, $PdCl_2$(dppf) turned out to be an efficient coupling catalyst and the 5-benzylated products **21** and **22** were isolated in 65 and 69% yield. Hydrolysis of the trifluoromethyl group of compound **21** led to a mixture of 3-carboxylic acid **23** and the corresponding 3,4-bis-carboxylic acid. Upon prolonged heating, the former became the only product, which was isolated in 82% yield. From the 4-chloro derivative **22**, hydrolysis into acid **24** was achieved in 65% yield.

3. Conclusion

In the course of the study of the scope of this 3/5-trifluromethylpyrazole hydrolysis into 3/5-*NH*-pyrazole carboxylic acid, we have also demonstrated the versatility of the 3-trifluoromethyl-bearing iodopyrazoles **7**, **8**, **12**, and **13** as building blocks. Indeed, these along with parallel experimentation techniques led to derivatives featuring a 3-trifluoromethyl or a 3-carboxyl moiety in two steps and in quantities suitable for any biological evaluations, which should thus simplify the work of medicinal chemists.

4. Experimental section

4.1. General

A Biotage initiator 2 microwave oven was used for reactions mentioning such heating method. This apparatus is of a mono mode type, temperature is set as described and is automatically monitored by an infrared detector and thus automatically regulated by the microwave power adjustments (between 0 and 400 W). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively. Shifts (δ) are given in parts per million with respect to the TMS signal and coupling constants (J) are given in hertz. Except for the purification of compounds **10a**–**p**, column chromatography was performed either on Merck silica gel 60 (0.035–0.070 mm) or neutral alumina using a solvent pump and an automated collecting system driven by an UV detector set to 254 nm unless required otherwise. Sample deposition was carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition of the top of the column. The low resolution mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system and the high resolution mass spectra (HRMS) were obtained using a Waters Micromass Q-Tof with an electrospray ion source.

4.2. Preparation of trifluoromethylpyrazoles 5b–d and 5f

The relevant acetoacetate (10 mmol) and hydrazine hydrate (0.53 mL, 11 mmol) were refluxed in ethanol (100 mL) overnight. The reaction mixture was concentrated to dryness and the resulting 5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-5-ol was boiled in 2 N hydrochloric acid (40 mL) for 1 min. After cooling, the precipitate was filtered, washed with water, and dried under vacuum to yield the trifluoromethylpyrazoles **5b**–**d** and **5f** as described below.

*4.2.1. 5-Phenyl-3-(trifluoromethyl)-1H-pyrazole (**5b**).* This compound was obtained as previously described.[15] Alternatively, it was obtained by heating compound **14** (0.33 mmol) in a 66% solution of sulfuric acid at 130 °C for 5 h. After cooling to room temperature, the solution was diluted with water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to afford **5b** in 84% yield.

*4.2.2. 5-(Furan-2-yl)-3-(trifluoromethyl)-1H-pyrazole (**5c**).* This compound was obtained in 78% yield; analytical data were in accord to the data previously reported.[33] ^{1}H NMR (DMSO-d_6): 6.65 (m, 1H); 6.95 (m, 2H); 7.82 (m, 1H); 14.15 (br s, 1H). ^{13}C NMR (DMSO-d_6): 100.4; 108.7; 112.4; 122.0 (q, J=266 Hz); 136.1; 142.1 (q, J=33 Hz); 143.8; 144.1.

*4.2.3. 5-(Thiophen-2-yl)-3-(trifluoromethyl)-1H-pyrazole (**5d**).* This compound was obtained in 81% yield; analytical data were in accord to the data previously reported.[33] ^{1}H NMR (DMSO-d_6): 6.99 (s, 1H); 7.17 (m, 1H); 7.57 (m, 1H); 7.66 (m, 1H); 14.09 (br s, 1H). ^{13}C NMR (DMSO-d_6): 101.5; 122.0 (q, J=267 Hz); 126.4; 127.5; 128.6; 130.2 (br); 139.0 (br); 142.6 (br).

*4.2.4. 3-(Trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole (**5f**).* To a solution of 1-(4-morpholino)cyclohexane (2.01 g, 11.9 mmol) and triethylamine (1.21 g, 11.9 mmol) in dichloromethane (15 mL) cooled to 0 °C was added trifluoroacetic anhydride (2.31 g, 11.9 mmol). The mixture was allowed to warm up to room temperature and stirred overnight. The resulting solution was concentrated to dryness and the residue dissolved in ethanol (15 mL) and cooled to 0 °C. Hydrazine hydrate (0.6 mL, 12.5 mmol) was added and the solution was heated to reflux for 4 h. This was concentrated to dryness and the residue was purified by a chromatography over silica gel (dichloromethane), followed by extensive drying under vacuum to remove a volatile impurity, to yield compound **5f** as pale yellow powder (1.50 g, 66%); mp 116 °C (lit.[34] mp 125 °C). ^{1}H NMR ($CDCl_3$): 1.81 (m, 4H); 2.63 (m, 2H); 2.69 (m, 2H), 12.0 (br s, 1/2H); 16.5 (br s, 1/2H). ^{13}C NMR ($CDCl_3$): 19.7; 20.8; 22.1; 22.5; 114.2; 122.2 (q, J=267 Hz); 139.0 (q, J=36 Hz); 141.4. HRMS: calcd for $C_8H_9N_2F_3$+H: 191.0796; found: 191.0752.

4.3. General method for the hydrolysis of the pyrazole trifluoromethyl group

In a Biotage tube, the relevant trifluoromethylpyrazole (1 mmol) and sodium hydroxide (0.2 g, 5 mmol) were stirred in ethanol/water 1:3 (1.2 mL). The tube was sealed and heated at 120 or 150 °C, as mentioned in the text for 1 h in a microwave oven. The resulting suspension was dissolved in water; the aqueous phase was washed with dichloromethane twice and made acidic with 2 N hydrochloric acid. This was extracted with ethyl acetate twice; the organic layer was washed with brine, dried over magnesium sulfate, and concentrated to dryness to yield the corresponding acid as described below. *CAUTION*: the reaction conditions used lead to the release of fluorine ions that attack the glass tubes. *Never recycle the reaction tubes as their resistance toward pressure and temperature may have been weakened in a process, which is releasing sodium fluoride*.

*4.3.1. 3-Ethoxy-1H-pyrazole-5-carboxylic acid (**3**).* Obtained as a white powder in 94% yield; mp 154 °C (lit.[35] mp 162–164 °C). ^{1}H NMR (DMSO-d_6): 1.29 (t, 3H, J=7.1 Hz); 4.11 (q, 2H, J=7.1 Hz); 6.13 (s, 1H); 13.02 (br s, 2H). ^{13}C NMR (DMSO-d_6): 15.1; 65.0; 92.4; 135.7; 161.0; 162.7 (in accord with the NMR data previously reported for this compound[36]). HRMS: calcd for $C_6H_8N_2O_3$+H]: 157.0613; found: 157.0666.

*4.3.2. 1H-Pyrazole-3-carboxylic acid (**6a**).* The residue was further purified by a recrystallization in acetic acid to yield compound **6a** in 7% yield; mp 212 °C (lit.[37] mp 213–215 °C). ^{1}H NMR (MeOH-d_4):

5.01 (br s, 2H); 6.83 (d, 1H, J=1.5 Hz); 7.70 (d, 1H, J=1.5 Hz). ^{13}C NMR (MeOH-d_4): 109.4; 134.1; 143.1; 165.1. LC/MS: m/z 113 $(M+H)^+$.

*4.3.3. 5-Phenyl-1H-pyrazole-3-carboxylic acid (**6b**).* Obtained from compound **5b** as a white powder in 97% yield with analytical data identical to a commercially available sample. Alternatively, as mentioned in the text compound **6b** was obtained from compound **14** in 90% yield when 7 equiv of sodium hydroxide was used and the reaction mixture was heated at 150 °C for 2 h.

*4.3.4. 5-(Furan-2-yl)-1H-pyrazole-3-carboxylic acid (**6c**).* Obtained as a white powder in 73% yield; mp 219 °C (lit.[38] mp 219 °C). ^{1}H NMR (DMSO-d_6): 6.59 (m, 1H); 6.82 (m, 1H); 6.95 (m, 1H); 7.74 (d, 1H, J=1.1 Hz); 13.5 (br s, 2H). ^{13}C NMR (DMSO-d_6; D1 set to 5 s): 105.0; 107.2; 118.8; 139.6 (br); 140.7 (br); 143.2; 146.8; 161.9. HRMS: calcd for $C_8H_6N_2O_3$+H: 179.0457; found: 179.0477.

*4.3.5. 5-(Thiophen-2-yl)-1H-pyrazole-3-carboxylic acid (**6d**).* Obtained as a white powder in 82% yield; mp 227 °C. ^{1}H NMR (DMSO-d_6): 7.07 (s, 1H); 7.10 (m, 1H); 7.49 (m, 2H); 13.5 (br s, 2H). ^{13}C NMR (DMSO-d_6; D1 set to 5 s): 105.5; 125.1; 125.9; 128.3; 135.2 (br); 138.0 (br); 145.8 (br); 172.5. HRMS: calcd for $C_8H_6N_2O_2S$+H: 195.0228; found: 195.0208.

*4.3.6. 5-Methyl-1H-pyrazole-3-carboxylic acid (**6e**).* Obtained as a white powder in 61% yield; mp 245 °C (lit.[39] mp 241–243 °C). ^{1}H NMR (DMSO-d_6): 2.24 (s, 3H); 6.45 (s, 2H); 12.87 (br s, 1H). ^{13}C NMR (DMSO-d_6): 11.9; 107.6; 142.2; 143.8; 163.7. LC/MS: m/z=125 $(M-H)^-$.

*4.3.7. 4,5,6,7-Tetrahydro-1H-indazole-3-carboxylic acid (**6f**).* Obtained as a white powder in 51% yield after a recrystallization from a mixture of ethanol and water; mp >240 °C (lit.[40] mp 250 °C). ^{1}H NMR (DMSO-d_6): 1.74 (m, 4H); 2.58 (m, 2H); 2.67 (m, 2H); 14.70 (br s, 2H). ^{13}C NMR (DMSO-d_6): 21.7; 22.1; 22.7; 23.1; 118.7; 135.7 (br); 144.3 (br); 163.2. HRMS: calcd for $C_8H_{10}N_2O_2$–H: 165.0664; found: 165.0645.

*4.3.8. 4-Chloro-1H-pyrazole-3-carboxylic acid (**6g**).* The residue was further purified by recrystallization from acetic acid to yield compound **6g** in 23% yield; mp 250 °C (lit.[37] mp 244–245 °C). ^{1}H NMR (MeOH-d_4): 4.95 (s (br), 2H); 7.73. ^{13}C NMR (MeOH-d_4): 114.7; 135.0 (br); 163.0. LC/MS: m/z 145/147 $(M-H)^-$.

*4.3.9. 3-Ethoxy-4-phenyl-1H-pyrazole-5-carboxylic acid (**11a**).* Obtained as a white powder in 78% yield; mp >260 °C. ^{1}H NMR (DMSO-d_6): 1.28 (t, 3H, J=7.0 Hz); 4.22 (q, 2H, J=7.0 Hz); 7.25 (m, 1H); 7.32 (m, 2H); 7.46 (m, 2H); 12.99 (br s, 1H); 13.28 (br s, 1H). ^{13}C NMR (DMSO-d_6): 14.7; 64.2; 108.1; 126.4; 127.5; 129.9; 130.5 (two signals); 159.9; 160.6. HRMS: calcd for $C_{12}H_{12}N_2O_3$+H: 233.0926; found: 233.0883.

*4.3.10. 4-(2-Chlorophenyl)-3-ethoxy-1H-pyrazole-5-carboxylic acid (**11b**).* Obtained as a white powder in 85% yield; mp 169 °C. ^{1}H NMR (DMSO-d_6): 1.21 (t, 3H, J=7.0 Hz); 4.18 (q, 2H, J=7.0 Hz); 7.32 (m, 3H); 7.49 (m, 1H); 13.04 (br s, 2H). ^{13}C NMR (DMSO-d_6): 14.7; 64.2; 105.4; 126.4 (two signals); 128.8; 130.3; 132.2; 132.8; 133.7; 159.9; 160.2. HRMS: calcd for $C_{12}H_{11}ClN_2O_3$+H: 267.0536; found: 267.0519.

*4.3.11. 4-(3-Chlorophenyl)-3-ethoxy-1H-pyrazole-5-carboxylic acid (**11c**).* Obtained as a white powder in 87% yield; mp 233 °C. ^{1}H NMR (DMSO-d_6): 1.29 (t, 3H, J=7.0 Hz); 4.25 (q, 2H, J=7.0 Hz); 7.29 (m, 1H); 7.37 (m, 1H); 7.45 (m, 1H); 7.53 (d, 1H, J=3.7 Hz); 13.1 (br s, 2H). ^{13}C NMR (DMSO-d_6): 15.1; 65.0; 107.0; 126.8; 128.9; 129.8; 129.9; 131.5; 132.6; 133.3; 160.4; 160.9. HRMS: calcd for $C_{12}H_{11}ClN_2O_3$+H: 267.0536; found: 267.0528.

*4.3.12. 4-(4-Chlorophenyl)-3-ethoxy-1H-pyrazole-5-carboxylic acid (**11d**).* Obtained as a white powder in 81% yield; mp >260 °C. ^{1}H NMR (DMSO-d_6): 1.25 (t, 3H, J=7.0 Hz); 4.22 (q, 2H, J=7.0 Hz); 7.41 (m, 2H); 7.48 (m, 2H); 13.04 (br s, 1H); 13.41 (br s, 1H). ^{13}C NMR (DMSO-d_6): 14.6; 64.3; 106.7; 127.5; 129.5; 130.8; 131.1; 131.6; 159.8; 160.5. HRMS: calcd for $C_{12}H_{11}ClN_2O_3$+H: 267.0536; found: 267.0522.

*4.3.13. 3-Ethoxy-4-(2-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (**11e**).* Obtained as a white powder in 89% yield; mp 196 °C. ^{1}H NMR (DMSO-d_6): 1.23 (t, 3H, J=7.0 Hz); 3.67 (s, 3H); 4.16 (q, 2H, J=7.0 Hz); 6.90 (m, 1H); 6.99 (d, 1H, J=7.7 Hz); 7.16 (m, 1H); 7.28 (m, 1H); 12.9 (br s, 2H). ^{13}C NMR (DMSO-d_6): 14.7; 55.1; 64.0; 104.1; 110.9; 119.6; 120.0; 128.3; 131.5; 132.3; 157.0; 160.1; 160.8. HRMS: calcd for $C_{13}H_{14}N_2O_4$+H: 263.1032; found: 263.1009.

*4.3.14. 3-Ethoxy-4-(3-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (**11f**).* Obtained as a white powder in 80% yield; mp 209 °C. ^{1}H NMR (DMSO-d_6): 1.29 (t, 3H, J=7.0 Hz); 3.75 (s, 3H); 4.23 (q, 2H, J=7.0 Hz); 6.83 (m, 1H); 7.06 (m, 2H); 7.25 (m, 1H); 13.0 (br s, 2H). ^{13}C NMR (DMSO-d_6): 14.7; 54.9; 64.3; 107.9; 112.0; 115.7; 122.3; 128.4; 130.8; 131.9; 158.5; 160.0; 160.6. HRMS: calcd for $C_{13}H_{14}N_2O_4$+H: 263.1032; found: 263.1013.

*4.3.15. 3-Ethoxy-4-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (**11g**).* Obtained as a white powder in 88% yield; mp 220 °C. ^{1}H NMR (DMSO-d_6): 1.27 (t, 3H, J=7.0 Hz); 3.75 (s, 3H); 4.22 (q, 2H, J=7.0 Hz); 6.92 (m, 2H); 7.42 (m, 2H); 13.0 (br s, 2H). ^{13}C NMR (DMSO-d_6): 15.2; 55.4; 64.7; 108.5; 113.4; 123.2; 130.7; 131.6; 158.4; 160.4; 161.2. HRMS: calcd for $C_{13}H_{14}N_2O_4$+H: 263.1032; found: 263.1028.

*4.3.16. 3-Ethoxy-4-(4-trifluoromethylphenyl)-1H-pyrazole-5-carboxylic acid (**11h**).* Obtained as a white powder in 86% yield; mp >260 °C. ^{1}H NMR (DMSO-d_6): 1.28 (t, 3H, J=7.0 Hz); 4.25 (q, 2H, J=7.0 Hz); 7.69 (s, 4H); 13.5 (br s, 2H). ^{13}C NMR (DMSO-d_6): 14.5; 64.4; 106.5; 124.3; 124.3 (q, J=269 Hz); 126.8 (q, J=36 Hz); 130.4; 131.0; 135.0; 160.0; 160.4. HRMS: calcd for $C_{13}H_{11}F_3N_2O_3$+H: 301.0800; found: 301.0749.

*4.3.17. 4-Phenyl-1H-pyrazole-3-carboxylic acid (**11i**).* Obtained as a white powder in 40% yield; when heating at 120 °C (see text); mp >260 °C (lit.[41] mp 252–253 °C). ^{1}H NMR (DMSO-d_6): 3.76 (s, 3H); 7.29 (m, 1H); 7.37 (m, 2H); 7.50 (m, 2H); 7.95 (s, 1H). ^{13}C NMR (MeOH-d_4): 52.5; 127.2; 128.7; 129.4; 130.7; 133.7; 135.7; 163.7. HRMS: calcd for $C_{10}H_8N_2O_2$+H: 189.0664; found: 189.0627.

*4.3.18. 4-(2-Chlorophenyl)-1H-pyrazole-3-carboxylic acid (**11j**).* Obtained as a white powder in 73% yield; mp >260 °C. ^{1}H NMR (DMSO-d_6): 7.35 (m, 3H); 7.48 (m, 1H); 7.80 (s, 1H); 12.70 (br s, 1H). ^{13}C NMR (DMSO-d_6): 121.3; 127.0; 129.3; 129.4; 132.4; 132.6; 133.5; 135.4 (br); 137.5 (br); 162.6. HRMS: calcd for $C_{10}H_7ClN_2O_2$+H: 223.0274; found: 223.0235.

*4.3.19. 4-(3-Chlorophenyl)-1H-pyrazole-3-carboxylic acid (**11k**).* Obtained as a white powder in 78% yield; mp >260 °C. ^{1}H NMR (DMSO-d_6): 7.35 (m, 2H); 7.50 (m, 1H); 7.64 (m, 1H); 7.97 (s, 1H); 13.1 (br s, 1H). ^{13}C NMR (DMSO-d_6): 123.2; 127.1; 128.0; 129.0; 130.2; 133.0; 134.7; 135.3 (br, two signals); 162.7. HRMS: calcd for $C_{10}H_7ClN_2O_2$+H: 223.0274; found: 223.0230.

*4.3.20. 4-(4-Chlorophenyl)-1H-pyrazole-3-carboxylic acid (**11l**).* Obtained as a white powder in 64% yield; mp >260 °C. ^{1}H (DMSO-d_6): 7.42 (m, 2H); 7.56 (m, 2H); 7.90 (s, 1H); 13.1 (br s, 1H). ^{13}C NMR (DMSO-d_6): 123.4; 128.3; 131.1; 131.5; 132.0; 135.4 (br, two signals); 162.7. HRMS: calcd for $C_{10}H_7ClN_2O_2$+H: 223.0274; found: 223.0226.

*4.3.21. 4-(2-Methoxyphenyl)-1H-pyrazole-3-carboxylic acid (**11m**).* Obtained as a white powder in 60% yield; mp 217 °C. ^{1}H NMR (DMSO-d_6): 3.69 (s, 3H); 6.92 (m, 1H); 7.01 (m, 1H); 7.26 (m, 2H); 7.73 (s, 1H); 13.05 (br s, 2H). ^{13}C NMR (DMSO-d_6): 55.6; 111.4; 120.0; 120.4;

121.9; 128.9; 131.5; 135.2; 137.3; 157.0; 163.2. HRMS: calcd for $C_{11}H_{10}N_2O_3$+H: 219.0770; found: 219.0723.

*4.3.22. 4-(3-Methoxyphenyl)-1H-pyrazole-3-carboxylic acid (**11n**).* Obtained as a white powder in 58% yield; mp 248 °C. ^{1}H NMR (DMSO-d_6): 3.77 (s, 3H); 6.85 (m, 1H); 7.13 (m, 1H); 7.17 (m, 1H); 7.25 (m, 1H); 7.89 (s, 1H); 13.1 (br s, 2H). ^{13}C NMR (DMSO-d_6): 55.4; 112.8; 115.2; 121.7; 124.4; 129.4; 133.9; 134.9 (br); 135.6 (br); 159.4; 162.8. HRMS: calcd for $C_{11}H_{10}N_2O_3$+H: 219.0770; found: 219.0735.

*4.3.23. 4-(4-Methoxyphenyl)-1H-pyrazole-3-carboxylic acid (**11o**).* Obtained as a white powder in 36% yield; mp >260 °C (lit.[42] mp 265 °C). ^{1}H NMR (DMSO-d_6): 3.76 (s, 3H); 6.93 (m, 2H); 7.48 (m, 2H); 7.80 (s, 1H); 12.5 (br s, 1H). ^{13}C NMR (DMSO-d_6): 55.5; 113.9; 124.5; 124.8; 130.6; 134.0 (br); 135.6 (br); 158.8; 162.7. HRMS: calcd for $C_{11}H_{10}N_2O_3$+H: 219.0770; found: 219.0730.

*4.3.24. 4-(4-Trifluoromethylphenyl)-1H-pyrazole-3-carboxylic acid (**11p**).* Obtained as a white powder in 71% yield; mp 257 °C. ^{1}H NMR (DMSO-d_6): 7.67 (m, 2H); 7.81 (m, 2H); 7.99 (s, 1H); 13.0 (br s, 2H). ^{13}C NMR (DMSO-d_6): 123.2; 124.8 (q, J=270 Hz); 125.2; 127.8 (q, J=31 Hz); 129.5; 130.0; 135.6 (br); 136.9; 162.7. HRMS: calcd for $C_{11}H_7F_3N_2O_2$+H: 257.0538; found: 257.0453.

*4.3.25. 4-Chloro-5-phenyl-1H-pyrazole-3-carboxylic acid (**16**).* Obtained as a white powder, in 83% yield following 1 h at 150 °C and 7 equiv of sodium hydroxide instead of **5**; mp >240 °C (lit.[43] mp 258–261 °C). ^{1}H NMR (DMSO-d_6): 7.46 (m, 3H); 7.80 (m, 2H); 14.07 (s, 2H). ^{13}C NMR (DMSO-d_6; D1 set to 5 s): 109.4; 127.6; 129.1; 129.5 (br); 135.3 (br); 144.7 (br); 160.9; one signal missing. HRMS: calcd for $C_{10}H_7ClN_2O_2$+H: 223.0274; found: 223.0235.

*4.3.26. 3-Ethoxy-4-benzyl-1H-pyrazole-3-carboxylic acid (**19**).* Obtained in 97% yield; mp 181 °C. ^{1}H NMR (DMSO-d_6): 1.26 (t, 3H, J=7.0 Hz); 3.89 (s, 2H); 4.17 (q, 2H, J=7.0 Hz); 7.12 (m, 1H); 7.21 (m, 3H); 12.9 (br s, 1H). ^{13}C NMR (DMSO-d_6): 15.2; 27.6; 64.6; 107.4; 126.1; 128.5; 128.6; 131.6; 141.4; 161.4; 161.5. HRMS: calcd for $C_{13}H_{14}N_2O_3$+H: 247.1083; found: 247.1031.

*4.3.27. 4-Benzyl-1H-pyrazole-3-carboxylic acid (**20**).* Obtained in 85% yield; mp 235 °C. ^{1}H NMR (DMSO-d_6): 4.04 (s, 2H); 7.19 (m, 5H); 7.47 (s, 1H). ^{13}C NMR (DMSO-d_6): 30.3; 124.0; 126.6; 129.1; 129.2; 136.0; 142.0; 163.5; one signal missing. HRMS: calcd for $C_{11}H_{10}N_2O_2$+H: 203.0821; found: 203.0763.

*4.3.28. 5-Benzyl-1H-pyrazole-3-carboxylic acid (**23**).* Obtained as a white powder in 82% yield following 2 h at 150 °C and 7 equiv of sodium hydroxide instead of **5**. NMR spectra of **23** in MeOH-d_4 have been previously reported;[40] mp 234 °C. ^{1}H NMR (DMSO-d_6): 3.97 (s, 2H); 6.45 (s, 1H). 7.19–7.32 (m, 5H); 13.0 (br s, 2H). ^{13}C NMR (DMSO-d_6, D1 set to 5 s): 32.5; 107.3; 126.7; 128.9; 128.92; 139.7; 140.9 (br); 147.1; 162.8 (br). HRMS: calcd for $C_{11}H_{10}N_2O_2$+H: 203.0821; found: 203.0764.

*4.3.29. 5-Benzyl-4-chloro-1H-pyrazole-3-carboxylic acid (**24**).* Obtained as an off-white powder in 65% yield heating 1 h at 150 °C, after a dispersion of the extracted material in boiling toluene followed by a filtration; mp 206 °C. ^{1}H NMR (DMSO-d_6): 3.97 (s, 2H); 7.18–7.31 (m, 5H); 13.5 (br s, 2H). ^{13}C NMR (DMSO-d_6): 30.2; 109.9; 126.3; 128.2; 128.4; 137.9; 144.0 (br); 161.5 (br); one signal missing. HRMS: calcd for $C_{11}H_9ClN_2O_2$+H: 237.0431; found: 237.0382.

4.4. General method for the preparation of 10a–p

A solution of the relevant 4-iodopyrazole[15] (1.0 mmol) and PPTS (2.5 mg, 0.01 mmol) in dichloromethane (1 mL) was treated with ethyl vinyl ether (0.2 mL, 2 equiv) at room temperature over 0.5 h. The volatiles were removed in vacuo, arylboronic acid (1.2 mmol) and potassium carbonate (335 mg, 2.4 mmol) were added under argon atmosphere, followed by dioxane (distilled under argon, 3 mL) and degassed water (1 mL). A catalyst solution, prepared by heating a pre-milled 1:2 mixture of palladium(II) acetate and XPhos (11.8 mg, 0.01 equiv [Pd]) in dioxane/H_2O (95:5; 1 mL) at 80 °C until the color of the solution turned green (ca. 5 min), was added and the reaction mixture (resulting substrate concentration: 0.2 M in dioxane/H_2O 4:1) was stirred at 80 °C for 3–6 h. Upon completion of the coupling (TLC control: silica gel, heptane/EtOAc 7:3), an aqueous 6 M HCl (5 mL) was carefully added (*CAUTION*: gas evolution!) and the mixture was vigorously stirred at 80 °C for 1 h. The mixture was cooled, neutralized by addition of aqueous 5 M NaOH (5 mL) followed by fine neutralization of the mixture by saturated aqueous solutions of $NaHCO_3$. A saturated aqueous solution of $Na_2S_2O_3$ (1 mL) was then added and the mixture was extracted by vigorous stirring with EtOAc (3×5 mL). Each portion of the organic extract was carefully separated from the aqueous phase with a pipette and successively passed through a cartridge filled with anhydrous Na_2SO_4 (3.5 g, ca. 2 mL) and silica gel (1 g, ca. 2 mL) followed by a final wash of the cartridge with ethyl acetate (10 mL). The organic solution was concentrated and the residue purified by chromatography. For parallel preparations, the ethoxyethyl-protected iodopyrazole (as a 1 M solution in dioxane), arylboronic acids (as a 0.5 M stock solutions in dioxane), Cs_2CO_3 (as a 2.4 M stock solution in water), and the catalyst solution could be conveniently dispatched over multiple parallel reactors of appropriate format and size. Within experimental error, the yield of reactions using K_2CO_3 and Cs_2CO_3 remains the same. On millimole scale, the parallel syntheses were performed on an STEM RS10 or Radleys' Carousel 12 reaction stations, while the purification of serial products was carried out by automated HPLC instrument (Knauer) on the Merck NW25 25×200 mm column packed with LiChrospher Si 60 (12 μm), operated at flow rate of 25 mL/min under a heptane/EtOAc gradient approximated to the formula below.

$$c(\text{EtOAc}) = \frac{\left(e^{\frac{at}{T}} - 1\right)(1-K)}{e^a - 1} + K$$

$$c(\text{heptane}) = 1 - c(\text{EtOAc})$$

where T=length of gradient (min), set to 16; K=c(EtOAc) at t=0, set to 0.3; a=exponential gradient parameter, set to 3; t=runtime.[44]

*4.4.1. 3-Ethoxy-4-phenyl-5-(trifluoromethyl)-1H-pyrazole (**10a**).* Obtained as a white powder in 82% yield; mp 126 °C. ^{1}H NMR ($CDCl_3$): 1.41 (t, 3H, J=7.1 Hz); 4.31 (q, 2H, J=7.1 Hz); 7.33–7.53 (m, 5H); 10.5 (br s, 1H). ^{13}C NMR ($CDCl_3$): 14.7; 65.9; 107.1; 120.1 (q, J=268 Hz); 127.5; 128.3; 128.8; 129.2; 131.0 (br); 159.6 (br). HRMS: calcd for $C_{12}H_{11}F_3N_2O$+H: 257.0902; found: 257.0885.

*4.4.2. 4-(2-Chlorophenyl)-3-ethoxy-5-(trifluoromethyl)-1H-pyrazole (**10b**).* Obtained as a white powder in 63% yield; mp 116 °C. ^{1}H NMR ($CDCl_3$): 1.34 (t, 3H, J=7.0 Hz); 4.23 (q, 2H, J=7.0 Hz); 7.38–7.37 (m, 3H); 7.50 (m, 1H); 10.9 (br s, 1H). ^{13}C NMR ($CDCl_3$): 14.8; 66.4; 104.1 (br); 119.9 (q, J=268 Hz); 126.5; 128.0; 129.5; 129.7; 131.0 (br); 132.7; 135.2; 158.9 (br). HRMS: calcd for $C_{12}H_{10}F_3ClN_2O$+H: 291.0512; found: 291.0494.

*4.4.3. 4-(3-Chlorophenyl)-3-ethoxy-5-(trifluoromethyl)-1H-pyrazole (**10c**).* Obtained as a white powder in 96% yield; mp 95 °C. ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, J=7.0 Hz); 4.31 (q, 2H, J=7.0 Hz); 7.31–7.38 (m, 3H); 7.49 (m, 1H); 10.9 (br s, 1H). ^{13}C NMR ($CDCl_3$): 14.7; 66.0; 105.7 (br); 119.8 (q, J=268 Hz); 127.2; 127.7; 129.1 (two signals ?); 130.0;

130.5; 134.2; 159.7 (br). HRMS: calcd for $C_{12}H_{10}F_3ClN_2O$+H: 291.0512; found: 291.0486.

*4.4.4. 4-(4-Chlorophenyl)-3-ethoxy-5-(trifluoromethyl)-1H-pyrazole (**10d**).* Obtained as a white powder in 84% yield; mp 120 °C. ^{1}H NMR ($CDCl_3$): 1.41 (t, 3H, *J*=7.0 Hz); 4.30 (q, 2H, *J*=7.0 Hz); 7.38–7.45 (m, 4H); 10.8 (br s, 1H). ^{13}C NMR ($CDCl_3$): 14.7; 65.9; 106.0; 119.9 (q, *J*=268 Hz); 127.2; 128.6; 130.4; 130.5 (br); 133.5; 159.7. HRMS: calcd for $C_{12}H_{10}F_3ClN_2O$+H: 291.0512; found: 291.0490.

*4.4.5. 3-Ethoxy-4-(2-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole (**10e**).* Obtained as a white powder in 88% yield; mp 117 °C. ^{1}H NMR ($CDCl_3$): 1.34 (t, 3H, *J*=7.1 Hz); 3.81 (s, 3H); 4.24 (q, 2H, *J*=7.1 Hz); 6.96–7.03 (m, 2H); 7.30–7.39 (m, 2H); 10.8 (br s, 1H). ^{13}C NMR ($CDCl_3$): 14.8; 55.3; 66.0; 102.9 (br); 110.8; 117.8; 119.3 (q, *J*=270 Hz); 120.3; 129.5; 131.9; 132.0 (br); 157.3; 159.7 (br). HRMS: calcd for $C_{12}H_{10}F_3N_2O_2$+H: 287.1007; found: 287.0961.

*4.4.6. 3-Ethoxy-4-(3-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole (**10f**).* Obtained as a white powder in 92% yield; mp 89 °C. ^{1}H NMR ($CDCl_3$): 1.41 (t, 3H, *J*=7.0 Hz); 3.80 (s, 3H); 4.30 (q, 2H, *J*=7.0 Hz); 6.89 (m, 1H); 7.10 (m, 2H); 7.32 (m, 1H); 11.2 (br s, 1H). ^{13}C NMR ($CDCl_3$): 14.7; 55.1; 65.9; 106.8 (br); 113.4; 114.5; 119.5 (q, *J*=270 Hz); 121.6; 129.3; 130.0; 131.0 (br); 159.3; 159.7 (br). HRMS: calcd for $C_{12}H_{10}F_3N_2O_2$+H: 287.1007; found: 287.0984.

*4.4.7. 3-Ethoxy-4-(4-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole (**10g**).* Obtained as a white powder in 96% yield; mp 145 °C. ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, *J*=7.1 Hz); 3.86 (s, 3H); 4.31 (q, 2H, *J*=7.1 Hz); 6.97 (m, 2H); 7.44 (m, 2H); 9.95 (br s, 1H). ^{13}C NMR ($CDCl_3$): 14.8; 55.2; 65.7; 107.2; 113.8; 119.8 (q, *J*=270 Hz); 121.0; 130.3; 138.8 (br); 159.0; 160.0. HRMS: calcd for $C_{12}H_{10}F_3N_2O_2$+H: 287.1007; found: 287.0966.

*4.4.8. 3-Ethoxy-4-(4-trifluoromethylphenyl)-5-(trifluoromethyl)-1H-pyrazole (**10h**).* Obtained as a white powder in 91% yield; mp 143 °C. ^{1}H NMR ($CDCl_3$): 1.43 (t, 3H, *J*=7.0 Hz); 4.34 (q, 2H, *J*=7.0 Hz); 7.61 (m, 2H); 7.67 (m, 2H); 10.70 (br s, 1H). ^{13}C NMR ($CDCl_3$): 14.7; 66.0; 106.0; 120.0 (q, *J*=268 Hz); 24.0 (q, *J*=253 Hz); 125.5; 129.3; 129.4; 129.7 (br); 132.5; 160.0. HRMS: calcd for $C_{13}H_{10}F_6N_2O_2$+H: 325.0776; found: 325.0752.

*4.4.9. 4-Phenyl-3-(trifluoromethyl)-1H-pyrazole (**10i**).* Obtained as a white powder, with a tendency to sublime under vacuum, in 91% yield; mp 125 °C. ^{1}H NMR ($CDCl_3$): 7.45 (m, 5H); 7.87 (s, 1H); 14.11 (br s, 1H) (as previously reported[24]). ^{13}C NMR ($CDCl_3$): 121.9 (q, *J*=267 Hz); 122.0; 127.9; 128.7; 129.9; 130.2; 136.9; 138.9 (q, *J*=36 Hz). HRMS: calcd for $C_{10}H_7F_3N_2$+H: 213.0640; found: 213.0594.

*4.4.10. 4-(2-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole (**10j**).* Obtained as an oil in 90% yield. ^{1}H NMR ($CDCl_3$): 7.35 (m, 3H); 7.54 (m, 1H); 7.87 (s, 1H); 14.05 (br s, 1H). ^{13}C NMR ($CDCl_3$): 118.0; 121.5 (q, *J*=267 Hz); 126.6; 129.1; 129.7 (two signals); 131.2; 132.1; 134.2; 140.0 (q, *J*=36 Hz). HRMS: calcd for $C_{10}H_6F_3N_2Cl$+H: 247.0250; found: 247.0209.

*4.4.11. 4-(3-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole (**10k**).* Obtained as a white powder in 92% yield; mp 85 °C. ^{1}H NMR ($CDCl_3$): 7.39 (m, 3H); 7.48 (m, 1H); 7.86 (s, 1H); 14.04 (br s, 1H). ^{13}C NMR ($CDCl_3$): 120.7; 121.8 (q, *J*=267 Hz); 126.3; 128.1; 128.7; 129.9; 130.1; 131.9; 134.5; 138.8 (q, *J*=36 Hz). HRMS: calcd for $C_{10}H_6F_3N_2Cl$+H: 247.0250; found: 247.0203.

*4.4.12. 4-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole (**10l**).* Obtained as a white powder in 50% yield; mp 130 °C. ^{1}H NMR ($CDCl_3$): 7.44 (m, 4H); 7.82 (s, 1H); 13.80 (br s, 1H). ^{13}C NMR ($CDCl_3$): 120.9; 121.8 (q, *J*=267 Hz); 128.6; 128.9; 129.9 (two signals); 134.1; 138.8 (q, *J*=36 Hz). HRMS: calcd for $C_{10}H_6F_3N_2Cl$+H: 247.0250; found: 213.0203.

*4.4.13. 4-(2-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazole (**10m**).* Obtained as a white powder in 93% yield; mp 100 °C. ^{1}H NMR ($CDCl_3$): 3.85 (s, 3H); 7.04 (m, 2H); 7.38 (m, 2H); 7.83 (s, 1H); 13.80 (br s, 1H). ^{13}C NMR ($CDCl_3$): 55.3; 110.8; 117.0; 119.4; 120.2; 121.9 (q, *J*=267 Hz); 129.4; 130.8; 131.2; 139.8 (q, *J*=36 Hz); 156.9. HRMS: calcd for $C_{11}H_9F_3N_2O$+H: 243.0745; found: 243.0692.

*4.4.14. 4-(3-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazole (**10n**).* Obtained as a white powder in 76% yield; mp 87 °C. ^{1}H NMR ($CDCl_3$): 3.84 (s, 3H); 6.95 (m, 1H); 7.06 (m, 2H); 7.39 (m, 1H); 7.84 (s, 1H); 13.70 (br s, 1H). ^{13}C NMR ($CDCl_3$): 55.2; 113.5; 114.4; 121.9 (q, *J*=267 Hz); 121.15; 121.9; 129.6; 129.9; 131.5; 138.7 (q, *J*=36 Hz); 159.5. HRMS: calcd for $C_{11}H_9F_3N_2O$+H: 243.0745; found: 243.0691.

*4.4.15. 4-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazole (**10o**).* Obtained as a white powder in 92% yield; mp 121 °C. ^{1}H NMR ($CDCl_3$): 3.88 (s, 3H); 7.00 (m, 2H); 7.42 (m, 2H); 7.77 (s, 1H); 13.90 (br s, 1H). ^{13}C NMR ($CDCl_3$): 55.3; 114.1; 121.6; 121.7 (q, *J*=267 Hz); 122.6; 129.6; 129.9; 138.6 (q, *J*=36 Hz); 159.4. HRMS: calcd for $C_{11}H_9F_3N_2O$+H: 243.0745; found: 243.0705.

*4.4.16. 4-(4-Trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazole (**10p**).* Obtained as a white powder in 82% yield; mp 137 °C. ^{1}H NMR ($CDCl_3$): 7.62 (m, 2H); 7.72 (m, 2H); 7.96 (s, 1H); 13.80 (br s, 1H). ^{13}C NMR ($CDCl_3$): 120.7; 121.7 (q, *J*=267 Hz); 124.0 (q, *J*=267 Hz); 125.6; 128.9; 130.2; 130.2 (q, *J*=36 Hz); 133.8; 139.0 (*J*=36 Hz). HRMS: calcd for $C_{11}H_6F_6N_2$+H: 281.0513; found: 281.0505.

4.5. Preparation of compounds 14 and 15

In a Biotage tube, the corresponding iodopyrazole[15] (0.735 mmol), benzene boronic acid (0.098 g, 0.80 mmol), and cesium carbonate (0.6 g, 1.83 mmol) were mixed in a 1:1 mixture of water and propanol (5 mL). This solution was degassed by a gentle stream of argon, [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.03 g, 0.036 mmol) was added, the tube was sealed and heated in a microwave oven at 110 °C for 1 h. The resulting suspension was diluted in water, extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness. The resulting residue was purified as described below.

*4.5.1. Ethyl 5-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (**14**).* Obtained as a white powder in 80% yield after a chromatography over silica gel (cyclohexane/dichloromethane from 1:4 to 0:1); mp 141 °C. ^{1}H NMR ($CDCl_3$): 1.26 (t, 3H, *J*=7.0 Hz); 4.26 (q, 2H, *J*=7.0 Hz); 7.47 (m, 3H); 7.55 (m, 2H); 11.45 (br s, 1H). ^{13}C NMR ($CDCl_3$): 13.7; 61.1; 109.5; 120.5 (q, *J*=269 Hz); 127.2; 128.5; 129.0; 130.3; 143.2 (q, *J*=38 Hz); 148.3; 161.6 (this ^{13}C NMR spectrum is more complete than the reported one[45]). HRMS: calcd for $C_{13}H_{11}F_3N_2O_2$+H: 285.0851; found: 285.0849.

*4.5.2. 4-Chloro-5-phenyl-3-(trifluoromethyl)-1H-pyrazole (**15**).* Obtained as a white powder in 83% yield after a chromatography over silica gel (cyclohexane/dichloromethane from 3:7); mp 188 °C. ^{1}H NMR (MeOH-d_4): 7.22 (m, 3H); 7.75 (m, 2H). ^{13}C NMR (MeOH-d_4): 104.6; 124.0 (q, *J*=269 Hz); 126.8; 127.8; 129.5; 130.1; 141.1. HRMS: calcd for $C_{10}H_6F_3N_2$+H: 247.0250; found: 247.0206.

4.6. Preparation of 17 and 18

In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw cap, the corresponding iodopyrazole (0.65 mmol) was degassed with a slow stream of argon for 10 min. A 0.5 M solution of benzylzinc bromide in THF (1.96 mmol) was added, followed by a pre-milled 1:2 mixture palladium(II) acetate/XPhos (0.032 mmol). The tube was sealed and heated at 85 °C for 5 h using an oil bath. After cooling to room temperature, the reaction mixture was diluted in ethyl acetate, washed with a 0.25 M solution of potassium-sodium tartrate twice. The organic phase was dried over sodium sulfate and concentrated to dryness. The resulting residue was further purified as described below.

*4.6.1. 3-Ethoxy-4-benzyl-5-(trifluoromethyl)-1H-pyrazole (**17**).* Obtained as a white powder in 51% yield after a chromatography over neutral alumina (1.5% water; dichloromethane/ethanol from 99:1 to 95:5) followed by a second chromatography over silica gel (dichloromethane); mp 72 °C. ^{1}H NMR ($CDCl_3$): 1.38 (t, 3H, J=7.0 Hz); 3.83 (s, 2H); 4.26 (q, 2H, J=7 Hz); 7.25 (m, 5H). ^{13}C NMR ($CDCl_3$): 14.7; 27.1; 65.3; 105.6; 120.2 (q, J=269 Hz); 126.1; 128.3; 131.1 (q, J=38 Hz); 139.5; 161.2. HRMS: calcd for $C_{13}H_{13}F_3N_2O$+H: 271.1058; found: 271.1002.

*4.6.2. 4-Benzyl-3-(trifluoromethyl)-1H-pyrazole (**18**).* Obtained as an oil in 64% yield after a chromatography over silica gel (cyclohexane/dichloromethane from 1:1 to 0:1). ^{1}H NMR ($CDCl_3$): 4.04 (s, 2H); 7.30 (m, 3H); 7.39 (m, 2H); 7.43 (s, H), 13.77 (br s, 1H). ^{13}C NMR ($CDCl_3$): 29.3; 119.5; 122.1 (q, J=266 Hz); 126.5; 128.5; 128.6; 130.2; 139.5; 139.7 (q, J=36 Hz). HRMS: calcd for $C_{11}H_9F_3N_2$+H: 227.0796; found: 227.0750.

4.7. Ethyl 5-benzyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (21)

In a glass tube sealable with a Teflon-coated joint, compound **12** (0.6 g, 1.79 mmol) was degassed with a slow stream of argon for 10 min. A 0.5 M solution of benzylzinc bromide in THF (10.6 mL, 5.38 mmol) was added, followed by [1,1′-bis(diphenylphosphino) ferrocene] dichloropalladium complexed with dichloromethane (0.072 g; 0.09 mmol). This mixture was sealed and heated at 120 °C for 60 min in an oil bath. After cooling to room temperature, the reaction mixture was diluted in ethyl acetate, washed with a 0.25 M solution of potassium-sodium tartrate twice. The organic phase was dried over sodium sulfate and concentrated to dryness and the residue was purified by a chromatography over silica gel (dichloromethane) to yield compound **21** (0.32 g, 65%), after drying this fraction under a high vacuum to remove some benzyl alcohol, as an off-white powder; mp 104 °C. ^{1}H NMR ($CDCl_3$): 1.39 (t, 3H, J=7.0 Hz); 4.37 (q, 2H, J=7.0 Hz); 4.40 (s, 2H); 7.38 (m, 5H). ^{13}C NMR ($CDCl_3$): 13.9; 31.7; 60.9; 109.1; 120.5 (q, J=269 Hz); 127.4; 128.8; 129.0; 135.6; 142.7 (q, J=37 Hz); 149.3; 161.8. HRMS: calcd for $C_{14}H_{16}F_3N_2O_2$+H: 299.1007; found: 299.0996.

4.8. 5-Benzyl-4-chloro-3-(trifluoromethyl)-1*H*-pyrazole (22)

By using the procedure described for the preparation of **21**, compound **22** was obtained in 69% yield as an off-white powder; mp 107 °C. ^{1}H NMR ($CDCl_3$): 4.05 (s, 2H); 7.23–7.38 (m, 5H); 9.99 (br s, 1H). ^{13}C NMR ($CDCl_3$): 30.0; 107.1; 120.5 (q, J=269 Hz); 127.5; 128.6; 129.1; 135.2; 139.2 (q, J=37 Hz); 141.6 (br). HRMS: calcd for $C_{11}H_8ClF_3N_2$+H: 261.0406; found: 261.0393.

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