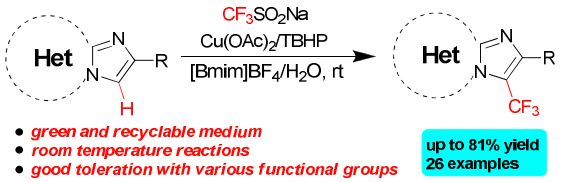
RSC Advances

This article can be cited before page numbers have been issued, to do this please use: X. Ji, L. Wei, F. Chen and R. Tang, *RSC Adv.*, 2015, DOI: 10.1039/C5RA02888D.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C5RA02888D



- *green and recyclable medium*
- *room temperature reactions*
- *good toleration with various functional groups*

up to 81% yield
26 examples

Dynamic Article Links ▶ View Article Online
DOI: 10.1039/C5RA02888D

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Direct Trifluoromethylation of Imidazoheterocycles in a Recyclable Medium at Room Temperature

Xiao-Ming Ji[a,b], Liang Wei[b], Fan Chen[b] and Ri-Yuan Tang*[a,b]

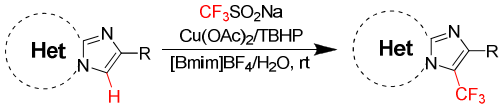
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Regioselective C−H trifluoromethylation of imidazoheterocycles with Langlois` reagent in a recyclable mixed medium of 1-butyl-3-methylimidazoliumtetrafluoroborate ([Bmim]BF_4) and water at room temperature has been developed. In the presence of catalytic cupric acetate and 2-methyl-2-(methylperoxy)propane (TBHP) , this green strategy tolerates a wide range of functional groups to afford diverse trifluoromethylated imidazoheterocycles in moderate to good yields.

Introduction

Imidazoheterocycles are privileged scaffolds with diverse bioactivity,[1] which have been used as SIRT1 activator,[2] RSK2 inhibitors,[3] anticancer agents,[4] and antiviral agents,[5] and in the treatment of Cystic Fibrosis.[6] Several commercially available drugs, such as alpidem, olprinone, necopidem, zolimidine, and saripidem, have been developed by the modification of imidazoheterocyclic skeletons.[7] Thus significant progress has been made in the functionalization of imidazoheterocycles.[8,9] C−H bond functionalization strategy is an ideal route to the preparation of diverse imidazoheterocycles as it is a straightforward, atom economical, and synthetic step economical method. C−H sulfenylation,[10] arylation,[11] alkenylation,[12] and carbonylation[13] have been employed to the functionalization of imidazoheterocycles. However, little attention has been paid to the C−H trifluoromethylation of imidazoheterocycles.[14]

The presence of trifluoromethyl group commonly strengthens the bioactivity of drug candidates,[15] which promotes us to focus on the C−H trifluoromethylation of imidazoheterocycles. Among the trifluoromethylating reagents (including Umemoto`s reagent,[16] Ruppert`s reagent,[17] Togni`s reagent,[18] and Langlois` reagent[19]), Langlois` reagent is a preferable trifluoromethylating reagent as it is stable, inexpensive, and environmental friendly, which has been extensively used in the preparation of diverse trifluoromethylated compounds.[19, 20] Baran group[20b-d, 20g] has made a great contribution to the field of the trifluoromethylation of heterocycles using Langlois` reagent. Despite great success has been achieved, green strategy for the trifluoromethylation remains scarce. The first example for C−H trifluoromethylation using water as a medium was recently reported by Lipshutz group.[20k] Despite the C−H trifluoromethylation of imidazoheterocycles was just carried out in DMSO using silver nitrate as catalyst,[14b] the development of C−H trifluoromethylation of imidazoheterocycles in an environmental friendly medium is highly desirable, which meets the guiding principles of green chemistry.[21] A challenge we are facing is the insolubility of imidazoheterocycles in water at room temperature. We hypothesized that the addition of an ionic liquid to the water may figure out the insolubility problem of imidazoheterocycles; additionally, ionic liquids are commonly stable, non-volatile, and recyclable, which are widely used as green mediums in various reactions.[22] As a part of our continuing interest in the C–H functionalization of imidazoheterocycles,[10h] we report a method for regioselective C–H trifluoromethylation of imidazoheterocycles in a mixed medium of [Bmim]BF_4 and water at room temperature.



Scheme 1 the trifluoromethylation of imidazoheterocycles.

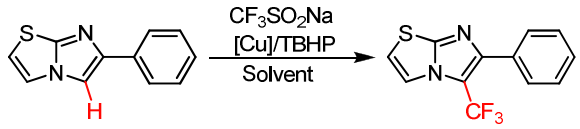
Results and discussion

Initially, we used the trifluoromethylation of 6-phenylimidazo[2,1-*b*]thiazole **1a** with sodium trifluoromethanesulfonate as the model reaction (table 1). Several organic solvents were investigated in the presence of 5 mol% of $Cu(OAc)_2$ and 3 equivalents of TBHP at 25 °C: DMSO was preferable for the trifluoromethylation to afford the product **2a** in 75% (entry 4); whereas other solvents such as CH_3CN, CH_3NO_2, and DMF gave low yields (entries 1–3). The trifluoromethylation of imidazoheterocycles was examined in water as a green solvent.[20k] Unfortunately, the insolubility of **1a** in water leads to the failure of the trifluoromethylation (entry 5). The commercially available [Bmim]BF_4 ionic liquid is a suitable reaction medium for the trifluoromethylation at room temperature, giving product **2a** in 62% yield (entry 6). To our delight, the yield of product **2a** was improved to 73% in the mixed medium of [Bmim]BF_4 and H_2O (*v*:*v* = 1:1) (entry 7). Increasing the proportion of water in the mixed medium decreased the yield of **2a** to 46% (entry 8). The reaction of **1a** at 40 °C appeared to have no change in the yield of **2a** (entry 9); whereas the reaction at 80 °C produced multi-ditrifluoromethylated products, leading to

View Article Online
DOI: 10.1039/C5RA02888D

lower yield of **2a** (entry 10). Other copper catalysts, including CuCl, $CuCl_2·2H_2O$, $Cu(OTf)_2$, and $Cu(TFA)_2$, were then evaluated in $[Bmim]BF_4/H_2O$ at 25 °C, all of these gave lower yields than that obtained with $Cu(OAc)_2$ (entries 11–14). The results show that using 2 equivalents of TBHP decreased the yield of **2a** to 61% (entry 15), and no product was obtained in the absence of TBHP (entry 16). It was demonstrated that only a small amount of **2a** was obtained in the absence of $Cu(OAc)_2$ (entry 17). These suggest that both TBHP and $Cu(OAc)_2$ are key to this transformation. The addition of 3 equivalents of 2,2,6,6-tetramethylpiperdin-1-oxyl (TEMPO) led to the failure of this reaction, suggesting that this reaction may undergo a radical pathway (entry 18).

Table 1. Screening of Optimal Conditions [a]



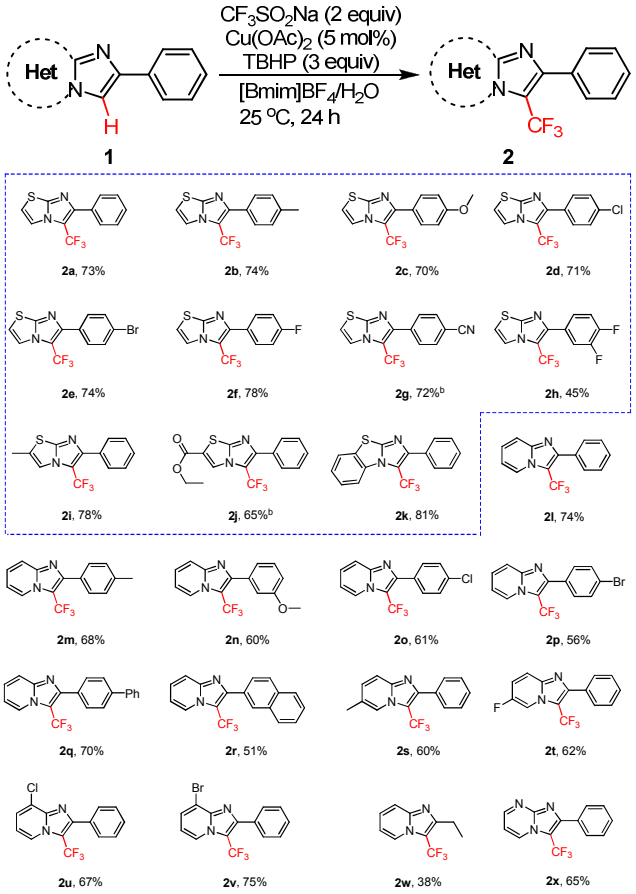
1a **2a**

Entry	[Cu]	Solvent	T (°C)	Isolated yield (%)
1	$Cu(OAc)_2$	CH_3CN	25	46
2	$Cu(OAc)_2$	CH_3NO_2	25	47
3	$Cu(OAc)_2$	DMF	25	43
4	$Cu(OAc)_2$	DMSO	25	75
5	$Cu(OAc)_2$	H_2O	25	0
6	$Cu(OAc)_2$	$[Bmim]BF_4$	25	62
7	$Cu(OAc)_2$	$[Bmim]BF_4/H_2O$	25	73
8[b]	$Cu(OAc)_2$	$[Bmim]BF_4/H_2O$	25	46
9	$Cu(OAc)_2$	$[Bmim]BF_4/H_2O$	40	73
10	$Cu(OAc)_2$	$[Bmim]BF_4/H_2O$	80	56
11	CuCl	$[Bmim]BF_4/H_2O$	25	53
12	$CuCl_2·2H_2O$	$[Bmim]BF_4/H_2O$	25	41
13	$Cu(OTf)_2$	$[Bmim]BF_4/H_2O$	25	52
14	$Cu(TFA)_2$	$[Bmim]BF_4/H_2O$	25	53
15[c]	$Cu(OAc)_2$	$[Bmim]BF_4/H_2O$	25	61
16[d]	$Cu(OAc)_2$	$[Bmim]BF_4/H_2O$	25	trace
17	—	$[Bmim]BF_4/H_2O$	25	<10
18[e]	$Cu(OAc)_2$	$[Bmim]BF_4/H_2O$	25	trace

[a] Reaction conditions: **1a** (0.2 mmol), CF_3SO_2Na (0.4 mmol, 2 equiv), [Cu] (5 mol%), TBHP (3 equiv, 5-6 M solution in decane), solvent (2 mL), $[Bmim]BF_4/H_2O$ (*v*:*v* = 1:1), at 25 °C, reaction for 24 h. [b] $[Bmim]BF_4/H_2O$ (*v*:*v* = 1:2). [c] TBHP (2 equiv). [d] in the absence of TBHP. [e] TEMPO (3 equiv) was added.

With this optimized reaction conditions in hand, the scope of imidazothiazoles was investigated (Table 2). 6-arylimidazo[2,1-*b*]thiazoles containing a methyl, methoxyl, chloro, bromo, fluoro, or cyano group on the benzene ring were well tolerated under the standard conditions. For example, both methyl and methoxyl substituted substrates underwent the reaction smoothly to give the corresponding products **2b** and **2c** in 74% and 70% yields, respectively. The halo-substituted substrates have good reactivity in the trifluoromethylation giving products **2d**–**2f** in good yields. These products are synthetically useful for further modification by coupling reaction at the halo groups. Cyano group also favoured the reaction in $[Bmim]BF_4$ to give product **2g** in 72% yield. Difluoro-substituted substrate also underwent the reaction successfully to afford product **2h** in 45% yield. Different substituents on the thiazole ring were also investigated (products **2i**–**2k**). It is noteworthy that the substrate bearing an ester group was well tolerated in $[Bmim]BF_4$ to give product **2j** in 65% yield, which enables a further chemical transformation at the ester group. To our delight, benzo[d]imidazo[2,1-*b*]thiazole exhibits good reactivity under the standard conditions, affording product **2k** in 81% yield.

Table 2. The Scope of Trifluoromethylation of Imidazoheterocycles [a]



[a] Reaction conditions: **1** (0.2 mmol), CF_3SO_2Na (0.4 mmol, 2 equiv), $Cu(OAc)_2$ (5 mol%), TBHP (3 equiv), $[Bmim]BF_4/H_2O$ (*v*:*v* = 1:1, 2 mL), at 25 °C, reaction for 24 h. [b] in $[Bmim]BF_4$ (2 mL).

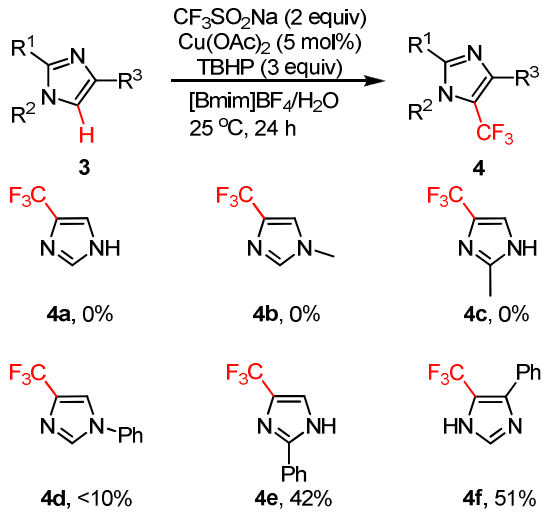
To further demonstrate the versatility of this trifluoromethylation strategy, the scope of imidazo[1,2-*a*]pyridines was investigated (products **2l**–**2w**). 2-Arylimidazo[1,2-*a*]pyridines with a methyl, methoxyl, chloro, bromo, or phenyl group on the benzene ring were well tolerated under the standard conditions, giving the corresponding product in moderate yield (products **2l**–**2q**). A 51% yield of **2r** was also obtained despite the hindrance of the naphthyl group. The results show that substrates with a halo group on the pyridine ring are suitable for this transformation (products **2t**–**2v**). For example, a 75% yield of product **2v** was obtained in the reaction of 8-bromo-2-phenylimidazo[1,2-*a*]pyridine, to which various functional groups can be introduced by the disconnection of C−Br bond. The reaction of 2-ethylimidazo[1,2-*a*]pyridine was also carried out under the standard conditions, albeit with a low yield of

View Article Online
DOI: 10.1039/C5RA02888D

product **2w** that cannot be obtained in the previous work[14b]. Finally, 2-phenylimidazo[1,2-*a*]pyrimidine was reacted with sodium trifluoromethanesulfonate to give product **2x** in 65% yield.

Next, we focused on the trifluoromethylation of imidazoles to expand the scope of application of this methodology (table 3). The results showed that the reactions of 1*H*-imidazole and methyl-substituted 1*H*-imidazoles did not proceed under the standard conditions. To our delight, a small amount of product **4d** was observed in the trifluoromethylation of 1-phenyl-1*H*-imidazole. Encouraged by this result, other phenyl-substituted imidazoles such as 2-phenyl-1*H*-imidazole and 4-phenyl-1*H*-imidazole were reacted with sodium trifluoromethanesulfonate, both reactions proceeded smoothly, giving products **4e** and **4f** in 42% and 51% yields, respectively. Based on these results, we can conclude that the phenyl substituent is essential to the trifluoromethylation of imidazoles. The presence of a phenyl group as a conjugated group in substrates **3e** and **3f** can stabilize the imidazole ring, which may facilitate the trifluoromethylation. Whereas the phenyl group on the nitrogen has weaker conjugation effect on the imidazole ring, leading to the bad result. Substrates **3a-c** did not work at all under the standard conditions may result from the absence of a conjugated group.

Table 3. The Scope of Trifluoromethylation of Imidazoles [a]



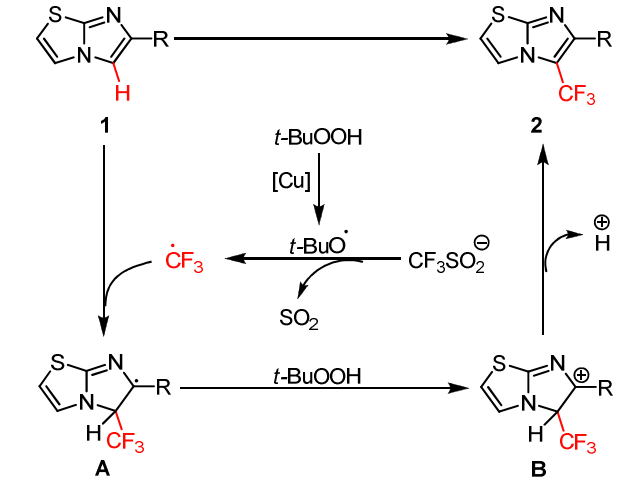
[a] Reaction conditions: **3** (0.2 mmol), CF_3SO_2Na (0.4 mmol, 2 equiv), $Cu(OAc)_2$ (5 mol%), TBHP (3 equiv), $[Bmim]BF_4/H_2O$ (*v*:*v* = 1:1, 2 mL), at 25 °C, reaction for 24 h.

To test their potential in large scale synthesis, the reaction of **1a** was conducted at 2.0 g (10 mmol) scale, and it performed well under the standard conditions to give **2a** in 70% yield (table 4). In the treatment of the reaction mixture with Et_2O, three-phase (from top to bottom is ether, water, and $[Bmim]BF_4$) can be observed. Thus product **2a** is readily isolated from the reaction medium, and cupric acetate was mainly distributed in $[Bmim]BF_4$ and water phases for the reaction cycle (table 4). The results show that the 1th–3th recycles appear to have no obvious change in term of yield of **2a** (entries 1−3); whereas the yield was reduced to 53% and 48% in the 4th and 5th recycles, respectively (entries 4 and 5). It is noteworthy that Et_2O used for extraction can be easily recovered for next extraction. These results suggest that the newly established strategy for the trifluoromethylation of imidazoheterocycles has potential for industrial applications.

Table 4. Recycling of the reaction medium

Entry	Cycle	Yield (%)
1	1[b]	70
2	2[b]	70
3	3[b]	65
4	4[b]	53
5	5	48

[a] Reaction conditions: **1a** (10 mmol), CF_3SO_2Na (20 mmol, 2 equiv), [Cu] (5 mol%), TBHP (3 equiv, 5-6 M solution in decane), $[Bmim]BF_4/H_2O$ (*v*:*v* = 1:1, 30 mL), at 25 °C, reaction for 24 h. [b] Extracted with Et_2O; $[Bmim]BF_4/H_2O$ medium was recycled for next reaction.



Scheme 2 A Possible Mechanism.

According to the present results and previous reports,[14b, 19, 20] a possible mechanism is proposed in scheme 2. The copper catalysts may facilitate the generation of *t*-butoxyl radical from TBHP, the *t*-butoxyl radical reacts with sodium trifluoromethanesulfonate to afford a trifluoromethyl radical in situ. The trifluoromethyl radical then reacts with compound **1** to produce intermediate **A**. The intermediate **A** is oxidized to a carboncation **B**, followed by an oxidative dehydrogenation process to afford target product **2**.

Conclusions

In summary, the mixture of $[Bmim]BF_4$ and H_2O has been found to be an effective reaction medium for the trifluoromethylation of imidazoheterocycles with Langlois` reagent at room temperature. In the presence of catalytic cupric acetate and TBHP, a wide range of functional groups were well tolerated to afford diverse trifluoromethylated imidazoheterocycles in moderate to good yields. Moreover, several phenyl-substituted 1*H*-imidazoles are also suitable for the trifluoromethylation under the standard conditions. This strategy has several advantages: (1) using green and recyclable reaction medium, (2) room temperature reactions, and (3) good toleration with various functional groups.

Experimental Section

View Article Online
DOI: 10.1039/C5RA02888D

General remarks

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-III 500 instrument (500 MHz for ^{1}H, 125 MHz for ^{13}C NMR spectroscopy) using $CDCl_3$ or DMSO-d_6 as the solvent. referenced to internal TMS (0.0 ppm) as the standard. Mass spectra were measured on a Shimadzu GC-MS-QP2010 Plus spectrometer (EI). HRMS (ESI) analysis was measured on a Bruker micrOTOF-Q II instrument. IR analysis was measured on Nicolet IS10 spectrometer (ATR).

General procedure for C−H trifluoromethylation of imidazoheterocycles.

A 15-mL tube with a Teflon cap, equipped with a magnetic stirring bar, was charged with substrate **1a** (0.20 mmol), CF_3SO_2Na (0.40 mmol, 2.0 equiv), $Cu(OAc)_2$ (5 mol%), TBHP (0.60 mmol, 3.0 equiv), and [Bmim]BF_4/H_2O (*v*:*v* = 1:1, 2 mL) was then added sequentially. The tube was then capped and stirred at 25 °C for 24 h. The product was extracted by Et_2O (3 × 10 mL), the ether phase was collected and dried (Na_2SO_4), filtered through a Celite pad, and washed with Et_2O. The filtrate was concentrated *in vacuo* (Et_2O was recovered for next extraction), and the resulting residue was purified by column chromatography (hexane-EtOAc) to afford product **2a** as a light yellow solid; yield: 39.1 mg (73%).

6-phenyl-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (2a). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 4.5 Hz, 1H), 7.46 – 7.39 (m, 3H), 6.98 (d, *J* = 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 149.3, 132.8, 129.0, 128.9, 128.5, 121.8 (q, $J_{C–F}$ = 265.3 Hz), 119.1 (q, $J_{C–F}$ = 2.8 Hz), 114.4, 112.0 (q, $J_{C–F}$ = 41.6 Hz). IR (ATR, cm^{-1}): 1576, 1433, 1335, 1187, 1132, 785. LRMS (EI, 70 eV) *m/z* (%): 268 (100), 249 (11), 229 (6), 134 (6), 58 (7). HRMS (ESI) for $C_{12}H_8F_3N_2S$ $(M+H)^+$: calcd 269.0355, found 269.0350.

6-(*p*-tolyl)-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (2b). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 4.5 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 4.5 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 149.2, 138.8, 129.8, 129.1, 128.6, 121.7 (q, $J_{C–F}$ = 265.6 Hz), 119.0 (q, $J_{C–F}$ = 2.8 Hz), 114.0, 111.5 (q, $J_{C–F}$ = 40.6 Hz), 21.3. IR (ATR, cm^{-1}): 2921, 1528, 1327, 1169, 1090, 832. LRMS (EI, 70 eV) *m/z* (%): 282 (100), 207 (14), 133 (8), 116 (7), 115 (8). HRMS (ESI) for $C_{13}H_{10}F_3N_2S$ $(M+H)^+$: calcd 283.0511, found 283.0520.

6-(4-methoxyphenyl)-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (2c). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 4.0 Hz, 1H), 6.98 – 6.96 (m, 3H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 151.4, 149.0 (d, $J_{C–F}$ = 2.4 Hz), 130.1, 125.2, 121.8 (q, $J_{C–F}$ = 265.3 Hz), 119.0 (q, $J_{C–F}$ = 2.8 Hz), 114.0, 113.9, 111.2 (q, $J_{C–F}$ = 40.5 Hz), 55.4. IR (ATR, cm^{-1}): 3059, 2966, 1428, 1353, 1275, 1182, 865. LRMS (EI, 70 eV) *m/z* (%): 298 (100), 283 (3), 281 (7), 73 (8). HRMS (ESI) for $C_{13}H_9F_3N_2NaOS$ $(M+Na)^+$: calcd 321.0280, found 321.0301.

6-(4-chlorophenyl)-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (2d). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 3H), 7.42 (d, *J* = 6.5 Hz, 2H), 7.05 – 7.02 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 147.9, 135.0, 131.1, 130.1, 128.7, 121.6 (q, $J_{C–F}$ = 265.5 Hz), 119.0, 114.6, 111.9 (q, $J_{C–F}$ = 45.3 Hz). IR (ATR, cm^{-1}): 1538, 1453, 1385, 1126, 1075, 986. LRMS (EI, 70 eV) *m/z* (%): 302 (100), 283 (9), 267 (6), 207 (11), 58 (8). HRMS (ESI) for $C_{12}H_7ClF_3N_2S$ $(M+H)^+$: calcd 302.9965, found 302.9960.

6-(4-bromophenyl)-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (2e). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.58 (m, 5H), 7.01 (d, *J* = 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 147.9, 131.6, 131.6, 130.4, 123.3, 121.5 (q, $J_{C–F}$ = 265.3 Hz), 119.0 (q, $J_{C–F}$ = 2.8 Hz), 114.6, 111.9 (q, $J_{C–F}$ = 42.3 Hz). IR (ATR, cm^{-1}): 1528, 1437, 1218, 1182, 1120, 973. LRMS (EI, 70 eV) *m/z* (%): 348 (100), 346 (93), 268 (6), 169 (9). HRMS (ESI) for $C_{12}H_7BrF_3N_2S$ $(M+H)^+$: calcd 346.9460, found 346.9456.

6-(4-fluorophenyl)-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (2f). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.59 (d, *J* = 4.5 Hz, 1H), 7.13 (t, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2 (d, $J_{C–F}$ = 247.1 Hz), 151.5, 148.1, 130.7 (d, $J_{C–F}$ = 8.4 Hz), 128.78 (d, $J_{C–F}$ = 3.3 Hz), 121.6 (q, $J_{C–F}$ = 265.4 Hz), 119.0 (q, $J_{C–F}$ = 2.8 Hz), 115.4 (d, $J_{C–F}$ = 21.6 Hz), 114.4, 111.7 (q, $J_{C–F}$ = 41.4 Hz). IR (ATR, cm^{-1}): 1487, 1243, 1187, 1169, 819, 765. LRMS (EI, 70 eV) *m/z* (%): 286 (100), 265 (7), 133 (6), 121 (7), 58 (6). HRMS (ESI) for $C_{12}H_7F_4N_2S$ $(M+H)^+$: calcd 287.0261, found 287.0276.

4-(5-(trifluoromethyl)imidazo[2,1-*b*]thiazol-6-yl)benzonitrile (2g). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.68 – 7.64 (m, 1H), 7.14 – 7.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 146.7, 137.0, 132.2, 129.3, 121.4 (q, $J_{C–F}$ = 265.6 Hz), 119.0 (q, $J_{C–F}$ = 2.8 Hz), 118.70, 115.4, 112.7 (q, $J_{C–F}$ = 41.0 Hz), 112.4. IR (ATR, cm^{-1}): 2226, 2098, 1517, 1480, 1175, 1149, 1082, 986, 971. LRMS (EI, 70 eV) *m/z* (%): 293 (100), 281 (17), 243 (7), 73 (7), 58 (7). HRMS (ESI) for $C_{13}H_7F_3N_3S$ $(M+H)^+$: calcd 294.0307, found 294.0309.

6-(3,4-difluorophenyl)-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (2h). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.46 (m, 3H), 7.26 – 7.04 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 150.8 (dd, $J_{C–F}$ = 242.4, 11.5 Hz), 150.2 (dd, $J_{C–F}$ = 244.9, 11.7 Hz), 146.8, 129.5, 125.0, 121.4 (q, $J_{C–F}$ = 265.5 Hz), 118.9, 117.8 (d, $J_{C–F}$ = 18.5 Hz), 117.3 (d, $J_{C–F}$ = 17.4 Hz), 114.7, 112.0 (q, $J_{C–F}$ = 43.4 Hz). IR (ATR, cm^{-1}): 3037, 1518, 1398, 1178, 1150, 1090, 969. LRMS (EI, 70 eV) *m/z* (%): 304 (100), 285 (17), 265 (7), 187 (9), 58 (8). HRMS (ESI) for $C_{12}H_6F_5N_2S$ $(M+H)^+$: calcd 305.0166, found 305.0186.

2-methyl-6-phenyl-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (2i). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.39 (m, 3H), 7.30 (s, 1H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 147.9, 132.8, 128.8, 128.7, 128.4, 128.4, 121.7 (q, $J_{C–F}$ = 265.5 Hz), 115.5 (q, $J_{C–F}$ = 2.8 Hz), 111.5 (q, $J_{C–F}$ = 40.4 Hz), 14.1. IR (ATR, cm^{-1}): 2931, 1435, 1352, 1183, 1150, 837. LRMS (EI, 70 eV) *m/z* (%): 282 (100), 263 (7), 261 (7), 103 (5), 72 (3). HRMS (ESI) for $C_{13}H_{10}F_3N_2S$ $(M+H)^+$: calcd 283.0511, found 283.0508.

Ethyl 6-phenyl-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole-2-carboxylate (2j). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.64 (d, *J* = 6.5 Hz, 2H), 7.38 – 7.37 (m, 3H), 4.35 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 151.0, 149.2, 130.8, 128.2, 127.7,

View Article Online
DOI: 10.1039/C5RA02888D

127.4, 123.3, 122.7, 120.2 (q, J_{C-F} = 265.7 Hz), 110.9 (q, J_{C-F} = 40.4 Hz), 61.4, 13.1. IR (ATR, cm^{-1}): 1735, 1600, 1563, 1387, 1162, 1139, 1089, 975. LRMS (EI, 70 eV) *m/z* (%): 340 (100), 312 (62), 207 (21), 267 (8), 73 (11). HRMS (ESI) for $C_{15}H_{12}F_3N_2O_2S$ $(M+H)^+$: calcd 341.0566, found 341.0559.

2-phenyl-3-(trifluoromethyl)benzo[d]imidazo[2,1-*b*]thiazole (2k)[14a]. Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.54 (m, 3H), 7.37 – 7.31 (m, 4H), 7.25 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 149.1, 131.9, 131.1, 129.1, 128.6, 127.9, 127.1, 125.8, 124.6, 123.3, 120.5 (q, J_{C-F} = 265.3 Hz), 113.7 (q, J_{C-F} = 4.6 Hz), 111.5 (q, J_{C-F} = 40.5 Hz). IR (ATR, cm^{-1}): 3072, 1551, 1478, 1296, 1178, 1157, 1093, 976, 773. LRMS (EI, 70 eV) *m/z* (%): 318 (100), 297 (10), 159 (11), 108 (10), 69 (10).

2-phenyl-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2l)[14a]. Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 3.0 Hz, 1H), 7.61 – 7.60 (m, 3H), 7.35 – 7.22 (m, 4H), 6.82 (t, *J* = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 145.1, 131.9, 128.5, 127.9, 127.1, 125.9, 124.5, 121.9 (q, J_{C-F} = 265.2 Hz), 117.0, 112.9, 108.5 (q, J_{C-F} = 38.4 Hz). IR (ATR, cm^{-1}): 3059, 1580, 1510, 1405, 1385, 1198, 1116, 1062, 995, 781. LRMS (EI, 70 eV) *m/z* (%): 262 (100), 241 (15), 212 (10), 192 (5), 78 (13).

2-(*p*-tolyl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2m). Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.2 Hz 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 6.5 Hz, 2H), 7.35 (s, 1H), 7.27 (d, *J* = 7.0 Hz, 2H), 6.94 (d, *J* = 6.5 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 146.2, 139.0, 130.0, 129.5, 129.0, 126.9, 125.5, 122.1 (q, J_{C-F} = 265.5 Hz), 118.0, 113.9, 109.4 (q, J_{C-F} = 40.6 Hz), 21.4. IR (ATR, cm^{-1}): 3045, 2973, 1539, 1462, 1327, 1251, 1152, 1073, 983, 754. LRMS (EI, 70 eV) *m/z* (%): 276 (100), 255 (5), 205 (7), 103 (5), 78 (11). HRMS (ESI) for $C_{15}H_{12}F_3N_2$ $(M+H)^+$: calcd 277.0947, found 277.0960.

2-(3-methoxyphenyl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2n). Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 4.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.28 – 7.25 (m, 2H), 7.00 (d, *J* = 6.0 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 147.9, 146.1, 134.2, 129.3, 127.1, 125.6, 122.1, 121.9 (q, J_{C-F} = 265.4 Hz), 118.1, 115.1, 114.7, 114.1, 109.7 (q, J_{C-F} = 36.0 Hz), 55.4. IR (ATR, cm^{-1}): 3021, 2962, 1538, 1458, 1397, 1263, 1082, 767. LRMS (EI, 70 eV) *m/z* (%): 292 (100), 273 (10), 241(10), 78 (3). HRMS (ESI) for $C_{15}H_{12}F_3N_2O$ $(M+H)^+$: calcd 293.0896, found 293.0898.

2-(4-chlorophenyl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2o). Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 6.5 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 146.0, 135.0, 131.3, 130.8, 128.3, 127.1, 125.4 (q, J_{C-F} = 3.3 Hz), 121.7 (q, J_{C-F} = 265.6 Hz), 117.9, 114.0, 109.5 (q, J_{C-F} = 39.0 Hz). IR (ATR, cm^{-1}): 1567, 1436, 1332, 1189, 1109, 1116, 752. LRMS (EI, 70 eV) *m/z* (%): 296 (100), 277 (9), 241 (6), 138 (7), 51 (14). HRMS (ESI) for $C_{14}H_9ClF_3N_2$ $(M+H)^+$: calcd 297.0401, found 297.0414.

2-(4-bromophenyl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2p). Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.0 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.60 – 7.57 (m, 4H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 146.2, 131.9, 131.5, 131.2, 127.3, 125.6 (q, J_{C-F} = 3.5 Hz), 123.5, 121.9 (q, J_{C-F} = 265.3 Hz), 118.1, 114.2, 109.7 (q, J_{C-F} = 39.4 Hz). IR (ATR, cm^{-1}): 1530, 1398, 1181, 1139, 726, 628. LRMS (EI, 70 eV) *m/z* (%): 340 (100), 342 (97), 261 (30), 207 (21), 73 (11). HRMS (ESI) for $C_{14}H_9BrF_3N_2$ $(M+H)^+$: calcd 340.9896, found 340.9891.

2-([1,1'-biphenyl]-4-yl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2q). Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 6.5 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.76 – 7.64 (m, 5H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.36 (d, *J* = 6.5 Hz, 2H), 6.97 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 146.2, 141.8, 140.6, 131.8, 130.0, 128.8, 127.6, 127.2, 127.0, 126.9, 125.4 (q, J_{C-F} = 3.6 Hz), 122.0 (q, J_{C-F} = 265.5 Hz), 118.0, 114.0, 109.6 (q, J_{C-F} = 39.3 Hz). IR (ATR, cm^{-1}): 1506, 1421, 1368, 1261, 1017, 729. LRMS (EI, 70 eV) *m/z* (%): 338 (100), 317 (5), 281 (5), 169 (4), 78 (7). HRMS (ESI) for $C_{20}H_{13}F_3N_2Na$ $(M+Na)^+$: calcd 361.0923, found 361.0940.

2-(naphthalen-2-yl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2r). Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.0 Hz, 1H), 8.21 (s, 1H), 7.93 – 7.81 (m, 4H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.51 – 7.50 (m, 2H), 7.36 – 7.33 (m, 1H), 6.94 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 146.2, 133.5, 133.1, 130.3, 129.3, 128.6, 127.8, 127.7, 127.0, 126.7, 126.3, 125.5 (q, J_{C-F} = 3.5 Hz), 122.0 (q, J_{C-F} = 265.4 Hz), 118.1, 114.0, 109.8 (q, J_{C-F} = 39.1 Hz). IR (ATR, cm^{-1}): 3019, 1526, 1366, 1157, 1075, 971. LRMS (EI, 70 eV) *m/z* (%): 312 (100), 291 (13), 273 (8), 156 (5), 73 (5). HRMS (ESI) for $C_{18}H_{12}F_3N_2$ $(M+H)^+$: calcd 313.0947, found 313.0962.

6-methyl-2-phenyl-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2s). Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.69 (d, *J* = 6.0 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 3H), 7.22 (d, *J* = 9.0 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 145.3, 133.2, 130.1, 129.6, 128.9, 128.2, 123.9, 123.2 (q, J_{C-F} = 3.5 Hz), 122.1 (q, J_{C-F} = 265.6 Hz), 117.3, 109.2 (q, J_{C-F} = 32.9 Hz), 18.4. IR (ATR, cm^{-1}): 2931, 1540, 1259, 1165, 1098, 825, 796. LRMS (EI, 70 eV) *m/z* (%): 276 (100), 237 (4), 226 (8), 128 (4), 92 (10). HRMS (ESI) for $C_{15}H_{12}F_3N_2$ $(M+H)^+$: calcd 277.0947, found 277.0964.

6-fluoro-2-phenyl-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2t). Light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.78 – 7.62 (m, 3H), 7.46 – 7.45 (m, 3H), 7.33 – 7.29 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 (d, J_{C-F} = 238.4 Hz), 149.1, 143.8, 132.6, 129.5, 129.2, 128.3, 121.7 (q, J_{C-F} = 265.5 Hz), 119.1 (d, J_{C-F} = 25.2 Hz), 118.6 (d, J_{C-F} = 8.9 Hz), 112.8 (dq, J_{C-F} = 42.5, 3.75 Hz), 111.0 (q, J_{C-F} = 39.4 Hz). IR (ATR, cm^{-1}): 1510, 1483, 1386, 1265, 1173, 916. LRMS (EI, 70 eV) *m/z* (%): 280 (100), 261 (10), 259 (17), 210 (6), 96 (17). HRMS (ESI) for $C_{14}H_9F_4N_2$ $(M+H)^+$: calcd 281.0696, found 281.0709.

8-chloro-2-phenyl-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2u). Light green solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.0 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 2H), 7.42 – 7.37 (m, 4H), 6.85 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 142.6, 131.4, 128.7, 128.2, 127.2, 124.9, 123.1 (q, J_{C-F} = 3.6 Hz), 123.0, 120.5 (q, J_{C-F} = 265.4 Hz), 112.6, 110.2 (q, J_{C-F} = 39.6 Hz). IR (ATR, cm^{-1}): 3029, 1550, 1376, 1187, 1117, 1090, 783, 687. LRMS (EI, 70 eV) *m/z* (%): 296 (100), 298 (33), 275 (12), 138 (8), 76 (10). HRMS (ESI) for $C_{14}H_8ClF_3N_2Na$ $(M+Na)^+$: calcd 319.0220, found 319.0227.

8-bromo-2-phenyl-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine

View Article Online
DOI: 10.1039/C5RA02888D

(2v). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 7.0 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.58 – 7.52 (m, 1H), 7.40 – 7.32 (m, 3H), 6.77 (t, J = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 143.3, 131.6, 128.9, 128.5, 128.3, 127.3, 123.9, 120.7 (q, $J_{C–F}$ = 265.3 Hz), 113.1, 111.4, 110.5 (q, $J_{C–F}$ = 39.6 Hz). IR (ATR, cm^{-1}): 1538, 1472, 1335, 1156, 980, 712. LRMS (EI, 70 eV) *m/z* (%): 340 (100), 342 (98), 321 (12), 170 (9), 158 (10). HRMS (ESI) for $C_{14}H_8BrF_3N_2Na$ $(M+Na)^+$: calcd 362.9715, found 362.9738.

2-ethyl-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2w). Brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 5.5 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 2.94 (q, J = 7.0 Hz, 2H), 1.36 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 135.9, 129.8, 126.3, 125.2, 120.7 (q, $J_{C–F}$ = 265.5 Hz), 117.4, 113.4, 31.1, 13.7. IR (ATR, cm^{-1}): 2931, 1512, 1255, 1221, 1186, 1122, 726. LRMS (EI, 70 eV) *m/z* (%): 214 (51), 213 (100), 195 (7), 145 (6), 78 (22). HRMS (ESI) for $C_{10}H_{10}F_3N_2$ $(M+H)^+$: calcd 215.0791, found 215.0795.

2-phenyl-3-(trifluoromethyl)imidazo[1,2-*a*]pyrimidine (2x). Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 – 8.64 (m, 2H), 7.78 (d, J = 4.0 Hz, 2H), 7.59 – 7.39 (m, 3H), 7.13 – 7.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 149.5, 148.6, 133.5, 132.1, 129.6, 129.5, 128.3, 121.5 (q, $J_{C–F}$ = 265.5 Hz), 110.2, 108.1 (q, $J_{C–F}$ = 39.6 Hz). IR (ATR, cm^{-1}):1636, 1510, 1483, 1381, 1215, 1172, 1086, 980, 712. LRMS (EI, 70 eV) *m/z* (%): 263 (100), 242 (19), 79 (2), 73 (11). HRMS (ESI) for $C_{13}H_8F_3N_3Na$ $(M+Na)^+$: calcd 286.0563, found 286.0562.

2-phenyl-4-(trifluoromethyl)-1*H*-imidazole (4e).[23] White solid. ^{1}H NMR (500 MHz, Acetone) δ 12.19 (brs, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.61 (s, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, Acetone) δ 148.7, 130.7, 130.1, 129.7, 127.0, 126.5, 123.4 (q, $J_{C–F}$ = 265.3 Hz), 118.9. IR (ATR, cm^{-1}): 2932, 2306, 1578, 1556, 1359, 1172, 1148, 975. LRMS (EI, 70 eV) *m/z* (%): 212 (100), 192 (18), 165 (49), 116 (36), 77 (23).

5-phenyl-4-(trifluoromethyl)-1*H*-imidazole (4f).[23] Light yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 13.22 (brs, 1H), 7.97 (s, 1H), 7.61 – 7.41 (m, 5H). ^{13}C NMR (125 MHz, DMSO) δ 136.5, 131.4, 128.8, 128.6, 128.4, 122.6 (q, $J_{C–F}$ = 265.5 Hz). IR (ATR, cm^{-1}): 2928, 1567, 1263, 1178, 1152, 798. LRMS (EI, 70 eV) *m/z* (%): 212 (100), 192 (18), 165 (23), 109 (21), 89 (29).

Notes and references

[a] *College of Science, South China Agricultural University, Guangzhou 510642, China. Tel:+86577-8668-9615; E-mail: try00312@163.com*
[b] *College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, China. Tel:+86577-8668-9615; E-mail: try@wzu.edu.cn*

† Electronic Supplementary Information (ESI) available: [coppies of ^{1}H and ^{13}C spectra for all compounds.]. See DOI: 10.1039/b000000x/

1 (a) C. Enguehard-Gueiffier and A. Gueiffier, *Mini-Rev. Med. Chem.,* 2007, **7**, 888. (b) F. Couty and G. Evano, Comprehensive Heterocyclic Chemistry; Elsevier: Oxford, 2008.

2 (a) C. B. Vu, J. E. Bemis, J. S. Disch, P. Y. Ng, J. J. Nunes, J. C. Milne, D. P. Carney, A. V. Lynch, J. J. Smith, S. Lavu, P. D. Lambert, D. J. Gagne, M. R. Jirousek, S. Schenk, J. M. Olefsky and R. B. Perni, *J. Med. Chem.,* 2009, **52**, 1275. (b) Y. Matsuya, Y. Kobayashi, S. Uchida, Y. Itoh, H. Sawada, T. Suzuki, N. Miyata, K. Sugimoto and N. Toyooka, *Bioorg. Med. Chem. Lett.,* 2013, **2317**, 4907.

3 A. Andreani, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, D. Lannigan, J. Smith, D. Scudiero, S. Kondapaka and R. H. Shoemaker, *Eur. J. Med. Chem.,* 2011, **46**, 4311.

4 Selected references, see: (a) J.-H. Park, M. I. El-Gamal, Y. Su. Lee and Ch.-H. Oh, *Eur. J. Med. Chem.,* 2011, **46**, 5769. (b) A. R. Ali, E. R. El-Bendary, M. A. Ghaly and I. A. Shehata, *Eur. J. Med. Chem.,* 2014, **75**, 492.

5 (a) J. S. Barradas, M. I. Errea, N. B. D'Accorso, C. S. Sepulveda and E. B. Damonte, *Eur. J. Med. Chem.,* 2010, **46**, 259. (b) T. Juspin, M. Laget, T. Terme, N. Azas and P. Vanelle, *Eur. J. Med. Chem.,* 2010, **45**, 840.

6 R. Budriesi, P. Ioan, A. Leoni, N. Pedemonte, A. Locatelli, M. Micucci, A. Chiarini and L. J. V. Galietta, *J. Med. Chem.,* 2011, **54**, 3885.

7 (a) D. Belohlavek and P. J. Malfertheiner, *Scand. Gastroenterol. Suppl.,* 1979, **54**, 44. (b) R. J. Boerner and H. J. Moller, *Psychopharmako. Therap.,*1997, **4**, 145. (c) Y. Abe, H. Kayakiri, S. Satoh, T. Inoue, Y. Sawada, N. Inamura, M. Asano, I. Aramori, C. Hatori, H. Sawai, T. Oku and H. Tanaka, *J. Med. Chem.,* 1998, **41**, 4587. (d) K. Mizushige, T. Ueda, K. Yukiiri and H. Suzuki, *Cardiovasc. Drug. Rev.,* 2002, **20**, 163. (e) T. Okubo, R. Yoshikawa, S. Chaki, S. Okuyama and A. Nakazato, *Bioorg. Med. Chem.,* 2004, **12**, 423. (f) H. Mori, M. Tanaka, R. Kayasuga, T. Masuda, Y. Ochi, H. Yamada, K. Ki shikawa, M. Ito and T. Nakamura, *Bone,* 2008, **43**, 840.

8 References for imidazo-[2,1-*b*]thiazoles, see: (a) G. Kolavi, V. Hegde and I. A. Khazi, *Tetrahedron Lett.,* 2006, **47**, 2811. (b) G. Huang, H. Sun, X. Qiu, C. Jin, C. Lin, Y. Shen, J. Jiang and L. Wang, *Org. Lett.,* 2011, **13**, 5224. (c) C. Mukherjee, K. T. Watanabe and E. R. Biehl, *Tetrahedron Lett.,* 2012, **53**, 6008.

9 References for imidazo-[1,2-*a*]pyridine, see: (a) N. Chernyak and V. Gevorgyan, *Angew. Chem., Int. Ed.,* 2010, **49**, 2743. (b) E. Kianmehr, M. Ghanbari, M. N. Niri and R. Faramarzi, *J. Comb. Chem.,* 2010, **12**, 41. (c) H. G. Wang, Y. Wang, D. D. Liang, L. Y. Liu, J. C. Zhang and Q. Zhu, *Angew. Chem., Int. Ed.,* 2011, **50**, 5678. (d) L. J. Ma, X. P. Wang, W. Yu and B. Han, *Chem. Commun.,* 2011, **47**, 11333. (e) Ł. Albrecht, A. Albrecht, L. K. Ransborg and K. A. Jørgensen, *Chem. Sci.,* 2011, **2**, 1273. (f) D. Sucunza, A. Samadi, M. Chioua, D. B. Silva, C. Yunta, L. Infantes, M. C. Carreiras, E. Soriano and J. Marco-Contelles, *Chem. Commun.,* 2011, **47**, 5043. (g) R. L. Yan, H. Yan, C. Ma, Z. Y. Ren, X. A. Gao, G. S. Huang and Y. M. Liang, *J. Org. Chem.,* 2012, **77**, 2024. (h) S. K. Guchhait, A. L. Chandgude and G. Priyadarshani, *J. Org. Chem.,* 2012, **77**, 4438. (i) D. K. Nair, S. M. Mobin and I. N. N. Namboothiri, *Org. Lett.,* 2012, **14**, 4580. (j) C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han and A. Lei, *Chem. Commun.,* 2012, **48**, 11073. (k) J. Zeng, Y. J. Tan, M. L. Leow and X.-W. Liu, *Org. Lett.,* 2012, **14**, 4386. (l) H. Yan, R. Yan, S. Yang, X. Gao, Y. Wang, G. Huang and Y. Liang, *Chem. Asian J.,* 2012, **7**, 2028. (m) M. Chioua, E. Soriano, L. Infantes, M. L. Jimeno, J. Marco-Contelles and A. Samadi, *Eur. J. Org. Chem.,* 2013, 35. (n) A. K. Bagdi, M. Rahman, S. Santra, A. Majee and A. Hajra, *Adv. Synth. Catal.,* 2013, **355**, 1741. (o) Y. Gao, M. Yin, W. Wu, H. Huang and H. Jiang, *Adv. Synth. Catal.,* 2013, **355**, 2263. (p) D. C. Mohan, S. N. Rao and S. Adimurthy, *J. Org. Chem.,* 2013, **78**, 1266. (q) D. C. Mohan, R. R. Donthiri, S. N. Rao and S. Adimurthy, *Adv. Synth. Catal.,* 2013, **355**, 2217. (r) J. Koubachi, S. El Kazzouli, M. Bousmina and G. Guillaumet, *Eur. J. Org. Chem.,* 2014, 5119. (s) S. Mishra, K. Monir, S. Mitra and A. Hajra, *Org. Lett.,* 2014, **16**, 6084. (t) A. K. Bagdi, S. Santra, K. Monir and A. Hajra, *Chem. Commun.,* 2015, **51**, 1555.

10 (a) D. C. Mohan, S. N. Rao, C. Ravi and S. Adimurthy, *Asian J. Org. Chem.,* 2014, **3**, 609. (b) Z. Li, J. Hong and X. Zhou, *Tetrahedron*, 2011, **67**, 3690; (c) W. Ge, X. Zhu and Y. Wei, *Eur. J. Org. Chem.,* 2013, 6015. (d) S. M. Patil, S. Kulkarni, M. Mascarenhas, R. Sharma, S. M. Roopan and A. Roychowdhury, *Tetrahedron,* 2013, **69**, 8255. (e) Z. Gao, X. Zhu and R. Zhang, *RSC Adv.,* 2014, **4**, 19891. (f) C. Ravi, D. C. Mohan and S. Adimurthy, *Org. Lett.,*

View Article Online
DOI: 10.1039/C5RA02888D

2014, **16**, 2978. (g) M.-A. Hiebel and S. Berteina-Raboin, *Green Chem.*, 2015, **17**, 937. (h) X.-M. Ji, S.-J. Zhou, F. Chen, X.-G. Zhang and R.-Y. Tang, *Synthesis*, 2015, 659.

11 (a) J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Synlett,* 2006, 3237. (b) B. B. Touré, B. S. Lane and D. Sames, *Org. Lett.,* 2006, **8**, 1979. (c) M. Aginagalde, Y. Vara, A. Arrieta, R. Zangi, V. L. Cebolla, A. Delgado-Camon and F. P. Cossio, *J. Org. Chem.,* 2010, **75**, 2776. (d) P.-V. Kumar, W.-S. Lin, J.-S. Shen, D. Nandi and H. M.Lee, *Organometallics,* 2011, **30**, 5160. (e) H. Cao, H. Zhan, Y. Lin, X.-L. Lin, Z. Du and H. Jiang, *Org. Lett.,* 2012, **14**, 1688. (f) H.-Y. Fu, L. Chen and H. Doucet, *J. Org. Chem.,* 2012, **77**, 4473. (g) H. -Y. Fu, L. Zhao, C. Bruneau and H. Doucet, *Synlett,* 2012, **23**, 2077. (h) H. Cao, Y. Lin, H. Zhan, Z. Du, X. Lin, Q.-M. Liang and H. Zhang, *RSC Adv.,* 2012, **2**, 5972. (i) F. Belkessam, F. Derridj, L. Zhao, A. Elias, M. Aidene, S. Djebbar and H. Doucet, *Tetrahedron Lett.,* 2013, **54**, 4888. (j) J. Lee, J. Chung, S.-M. Byun, B. M. Kim and C. Lee, *Tetrahedron,* 2013, **69**, 5660. (k) C.-H. Ke, B.-C. Kuo, D. Nandi and H. M. Lee, *Organometallics,* 2013, **32**, 4775. (l) S. Wang, W. Liu, J. Cen, J. Liao, J. Huang and H. Zhan, *Tetrahedron Lett.,* 2014, **55**, 1589. (m) L. Zhao, H. Zhan, J. Liao, J. Huang, Q. Chen, H. Qiu and H. Cao, *Catal. Commun.,* 2014, **56**, 65. (n) S. Huang, J. Qing, S. Wang, H. Wang, L. Zhang and Y. Tang, *Org. Biomol. Chem.,* 2014, **12**, 2344.

12 (a) J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Synthesis,* 2008, 2537. (b) J. Koubachi, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Synthesis,* 2009, 271. (c) H. Cao, S. Lei, J. Liao, J. Huang, H. Qiu, Q. Chen, S. Qiu and Y. Chen, *RSC Adv.,* 2014, **4**, 50137. (d) H. Zhan, L. Zhao, N. Li, L. Chen, J. Liu, J. Liao and H. Cao, *RSC Adv.,* 2014, **4**, 32013.

13 (a) T. Fukuyama, N. Chatani, F. Kakiuchi and S. Murai, *J. Am. Chem. Soc.,* 199**6**, **118**, 493. (b) N. Chatani, Y. Ie, F. Kakiuchi and S. Murai, *J. Org. Chem.,* 1997, **62**, 2604. (c) T. Fukuyama, N. Chatani, J. Tatsumi, F. Kakiuchi and S. Murai, *J. Am. Chem. Soc.,* 1998, **120**, 11522.

14 (a) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu and J.-C. Xiao, *Angew. Chem., Int. Ed*., 2011, **50**, 1896. (b) K. Monir, A. K. Bagdi, M. Ghosh and A. Hajra, *J. Org. Chem.,* 2015, **80**, 1332.

15 (a) P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications; Wiley-VCH: Weinheim, 2004. (b) I. Ojima, Fluorine in Medicinal Chemistry and Chemical Biology; W iley-Blackwell: Chichester, 2009. (c) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.,* 2008, **37**, 320. (d) W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Acena, K. Izawa, H. Liu and V. A. Soloshonok, *J. Fluorine Chem.,* 2014, **167**, 37.

16 C. Zhang, *Org. Biomol. Chem.,* 2014, **12**, 6580.

17 (a) L. Chu and F.-L. Qing, *Acc. Chem. Res.,* 2014, **47**, 1513. (b) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.,* 2015, **115**, 683.

18 J. Charpentier, N. Fruh and A. Togni, *Chem. Rev.,* 2015, **115**, 650.

19 C. Zhang, *Adv. Synth. Catal.,* 2014, **356**, 2895.

20 Selected references, see: (a) B. R. Langlois, E. Laurent and N. Roidot, *Tetrahedron Lett.,* 1991, **32**, 7525. (b) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci. U. S. A.,* 2011, **108**, 14411. (c) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature,* 2012, **492**, 95. (d) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.,* 2012, **134**, 1494. (e) A. Evitt, L. M. Tedaldi and G. K. Wagner, *Chem. Comm.,* 2012, **48**, 11856. (f) D. Musumeci, C. Irace, R. Santamaria and D. Montesarchio, *Med. Chem. Comm.,* 2013, **4**, 1405. (g) F. O'Hara, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.,* 2013, **135**, 12122. (h) Z. Li, Z. Cui and Z.-Q. Liu, *Org. Lett.,* 2013, **15**, 406. (i) M. Wu, X. Ji, W. Dai and S. Cao, *J. Org. Chem.,* 2014, **79**, 8984. (j) E. P. Stout, M. Y. Choi, J. E. Castro and T. F. Molinski, *J. Med. Chem.,* 2014, **57**, 5085. (k) J. C. Fennewald and B. H. Lipshutz, *Green Chem.,* 2014, **16**, 1097.

21 P. T. W. Anastas and J. C. Warner, Green Chemistry: Theory and Practice, Oxford University Press, New York, NY, 1998.

22 (a) G. Cevasco and C. Chiappe, *Green Chem.,* 2014, **16**, 2375. (b) A. Pathak, N. Jangid, R. Ameta and P. B. Punjabi, *Green Chem.,* 2014, **16**, 109.

23 H. Kimoto, S. Fujii and L. Cohen, *J. Org. Chem*., 1982, **47**, 2867.