An Efficient Protocol for the Synthesis of O-Fluoroalkylisoureas through Copper-Catalysed, Three-Component Reaction of Cyanamides, Fluoroalcohols and Diaryliodonium Triflates

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Abstract A copper-catalysed, three-component reaction involving cyanamides, fluoroalcohols and diaryliodonium triflates is disclosed for the synthesis of O-fluoroalkylisoureas. Various O-fluoroalkylisoureas were obtained in good yields by using simple and readily available substrates. Moreover, C–H activation of O-fluoroalkylisoureas mediated by PhI(OAc)\textsubscript{2} was established to obtain 2-fluoroalkoxybenzimidazoles in high yields at room temperature.

Key words copper-catalysis, three-component reaction, O-fluoroalkylisourea, 2-alkoxybenzimidazole, C–H activation

Isoureas, an important class of versatile organic reagent, have been widely used as guanyleting and alkylating agents.\textsuperscript{1} Additionally, they are key precursors for constructing various bioactive molecules, such as the hypertension drug Candesartan,\textsuperscript{2} glucocerebrosidase inhibitor fused oxazolidin-2-imines and nanomolar enzyme activity enhancer spiro oxazolidin-2-imines.\textsuperscript{3} Despite their widespread applications, only a limited number of synthetic routes to isoureas have been reported, mainly relying on nucleophilic addition of alcohols to carbodiimides (Scheme 1, a). Initially, thermal acid- or base-promoted reactions were developed by Stieglitz\textsuperscript{4} and Dains,\textsuperscript{5} which are only suitable for the synthesis of N-arylisoureas. Subsequently, copper and zinc catalysts were used to promote the reaction by Däbritz\textsuperscript{6} and Schmidt,\textsuperscript{7} respectively, providing more efficient routes for the preparation of both N-arylisoureas and N-alkylisoureas. Recently, uranium and thorium amide catalysts have also been applied to the reaction, which is reported by Eisen to be a highly efficient synthetic protocol.\textsuperscript{8} These approaches are all similar, and more diverse methodologies involving simple and easily available starting materials are clearly required for the synthesis of isoureas.

Inspired by our work on transition-metal-catalysed multicomponent reactions for the synthesis of N-molecules,\textsuperscript{9} we have recently developed a copper-catalysed, three-component reaction of cyanamides, amines and diaryliodoniums for the synthesis of guanidines. Here, an extension of this methodology to fluoroalcohols was explored for the rapid synthesis of O-fluoroalkylisoureas that can be useful synthons for potentially bioactive cyclic fluoro-isoureas\textsuperscript{10} (Scheme 1, b).

We started our study by investigating the reaction of p-tolylcyanamide (1a), di(p-tolyl)iodonium triflate (2a) and 2,2,2-trifluoroethanol (3a) in the presence of K\textsubscript{2}CO\textsubscript{3} using CuCl (5 mol%) as catalyst with bipy (2,2′-bipyridyl) in toluene under N\textsubscript{2} for 2 h (Table 1, entry 1). Gratifyingly, the reaction afforded the desired isourea 4a in 62% yield, and the reaction under air produced 4a in 47% yield (entry 2). The reaction conditions including bases, solvents, ligands, and copper catalysts were then screened in detail (Table 1). Other bases such as NaHCO\textsubscript{3}, Cs\textsubscript{2}CO\textsubscript{3}, K\textsubscript{3}PO\textsubscript{4},...
t-BuOK and Et$_3$N all afforded inferior yields (entries 3–7), and the reaction without base did not produce any product (entry 8).

The reactions with 1,10-phen or DMSO, H$_2$O, DMF or THF did not improve the reaction yield (entry 8). and the reaction without base did not produce any product no desired isourea formation (entry 20). Finally, the sub-

<table>
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<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
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<th>Cat.</th>
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$^a$ Reaction conditions: p-tolylocyanamide 1a (0.3 mmol), di(p-tolyliodonium triflate 2a (0.3 mmol), 2,2,2-trifluoroethanol 3a (0.2 mmol), copper salt (0.01 mmol), solvent (1.0 ml), stirred under N$_2$, 80 °C, 2 h.

$^b$ Isolated yield.

$^c$ The reaction was performed under air.

$^d$ CuCl (0.02 mmol) was used.

$^e$ Ratio 1a/2a/3a=1:1.5:1.5.

Replacing tolune with other solvents such as dioxane, DMSO, H$_2$O, DMF or THF did not improve the reaction yield (Table 1, entries 9–13). The reactions with 1,10-phen or PPh$_3$, as ligands did not provide higher yields (entries 14 and 15), and the reaction without ligand afforded a slightly higher yield (entry 16). Other catalysts such as CuBr and Cu were inferior to CuCl (entries 17 and 18). Increasing the amount of CuCl (10 mol%) did not enhance the reaction yield (entry 19), and the absence of copper catalyst led to no desired isourea formation (entry 20). Finally, the sub-

strate ratios (1a/2a/3a=1.5:1.5:1, 1:1.5:1.5, 1:1:1.5) were explored (entries 16, 21 and 22), and the 1a/2a/3a=1.5:1.5:1 ratio was found to be optimal.

With the optimised reaction conditions in hand, the scope of the reaction with respect to cyanamidine was evaluated (Scheme 2). Phenylcyanamidine gave 65% yield of 4b, and m- and o-tolyl cyanamides also formed the corresponding isoureas 4c and 4d, respectively, in good yields. Arylcyanamides with electron-donating or electron-donating groups likewise provided 4e and 4f in comparably good yields. Impressively, 1-nathlycyanamidine afforded the desired product 4g in high yield. Additionally, some aliphatic cyanamides were found to be suitable for the reaction. However, low yields were obtained for aliphatic cyanamides, as the cross-coupling products of the aliphatic cyanamides and di(p-tolyliodonium triflate were found to be major products. For instance, benzylcyanamidine and cyclohexylcyanamidine both produced the corresponding isoureas 4h and 4i with 24% and 20% yield, respectively, and t-butylcyanamidine did not afford any of desired product 4j, which is probably due to the extreme steric hindrance of the t-butyl group.

A variety of the diaryliodonium triflates was then examined, as shown in Table 2. Symmetric diaryliodoniums with either electron-poor or electron-rich aryls produced the desired isoureas in good yields (entries 1–4). For example, di[p-chlorophenyl]iodonium triflate and di[p-t-buty]phenyl]iodonium triflate gave 63% and 55% yield, respectively (entries 2 and 4). The reactions of sterically hindered di[2,5-dimethylphenyl]iodonium triflate and di[2,4,6-trimethylphenyl]iodonium triflate furnished the desired products in higher yields (entries 5 and 6), because the side reactions between cyanamides and sterically hindered diaryliodoniums were reduced. For the unsymmetrical diaryliodonium triflates, the reactions provide good yields comparable to those with symmetrical diaryliodoniums triflates. The phenyliodonium triflates with p-(t-buty]phenyl]phenyl and p-iodophenyl both afforded a mixture of products with low chemoselectivities (entries 7 and 8). Interestingly, phenyl(p-nitrophenyl]iodonium only produced a single product 4q in low yield (entry 9). Phenyl(2,5-dimethylphenyl]iodonium triflate yielded two products 4n and 4n' in 1:7:1 ratio (entry 10). These results suggest that the more electron-rich and bulkier aryl groups of the unsymmetrical diaryliodoniums were preferable transferred in this three-component reaction.

Finally, the scope of the reaction with respect to alcohol was explored (Scheme 3). We were pleased to find that the protocol was tolerant of many fluorne-substituted alcohols. Both mono- and di-fluoroethanols delivered the corresponding products 4r and 4s in 49% and 63% yield, respectively. 1,1,1,3,3,3-Hexafluoro-2-propanol furnished the desired product 4t in moderate yield (51%).
Moreover, ethanol was found to be suitable for the reaction, although a low yield of \(4u\) was obtained (34%), indicating that fluorine plays an important role in activation of the alcohol (4r vs. 4s vs. 4u). The reaction of phenol was complex, with formation of unidentified products.

Considering 2-alkoxybenzimidazole is the core of the hypertension drug candesartan,\(^2\) the C–H activation of the isoureas was explored for the synthesis of 2-fluoroalkoxybenzimidazoles, which may have interesting bioactivities (Scheme 4).\(^10\)

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**Scheme 2** Scope of the reaction with respect to cyanamide. Regents and conditions: Cyanamide 1/diaryliodonium triflate (2a or 2b)/2,2,2-trifluoroethanol 3a (1/2a or 2b)/3a = 1.5:1.5:1.0, CuCl (0.05 equiv), K2CO3 (2.25 equiv).

**Table 2** Scope of the Reaction with Respect to Diaryliodonium Triflate\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(\text{Ar}^1)</th>
<th>(\text{Ar}^2)</th>
<th>(4/4') (ratio)</th>
<th>Yield (%)(^b)</th>
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<tbody>
<tr>
<td>1</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>4b/4'-(-)</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl(\text{C}_6\text{H}_4)</td>
<td>4-Cl(\text{C}_6\text{H}_4)</td>
<td>4k/4'(-)</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>4-Br(\text{C}_6\text{H}_4)</td>
<td>4-Br(\text{C}_6\text{H}_4)</td>
<td>4l/(-)</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>4-(t-butyl)(\text{C}_6\text{H}_4)</td>
<td>4-(t-butyl)(\text{C}_6\text{H}_4)</td>
<td>4m/4'(-)</td>
<td>55</td>
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<td>5</td>
<td>2,5-(CH(_3))(_3)(\text{C}_6\text{H}_3)</td>
<td>2,5-(CH(_3))(_3)(\text{C}_6\text{H}_3)</td>
<td>4n/(-)</td>
<td>76</td>
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<tr>
<td>6</td>
<td>2,4,6-(CH(_3))(_3)(\text{C}_6\text{H}_2)</td>
<td>2,4,6-(CH(_3))(_3)(\text{C}_6\text{H}_2)</td>
<td>4o/(-)</td>
<td>73</td>
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<tr>
<td>7</td>
<td>4-(t-butyl)(\text{C}_6\text{H}_4)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>4m/4m' (1.5:1)(^c)</td>
<td>64</td>
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<tr>
<td>8</td>
<td>4-(\text{IC}_6\text{H}_4)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>4p/4p' (1:1.1)(^d)</td>
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<td>4-(\text{NO}_2)(\text{C}_6\text{H}_4)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>4q/4'q (0:1)</td>
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<tr>
<td>10</td>
<td>2,5-(CH(_3))(_3)(\text{C}_6\text{H}_3)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>4n/4n' (1:7:1)</td>
<td>70</td>
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</tbody>
</table>

\(^a\) Reaction conditions: p-tolylcyanamide 1a/diaryliodonium triflate 2/2,2,2-trifluoroethanol 3a (1a/2/3a = 1.5:1.5:1.0), CuCl (0.05 equiv), K\(_2\)CO\(_3\) (2.25 equiv).

\(^b\) Isolated yield.

\(^c\) Ratio based on \(^1\)H NMR spectroscopic analysis.
We were pleased to find that the C–H activation of isourea 4a can be mediated by PhI(OAc)2 to form 2-(2,2,2-trifluoroethoxy)benzimidazole 5a in 91% yield at room temperature. The mild reaction conditions of this protocol mean that it could potentially have wide application.

Control experiments were also carried out for mechanistic studies. Nucleophilic addition of p-tolylcyanamide (1a) and 2,2,2-trifluoroethanol (3a) did not take place under the optimal conditions, with most of the p-tolylcyanamide being recovered (Scheme 5a).

In addition, the nucleophilic addition product 6 was not detected during the three-component reaction. Together, these results suggest that the reaction pathway involving nucleophilic addition of cyanamide 1 and fluoroalcohol 3 followed by C–N coupling with diaryliodonium triflate 2 is unlikely (Scheme 6, a).

The addition of the radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) did not reduce product formation (Scheme 5, b), ruling out a radical process.12 Thus, a plausible pathway is proposed (Scheme 6, b), involving oxidative addition of diaryliodonium triflate 2 with CuCl13 followed by coordination with cyanamide 1 and isomerisation promoted by K2CO3 to form intermediate D. Then, D may undergo reductive elimination and nucleophilic addition with fluoroalcohol 3 to generate the desired product 4 via intermediate E or F. The N-arylation products of diarylcyranamides have been proposed as intermediates for the copper-catalysed, three-component reaction of diarylcyranamides, diaryliodoniums and H2O.14 However, the N-arylation product E is barely detected in this reaction. Thus, it is reasonable to conclude that the desired product is produced via intermediate F.

In summary, an efficient copper-catalysed, three-component reaction of cyanamide, fluoroalcohol and diaryliodonium triflate has been developed for the synthesis of O-fluoralkoxyisoureas in good yields. The use of simple and readily available starting materials is a major practical advantage of this protocol. In addition, the PhI(OAc)2-promoted C–H activation of O-fluoralkoxyisoureas provides a convenient access to potentially valuable 2-fluoroalkoxybenzimidazoles. Further exploration of such three-component reactions to expand the diversity of this methodology is under way in our laboratory.
1H NMR spectra were recorded at 400 MHz or 500 MHz with a Bruker AC-500 spectrometer. 13C NMR spectra were similarly recorded at 101 MHz or 125 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual proton signals in CDCl3 (δ = 7.26, 77.00 ppm). Coupling constants (J) are reported in Hertz (Hz) and refer to apparent multiplicities; the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), quin (quinet), sept (septet), hept (heptet), m (multiplet), br (broad signal). Because of the presence of tautomers, we found that some 13C NMR signals were barely detectable for some isoureas, guanidines, and isothioureas; therefore, the total number of 13C NMR signals is more than the total number of non-equivalent carbon atoms in some isoureas, which may be due to the presence of E/Z-isomers. Mass spectra were obtained either from an LCMS-IT-TOF (ESI or APCI) using positive or negative electron spray (ES+ or ES−), or from high-resolution mass spectra (HRMS). Flash chromatography was performed using silica gel 60 (35–70 μm). Preparative thin-layer chromatography (TLC) was carried out on 20 × 20 cm plates with a thickness of 0.5 or 1 mm (SDS Silicagel F254).

All reagents were obtained from commercial suppliers unless otherwise stated. When necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. The starting cyanamides and diaryliodonium triflates are and/or distilled prior to use and stored over molecular sieves under argon. To a round-bottom sidearm flask, CuCl (0.01 mmol, 0.05 equiv), cyanamide (0.2 mmol, 1 equiv) and K2CO3 (0.45 mmol, 2.25 equiv) were sequentially added and the mixture was heated to 80 °C, with stirring for 2 h. The mixture was cooled, the reaction was quenched with water and the vessel was degassed and backfilled with nitrogen (balloon). Toluene (1 mL) and fluoroalcohol (0.2 mmol, 1 equiv) were sequentially added and the mixture was heated to 80 °C, with stirring for 2 h. The mixture was cooled, the reaction was quenched with water and the mixture was extracted with EtOAc. The organic layers were combined, dried over MgSO4 and concentrated under reduced pressure to give a residue that was purified by preparative TLC (SiO2) to obtain O-fluooralkylosourea 4.

### 2,2,2-Trifluoroethyl N′-Phenyl-N-(m-toly)carbamimidate (4a)

Yield: 42 mg (65%); colourless waxy solid.

1H NMR (400 MHz, CDCl3): δ = 7.18 (d, J = 7.1 Hz, 2 H), 7.08 (d, J = 7.3 Hz, 2 H), 7.98 (d, J = 7.4 Hz, 2 H), 7.87 (d, J = 7.2 Hz, 2 H), 5.90 (br, NH), 4.76 (q, J = 8.6 Hz, 2 H), 2.39–2.27 (m, 6 H).

13C NMR (101 MHz, CDCl3): δ = 148.66, 143.98, 134.98, 133.49, 132.88, 130.41, 129.48, 122.16, 123.40 (q, J = 277.2 Hz), 121.12, 62.52 (q, J = 36.4 Hz), 20.76, 20.68.

IR: 3405.37, 2923.81, 1672.99, 1610.85, 1509.22, 1358.83, 1270.01, 1107.32, 766.34, 697.09 cm−1.


### 2,2,2-Trifluoroethyl N′-Phenyl-N-(o-toly)carbamimidate (4d)

Yield: 47 mg (76%); colourless oil.

1H NMR (400 MHz, CDCl3): δ = 6.93–7.42 (m, 9 H), 5.80–5.86 (m, NH), 4.82–4.90 (m, 2 H), 2.16–2.26 (m, 3 H).

13C NMR (101 MHz, CDCl3): δ = 147.76, 144.78, 137.48, 128.97, 123.83, 123.71, 123.36 (q, J = 277.4 Hz), 122.31, 121.98, 120.94, 119.20, 62.43 (q, J = 36.4 Hz), 17.67.

IR: 3404.15, 2925.72, 1674.72, 1595.07, 1498.11, 1361.69, 1270.72, 1166.90, 1103.05, 747.11 cm−1.


### 2,2,2-Trifluoroethyl N-2(2-Fluorophenyl)-N′-phenylcarbamimide (4e)

Yield: 39 mg (60%); pale-yellow oil.

1H NMR (400 MHz, CDCl3): δ = 6.97–7.46 (m, 8 H), 6.19 (br, 0.35 H), 5.82 (br, 0.59 H), 4.78 (q, J = 8.4 Hz, 2 H), 2.32 (s, 3 H).

13C NMR (101 MHz, CDCl3): δ = 149.23, 134.54, 134.18, 130.53, 129.55, 124.98, 124.45, 123.38 (q, J = 276.7 Hz), 122.95, 121.92, 116.68, 116.48, 115.30, 62.86 (q, J = 36.5 Hz), 20.80.

IR: 3411.56, 2925.80, 1674.91, 1610.99, 1513.44, 1415.46, 1363.78, 1272.02, 1167.65, 1103.94, 982.73, 753.19 cm−1.


### 2,2,2-Trifluoroethyl N-(4-Methoxyphenyl)-N′-phenylcarbamimide (4f)

Yield: 41 mg (63%); pale-yellow waxy solid.

1H NMR (400 MHz, CDCl3): δ = 7.26–7.36 (m, 2 H), 6.83–6.70 (m, 7 H), 5.83–5.97 (m, NH), 4.46 (q, J = 7.6 Hz, 2 H), 3.79 (s, 3 H).

13C NMR (101 MHz, CDCl3): δ = 156.57, 155.99, 148.8, 146.79, 139.46, 137.60, 130.35, 129.79, 128.99, 123.61, 123.44, 123.37 (q, J = 278.0 Hz), 123.15, 122.42, 121.99, 120.72, 115.16, 114.11, 62.52 (q, J = 36.6 Hz), 55.42.
IR: 3407.63, 2924.93, 1672.11, 1513.56, 1488.70, 1359.04, 1269.88, 1166.53, 824.92 cm⁻¹.

2,2,2-Trifluoroethyl N-(4-Chlorophenyl)-N′-(p-toly)carbamimidate (4k)

Yield: 42 mg (62%); colourless waxy solid.

1H NMR (400 MHz, CDCl₃): δ = 6.78–7.42 (m, 8 H), 5.81–5.93 (m, NH), 4.75 (q, J = 8.2 Hz, 1 H), 4.56 (q, J = 8.0 Hz, 2 H), 2.32 (s, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 148.81, 145.28, 130.48, 129.84, 129.54, 129.98, 123.77, 123.29 (q, J = 277.4 Hz), 122.02, 121.38, 62.63 (q, J = 36.5 Hz), 20.70.

IR: 3404.79, 2925.49, 1672.80, 1492.03, 1360.44, 1270.70, 1167.44, 1096.49, 824.27 cm⁻¹.

2,2,2-Trifluoroethyl N′-(4-(Bromophenyl))-N-(p-toly)carbamimidate (4l)

Yield: 27 mg (35%); colourless waxy solid.

1H NMR (400 MHz, CDCl₃): δ = 7.39–7.45 (m, 2 H), 6.71–7.20 (m, 6 H), 5.80–5.92 (m, NH), 4.75 (q, J = 8.3 Hz, 1.79 H), 4.55 (q, J = 8.2 Hz, 0.11 H), 2.31 (s, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 148.66, 132.79, 131.93, 130.41, 129.55, 124.23, 123.24 (q, J = 279.0 Hz), 122.32, 121.91, 121.41, 116.34, 62.66 (q, J = 36.4 Hz), 20.74.

IR: 3407.63, 2924.93, 1672.11, 1513.56, 1488.70, 1359.04, 1269.88, 1166.53, 824.92 cm⁻¹.

2,2,2-Trifluoroethyl N′-(4-(tert-Butyl)phenyl)-N-(p-toly)carbamimidate (4m)

Yield: 40 mg (55%); colourless oil.

1H NMR (400 MHz, CDCl₃): δ = 7.30–7.37 (m, 2 H), 7.08–7.16 (m, 2 H), 6.87–6.98 (m, 4 H), 5.93 (br, NH), 4.77 (q, J = 8.0 Hz, 2 H), 2.31–2.54 (m, 3 H), 1.32 (s, 9 H).

13C NMR (101 MHz, CDCl₃): δ = 148.56, 130.40, 129.48, 126.67, 125.84, 122.15, 121.84, 121.26, 120.31, 62.51 (q, J = 35.9 Hz), 34.26, 31.38, 20.74.

IR: 3405.39, 2926.92, 1673.61, 1609.49, 1513.14, 1361.23, 1270.55, 1166.57, 1103.66, 824.92 cm⁻¹.

2,2,2-Trifluoroethyl N′-(2,5-Dimethylphenyl)-N-(p-toly)carbamimidate (4n)

Yield: 51 mg (76%); colourless oil.

1H NMR (400 MHz, CDCl₃): δ = 6.73–7.15 (m, 7 H), 5.75 (br, NH), 4.81–4.85 (m, 2 H), 2.33 (s, 3 H), 3.32 (s, 3 H), 2.08–2.17 (m, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 147.70, 144.76, 139.62, 135.0, 133.64, 130.95, 130.43, 129.54, 127.34, 124.41, 122.47, 121.14, 121.38, 62.39 (q, J = 36.4 Hz), 21.02, 20.74, 17.27.

IR: 3408.34, 2924.07, 1673.26, 1611.24, 1514.20, 1358.85, 1270.39, 1166.19, 811.07 cm⁻¹.

2,2,2-Trifluoroethyl N′-Mesityl-N-(p-toly)carbamimidate (4o)

Yield: 51 mg (73%); colourless oil.

1H NMR (400 MHz, CDCl₃): δ = 7.07–7.17 (m, 2 H), 6.85–6.96 (m, 4 H), 5.57 (br, 0.74 H), 5.32 (br, 0.23 H), 4.89 (q, J = 8.4 Hz, 1.52 H), 4.70 (q, J = 8.1 Hz, 0.44 Hz), 2.29–2.34 (m, 6 H), 2.14–2.18 (m, 6 H).

13C NMR (101 MHz, CDCl₃): δ = 147.01, 140.48, 134.91, 133.58, 132.53, 129.54, 129.20, 127.56, 124.80, 123.42 (q, J = 278.6 Hz), 122.26, 121.44, 119.28, 62.20 (q, J = 36.4 Hz), 20.68, 20.66, 17.97, 17.80.
IR: 3396.09, 2922.11, 1675.51, 1611.58, 1514.45, 1357.22, 1271.30, 1167.24, 1104.41, 981.66, 820.59 cm⁻¹.

2,2-Trifluoroethyl N'-4(tert-Butyl)phenyl-N-(p-tolyl)carbimidamide / 2,2-Trifluoroethyl N'-Phenyl-N-(p-tolyl)carbimidamide (4m/4m')
Yield: 44 mg (64%); 4m/4m' = 1:1; pale-yellow oil.

1H NMR (400 MHz, CDCl₃): δ = 7.30–7.34 (m, 2.95 H), 7.89–7.17 (m, 10.23 H), 5.94 (br, 1.54 H), 4.78 (m, 3.12 H), 2.33 (br, 5.42 H), 1.33 (s, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 124.59, 124.33, 134.99, 129.83, 125.83, 124.76, 122.40, 120.05, 121.24, 62.57 (q, J = 36.4 Hz), 62.51 (q, J = 36.4 Hz), 34.25, 31.36, 20.73.

2,2-Trifluoroethyl N'-4(1-Iodophenyl)-N-(p-tolyl)carbimidamide / 2,2-Trifluoroethyl N'-Phenyl-N-(p-tolyl)carbimidamide (4p/4p')
Yield: 45 mg (61%); 4p/4p' = 1:1:1; pale-yellow oil.

1H NMR (400 MHz, CDCl₃): δ = 7.57–7.64 (m, 0.88 H), 7.28–7.36 (m, 8 H), 6.56 (hept, J = 7.6 Hz, 2 H), 6.94 (d, J = 2.3 Hz, 1 H), 6.22 (tt, J = 8.2 Hz, 2 H), 7.19 (d, J = 8.2 Hz, 2 H), 4.41 (t, J = 7.5 Hz, 2 H), 2.32 (s, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 148.59, 146.53, 138.82, 137.97, 130.47, 129.86, 129.59, 129.03, 124.82, 123.58, 122.06, 121.92, 121.46, 121.29, 120.82, 86.90, 62.68 (q, J = 36.0 Hz), 62.64 (q, J = 36.3 Hz), 21.63, 21.14.

Ethyl N,N'-Di-p-tolylicarbimidamide (4q)
Yield: 18 mg (34%); colourless waxy solid.

1H NMR (400 MHz, CDCl₃): δ = 7.19–7.01 (m, 4 H), 6.88–6.94 (m, 4 H), 5.80 (br, NH), 4.40 (q, J = 7.0 Hz, 2 H), 2.31 (s, 6 H), 1.40 (t, J = 7.1 Hz, 3 H).

13CNMR (101 MHz, CDCl₃): δ = 150.36, 136.07, 132.53, 132.12, 130.25, 129.85, 129.32, 122.52, 120.61, 62.57, 20.74, 20.66, 14.32.
IR: 3412.51, 1657.62, 1610.38, 1510.33, 1381.07, 1327.68, 1232.22, 1064.68, 813.77 cm⁻¹.

Synthesis of 2-Fluoroalkoxybenzimidazoles through PhI(OAc)₂-Imidate / 2,2,2-Trifluoroethyl Isoureas; General Procedure
To a round-bottom flask, 2-fluoroalkoxybenzimidazole (5a) obtained under reduced pressure to give a residue, which was purified to yield 2-fluoroalkoxybenzimidazole 5 after preparative TLC (SiO₂).

2-Methyl-1-(p-tolylicarbimidazole) (5a)
Yield: 58 mg (91%); pale-yellow waxy solid.

1H NMR (400 MHz, CDCl₃): δ = 7.49 (d, J = 8.1 Hz, 1 H), 7.41–7.30 (m, 4 H), 7.07 (d, J = 7.9 Hz, 2 H), 7.00 (d, J = 7.9 Hz, 2 H), 4.41 (t, J = 7.5 Hz, 2 H), 3.99 (t, J = 7.5 Hz, 2 H), 2.35 (s, 3 H), 2.32 (s, 3 H).

13CNMR (101 MHz, CDCl₃): δ = 149.26, 144.84, 137.22, 132.45, 131.55, 129.28, 120.99, 119.82, 63.60, 46.55, 20.79, 20.68.
IR: 3425.30, 2920.65, 1673.61, 1606.30, 1508.24, 1400.43, 1312.80, 1201.39, 1101.60, 1041.78, 809.95 cm⁻¹.
HRMS (ESI): no molecular ion peak was found.

2,2-Difluoroethyl N,N'-Di-p-tolylicarbimidazole (4s)
Yield: 52 mg with di(p-tolylicyanamide) (63%); pale-yellow waxy solid.

1H NMR (400 MHz, CDCl₃): δ = 7.11–7.28 (m, 8 H), 6.22 (t, J = 5.5 Hz, 1 H), 5.95 (br, NH), 4.60 (td, J = 13.6, 3.9 Hz, 2 H), 2.40 (s, 3 H), 2.37 (s, 3 H).
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